Cosmetic Formulation of Skin Care Products

edited by

Zoe Diana Draelos
Lauren A. Thaman

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COSMETIC SCIENCE AND TECHNOLOGY

Series Editor
ERIC JUNGERMANN
Jungermann Associates, Inc.
Phoenix, Arizona

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edited by

Zoe Diana Draelos

Wake Forest University School of Medicine
Winston-Salem, North Carolina, U.S.A.

Lauren A. Thaman

P&G Beauty
Cincinnati, Ohio, U.S.A.

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About the Series

The Cosmetic Science and Technology series was conceived to permit discussion of a broad range of current knowledge and theories of cosmetic science and technology. The series is composed of books written by either one or two authors or edited volumes with a number of contributors. Authorities from industry, academia, and the government participate in writing these books.

The aim of the series is to cover the many facets of cosmetic science and technology. Topics are drawn from a wide spectrum of disciplines ranging from chemistry, physics, biochemistry and dermatology to consumer evaluations, safety issues, efficacy, toxicity and regulatory questions. Organic, inorganic, physical, analytical and polymer chemistry, microbiology, emulsion and lipid technology all play important roles in cosmetic science.

There is little commonality in the scientific methods, processes and formulations required for the wide variety of toiletries and cosmetics in the market. Products range from hair, skin, and oral care products to lipsticks, nail polishes, deodorants, body powders and aerosols, to cosmeceuticals which are quasi-pharmaceutical over-the-counter products such as antiperspirants, dandruff shampoos, wrinkle reducers, antimicrobial soaps, acne treatments, or sun screen products.

Emphasis in the Cosmetic Science and Technology series is placed on reporting the current status of cosmetic science and technology, the ever-changing regulatory climate, and historical reviews. The series has now grown to 30 books dealing with the constantly changing trends in the cosmetic industry, including globalization. Several of the books have been translated into Japanese and Chinese. Contributions range from highly sophisticated and scientific treaties to primers and presentations of practical applications. Authors are encouraged to present their own concepts as well as established theories. Contributors have been asked not to shy away from fields that are in a state of transition or somewhat controversial, and not to hesitate to present detailed discussions of their own work. Altogether, we intend to develop in this series a collection of critical surveys and ideas covering the diverse phases of the cosmetic industry.

The thirtieth book in this series, *Cosmetic Formulation of Skin Care Products* edited by Zoe Diana Draelos, MD and Lauren Thaman, MS comprises 22 chapters authored or co-authored by over 30 experts in the field. The development of cosmetics and toiletries represents a highly diversified field involving many subsections of science and "art." It covers the discovery of novel raw materials, development and manufacture of unique formulations, ever more sophisticated testing methods particularly in the areas of safety, clinical and performance efficacy evaluations, and claim substantiation. But even in these days of high technology and ever increasing scientific sophistication, art and intuition continue to play an important part in the development of formulations, their evaluation,

selection of raw materials, and, perhaps most importantly, the successful marketing of new products. Aesthetic considerations, such as fragrance, color, packaging and product positioning often can be as important to the success of a new cosmetic product as delivering the promised (implied) performance or the use of a new magic ingredient.

The application of more sophisticated methodologies to the evaluation of cosmetics that began in the 1980s has continued and has greatly impacted such areas as claim substantiation, safety and efficacy testing, product evaluations and testing, development of new raw materials, such as biotechnology products, for example products produced by microorganisms where genes are modified by recombinant DNA technologies. But regardless how great the science and the medical proofs behind a new product, bad or just indifferent aesthetics can hurt the performance in the marketplace.

New cosmetic formulations usually are the result of systematic development programs sponsored by corporations and carried out either in their own laboratories or by sponsored programs in cooperation with consulting laboratories. Their development involves individuals with diverse backgrounds, experience, and objectives. Though multi-tasking has become a favorite buzzword, there are obvious limitations. Top management and marketing and advertising executives identify areas of new product development that were either developed internally or brought to their attention by various outsides sources. This sometimes leads to a push for extravagant claims that might require the repeal of one or more laws of nature. The product development chemists (formulators) in the laboratory are then charged with meeting the performance objectives and product parameters set by management. In addition, they have to be concerned with a host of considerations, ranging from safety issues, global regulations, raw material cost and availability, awareness of the competitive climate, patent status, adequate preservation, stability and compatibility issues, product scale-up and production problems, to cosmetic elegance considerations, such as fragrance selection, color, and packaging. Finally, there is the medical fraternity, often dermatologists, devising and supervising efficacy and safety tests concerned with the performance of the products. This can be a key activity particularly with cosmeceuticals and other products making clinical claims that need substantiation and scientific credibility.

When looking at the total process of developing and commercializing a new cosmetic product, there are a number of stakeholders: top management, marketing and sales, R&D and operations, academic support groups, and consultants. These groups may have quite different philosophical approaches and goals. While all share a common goal of coming up with a commercially successful product, there are often real differences in how the various groups view or perceive the project. Some are clearly business-driven; others are science-driven.

This book tries to bridge some of these differences. Business-driven activities include top management's desire to have the product in the market place with good customer acceptance, a strong business plan and strategy, and good profit margins; involvement in the details on how this is achieved is secondary. To quote a speaker (Harvey Gedeon, Estee Lauder Companies) at the 2005 Annual meeting of Society of Cosmetic Chemists, "Management expects us to create low-cost breakthrough products that are the best-in-category." Marketing and sales are concerned with developing the marketing strategies and coordinating and directing the management of the new product or brand. Science-driven activities predominate in the laboratory. The formulators and the clinical workers attacking the various technical problems will be intrigued by the use of new chemicals, clever processing techniques, patentability and new testing techniques, often involving expensive new and intriguing new technical tools to solve the technical challenges presented by the project. Sometimes too many technical

tangents can delay the timely resolution of new product development projects. Building a good communication bridge between the business and different science-driven groups is the key to the success of a new cosmetic product.

I want to thank all the contributors and the editors, Zoe Diana Draelos, MD and Lauren Thaman, MS for participating in the Cosmetic Science and Technology series and the Informa Healthcare organization, particularly Sandra Beberman, with whom I have worked since the inception of this series twenty-five years ago, for their support and help.

Eric Jungermann, PhD

I dedicate this book to my two sons, Mark and Matthew,
who constantly challenge me to see the world in new fresh ways!

Zoe Diana Draelos

I dedicate this book to my many P&G colleagues
who consistently demand and force me to think what's next.

Lauren Thaman

Preface

Cosmetic formulation is becoming increasingly complex given the challenges of formulating for a technologically sophisticated consumer. This text is designed to meet the needs of the cosmetic chemist, scientist, dermatologist and formulator who must understand a wide range of issues to create successful, novel skin care products for a diverse population. To accomplish this end, the text is divided into the key knowledge areas of cutaneous formulation issues, formulation development, raw materials and active ingredients, and product testing, efficacy, and clinical assessment. The section on cutaneous formulation deals with the unique aspects of formulating for specific body areas, such as the face, eyelids, lips, hands, underarms, etc., while discussing the needs of special populations, such as individuals with sensitive skin, rosacea, atopic dermatitis, etc. Issues specific to both genders and all skin color types are presented. This initial section presents the framework necessary to design products that successfully perform in body areas with unique anatomic considerations while considering gender and ethnic differences.

The text continues by delving into formulation development by product category: cleansers, moisturizers, toners, antiperspirants, and sunscreens. This allows the reader to take the information learned in section one regarding unique anatomic needs and create skin care products by employing state-of-the-art formulation chemistry. However, the skin care industry has moved beyond basic skin maintenance product categories into actives designed to deliver skin-enhancing benefits. These areas of skin treatment include the realms of acne, photoaging, dyspigmentation, and inflammation. Actives that are important in these areas include salicylic acid, benzoyl peroxide, hydroxy acids, retinoids, vitamins, hydroquinone, antioxidants, botanicals, etc. Understanding the mechanism of action and formulation issues regarding these actives allows the creation of skin care products that deliver benefits into the treatment realm beyond maintenance.

In summary, the text presents diverse knowledge sets from dermatology, cosmetic chemistry, and product formulation. It synthesizes the information into one cohesive unit for practical application by the dermatologist, cosmetic chemist, formulator, or testing facility. Only by understanding all aspects of cosmetic formulation can technology expand the skin care marketplace.

Zoe Diana Draelos
Lauren A. Thaman

Contents

Contributors

Yohini Appa   Neutrogena Skincare Institute, Los Angeles, California, U.S.A.

Donald L. Bissett   P&G Beauty, Miami Valley Innovation Center, Cincinnati, Ohio, U.S.A.

M. Elizabeth Briden   Advanced Dermatology and Cosmetic Institute, Edina, Minnesota, U.S.A.

Karen E. Burke   Department of Dermatology, Mount Sinai Medical Center and Department of Medicine, Cabrini Medical Center, New York, New York, U.S.A.

Theresa Chen   Neutrogena Skincare Institute, Los Angeles, California, U.S.A.

Tracy Cornuelle   Research and Development, Nu Skin Enterprises, Provo, Utah, U.S.A.

James Q. Del Rosso   Department of Dermatology, University of Nevada School of Medicine, Las Vegas, Nevada, U.S.A.

Joseph DiNardo   Pharma Cosmetix Research, LLC, Richmond, Virginia, U.S.A.

Zoe Diana Draelos   Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, and Dermatology Consulting Services, High Point, North Carolina, U.S.A.

Keith Ertel   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Emmy M. Fernandez   Department of Dermatology, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania, U.S.A.

Bryan B. Fuller   Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.

Jorge I. Gaviria   Medical Hair Research Group, Inc. and Clinical Research, Skin Care Research, Inc., Boca Raton, Florida, U.S.A.

Barbara A. Green   NeoStrata Company, Inc., Princeton, New Jersey, U.S.A.

A. C. Lanzalaco   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Jan Lephart   Research and Development, Nu Skin Enterprises, Provo, Utah, U.S.A.

Joseph Lewis   Pharma Cosmetix Research, LLC, Richmond, Virginia, U.S.A.

Paul J. Matts   P&G Beauty, Rusham Park Technical Center, Egham, Surrey, U.K.

David H. McDaniel   The Institute of Anti-Aging Research, Virginia Beach, Virginia, U.S.A.

J. F. Nash   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Nathalie Nguyen   Department of Dermatology, New York University School of Medicine, New York, New York, U.S.A.

Anthony V. Rawlings   AVR Consulting Ltd., Northwich, Cheshire, U.K.

Marta I. Rendon   Dermatology and Aesthetic Center and University of Miami, Miami, and Florida Atlantic University, Boca Raton, Florida, U.S.A.

Darrell S. Rigel   Department of Dermatology, New York University School of Medicine, New York, New York, U.S.A.

Dustin R. Smith   Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.

Melanie Smith   Mary Kay Inc., Dallas, Texas, U.S.A.

D. F. Swaile   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Paul R. Tanner   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Lauren A. Thaman   P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

Diane M. Thiboutot   Department of Dermatology, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania, U.S.A.

Carl Thornfeldt   Episciences, Inc., Boise, and CT Derm, Fruitland, Idaho, and Oregon Health Sciences University, Portland, Oregon, U.S.A.

John E. Wild   Hill Top Research, Miamiville, Ohio, U.S.A.

Andrea L. Zaenglein   Department of Dermatology, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania, U.S.A.

Ru-Zhi Zhang   Department of Dermatology, The Affiliated Hospital, BangBu Medical College, BangBu, P.R. China

Wen-Yuan Zhu   Department of Dermatology, The First Affiliated Hospital, Nanjing Medical University, Nanjing, P.R. China

1
Cosmetic Formulation of Skin Care Products

Zoe Diana Draelos
*Department of Dermatology, Wake Forest University School of Medicine,
Winston-Salem, and Dermatology Consulting Services, High Point,
North Carolina, U.S.A.*

INTRODUCTION: HOW TO UTILIZE THIS TEXT

The formulation of skin care products requires a cross-disciplinary knowledge base, which can be difficult to obtain. How can any individual obtain the knowledge of a dermatologist, the expertise of a PhD biochemist, the experience of a cosmetic chemist, and the insight of a research and development scientist? There is not enough time in one lifetime to master all of these disciplines. It takes eight years after college to become a dermatologist, at least five years to obtain a PhD, 10 years to become an experienced cosmetic chemist, and 10 years to mature into a research and development scientist. Thus, after 33 years of work experience and schooling the cross-disciplinary knowledge base would be complete! This text aims to condense 33 years into 400 pages, allowing mastery of the field of skin care formulation by the exchange of knowledge.

In order to accomplish this goal, the text contains chapters written by dermatologists, PhD basic scientists, cosmetic chemists, and industry research and design (R&D) applied scientists. The book is organized sequentially in three sections: cutaneous formulation issues, formulation development and application, and active ingredients for skin treatment. Cutaneous formulation issues deals with the unique skin needs of each area of the body and the differences in skin response in various populations. This knowledge base comes from dermatology. For example, the skin care needs of the face and the hands are quite different. There are numerous sebaceous glands and small vellus hairs on the face, but none on the palms of the hands. This means that reactions to products and product design must be different for these two areas. Furthermore, a product that might perform well in fair skin might not meet the needs of persons of color. Titanium dioxide sunscreens are a good example. The titanium dioxide is not perceptible on the skin of a Caucasian individual, but causes unacceptable whitening in an African American individual. These first two chapters of the text are designed to offer specific ideas for skin care needs. The chapters can be read either in their entirety or by using the outline format to select on those body areas or special populations of interest.

The next section of the book discusses formulation development and application in the basic skin care areas: cleansers, toners, moisturizers, and antiperspirants. These chapters are all written by research and development scientists in industry with an understanding of how these products function. The chapters present the basic anatomy and physiology of the skin impacted by the product, ingredients, key considerations, and methods for product evaluation and testing. The dermatologic perspective on the use and selection of these skin care products is also presented.

Lastly, the book presents an up-to-date look at many of the active products that form the cosmeceutical arena to include: sunscreens, skin lightening agents, exfoliants, and anti-aging skin care products. The dermatologic perspective on each of these areas follows with a discussion of sunscreens in relation to skin cancer prevention, the impact of cosmeceuticals on the skin, medical therapies for skin lightening, and acne treatment methodologies. This approach allows the dermatologist to better understand how these products are constructed, but also helps the industry researcher to view products from a medical perspective that bridges the over-the-counter and prescription worlds. The text then looks at the world of botanicals, anti-inflammatories, and antioxidants. Specific raw materials are discussed by both industry researchers and dermatologists with an encyclopedic review of botanicals that are relevant to skin care.

Thus, the text presents skin care, formulation, and raw material selection issues pursuing a unique multidisciplinary approach to the topic. As part of the Marcel Dekker Cosmetic Science and Technology series, this text can serve as an introduction to some of the more product specific texts in the series that deal solely with moisturizers, cleansers, antiperspirants, etc. This text can provide the 33 years of knowledge necessary to understand skin care formulation.

2

Cutaneous Formulation Issues

Zoe Diana Draelos
*Department of Dermatology, Wake Forest University School of Medicine,
Winston-Salem, and Dermatology Consulting Services, High Point,
North Carolina, U.S.A.*

An important consideration in formulation technology is the target site for product application. Should a skin care product be formulated for the entire body or are there unique needs for specific body sites? As a dermatologist, I am keenly aware of the need to look at each anatomic area individually to achieve optimal product functioning. Failure to do so leads to development of a product that works everywhere and nowhere. The goal of this section of the text is to explore the uniqueness of the skin in various body locations to provide a foundation for anatomic formulation considerations.

To understand formulation needs of each body area, several basic concepts must be elucidated. First, the anatomy and physiology of the body site must be identified. For example, is the skin in the area bearing hair, sebaceous gland rich, transitional between dry and moist, marked by the presence of sweat glands, hormonally mediated, acne prone, age related, etc. The second basic consideration is a discussion of the dermatologic diseases that may afflict the given skin area. Good skin care products should supplement prescription medications when disease is present, but also maintain the health of the skin and prevent disease recurrence once resolution of the dermatologic problem has occurred. Third, the hygiene needs of the skin should be considered. Is there natural bacterial colonization of the site? Is the site a mucous membrane with little resistance to viral particle penetration? Lastly, thought should be given what constitutes skin health in the area and what skin care needs should be met to allow maintenance of this health.

Only after all of these particular formulation issues have been considered can a truly quality product begin the development process. Failure to give the necessary forethought will result in a product that is met with initial enthusiasm, due to well-constructed marketing claims, but poor long-term product performance, due to lack of efficacy. This formulation textbook begins with this chapter, since these ideas form the next logical step in product development following product conception.

SITE-SPECIFIC CUTANEOUS NEEDS

Many unique body areas require consideration. The face can be considered as a whole; however, the eyelids and the lips represent unique facial areas that demand separate

3

evaluation. The thicker skin of the hands and feet is different from anywhere on the body with a transitional area occurring between the rigid nails and the surrounding cuticle and soft tissue. The abundant sebaceous glands and terminal hair follicles on the scalp make this a separate skin environment, along with skin that expands and contracts with movement in intertrigenous areas such as the neck and the underarms. The female and male genitalia are also unique with numerous glandular and follicular structures that present a hygiene challenge. Everything else that is covered by skin can be simply labeled as the body. Let us begin by examining each of these skin environment areas separately.

Face

The face begins at the anterior hairline, stops at the ears, and is bounded by the lateral jawline and chin. It is the most complex and challenging area of the body for the formulator, yet more products are designed for facial use than any other. Why? Because the face is the purveyor of our image, our personality, our health, and our age. It identifies who we are, how we are, where we are, and sometimes what we hope to be. From a dermatologic standpoint, the face possesses unique medical attributes. It contains all of the glandular structures of the body, including hair, and is characterized by dry skin and transitional skin. The transitional skin is found around the eyes, nose, and mouth. It is also frequently afflicted by a variety of skin diseases that complicate product development.

Anatomy and Physiology

Let us begin by considering the anatomy and physiology of the face. The facial skin is the thinnest on the body, except for that around the eyelids. This means that the skin is easy to injure, but also readily healed. It is for this reason that skin surgeons prefer to operate on facial skin. Incisions heal imperceptibly due to the minimal movement of skin on the face and the fact that the face is not weight bearing. Compare the facial skin to that of the upper chest, which heals extremely poorly. The chest skin is constantly subject to pulling and pushing as the arms move, which predisposes any chest incision to healing with a thickened hypertrophic scar. Compare the facial skin to that of the lower ankles, which is some of the slowest healing skin on the body, because it must bear a load with walking accompanied by constant movement. Indeed, the facial skin is some of the most forgiving on the body when it comes to surgical manipulation.

On the other hand, the facial skin is some of the least forgiving when it comes to irritation and allergy. The thinness of the facial skin that is so desirable for healing purposes allows the ready penetration of irritants and allergens, making product formulation more challenging. The face is also characterized by numerous follicular structures in the form of pigmented terminal or full thickness hairs in the eyebrows, eyelashes, and male beard combined with white fine downy vellus hairs over the rest of the face. These follicular structures are the transition between the skin on the surface of the face and the ostia, or openings, that lead down into the follicle itself and the associated sebaceous or oil glands. The follicular ostia forms the structure that is commonly referred to as a pore. The follicle creates the interesting topography of the facial skin with mountains occurring around each follicular structure and intervening valleys in between. This unique topography is known as dermatoglyphics, which forms the pattern and texture of the skin. Prominent dermatoglyphics lead to what is termed coarse skin while a more even skin surface with smaller pores leads to fine skin and better texture.

At the base of the pore lies the hair follicle just below the oily sebaceous gland. The skin lining of the pore connecting the surface to the depth of the follicle is an important

transitional area. This is the skin that sloughs improperly creating the environment appropriate for acne. It is also the skin that is easily irritated resulting in the "breakouts" experienced following the use of products that cause the formation of red bumps, known as papules, and pus bumps, known as pustules. This skin cannot be reached by traditional cosmetics and skin care products, but irritant or allergic reactions that occur at the skin surface can impact this follicular lining.

The pore is not only connected to the hair, but also to the sebaceous gland. The sebaceous gland is the structure that produces sebum. Sebum is the oil of the body that lubricates the skin surface, but also provides a food supply for bacteria, such as *Propionibacterium acnes*, and fungal elements, such as pityrosporum species. The bacteria *propionibacterium acnes* digests the sebum releasing free fatty acids that initiate inflammation characterized by the influx of white blood cells. These white blood cells form the pus that is seen with acne. Pityrosporum species are responsible for the initiation of the inflammation, also due to the release of free fatty acids, which is associated with the onset of dandruff of the scalp and face. Dandruff of the face is medically termed seborrheic dermatitis.

The facial skin also contains two types of sweat glands, known as eccrine and apocrine glands. Eccrine glands are the sweat glands that produce a sterile watery liquid associated with the maintenance of body temperature. It is the evaporation of the sweat from the skin surface that allows excess heat to be rapidly removed from the body. However, on the face sweating can occur in response to emotion and the ingestion of spicy food. This type of sweating is under a different neural control than that associated with thermoregulation. The other type of sweat gland, known as an apocrine gland, produces a scented sweat that is unique to each individual. This apocrine sweat contributes to body odor and allows certain perfumes to smell differently on each individual. The apocrine sweat glands are uniquely located around the eyes.

Our discussion to this point has focused on the anatomic structures present on the facial skin to include pores (follicular ostia), terminal hairs, vellus hairs, sebaceous glands, eccrine glands, and apocrine glands. The face possesses a larger variety of these structures than any other skin on the body, which makes it unique. But, the skin on the face is structurally identical to any other skin on the body in that it is composed of two layers, to include the epidermis and the dermis. The epidermis is the outer layer of skin, which is covered by a thin layer of nonliving skin cells, known as the stratum corneum. The stratum corneum is the layer of skin with which all skin care products interact. It is this structure that is impacted by the majority of formulations concocted by the cosmetic chemist. Beneath the epidermis lies the dermis. The dermis is the collagen-rich, structurally strong layer of skin. It is the dermis of cow hides that is turned into leather. The dermis actively participates in the immunologic surveillance of the body and produces a scar if injured. For all practical purposes, the cosmetic chemist is not concerned with the dermis as this is the realm of prescription drugs.

The stratum corneum represents the skin barrier and is integral in differentiating those substances that must remain outside the body from those that are allowed to enter through the skin. It accomplishes this end by a unique arrangement of dehydrated skin cells, known as corneocytes, interspersed between a combination of oily substances, known as intercellular lipids. The intercellular lipids implicated in epidermal barrier function include sphingolipids, free sterols, and free fatty acids[a]. This organization has been likened to a brick wall where the bricks are represented by the nonliving corneocytes

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[a] Elias PM: Lipids and the epidermal permeability barrier. Arch Dermatol Res 270:95–117, 1981.

and the mortar is represented by the intercellular lipids. Any disruption in this organization, either through removal of the coreneocytes or intercellular lipids, results in a barrier defect that can ultimately result in skin disease, our next topic of discussion.

Common Dermatologic Disease Considerations

The causes of most facial skin diseases that can be impacted by skin care products are due to barrier defects. The barrier defects are mostly due to removal of the intercellular lipids resulting in excessive water loss from the skin surface, a phenomenon known as transepidermal water loss. This loss of water from the skin produces dryness, known as xerosis, with the onset of flaking of the facial skin later accompanied by redness and swelling. These physical findings are associated with the subjective findings of tightness, itching, stinging, burning, and pain, in order of increasing skin disease severity. It is the onset of this transepidermal water loss that is necessary to initiate synthesis of intercellular lipids to allow barrier repair[b,c].

The skin disease that results from dryness is known as eczema. Eczema is treated by creating an environment suitable for barrier repair to occur. Most dermatologists recommend decreased bathing and use of a mild detergent to prevent further undesirable removal of the intercellular lipids. They also recommend the use of oily moisturizers to create an artificial barrier soothing irritated nerve endings, thus preventing itching and pain, and to decrease transepidermal water loss. Moisturizers are used not to hydrate the skin, but rather to minimize further damage while the skin is healing the barrier endogenously.

It is worth mentioning that some individuals are more susceptible to barrier damage than others. For unknown reasons, some persons may have defective intercellular lipids, insufficient secretion of intercellular lipids, or corneocytes that are less resistant to structural damage. These persons will demonstrate barrier defects more readily than others and will have eczema that is harder to control and sometimes impossible to cure. These individuals are classified as possessing sensitive skin and are used in cosmetic testing panels for this reason.

The other common facial skin conditions of acne, acne rosacea, and seborrheic dermatitis are due to a completely different mechanism of action. They may ultimately result in a facial skin barrier defect, but can be considered diseases of the facial skin biofilm. The biofilm is that thin layer of sebum, eccrine sweat, apocrine sweat, skin care products, cosmetics, medications, environmental dirt, bacteria, and fungus that is present on the skin surface. A healthy biofilm will lead to skin health while biofilm abnormalities will ultimately lead to disease. For example, as has been mentioned previously, an overgrowth in the facial flora of *propionibacterium acnes* will lead to acne. Without *propionibacterium acnes* there can be no acne. Thus, skin care products can impact facial acne by minimizing the growth of this organism on the face. Propionibacterium acnes is also felt to be operative in an adult acne condition associated with facial redness and papules and pustules known as acne rosacea.

Seborrheic dermatitis is different from acne in that it is caused by a fungus, known as pityrosporum. This fungus is normally found on the facial skin in small numbers with its growth kept in check by the immune system. Seborrheic dermatitis, characterized as dandruff of the face, is more common in the elderly, persons with AIDS, after severe

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[b] Jass HE, Elias PM: The living stratum corneum: implications for cosmetic formulation. Cosmet Toilet 106 October 1991:47–53.
[c] Holleran W, Feingold K, Man MQ, Gao W, Lee J, Elias PM: Regulation of epidermal sphingolipid synthesis by permeability barrier function. J Lipid Res 32:1151–1158, 1991.

medical illnesses, and following chemotherapy. Sometimes severe untreatable seborrheic dermatitis is the first indication that an immune problem may be present. Skin care products can dramatically affect the presence of fungal elements on the facial skin, thus minimizing or maximizing the chances of developing seborrheic dermatitis through proper hygiene, discussed next.

Hygiene Needs

The hygiene needs of the face are more complex than any body area, except for perhaps the genitalia. This is due to the interplay between the skin, the hair, the sebaceous glands, the eccrine glands, and the transitional skin around the eyes, nose, and mouth. The moist skin of the nasal mucosa and the oral mucosa is an environment perfect for bacterial colonization and growth. Bacteria from these sites can easily move onto the facial skin covered with a mixture of sebum and sweat perfect for encouraging bacterial growth and spreading infection. The presence of hair also provides added surface area for bacterial growth to occur, thus the facial skin is a common site of infection.

Good facial hygiene is a careful balance between maintaining a healthy biofilm while preserving the integrity of the barrier by leaving the intercellular lipids intact. This can be challenging in light of the fact that cleansers cannot accurately differentiate between sebum and intercellular lipids. It is further challenged by the ever changing sebum production of the facial glands, which varies by both age and climate, and the different bacteria with which the body comes in contact. Many dry complected individuals fail to clean the face due to the fear that dryness will result. Ultimately, disease results. Thus, facial skin must be kept clean, but not too clean.

Skin Care Needs

In many cases, barrier damage from meeting the hygiene needs of the skin must be balanced by the use of additional skin care products. Thus, the skin care needs of the face are influenced not only by the unique attributes of the facial skin, but also by the needs created through the use of other skin care products. What are the skin care needs of the face? They are the maintenance of skin health and the enhancement of skin beauty. These are two very different goals. The maintenance of skin health has already been discussed as optimization of the biofilm, which is a careful balance between cleansing (Chapter 4) and moisturizing (Chapters 6, 7). Yet, there are other skin needs. These include the creation of an even skin surface and the prevention and reversal of skin damage.

The image of healthy facial skin is shiny skin due to abundant light reflection. This light reflection is due to an even surface. Causes of uneven facial skin include scars, facial growths such as moles, skin disease such as acne, and retained dead skin cells from the stratum corneum, known as corneocytes. Little can be done cosmetically to affect facial scars and moles, while acne issues have already been discussed. One area that deserves further mention is the issue of retained corneocytes. During youth the corneocytes slough easily as the cellular message for cell disadhesion is well transmitted. With advancing age, the cells do not disadhese or desquamate as readily leading to retained dead skin scale. This skin scale, or dander, creates an uneven skin surface. This has led to the concept of exfoliation, which uses chemical or mechanical means to encourage the removal of the dead skin scale. Exfoliants (Chapter 15) are the product category addressing this need. Exfoliation through the use of mild acids in astringent formulations (Chapter 5), such as glycolic or lactic acid, or the use of abrasive scrubs or textured cleansing cloths removes the skin scale improving skin texture and skin shine.

The other major skin need is the prevention and reversal of skin damage from sun exposure. Sun contains UVB and UVA radiation, both of which damage the skin. This damage can be seen in the form of collagen loss resulting in premature skin wrinkling or abnormal pigmentation resulting in uneven skin color. Facial skin care products have been developed to meet these needs. Sunscreens (Chapter 9) are themost important anti-aging facial skin care products currently available for their ability to absorb, scatter, or reflect UVB and/or UVA radiation. After cleansing for good facial skin hygiene, sunscreen is the most important facial skin care product to maintain skin health. Unfortunately, sunscreen is not completely effective in preventing UV damage and compliance, especially during youth, is not 100%. Thus, skin lightening preparations (Chapters 13, 14) are available to even irregular pigmentation and antiaging products (Chapters 9, 10, 11, 12) attempt to reverse facial skin damage once it has occurred.

Eyelids

From the face, we will now move to a discussion of the eyelids. The eyelid skin is some of the most interesting on the body. It moves constantly as the eyes open and close; thus, it must possess unique mechanical properties. It must be thin enough for rapid movement, yet strong enough to protect the tender eye tissues. Eyelid tissue shows the state of health and age of an individual more rapidly than any other skin of the body. When others comment on a tired appearance, they are usually assessing the appearance of the eyes and the eyelid tissue. When others comment on a sickly appearance, they are also assessing the appearance of the eyes and the eyelid tissue. The eyelid skin appears to age quickly resulting in the presence of redundant upper eyelid tissue and lower eyelid bags. The redundant upper eyelid tissue is due to loss of facial fat, cumulative collagen loss in the eyelid skin from UV exposure, and the effect of gravity pulling down the upper eyelid skin. Lower eyelid bags are also due to the effect UV damage and gravity, but edema or swelling may also contribute. This edema may be due to retained body fluids or the release of histamine from inhaled allergens. All of these factors contribute to the complexity of the eyelid skin.

Anatomy and Physiology

The eyelids are indeed composed of unique skin. It is the thinnest skin on the body, accounting for the eyelids as the most common site of irritant contact dermatitis and allergic contact dermatitis, either from products that are directly applied to the eyelids or from products transferred to the eyelids by the hands. The eyelid skin also has a paucity of sebaceous glands, making it a common area of skin dryness. While there are no hairs on the eyelids themselves, the eyelashes form an interesting transition between the keratinized eyelid skin and the cartilage of the tarsal plate giving structure to the edge of the eyelid. Tearing from the eye impacts the skin of the eyelid, since wetting and drying of the eyelid tissues can predispose to dermatitis.

The eyelids are also a common source of symptoms induced by allergies. These symptoms can be itching, stinging, and/or burning. Most persons with these symptoms respond by vigorously rubbing the eyelids. This can cause mechanical damage to the eyelid skin, from minor trauma resulting in sloughing of portions of the protective stratum corneum to major trauma resulting in small tears in the skin. Most of the skin on the body responds by thickening or callousing when rubbed. Eyelid skin will also thicken, but this predisposes to decreased functioning and worsening of the symptoms.

Eyelids are also a common site for cosmetic adornment. There are more individual colored cosmetics for the eyelid area than any other body area to include mascara, eyeliner, eye shadow, and eyebrow pencil. These cosmetics and the products used to remove them can be a source of both allergic and irritant contact dermatitis, the next topic of discussion.

Common Dermatologic Disease Considerations

As mentioned previously, the eyelid skin is the most common body site afflicted with irritant and allergic contact dermatitis. Some of this predisposition is due to the thinness of the eyelid skin, but the transitional nature of the tissue is also important. The eyelid bridges the transitional area between the well-keratinized skin of the face and the moist tissue of the conjunctiva that lines the inner eyelid and the eyeball. The moisture from tearing wets the eyelid skin and enhances irritant and allergen penetration. It can also help dissolve any allergen or irritant, possibly enhancing the adverse reaction. The eyes are also uniquely designed to sense substances that might cause vision damage, and thus the eyelids have a heightened immune response. Swelling induced by topical, inhaled, or ingested allergens are frequently seen initially in the eyelids. The thin nature of the skin also allows the swelling, due to tissue edema, to appear more dramatic than on other body areas where the skin is thicker and less mobile.

In addition to irritant and allergic contact dermatitis involving the eyelid skin, there are also eyelid diseases involving the eyelid sebaceous glands found at the base of the eyelash follicular unit. This condition is basically acne of the eyelashes and is found both in adolescents and the elderly. It is treated with oral antibiotics, much like traditional facial acne, but superb eyelid hygiene is necessary to prevent recurrence and the avoidance of oily substances in the eye area that might block the sebaceous gland orifice is mandatory.

A type of dandruff, known as seborrheic blepharitis, can also affect the eyelids. This represents the eyelash equivalent of the seborrheic dermatitis, mentioned earlier, that can affect primarily the scalp and sometimes the folds of the face, such as the skin around the nose and mouth. Seborrheic blepharitis is also caused by fungus; thus, proper eyelash hygiene is the key to control. Most individuals with scaling in the eyelash area will also present with facial and scalp scaling as well, thus necessitating treatment of the entire scalp and face.

The eyelid skin is also uniquely affected by the immune status of the individual. Most persons with inhaled allergies to pollen, fragrance, dust, etc. will complain not only of a runny nose, but also of itchy eyes. The eyelids and the nose both represent areas possessing transitional skin bridging the wet mucosa with the traditional dry keratinized skin. Since the wet mucosa is devoid of a skin barrier to allergens and infection, the immune system is particularly fortified in these locations. For this reason, hyperimmune states that affect the overall body skin are keenly present in the eyelid area. The most common of these conditions is known as atopic dermatitis. Atopic dermatitis is a combination of dry skin, asthma, and hay fever. Thus, these individuals have chronic itchy skin, problems breathing, and bad inhaled allergies. One of the most common sites for this condition to manifest is the eyelid. These atopic persons have chronically itchy eyelids that become red, swollen, and tender. They represent a unique population of sensitive eyelid persons that have problems with many eye area cosmetics and skin care products. Treatment of these individuals usually involves the use of high-potency topical corticosteroids and oral antihistamines.

By far the most common dermatologic disease to afflict the eyelid is eczema, more commonly known as bad dry skin. Since the eyelid is relatively poor in oil glands, dry

eyelid skin is frequently seen due to over-aggressive removal of lipids. This may be due to the use of a strong cleanser or products designed to solubulize oil-based waterproof cosmetics, such as mascara and eyeliner. Anything that damages the intercellular lipids or the corneocytes will result in eyelid eczema. Thus, eyelid hygiene must achieve a careful balance between the removal of excess sebum and old cosmetics to prevent eyelash infections and seborrheic blepharitis, while preventing damage to the intercellular lipids and ensuing eyelid eczema.

Hygiene Needs

Cleansing of the eyelid tissue is indeed a delicate task. Typically, the skin should be handled very gently, due to its thin nature, and cleansing should remove excess sebum while preserving the intercellular lipids. If more aggressive cleansing is required, an appropriate moisturizer must be selected that will provide an environment for healing while the intercellular lipids are resynthesized. The typical cleanser used in the eye area by dermatologists is baby shampoo. This non-stinging shampoo formula allows cleansing of the eyelashes to prevent seborrheic blepharitis, while minimizing further eyelid irritation. Typically, the cleanser is applied with the fingertips and not a washcloth or other cleansing implement, since the fingers can easily sense if too much pressure or force is being used to clean the thin eyelid tissue. Most of the diseases of the eyelid and the eye itself are related to poor eye area hygiene and the onset of infection. Thus, appropriate eyelid hygiene is medically and cosmetically important.

Skin Care Needs

After maintaining good eyelid hygiene through proper cleansing, the issues of moisturization and sun protection must be addressed. These are the skin care needs of the eyelid skin. The recurring theme throughout this discussion of the eyelid has been the unique thinness of the skin. This consideration becomes extremely important when formulating eyelid moisturizers and sunscreens. Any eyelid moisturizer selected must spread easily to prevent bruising or tearing. Thus, highly lubricious emollient formulations are best. They should occlude the eyelid skin enough to allow the skin barrier to repair, but should not be too oily such that they interfere with vision if accidentally introduced into the eye.

The thinness of the eyelid skin also makes the use of sunscreens important. UVA radiation can easily penetrate to the dermis of the thin eyelid skin, causing premature wrinkling. The eyelids are also a common site for UVB-induced sunburn. This makes UVA and UVB broad spectrum sun protection vital, a topic more fully discussed in Chapter 9. It should come as no surprise that most men and women notice aging first in the upper and lower eyelid tissue. This thin skin quickly looses elasticity from photodamage, which can be exaggerated by familial tendencies toward eyelid skin laxity, a condition known as blepharochalasis. Eyelid sunscreens must be carefully formulated to avoid allergic and irritant contact dermatitis, stinging, and burning should the product enter the eye, and limited photoprotection. In addition to sunscreens, excellent eyelid skin protection can obtained through the use of sunglasses and hats.

Lips

The lips present many of the same challenges as discussed previously for the eyes. They both represent transitional skin between traditional keratinized dry skin and moist mucosal skin and they both are portals of entry for foreign invaders, such as bacteria and

viruses, and other substances entering the body, such as medications. However, the lips are much more complex in terms of the substances they contact, since the lips are instrumental in eating. They contact many different foods, chemicals, and cosmetics. They are also in constant motion, much more so than any other part of the body, due to their participation in the phonation associated with speech. Yet, their cosmetic value cannot be minimized. They are an instrument of affection as delivered by a kiss and the focal point of the face. Much poetry has been written about beautiful ruby red lips through the ages.

Anatomy and Physiology

The lips must sustain pulling, twisting, and contracting forces in many different directions in order to eat and speak. To accomplish this engineering feat, they contain a transitional skin surface, known as the vermillion, overlying a complex array of muscles with supporting fat. The vermillion is the portion of the lip that is visible and adorned by lip cosmetics. It has a rich vascular supply that is visible through the thin overlying skin. The lip skin is unique in that it does not have a well-developed stratum corneum making it different than the rest of opaque facial skin. Damage to the lip tissue, from sun or cigarette heat, results in formation of a dysfunctional stratum corneum that causes the lips to lose their characteristic red color. This causes a whitening of the lips, medically known as leukoplakia, literally translated as white plaque.

As the lips age, they begin to thin and lose their characteristic shape. This is due to loss of the fat that gives the lip substance. A profile view of a child will reveal lips that protrude from the face, while the profile of a 70-year-old woman will reveal lips that are flat and even depressed from the facial surface. Many of the new cosmetic fillers, such as hyaluronic acid, are designed to replace this lost fat. The loss of lip shape is also accentuated by loss of teeth and bony gum structures that give the lips their characteristic Cupid's bow shape. The lip muscles remain intact throughout life, but cannot make up for the loss of the underlying fat suspended over a bony frame.

Common Dermatologic Disease Conditions

The lips not only are subject to the effects of aging, but also to the insults of dermatologic disease. Infection is probably the most common serious lip problem. This is typically due to the herpes simplex type 1 virus that is responsible for fever blisters. This infection is seen as a group of clustered tiny blisters, known as vesicles, at the margin of the red vermillion. The herpes simplex virus is usually contracted during youth and remains dormant under the watchful eye of the immune system until reactivated and allowed to migrate from the nerve root to the skin surface. The virus reactivates when the immune system is overburdened. This most commonly occurs when the body is sick with another infection, hence the name "fever blister" for the herpes infection. When the body is busy fighting an infection war at another location, the herpes virus takes the opportunity to reproduce and migrate to the lip causing further pain and misery. The fever blister is contagious during the time when the blisters are filled with liquid. Once a scab has formed over the blister, the infection is no longer transmissible. This is important to the cosmetic industry, since shared lip balms and lipsticks can transmit the virus as long as the blister fluid remains moist. Herpes simplex infections are usually treated with antiviral drugs, such as acyclovir, that stop the virus from reproducing, but unfortunately cannot eradicate the virus from the body. For this reason, fever blisters are recurrent.

The lip is also the site of other infections, such as those caused by yeast. Yeast organisms may be present in the mouth and can migrate to the lips under certain

conditions. Yeast most commonly infects the corners of the mouth, a condition known as perleche. The corners of the mouth are a frequent site of saliva collection, especially in children who drool, adolescents with braces, and the elderly with poor dentition. The moisture remains in the mouth corners overnight, creating a condition known as maceration, and provides a perfect environment for the growth of yeast. Yeast typically is not transferred person to person like the herpes virus previously discussed, but can be a source of pain when cosmetics are applied or a complication of chapped-appearing lips. Perleche is usually treated with a combination of topical low potency corticosteroids and topical antifungal/antiyeast creams.

The last common lip disease to be discussed is chelitis, which simply means inflammation of the lips. Chelitis can be due to chapped lips, a condition akin to dry skin. This can result from insufficient oil being produced by the tiny yellow oil glands lining the edge of the vermillion border, as seen in elderly individuals, or due to chronic wetting and drying of the lips from lip licking, as seen in children. Both of these conditions can be remedied by the use of lip balms, lip moisturizers, or lip sticks. Good occlusion is typically required to allow these conditions to resolve, achieved through the use of oily substances, such as petrolatum, waxes, and silicones. Some elderly individuals may appear to have chronic chelitis or chapped lips due to the continual presence of peeling skin over the lips. This may be due to dryness, but may also be due to insufficient exfoliation of the lip surface or another condition known as actinic chelitis.

Actinic chelitis presents as whitish lips with unrelenting skin scale. The word "actinic" means sun. The dry skin can be removed, but is quickly replaced by the lip renewal process that is unable to make quality smooth skin. Instead, the lip is replaced every two weeks by skin made by cells containing sun damaged DNA. Actinic chelitis is a precancerous condition that can possibly culminate in skin cancer after years of neglect. Actinic chelitis is cosmetically unattractive, since the lips lose their distinct outline and red color, and is best prevented through the use of sunscreen-containing lip balms and opaque lipsticks.

Hygiene Needs

From the preceding discussion, it is apparent that the lips have some unique hygiene needs, because they are the gatekeeper of everything that is consumed orally. Typically, the lips are washed with the face, but they are regularly cleansed with saliva. They are most frequently infected by direct contact with other infected individuals through kissing. Infection that enters the body through the mouth via hand/oral transmission is far more common than infection of the lips themselves.

Skin Care Needs

The best method for keeping the lips infection free is to maintain the vermillion intact, free of fissures or openings. This requires the use of waxy, thick moisturizers designed to stay on the lips through saliva and food contact. The tiny yellow sebaceous glands that can be seen along the edge of the lips in elderly individuals do not function as abundantly with advancing age. Dry lips are also more common in the elderly due to nasal obstruction promoting mouth breathing and dentures that may not fit properly. Dry lips may also be seen at the other end of the spectrum in children who are endentulous or thumb suckers. Occlusive lip balms that prevent saliva from repeatedly wetting the skin surface are the most successful at alleviating the dry skin.

Lip balms can be further adapted to provide both lip moisturization and sun protection. A quality lip balm used on a daily basis with an SPF of at least 15 can prevent

actinic chelitis, a medically and cosmetically significant condition. A sunscreen-containing lip balm is also the best way to prevent the recurrence of a herpes simplex fever blister, since the virus is photo-reactivated. Lastly, sunscreen-containing lip balms can prevent skin cancer of the lip, a serious medical condition.

Hands

The hands are one of the most expressive parts of the body, providing the structures needed to write, draw, paint, dance, and express affection. It is frequently said that much can be said about people from their handshake, which is an assessment of the skin, muscle, and bone that form the hand. The hand can express gender, occupation, and age. Female hands are small while male hands are large and muscular. People who work with their hands outdoors have a much different skin feel than persons who type on a computer for much of the day. Children have soft, doughy, padded hands while the elderly have thin, sinewy, bony, arthritic hands. Hands are what make humans unique from every other living thing on the earth.

Anatomy and Physiology

The hands are formed of many tiny muscles and bones that account for their agility. They are that part of the body that most frequently touches the outside world and can serve as a vector, bringing infection to the vulnerable nose, eye, and mouth tissues. The hands also sustain considerable chemical and physical trauma. They are washed more than any other body area, yet are completely devoid of oil glands on the palmar surface.

While the stratum corneum of the palm is uniquely designed to withstand physical trauma, it is not designed to function optimally when wet. Water destroys the resistive physical strength of the palmar skin, which is why hand blisters are more common when the hand is perspiring heavily. The palmar surface of the hand has numerous sweat glands, known as eccrine glands, which are largely under emotional control. Palm sweating may occur in warm weather, but may also occur under stressful conditions.

The hand responds to trauma by forming thickened skin, known as a callus. Calluses are formed from retained layers of keratin that form a dead skin pad over the area subjected to repeated physical trauma. For example, the palm of the hand will callus to protect the small bones in persons who use a hammer. The finger will callus in the location where a pencil is held in both children and adults. While the body forms a callus to protect underlying tender tissues, the callus can also cause dermatologic problems. Since a callus is made of retained keratin, it is dehydrated and inflexible and will fissure readily with trauma. Once the keratin is fissured, it cannot be repaired, since the callus is nonliving. This leads to a discussion of the most common dermatologic disease considerations involving the hand.

Common Dermatologic Disease Considerations

Dermatologic disease needs to be divided into those conditions that affect the dorsum or back of the hand and those that affect the palm of the hand. This is an important distinction because the two skin surfaces are quite different. The dorsum of the hand is thinner skin that becomes increasingly thinner with age. After the face, the back of the hand is generally the most photoaged skin location. The skin of the hand loses its dermal strength early leading to decreased skin elasticity, which can be simply measured by pinching the skin on the back of the hand and watching for the amount of time it takes for the skin to

rebound to its original conformation. This easy to perform test is an excellent measure of the hand skin age. Skin that takes a long time to return to normal configuration is more photoaged than youthful skin that bounces back energetically. In addition to losing elasticity, photoaged skin also becomes irregularly pigmented leading to dark areas, known as lentigenes, and light areas, known as idiopathic guttate hypomelanosis. This irregular pigmentation is also accompanied by skin that is easily injured. Injury may be seen in the form of red bruises, affectionately named senile purpura, and tissue tears from minimal trauma, which heal with unattractive white scars.

The palm of the hand is affected uniquely by inflammatory conditions like eczema and palmar psoriasis. Because the palm is the surface that the body uses to pick and touch, it more commonly is affected by chemical and physical trauma. This trauma may manifest as hand eczema, which is usually treated with high potency corticosteroids. In addition, highly occlusive and emollient hand creams are necessary to rehydrate damaged keratin and create an optimal environment for barrier repair. Hand creams are also important in the treatment of psoriasis where too much poor quality skin is produced too quickly. Both of these conditions require carefully selected cleansers and moisturizers, in addition to prescription therapy.

Lastly, the palms can be affected by excessive sweating, a condition medically known as hyperhidrosis. Palmar hyperhidrosis can be physically disabling to persons such that they cannot hold a pen to write or emotionally disabling such that they are uncomfortable shaking hands. As mentioned previously, the eccrine sweat glands on the palms are under temperature and emotional control. Palmar hyperhidrosis is usually more of an emotional condition, since the sweat released by the hands does little to cool the body. The treatment of hyperhidrosis is addressed in Chapter 8.

Hygiene Needs

The hands receive more cleansing than any other part of the body. The basic ritual of "wash your hands before you eat" is an effective method of preventing disease transmission, but may take its toll on the physiologically sebum-lacking skin of the palms. Excessive hand washing can even be considered a medical disease, especially in persons with obsessive-compulsive disorder. There are a variety of methods of washing the hands. Basic hand washing is usually performed with a bar or liquid soap followed by water rinsing. Regimented timed hand washing routines are used to thoroughly remove all bacteria from the hands prior to surgery. Lastly, a variety of hand cleansing antibacterial gels have been introduced, usually based on triclosan, that can be used without water to clean the hands. In general, it is felt that the physical rubbing of the hands to lather the cleanser followed by rubbing in a running stream of water to rinse away the cleanser is important. Both the physical rubbing of the hands and the chemical interaction of the cleanser and water are necessary for optimal hand hygiene.

Skin Care Needs

The skin care needs of the hands go beyond basic cleansing to moisturization, healing, photoprotection, and skin lightening. As mentioned previously, hand moisturization is very important due to frequent cleansing. Hand moisturizers should be designed to occlude the skin reducing transepidermal water loss, rehydrate the skin through the use of humectants, alleviate itch and pain, and smooth the skin surface with emollients. Hand moisturizers with this type of construction can be used for simple dry skin, as well as providing healing qualities for the dermatologic conditions previously discussed.

In addition to moisturization, the hands also need photoprotection both during sports and while driving a car, since photoaging UVA radiation passes through the windshield of a car. Sun protection is a unique challenge for the hands because they are frequently aggressively washed, removing the sunscreen. However, the need for sun protection is obvious when one considers the thin dyspigmented skin that characterizes mature hands. This means that the hands require aggressive anti-aging therapy, discussed in Chapter 11, and skin lightening, discussed in Chapters 13, 14.

Feet

The hands and the feet have much in common. They both have a different type of epithelium on the dorsal and plantar surface, they both have hair on the dorsal surface and none on the plantar surface, and they both have few sebaceous glands and numerous sweat glands on the plantar surface. However, there are many differences between the hands and the feet, the most important being that the feet constantly bear the weight of the body while the hands do not. The feet are used for locomotion, competitive athletics, and personal expression in the form of dance. They are forced into shoes that can function both as protection while walking and the source of bony deformity. One only need look at the bunions and overlapping toes of the woman who wore tall, spiked heel, pointed toe shoes during her youth who cannot walk normally today due to misshapen feet that cannot properly bear weight.

Anatomy of Physiology

The feet form our most important point of contact between the body and the earth. They grow proportionately as we grow during adolescence, pregnancy, and old age to provide the body with stable balance. Unfortunately, their bones wear out with continued use and chronic inflammation to yield crippling arthritis. The sole of the foot is made of keratin remarkably resistant to trauma from torque and pressure, but this resiliency is decreased when the keratin is wet. This most commonly occurs in individuals with sweaty feet. The interaction of sweat with the plantar keratin in the environment of the shoe creates unique hygiene challenges. The lack of oil glands on the sole of the foot also predisposes it to dry skin. This leads to our next topic of discussion, which is dermatologic disease of the feet.

Common Dermatologic Disease Considerations

As might be expected, the warm, moist, dark environment of the foot in the shoe is perfect for infection of all types, especially between the toes. The foot is a common site for bacterial, fungal, and yeast infections. These organisms can live on the surface of the foot or enter into the body through small wounds. Foot infection is a major medical issue in diabetics who have a reduced capacity to fight infection, poor blood circulation to the feet, and reduced sensation. In normal individuals, the most common infection of the feet is fungal, a condition known as tinea pedis. Tinea is the medical word for fungal infections of all types with pedis referring to the feet. Tinea pedis most commonly occurs between the toes, especially between the fourth and fifth toes, since these toes are usually closely spaced. Mild infections of this type can occur in otherwise healthy athletic individuals; however, the incidence of fungal infection increases with advancing age due to deterioration of the body's immune system. Most fungal infections of the toes or the sole of the foot can be easily treated with two weeks of a topical antifungal. However, fungal infections of the nail require oral medication, usually for three months.

The foot is also the site of frequent viral infections in the form of plantar warts. The highly infectious human papilloma virus causes warts. This virus only affects humans, thus warts are passed by person-to-person contact through wounds in the foot. Common places to contract warts include public pools, exercise facilities, dance studios, public showers, etc., basically any place where there is moisture and lots of bare feet.

Other noninfectious growths that occur on the foot include calluses and corns. Calluses form over areas of the feet that are commonly traumatized, such as the side of the great toe, the side of the little toe, and the heel. Corns, on the other hand, occur over bony prominences. Hard corns occur on the sole of the foot at the base of the toes while soft corns occur over bones between the toes. Both calluses and corns are deposits of excess keratin designed to protect the foot from undue injury while walking. Unfortunately, the calluses and corns themselves may produce pain while walking. Substances can be applied to the growths to remove the keratin, but the callus or corn will return unless the exact cause for their formation has been determined. This can be ill-fitting shoes, arthritic changes, or improper weight transfer over the foot while walking.

The foot is also a common site for eczema or dry skin due to the complete lack of oil glands on the sole and the reduced number of oil glands on the top of the foot. The feet receive the most cleanser and water contact of any part of the body while showering, thus excessive removal of sebum on the feet is common. For all of the reasons put forth here, the feet have unique hygiene needs to balance the predilection for infection with the dryness of overcleansing.

Hygiene Needs

The feet need aggressive hygiene, not only to prevent infection, but also to control odor. Foot odor is primarily due to the mixture of sweat with bacteria in the closed environment of the shoe. Bacteria digest the sweat to obtain nutrition and reproduce. Most individuals have several types of bacteria present in low numbers on the feet. The difference between individuals with minimal foot odor and extreme foot malodor is the number and type of bacteria present on the feet. Foot malodor is a much greater problem in persons with hyperhidrosis. Hyperhidrosis of the feet is identical in cause to hyperhidrosis of the palms, in that both are primarily under emotional control, although feet tend to sweat more for thermoregulatory purposes due to the presence of warm socks and shoes.

Good cleansing of the feet is a prerequisite to skin health, but overly aggressive cleansing may set the stage for dry skin and foot eczema. Thus, foot cleansing must be carefully balanced with proper moisturization, our next topic of discussion.

Skin Care Needs

One way to minimize the dryness that may be associated with foot cleansing is through the use of moisturizers. Moisturizers can be used to prevent foot dryness and soften calluses utilizing substances such as urea and lactic acid to open up water binding sites on dehydrated keratin. The physical act of rubbing a moisturizer on the feet can also help desquamate dead skin that may build up between the toes and on the arch of the foot, especially in elderly individuals. Foot moisturizers must be similar to hand moisturizers in that both occlusive and humectant substances must be incorporated.

Nails and Cuticles

No discussion of the hands and feet would be complete without consideration of the nails and cuticles. Even though the nails are made of nonliving keratin, they are the source of

considerable cosmetic attention. Manicures, pedicures, artificial nails, nail polish application, etc. are all popular activities. Certainly, the nails add glamour and enhance the appearance of the hands and feet. In certain cultures, the fingernails are used to designate class status. For example, Greek males allow their little fingernail to grow longer than the rest to show that they work at a desk job rather than performing manual labor, since a long little fingernail cannot be maintained if people use their hands to make a living. Similarly, women in United States use long nails for much the same purpose. Since the nails are made of nonliving tissue, their cosmetic needs are much different than any of the other body areas previously discussed.

Anatomy and Physiology

The nail is a thin plate of nonliving keratin designed to protect the tip of the finger and toes. The nail is produced by a group of cells designated as the nail matrix that lies approximately one-quarter inch below the visible nail. The nail matrix cells are formed at birth and cannot regenerate following injury. For this reason, trauma to the nail matrix can result in a permanently deformed nail that cannot repair and will not grow normally. One of the most important structures adjoining the nail from a dermatologic standpoint is the cuticle. The cuticle is a like a rubber gasket forming a watertight seal between the nonliving nail and the skin of the fingertip. Damage to the cuticle results in water, chemicals, or anything the hand touches reaching the nail matrix cells. It is for this reason that dermatologists recommend that the cuticle not be dislodged, pushed back, trimmed, or manipulated in any way. Many of the abnormalities and diseases of the nail tissue can be traced back to a damaged cuticle.

Common Dermatologic Disease Considerations

Nail abnormalities and disease are extremely hard to treat because the visible nail cannot be repaired; only the growth of new nail can be influenced. In most individuals, it takes six months to grow a new fingernail and one year to grow a new toenail. This means that creation of a new nail to replace a damaged nail is a long process requiring patience before the effects of successful treatment are visible. The common nail problem is loosening of the nail plate from the nail bed, a condition known as onycholysis. Onycholysis is usually traumatic in nature and is more common in individuals who wear artificial nails in the form of sculptures or tips. The bond between the artificial nail and the natural nail is stronger than the bond between the natural nail and the underlying skin. This means that the natural nail plate will rip from the skin causing pain and swelling of the finger. The natural nail now appears white, because the nail is no longer attached to the pink flesh, and a space is created beneath the nail plate and the skin where infection can occur. Onycholysis is the most common condition predating a nail fungal infection.

Fungal infections of the nail, medically known as tinea unguinum, are extremely common with advancing age. It is estimated that 80% of persons age 80 or older will develop a nail fungal infection. The infection becomes more common with advancing age as the immune system's ability to protect against a fungal invader is diminished. The same fungus that causes infection of the feet also causes nail fungus, as mentioned previously during our discussion of foot diseases. Nail fungal infections of the hands and feet are very difficult to treat since medication cannot be administered to the nonliving nail. The site of the nail fungal infection is not actually the nail itself, but the living tissues beneath the nail. This makes topical treatment minimally effective because any topically applied medication must penetrate the hard nail plate to reach the infected tissues below. For this reason, fungal nail infections are traditionally treated orally with medications that

must be taken for three months. The oral medication allows an antifungal to be incorporated into the newly grown nail, forming a barrier for the advancing fungal infection. The old infected nail is then cut away to physically remove the infected nail plate, and eventually the treated nail, resistant to fungal invasion, is formed. However, the nail containing the oral antifungal medication is removed with further nail growth and reinfection commonly occurs.

Nail fungus is actually transmitted through fungal spores which are extremely resistant to destruction. Traditional disinfectants used to clean manicure and pedicure instruments are ineffective against the spores, thus fungal disease can be transmitted through nail salons. Nail fungus is also not susceptible to triclosan or other antibacterial agents traditionally used in soaps and cleansers. Thus, the best protection against a nail fungus infection is an intact nail and surrounding cuticle.

Another common nail problem is peeling and cracking of the nail plate. While these are largely cosmetic concerns, they can result in pain and leave the nail weakened to infection. Nail peeling and cracking are more common with advancing age. This may be due to decreased blood flow to the cells of the nail matrix from arthritis or blood vessel disease or due to declining nutritional intake. The body certainly recognizes that the nails are not essential to maintain life, thus under times of stress or illness nail growth is not optimal. However, there are conditions where nutrients may not be absorbed from the intestinal tract that becomes more common with advancing age. One of these nutrients is biotin. Biotin is necessary for hard nails and may not be properly absorbed. For this reason, one of the main treatments for peeling, cracking nails is an oral biotin supplement. Nail dehydration may contribute as well, but this topic is addressed under skin and nail care needs.

There are a variety of inherited or acquired nail deformities for which no treatment exists. For this reason, many dermatologists run the other way when a patient presents with nail problems. Probably the common somewhat treatable nail deformity is psoriasis. As we discussed previously, psoriasis is the production of too much poor quality skin too quickly. Psoriasis of the nail is similar in that the nail that is produced is also poor quality such that little chunks of the nail plate fall out leaving tiny holes or pits. Thus, the hallmark of nail psoriasis is pitted nails. The nails improve slowly as the body psoriasis improves, but methods of camouflaging the problem with nail polish or artificial nails are a more rapid solution. Most dermatologic nail conditions are best treated in the short term with cosmetic techniques, which are beyond the scope of this text.

Hygiene Needs

As mentioned previously, the most important way to keep the nail plate healthy is to leave the cuticle undisturbed. For some, this answer is almost too simple. The nail is designed to take care of itself, and any manipulation interferes with the perfect design. Typically, hand hygiene and nail hygiene are taken care of simultaneously with good hand washing.

The most common infection that affects the nail is known as a paronychia. A paronychia is actually an infection of the skin surrounding the nail to include the cuticle. Here the cuticle is disrupted and water enters the tissue around the nail. This forms a warm, dark, moist space perfect for the growth of yeast organisms. The yeast breakdown the skin and make an environment appropriate for bacterial infection, which occurs secondarily. The bacteria then multiply and produce pain and pus. Use of antibacterial cleansers containing triclosan are very helpful in preventing a paronychial infection along with good moisturization of the tissues around the nail to prevent cracking. Oral antibiotics are usually required to treat nail and cuticle infections of this type.

Skin and Nail Care Needs

Moisturizing the nail and the cuticle are important to prevent disease. Usually these structures are moisturized at the same time the hands are moisturized, but there are some key differences to consider. The outer stratum corneum layer of the skin of the hands is replaced every two weeks, but the nails are nonliving, thus, any dehydration damage inflicted is permanent. Remoisturizing the nails can be minimally enhanced with urea and lactic acid, which increase the water binding sites on the nail keratin, but their effect is temporary until the next hand washing. Also, too much urea and lactic acid can over soften the nail plate, making it more susceptible to fracture. Water is the main plasticizer of the nail plate and it should not be removed with aggressive cleansing.

Scalp

The scalp/hair interface is very similar to the nail/cuticle interface in many respects. Here the nonliving hair abuts the living scalp, just like the nonliving nail abuts the living cuticle. The skin needs of the scalp are complex due to the presence of abundant sweat, sebum, and nerves all complicated by the presence of numerous hair follicles. It is beyond the scope of this text to deal with the many issues surrounding hair growth and cleansing, thus this section will focus strictly on the skin forming the scalp.

Anatomy and Physiology

It is important to recognize that healthy hair begins with a healthy scalp. The hair grows actually below the skin of the scalp with follicles protected in the subcutaneous fat covering the skull. The scalp has an abundant blood supply to provide the necessary nutrients for hair growth and an extensive nerve network. This is why injuries to the scalp bleed profusely and are quite painful. In addition to blood vessels and nerves, the scalp also has numerous eccrine sweat glands and sebaceous glands. These secretions provide nutrients for bacteria and fungus that can infect the skin of the scalp. The hair also increases the chances for infection by providing abundant surface area for organisms to grow. Lastly, sweat can function as an irritant, accounting for the frequent itching associated with areas of sweat collection, such as the nape of the neck. The presence of the neural network around the hairs also provides more opportunities for sensation of itch to be induced.

Common Dermatologic Disease Considerations

The scalp is the site of many dermatologic diseases, the most common of which is dandruff. Dandruff lies on a spectrum between occasional mild flaking of the scalp to thick oozing plaques devoid of hair, known as seborrheic dermatitis. Both of the conditions are caused by the same fungal organism named Malassezia globosa. This fungal organism is present in the air and lands on the scalp rich in sebum. It consumes the sebum and leaves behind free fatty acids that are extremely irritating to the scalp skin. These free fatty acids induce itching, inflammation, and increase the scalp skin turnover resulting in flaking. If the immune system is intact, the body will not allow the Malassezia to proliferate and the skin remains healthy. If the immune system is not intact, such as with advancing age, the presence of illness, or human immunodeficiency virus (HIV) infection, the Malassezia organisms will multiply and their sheer number will induce an infection. A mild infection may be perceived as dandruff, but a more severe infection is termed seborrheic dermatitis. The key to preventing a Malassezia

scalp infection is the use of topical antifungals in the form of shampoos containing zinc pyrithione or selenium sulfide or ketoconazole. Active infection can be treated with prescription oral and/or topical antifungals.

It should be mentioned that other fungal organisms, besides Malassezia, could also infect the scalp. These include the same fungal organisms that cause athlete's foot (tinea pedis) and nail fungal infections (tinea unguinum). Fungal infections of the scalp, medically known as tinea capitas, are commonly termed ringworm. A worm is not involved, but the areas of hair loss are round, hence the early misnomer that a round worm was causing the problem. The organisms that cause scalp fungal infections can be transmitted person to person on combs or through direct contact. For this reason, tinea capitas is mainly seen in children. It is a highly contagious infection requiring the use of oral prescription antifungal medication for eradication.

Bacteria can also affect the scalp creating an infection known as folliculitis. In this condition, the bacteria enter the scalp at the site where the hair exits the scalp, known as the follicular ostia. This is the weakest point of the scalp to infection, since the hair slightly tents the scalp, allowing this skin to sit above the rest of the scalp. When the scalp is scratched, the skin around the hair is preferentially injured and bacteria from beneath the fingernail placed in the scalp skin causes infection. As might be expected, folliculitis is a common complication of an itchy scalp. Folliculitis is usually treated with shampooing for good scalp hygiene, treatment of the scalp itch with topical corticosteroids, and oral antibiotics for the scalp bacterial infection. Shampoos and scalp products that prevent itch are important for maintenance therapy, since an itchy scalp is usually the initiating factor for scalp folliculitis.

Lastly, no discussion of scalp skin could be complete without the mention of psoriasis. As in all other body areas, psoriasis of the scalp is due to the production of too much poor quality skin too quickly. It presents with severe thick silvery plaques of scalp scale that may interfere with hair growth. It is best treated medically; however, shampoos and scalp solutions containing keratolytics, such as salicylic acid, or anti-inflammatories, such as tar derivatives, are helpful. Antidandruff preparations, as discussed previously, may be helpful since the presence of Malassezia my initiate a flare of scalp psoriasis.

Hygiene Needs

The hygiene of the scalp must be maintained while beautifying the hair, which can be a cosmetic challenge. Cleanliness of the scalp is very important to prevent fungal and bacterial infection that can induce subclinical and clinical disease, without overdrying the nonliving hair. It is interesting to note that shaving the hair, which provides a ready surface for infection, can cure many scalp diseases. Certainly, this is not an alternative that would be considered by many!

Skin Care Needs

The skin care needs of the scalp are to remove excess skin scale, loosen shedding hair, and maintain the biofilm of sweat, sebum, and organisms in balance. Many might suggest that the scalp should be moisturized to smooth down the skin scale and allow barrier repair to occur. While this is generally the case in other body areas, this logic does not pertain to the scalp. Skin scale provides a home for the fungal and bacterial organisms and allows sweat and sebum to accumulate on the scalp. Removal of the skin scale is key to scalp skin health.

Neck

The neck is an interesting area of highly mobile skin that provides a transition between the thin skin of the neck and the thicker skin of the upper chest and back. It contains fully mature hairs in the male and thin vellus hairs in the female. It is an important area from a cosmetic standpoint since it is an area affected by shaving in the male, fragrance application in the female, and photodamage in both sexes.

Anatomy and Physiology

The neck skin covers important underlying structures, such as the blood and nerve supply to the head. The neck also contains the cervical spine and numerous muscles allowing the head to move side to side. It is for this reason that the neck is a difficult area cosmetically. It does not heal well from cosmetic surgical or traumatic injuries due to this continuous movement. It is also is subject to photodamage, since many forget to wear protective clothing or apply sunscreen to the neck. Most hats do not provide adequate neck protection, thus the neck skin tends to show age more quickly than other body areas.

Common Dermatologic Disease Considerations

The photodamage condition that most commonly affects the neck is known as poikiloderma. Poikiloderma describes the thinned skin present from lost dermal collagen. It resembles chicken skin because the lower dermal oil glands become more visible as little tiny yellow dots. The thinned skin also allows better visualization of the underlying small vessel network creating the "red neck" terminology, used to describe those who work out of doors, such as cowboys. Lastly, poikiloderma describes the irregular pigmentation that results from prolonged photodamage characterized by both lighter and darker areas in almost a lace-like pattern. It is interesting to note that the neck skin beneath the chin is sun protected. For this reason, neck photodamage is almost in the shape of a butterfly being more pronounced on the sides of the neck. The degree of photodamage present on the skin of an individual can be easily determined by comparing the sun protected skin beneath the chin with the appearance of the sun damaged skin on the sides of the neck.

The neck is also the site where women apply fragrance. For this reason, the neck is a common site of fragrance allergy. This allergy can manifest as allergic contact dermatitis, which presents as red skin with little tiny bumps, known as papules, and blisters, known as vesicles. Patch testing fragrances is usually performed to determine the exact cause after treatment with topical corticosteroids. Fragrances can also cause irritant contact dermatitis, which presents as simply red, itchy skin, due to the drying volatile vehicle in the perfume.

Hygiene Needs

The hygiene needs of the neck are similar to the rest of the body. The neck does not contain many oil glands and thus cleansing should be thorough, but not over drying. Probably the most unique hygiene need for the neck area is in males who shave the hair in this location. The neck is a transition area for hair growth between the beard of the face and the body hair of the chest. For this reason, the hair exits the skin in many different directions, which predisposes to inflammation of the hair follicular ostia, more commonly known as razor burn. Severe razor burn accompanied by ingrown hairs in African-American males is known as pseudofolliculitis barbae. In this condition, the curved hair shafts re-enter the skin causing inflammation and infection. It is a difficult condition to treat. Growing a beard

and not shaving obtain the best results, since the long hairs cannot ingrow. The second best option to shave frequently and keep the hairs so short that they cannot ingrow.

Skin Care Needs

The major skin care needs of the neck are good moisturization accompanied by sun protection. The neck receives almost as much sun as the face and is a common site for precancerous and cancerous growths.

Body

The body encompasses all the rest of the skin not previously discussed, except for the skin fold areas. Most notable body areas for discussion are the back, chest, arms, and legs. The skin on the body does not heal as well as the face and neck. The further the skin is away from the face, the poorer the surgical result. This is due to the thicker skin in these locations accompanied by the distance away from the heart and a poorer blood supply.

Anatomy and Physiology

The thickest skin of the body is present on the upper back due to the need to sustain pulling and twisting movements from arm motion. This thick skin does not heal well and is a common site of unsightly scars. The poorest healing parts of the body are the upper chest, upper arms, and upper back where hypertrophic scars (thickened scars) and keloids (scars that extend beyond the boundary of the injury) may form with increased frequency. Oil glands are also reduced in these areas making careful cleanser selection and the use of moisturizers important. One of the itchiest spots on the entire body is at the base of the shoulder blade on the back. It is not quite clear why is this the case; however, this spot is extraordinarily difficult to reach and is a common place where people routinely rub against a doorframe!

The arms and legs form another anatomic area. Both sites possess skin that is designed for movement accompanied by hair growth. The oil glands are more numerous here than on the back and chest, but these are frequent sites of skin dryness in the elderly.

Common Dermatologic Disease Considerations

Most dermatologic diseases affect the body, thus a complete discussion of this topic is beyond the scope of this text. For those who wish additional information, a recommended reading list is presented at the end of the chapter. However, it is worthwhile mentioning that the most common skin disease of the body seen by the dermatologist is dry skin, known as eczema. Why is this the case? The reason can be simply stated as overbathing. Many people feel a need to bathe daily and some twice daily. Bathing the body has become a ritual. Some bathe to relax prior to retiring for the night while others bathe to wake up. Athletically inclined individuals bathe after each exercise session. The elderly, who are otherwise inactive, may bathe frequently as they find the warm water soothing for achy muscles and joints. This excessive amount of cleanser and water contact eventually removes not only the sebum, but also the intercellular lipids, causing dry skin. The skin cracks, exposing tender dermal nerve endings, and itching ensues followed by scratching. This further damages the skin barrier and more itching and more scratching occur. Finally, the skin barrier is in complete disarray and the dermatologic disease of eczema is present. This sequence of events is known as the itch-scratch cycle. Successfully controlling the

eczema depends on stopping the itching, repairing the barrier, and restoring the skin to health.

Hygiene Needs

This means body hygiene is a careful balance between removing enough bacteria to prevent disease and body odor while leaving the skin barrier undamaged. This is indeed quite a challenge. It would be nice to somehow develop a cleanser that could distinguish between sebum and intercellular lipids, removing the former while leaving the later untouched. This should be the goal of all therapeutic body cleansers.

Skin Care Needs

The desire to bathe frequently has created moisturization as the major skin need of the body. Body moisturizers should create an optimal environment for healing and quell itch, leaving the skin smooth and soft. The moisturizer must function in hairy body areas and leave behind a breathable film that does not prevent sweat from evaporating from the body surface. The construction of moisturizers for this purpose is discussed in Chapter 6.

Underarms

The underarms have been removed from the general body discussion as they represent a unique body area medically known as an intertrigenous site. Intertrigenous sites are body areas where two skin surfaces meet. They include the armpit, beneath the female breasts, and between the upper inner thighs. In persons who are obese, other intertrigenous sites may be present beneath the chin, beneath the abdomen, behind the knees, etc. Intertrigenous sites are characterized by moisture retention, skin movement, and warmth. This environment, as mentioned previously, is perfect for the growth of fungus, yeast, and bacteria, thus the intertrigenous sites are frequent sites of dermatologic disease.

Anatomy and Physiology

The armpit is a particularly interesting intertrigenous site because it combines the aforementioned factors with hair and abundant sweat glands. The armpit contains two types of sweat glands, eccrine and apocrine. Up to this point, the discussion regarding sweat glands has referred to eccrine sweat glands that produce a clear odorless sweat designed to cool the body and prevent overheating. Apocrine sweat glands do not participate in thermoregulation, but rather produce a yellowish scented sweat. Apocrine glands are well developed in skunks and deer, but not so well developed in humans. It is the scented apocrine sweat that interacts with special perfumes to produce a unique smell. It is theorized that babies who cannot see recognize their mother from the unique scent of her apocrine sweat. Indeed, there are abundant apocrine sweat glands around the areola of the breast. Other locations of apocrine sweat glands include the groin, buttocks, and scalp. Apocrine sweat provides a perfect growth media for odor producing bacteria. Further growth of these bacteria, in combination with fungus and yeast, can result in infections seen in the armpit, our next topic of discussion.

Common Dermatologic Disease Considerations

Infection is clearly the most common dermatologic condition seen in the armpits. Infection may be due to fungus, yeast, or bacteria. The most common condition seen in the armpit is known as intertrigo. This is the growth of yeast and possibly fungus in the warm moist

environment of the armpit that has had the skin barrier damaged by overhydration with eccrine sweat. Intertrigo presents as red, inflamed skin that may itch or burn. It is typically treated with a combination of topical antiyeast/antifungals and topical corticosteroid creams. Elimination of the sweat can prevent recurrence through the use of antiperspirants, discussed in Chapter 8.

Bacterial infections of the armpit are usually due to staph or strep organisms. These are the most common pathogens found in the environment and on the body. The apocrine sweat in the armpit provides an excellent bacterial growth media. If the bacterial infection involves the skin of the armpit, it is known as impetigo. If the bacterial infection involves the skin around the exit of the hair from the skin, it is known as folliculitis. Open wounds that may be scabbed or oozing pus characterize both conditions. They are treated with oral and/or topical antibiotics. Again, elimination of the sweat is key to prevention.

Hygiene Needs

It comes as no surprise that the key hygiene need in the armpit is the elimination of eccrine and apocrine sweat. Sweating is normal part of human physiology, but excessive sweating may occur in the armpits, just like on the hands and feet, and is characterized as hyperhidrosis. Controlling the sweat prevents body odor, skin barrier damage, infection, and emotionally disturbing wetness. This is the realm of antiperspirants, but oral medications and chemodenervation through botulinum toxin A are also used. These topics are more fully explored in Chapter 8.

Skin Care Needs

The skin care needs of the armpit are mainly irritation reduction from the aluminum salts used in antiperspirants and hair removal. Unfortunately, most topical antiperspirants cause irritation in the sensitive skin of the armpit. This can result in irritant contact dermatitis, especially if the skin barrier has already been damaged from overhydration. Thus, the best way to maintain the health of the armpit is to use an effective, nonirritating antiperspirant.

The armpit skin barrier may be further irritated from hair removal techniques, especially in the female. The armpit is a challenging area to shave with a razor due to its concave nature. Using a well-designed razor and shaving cream to both soften and reduce friction are key in the armpit. Depilatories are typically too irritating for armpit hair removal. However, hair removal is an important method to control armpit odor, since the hair provides a large surface area for bacterial growth. Removal of the hair limits the amount of bacteria that can be present in the armpit.

Female Genitalia

Our last body areas to discuss are the female and male genitalia. These areas have been separated for individual discussion because they represent unique skin interfaces with important hygiene and skin care needs.

Anatomy and Physiology

The female genitalia forms several skin interfaces. The hair bearing skin of the mons pubis joins the nonhair bearing skin of the labia and the mucosal surface of the labia abuts the urethra and vagina. A further skin interface is created where the keratinized skin of the

inner thigh joins the transitional skin of the anus. Each of these sites form a location where skin disease can occur.

The female genitalia is one of the intertrigenous zones previously discussed and as such is a warm, moist, dark place prone to infection from fungus, yeast, bacteria, and viruses. It is easily irritated and fragile with worsening fragility arising from the mucosal thinning that occurs with menopause.

Common Dermatologic Disease Considerations

The most common dermatologic conditions involving the genitalia would then be infection and irritation. Infection is frequent, since the mucosa presents little barrier to infection. Common infections of the genitalia include herpes simplex, genital warts, yeast (usually Candida albicans), and fungus. Fungal infections of the groin, medically known as tinea cruris, occur from the same organism that causes fungal foot and toenail infections.

Irritation in the groin usually arises from tight fitting clothing that does not control moisture. Just like other skin areas, overhydrated skin is easily damaged. Since this is an area of abundant apocrine and eccrine sweat glands accompanied by the wetness of vaginal secretions and urine, hygiene assumes great importance.

Hygiene Needs

Hygiene of the female genitalia is an important, but overlooked, area. Most cleansers that are designed for keratinized body skin do not function well as cleansers for the mucous membranes of the female genitalia. They damage the mucosa causing itching, stinging, and pain. Yet, there is a need for cleansing to prevent infection and control odor.

Skin Care Needs

Thus, the basic skin care need of the female genitalia is the management of wetness without the removal of the natural vaginal lubricants necessary to keep the tissues soft and supple. This is quite a challenge, which has not yet been met. It is desirable to absorb and remove the sweat, but the mucous secretions must remain in place to lubricate the tissues as they glide across one another with walking and movement.

Male Genitalia

The male genitalia also form an interface between various skin types with and without hair. The lack of a large mucosal surface makes infection less of a problem, but the presence of hair is a complicating factor.

Anatomy and Physiology

The male genitalia is characterized by the thin skin of the scrotum interfacing with the keratinized skin of the penis abuting the transitional mucosal skin of the head of the penis. In uncircumcised males, the head of the penis and the part of the penis beneath the foreskin is true mucosa. This true mucosa is a common site of infection, but is not found in the circumcised male.

Common Dermatologic Disease Considerations

The most common dermatologic disease seen in the male is known as "jock itch." It represents a fungal infection, medically known as tinea cruris, again due to the same organisms that cause ringworm and toenail infections. The fungus can be passed between partners with direct contact, which is usually how females acquire the infection. Yeast infections of the penis can also occur, but this is less common in the circumcised male. Other infections, such as venereal disease may occur, but this is beyond the scope of this discussion.

Hygiene Needs

The hygiene needs of the male genitalia mainly focus around moisture and body odor control. Both are related because moisture is necessary for the growth of bacteria that cause body odor, thus eliminating wetness solves both problems. No personal antiperspirants exist for the area and moisture-absorbing powders usually become sticky, creating another problem.

Skin Care Needs

The need for skin lubrication does not exist for the male like it does for the female. All of the body surfaces that move with locomotion are keratinized and do not require lubrication.

Summary

This section has presented an overview of cutaneous formulation issues that must be considered when developing successful products for a given body area. Each major body area has been discussed in terms of anatomy and physiology of the anatomic site, common dermatologic disease considerations, hygiene needs, and skin care needs. Yet, there is much more that could be written for the person who wishes further study. This list contains major dermatology textbooks that should consulted for additional information.

SUGGESTED READINGS

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3
Formulation for Special Populations

Zoe Diana Draelos

*Department of Dermatology, Wake Forest University School of Medicine,
Winston-Salem, and Dermatology Consulting Services, High Point,
North Carolina, U.S.A.*

Not all skin is the same. This is one of the key challenges in the treatment of dermatologic disease and successful global cosmetic formulation. The same skin disease can look very different in Caucasian versus African American skin. The pigmentation problems common in Asian skin are not seen in northern Europeans. The effects of aging are much different in men versus women. Adolescents are more likely to develop acne in response to product use than mature individuals. Persons with easy flushing experience stinging and burning in response to product application more frequently. Thus, issues of ethnicity, skin color, age, gender, and skin sensitivity must be considered when formulating skin care products for a global market. This chapter discusses these important formulation issues.

GENDER

Gender difference issues are some of the most basic when considering cosmetic formulation. Male skin is visually much different than female skin and has a unique response to aging and adverse product reactions. When discussing female versus male skin, we shall be talking about fully mature individuals. The unique skin care needs of children will be discussed later.

Probably the most important difference between male and female skin is the skin thickness. Male skin is thicker than female skin, in part due to the presence of terminal hair follicles over much of the body. This difference is most pronounced on the face where women have only vellus hairs while men have fully developed terminal hairs taking up space within the skin. The presence of male facial hair is partially responsible for the more favorable appearance of mature men over mature women. As UV radiation activates collagenase to destroy dermal collagen, the male beard allows the skin to resist wrinkling, which is not the case in females. Thus, photoaged males do not exhibit the pronounced redundant facial skin seen in photoaged females. The thicker male skin is also better at diffusing UV radiation, especially in the UVA range, which penetrates more deeply causing greater damage in female skin. The media that tends to prefer images of younger women and older men further magnifies the gender differences in photoaging.

Differences in skin thickness also impact the frequency of adverse product reactions suffered by the two sexes. Women experience adverse reactions more commonly than men. The thinner skin may allow irritants and allergens to penetrate deeper in female skin, but the increased incidence may also be due to greater product usage. Women overall use more skin care products and cosmetics than men. This increased usage magnifies the chances of contacting an irritant or an allergen. Women are also more likely to undergo procedures that destroy the skin barrier, such as facial peels, microdermabrasion, spa treatments, etc. Furthermore, women are more likely to engage in anti-aging topical products that can create barrier damage, such as topical tretinoin, glycolic acid, lactic acid, etc. This damage to the stratum corneum further increases the chance for magnification of a mild adverse reaction into a more major problem. This artificially created increase in adverse reactions experienced by women has been termed "polypharmacy" by some who wish to impart the concept of overusage of prescription and over-the-counter products by youth-seeking women. Others use the term "iatrogenic sensitive skin" to emphasize the skin sensitivity created by exaggerated product use.

Perhaps one of the most important differences between male and female skin is the relative balance between male testosterone and female estrogen and progesterone. Male and female skin is quite similar up until puberty, at which time sexual differences become more pronounced. Both testosterone and estrogen cause the production of facial and body sebum. This onset of oil production sets the stage for acne whereby the (*Propionibacterium acnes*) bacteria now has a food supply to encourage abundant growth. More sebum production is triggered by testosterone accounting for the generally greater severity of acne in males over females. However, females with higher than normal testosterone production, due to hormonal abnormalities, such as polycystic ovary disease, may experience acne equally severe to any male. The onset of hormones also triggers an increase in apocrine sweat, the scented type of sweat that is produced by specialized sweat glands on the eyelids, breasts, scalp, buttocks, and in the armpits. Both sebum and apocrine sweat create different skin cleansing needs and alter the skin biofilm in ways that can dramatically affect cosmetics and skin care products. The formulator must consider the substances on top of the skin.

AGE ISSUES

In addition to gender issues, age issues are also important to the formulator. Newborn children produce little sebum and eccrine sweat. Sebum production typically does not begin until the hormonal changes of puberty occur, as discussed previously; thus, most children have dry skin. This creates a challenge, since children frequently get their skin dirty, which necessitates washing. The child may not produce enough sebum to combat the effect of cleansing that may remove the intercellular lipids resulting in barrier damage. This creates the need for thorough mild cleansers and moisturizers for children. Careful formulation is essential, since the skin of children is also thin and their well-functioning immune system is likely to respond aggressively to irritants and allergens. It is for this reason that children are considered to have sensitive skin.

Puberty brings full functioning of the sebaceous, apocrine, and eccrine glands. This may be advantageous to dry skinned children who will no longer suffer from eczema. Many times allergies also become attenuated at this age. But, of course, oil, and sweat removal become more of a problem as acne and body odor emerge. The next complexion change generally occurs around age 40 as sebum production begins to decline. There is great variability in the age at which sebum production changes. In women, dramatically

decreased sebum production occurs at menopause, which usually begins by age 50 and is completed by age 60.

Usually about age 60 there is a transition in both men and women to geriatric skin. While this is not a proper medical term, there are unique skin needs of the elderly. These include skin fragility that results in easy skin tears and bruising due to loss of dermal collagen, which confers the skin's strength. Even the rubbing of thick viscous skin creams can cause bruising in elderly skin, medically known as senile purpura. Elderly skin is also unique in that it appears chronically dry, even though noninvasive skin measurements, such as transepidermal water loss, are normal. This may be due to the decreased ability of dead skin scale to slough in a timely manner. The buildup of corneocytes appears like dry skin even though the viable epidermis is well moisturized. This means that moisturizers designed for geriatric skin should encourage desquamation and provide superior emolliency to smooth the dry-appearing corneocytes.

The last area to discuss in elderly skin is itching. Geriatric skin is uniquely itchy, even though there is little visible evidence of barrier disruption. Itching is typically due to barrier disruption, medically termed dermatitis, and lack of protection of underlying dermal nerve endings. In the elderly, severe itching may be reported even though no dermatitis is present. This is a diagnostic enigma for the dermatologist. Skin itching appears to become worse in the postmenopausal female; thus, estrogen may play a role. However, the exact cause of the itching is not always apparent. It may be due to depression, poor dermal support of the nerve endings, abnormal intercellular lipids, etc. Thus, itch reduction is a skin care need in the elderly, not frequently seen in younger populations.

SKIN COLOR

We shall now turn our discussion to skin color. Skin color produces as many variations in skin care needs as age. All colors of skin possess melanin, but the differences arise from how the melanin is packaged within the skin. This difference in melanin packaging gives rise to light and dark skin and also to the skin sunburn characteristics. These topics are covered in more detail in the sunscreen chapter; however, here we shall address the unique differences between skin color and skin care product response. Very light skin that does not tan well typically does not respond to injury with pigmentation problems. There may be some transient hypopigmentation, or reduced skin color, especially with skin dryness where the skin does not tan well, a condition medically known as pityriasis alba. Hypopigmentation may also be seen following a traumatic skin injury, especially if the melanocytes have been damaged. However, a burn injury usually results in increased pigmentation, medically known as post-inflammatory hyperpigmentation. This is in contrast to persons with darker skin, to include Asian, Mediterranean, African American, and Hispanic persons, who experience frequent post-inflammatory hyperpigmentation, which is a larger cosmetic concern than wrinkling in these ethnic groups.

Postinflammatory hyperpigmentation is darkening of the skin in response to injury. The injury can be from acne, sunburn, skin disease, irritant contact dermatitis, allgeric contact dermatitis, or a traumatic scratch. Since melanocytes are felt to be an important part of the immune system, it is postulated that this hyperpigmentation is an immune response to skin injury, but the exact reason for this reaction is largely unknown. Thus, products designed for skin of color must be carefully formulated to minimize any skin irritation, since postinflammatory hyperpigmentation is the inevitable result. It may take six months to one year to return the skin to normal color after the injury, which accounts for the tremendous skin lightening product focus in cultures with darker complected

individuals. In order to return the skin to proper color, the extra melanin produced must be phagocytized or consumed by white blood cells and then removed from the skin. More superficial pigmentation can be readily removed while some deeper dermal pigmentation may be permanent.

Skin color also confers photoprotection. Darker skin can sunburn and tan just like fair skin, but deepening of the skin color is generally considered undesirable. This is not the case in fair complected individuals who try to achieve a tan by natural sun exposure, the use of artificial UVA radiation in a tanning booth, or dyeing of the skin with self-tanning products containing dihydroxyacetone. Melanin is basically an unstable radical that can absorb an electron from highly energetic unstable oxygen species, preventing the activation of collagenase and the resulting dermal damage. This is why darker complected persons typically do not demonstrate photoaging to the same degree as their lighter age-matched counterparts.

In addition to the different skin color responses to injury and photoaging, another important reaction pattern, known as follicular predilection, is unique to skin of color. Follicular predilection refers to the presence of disease around the follicle and at the opening of the hair onto the skin surface, known as the follicular ostia. For example, eczema due to dry skin usually occurs evenly over the skin surface in fair complected individuals, but in African American persons, the eczema occurs around the follicular ostia giving the skin a unique goose bump type of appearance. Whether this reaction pattern is due to the increased melanin or the kinky hair is unknown, but this type of eczema is considerably more difficult to treat. Mild skin irritation or full blown irritant contact dermatitis may also be present with this follicular pattern. Thus, problems associated with skin care products or cosmetics may appear differently in skin of color, sometimes confusing the proper diagnosis.

HAIR SHAFT ARCHITECTURE

No discussion of skin is complete without considering the contribution of the hair to the physiology of the skin. Different hair architecture accompanies different skin colors; thus, the hair and the skin are inter-related special considerations. Caucasian persons with very fair skin typically have straight to slightly curly hair while African American persons with dark skin typically have kinky hair; however, many variations exist. Follicular skin problems are usually minimal in Caucasian, Asian, Hispanic, and Mediterranean individuals where the oval to elliptical hair cross-section yields body hair that is straight to curly. Unique follicular problems exist in African American persons where the flattened elliptical hair cross-section yields tightly kinked hair. This tight kink predisposes the hair to ingrowing, especially on the face, in the armpits and groin, and on the legs. Shaving of the hair in any of these areas cuts the hair at an angle and the tight kink of the hair shaft allows the short hair to re-enter the skin after exiting the follicular ostia due to the sharp tip. The ingrown hair then burrows beneath the skin surface causing inflammation, which can result in the formation of a pustule, the appearance of post-inflammatory hyperpigmentation, and/or a scar. When these findings arise in connection with ingrown facial hairs, it is known as pseudofolliculitis barbae.

This means that African American persons can develop skin disease based on the manner in which they groom their body hair. This problem with ingrown hairs explains why many African American women do not shave their armpits, groin, and legs. It also explains why many African American men wear a short beard. The only way to avoid the ingrown hair is to keep the hair so short that it cannot ingrow, which may mean twice daily

shaving for some, or to allow the hair to grow so long that it cannot ingrow, which is much simpler. Depilatories, waxing, and laser hair removal techniques are generally not an option in African American individuals, since these methods do not work well on the deeply pigmented kinky hair shafts.

SENSITIVE SKIN

Probably the biggest formulation challenge for the cosmetic chemist and the biggest treatment challenge for the dermatologist is sensitive skin. Sensitive skin can present with visible outward changes, easily recognized by the dermatologist, or invisible signs with marked symptoms presenting a treatment challenge.

Visible sensitive skin is the easiest condition to diagnose, since the outward manifestations of erythema, desquamation, lichenification, and inflammation identify the presence of a severe barrier defect. Any patient with a barrier defect will possess the signs and symptoms of sensitive skin until complete healing occurs. The three most common causes of barrier defect induced facial sensitive skin are eczema, atopic dermatitis, and rosacea. These three diseases nicely illustrate the three components of sensitive skin, which include barrier disruption, immune hyper-reactivity, and heightened neurosensory response.

Eczema

Eczema is characterized by barrier disruption, which is the most common cause of sensitive skin. The barrier can be disrupted chemically through the use of cleansers and cosmetics that remove intercellular lipids or physically through the use of abrasive substances that induce stratum corneum exfoliation. In some cases, the barrier may be defective due to insufficient sebum production, inadequate intercellular lipids, abnormal keratinocyte organization, etc. The end result is the induction of the inflammatory cascade accompanied by erythema, desquamation, itching, stinging, burning, and possibly pain. The immediate goal of treatment is to stop the inflammation through the use of topical, oral, or injectable corticosteroids, depending on the severity of the eczema and the percent of body surface area involved, and proper skin care products and cosmetics.

Atopic Dermatitis

Sensitive skin due to eczema is predicated only on physical barrier disruption, while the sensitive skin associated with atopic dermatitis is predicated both on a barrier defect and an immune hyper-reactivity, as manifested by the association of asthma and hay fever. Patients with atopic dermatitis not only have sensitive skin on the exterior of the body, but also sensitive mucosa lining the eyes, nose, and lungs. Thus, the treatment of sensitive skin in the atopic population involves topical and systemic considerations. There is also a prominent link between the worsening of hay fever and the onset of skin symptoms, requiring broader treatment considerations.

All of the treatments previously described for eczema also apply to atopic dermatitis, but additional therapy is required to minimize the immune hyper-reactivity. While this may take the form of oral or injectable corticosteroids, antihistamines (hydroxyzine, cetirizine hydrochloride, diphenhydramine, fexofenadine hydrochloride, etc.) are typically added to decrease cutaneous and ocular itching. Antihistamines also improve the symptoms of hay fever and may prevent a flare up should the patient be exposed to pollens or other inhaled allergens. The avoidance of sensitive skin in the atopic patient is largely predicated on avoidance of inciting substances. This means creating an

allergy-free environment by removing old carpet, nonwashable drapes, items likely to collect dust, feather pillows and bedding, stuffed animal toys, heavy pollinating trees and plants, pets, etc. The prevention of the release of histamine is the key to controlling the sensitive skin of atopic dermatitis.

Rosacea

Rosacea is an example of the third component of sensitive skin, which is heightened neurosensory response. This means that patients with rosacea experience stinging and burning to minor irritants more frequently than the general population. For example, I demonstrated that 62.5% of randomly selected rosacea patients demonstrated a positive lactic acid sting test for sensitive skin (1). Furthermore, rapid prolonged facial flushing is one of the main diagnostic criteria for rosacea. Whether this sensitive skin is due to nerve alterations from chronic photodamage, vasomotor instability, altered systemic effects to ingested histamine, or central facial lymphedema is unclear.

The treatments for rosacea-induced sensitive skin are much different than those for eczema or atopic dermatitis. Anti-inflammatories in the form of oral and topical antibiotics form the therapeutic armamentarium. Antibiotics of the tetracycline family are most commonly used orally, while azelaic acid, metronidazole, sulfur, and sodium sulfacetamide are the most popular topical agents. However, the effect of the anti-inflammatory antibiotic can be enhanced through the use of complementary skin care products that enhance barrier function.

Eczema, atopic dermatitis, and rosacea are in some ways the easiest forms of sensitive skin to treat. The skin disease is easily seen and treatment success can be monitored visibly. If the skin looks more normal, generally the symptoms of itching, stinging, burning, and pain will also be improved. Unfortunately, there are some patients who present with sensitive skin and no clinical findings. These patients typically present with a bag full of skin care products they claim cannot be used because they cause facial acne, rashes, and/or discomfort. This situation presents a challenge for the physician, since it is unclear how to proceed.

Several treatment ideas are worth considering. The patient may have subclinical barrier disruption. For this reason, treatment with an appropriate strength topical corticosteroid for two weeks may be advisable. If symptoms improve, then the answer is clear. The patient may have subclinical eczematous disease. If the symptoms do not improve, it is then worthwhile to examine the next most common cause of invisible sensitive skin, which is contact dermatitis. This is accomplished by considering the ideas presented in Table 1 (2). Sometimes a more regimented approach to contact dermatitis is required, as represented by the basic product selection ideas presented in Table 2.

Sensitive skin products are increasing in the marketplace, since many individuals consider themselves to possess sensitive skin while others feel that products labeled for sensitive skin are less likely to cause problems in all populations. Exactly what is unique to sensitive skin products is unclear. In many ways, it is simply a marketing statement; however, some manufacturers will elect to test their formulations on persons with eczema, atopic dermatitis, and rosacea as part of a sensitive skin panel to substantiate the claim.

CONTACT DERMATITIS ISSUES

Our prior discussion of sensitive skin focused on those special skin conditions, namely eczema, atopic dermatitis, and rosacea, which form the basis for a sensitive skin panel. However, we must also consider issues of contact dermatitis. Traditionally, issues of

Table 1 Considerations for the Minimization of Contact Dermatitis from Skin Care Products and Cosmetics

1. Eliminate common allergens and irritants, or reduce their concentration
2. Select products from a reputable manufacturer that uses high-quality pure ingredients free of contaminants
3. Products should be well-preserved to prevent the formation of auto-oxidation byproducts
4. Paraben preservatives have proven to be the least problematic
5. Avoid solvents, volatile vehicles, vasodilatory substances, and sensory stimulators in all products
6. Minimize the use of surfactants and select minimally irritating emulsifier systems

irritant contact dermatitis are implied under the claim umbrella of sensitive skin, but allergic contact dermatitis issues are sometimes separately claimed. Allergic contact dermatitis issues may fall under the claim of hypoallergenic. Exactly what hypoallergenic means is unclear. In the strictest sense, the word hypoallergenic is used to indicate reduced allergy. Many products that are labeled hypoallergenic are also labeled as appropriate for sensitive skin, but the claims are somewhat different. All sensitive skin products should be hypoallergenic, but all hypoallergenic products are not necessarily appropriate for sensitive skin. In my mind, hypoallergenic simply means that common allergens have been removed from the formulation, but irritants may still be present.

Formulating products with reduced allergy is sometimes difficult. It is obvious that poison ivy, a common allergen, should never be included as an ingredient, but other guidelines are sometimes difficult to develop. It is probably for this reason that hypoallergenic has never been defined by any regulatory body. Hypoallergenic products are probably best formulated by using the fewest, purest ingredients possible and staying away from unusual botanical extracts. A poor approach would be to put anti-inflammatory substances, such as bisabolol or allantoin, in the formulation to minimize any allergic reaction. A quick review of the contact dermatitis literature shows that the most commonly cited cases of skin care product induced problems arise when contaminated raw materials are used, such as nickel-contaminated eye shadow pigments or oxidized vitamin E, or when product preservatives break down. The best guarantee of formulating a hypoallergenic product is to use time-tested ingredients in a stable formulation.

Table 2 Cosmetic Selection Criteria in Sensitive Skin Patients

1. Powder cosmetics should be selected
2. Cosmetics should be water removable
3. Old cosmetics should be discarded
4. Eyeliner and mascara should be black
5. Pencil formulations should be used for eyeliner and eyebrow cosmetics
6. Eye shadows should be earth-toned (tan, beige, light pink, cream)
7. Avoid chemical sunscreens in cosmetic formulations
8. Select cosmetic formulations with as few ingredients as possible
9. Avoid nail polishes
10. Select cream/powder facial foundations or, if liquid, silicone-based formulations

ACNE ISSUES

The last two claims for special populations are non-comedogenic and non-acnegenic. These claims are aimed at individuals who develop acne in response to the facial use of skin care products and cosmetics. Non-comedogenic refers to the testing of products to determine that they do not produce blackheads, known as open comedones, or whiteheads, known as closed comedones, after wearing. Comedogenicity was a much greater problem when petrolatum was contaminated with tar, a known comedogen. Presently, comedogenicity is not a great problem, except in the ethnic hair care market where comedogenic vegetable oils, such as olive oil, are used in pomades to moisturize the hair.

Testing must be done to substantiate the non-comedogenic claim. In the past, comedogenicity was assessed in the rabbit ear assay by applying the final formulation inside a rabbit ear and then visually assessing the presence or absence of comedones. This test was not felt to have much human validity and animal testing has fallen out of favor; thus, the rabbit ear assay has given way to testing on human volunteers. Typically, the final formulation for testing is applied to the upper back in persons capable of forming comedones on the upper back daily for 14 days. A positive control, in the form of tar, is applied, and a negative control, in the form of pure petroleum jelly, is also used. The comedones are extracted from the upper back with cyanoacrylate glue placed on a microscope slide. Any increase in comedone formation following the 14-day exposure to the final cosmetic formulation is considered comedogenic.

The non-acnegenic claim is much different. It implies that the finished product does not produce true acne, which is identified as red bumps, known as papules, or pus bumps, known as pustules. It takes much longer for acne to develop from product use, typically about four weeks. There is no standard test done for acnegenicity, except for use testing. Volunteers use the product as intended for one month and are examined for the presence of papules and pustules. Yet, there are a number of individuals who will develop tiny perifollicular papules and pustules within 48 hours of wearing a skin care product or cosmetic. Is this acne? The answer is no. True acne cannot develop in 48 hours. In my opinion, this is perifollicular irritant contact dermatitis. It looks much like acne, but the presence of lesions at the follicular ostia and the rapid onset lead to the diagnosis of perifollicular contact dermatitis. This problem is best avoided by minimizing the presence of irritants in the formulation as previously discussed.

SUMMARY

Formulating for special populations is indeed a challenge. There are unique dermatologic reaction patterns that must be considered. Failure to consider these reaction patterns could result in a product that is not globally acceptable. The globalization of the cosmetics industry means that skin care and cosmetic products must be suitable for both sexes, all ages, all skin types, all ethnic groups, all skin colors, etc. Understanding the unique needs of all world populations is vital to success.

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Personal Cleansing Products: Properties and Use

Keith Ertel
P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

INTRODUCTION

> *"Let it be observed, that slovenliness is no part of religion, that neither this, nor any text of Scripture condemns neatness of apparel. Certainly this is a duty not a sin. Cleanliness, indeed, is next to Godliness."*
> —John Wesley (1703-1791), Sermon XCII

> *"Cleanliness becomes more important when Godliness is unlikely."*
> —P. J. O'Rourke

In today's marketplace personal cleansing products are found on the shelves of mass retailers and behind cosmetic counters at prestige stores, where they are offered as part of a total skin care and beauty package. Nearly every shopping mall has a purveyor of specialty cleansing products and a simple search on the Internet reveals a number of suppliers whose distinctive personal cleansers are purported to remedy the deficiencies of the products made by large-scale manufacturers. New cleanser forms offer increased convenience and consumers can choose from myriad product scents, colors, and functional ingredients intended to help them achieve relaxation and escape from the cares of everyday life, and to improve their skin's health and appearance (1–4). Yet despite their increased variety and complexity, present day cleansers have the same basic function as their counterparts of times past: to cleanse the skin.

SKIN CLEANSING

Soil Removal

The skin is covered with a hydrolipid film that, depending on the area of the body, comprises secretions from sebaceous glands and from apocrine and eccrine sweat glands. Decomposition products from cornification (cellular debris and stratum corneum lipids) and corneocytes in the process of being shed are also present. This film provides a degree of waterproofing to the skin's surface, traps water to help maintain skin pliability, and provides a natural defense against pathogenic organisms. But this film also attracts

and holds dirt and pollutants from the environment. The skin's surface is also home to a variety of microorganisms. In most cases these organisms, the so-called resident flora, cause no harm and provide an additional defense against overgrowth by potential pathogens. But these organisms can act on components of the surface film and create undesirable by-products, such as those resulting from the metabolism of compounds found in apocrine sweat that create body odor. Thus, while the surface hydrolipid film is an important skin integument, periodic cleansing to remove dirt, debris, and odor is essential to maintaining skin health and in many cultures, social acceptance. Additionally, periodic cleansing is necessary to remove soil (including bacteria) from the skin surface that is acquired by incidental contact or by intentional application, e.g., medications or makeup and other cosmetic products.

Water alone is capable of removing much of the soil from the skin's surface (5). However, water has a limited ability to dissolve and remove oils; as the old adage goes, "oil and water don't mix." The surfactants that make up the bulk of most personal cleansing products aid this process. A surfactant, or surface active agent, is a material that lowers the interfacial tension of the medium it is dissolved in, and the interfacial tension with other phases. Said more simply, a surfactant increases the affinity of dissimilar phases for each other. This ability is based on surfactants' unique structure, which combines both hydrophilic and hydrophobic moieties at opposite ends of the surfactant molecule. In a dilute aqueous solution, surfactant molecules will arrange themselves such that the hydrophilic portion of the molecule is oriented toward the bulk solution while the hydrophobic portion orients itself in the opposite direction. For water in contact with skin the presence of surfactant molecules at the interface lowers the interfacial tension and aids wetting, which improves water's ability to spread over the skin's surface. This, along with the mechanical action of applying the cleanser, helps to remove soil. As the concentration of surfactant in solution increases a point is reached at which the surfactant molecules begin self-association into micellar structures. This point is known as the critical micelle concentration (CMC). Surfactants in aqueous micelles have their hydrophilic end oriented toward the bulk (water) phase and their hydrophobic end oriented toward the interior of the micelle. The hydrophobic interior provides a good environment for dissolving lipids, and micellar solubilization is an important mechanism by which surfactants remove oily soils from the skin's surface and help keep the soils suspended until they are rinsed away. Other factors may aid this process. For example, the skin's surface possesses a net negative charge at physiological pH and repulsive forces between the skin and anionic surfactants or their associated micelles help keep suspended soils from redepositing, making these surfactants particularly good cleansers.

Tests of Cleansing Efficiency

A personal cleanser's ability to clean the skin is dependent on a number of factors including its (surfactant) composition, its in-use concentration, the application time and method, the soil load, and the surface characteristics of the particular skin being cleaned. The past several decades saw a change in how personal cleansers are viewed, the focus shifting from their role as skin cleansing aids to their role as agents with a potential to damage skin (6). Thus, while numerous publications describing methods to assess and compare personal cleansers' skin compatibility appeared in this time frame, in-use cleansing performance was largely ignored. However, this question deserves consideration given the greatly expanded range of personal cleansing products now available, both in terms of forms and ingredients.

Weber described a method to assess cleansing that employed a device designed to wash forearm skin in a controlled manner (7). A colored model soil was applied to forearm skin of normal subjects and three subject groups with psoriasis, atopic dermatitis, or non-lesional skin disease. Four cleansing bars ranging from full soap to synthetic detergent (syndet) were tested on each subject group. The amount of color on skin was measured photometrically before and after cleansing. Weber found differences in cleansing, not only between the cleaner types but also between subject populations. Skin cleansing was in all cases best with the syndet bar, poorest with the soap. The measured cleansing response was greatest in psoriatics, which could reflect soil removal by detergency and the mechanical removal of stained psoriatic plaques by the washing process. Cleansing was poorest in atopics, which the author attributed to higher skin dryness (roughness) and greater adherence of the model soil.

Schrader and Rohr also used a device to assess personal cleansers' skin cleansing ability under controlled conditions (8). Their device was designed for use on the forearm, with a dual-chamber arrangement for simultaneous testing of two products. Agitators with felt inserts rested on the forearm surface at a controlled pressure and moved in a back-and-forth motion to effect washing. A mixture comprising oleaginous materials (including lanolin, petrolatum, and mineral oil) and lipid- and water-soluble dyes was used as a model soil. The published study compared soap-based and syndet-based liquid cleansers at 2% and 8% concentrations. Water and a 2% solution of sodium lauryl sulfate (SLS) were used as controls. The color (L^*-value) on skin before and after "washing" was measured with a chromameter. This work showed greater cleansing efficiency for the soap-based cleanser.

These authors conducted a separate experiment to assess the skin roughening effect of the test cleansers. Subjects used the test solutions for forearm washing over a two-week period. Skin roughness was assessed using silicon replicas taken at baseline and study end and analyzed by laser profilometry. The 2% solution of the soap-based cleanser produced greater roughening than did the 2% solution of the syndet-based cleanser. Changing the concentration of soap-based cleanser from 2% to 8% did not increase skin roughness. However, skin roughening for the syndet-based cleanser showed a concentration effect and at the higher concentration skin roughening was comparable to that produced by the soap-based cleanser. This illustrates the concentration-dependence of cleanser effects on skin and, since an 8% concentration is representative of cleansers' concentration on the skin during actual use (9), the importance of understanding test conditions when judging how a cleanser will affect skin. This is particularly important when attempting to predict cleansers' in-use skin effects.

Wolf and Friedman used a modification of Schrader's method to assess the skin cleansing effect of soaps (10). An oleaginous mixture (petrolatum, lanolin, mineral oil) was again used as a model soil but in this case it was applied to the dorsum of the hand. The soiled hand was immersed for five minutes in a beaker filled with a stirred, 1% solution of the test cleanser maintained at 37°C. Sebumeter® readings made before and 30 minutes after immersion were used to determine the amount of soil removed. The authors report that this method is a convenient and economical alternative to the method of Schrader that can reliably and reproducibly measure and discriminate the skin cleansing ability of different products. A study comparing a syndet to a mild cleanser containing "25% hydrating soothing cream" showed that the latter product removed less of the model soil from the skin, i.e., it was a poorer cleanser. The authors conclude that for a product to function as an effective cleanser it must also dry the skin to a certain degree.

Imokawa used a model soil consisting of a mixture of triolein, cholesterol, squalene, palmitic acid, and Sudan Black dye (11). This mixture was applied to six glass slides, which were placed into a beaker containing 40°C surfactant solution and stirred at

1300 rpm for 10 or 30 minutes. Cleansing efficiency was judged by spectrophoto-metrically or gravimetrically measuring the amount of soil removed from the slides.

Lockhart and Lazer presented work that examined the impact of various physical conditions on cleansing (12). Charcoal applied to the dorsum of the hand served as a model soil. Four "wash" conditions were examined: simple soaking and placing the hand in a whirlpool, a simulated shower, or in an ultrasonic bath. Water temperature was maintained between 32°C and 38°C in all cases. Cleansing efficacy was judged by measuring color at the charcoal-stained area with a chromameter before and after washing. The results showed that the conditions ranked, in order of increasing cleansing effectiveness, soaking $<$ whirlpool $<$ shower $<$ ultrasonic bath. While this study did not involve a cleansing agent or oleaginous soil, it demonstrates the potential for physical conditions and mechanical action to influence removal of a simple soil from the skin's surface. Personal cleansers are used under a range of conditions and with a variety of implements, and these factors will affect overall cleansing efficacy.

The above methods all used a device in an attempt to reduce variability associated with the washing process. Other authors describe cleansing efficacy methods that more closely approximate in-use conditions. Sauermann et al. used mineral oil containing 0.1% anthracene as a model soil (13). The material was applied to the lower inner forearm, and the site was washed in a regular manner for 30 seconds with warm (32°C) water and then gently blotted dry. Cleansing efficacy was calculated based on fluorescence measured at the site before and after washing. These authors reported greater cleansing efficacy for soap bars than for syndet bars.

Puvvada et al. describe a method using makeup materials (e.g., lipstick or mascara) as model soils (14). Washing involved rubbing a (wetted) bar on the skin for one minute, rinsing with 35°C water for 30 seconds, and then patting dry. Cleansing efficacy was estimated from the difference in chromameter measurements taken before and after washing. While this method employs model soils that represent everyday cleansing needs, the wash conditions are exaggerated beyond expected use. Mills et al. also described a method using makeup (opaque camouflage cream) as a model soil (15). The makeup was applied to nine test sites on the ventral forearms, and then a technician washed each site in a controlled manner with a pad lathered with one of the test cleansers. The sites were rinsed to remove all traces of lather then rank-ordered based on the level of cleansing. Of the cleanser types tested, a bar soap product was ranked among those with the poorest cleansing efficacy, followed by a liquid soap marketed for sensitive skin. Cleansing products based on sugar surfactants (polyhydroxy fatty acid amides) were ranked as having the best cleansing efficacy. These products were also found to have the best skin compatibility in a chamber scarification test (16).

We also assess cleansing efficacy using a makeup removal model. Subjects are screened on the basis of skin tone (chromameter L^*-value); only subjects with sufficiently light skin are enrolled to assure good contrast with the model soil. A dark, oil-based makeup is applied to application areas marked on the volar forearms, and 30 minutes later the color at each site is measured again. Then a bar or liquid cleanser lather is generated, and a technician washes a randomly assigned site with lathered fingers for 10 seconds; the site is rinsed for 10 seconds with warm water and gently patted dry. A water-only wash is commonly included as a control. Thirty minutes after rinsing the color at the site is measured again. The color difference (ΔE) is calculated from the pre- and post-wash $L^* a^* b^*$ values as an indicator of cleansing efficacy. This method is useful for assessing the relative cleansing efficacy of a variety of personal cleanser types. For example, the makeup removal method was used to compare cleansing efficacy of traditional soap bars
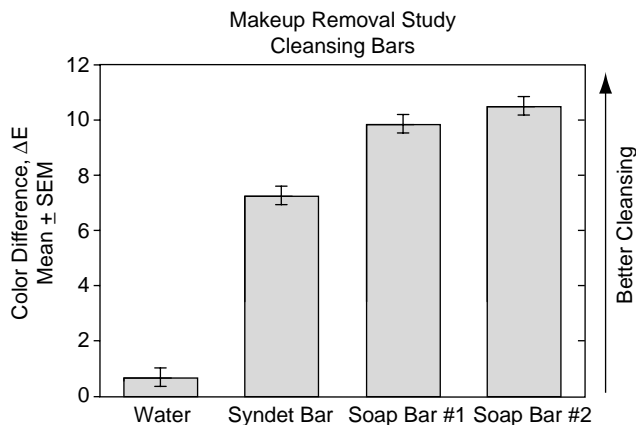
Figure 1 Results from a makeup removal study comparing two soap bars and a syndet bar. The soap bars cleaned significantly better than the syndet bar ($P < 0.05$), and all of the cleansing products removed significantly more of the model soil than water.

and a syndet bar. The cleansing efficacy for the soap bars was significantly better than that for the syndet bar under this method (Fig. 1).

Liquid personal cleanser forms are becoming increasingly popular, and some of these cleansers incorporate benefit agents such as petrolatum that deposit on skin during use. This product performance model seems inconsistent with a cleanser's purpose, i.e., how can products that are designed to deposit material onto the skin function effectively as cleansers? One strategy involves employing technology that takes advantage of varying conditions that exist at different stages of the wash process. The benefit agent remains suspended in the lather during cleansing but upon rinsing this lather becomes dilute and the emulsion suspending the benefit agent "breaks," depositing the benefit agent onto the skin. To demonstrate that this type of cleanser can effectively remove soil, we used the makeup removal test to assess the cleansing efficacy of two marketed liquid hand cleansers and three prototype liquid hand cleansers containing different levels of petrolatum (Fig. 2). The petrolatum-depositing products showed significantly better cleansing efficacy than the marketed cleansers under this model, and the results suggest that cleansing efficacy improved with increasing petrolatum level. Since the model soil is an oil-based makeup product this could reflect a "like dissolves like" phenomenon, which should translate to good removal of lipophilic soils from the skin in actual use. There are other examples of using lipophilic materials to aid soil removal. In ancient times the Romans applied oil to their skin during the cleansing process (17), and lipid-based washing products are again being promoted for use by patients with sensitive skin and atopic dermatitis (18,19).

Cleansing efficacy is important but for a product like a hand wash, which is used multiple times each day for washing, good skin compatibility is also necessary. We conducted a controlled application pilot study simulating in-use exposure to assess this parameter for the petrolatum-depositing hand wash (25% petrolatum). Healthy adult females were enrolled in a hand washing study comprising a seven-day pre-treatment period and a five-day treatment period. Subjects were provided with a regular liquid hand cleanser for hand washing and a syndet-based bar to use for showering. They were instructed not to apply cleansing products to the dorsal part of their hands and to avoid any activity that required hand immersion in a surfactant solution, e.g., washing dishes. Moisturizer use was prohibited. Ten subjects who exhibited a sufficient level of hand dryness entered the treatment phase. Treatment was conducted as a paired comparison.

Makeup Removal Study
Liquid Hand Wash Products
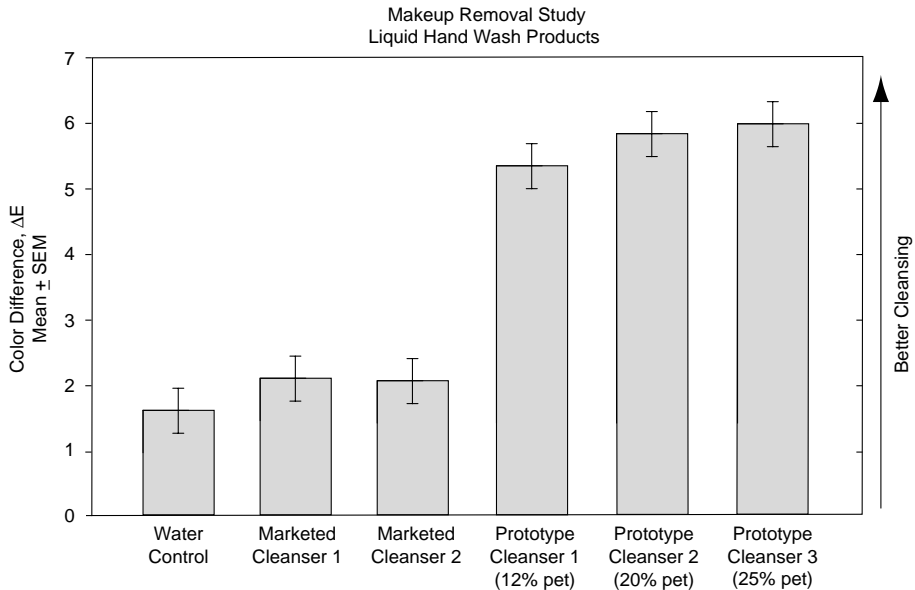
Figure 2 Results from a makeup removal study comparing three prototype petrolatum-depositing hand wash formulas to two marketed hand wash products. The percentages of petrolatum are shown in parentheses. The prototype formulas cleaned significantly better than the marketed hand washes and water ($P < 0.05$).

A technician washed one randomly assigned hand with the petrolatum-depositing hand wash product for 10 seconds following a prescribed procedure; the other hand was wet, rinsed, and patted dry. There were five wash visits each day, spaced by 30 minutes, with the washing procedure conducted four times in succession at each visit. Thus, subjects' hands were washed a total of 20 times each day. Hand condition was evaluated visually (20) and instrumentally (CM-825) at baseline, before washing, and two hours after the final wash each day. Subjects acclimatized for 30 minutes in a controlled environment room before each evaluation.

Expert visual evaluation showed little difference in erythema production between the hand wash and control (Fig. 3). In fact, the hand wash generally produced somewhat *less* erythema than the control. In addition, the hand wash produced marked dryness improvement compared to control at the post-wash evaluations, and there was progressive improvement in dryness observed at the pre-wash evaluations over the course of treatment (Fig. 3). Trends in the skin capacitance measurements, which provide an indirect assessment of stratum corneum hydration, paralleled the expert dryness scores. These results demonstrate that this petrolatum-depositing hand wash shows good skin compatibility and can actually improve dry skin condition, even under exaggerated exposure conditions.

PERSONAL CLEANSER EFFECTS ON SKIN

Surfactant Types Commonly Used in Personal Cleansers

While some new cleanser technologies can combine effective cleansing with the potential to improve skin condition, the focus for the majority of personal cleansing products remains on minimizing the potential for skin damage. Surfactants make up the bulk of most personal cleansing products and are primarily responsible for a product's in-use

Expert Visual Assessment - 20 Daily Washes
Petrolatum-Depositing Hand Wash Relative to Water Control
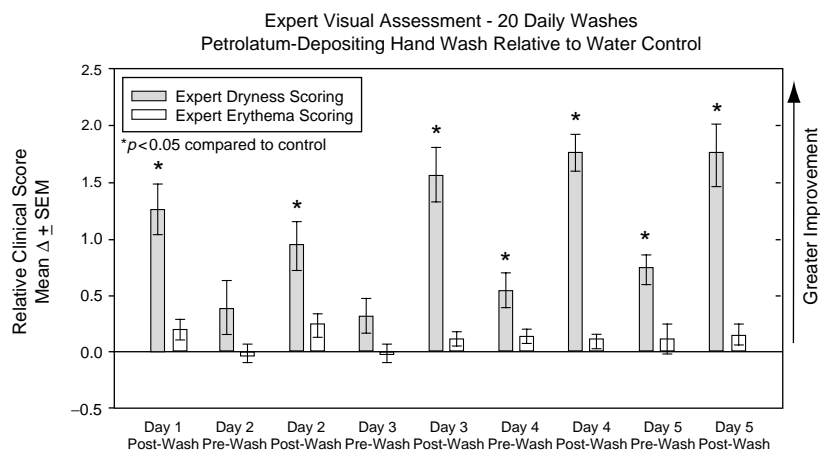
Figure 3 Expert visual dryness and erythema results from a hand washing pilot study comparing a petrolatum-depositing hand wash product to a water control. The hand wash product improved dry skin condition, even when used for washing hands 20 times daily.

properties, e.g., lather, and for its effects on skin. While all surfactant molecules are amphiphilic, there are distinct surfactant types. A surfactant's dissociation behavior in water provides a convenient basis for classification.

Anionic Surfactants

These surfactants dissociate in water to yield a surfactant with a negatively charged hydrophilic group and a cation that is usually an alkali metal (sodium or potassium) or a quaternary ammonium species. Anionic surfactants are used in a wide variety of bar and liquid personal cleansing products and account for about 50% of worldwide surfactant production (21,22). Soap, which is chemically the alkali salt of a fatty acid, is the best-known anionic surfactant, but a variety of synthetic (i.e., non-soap) anionic surfactants are commonly used in personal cleansing products, including the acyl isethionates, alkyl sulfates, and alkyl ether sulfates (AES). The acyl isethionates have good skin compatibility and are good detergents and lime soap dispersants, viz they inhibit the formation of hard water scum. Sodium cocoyl isethionate is an example; this surfactant is a common primary surfactant in "mild" cleansing bars. The alkyl sulfates are widely used in cosmetic products ranging from skin cleansers to toothpastes. They have good foam-forming properties and produce creamy lather but do not perform well in hard water. Alkyl sulfates have a marked potential to irritate skin. Sodium lauryl sulfate (SLS), an alkyl sulfate found in many personal care products, is often used as a model irritant. The AES are similar to the alkyl sulfates but their hydrophobic portion comprises ethylene oxide units rather than a straight-chain hydrocarbon. This gives AES a number of advantages over alkyl sulfates, including better lather formation in hard water and better lime soap dispersion. AES are also less irritating than alkyl sulfates, and their skin compatibility is improved by increasing the degree of ethoxylation (23,24). Sodium laureth sulfate is an example of an AES that is commonly found in personal cleansing products.

Cationic Surfactants

These surfactants dissociate in water to yield a surfactant with a positively charged hydrophilic group and an anion. Fatty amine or ammonium salts and quaternary ammonium salts are examples. Cationic surfactants are generally not good detergents or

foaming agents, and they are usually incompatible with anionic surfactants. However, being positively charged they adsorb to biological (and other) surfaces, which tend to have a net negative charge at a neutral pH. This property makes cationic surfactants useful as antistatic agents in hair conditioning products. The quaternary ammonium compounds have marked antibacterial activity and are often found in toiletries such as deodorants and mouthwashes.

Nonionic

These surfactants do not dissociate in water. Instead, their hydrophilic group is commonly an alcohol, phenol, ether, ester, or an amide. Alcohol ethoxylates and alkylphenyl ethoxylates are two common examples of this type of surfactant. A "new" class of nonionic surfactants employs various sugars as hydrophilic groups. The uncharged nature of nonionic surfactants makes them compatible with other surfactant types, and they also show reduced sensitivity to conditions such as water hardness or salinity and to formulation pH. Common examples are the sorbitan esters (marketed as SPAN) and their ethoxylated counterparts (marketed as TWEEN). As a class, nonionic surfactants tend to exhibit good skin compatibility (15,25), but they still have a potential to interact with and negatively impact the stratum corneum (26).

Amphoteric Surfactants

These surfactants have two functional groups, one anionic and one cationic. Their character is determined by the pH of their environment; amphoteric surfactants are anionic under alkaline conditions and cationic near or below their isoelectric point, i.e., the point at which the surfactant molecule carries no net charge. Betaines, which actually carry a positive charge in both acidic and alkaline media (27), are among the most widely used amphoteric surfactants and are found in both bar and liquid cleanser formulations. Betaines are used to improve lather quality or to increase the viscosity of liquid formulations. They generally show good skin compatibility and can decrease the skin irritation potential of harsher anionic surfactants when used in combination with them (24,28). But betaines are not without issues. There are a number of reported cases of contact allergy to cocamidopropyl betaine (29–32), one of the most commonly used surfactants in this group, and this surfactant was named the contact allergen of the year in 2004 (30). However, the effective incidence of issues is low given the widespread use of this surfactant in personal care products. Still, manufacturers may be able to reduce the risk of contact allergy by using a higher grade of betaine material as data suggest the allergic response is caused by impurities rather than by the surfactant itself (32–34).

Surfactant Interactions with the Skin

Personal cleansing products are complex systems that often contain several surfactants. Even a seemingly simple cleanser such as a soap bar comprises a mixture of soap species. Several of the mechanisms believed to drive surfactant interactions with the skin are discussed below. These are presented separately for convenience but the mechanisms are undoubtedly interdependent to some degree.

Surfactant Structural Considerations

The surfactant composition of a personal cleanser in large part determines the product's potential to impact skin, and there are numerous published studies that compare and

contrast the skin effects of individual surfactants and full formula cleansers. But skin compatibility can vary even within a given surfactant type. Soap provides a good example. As defined previously, soap is the alkali salt of a fatty acid. The regulatory definition of soap is quite narrow and only a few true soaps remain on the market in the United States (35–37), but products based on soap-syndet mixtures (so-called combo bars) persist in the U.S. market, and soap remains a popular cleansing form in many other countries. The raw material used in soap manufacture is often a mixture derived from tallow, vegetable oils, and their processed derivatives (38,39). Being derived from natural sources, these raw materials comprise a mixture of fatty acid species. The fatty acid compositions of triglycerides from several different sources that are used in soap manufacture are shown in Figure 4 (21).

The varying composition of the raw materials used in soap manufacture means that saponfication, i.e., reacting triglyceride with alkali to form soap and glycerin, yields a mixture of soap species. The chemical composition of the finished soap product determines its skin compatibility. For example, Dahlgren et al. used soap bars prepared with different relative amounts of tallowate and cocoate soaps to demonstrate that the level of dryness and erythema following controlled washing is dependent on the ratio of these soap species (40). In this work a bar based entirely on coconut-derived soap was harshest to skin, while a bar based entirely on tallow-derived soap was mildest. The mildness of bars based on intermediate combinations of cocoate and tallowate soap fell between these extremes. These results, and the differences in the fatty acid compositions of the raw materials (Fig. 4), indicate that the distribution of soap species in a personal cleansing product is an important determinant of its skin compatibility.

Studies conducted with pure fatty acids demonstrate this effect at a more fundamental level. Blank conducted patch tests using coconut oil and pure fatty acids commonly found in soap (41). Patches were applied for 24 hours to intact skin on the upper arms of normal (healthy) subjects, subjects who previously exhibited a reaction to soap (pruritus or vessiculation), and subjects with evidence of contact or atopic dermatitis. Reactions were read one hour after patch removal. The results are summarized in Fig. 5. The percentage of positive reactions in each test group shows clear fatty acid chain length dependence, with the incidence decreasing as the chain length increases. Kellum
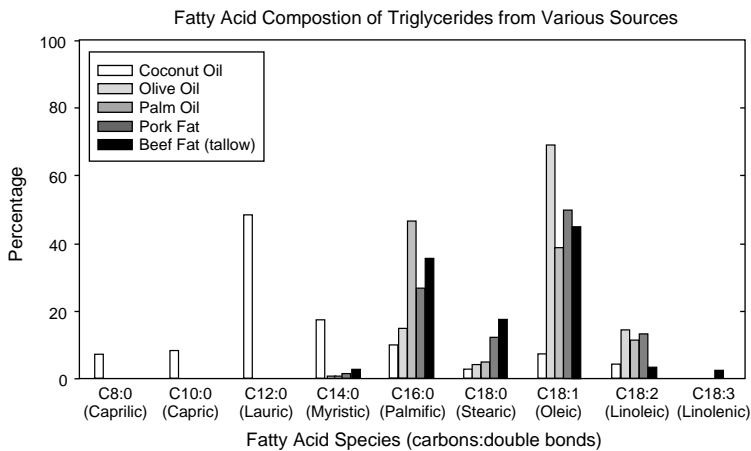

Figure 4 Typical fatty acid composition of some triglycerides commonly used to manufacture soap. *Source*: From Ref. 21.
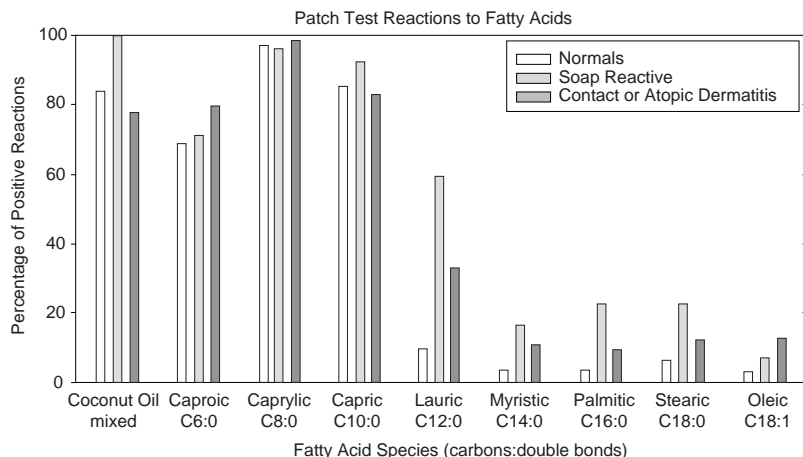
Figure 5 Results from a patch test study conducted among normals, soap reactive individuals, and individuals with contact or atopic dermatitis. There is a decreased irritation potential with increasing fatty acid chain length. *Source*: From Ref. 41.

conducted a similar study, patching saturated fatty acids with even-numbered chain lengths from C_2-C_{16} on the backs of healthy volunteers for up to 15 days (42). Response was greatest to the C_8-C_{12} acids, with the C_{12} homologue producing the most severe reactions. The author hypothesized that the C_{12} chain length might be optimum for incorporation into or passage through biological membranes. Stillman et al. conducted patch testing with even- and odd-numbered saturated fatty acids ranging from C_3-C_{18}; several unsaturated C_{18} species were also tested (43). The results again showed the greatest reaction to the C_8-C_{12} acids. Of the unsaturated species tested, only linoleic acid (C18:2) produced irritation.

García-Domínguez and coworkers proposed a five-step model to account for the increased irritancy of C_{12} ionic surfactants (44). The model involves both ionic and hydrophobic interaction between the surfactant molecule and proteins at the skin surface, ultimately leading to migration of the charged and hydrophobic portions of the surfactant molecule into the protein. Irritation results from localized environmental changes within the protein structure induced by the presence of surfactant. Thus, the higher irritancy of C_{12} surfactants is again attributed to structural characteristics that favor their interaction with the skin.

These studies show that soap composition, in particular the chain length distribution of fatty acids in the soap, is an important determinant of soaps' skin compatibility. Using tailored mixtures of fatty acid starting material, in which the longer chain length species predominate, is one approach that is used to effectively improve the skin compatibility of soap bars (45,46).

The skin compatibility of many synthetic detergents exhibits a structural dependence similar to that of soap. Kligman and Wooding used patch testing to estimate the ID_{50}, the concentration needed to produce a discernible irritant reaction in 50% of the study population in 24 hours, and the IT_{50}, the number of days of continuous exposure to produce a threshold reaction in 50% of the study population, for a series of sodium alkyl sulfates (47). They observed minimum values for both parameters, i.e., greatest irritancy, for the C_{12} chain length (SLS). Dugard and Scheuplein measured the effect of C_8-C_{16} homologues of the sodium salts of primary aliphatic acids (soap), sodium *n*-alkyl sulphates, and *n*-alkylamine hydrochlorides on the permeability of human epidermal

membranes (48). They observed the greatest permeability increase with the C_{12} and C_{14} members in each series. Robbins and Fernee reported a maximum in the swelling behavior of epidermal membrane, a parameter reported to parallel anionic surfactants' ability to elicit erythema in vivo, for the C_{12} homologue in a series of alkyl sulfates (49). They note that surfactant binding to keratin is also optimal at this chain length. Rhein et al. used a similar experimental procedure and reported maximal swelling for the C_{12} or C_{14} homologues of alpha olefin sulfonates, paraffin sulfonates, linear alkylbenzene sulfonates, and alkyl sulfates (23). Increases in swelling response with time suggested surfactant effects on keratin secondary and tertiary structure. Imokawa and co-workers conducted experiments using a surfactant solution circulation apparatus to assess the skin roughening potential of C_8-C_{14} soaps and of homologous series of various synthetic surfactants (50,51). The C_{12} soap and synthetic surfactants produced the greatest skin roughening effect within each homologous series.

These examples illustrate a common surfactant feature that reduces skin compatibility, namely, a chain length of about C_{12}. Thus, one way to improve skin compatibility of syndet-based cleansers is to minimize their content of short-chained surfactants, especially C_{12} species, analogous to the soap bar example given earlier. Using a modified surfactant can also improve skin compatibility. For example, Rhein et al. reported a reduction in stratum corneum swelling produced by C_{12}-C_{14} alkyl ethoxy sulfates as the degree of ethoxylation increases (23). Finally, personal cleansers' skin compatibility is often improved by using mixtures of different synthetic surfactants (23,24,28,52).

Removal of Skin Lipids (Delipidization)

As noted earlier, the hydrolipid film on the surface of the skin is important for maintaining skin health. Epidermal lipids, which serve as the "mortar" between the corneocyte "bricks" in the stratum corneum, are also important to maintaining skin health and stratum corneum barrier function (53–55). Patient populations that exhibit heightened sensitivity to personal cleansing products, such as individuals with atopic dermatitis, often exhibit aberrant epidermal lipid composition or structure (56,57), and di Nardo et al. found an inverse relationship between susceptibility to irritation from SLS and levels of certain stratum corneum ceramides in normals (58). Visscher et al. reported an increase in transepidermal water loss rate, consistent with stratum corneum barrier compromise, following acetone/ether extraction of lipid from the skin surface and upper stratum corneum (59). Findings such as these, coupled with surfactants' natural ability to emulsify oils and lipids, suggest that surfactants' negative impact on skin could result from delipidization or selective removal of lipid components from the stratum corneum.

Kirk examined the amount of casual lipid, i.e., lipid on the skin surface, removed by one minute of controlled hand washing (60). Results from washing with water and with several bar cleansers are summarized in Figure 6. As expected, water is relatively inefficient at removing skin surface lipid. The surfactant bars are more efficient but still do not completely strip the skin surface of lipid. However, even partial removal of the hydrolipid film may effect changes in skin condition. Morganti reported that washing the skin with water decreases surface lipids by about 24%, while washing with soap reduces surface lipids by about 36% (61). Surprisingly, using a syndet bar to wash the skin reduced surface lipids by about 50%. Removal of skin surface lipids was hypothesized to decrease the skin's ability to retain natural moisturizing factors (NMF), ultimately leading to dry skin. Sauermann et al. also reported removal of NMF by exposure to water and to soap or syndet solutions, but these authors did not measure lipid removal (13).
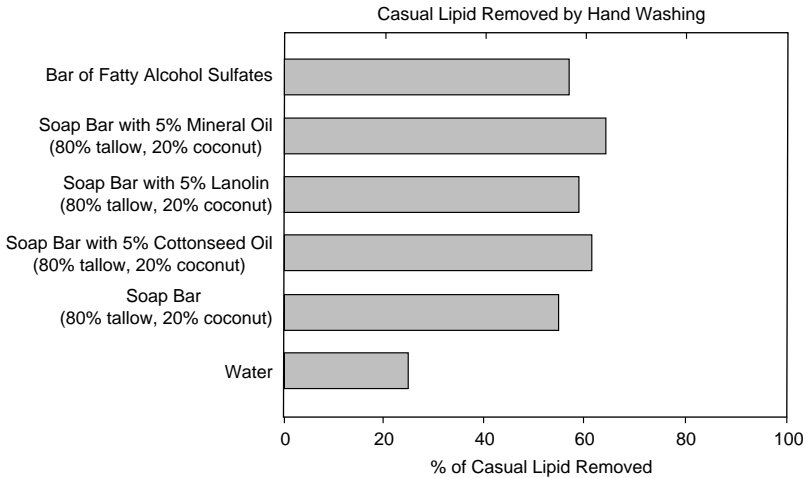
Casual Lipid Removed by Hand Washing

Figure 6　Percentage of casual lipid removed by 1 minute of hand washing. Washing with water alone removes about 25% of casual lipid; the amount of casual lipid removed increases to 50%–60% when a cleanser is used. *Source*: From Ref. 60.

Bechor et al. reported $>70\%$ relative change in casual sebum levels after washing the cheek for 30 seconds with water or various personal cleansing products (62). Sebum removal was not linked with clinical symptoms in this study, and sebum levels returned to baseline values in about one to two hours. Gfatter et al. examined the effect of washing on skin surface lipid content in a group of infants aged two weeks to 16 months (mean age 3.2 months) (63). Treatment consisted of a one-minute wash performed on each child's chest and buttock with tap water (control), a synthetic detergent liquid, a synthetic detergent bar, or a soap bar. Skin surface lipid content and several other parameters were measured 10 minutes after washing. All of the washes removed a significant amount of skin surface lipid. Not unexpectedly the least removal was observed for the control group $(-0.93\ \mu g/cm^2)$, the greatest removal for the soap bar group $(-4.81\ \mu g/cm^2)$. The authors conclude that removal of surface lipid might reduce stratum corneum hydration and lead to dryness and scaling.

　　　Personal cleansers can also induce changes in epidermal lipids, which are responsible for maintaining the skin's barrier function. Imokawa et al. reported that the stratum corneum lipid lamellar structure of forearm skin was disrupted following a 30-minute exposure to 5% aqueous sodium dodecyl sulfate (64). Post-exposure analysis showed a selective loss of various lipid components including cholesterol, cholesterol ester, free fatty acids, and sphingolipid. The authors noted that surfactant exposure produced an enduring chapped, scaly appearance and reduced hydration. Recovery studies conducted by applying isolated lipid fractions to surfactant-treated skin suggested a role for sphingolipids in helping to restore the skin's ability to retain water. Rawlings et al. examined lipid structure and composition in the normal skin of adult females and in xerotic skin induced by soap washing (65). Xerotic skin samples were obtained by tape stripping the backs of subjects' hands following one week of three-times-daily washing with soap; normal skin samples were obtained from a control group of subjects. The authors noted an apparent perturbation of desmosomal degradation, with intact desmosomes persisting to higher levels in the stratum corneum in soap-treated skin. The lipid bilayer structure in the outer stratum corneum was degraded in both skin types, but the normal and soap-treated structures had a different appearance. The authors found a decreased stratum corneum

ceramide content in soap-treated skin, with a progressive, deeper loss accompanying more severe dry skin grades. However, the relative levels of the various ceramide species were not different in the two skin types. The authors concluded that alterations in stratum corneum lipid composition and organization, along with reduced desmosomal degradation, are responsible for the scaling that accompanies soap washing.

Fulmer and Kramer compared lipid content in normal and surfactant-induced dry skin in a paired, dry leg study (66). Subjects washed one randomly assigned leg three times daily with 4% sodium dodecyl sulfate solution for a period of two weeks; the other leg remained untreated as a control. At the end of treatment shave biopsies were taken for lipid analysis. In contrast to the results reported by some other groups, no alteration in the total amount of lipid per gram of stratum corneum protein resulted from the surfactant washing. In particular, the total ceramide level was not changed. However, ceramide, cholesterol, and free fatty acid profiles were altered in the surfactant-treated skin compared to control. The authors concluded that surfactant washing affects the quality, but not the quantity, of stratum corneum lipids, suggesting that surfactants' role in the dry skin process is related to perturbation of the stratum corneum formation process, not lipid extraction.

Other studies also call the hypothesized relationship between lipid extraction and surfactant-induced skin damage into question. Scheuplein and Ross examined the effect of three classes of compounds on human epidermal membrane permeability to tritiated water: lipid solvents (e.g., chloroform:methanol), hydrogen-bonded solvents (e.g., water, DMSO), and surfactants (sodium laurate, SLS) (67). Lipid extraction decreased the dry weight of the stratum corneum by up to 20% even though its gross appearance remained unchanged. Solvent extraction of epidermal lipids resulted in a large increase in membrane permeability; this effect was irreversible. Hydrogen-bonded solvents also increased permeability, which was attributed to resolvation and membrane expansion. Unlike solvent extraction, the increase in permeability from hydrogen-bonded solvents was largely reversible. Exposure to surfactant caused visible expansion in the plane of the tissue, suggesting that the anionic surfactants initiate uncoiling of alpha-keratin molecules to form beta-keratin. The effect was reversible for mild surfactant exposures but irreversible for more severe exposures. Follow-up work by Dugard and Scheuplein again showed reversible changes in human epidermal membrane permeability following exposure to surfactants belonging to three *n*-alkyl homologous series (48). They concluded that extraction of lipids or other epidermal components was not the primary mechanism responsible for the increased membrane permeability, and instead suggested that surfactants act on membrane proteins. Rhein et al. reported that the swelling response of stratum corneum exposed to surfactant solutions was reversible, again suggesting a limited role for lipid extraction in surfactant interactions with skin (23). Froebe et al. examined in vitro stratum corneum lipid removal by SLS and linear alkyl benzene sulfonate (68). Both materials removed detectable levels of lipid only above their CMC, demonstrating that lipid removal is a micellar phenomenon. The primary lipid species involved were cholesterol and free fatty acids; little or no ceramide was extracted. Even at the highest surfactant concentration used (2%), the amount of lipid material removed from the skin represented less than 7% of the total stratum corneum lipid, indicating that delipidization, or at least the removal of sizable amounts of stratum corneum lipid, is not a primary mechanism for surfactant-induced irritation.

Surfactant Binding to Stratum Corneum Proteins and Surfactant Penetration

Other studies also support a role for surfactant-protein interaction in the development of skin irritation. Imokawa et al. measured the specific rotation of bovine serum

albumin (BSA) in the presence of surfactant to assess surfactant-protein interaction (69). Changes in the specific rotation were the result of conformational changes in BSA due to interactions with surfactant. Studies conducted with a range of surfactants suggested that both ionic and hydrophobic interactions between the surfactant molecule and BSA determine the extent of denaturation. For example, the authors proposed a stepwise interaction between ionic surfactants and BSA that would ultimately lead to complete denaturation of the protein molecule. They reported an excellent correlation between surfactant-protein interaction, as determined by the BSA specific rotation method, and skin roughness measurements made with a circulation apparatus (69).

Imokawa also used a technique based on indigo carmine dye displacement to examine binding of surfactant to stratum corneum and reported that the skin roughening effects of surfactants are related to their ability to adsorb onto skin (11,51,70). Keratin denaturation was believed to follow surfactant adsorption, as in the BSA model, ultimately leading to skin roughness. Kawai and Imokawa later extended this model to explain the sensation of tightness (71). Their work showed that lipid removal from skin was related to tightness induction; however, delipidization of the skin with ether did not result in marked tightness, and surfactants' ability to remove lipids did not always parallel their potential to induce tightness. There was, however, a strong correlation between surfactant adsorption and tightness, and removal of skin surface lipids enhanced tightness upon subsequent surfactant exposure. The authors proposed a model in which stratum corneum lipid extraction by surfactant is a necessary step to induce skin tightness, but is itself not sufficient to cause tightness.

Prottey et al. analyzed tape strip or cup scrub samples collected from the backs of hands following immersion in surfactant solutions or water for acid phosphatase activity (72). They found a decrease in enzyme activity following surfactant exposure, which was attributed to acid phosphatase denaturation and subsequent enzymatic inactivation resulting from surfactant interaction with the protein. The authors reported an inverse relationship between remaining acid phosphatase activity and hand dryness, and proposed this enzyme as a marker for monitoring interactions between surfactants and stratum corneum proteins. Ananthapadmanabhan et al. examined the binding behavior of several surfactants to isolated guinea pig or human stratum corneum and reported that the extent of surfactant binding to stratum corneum correlated well with the irritation potential predicted by in vitro and in vivo methods (73). Rhein et al. noted a time-dependent effect on stratum corneum swelling for SLS, which was attributed to the interaction of surfactant with keratin and disruption of the keratin's secondary and tertiary structure (23). As noted earlier, swelling induced by this and other surfactants studied exhibited a maximum for C_{12}-C_{14} chain lengths. The swelling response was for the most part reversible except following exposure to soap concentrations $> 1\%$ or prolonged (> 24 hours) soap exposure. In a later review Rhein proposed a model by which surfactants interact with stratum corneum proteins that explains the observed swelling behavior (74). This model incorporates ionic and hydrophobic binding interactions and accounts for the effect of pH on both stratum corneum proteins and on anionic and cationic surfactants.

Mukherjee et al. examined the interaction of pure anionic surfactants and cleansing bars based on anionic surfactants with isolated stratum corneum in vitro by measuring displacement of 1-anilinonaphthalene-8-sulfonic acid (ANS), a fluorescent probe known to bind to stratum corneum proteins (75). Their results showed agreement between surfactants' ability to displace ANS from stratum corneum samples and their potential to irritate skin as predicted by in vitro and in vivo methods, suggesting that surfactants' potential for binding to stratum corneum proteins determines their in-use skin

compatibility. López et al. exposed porcine stratum corneum to solvent (chloroform-methanol) and nonionic surfactant (octyl glucoside) solutions (26). Solvent exposure removed stratum corneum lipids but did not affect stratum corneum adhesion. In contrast, surfactant exposure preserved epidermal lipids; however, the lipid domain structure was disrupted. The surfactant also damaged corneocyte envelopes and caused corneocyte dishesion, suggesting that surfactant-protein interaction plays a role in irritation development. Shukuwa et al. studied the impact of pure surfactants and 1% solutions prepared from full formula bars on corneocyte disaggregation and swelling, and on morphologic deterioration using stratum corneum disks isolated from forearm suction blisters (76). The test materials' tendency to induce corneocyte disaggregation did not correspond well with induced swelling behavior, e.g., SLS caused significant corneocyte disaggregation but only slightly greater swelling than water. The ranking of the test soaps based on corneocyte swelling was consistent with irritation potential predicted by the soap chamber test (77), and the authors propose corneocyte swelling as an in vitro model for predicting cleansers' skin effects. One caution with the extrapolations made in several of these studies, however, is that the results generated under controlled exposure protocols that are used to "validate" the in vitro test data are themselves not always predictive of consumer experience with personal care products (9,78,79).

Factors related to the personal cleanser use environment will also influence surfactant-skin interactions. For example, Berardesca et al. examined irritation resulting from 5% SLS applied to the forearm at temperatures of 4°C, 20°C, and 40°C (80). Measurements made after four days of once-daily treatment showed that barrier compromise and erythema production increased with temperature. Desquamation and reflectance (L^*-value) also exhibited temperature-dependent behavior. Clarys et al. demonstrated a temperature-dependent increase in the irritant response to two dish washing liquids over a much narrower temperature range: 37°C and 40°C (81). In both of these studies the increase in irritation with temperature was attributed to greater fluidity of the epidermal lipids and enhanced irritant penetration.

Water hardness is another variable that varies in different use situations. We showed that water hardness impacts the absolute and relative skin compatibility of commercial personal cleansing products; soap-containing bars being more affected than syndet-based cleansers (82). Fujiwara and coworkers conducted arm immersion experiments using solutions of sodium laurate to examine the relationship between water hardness (calcium ion) and calcium soap-deposition onto skin (83). They found that hardness in water increased soap deposition, driven especially by the presence of calcium in the rinse water. We extended this work using marketed cleansing bars tested under a consumer-relevant arm wash protocol (84,85). A syndet bar, a triethanolamine (TEA) soap bar, and a sodium soap bar were tested. Washing was divided into two phases: a wash phase and a rinse phase conducted with various combinations of deionized water and hardened water (11 grains/gallon calcium). The syndet and TEA soap bars produced significantly less dryness and erythema than the sodium soap bar in the presence of calcium, but the difference between the products was negligible in deionized water ($P \geq 0.48$ for inter-product comparisons). Greater deposition of calcium soap onto skin occurred under the hard water conditions. As reported by Fujiwara, the rinse step was particularly important in determining the compatibility of these cleansing bars with the skin. Although the specific interaction between the calcium soap and skin was not examined in either of the above studies, both provide an example of the role surfactant-skin interaction (i.e., calcium soap deposition) plays in determining personal cleansers' skin compatibility.

Effect of Personal Cleanser pH

The pH is thermodynamically defined as the negative logarithm of the hydrogen ion activity in aqueous solution. The pH is often defined in more practical terms as the negative logarithm of hydrogen ion *concentration*. Strictly speaking the hydrogen ion activity and concentration are not identical but in dilute solution this is a reasonable assumption. Many publications refer to the pH of the skin, but since the skin is not an aqueous solution it clearly does not have a pH. When a wet pH electrode is placed onto the skin, water-soluble materials on the skin surface dissolve; the pH of this solution is what is actually measured. Also, personal cleansing products, and even the preparations made from them, are usually not dilute solutions. In what follows, "pH" is used to remain consistent with the original references, even though in many instances what is measured is more correctly called an apparent pH.

Soap dissolves in water to form free fatty acid and strong base, e.g., sodium soap will react with water to produce small quantities of free fatty acid and sodium hydroxide. As a result soap-based cleansing bars usually produce lather with a higher pH than do products based on synthetic detergents. The inherent tendency for soap-based cleansers to produce lather/solutions with pH values in the range of about 9–10, coupled with their generally poor skin compatibility, frequently forms the basis for a hypothesized cause-and-effect relationship between a cleanser's pH and its potential to irritate the skin.

At a fundamental level, Ananthapadmanabhan et al. reported a pH dependence for sodium lauroyl isethionate adsorption to skin, showing a minimum from pH 7 to pH 9, suggesting that pH might play a role in determining surfactant-skin interactions (73). However, van Scott and Lyon examined the potential for tap water with its pH adjusted from 4.5-10.5 or 1% solutions of various soap and detergent products to denature keratin (86). Water had no effect on the denaturation of defatted keratin or keratin plus 1% sebum over the pH range studied. Similarly, there was no significant relationship between product pH values, which ranged from pH 6.7 to pH 10.1, and denaturation of any of the keratins studied. Robbins and Fernee reported no significant in vitro swelling change when stratum corneum was exposed to water with pH values adjusted to between 3 and 9 (49). They also examined the effect of pH on stratum corneum swelling response to three different surfactants: SLS, linear alkylbenzene sulfonate (LAS), or dodecyl trimethyl ammonium bromide (DTAB). SLS and LAS are anionic; DTAB is cationic. Decreasing the pH value from 9 to 3 reduced the swelling responses for SLS and LAS. However, the swelling response was unchanged or increased when the pH was lowered from pH 9 to 6, a range that is relevant to many personal cleansers. The swelling response for DTAB increased when the pH was lowered from pH 9 to pH 3. Dugard and Schueplein observed that buffer in the pH range 3.0–9.5 produced no increase in stratum corneum permeability in the absence of surfactant (48). These authors found no change in the rate of permeability increase as a function of pH for the three surfactants studied: sodium dodecanoate (pH range 7.5-9.5), sodium dodecyl sulphate (pH range 5.0–9.0), and sodium dodecylamine hydrochloride (pH range 3.0–7.5). Bettley and Donoghue also performed water permeability experiments using isolated human stratum corneum (87). Their work showed that water, pH 10 buffer, and "Teepol" (2° alkyl sulphate detergent) at its natural pH or buffered to pH 10 had a minimal effect on membrane permeability. However, membrane permeability was markedly increased by exposure to 1% or 5% solutions of sodium palmitate. Membrane permeability gradually recovered upon removal of the soap, which as mentioned earlier argues against epidermal lipid extraction as a mechanism of irritation. The authors instead suggested that irritancy is related to a surfactant's ability to penetrate the stratum corneum.

In vivo studies show a similar trend. Bettley and Donoghue also conducted patch testing with toilet soap and TEA soap (88). The TEA soap was less irritating than the toilet soap even though the solutions prepared from each product had a comparable pH value. This may reflect a counterion effect; Rhein et al. also reported reduction in swelling response, i.e., a reduced potential for skin irritation, from TEA salts of surfactants (23). Frosch reported the relative skin irritation potential of 23 cleansing bars marketed in the United States and Germany determined using a soap chamber test (9). These products represented a range of surfactant compositions and covered a pH range from 5.4 to 10.7. The published results do not support a cause-and-effect relationship between a cleanser's potential to irritate skin and its pH value. Van der Valk et al. conducted a similar experiment and assessed the skin compatibility of 13 marketed personal cleansers (89). Irritation from 2% aqueous solutions of the products applied to subjects' volar forearms on stratum corneum barrier function was assessed by evaporimetry. All of the cleansers significantly increased transepidermal water loss (TEWL) compared to control, but the results showed no relationship between cleanser pH and irritation TEWL. In a similar study, van der Valk conducted patch testing with pure surfactant solutions on unaffected forearm skin of healthy subjects and subjects with irritant contact dermatitis or atopic dermatitis (90). The results again did not support a relationship between surfactant pH and irritation. Van Ketel et al. examined the irritation potential of several liquid hand cleansers spanning a pH range from 3.5 to 10.0 by applying 8% aqueous solutions of each product under patch (91). These authors concluded that the pH value of a cleanser is not a useful parameter for predicting its irritancy. Murahata et al. used a modified soap chamber test to study the skin irritation from a series of buffer solutions covering a pH range from 4.0 to 10.5, 8% (w/w) detergent solutions prepared from marketed syndet and soap bars, and 8% solutions prepared from altered soap base in which low molecular weight free fatty acids were added to the bars during processing (92). The buffers altered the skin surface pH but did not produce irritation. Likewise, the cleanser preparations changed the skin surface pH, but there was no correlation between pH and irritancy. One seeming exception is a patch test study by Baranda et al. conducted with 27 cleansing bars (tested as 8% emulsions), two undiluted liquid cleansers, and water (93). These authors reported a significant correlation between irritation and cleanser pH. However, the coefficient of determination calculated from the reported results is $r^2 = 0.244$. Thus, only about 25% of the variability in irritation that was observed in the study is explained by differences in cleanser pH.

Taken together, these in vitro and in vivo results suggest that the skin irritation potential of a personal cleansing product is primarily driven by differences in the chemical and physical properties of its component surfactants rather than by the pH value. However, personal cleansing products could affect skin condition in other ways. For example, Ananthapadmanabhan et al. conducted experiments to study the effect of pH on the physical properties of the stratum corneum (94). A series of in vitro experiments was conducted using Yucatan piglet skin as a model substrate. Sections of isolated stratum corneum were placed into the wells of microtiter plates and buffer or buffered surfactant solutions were added. Samples intended for swelling analysis (optical coherence tomography) were soaked for five or 21 hours at 37°C. Samples intended for lipid fluidity analysis were soaked for about 16 hours at room temperature. These experiments showed an increase in stratum corneum swelling at pH 10 compared to the other pH values; this effect was increased by the addition of surfactant. Lipid fluidity decreased at pH 10 relative to the other pH values; surfactant again increased this effect. The authors conclude that there is a direct effect of pH on stratum corneum protein swelling and lipid rigidity; both are greater at pH 10 than at pH 6.5 or pH 4.

Sznitowska et al. studied the effect of pH on the lipoidal route of stratum corneum penetration (95). Suspensions of two model compounds, hydrocortisone and testosterone, were prepared at pH values ranging from 2.0 to 10.0 (hydrocortisone) and from 1.0 to 12.0 (testosterone). Penetration was studied using full thickness cadaver skin mounted in flow-through diffusion cells. The studies were conducted with untreated skin and with skin pretreated with methanol-chloroform (11) or Azone, a material that alters stratum corneum lipid organization. The results from the experiments conducted with intact skin showed no significant effect of pH on the penetration of the model compounds in the range from 1.0 to 11.0. Removal of skin lipids with methanol-chloroform increased penetration, as did pretreatment with Azone. However, no significant pH effect on penetration was found for either pre-treatment method. A follow-up study was conducted to examine the effect of pH on lipid and free fatty acid extraction, lipid packing, and keratin conformation (96). Human stratum corneum samples were shaken for 24 hours with buffers ranging from pH 1 to 12. Buffer pH had no large impact on the amount of sterols or ceramides extracted, but free fatty acid extraction was pH-dependent, being maximal at pH 11 and 12. Differential scanning calorimetry showed some disordering of lipid packing in alkaline-treated samples. The changes were not instantaneous and required >1 hour exposure, becoming maximal after about eight hours. Fourier transform infrared spectroscopic analysis showed that the stratum corneum was largely unaffected by exposure to the buffer solutions, with no major changes to lipid packing motifs. Keratin conformation also appeared to be largely unaffected by buffer exposure, though there was some evidence that intracellular keratin took on a more ordered conformation at alkaline pH values. These authors concluded that the stratum corneum is remarkably resilient to extended exposure to both highly acidic and highly alkaline environments.

In adults the skin surface is normally slightly acidic, giving rise to the concept of the so-called "acid mantle." Healthy adult skin exhibits a very good ability to recover from pH changes even when challenged with alkaline solutions having a pH value around 13 (97). Literature indicates that personal cleansing products can transiently affect the skin surface pH in both adults and infants. As was mentioned previously, Gfatter et al. examined the effect of washing infants' skin with synthetic detergent and soap-based cleansing products (63). Washes were conducted with water (pH 7.9–8.2), a synthetic detergent bar (pH 5.5), a liquid synthetic detergent cleanser (pH 5.5), or a soap bar (pH 9.5). Skin surface pH measurements were made 10 minutes after washing. All washes increased the skin surface pH, with the water control producing the smallest increase (+0.20 units). Both synthetic detergent cleansers increased the skin surface pH by +0.29 units, significantly greater than the control. The soap produced the greatest skin surface pH increase, +0.45 units. This increase was significantly greater than that produced by the control or the synthetic detergent cleansers.

Changes in the skin surface pH resulting from washing with personal cleansing products can persist for longer periods. Bechor et al. examined the time course of changes in skin surface pH following controlled washing (62). Adult volunteers washed their faces for 30 seconds with one of 41 cleansing products covering the surfactant composition range from soap to synthetic. The skin surface pH was measured at defined times for up to 200 minutes after washing. The results from this study show that cleanser-induced elevation of skin surface pH persisted for as long as 94 minutes after washing.

Korting et al. conducted eight-week crossover studies to demonstrate the potential for personal cleansers to alter skin surface pH. Liquid syndet cleansing preparations adjusted to pH 5.5 or 8.5 were used as test products. Subjects washed sites on their forehead and the ventral forearm twice daily for one minute. One cleanser was used for the first four weeks, the other for the remaining four weeks. Skin parameters were assessed at

various times during each period, at least six hours after the previous wash. Both studies showed that washing with the pH 8.5 product resulted in a higher skin surface pH than washing with the pH 5.5 product. The cleansers produced no consistent difference in TEWL or skin surface roughness (98) but did influence the skin's microflora (99). No cleanser effect was observed on coagulase-negative Staphylococci populations, but Propionibacteria counts were increased when the cleanser at pH 8.5 was used. A similar effect on bacterial populations was demonstrated in a crossover study in which subjects used a full syndet bar or a soap bar for cleansing (100). The authors report that overall the skin surface pH was higher by 0.3 units and that Propionibacteria counts were elevated during the period of soap washing. These products were later compared in a three-month use study conducted among adolescents and young adults with acne (101). Fewer inflammatory lesions were observed in the group using the full syndet bar product. The authors extrapolate results from the earlier study conducted with liquid cleansers to rule out an effect due to differences in cleanser composition.

Alteration of skin surface pH might also effect more fundamental changes in the stratum corneum. For example, Fluhr et al. examined the impact of pH on stratum corneum acidification and integrity in a murine model (102). The backs and flanks of hairless mice were treated twice daily for three days with secretory phospholipase inhibitor (bromphenacylbromide or 1-hexadecyl-3-trifluoroethylglycero-sn-2-phospho-methanol) or vehicle control. Free fatty acid (palmitic, stearic, or linoleic acid) was co-applied to some animals. The effect of pH was examined by immersing flanks of anesthetized mice in bffer solution (pH 5.5 or pH 7.4) for three hours. The authors found that treatment with secretory phospholipase inhibitor increased skin surface pH and decreased barrier function (TEWL) and integrity (tape stripping), demonstrating a role for phospholipid metabolism in both these processes. Co-application of free fatty acid or exposure to pH 5.5 buffer normalized these effects. However, exposure to pH 7.4 buffer alone produced barrier alterations similar to the inhibitors, and exacerbated barrier effects in inhibitor-treated mice.

Barel et al. compared the skin effects resulting from use of a syndet bar (pH of 2% solution = 6.9) or a soap bar (pH of 2% solution = 9.6) in a blinded home-use test (103). Subjects washed their entire body with the assigned product at least once daily for a period of 10 weeks. Skin surface pH, TEWL, redness (chromameter a*-value) and stratum corneum hydration were measured at baseline and endpoint on the hand, forearm, upper arm, neck, and leg. The skin surface pH after using with soap was significantly higher than after using the syndet bar on the upper arm, neck, and leg. The difference between the mean pH values measured at study end was ≤0.4 unit, and the mean skin surface pH was in all cases ≤6.0. None of the other instrumental measurements showed a difference between the two treatment groups, and expert evaluation of dryness and erythema showed that daily use of the products did not induce visible skin changes. Subjective ratings of overall irritation/mildness showed a trend favoring the syndet bar at the end of the 10-week use period, but it seems likely based on the earlier discussion (e.g., the work of Imokawa) that this was due to a factor other than the product pH. The results of this study again highlight the difficulty of predicting in-use experience with controlled exposure models.

Other Ingredient Considerations

Surfactants determine many of the actions personal cleansing products have on the skin, but other ingredients can also have an effect. For example, certain polymers are used in personal cleansing products as formulation aids, to alter skin feel, or are substantive on skin, providing skin-protective properties (104–106). Glycerin is a

humectant ingredient used in many leave-on moisturizers that can also facilitate desmosome degradation (107). But being water soluble, it is difficult to deposit an effective level of glycerin on the skin in the rinse-off context that applies to most personal cleansers. However, glycerin can have other effects when used in personal cleansers. For example, Dahlgren et al. showed that incorporating glycerin into a soap bar improved the product's perceived moisturization benefit even though clinical endpoints are unchanged (40). As was mentioned earlier, some personal cleansers can now deposit effective levels of petrolatum onto the skin during use. These new petrolatum-depositing cleansers can produce marked improvement in dry skin condition; the prototype hand wash products described earlier are an example. Beyond this, there is evidence that topically applied petrolatum permeates the stratum corneum and improves barrier function (108), and that petrolatum deposited from a body wash can improve lipid bilayer structure in the outer stratum corneum (109) and improve stratum corneum barrier function (110).

Ancillary ingredients can also negatively impact skin condition. Fragrances are widely used in personal cleansing products. These materials often serve a functional role, covering the base odor of other formula components, and enhance product aesthetics and the cleansing experience. However, fragrances are frequently implicated as a cause of contact dermatitis and as a potential triggering factor in disease conditions such as atopic dermatitis. Since manufacturers rarely identify specific fragrances or fragrance components, identifying an offending agent is difficult. Using a cleanser that is labeled as "unscented" or "fragrance-free" does not guarantee that fragrance will not be an issue. Fragrance-free, for example, implies that a product has no perceptible odor, but these products can contain a low level of fragrance, smaller than the amount needed to impart a noticeable scent, to mask the odor from raw materials (111). A complicating factor is that some fragrance-free products contain ingredients such as preservatives or natural oils that provide scent as a secondary function, but that can also be a covert source of dermatitis (112,113).

SOME PRACTICAL CONSIDERATIONS WHEN CHOOSING A PERSONAL CLEANSER

Dermatologists and consumers are faced with a variety of choices when recommending or selecting a personal cleansing product. The previous sections of this chapter reviewed some of the available literature that examines factors governing the interaction between surfactants and the skin from a theoretical standpoint. While many of the studies presented were not conducted under in-use conditions, and some of the conclusions differ, they demonstrate that personal cleansers can impact skin in a number of ways and produce a range of skin effects. What does this mean from a practical standpoint?

Facial Cleansing

Facial cleansing is a primary need for most individuals. Apart from being a key interface for social interaction ("put your best face forward"), the face is a prime location for the accumulation of endogenous and exogenous soils. Sebaceous gland size and density are greatest on the face, upper back, and chest. The secretions from these glands, in conjunction with applied cosmetic products, help create a hydrolipid film on the skin surface that can effectively trap environmental pollutants (e.g., dust, and cigarette smoke). But while the accumulation of soil necessitates effective facial cleansing there are also

considerations that argue against excessive cleansing. For example, the facial stratum corneum has fewer cell layers than other parts of the body, except for the genitalia (114). A thinner stratum corneum barrier could increase susceptibility to irritation. The face is a site commonly associated with "sensitive skin," which by definition is based on subjective irritation and excludes individuals with pre-existing skin disease (115). This condition, which is estimated to affect about 50% of females, is reportedly associated with a defective stratum corneum barrier and to improve with a controlled skin care regimen (116). Facial skin is also moveable and rich in sensory nerves, so sensations such as tightness or tautness are more easily noticed. A retrospective study conducted by de Groot showed that the face far exceeded other body sites as an area for adverse effects from cosmetics among both females and males surveyed (117). Both sexes identified cleansers (soaps) as the agents most often responsible for these effects.

Bars are a convenient and popular facial cleansing option. These cleansers are available in a wide range of compositions. Traditional soaps provide effective cleansing and results presented previously indicate that with normal washing even soap bars do not completely strip the hydrolipid layer from the skin surface. However, soap may still induce or predispose the skin to sensations of tightness. Cleansing in adolescents or acne-prone populations requires special consideration. Acne is not caused by dirt on the skin surface, but regular cleansing is important. While soap is an effective cleanser, some evidence suggests that soap washing may predispose the skin to acne (101). More importantly, soap can irritate already inflamed acne lesions. Washing with a mild cleanser and warm water is recommended (118).

Exfoliating agents help to physically remove dirt and cellular debris from the surface of the skin, provide a rejuvenated look, stimulate the skin through a massage effect, and smooth the skin surface (119). The latter can increase the cleansing efficacy of personal cleansers. Exfoliating agents take several forms. There are exfoliating implements; those intended for use on the face are often made of a non-woven polyester material and are used to apply a cleansing product to the skin; some incorporate a cleanser that is activated by wetting. Proper use is important to avoid damaging the stratum corneum barrier, which will increase the likelihood of cleanser irritation, and manufacturers' directions for use should be followed. Some bar and liquid cleansers incorporate particles intended to act as exfoliating agents. Materials such as polyethylene, silica, various ground seeds (e.g., apricot, almond, or walnut seed), jojoba esters, loofa powder, cross-linked polymethacrylate, or calcium carbonate are used for these beads. The effectiveness of these exfoliating products and their potential to impact the skin is dependent on the concentration of the exfoliating agent and the properties of the particular agent used (119–121). As with exfoliating implements, manufacturers' directions for use should be followed to avoid damaging the skin when using these products.

Cleansing cloths are a relatively new introduction into the personal cleansing market. These cloths are available in dry and wet forms. The former, like the cleansing sponges mentioned above, incorporate cleansers that are activated when the cloth is wet. The textured surface of these cloths provides exfoliation and, in conjunction with the integrated surfactants, effective cleansing (122). These cloths can incorporate additional agents, such as petrolatum, that are transferred to the skin during use to provide skin benefits such as improved hydration. A four-week study conducted among a subject population with stage 1 or stage 2 rosacea showed good in-use tolerance for a dry lathering facial cleansing cloth with petrolatum (123). Thus, these facial cleansing cloths may provide a good cleansing option for individuals with sensitive skin.

Astringents and toners are sometimes used after cleansing to remove soap residue or remaining oil. These products may contain water, alcohol, propylene glycol, witch hazel,

or salicylic acid (124). Astringents and toners can dry the skin and leave it with a tight feeling, a cleansing endpoint that is considered desirable by some consumers. However, Wortzman reported that using a toner after cleansing increases irritation (125), either by a direct effect for toners with high alcohol content, or paradoxically for toners with moderate to low alcohol content. Propylene glycol that is found in some products is a mild irritant that may cause stinging in some individuals, and is also a potential contact allergen.

Body Cleansing

The number of cleansing forms available for use on the body is more limited than for the face, but the range of surfactants used in these products is no less varied. Soap is a cleanser used since antiquity, and it remains a popular cleanser despite much negative press and the introduction of syndets. In fact, soap is an effective, economical, and acceptable cleansing alternative for many people. The large number of soap-based products sold by large-scale and specialty manufacturers attests to this, and results from studies like the one conduced by Barel et al. suggest its effects on healthy skin may be limited in normal use (103). But numerous controlled application studies demonstrate the *potential* for soap to negatively impact skin and for this reason prudence dictates choosing an alternative cleanser in certain situations. For example, while some studies suggest that soap is well-tolerated in and may actually benefit conditions such as atopic dermatitis (126,127), there are better options for cleansing diseased skin. For patients who prefer a bar form, syndet cleansing bars provide good cleansing and are usually well-tolerated. Those who prefer a liquid cleanser form can benefit from using one of the newer body wash technologies, such as a product that will deposit petrolatum on the skin during use (128). An added benefit to using a body wash product is that they are applied with a polyethylene mesh "cleansing puff." This type of implement provides a mild exfoliation benefit (129) that can help remove the dry skin that accompanies many dermatoses.

There are situations were personal cleanser choice can be important, even for individuals with healthy skin. As mentioned above, the stratum corneum is thinnest on the genitalia (114), and the presence of a thin barrier in this intertriginous area seems a formula for personal cleanser issues. Cleanser irritation of the external genitalia is a greater issue for females than for males (130), and cleansing residue may also be a source of discomfort in females (131). In both sexes, cleansing with water only is advised, or if a cleanser must be used, a syndet-based product followed by thorough rinsing (130).

Aged skin also presents a cleansing challenge. The skin undergoes many changes with age, some of which can impact the response to personal cleansing products: the microvasculature that supplies the epidermis degrades and circulation decreases (132,133), the stratum corneum lipid content decreases (134), the stratum corneum turnover rate decreases (135), and the skin becomes drier and rougher (136). Resting TEWL values are lower in aged skin than in young skin, (134,137) which is usually associated with better barrier function. Aged skin does show a decreased response to irritants (133,137), but it also shows altered permeability to a variety of topically applied materials, suggesting that the decreased irritation reflects an attenuated inflammatory response rather than an improved barrier. Once perturbed, barrier recovery occurs more slowly in old than in young skin (134).

Cleanser choice can impact the elderly in a number of ways. The natural decrease in stratum corneum lipids and increased dryness can predispose aged skin to the drying effects of cleansers. Apart from its affect on skin appearance, increased dryness can worsen pruritus that commonly accompanies aging, which can lead to scratching, excoriation, and

infection (138). The loss of hydration and elasticity also makes the stratum corneum more susceptible to mechanical damage; a study conducted among residents of a long-term care facility showed an increased incidence of skin tears during periods when a non-emollient soap was used, compared to periods of emollient soap use (139). Regular skin cleansing remains important, but decreasing bathing or showering frequency and using a non-soap cleanser is recommended (140,141). Emollient cleansers can help, but their benefit must be balanced with the potential for slipping in the tub or shower (140). Since water temperature impacts skin-cleanser interactions (80,81), bathing in warm rather than hot water can help reduce drying and irritation. If a cleanser is used, thorough rinsing is important to assure that the cleanser residue is removed from the furrowed skin surface (142).

Race can also be a consideration when recommending or choosing a personal cleansing product. There are numerous published works describing physiological differences between different racial groups and controlled exposure studies that examine differences in irritant susceptibility (143–149), but the practical implications of the reported results in terms of susceptibility to in-use irritation remain unclear. Regardless of whether there are differences in the magnitude of the physiological response to personal cleansing products, the potential to induce some level of dryness or irritation undoubtedly exists for all skin types and this could have different implications for different groups. For
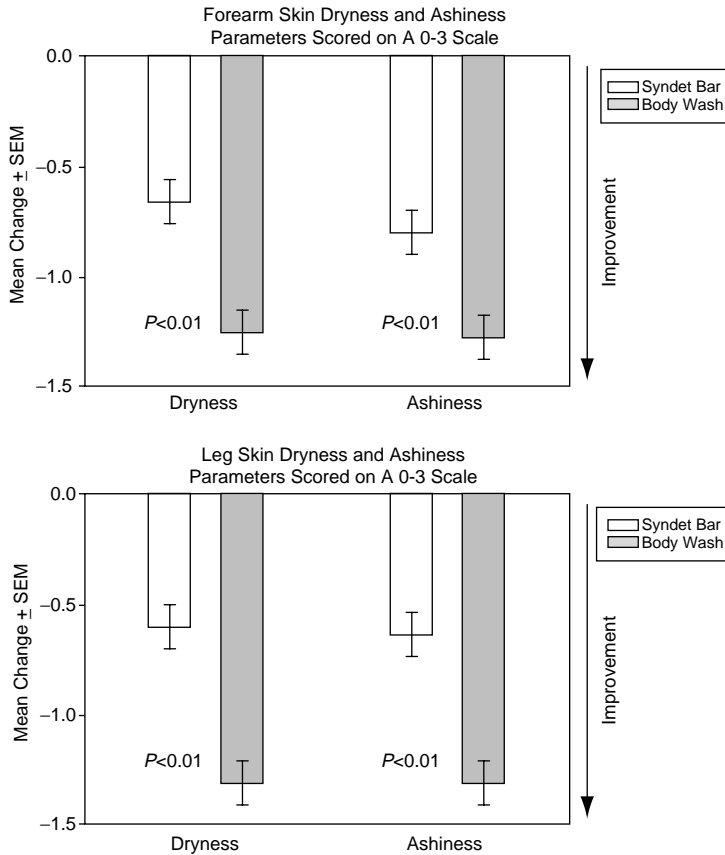

Figure 7 Change in dryness and ashiness on African American subjects' arms (*top*) and legs (*bottom*) assessed by the dermatologist investigator during a four-week home use study.

example, dry skin flakes are more visible when viewed against a dark background and light scattered by dry skin gives dark skin a dull, gray, "ashy" appearance, a condition that is considered undesirable or even disturbing to individuals with skin of color. Moisturizers are often used to mitigate skin dryness and the ashy appearance, but proper cleanser selection is also important to help minimize dry skin production.

To demonstrate the potential impact of personal cleanser choice on dryness and ashiness, we conducted a blinded, parallel group study among African American women with self-perceived dry/ashy skin, especially on their legs (150). Approximately half of the 83 women enrolled were randomly assigned to use a petrolatum-depositing body wash for daily showering for four weeks, and the remainder of the subjects were assigned to use a syndet bar. Moisturizer use was prohibited to eliminate this variable as a potential confounding effect and tub bathing was restricted. The dermatologist investigator scored dryness and ashiness on the lateral surface of subjects' arms and legs at baseline and study
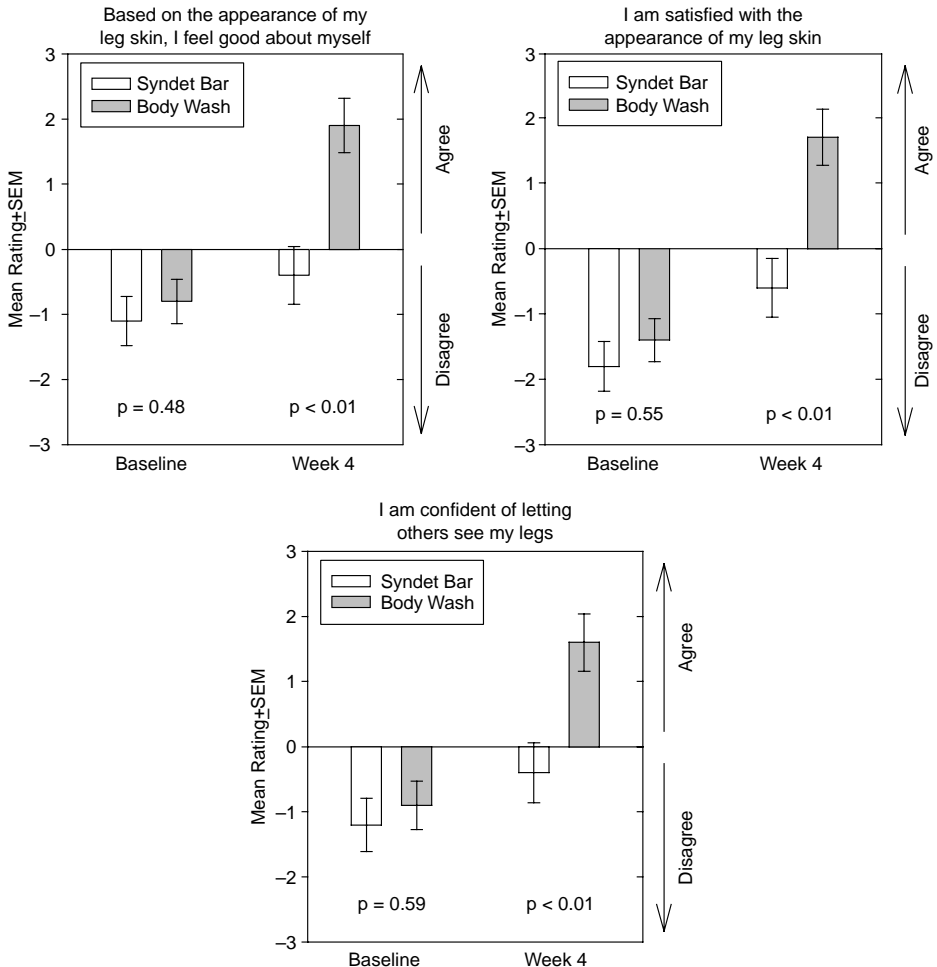

Figure 8   African American subjects' responses to a psychosocial questionnaire administered at baseline and after four weeks of using a petrolatum-depositing body wash or a syndet bar. The responses from subjects who used the body wash showed a marked improvement over the course of the study.

end. Subjects also completed a brief psychosocial questionnaire at these times to assess the impact of their dry/ashy leg skin on self-image. The dermatologist's evaluations showed that both personal cleansing products reduced dryness and ashiness over the course of treatment; a significantly greater reduction was observed for those subjects using the petrolatum-depositing body wash (Fig. 7). Weather conditions were reasonably consistent during the study, but a baseline habits and practices questionnaire showed that a high percentage of the enrolled subjects used a soap or combo bar (soap + syndet) as their usual cleanser. Since the study did not include a pretreatment period, some improvement in dryness and ashiness was expected as a result of switching to a less drying (i.e., non-soap) cleanser. While the test cleansers had a positive impact on these clinical parameters, an even more striking effect was shown on subjects' self-image (Fig. 8). Mean responses to these questions were relatively poor at baseline. Responses for subjects using the syndet bar exhibited a shift toward neutrality over the course of the study. However, responses for subjects who used the petrolatum-depositing body wash exhibited a strong positive shift, demonstrating that modern personal cleansing products can have a much broader impact than simply providing a means to remove soil from the skin.

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5

Toners and Astringents

Melanie Smith
Mary Kay Inc., Dallas, Texas, U.S.A.

INTRODUCTION

Skin care sales continue to grow globally, driven by innovative new product forms, multifunctional products, consumer interest in reducing the signs of aging, a rise in disposable income, and the availability of foreign product lines in formerly less-developed countries. Most of the increase in sales is generated by anti-aging/nourishing products. Dermatologists' skin care lines with scientific-sounding names and minimalist packaging are increasingly popular with the consumer who feels these lines may provide efficacy at an affordable price without a prescription. Euromonitor (1) reported toner sales worldwide in 2004 at $4.7 billion, growing at a lower rate than other skin care categories. Growth in toner sales in 2004 came from Asia-Pacific, Western Europe, Eastern Europe, and Latin America where multistep regimens are well received. In the U.S., where convenience is a key factor in product usage, sales peaked at $384.7 million in 1999 and then began a gradual decline which is forecasted to continue. The perception among some consumers that toners are unnecessary or harmful because they "strip" the skin, the lack of innovation in the product form, and inconvenience are among the reasons toner sales have declined. Toners are often perceived as harmful because consumers tend to associate them with drying of the skin and high alcohol levels. At one time toners were touted as pH balancers and necessary to remove the highly alkaline, drying, irritating residue of cleansers and soaps of the past. Most cleansers marketed today are mild and well formulated so as not to disrupt the skin's pH level, thus minimizing the perceived need for toners. In addition, toners have not advanced from the traditional solution form. Consumers prefer the convenience of facial cleansing wipes and multifunctional products, such as two-in-one cleanser/toner and three-in-one cleanser/toner/mask products, rather than the additional step of a toner. Despite this, there are opportunities for the dermatologist, aesthetician, and consumer to use a toner that is cosmetically acceptable, provides a sensorial experience, is suitable as a delivery vehicle, and is formulated appropriately for skin type.

PRODUCT NOMENCLATURE

Toners, astringents, skin fresheners, skin lotions, softeners, tonics, balancers, cleansing waters and other terms are used for products in this category. The choice of nomenclature

can vary by manufacturer and even within product lines. Also, the product name does not necessarily indicate strength or inclusion of a particular ingredient. For this chapter the term toners will be used to cover all these nomenclatures unless specified. Toners may be categorized as cosmetics or over-the-counter (OTC) drug products, depending upon the claims and ingredients. There is an astringent category under the Food and Drug Administration's (FDA's) Skin Protectant Drug Products for Over-the-Counter Human Use (2) defining astringents as "… (products) applied to the skin or mucous membranes for a local and limited protein coagulant effect." This definition covers the use of aluminum acetate, aluminum sulfate, and witch hazel. Active ingredients and labeling claims in astringent drug products are dictated by the FDA OTC Monograph (2). Except for witch hazel (*hamamelis water*) USP, these actives are reserved for OTC uses and are not typically used in cosmetic toners and, therefore, will not be considered for purposes of this chapter. To add to this confusion, there are products branded as toners and astringents containing cosmetic ingredients as well as toners and astringents containing salicylic acid that are sold in accordance with the FDA's OTC Acne Drug Monograph (3).

FUNCTION AND ORDER OF APPLICATION WITHIN A SKIN CARE REGIMEN

Toners are leave-on products. They are the second cleansing step within a skin care regimen designed to freshen and tone, and they also prepare the skin for the application of moisturizer. After cleansing, toners are typically applied by saturating a cotton ball or pad and wiping this across the face. Men may use them as a splash-on after shaving. Toners remove any makeup residue, and oily skin patients find them beneficial to remove excess sebaceous secretions. Toners can provide a mild exfoliating action and a stimulating or cooling sensation. Toners may also serve as a delivery vehicle for active or cosmeticeutically important ingredients such as anti-acne, anti-aging, and whitening/lightening. Although toners are typically designed for facial use, they may also be used for the upper chest and back in acne treatment.

FORMULATION CONSIDERATIONS

Product Forms and Ingredients

Toners are typically clear to translucent aqueous or hydroalcoholic solutions. The choice of ingredients, function of these ingredients, and claims determine the product's appearance and type of solution. A generic base formulation is shown in Table 1. Water is typically the major component and main vehicle or delivery system for active or other cosmetically important ingredients. Ethanol may be added as part of the vehicle as desired for skin type and/or ingredient solubility. Ethanol is generally not used in toners formulated for dry or sensitive skin or in the Asia-Pacific market, but it is found at varying levels in normal, combination, oily, and acne-prone skin types. Ethanol also serves as a preservative when used at levels of 20% or higher. Various types of denatured ethanol are used in toners, depending on country regulations on the denaturant. Isopropanol was used years ago, but it is now out of favor because of its strong odor.

Humectants are added to attract moisture to the skin, mitigate the drying effects of alcohol, lower the freeze point to ensure stability in cold temperatures, solubilize other

Table 1 Skin Toner—Base Formula with Typical Concentration Ranges

Ingredients	%
Water	Qs to 100.00%
Ethanol	0.00–65.00
Humectants	1.00–5.00
Key ingredients	0.10–10.00
Emollients	0.10–3.00
Cosolubilizers	0.10–0.50
Thickeners/film formers	0.05–0.20
Preservatives	As needed
Color, fragrance	Qs

ingredients, and adjust the aesthetics. Glycerin and sorbitol are the most cost effective humectants, but they can lend a tacky afterfeel. Sodium polycarboxylic acid (PCA) is less tacky, but more importantly, it is similar to the PCA which is found in the skin's own natural moisturizing factor (NMF). When additional solubility and an elegant, smooth, non-tacky feel is desirable, propylene glycol, butylene glycol, polyethylene glycols, and the ethoxylated glycerins, such as methyl gluceth-10 or methyl gluceth-20, are used. Sodium hyaluronate and other water-soluble moisturizing agents may be added.

Emollients, such as dimethicone copolyols and small amounts of natural oils, are beneficial for skin lubricity and soothing. They require the use of cosolubilizers to assure ingredient solubility to maintain product clarity and stability. Cosolubilizers include ethoxylates and propoxylates, such as PEG-40 hydrogenated castor oil, PPG-5-ceteth-20, or polysorbate 20. They are added at concentrations of 0.10–0.50%, depending on the oil-soluble ingredient and level used. The ethoxylated and proproxylated humectants are also useful but less efficient cosolubilizers.

Botanical extracts are added for a variety of reasons (4–6). The concentration is dependent on many factors, including the type of extraction and the percent solids of the extract. For example, aloe extract and witch hazel distillate are often used as vehicles. Frequently, several botanicals will be incorporated into a toner. Some extracts are more suitable for specific skin types; some offer multiple benefits. They are frequently touted as the key ingredient that offers benefits such as astringency, anti-inflammation, antioxidant, exfoliating, soothing, and cooling. It is the extracts' polyphenolic content that offers one or more of these benefits. Especially popular and beneficial are the polyphenolic bioflavinoids found in green tea, rosemary, blueberry, raspberry, strawberry, red wine, grapeseed, and pine bark extracts. They provide antioxidant and anti-inflammatory benefits. The anti-inflammatory benefits equate to soothing the skin by reducing skin stinging, itching, and redness. Extracts of honey, mallow, soy, aloe, lavender, green tea, algae, licorice, and chamomile may be added for their soothing and conditioning effects on the skin. The high tannin levels in botanical extracts such as witch hazel, sage, horsechestnut, and *quercus lusitanica* oak provide astringency. In addition to its astringency, the distillate of witch hazel, which contains 14% ethanol, also provides a cooling effect on the skin. It may be claimed as an OTC drug product astringent under the Skin Protectant Monograph (2), but both the distillate and extracts forms are more frequently used as a cosmetic ingredient in skin toners. Isoflavones, such as soy extract, known for their phytoestrogen content, are beneficial to more mature and dry skins.

Other beneficial ingredients used in toners are allantoin and panthenol for conditioning and soothing of the skin, and free radical scavenging antioxidants, such as alpha lipoic acid, superoxide dismutase, and vitamins A, C, and E. Vitamin E and its derivative, tocopheryl acetate, can also be used to protect the product and its constituents from oxidization.

Alpha-hydroxy acids (AHAs) such as glycolic, lactic, malic, citric, and mixed fruit acids are used for exfoliation and/or pH adjustment. While they are not marketed as toners, the toner product form has been used by aestheticians and dermatologists to deliver high levels of hydroxy acids in chemical peels for years, and more recently chemical peels with lower levels of AHAs have been introduced through the retail market. AHAs at efficacious exfoliating levels of pH <5 may cause skin stinging and redness, so the addition of anti-inflammatory and soothing botanical extracts is recommended. Although neutral pH ranges offer less irritation potential, they do not offer the same exfoliation activity. Polyhydroxy acids (PHAs), larger molecular weight variants of AHAs, are designed to be less irritating (7). Both AHAs and PHAs may be used in both aqueous and hydroalcoholic solutions. When used as a pH adjuster, AHAs are added at levels of 0.01–0.20%. The beta hydroxy acid (BHA), salicylic acid, is used for its keratolytic/exfoliating activity and is monographed as an OTC anti-acne drug (3).

Whitening agents have a long history of use in Asia. They are highly regulated in Asia as quasi-drugs. They have gained popularity in the rest of the world for the cosmetic claim of even skin tone, where the term whitening is considered a drug claim. Licorice, mulberry, and bearberry are popular skin lightening botanical extracts. The oil-soluble form of licorice at 0.05% is regulated as a functional drug in Korea (8). The water-soluble vitamin C derivatives, magnesium ascorbyl phosphate (MAP) used at 3%, and ascorbyl glucoside at 2%, are recognized as quasi-drugs in most of Asia (9). MAP is highly unstable and turns brown readily with time, high temperatures, and exposure to light. Ascorbyl glucoside is preferred for its acceptable stability profile.

Thickening ingredients are added when a slightly viscous and/or film forming property is desired. They also provide a more lubricious application and afterfeel than a solution. Xanthan gum, polyacrylic acids such as carbomer, and cellulose gum derivatives, such as methylcellulose, hydroxypropylcellulose, and hydroxyethylcellulose, are used.

Fragrance oils or naturally derived extracts and oils may be added to impart a pleasant scent to the formula or cover off-odors that develop when the product is exposed to excessive heat, light, or other parameters associated with shelf life. They also can be used to support a toner's marketing position and enhance the message that the toner is soothing or refreshing or, in the case of anti-acne toners, medicinal. Rose and lavender extracts can be used for soothing and dry skin formulas. Rosemary, peppermint, and citrus extracts may be added to toners designed for oily and combination skins or when a refreshing, stimulating signal or scent is desired. Menthol, peppermint, and eucalyptus odors are associated with a medicinal benefit.

Like fragrance, color is included to deliver a sensorial signal, such as soothing, refreshing or therapeutic, or to enhance the product's appearance, or to cover product color stability issues. Water-soluble Food, Drug, and Cosmetic (FD&C) and Drug and Cosmetic (D&C) colorants are used.

New and Patented Ingredients/Applications

Toners have historically contained plant-derived key ingredients. With recent controversies in the cosmetic industry concerning the use of animal-derived ingredients, the use of collagen and other animal-derived ingredients has diminished, and they are very

rarely found in toners outside of Japan. A recent U.S. patent discloses the use of extensions, plant-derived hydroxyproline-rich glycoproteins that can be incorporated into toners as substitutes for animal collagen (10). The use of *Morinda Citrifolia* or Noni from the Indian Mulberry plant in a toner is disclosed in a recent patent. Noni provides antioxidant benefits and is high in linoleic acid to nourish the skin (11). *Sanguisorba,* a plant native to Korea, China, and Japan, produces a root extract widely used in Asian cosmetics for its astringent effect. It is said to offer antimicrobial and anti-inflammatory effects as well, and it functions much like superoxide dismutase as an antioxidant (12). A recent patent discloses the preparation zinc glycyrrhizinate for use as an astringent in medical and cosmetic preparations (13). A mixture of butylene glycol and mushroom extract is used as an astringent additive for its skin tightening benefits (14). Pycogenol or pine bark extract and blueberry extract exhibit potent antioxidant and anti-inflammatory actions. They are useful as soothing and antioxidant agents in toners (15). Another recent patent (16) discloses the use of solvent extracts of plants including *Spondias mombin, Maprounea guianesis, Waltheria indica, Gouania blanchetiana, Cordia schmoburgkii, Randia armata*, and *Hibiscus furcellatu*s to stimulate autosynthesis of reduced glutathione. A skin toner formulation patent (17) covers the use of butylene oxide-based ethers and propylene oxide-based ethers. It is purported to remove sebum from the skin without significant removal of moisture-retaining intercellular lipids.

Formulation Challenges

Skin Types

Toners have two key formulating challenges—formulating for specific skin types and vehicle/ingredient stability and compatibility. Varying skin types, including dry, normal, oily, combination, sensitive, and acne-prone, require different and skin-type specific ingredients and vehicles. Free radical scavenging antioxidants are used regardless of skin type. Most toners are used within a skin care regimen. The patient's concern about toners being drying or harmful may be mitigated by using a regimen and toner appropriate for skin type.

Alcohol-free formulas with humectants, emollients, and soothing agents are most suitable for the dry and sensitive skin patient (Table 2). This, in conjunction with the use of a moisturizer, allays the concern of a toner being drying. The addition of humectants and emollient agents will help maintain moisture balance. Soothing ingredients are beneficial to alleviate the redness and irritation often experienced with these skin types. Sensitive

Table 2 Skin Toner for Dry Skin

Ingredients	%	Function
Water	QS to 100%	Vehicle
Sodium PCA	5.0	Humectant
Green tea extract	3.0	Botanical extract with soothing, anti-inflammatory, mild astringency, free radical scavenger benefits
Soy extract	2.0	Botanical extract with moisturizing benefits
Xanthan gum	0.2	Film former, thickener
Fragrance, color, preservative	As needed	

skin toners are formulated similar to dry skin formulas with the addition of anti-irritants such as allantoin, green tea, or licorice extract.

Toners designed for normal to combination skin types typically contain low levels of ethanol, humectants, and appropriate key ingredients. Botanical extracts with high tannin levels offer skin tightening effects without stripping the skin of its natural oils to mitigate the potentially drying effect of ethanol. It is recommended that soothing agents and humectants be added and that toner use be followed by a moisturizer designed for normal skin.

Oily skin toners, such as the formula in Table 3, are designed to provide a high degree of astringency and to control and/or remove excess sebum. This is achieved by using higher levels of ethanol and highly astringent and oil-absorbing ingredients. Levels of 20–50% ethanol may be used. The sebum removing and cooling effects of ethanol are highly desirable to the oily skin patient. High tannin-containing ingredients provide astringency. Astringent botanicals to consider include extracts of witch hazel, rosemary, lemon, grapefruit, horse chestnut, and stinging nettle. Natural sources of glycolic acid found in sugar cane extract, lactic acid found in milk, and salicylic acid found in willow bark extracts are often added for exfoliation. If a stimulating sensation is desired, peppermint, menthol, or eucalyptus is added. Kaolin, polyamides (nylon-6 and -12), methylmethacrylate crosspolymer, and silica absorb skin oil and minimize the appearance of oily shine on the skin. Silica settles slowly and gives the product a hazy appearance. The other oil-absorbing particulates settle readily, so a shake-well instruction prior to use is required. Soothing botanical agents and allantoin may be added to lessen any irritating dryness associated with higher ethanol concentrations.

Toners formulated for acne-prone skin typically contain high levels of ethanol, salicylic acid, and naturally derived antibacterials such as cinnamon, neem, and tea tree oil. Recently, there have been several references on the allergenic characteristics of tea tree oil (18–21). The ethanol level should be kept to the minimum necessary to solubilize the salicylic acid in order to minimize excessive drying to the skin. The FDA OTC Acne Monograph (3) dictates levels of salicylic acid from 0.5–2.0% as well as the acne treatment claim that may be listed on the product. A pH <4 is needed to assure delivery of the acid form. Formulations containing salicylic acid typically use 35–60% ethanol to maintain its solubility and stability. Levels as low as 20% ethanol in conjunction with the humectants glycerin and butylene glycol as cosolvents have been shown to provide acceptable salicylic acid solubility at room-temperature and low-temperature (5°C) conditions (22). To further enhance the perception of medicinal benefits of an anti-acne toner, scent and skin sensorial-stimulating agents such as menthol, eucalyptus, peppermint, or camphor may be added. Soothing botanical extracts and humectants are beneficial to minimize the potentially irritating and drying effects of high alcohol levels.

Table 3 Skin Toner for Oily Skin

Ingredients	%	Function
Water	QS to 100%	Vehicle
Ethanol	20.0	Vehicle, astringent, preservative, oil removal
Witch hazel distillate	20.0	Astringent, cooling and soothing effect
Glycerin	5.0	Humectant
Fragrance, color	As needed	

Alcohol-free toners may be used as a last step in cleansing, a preparation step to moisturizing, or as a whitening treatment product in the Far East. Toners are frequently sold under the "softener" nomenclature in Asia. Asian consumers have a negative perception of alcohol in terms of both skin reactions and odor of ethanol. They exhibit a higher degree of sensitivity to the skin effects of alcohol (23). It is advisable to avoid the use of alcohol and sensorial-stimulating agents to minimize the chance of irritation. Botanical extracts and the quasi-drug ascorbyl glucoside are used for whitening effects in toners. Another popular toner form in Asia is the lightweight, low-viscosity milky lotion. These are frequently used to prepare the skin as the first step of the moisturizing regimen. The milky lotions are alcohol-free. Collagen, hyaluronic acid, and whitening agents are popular in these products.

Ingredient and Vehicle Stability and Compatibility Considerations

Requirements of pH, ingredient solubility and compability, and product stability influence the choice of ethanol-to-water ratios, humectants, and cosolubilizers. Hydroxy acids require low pH to be effective as exfoliants. Fortunately, they also act as pH adjusters when a low pH is desired. This low pH limits the choice of film formers and thickeners. There are also pH and concentration limitations when using AHAs in retail products sold in the U.S. The Cosmetic, Toiletry, and Fragrance Association's Cosmetic Ingredient Review (CIR) Expert Panel recommends that cosmetic products containing glycolic and lactic acids and their salts and esters be formulated at pH ≥ 3.5 and at concentrations $\leq 10\%$ (24). Oil-soluble ingredients such as emollients, fragrance oils, and vitamins A and E require cosolubilizers to assure ingredient solubility to maintain product clarity and stability. The use of these cosolubilizers may cause product foaming during production filling and consumer use. This foaming can be minimized by adding an ingredient such as simethicone to reduce surface tension. Tea tree oil, found in many anti-acne and oily skin toners for its antibacterial activity, requires solubilizing agents for a clear solution, has a distinctive odor and its terpene constituents are highly susceptible to oxidation. The oxidation potential impacts the safety of the product (18–21); therefore, a recent European Cosmetic Toiletry and Perfumery Association (COLIPA) report recommended that manufacturers add antioxidants and/or packaging that minimizes the product's exposure to light (25).

High levels of ethanol in a toner can solubilize oil-soluble ingredients without the need for additional cosolubilizers. Easier to use water-soluble botanical extracts are more commonly used to provide antioxidant, anti-irritant, and soothing benefits, thus negating the need for cosolubilizers and mitigating any drying effects of alcohol. Alcohol-free toners or toners with less than 20% alcohol require preservatives to maintain microbiological quality.

PRODUCT CLAIMS

Toners on the market tout a plethora of skin benefit claims. It is these benefits that offer a prime opportunity for toner acceptance. The benefit most frequently associated with toners is a reduction of apparent pore size. Although no cosmetic product can alter the actual size of the pores, this claim is achieved because the pores appear less prominent due to an astringent effect that results in swelling of the skin surrounding the pore or removal of oil and dirt from the pore. "Purifies skin by removing dirt and oils" and "removing (or)

controlling oil" are claims used in oily skin toners. The toner claims, "restores the acid/alkali balance of the skin" and "pH balanced," still resonate well with consumers although they go back to the days of highly alkaline cleansers. Sensorial claims include "skin looks healthy," "even skin tone," "softens," "soothes," "refreshes," "energizes," "cools skin," "warms skin," and "tightens." Lightening and whitening claims such as "whitens (or lightens) the skin" and "reduces dark spots" are popular in Far East whitening toners. These claims may be quasi-drug or cosmetic depending on the country, ingredient, and claims. The "evens skin tone" claim is gaining popularity in the rest of the world.

CLAIMS TESTING METHODS

Toner claims are substantiated by subjective and objective measurements. Many claims are substantiated by using both measurements. These tools are useful in the screening of ingredients and final product efficacy. Subjective measurements include consumer perception testing and panelists self-assessment on clinical trials. These tests include yes/no, like/dislike, agree/disagree, and point scales to rate consumer perception. Point scales may be a three-, five-, seven-, or 10-point scale. For example, using a five-point scale of "much worse," "slightly worse," "no change," "slightly improved," or "much improved" would offer the panelists the option to rate the skin's appearance and condition. Another method is the use of a line marked in units from one to 10 designating least to most, where the panelists mark product attribute agreement.

Objective measurements include expert grading, photography, and instrument measurements. The expert grader is trained in visually assessing the skin for changes in color for evenness of skin tone, reduction of pore size for tightening and astringent claims, and reduction of the appearance of fine lines and wrinkles for anti-aging claims. Photography and more recently VISIA CR™ is used to capture these same measures on a permanent record. Instrumental measures include the Sebumeter™ and Sebutape (CuDerm Corporation, Dallas, TX) (Fig. 1) to measure oil control. The Gas Bearing Electrodynamometer™ assesses skin softness, and the Minolta chromameter measures skin tone and color. Chromameter measurements are useful in measuring skin tone and color in products claiming evenness of skin tone or skin whitening as well as the reduction of redness when measuring anti-irritant and anti-inflammatory benefits.

USES IN DERMATOLOGY

Until recently, the use of astringents and toners in dermatology was primarily limited to their anti-acne and astringent properties, although some also functioned as mild antiseptic agents suitable for mild or limited bacterial infections of the skin surface (24). Today soothing toners are increasingly being used by dermatologists and aestheticians for their anti-inflammatory and anti-irritant benefits as part of a post-cosmetic surgery regimen such as laser, chemical peel, or light-modulated procedures. The perceptual attributes of clean and refreshing for oily and acne-prone skins and soothing and calming for dry and sensitive skins in a cosmetically acceptable toner formulation assure patient compliance when compared with traditional drug vehicles that lack the aesthetic characteristics preferred by patients (26).
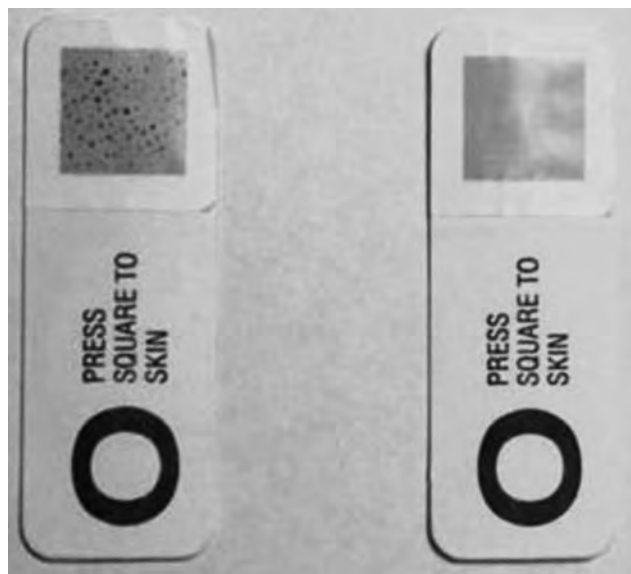
Figure 1 Macroscopic view of Sebutapes taken from oily skin surface before (*left*) and after (*right*) toner treatment. The fewer and smaller black spots on the right indicate a reduction in sebum after treating the skin with an oily skin toner. The number of pores and amount of sebum secreted can also be determined via image analysis.

ADVERSE REACTIONS

Adverse reactions in toners include transient contact irritation, contact allergy, and sensitization. Contact allergy is most often seen with more pharmacologically complex products, such as those containing multiple botanical extracts and penetration enhancers (27). Propylene glycol is often used as a humectant and sometimes as a solvent in toners. It is approved for use in concentrations up to 50% by the CIR (28), but caution is advised in using it above 10% as it can act as a penetration enhancer and cause irritation which, in patch testing, is often confused with comedones. Although tea tree oil is not recognized by the FDA as an anti-acne, antiseptic or antibacterial active ingredient, it is found in many anti-acne and oily skin toners. It also has a distinctive odor, and recently there have been several reports on the allergic, sensitization, and irritation potential of tea tree oil (18–21,29). COLIPA recommended that it not be used in cosmetic products at concentrations greater than 1% (25). Increased sun sensitivity occurs from topical application of AHA-containing products. Recently, the FDA issued industry guidance for labeling these products with a sunburn alert to minimize this risk (30). Toners have very low rates of reported adverse reactions compared to other skin care products. FDA statistics for the years 1991–1994 show 7.07 reported adverse reactions to toners and fresheners per million units sold, (31) and no consumer complaints were reported from 1995–2003 (32).

SUMMARY

Toners have a beneficial role in a patient's skin care regimen. They reduce the appearance of pore size; exfoliate; remove or control sebum; soothe skin aggravated by the environment,

dryness, or dermatological procedures, and provide a clean, refreshing skin feel. When properly formulated for skin type and skin benefits, they offer a cosmetically acceptable vehicle for delivery of ingredients used in cosmetic, cosmetology, post-cosmetic surgery, and acne treatment applications.

ACKNOWLEDGMENTS

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6
The Dry Skin Cycle

Paul J. Matts
P&G Beauty, Rusham Park Technical Center, Egham, Surrey, U.K.

Anthony V. Rawlings
AVR Consulting Ltd., Northwich, Cheshire, U.K.

INTRODUCTION

In 1994 two key publications summarized the knowledge on the state of the art of stratum corneum biology and dry skin, namely: "Stratum corneum moisturization at the molecular level" (1) and "The correlation of water content with ultrastructure in the stratum corneum." Since then, significant advances have been made in our understanding of the pathophysiology of dry skin. This chapter will review these recent findings and from these propose a new model of a dry skin cycle (Fig. 1).

First, however, we need to consider the role of water loss through the stratum corneum (SC). Under normal circumstances, the SC must be as impermeable as possible except for a small amount of water loss to (i) hydrate the outer layers of the SC to maintain its flexibility and (ii) to provide enough water to allow enzyme reactions that facilitate SC maturation events, together with corneodesmolysis and ultimately desquamation (Fig. 2) (4–6). This inbuilt water loss is vital for the normal functioning of the SC. This does, however, generate water gradients within the tissue. Key in precipitating the condition we call "dry skin" is a perturbation of these water gradients within the SC. Scientists at Procter and Gamble were the first to demonstrate changes in SC water gradients in dry skin (7) where about one-third of the outer layers of the SC are reported to contain less than 10% water content (Fig. 3). At this level of water content the SC will be dysfunctional and brittle (8).

The SC uses three main mechanisms to hold onto water:

- the intercellular lamellar lipids whose physical conformation, predominantly an orthorhombic laterally-packed gel and 13 nm long periodicity (LPP) lamellar phase induced by linoleate containing long chain ceramides, provide a tight and semi-permeable barrier to the passage of water through the tissue
- the presence of fully matured, rigid, corneodesmosome-bound, and ceramide hydrophobed corneocytes which influence the tortuosity of the SC and thereby the diffusion path length of water
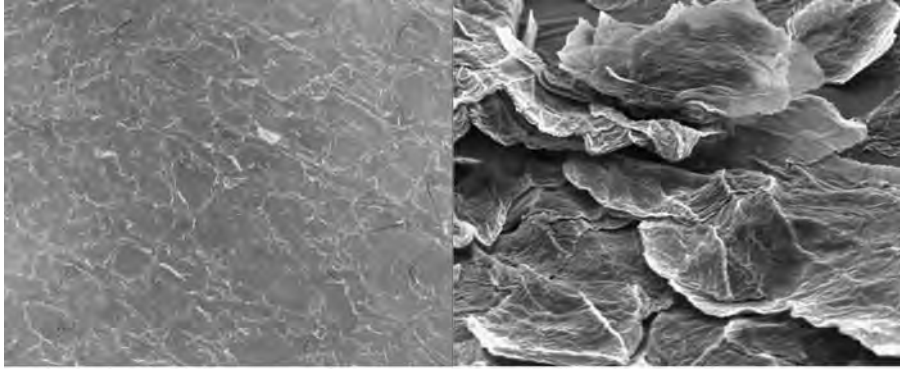
Visible light macrograph of dry skin
on the outer lower leg (approx 50x),
showing lifting squame

SEM micrograph of carbon tape
applied to dry outer lower leg skin (500x);
note compacted corneocytes in disarray

Figure 1   Typical photographs of cosmetic dry skin. *Source*: From Ref. 2.

-the presence of both intracellular and extracellular hygroscopic materials called
"natural moisturizing factors" (NMF)

STRATUM CORNEUM AND EPIDERMAL STRUCTURE

Our original concept of the SC with a "basket weave" appearance at the histological level
and a stratum compactum–stratum disjunctum at the electron microscope level has come
under scrutiny over the last decade. For instance, Pfeiffer et al. (9) developed new high-
pressure freezing followed by freeze substitution techniques for electron microscopy
methods and visualized an SC that appeared more compact with smaller intercellular
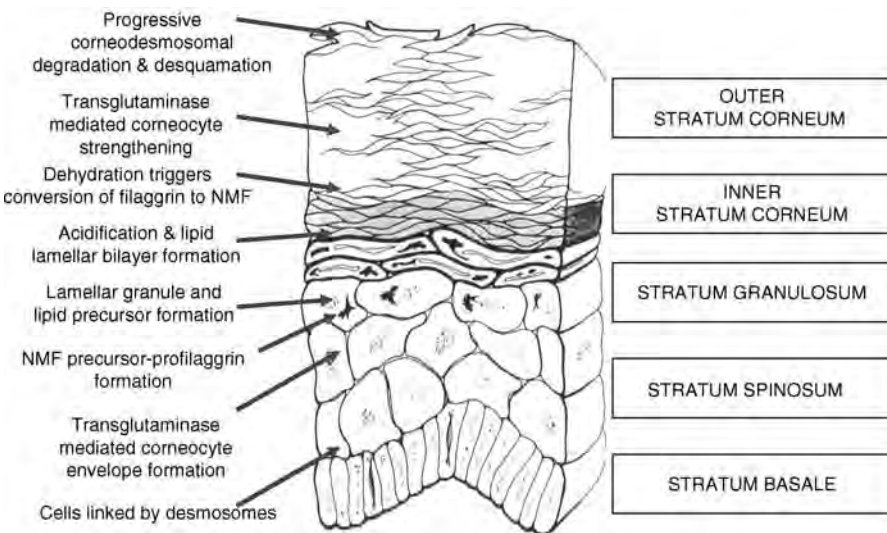
Figure 2   Typical structure of the epidermis and critical steps in formation of the stratum corneum.
Source: From Refs. 1, 3.
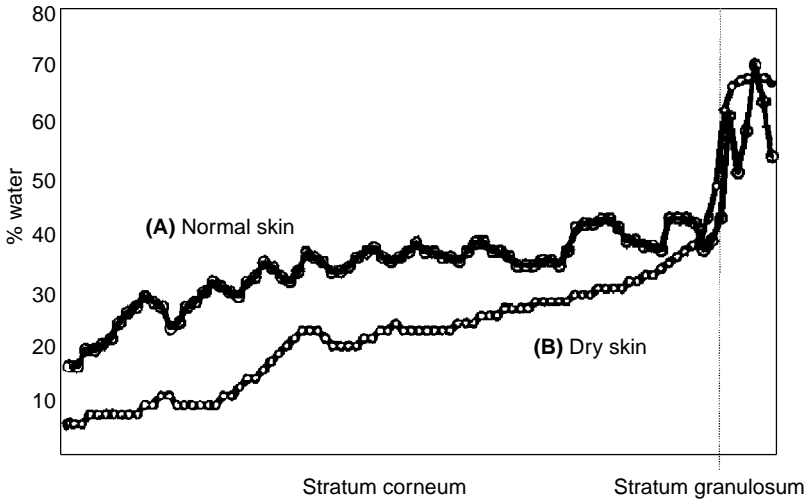
Figure 3 Water profile averaged over a single rectangular region of a cryosection obtained from an individual with (**A**) good skin, grade 0.5. The horizontal axis is distance across the SC with the SC/granulosum junction indicated by a vertical line. Water profile averaged over a single rectangular region of a cryosection obtained from an individual with (**B**) dry skin, grade 4. *Source*: From Ref. 7.

spaces and hence tighter cell-cell interactions. More controversial, however, was the lack of presence of keratohyalin granules in the epidermis. Lars Norlen (10) has also developed novel cryo-transmission electron microscopy techniques to image vitreous sections of skin without the use of cryo-protectants and, again, more densely-packed SC cells were apparent compared with conventional images and new organelles or tubular structures were observed in the epidermis. Norlen (11) has further proposed a cubic rod packing model for SC keratin structures. However, even with a more compacted SC, several SC swelling regions have been established by Bouwstra et al. (12) and Richter et al. (13) upon skin hydration which appear to be related to loss of barrier function and loss of NMF in the outer layers of the SC, hydrolysis of filaggrin to NMF, and lysis of non-peripheral corneodesmosomes, allowing greater intercorneocyte freedom and transglutaminase-mediated maturation of corneocytes towards the surface layers of the SC. As will be discussed, all of these events become aberrant in dry skin.

STRATUM CORNEUM LIPID CHEMISTRY AND BIOPHYSICS

All SC lipids are important for barrier function of the skin but due to their unique properties and structure the ceramides have been of most interest in recent years. Ceramides constitute (on a weight basis) approximately 47% of the SC lipids (14). Given this diversity, together with the identification of new ceramides, a new nomenclature based on structure, rather than the original chromatographic migration characteristics, was proposed by Motta et al. (15). In this system, ceramides are classified in general as CER FB, where F is the type of fatty acid and B indicates the type of base. When an ester linked fatty acid is present, a prefix of E is used. Normal fatty acids (saturated or unsaturated), alpha-hydroxy fatty acids, and omega-hydroxy fatty acids are N, A, O respectively, whereas sphingosines, phytosphingosines, and 6-hydroxysphingosine are indicated by S, P, and H. Sphinganine (not previously classified) is proposed to be SP in this nomenclature

system. A novel long-chain ceramide containing branched chain fatty acids is also found in vernix caseosa (16). Typical structures of human ceramides are given in Figure 4. Newly identified ceramides have also been found attached to the corneocyte envelope (CE). In addition to ceramide A (sphingosine) and ceramide B (6-hydroxysphingosine), Chopart et al. (17) recently identified covalently-bound omega hydroxyl fatty acid containing sphinganine and phytosphingosine ceramides. These covalently-bound ceramides should now be named CER OS, CER OH, CER OSP, and CER OP.

Ceramides are synthesised from either glucosylceramides, epidermosides, or sphingomyelin. Epidermosides are glycated precursors of omega, hydroxyl–containing ceramides. The studies of Hamanaka et al. (18) have demonstrated that sphingomyelin provides a proportion of CER NS and CER AS whereas the glucosylceramides are precursors to ceramides and epidermosides are precursors to the covalently bound ceramides, together with CER EOS, CER EOH, and CER EOP.

It is the packing states, however, and not only the structures of the SC lipids that are important for barrier function. Lipids in vivo appear to exist as a balance between a solid crystalline state (orthorhombic packing) and gel (hexagonal packing) or liquid crystalline states. The orthorhombically-packed lipids are the most tightly packed conformation and have optimal barrier properties. However, a greater proportion of hexagonally-packed lipid conformations are observed in the outer layers of the SC (19). This is consistent with a weakening of the barrier towards the outer layers of the SC. It is believed that short chain fatty acids from sebum contribute to the crystalline to gel transition in the upper stratum corneum layers (20).

Bouwstra et al. (21) recently proposed a new sandwich model consisting of two broad lipid layers with a crystalline structure separated by a narrow central lipid layer with
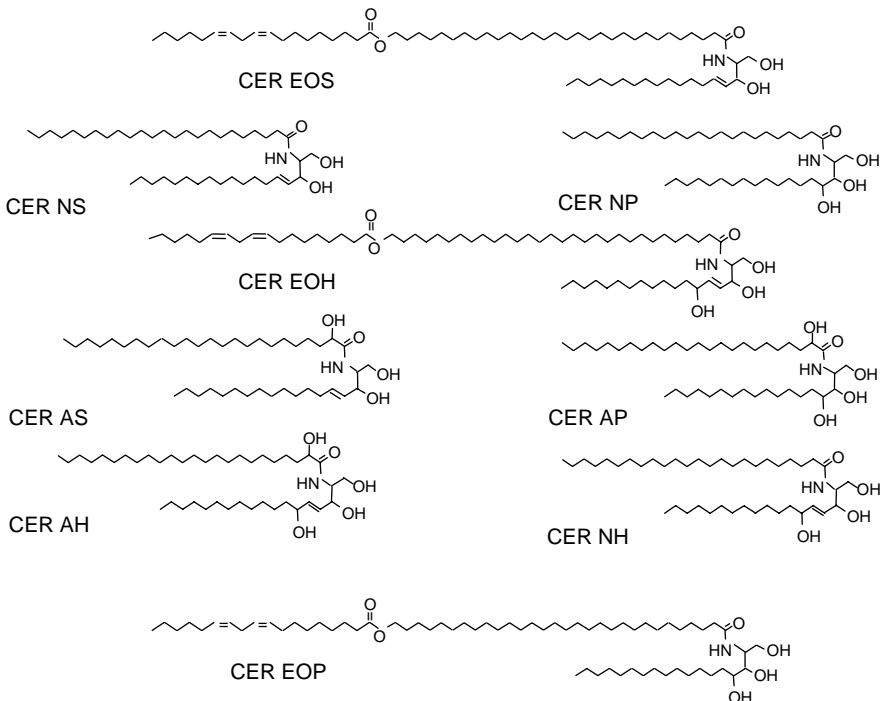
Figure 4   Structures of human stratum corneum ceramides.

fluid domains (Fig. 5). Cholesterol and ceramides are important for the formation of the lamellar phase, whereas fatty acids play a greater role in the lateral packing of the lipids. Cholesterol is proposed to be located with the fatty acid tail of CER EOS in the fluid phase. CER EOS, EOH, and EOP play an essential role in formation of the additional lamellar arrangements. The repeated distances were found to be 13 nm in dimension, composed of two units measuring approximately 5 nm each and one unit measuring approximately 3 nm in thickness. These repeat lamellar patterns were also observed by X-ray diffraction studies and were named the "LPP" and "short periodicity" (SPP) phases respectively.

Mostly hexagonal phases are also observed for total lipid mixtures in the absence of CER EOS. Equally no LPP phase is formed. Moreover, the importance of ceramide 1 or CER EOS in facilitating the formation of the LPP has been further elaborated by
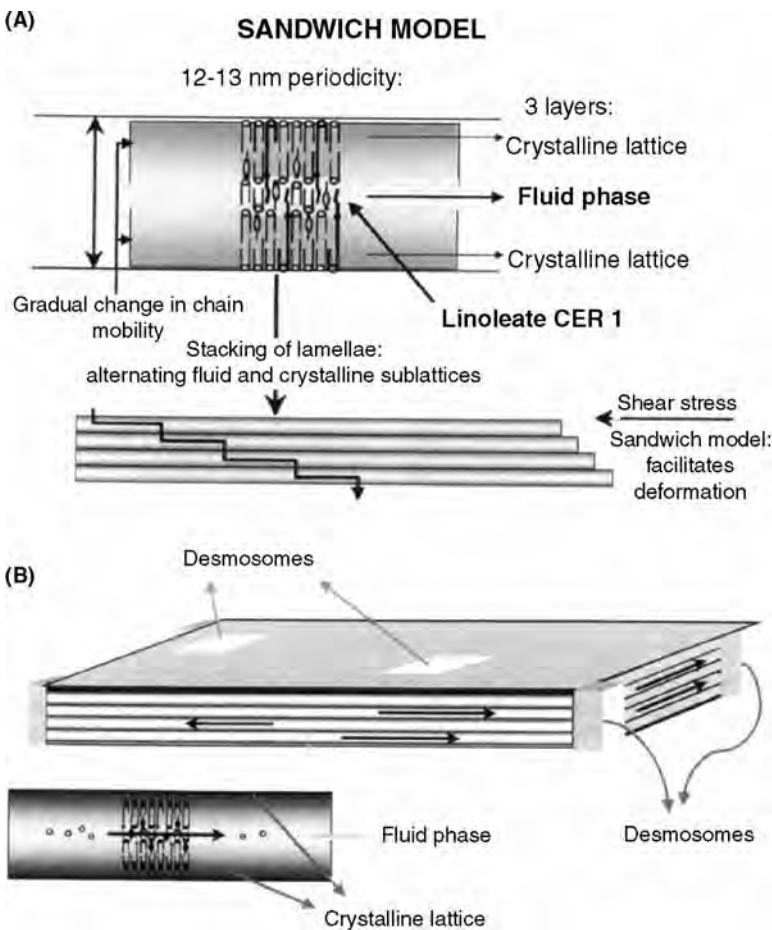
Figure 5 (**A**) "Sandwich model," the characteristics of which are: (1) the liquid sublattice is located in the central lipid layer of this phase, and in this layer mainly unsaturated linoleic acid and cholesterol are present; (2) in the sublattice adjacent to the central layer a gradual change in lipid mobility occurs due to the presence of less mobile long saturated hydrocarbon chains; (3) only a small fraction of lipids forms a fluid phase in the SC, and therefore one can assume that this central lipid layer is not a continuous phase. (**B**) The liquid phase parallel to the basal layers of the lamellae facilitates transport and therefore communication between the desmosomes. *Source*: From Ref. 21.
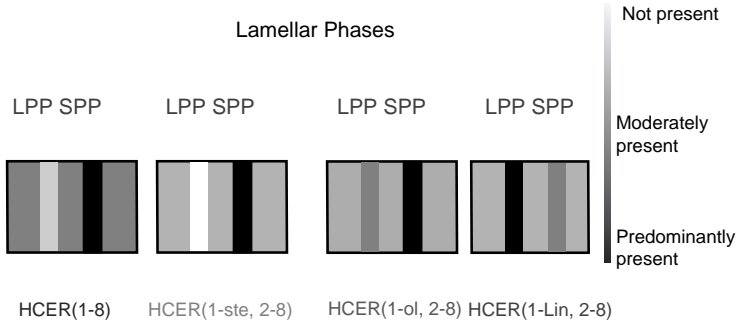
Figure 6 A summary of the lamellar phases and CER EOS in various lipid mixtures. HCER (1–8) mixtures in which HCER (EOS) is replaced with either synthetic stearate-containing CER (EOS), oleate-containing CER (EOS), or linoleate-containing CER (EOS). *Source*: From Ref. 22.

understanding the influence of the type of fatty acid esterified to the omega-hydroxyl fatty acid (Fig. 6) (22). As a consequence, the LPP is seen mainly with linoleate-containing CER EOS, less with oleate-containing CER EOS and is absent if only stearate-containing CER EOS is present in the lipid mixtures. These studies indicate that for formation of the LPP, a certain fraction of the lipids has to form a liquid phase. If the liquid phase is too high (as with the oleate-containing CER EOS) or too low (as with stearate-containing CER EOS), the levels of the SPP increase at the expense of the LPP. It is important to remember in vivo that the fatty acid composition of CER EOS is highly complex but contains a large proportion of linoleic acid.

Changes to the composition of the SC lipids could, therefore, dramatically influence the condition of the skin. In this respect, using electron microscopy of tape strippings from the outer layers of normal healthy skin, Rawlings et al. (23) reported complete loss of lamellar ordering in the outer layers of the SC (Fig. 7). These results have been confirmed by Warner et al. (24) and more recently by Berry et al. (25).

STRATUM CORNEUM CORNEODESMOSOMES AND CORNEODESMOLYSIS

The "brick and mortar" model of the SC has been known for many years. However, a more complete description of this model includes "corneodesmosomes." Corneodesmosomes (26) are macromolecular glycoprotein complexes incorporated into the CE and consist of the cadherin family of transmembrane glycoproteins, desmoglein 1 (Dsg 1) and desmocollin 1 (Dsc 1). These glycoproteins span the cornified envelope into the lipid-enriched intercellular space between the corneocytes and provide cohesion by binding homeophilically with proteins on adjacent cells. Within the corneocytes, Dsg 1 and Dsc 1are linked to keratin filaments via corneodesmosomal plaque proteins such as plakoglobin, desmoplakins, and plakophilins. The corneodesmosomal protein, corneodesmosin (Cdsn), after secretion by the lamellar bodies with the intercellular lipids and certain proteases, becomes associated with the desmosomal proteins just before transformation of desmosomes into corneodesmosomes. As these proteins are cross-linked into the complex by transglutaminase, their controlled disruption must occur by proteolysis to allow

(A)
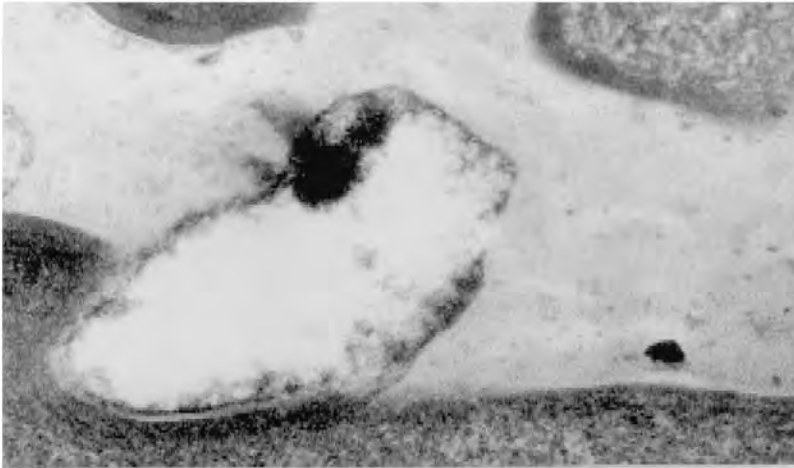
(B)   (C)
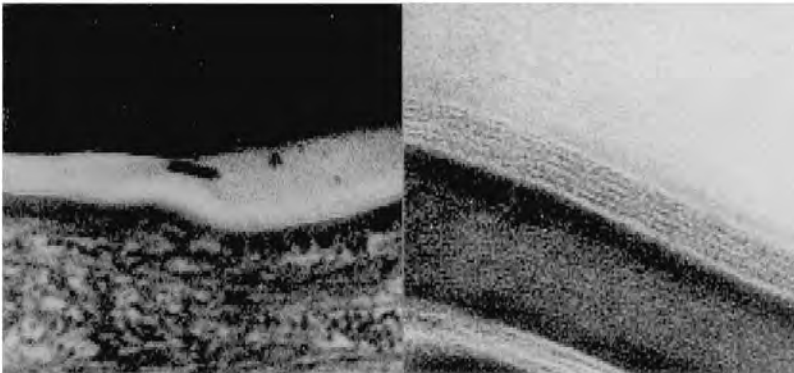
Figure 7   Organization of stratum corneum lipids in tape strippings of individuals with clinically normal skin. Transmission electron micrographs of tape strippings. Ultrastructural changes in lipid organization towards the surface of the stratum corneum: (**A**) First strip; absence of bilayers and presence of amorphous lipidic material. (**B**) Second strip; disruption of lipid lamellae. (**C**) Third strip; normal lipid lamellae. x200,000. *Source*: From Ref. 23.

desquamation to proceed. Indeed, Rawlings et al. (Fig. 8) (23) demonstrated degradation of the corneodesmosomes towards the surface of the SC in humans.

Desquamation is facilitated by the action of specific hydrolytic enzymes in the SC that degrade the corneodesmosomal linkages. Currently, several serine, cysteine, and aspartic enzymes are believed to be involved in this process, namely stratum corneum chymotryptic enzyme (SCCE), stratum corneum tryptic enzyme (SCTE), stratum corneum thiol protease (SCTP, now known as Cathepsin L-2), cathepsin E, and the aspartic protease cathepsin D. SCCE and SCTE are alkaline-optimal enzymes whereas the latter ones are acidic-optimum enzymes (27–31). Cathepsin L has also recently been implicated in Cdsn hydrolysis (32). Only SCTE and not SCCE, however, was capable of degrading Dsg 1 (33). This enzyme was also reported to be involved in the processing of pro-SCCE. Bernard et al. (34) have also identified an endoglycosidase, heparanase 1, within the SC, thought to play a role in the pre-proteolytic processing of the protecting sugar moieties on corneodesmosomal proteins.
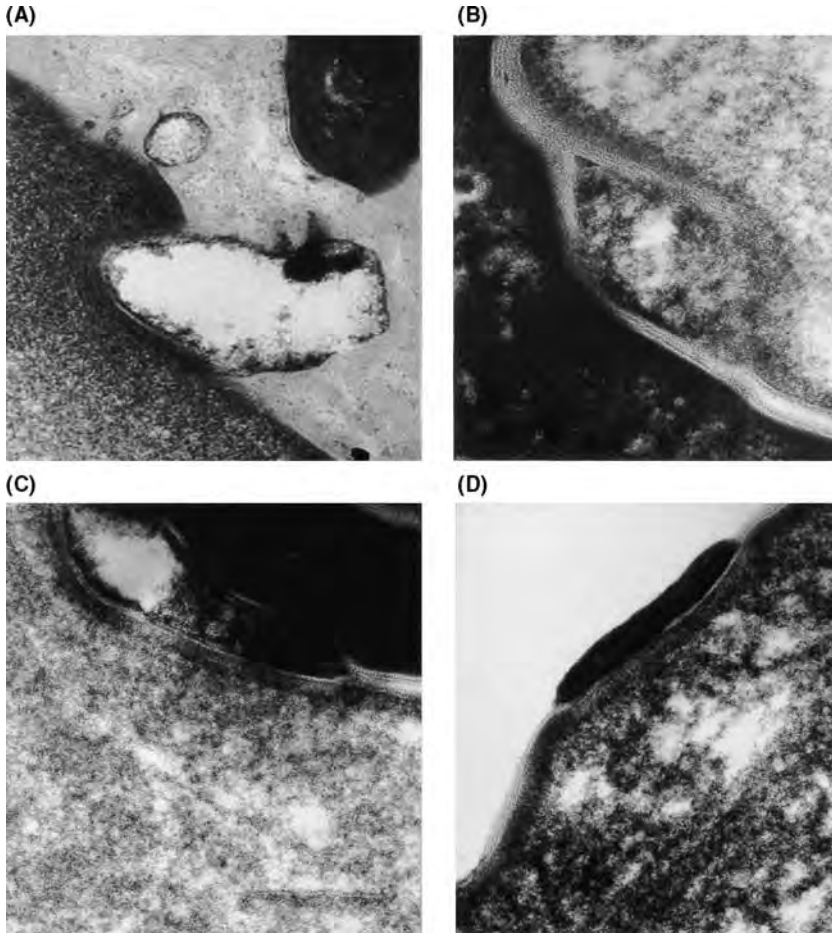
Figure 8 Electron micrographs of tape strippings of normal skin (grade 1). Degradation of corneodesmosomes (CD) toward the surface of the stratum corneum: (**A**) First strip; CD fully degraded. (**B**) Second strip; CD partially degraded and encapsulated by lipid lamellae. (**C**) Third strip; CD partially degraded, vaculation of structure. (**D**) Third strip, normal CD in contact with lamellar lipids. *Source*: From Ref. 23.

Cdsn undergoes several proteolytic steps. Cleavage of the N terminal glycine loop domain occurs first at the compactum disjunctum interface (48–46 KDa to 36–30 KDa transition), followed by cleavage of the C terminal glycine loop domain in exfoliated corneocytes (36–30KDa to 15KDa transition) (35). The last step appears to be inhibited by calcium resulting in residual intercorneocyte cohesion. Nevertheless, the presence of oligosaccharides did not protect Cdsn against proteolysis by SCCE (33). A complete list of the putuative desquamatory enzymes is given in Table 1.

These enzymes largely exist as proforms, and as they are secreted with the lamellar bodies, they have been immunolocalized to the intercorneocyte lipid lamellae. Sondell et al. (36) used antibodies that immuno-react precisely with pro-SCCE to confirm that this enzyme is transported to the SC extracellular space via lamellar bodies. In later studies, using antibodies to both pro-SCCE and SCCE, Watkinson et al. (37) demonstrated that the processed enzyme was more associated with the corneodesmosomal plaque. More recently, Igarashi et al. (38) have immunolocalized cathepsin D to the intercellular space,

Table 1 Desquamatory Enzymes

Sphingoid hydrolases	Cermidase
	Glucocerebrosidase
	Sphingomylinase
	Sphingomyelin deacylase
	Glucosylceramidedeacylase
Sulphatases	Steroid sulphatase
Glycosidases	Heparanase 1
Serine proteases	Stratum corneum chymotryptic-like enzyme (SCCE/KLK7)
	Stratum corneum tryptic-like enzyme (SCTE/KLK5)
Cysteine proteases	Stratum corneum thiol protease (SCTP/L2)
	Stratum corneum cathepsin L-like enzyme (SCCL)
Aspartic proteases	Stratum corneum cathepsin D-like enzyme (SCCDE)
	Stratum corneum cathepsin E-like enzyme (SCCEE)
	Skin aspartic protease (SASPase)
	Caspase 14

whereas cathepsin E was localized within the corneocytes. Finally, KLK8 has also been reported to be localized to the intercellular spaces of the SC (39).

As the desquamatory enzymes are present in the intercellular space, the physical properties of the SC lipids, together with the water activity in this microenvironment, will influence the activity of these enzymes. Interestingly, however, SCCE appears to have a greater tolerance to water deprivation than other proteolytic enzymes, and this may be an adaptation to maintain enzyme activity even within the water-depleted SC intercellular space (40). However, a variety of inhibitors are also present to attenuate their activities, cholesterol sulphate being one of them. Other protein and peptide inhibitors are present such as elfin, covalently bound to the CE, antileukoproteinase, alpha-1-antitrypsin, alpha-1-antichymotrypsin, and the SPINK5-derived peptides (41). Nevertheless, anti-leukoprotease is believed to be the major physiological inhibitor of SCCE; the serpins are too low in concentration to be physiologically relevant (42). Caubet et al. (33) recently speculated in a new model of desquamation that SPINK5 may also inhibit SCTE.

Currently, little is understood of the molecular activation mechanisms of SCCE or other enzymes within the SC, but Brattsand et al. (43) has proposed a model recently for the activation of the kallikreins (Fig. 9). Clearly, SC pH and water content will influence enzymic activity. As the SC pH declines towards the surface of the skin, the activity of SCTE and SCCE may be reduced and perhaps the acid optimal cathepsin enzymes mediate the final desquamatory steps. The role of the newly identified skin aspartic protease and caspase 14 in this process is still awaiting clarification.

CORNEOCYTE ENVELOPE MATURATION AND THE ROLE OF TRANSGLUTAMINASES

The CE is an extremely stable and insoluble proteinaceous layered structure. The stability of the envelope is attributed to the degree of cross-linking of envelope proteins by either disulphide, glutamyl-lysine isodipeptide bonds, or glutamyl polyamine cross-linking of glutamine residues of several CE proteins (44). The enzymes, responsible for catalysing the gamma-glutamyl-epsilon-lysine isodipeptide bond formation, are the calcium-dependent transglutaminases (TGase; glutamyl-amine aminotransferases EC 2.3.2.13),
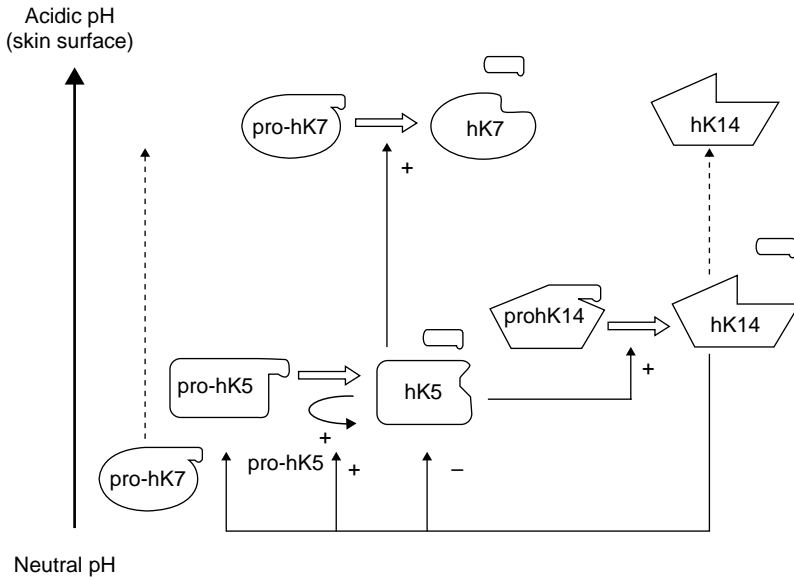
Figure 9 Proposed kallikrein activation cascade in human stratum corneum. *Source*: From Ref. 43.

of which four are expressed in the epidermis: TGase 1, 2, 3, and 5. However, only TGase 1, 3, and 5 are thought to be involved in keratinocyte differentiation.

At early time points in the keratinocyte differentiation process, envoplakin and periplakin are expressed and become associated with desmosomes in the viable epidermis. Subsequently, involucrin (the glutamyl-rich protein that covalently-bound lipids become attached to) is expressed at the same time as TGase 1 (45–47). TGase 1 then cross-links involucrin to the other early expressed proteins, such as members of the small proline-rich family of proteins. Subsequently, other plasma membrane proteins become cross-linked, and these form a scaffold for further reinforcement and maturation events (48).

By Normarski microscopy, CEs (CE's) were shown to have a crumpled surface when isolated from the lower layers of the SC and a smoother, more flattened surface when isolated from the upper SC. These two populations of CEs were named fragile (CEf) and rigid (CEr). Mils et al. (49) reported that about 80% of corneocytes from volar forearm skin were smooth and rigid, whereas 90% from foot sole were rough or fragile cells. They can also be further differentiated by their binding of tetra-methyl rhodamine isothiocyanate (TRITC), with the rigid envelopes staining to a greater extent (Fig. 10) (50). However, Hirao et al. (51) have used a more elegant method to identify CEs based upon their hydrophobicity (staining with Nile red) and antigenicity (to anti-involucrin) (Fig. 11). It is clear from these studies that immature envelopes (CEf) occur in the deeper layers of the SC (involucrin-positive and weak staining to Nile red or TRITC) and that mature envelopes occur in the surface layers of healthy skin (apparent involucrin staining lessened and increased staining with Nile red or TRITC). More recent work from Kashibuchi et al. (52) using atomic force microscopy confirmed these structural changes in corneocytes from the deeper layers of the SC.

The classification of fragile and rigid envelopes has subsequently been found to be a pertinent classification system as, mechanically, they have fragile and rigid characteristics
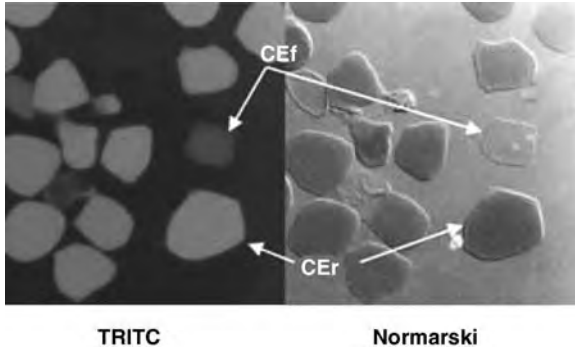
Figure 10 Fluorescence and Normaski phase contrast microscopy of TRITC stained cornified envelopes demonstrating increased fluorescence labelling of CEr compared with CEf. *Source*: From Ref. 50.

under compressional force (Fig. 12) (50). Supporting this concept of increasing CE strength, gamma glutamyl-lysine cross-links also increase in the subsequent layers of the SC, due to enhanced TGase activity. Three pools of TGase activity have been identified in the SC which have been classified based upon their solubility characteristics: a water-soluble TGase (mainly TGase 1 and 3), a detergent-soluble TGase (TGase 1), and a particulate form that cannot be liberated from the corneocyte. Whether all enzyme fractions are active in this maturation process of CEf to CEr is currently not known.

STRATUM CORNEUM NATURAL MOISTURIZING FACTORS (NMF)

A historical perspective on filaggrin biology was given by Rawlings et al. (1). Biologically, NMF allows the outermost layers of the SC to retain moisture against the
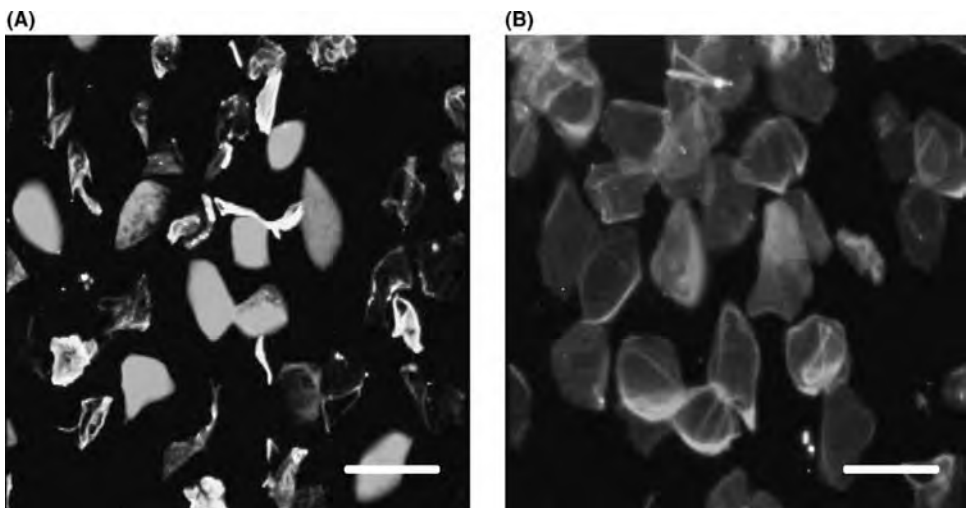
Figure 11 Double staining of CEs with Nile red and anti-involucrin (shown here in gray scale). (**A**) Face and (**B**) upper arm. *Source*: From Ref. 51.

CE*r*

Population mean = 832.94μN

CE*f*

Sample mean = 135.1μN
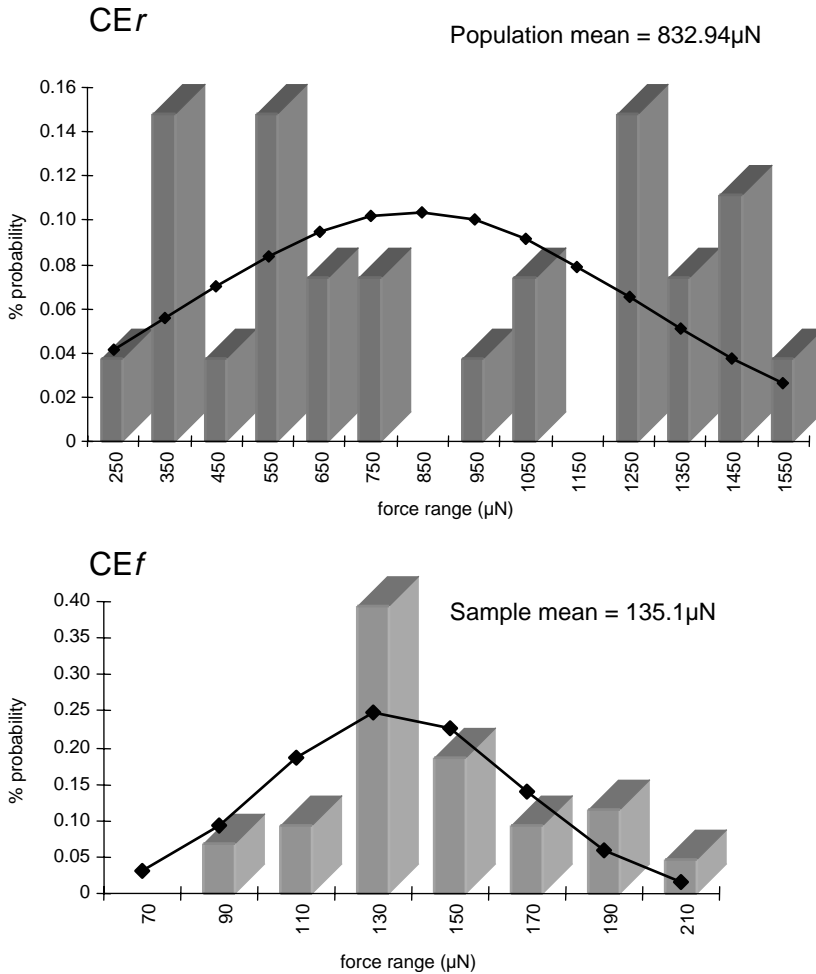
Figure 12 Distribution profile of the maximal compressional forces (uN) of individual CEs. Top panel shows the force range for CEr and the bottom for CEf. The maximal compression force was significantly different between the corneocytes. *Source*: From Ref. 50.

desiccating action of the environment. Traditionally, it was believed that this water plasticized the SC, keeping it resilient by preventing cracking and flaking which might occur due to mechanical stresses. The general mechanisms by which these NMF components influence SC functionality have been studied extensively. From a physical chemistry perspective, the specific ionic interaction between keratin and NMF, accompanied by a decreased mobility of water, leads to a reduction of intermolecular forces between the keratin fibers and increased elastic behavior. Recent studies have emphasized that it is the neutral and basic free amino acids (53), in particular, that are important for the plasticization properties of the SC. The generation of NMF is summarized by Mechin et al. (Fig. 13) (54) which also highlights the importance of peptidylarginine deminases involved in the processing of filaggrin and thereby allowing its hydrolysis to NMF.

Recently, hyaluronic acid has been shown to be present naturally in the SC (55) as has glycerol. Glycerol will also be derived from sebaceous triglyceride breakdown and

again, to emphasize the importance of this molecule, studies by Fluhr et al. (56) have indicated that topically-applied glycerol can completely restore the poor quality of SC observed in asebic mice (that are lacking sebaceous secretions) to normal. The importance of glycerol as a natural skin moisturizing molecule has also been shown by Elias et al. (57) However, typically, these two molecules have been largely ignored in descriptions of NMF composition (1). Recent data also indicates that lactate plays a critical role in influencing the physical properties of the SC. Lactate and potassium were found to be the only components of the NMF analyzed that correlated significantly with the state of hydration, stiffness, and pH in the SC (58).

The generation and maintenance of an acid pH within the SC, the so-called "acid mantle," is critical to the correct functioning of this tissue. Studies point to an essential role of free fatty acids generated through phospholipase activity as being vital for SC acidification (59), while Krein and Kermici (60) have recently proposed that urocanic acid plays a vital role in the regulation of SC pH. Although this is in dispute, it is likely that all NMF components contribute significantly to the overall maintenance of pH.

Other components of NMF are also not derived from filaggrin, and urea, like lactate, may also be derived in part from sweat. However, the presence of sugars in the SC represents primarily the activity of the enzyme beta-D-glucocerebrosidase, as it catalyzes the removal of glucose from glucosylceramides to initiate lipid lamellae organization in the deep SC (1).

New measurement tools have been developed in the last decade for the measurement of such compounds in vivo. Caspers et al. (61) have pioneered the use of confocal Raman microspectroscopy to determine the concentration of defined NMF components, non-invasively, in vivo within the SC. Typical depth-concentration profiles can be seen in Figure 14.
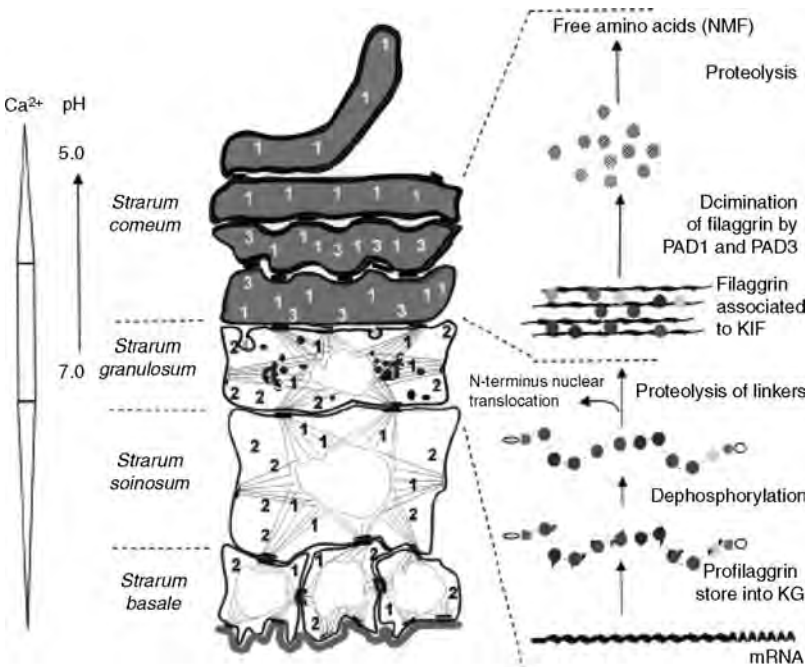
Figure 13 Schematic representation of profilaggrin catabolism and filaggrin hydrolysis to NMF and activation of peptidylarginine deiminase. *Source*: From Ref. 54.
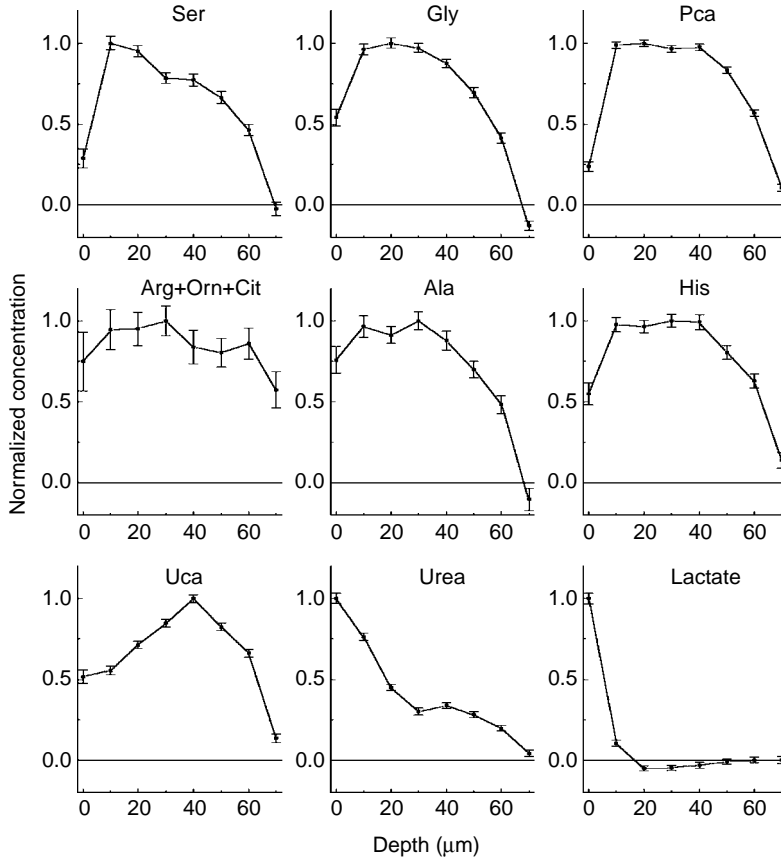
Figure 14 Semiquantitative in vivo concentration profiles of NMF and sweat constituents in the stratum corneum of the thenar as determined by Raman spectroscopy. *Source*: From Ref. 61.

THE EFFECT OF HUMIDITY ON EPIDERMAL DIFFERENTIATION AND STRATUM CORNEUM QUALITY

Before considering the biology of dry skin and the dry skin cycle, it is important to review the effect of environmental conditions on the SC, as these are the primary initiating events for the precipitation of the condition. In studies conducted in the different seasons of the year in the U.K., Rogers et al. (62) demonstrated that there was a significant reduction in the levels of SC ceramides and fatty acids, together with linoleate-containing CER EOS in subjects in winter. Similar differences in scalp lipid levels have been observed between the wet and dry seasons in Thailand (63). Nevertheless, more importantly, Declercq et al. (64) have reported an adaptive response in human barrier function, where subjects living in a dry climate such as Arizona (compared with a humid climate in New York) had much stronger barrier function and less dry skin due to increased ceramide levels and increased desquamatory enzyme levels (SCCE and SCTE).

Several animal studies have been conducted that support these findings. TEWL was reduced by approximately 30% in animals exposed to a dry ($<10\%$RH) environment due to increased lipid biosynthesis, increased lamellar body extrusion, and a slightly thicker SC layer, whereas, in animals exposed to a high humidity environment (80%RH), this induction of lipid biosynthesis was reduced (65). However, abrupt changes in environmental humidity

can also influence stratum corneum moisturization (66). After transferring animals from a humid (80%RH) to dry (<10%RH) environment, a six-fold increase in TEWL occurred. Barrier function returned to normal within seven days due to normal lipid repair processes. These changes did not occur in animals transferred from a normal to dry humidity environment. These changes in barrier function have also recently been reported in a group of Chinese workers who are exposed to very low humidity conditions. However, the changes in barrier function take longer to reach equilibrium than anticipated from the animal studies (Fig. 15) (67).

Similarly, findings were reported for the water-holding capacity and free amino acid content of the SC. Katagiri et al. (68) demonstrated that exposure of mice to a humid environment, and subsequent transfer to a dry one, reduced skin conductance and amino acid levels even after seven days following transfer; after transfer from a normal environment, however, decreased amino acid levels recovered within three days.

Exposure to low humidity conditions also increases epidermal DNA synthesis and amplifies the DNA synthetic response to barrier disruption (69). Equally, when in a dry environment epidermal IL-1 levels increased and increased levels of this cytokine were greater when the barrier was experimentally-challenged (70). More recently, the same group also reported increased numbers of mast cells and increased dermal histamine levels (but unchanged epidermal histamine levels) (71). These changes in barrier properties of the SC are attributable to changes in SC moisture content and provide evidence that changes in environmental humidities contribute to the seasonal exacerbation or amelioration of xerotic skin conditions which are characterized by a defective barrier, epidermal hyperplasia, and inflammation.

THE PATHOPHYSIOLOGY OF WINTER- AND SOAP-INDUCED DRY SKIN

The differences in SC water concentration profiles between normal and dry skin influence the enzymic reactions in the SC. In dry flaky skin conditions, corneodesmosomes are not
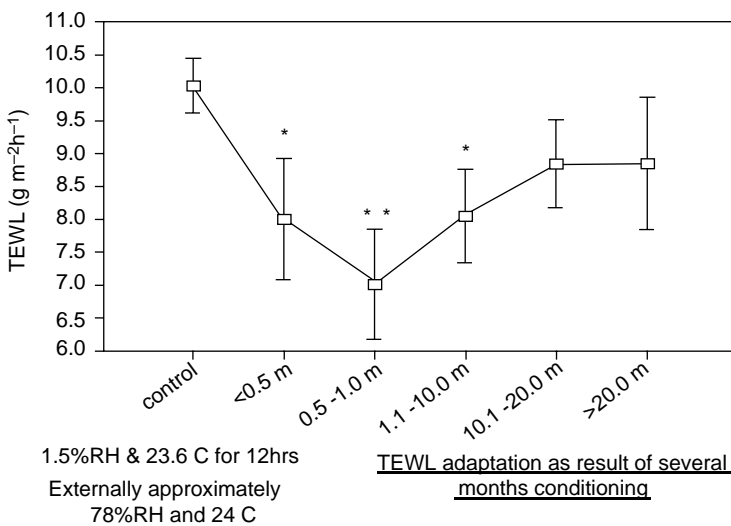
Figure 15 Time course of TEWL adaptation in humans working in an ultra-low humidity environment (1.5%RH). *Source*: From Ref. 67.

degraded efficiently and corneocytes accumulate on the skin's surface layer leading to scaling and flaking. Increased levels of corneodesmosomes in soap-induced dry skin were first reported by Rawlings et al. (23) but have been confirmed more recently by Simon et al. (72). Many corneodesmosomal proteins are now also reported to be increased in the surface layers of xerotic skin. Increased SC corneodesmosomal proteins have also been reported (23,71–73). Interestingly, however, in winter xerosis, the accumulation of the corneodemosomal proteins, Dsg 1 and plakoglobin, correlate with each. Cdsn protein levels, which were also increased, do not, however, have such an association, suggesting that different proteolytic mechanisms occur for the different corneodesmosomal components during desquamation. As suggested by Simon et al. (72), as plakoglobin is a cytoplasmic protein, this would indicate that at least the cytoplasmic domain of Dsg 1 may be cleaved. In fact, immunoreactivity to the carboxy terminal tail of the cytoplasmic portion of Dsg 1 was observed. Perhaps the intracellular portions of Dsg 1 are also degraded within the corneocyte (for example, plakoglobin by the trypsin-like activity or cathepsin E activity reported within the corneocyte matrix). Conversely, Cdsn might be degraded by SCCE, SCTE, or cathepsin D in the lamellar matrix. This is consistent with the early electron microscope images of Rawlings et al. (23) showing that corneodesmosomes become internally vacuolated, followed by complete detachment of the protein structures from the CE (Fig. 8).

The lamellar lipid matrix is also perturbed dramatically in dry skin (Fig. 16) (23). As the main desquamatory enzymes are found within this lipid matrix, the physical properties of the lamellar lipids will, therefore, influence enzyme activity.

Rawlings et al. (5) originally reported that SC SCCE levels were reduced in the outer layers of xerotic SC compared with normal skin. This has been confirmed recently in more extensive studies by Van Overloop et al. (74) who also found that the equally important SC SCTE activities were also reduced. Conversely, in SLS-induced dry skin, increased activities of these enzymes were reported (28). More recently, the over-activation of the plasminogen cascade has been associated with dry skin. Normally, only observed in the epidermal basal layers, skin plasmin is widely distributed through the epidermis in dry skin. Interestingly, a urokinase-type plasminogen activator also exists in the SC (75). Clearly these and other enzymes are potentially involved in the inflammatory and hyperproliferative aspects of dry skin.

It has been well established that, in hyperproliferative disorders such as dry skin, there is a change in SC lipid composition. In particular, the composition of the ceramide subtypes change and a predominance of sphingosine-containing ceramides (at the expense of the phytosphingosine-containing ceramides) has been observed in the SC of subjects with dry skin. Fulmer and Kramer (76) first identified these changes in SDS-induced dry skin (increased levels of ceramide 2 and 4, and reduced levels of ceramide 3). However, Saint-Leger et al. (77) could not find any changes in ceramide levels in dry skin, but found increased fatty acid levels. Rawlings et al. demonstrated the reduced levels of ceramides at the surface of the SC in winter xerosis (23). At this time, the full complexity of the different ceramide structure was not known, but, more recently, Chopart et al. (78) observed dramatic reductions in the levels of phytosphingosine-containing ceramides in dry skin (approximately 50%), together with a shortening and lengthening of the acyl sphingoid bases sphingosine and 6-hydroxysphingosine, respectively. Van Overloop et al. (74) also clearly demonstrated that the phyto-sphingosine-containing ceramides were reduced to a greater extent than other ceramides, with increasing dryness levels. Fulmer and Kramer at P&G also observed dramatic reductions in the levels of long chain fatty acids in dry skin (76). Imokawa et al. (79) did
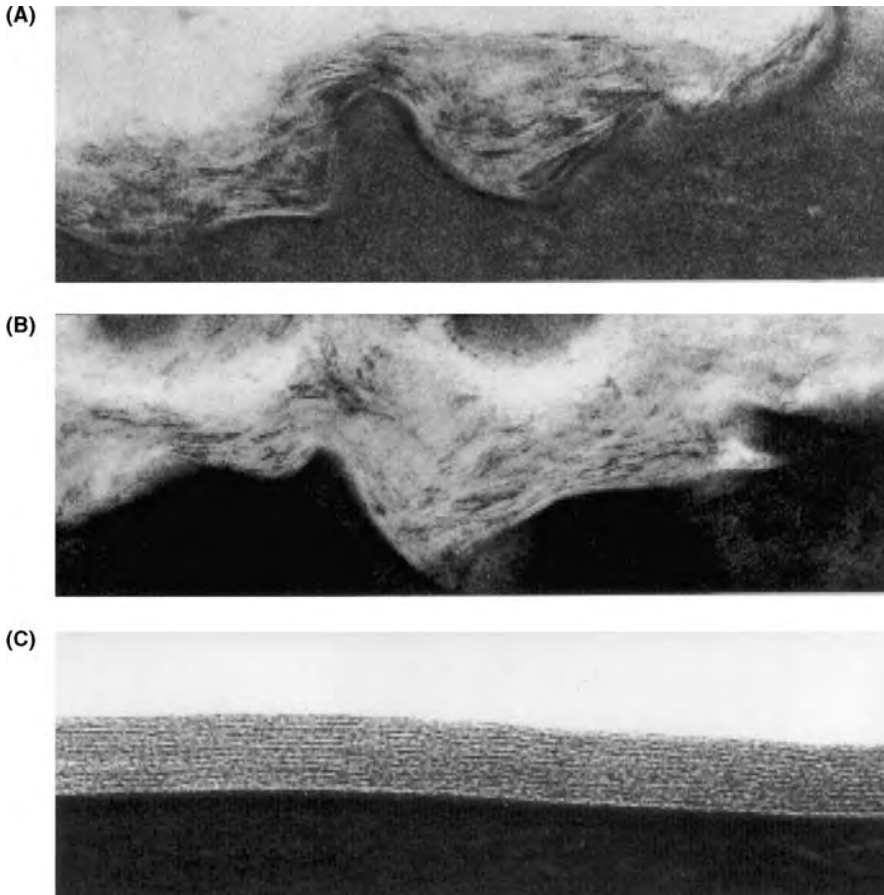
Figure 16 Organization of stratum corneum lipids in tape stripping of subjects with winter xerosis. Transmission electron micrographs of tape strippings of individuals with severe xerosis. Perturbation in lipid organization towards the surface of the stratum corneum. (**A**) First strip; disorganized lipid lamellae. (**B**) Second strip; disorganized lipid lamellae. (**C**) Third strip; normal lipid lamellae (x200,000). *Source*: From Ref. 23.

not find reduced ceramide levels in xerotic skin (but only average levels, rather than superficial levels, were measured).

These changes in lipid composition will, of course, influence the lamellar packing of the lipids. In fact, Schreiner et al. (80) established a reduction of CER EOS and EOH with increased concentrations of sphingosine-containing ceramides (CER NS and CER AS) and crystalline cholesterol in association with a loss of the LPP. However, although the lipid ultrastructure is clearly aberrant in the outer layers of dry skin (23), more work is needed to ascribe a particular lipid phase.

The proportions of the different CE phenotypes also change in subjects with dry skin (43,50). Soap washing leads to a dramatic increase in the levels of the fragile envelope phenotype at the expense of the rigid phenotype (Fig. 17). It is known that SC transglutaminase activities increase towards the surface of the SC, particularly the detergent-soluble and particulate fractions. Although the same trend of the relative increase in TGase between the inner and outer corneum is true of dry skin, TGase activities
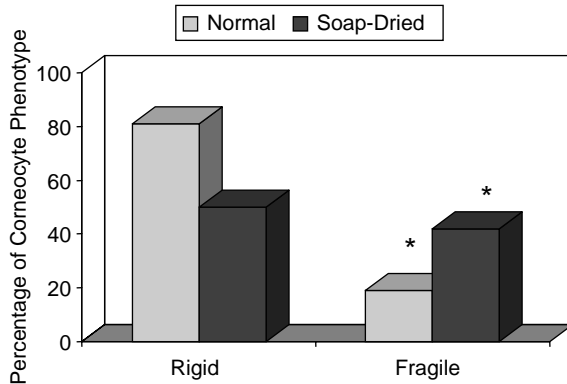
Figure 17   Percentage distribution of CEr and CEf in normal and soap-dried dry skin. *p<0.05.
Source: From Ref. 50.

are dramatically lowered in dry skin compared with healthy skin, particularly the detergent-soluble fraction, which contains mainly TGase 1.

Reduced NMF levels are also implicated in dry skin conditions. The loss of NMF generally reported with increased aging, however, is not consistent with the recent observations of Takahashi and Tezuka (81) of increased NMF in subjects with senile xerosis, and suggests that our understanding of this process is far from complete.

THE "DRY SKIN CYCLE" MODEL: A NEW WAY TO DESCRIBE INDUCTION AND PROPAGATION OF THE XEROSIS

Classically, dry skin has been described in two ways—(1) as a condition that is simply either present or not or (2) as a linear progression of sequelae, resulting in the concomitant development of clinical tools such as linear visual grading scales, etc. While not refuting the validity of these, it is proposed that the induction and propagation of dry skin conditions may be best and most intuitively expressed as a *cyclical* model, dependent on SC integrity and particularly upon barrier function and homeostasis.

A cyclical model implies a spiralling deterioration in outcome that, without intervention, would lead to a progressive worsening in model endpoints. Additionally, it is implicit that intervention at one, or preferably multiple, points within this cycle is necessary to arrest the progression of this continuing downward spiral. This is indeed the case with most dry skin conditions and, moreover, reflects extremely well consumer perception of dry skin—the seeming repetitive cycle of product usage, re-usage, disappointment with treatment outcome, and, often, a corresponding loss of compliance. The model described below describes several phases within this cycle and, therefore, possible targets against which treatments could be directed. Reference to the graphical depiction of the model below (Fig. 18) may facilitate complete understanding of the relationship of these phases, one with another.

As discussed the induction phase can be mediated by a variety of different factors:

-low environmental temperature and humidity
-abrupt changes in environmental conditions which includes the effect of modern
    indoor climate-controlled environments
-surfactant dissolution of SC lipid and NMF
-chronological aging and genetics

Once the skin has been provoked by one or more of these mechanisms, there is an inevitable sequence of events that may be described conveniently as a cycle.

Initially a mini-cycle of barrier deterioration is initiated and perpetuated. Blank estimated that the SC loses its flexibility once its water content falls below approximately 10% (8), the provocation for which may constitute one or a combination of the factors noted above. Without intervention, this quickly leads to a steeper SC hydration gradient, a decrease in net recondensation on the SC surface, a corresponding increase in evaporative water loss from the SC surface, a consequent further drop in SC water concentration, and so on. The inevitable rapid consequence of this series of events is a decrease in the plastic or viscous properties of the SC (commonly interpreted as skin "softness" or "suppleness"), an increase in SC fragility/brittleness, and an impairment of SC barrier function (82–85). This surface dehydration is the first step in the development of the dry skin cycle and is further exacerbated by destruction of the normal barrier lipid lamellae in the outer layers of the SC during bathing (23). The impaired barrier in the superficial layers of the SC allows leaching of NMF from the outermost skin cells, thereby reducing SC water activity. Whiteness between the dermatoglyphics (caused by backscatter from multiple tissue-air interfaces) and minor scaling due to the dehydration of individual corneocytes are the first visible steps in the cycle. Perturbation to the barrier then leads to further development of dry skin.

Due to the cyclical nature of these processes, therefore, it becomes virtually impossible to distinguish between dry skin conditions that are provoked initially by barrier disruption or by dehydration of the SC. However, once the barrier has been disrupted, even superficially, a new cascade of events is started primarily through the induction of a hyperproliferative state.
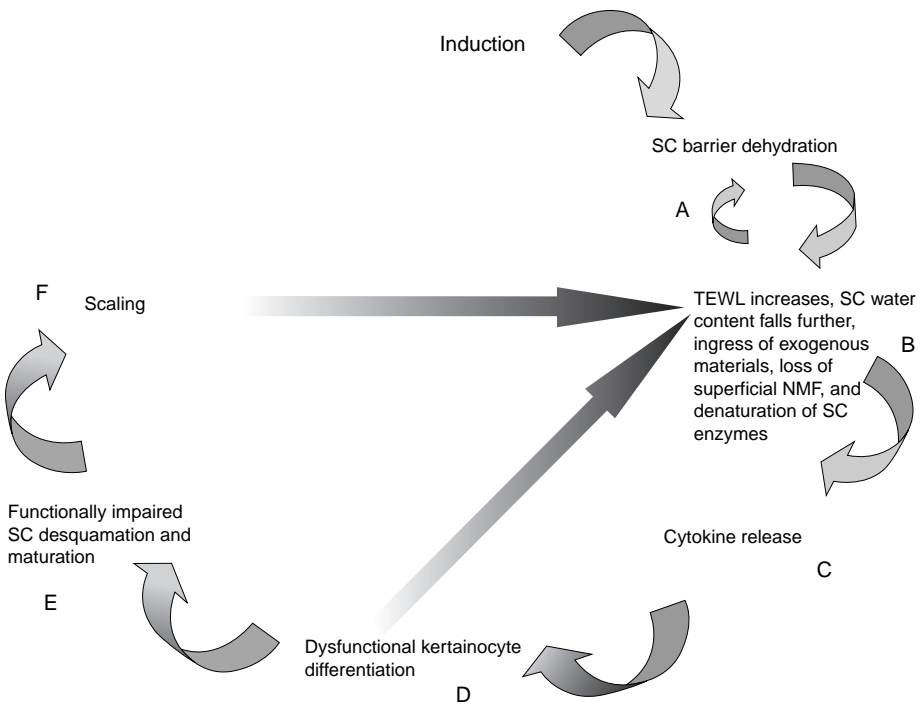
Figure 18   Schematic diagram showing pivotal events within the "dry skin cycle." *Source*: From Ref. 2.

Acute and chronic insults to the SC barrier will lead to enhanced keratinocyte proliferation, consequent hyperkeratosis, and mild inflammatory changes, one of the hallmarks of dry skin conditions, as the skin attempts to repair itself. This response is mediated via production and secretion of cytokines and growth factors, many researchers citing the ratio between interleukin 1 receptor antagonist protein and interleukin-1 alpha (IL-1 alpha) as a key marker of this process (86–89). The degree of hyperprofileration has been shown to be dependent upon the corresponding degree of barrier perturbation (90), probably reflecting both the ingress of exogenous irritants through the impaired barrier and the growing realization that the SC barrier is itself a biosensor and that corneocytes and keratinocytes themselves participating in the release of these messengers. The hyperproliferation of the epidermis probably occurs as a result of the double paracrine signaling events between the epidermis and dermis. IL-1 acts on fibroblasts which in turn secrete KGF and GMCSF inducing hyperproliferation and dysfunctional differentiation of keratinocytes (91).

The induction of this inflammatory hyperproliferative state is absolutely key in the cycle of dry skin as it fundamentally leads to aberrant differentiation and the over-hasty production of a variety of poor quality materials and structures vital to the proper functioning of the SC barrier and normal healthy skin. These include:

1. the production of smaller and immature CEs
2. changes in epidermal lipid and particular ceramide biology
3. reduced transglutaminase activity
4. reduced filaggrin synthesis and NMF levels

Finally a loss in efficiency of desquamation, due to reduced activity of desquamatory enzymes at the surface of the SC, and ensuing scaling, thickening, and loss of hygroscopicity of the SC occurs. Marked scaling is, of course, one of the obvious consumer-noticeable expressions of "dry skin." The formation of a thicker SC with impaired desquamation has, again, immense biophysical importance. The water gradient across the thicker SC becomes steeper, leading to further increases in evaporative water loss, reducing further water concentration in the outer SC, and propagating directly another round of the dry skin cycle.

Corneocytes that should be in a mature fully hydrophobed format are now replaced by fragile corneocytes. The resulting barrier protecting these corneocytes and their contents is now weaker due to changes in barrier lipid profiles and surface hydrophobicity. Equally, the hygroscopic (though highly water-labile) NMF present within corneocytes of normal SC, are depleted gradually through normal everyday activities such as cleansing and/or occupational duties (1,61). The corneocytes of dry SC are, therefore, subject to exaggerated insult such due to their changed biochemical and biophysical properties. The dry skin cycle, thus, is propagated further by an increased loss of NMF relative to normal skin and a corresponding loss in SC hygroscopicity.

Finally and most importantly, the development of an increasingly thick, dry SC results in a layer characterized, from a biomechanical viewpoint, by a dramatic increase in hardness and brittleness. The consumer perceives this as tightness. These properties create an SC barrier inherently susceptible to mechanical stress and fracture, another factor driving the impairment in barrier function cyclical nature of the dry skin cycle.

The clinical endpoint of "dry skin" cannot be regarded as static but rather is most fully described as a cycle that, without intervention, tends to perpetuate itself. Pivotal to every stage of this cycle and its propagation is a compromised SC barrier. Interventions that truly break the dry skin cycle, therefore, by definition need not only to treat symptomatic manifestations, but repair and augment SC barrier function. This will yield a

skin that is inherently better able to cope with the constantly changing external environment of the modern world.

MANAGEMENT OF DRY SKIN

Although a major analysis of dry skin treatments are outside of the scope of this review it is worth mentioning just briefly the biology that needs to be corrected in cosmetic dry skin conditions and some key examples of suitable treatments.

Traditionally, humectants, occlusives, and emollients have been, and will continue to be, the mainstay of cosmetic treatments (92):

Arguably, the most widely used and effective humectant used in cosmetic treatments for xerotic skin is glycerol, due to its excellent safety profile, cost, and simply outstanding water-retaining (humectant) and hygroscopic properties. There is now much evidence, however, that glycerol is not only a "mere" humectant, but also (i) is a lipid fluidizer (93), modulating the temperature-dependent rheology of SC lipid, thus preventing a loss of fluidity of their lamellar structure at low relative humidities and (ii) has corneodesmolytic activity, facilitating the proteolytic digestion of superficial corneodesmosomes in dry skin (94). Humectants are also an essential requirement for most of the additional approaches. In O/W creams occlusives and bilayers-forming lipids (described below) also require glycerol to alleviate dry skin. Moreover, humectants are required for the transglutaminase-mediated CE maturation that is required for a healthy SC (95). In this respect, combinations of humectants including glycerol have been shown to be more effective than just using glycerol alone. Glycerol has also been shown to enhance the barrier function of the SC (96).

Like glycerol, urea is a natural component of the SC NMF and has been used as a humectant in creams since 1943 (97). Ten-percent urea has been shown to be more efficacious than salicylic acid and petroleum jelly. Urea-containing moisturizers have been reported to improve barrier function and reduce TEWL, increase skin capacitance, and reduce irritation reactions (98–101).

As a principal component of NMF, considerable interest has been paid to the ability of PCA and its derivatives to moisturise the SC. Creams and lotions containing the sodium salt of PCA are widely reported to help hydrate the SC and improve dry flaky skin conditions (102–106).

Petroleum jelly acts primarily as an occlusive agent having been shown to reduce TEWL by over 98%, whereas other oils only manage a 20–30% reduction. Yet this agent does not simply act as an occlusive film over the surface of the skin; it has been shown to diffuse into the SC intercellular domains which may add to its efficacy. On penetrating the epidermis it was also shown to accelerate lipid biosynthesis, thereby aiding barrier repair (107).

Recent years, however, have seen a dramatic increase in the development and inclusion of novel technologies that complement these mainstays of moisturization.

Bilayer-Forming Lipid

From the current understanding of the compositional changes in dry skin five aspects of stratum corneum lipid biochemistry need to be corrected:

The lowered levels of ceramides generally.
The phytosphingosine-containing ceramide insufficiency.

    The ceramide one linoleate (CEOS) insufficiency.

    The lowered covalently bound ceramides.

    The precise chain length of the ceramide sphingoid bases and free fatty acids.

Overall, however, the lipid lamellar architecture in the outer layers of the stratum corneum needs to be normalized in dry flaky skin conditions. Evidence also indicates that a reduction in long chain fatty acids also occurs in SLS-induced dry skin. As these lipids are important for inducing an orthorhombic lateral packing state, these will also need to be supplied to the skin to more effectively correct barrier function. Moreover correction of the reduction of SC NMF levels, correction of the aberration of CE maturation, and the impaired corneodesmolysis are needed for dry skin treatments.

Several clinical studies evaluating the effects of ceramides have been conducted recently. However, it is important to remember that to derive the full benefits of ceramide technology formulation into heavy emulsions where other emollients dominant the formulation will be difficult to discern unless the ceramides are at a high enough concentration. Nevertheless, two studies investigating the properties of Locobase Repair cream have found opposite effects on barrier recovery. Barany et al. (108) could not find any improvements to placebo whereas Kucharekova et al. (109) found that the CER NP-containing cream significantly reduced TEWL, erythema, and epidermal proliferation compared with placebo cream. Nevertheless, further improvements in function are observed with complete lipid mixtures. De Paepe et al. (110) have demonstrated improvements in barrier functionality and SC hydration from a lipid mixture of CER NP (0.2%), CER AS (0.1%), and CER UP (0.2%) together with cholesterol (0.25%), linoleic acid (0.25%), and phytosphingosine (0.5%) compared with placebo lotions and a lotion containing only CER NP (0.6%) and CER UP (0.4%). The percentage increases in TEWL and SC hydration are shown in Figure 15. Berardesca et al. (111) have also established that balanced lipid mixtures containing CER NP are effective in improving the barrier properties and clinical condition of skin in subjects with contact dermatitis. Equally convincing are the studies of Chamlin et al. (112) showing that a ceramide dominant barrier repair lipid cream alleviates childhood atopic dermatitis. Over the six-week treatment period TEWL values decreased by 50% and the number of D-squame tape strippings required to break the barrier increased from approximately 12 to 22 strippings, indicating a stronger SC barrier function.

In addition to ceramides, which have been introduced to supplement the SC barrier, (113) phospholipids are also bilayers-forming lipids and when combined with glycerol have been demonstrated to be clinically superior to petroleum jelly in relieving dry skin (114).

Hydroxy Acids

Hydroxy acids are being used to facilitate desquamation and improve lipid biosynthesis together with barrier function. The influence of alpha-and beta-hydroxy acids (115) on desquamation is now well established, but new lipophillic variants of salicylic acid appear to influence corneodesmolysis differently. Whereas lactic and salicylic acid act on all corneodesmosomes, LSA only acted in the stratum disjunctum corneodesmosomes. These lipophillic variants appear to act on the whole structure of the corneodesmosomes whereas the "ordinary" acids fractionate the corneodesmosomes. Fartarsch et al. (116) also demonstrated that the action of glycolic acid on corneodesmolysis was restricted to the stratum disjunctum suggesting a targeted action without compromising barrier function. Medium chain fatty acids have also been reported to not only improve SC flexibility but

also assist in the relief of dry skin in combination with barrier lipids. Further enhanced dry skin relief was observed in the presence of barrier lipids (117), and the L isomer, in particular, increased SC extensibility and keratinocyte proliferation as reported by Rawlings et al. (118). Rawlings et al. also reported that longer chain hydroxy acids were more effective than short chain fatty acids at facilitating corneocyte cell release in the presence of several calcium chelators. This may be due to a fluidizing effect of these longer chain fatty acids on the lamellar lipids as in SC extensibility studies using extensions where only lipids are believed to being extended longer chain alpha-hydroxy acids plasticize the corneum (119).

SC turnover time measured by dansyl chloride (a measure of epidermal proliferation matched by desquamation) increased by 15% by applying a moisturizing cream at pH 3.8. However, further increases were observed with increasing concentration of the free acid of glycolic acid or by decreasing the pH of the base. At 8% glycolic acid concentration (4% free acid) Johnson (120) reported approximately 30% increase in SC turnover time. The increased turnover time needs to be matched by increased desquamation; otherwise, retention hyperkeratosis would occur, which clearly it does not. In fact, the opposite occurs. So desquamation must also be enhanced by further activating acidic optimum enzymes or by also chelating calcium, which is known to reduce the final processing steps involved in Cdsn degradation.

Nevertheless, not all hydroxy acids perform equally, and, in fact, some appear to enhance the skin's sensitivity to UV irradiation, especially glycolic acid. However, glucanolactone and tartaric acid have been shown to be not only superior to glycolic acid and lactic acid in improving barrier function but have been shown to not increase in sunburn cell formation (121).

SC Barrier Augmentation by Inducing Epidermal Differentiation

Ligands for nuclear receptors such as the peroxisomal proliferator activated receptor have been shown to improve epidermal differentiation, increasing ceramide and filaggrin levels (122). This superfamily of nuclear transcription receptors includes the retinoic acid receptors, the steroid receptors, the thyroid receptors, and the vitamin D receptors and also the peroxisome proliferator activated receptor (PPAR), together with farnesol activated receptor (FXR) and the liver activated receptor (LXR). These transcription factors bind their respective ligands and regulate many of the aspects of cellular proliferation and differentiation. Fatty acids are important ligands for the PPAR receptor, farnesol for the FXR, and hydroxylated cholesterol derivatives or cholestenoic acid for the LXR. All of these pathways stimulated epidermal differentiation and increased the synthesis of involucrin, filaggrin, and enzymes of the ceramide synthesis pathway.

The transcription factor most intensively investigated is the PPAR. There are three main PPAR isoforms: alpha, beta/delta, and gamma. Nevertheless, PPAR delta was recently observed to be the predominant PPAR subtype in human keratinocytes, whereas PPAR alpha and gamma were only induced during epidermal differentiation, suggesting non-redundant functions during differentiation (123). Respective ligands for all of these isoforms increased epidermal differentiation. Pharmaceutical ligands for the PPAR receptors increase ceramide synthesis in vitro by increasing the expression of SPT, glucosyl ceramide synthase, and glucocerebrosidase but not sphingomyelinase (124). More recently PPAR delta ligands were found to be the most potent in inducing epidermal differentiation (tetrathioacetic acid) by increasing involucrin and transglutaminase while decreasing proliferation.

Petroselinic acid (125) and conjugated linoleic acid (126) have been identified as potent PPAR alpha activators improving epidermal differentiation, reducing inflammation, increasing extracellular matrix components, and eliciting skin lightening. In vitro increased levels of transglutaminase, involucrin, filaggrin, and CE formation were observed in keratinocytes after treatment with petroselinic acid. These effects were confirmed in vivo by short-term patch testing studies over three weeks and increases in involucrin and filaggrin were also observed. Using this technology, improvements in the signs of photodamage, skin tone and dry skin were observed in a 12-week clinical study on forearm skin (127). Octadecenedioic acid has also recently been identified as a pan-PPAR agonist (with a preference for PPAR gamma) and has been shown to reduce skin hyperpigmentation, but with its PPAR agonist activities it is also expected to improve epidermal differentiation (128).

SC Barrier Augmentation by Inducing Epidermal Lipogenesis

Changes in lipid levels and types can be corrected by topically applying agents to manipulate the lipid synthesis process within the viable epidermis. However, as described above, in dry skin conditions the epidermis makes less phytosphingosine-containing ceramides, changes the carbon chain lengths of other sphingoid bases and synthesis less long chain fatty acids. These results suggest that changes in the levels or activities of the different fatty acid synthetases, as well as the enzymes involved in phytosphingosine synthesis, occur in dry skin. The biology of these enzymes is yet to be described in these conditions.

Elias et al. (129), however, has used lipid mixtures to aid barrier recovery in acetone damaged barrier studies. Cholesterol itself was shown to aid barrier recovery in a tape stripping model in aged skin but not young skin. In fact any incomplete mixture of one or two of the three major lipid species slows barrier recovery in this model. The equimolar mixture of the three dominant SC lipids allows normal rates of barrier recovery in normal skin, whereas its further adjustment to a 3:1:1 molar ratio accelerates barrier recovery. As expected the requirements for optimal barrier recovery in aged skin is different, and it has been shown that a cholesterol dominant lipid mixture accelerates barrier recovery in aged skin whereas a fatty acid dominant mixture delays barrier recovery. In young skin any of the lipid species can be the dominant lipid and the barrier will recover more quickly with one exception, and that is in atopic dermatitis where a ceramide dominant mixture is required (130). Further studies on the use of long chain fatty acids are recommended. Exploiting these facts it has been shown that (131) mevalonic acid, the product of the rate limiting enzyme HMGCoA reductase, increases cholesterol biosynthesis.

Several other routes have been shown to increase ceramide synthesis in vivo and improve barrier function. As described above alpha-hydroxy acids well known for their desquamatory properties also stimulate lipid biosynthesis. Lactic acid, and especially the L isomer, increases ceramide biosynthesis in vitro and in vivo. Presumably lactic acid achieves this by acting as a general lipid precursor by providing acetate and providing more reducing power in the form of NADH or NADPH (132). Corresponding improvements in barrier function were reported. Interestingly, lactic acid also increased the levels of linoleate-containing CER EOS which may be contributing to these improvements in skin functionality.

The pleotropic skin benefits of niacinamide have been the subject of intense study by Procter & Gamble and have been excellently reviewed by Matts et al. (133). Niacinamide has been reported to stimulate the synthesis of glucosylceramides, sphingomeylin, cholesterol, and fatty acids by keratinocytes in vitro (127). The increases in ceramide synthesis were achieved by enhancing the activity of SPT together with the expression of

Table 2 Agents That Increase Ceramide Biosynthesis

Lipids	Optimized mixtures of ceramides, cholerterol & fatty acids
Lipid precursors	Phytosphingosine, tetra-acetylphytosphingosine, omega-hydrosy-fatty acides, linoleic acid
Alpha-hydroxy acids	L-Lactic acid
Humectants	Glycerol, urea
Vitamins	Niacinamide, lipoic acid, ascorbic acid
Protease inhibitors	Aminocyclohexanecarboxylic acid, egg white lysozyme
Monerals	Magnesium, calcium
Histamine receptor	H1 receptor antagonist
Antagonists	H2 receptor antagonist
PPAR	PPAR alpha agonists
Electrical potential	Negative potential
Triterpenoids	Ursolic acid
GABA agonists	GABA type A agonists (musimol, isoguvacine)
Purinergic receptor	P2Y antagonists
Fragrances	Fragrances
GC receptor	Glucocorticoid receptor antagonists

LCB 1 and 2. In vivo, however, increased levels of stratum corneum fatty acid (67%) and ceramide (34%) levels were observed. Similar to studies with lactic acid, increases in the levels of stratum corneum cholesterol seem to be refractory to change. In their further studies Tanno et al. (134) at Kanebo have also been researching the changes in skin functionality with presence of sensitive skin. In their most recent studies topical application of niacinamide improved the barrier of the most severely affected subject with
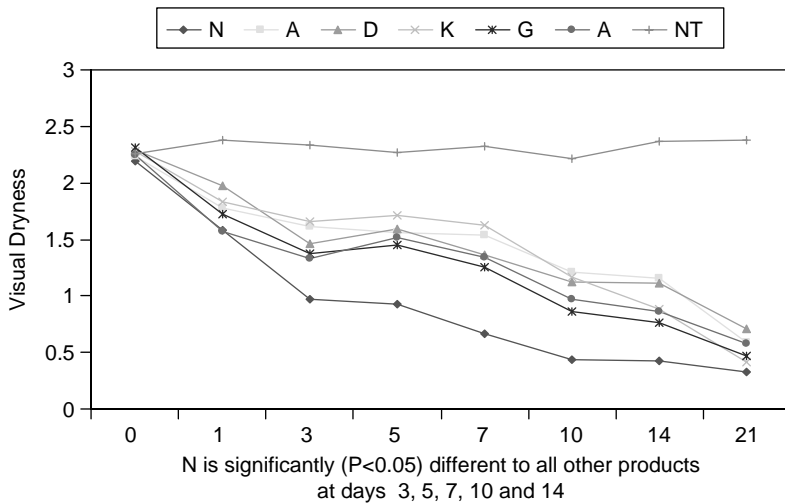
Figure 19 Results from the treatment phase of a Kligman-type regression study (products applied twice-daily at 2 mg/cm^2 to randomized sites on the outer, lower leg of female subjects [n = 36] with inclusion of a no-treament control). Products represented high-efficacy commercial moisturizers with ingredients of differing dry skin relief mechanism. *Abbreviations*: NT, no treatment control; N, niacinamide-containing lotion; A, lactic acid-containing moisturizer; other product codes represent commercial products with high loadings of traditional humectants and emollients (including glycerin and petrolatum). *Source*: From Ref. 2.
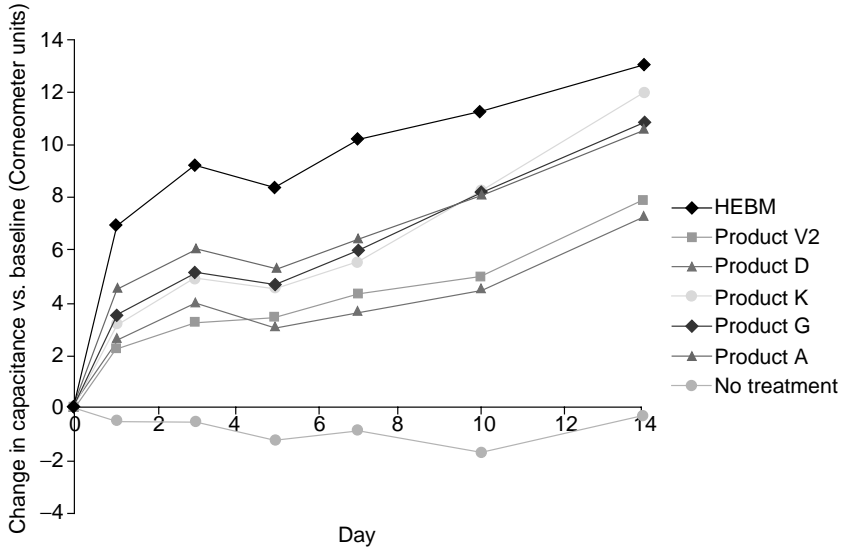
Figure 20 Change in capacitance during treatment with several moisturizers expressed as difference from baseline. *Source*: From Ref. 144.

sensitive skin with a concomitant improvement in stinging score. Ertel et al. (135) observed similar improvements in barrier functionality together with an increased SC turnover rate using a 2% niacinamide cream. Draelos et al. (136) similarly observed a significant improvement in SC barrier function and improvement in global skin condition in subjects with stage 1/11 Rosacea.

Topical application of phytosphingosine and its derivatives have also been shown to increase SC ceramide levels and barrier function (137). This is especially important as the phytosphingosine-containing ceramides are deficient in dry skin. Although increases in the total levels of ceramides were observed, greater increases in CER EOS and CER AS were found when combined with juniperic acid and linoleic acid. Linoleic acid on its own has
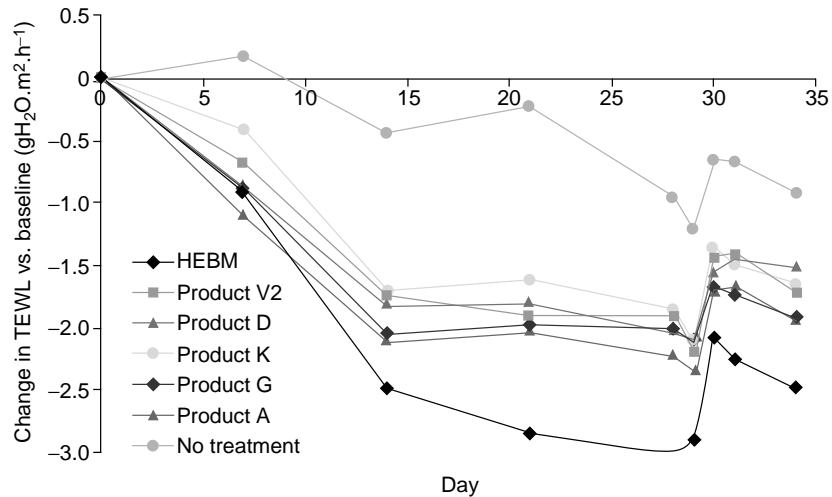
Figure 21 Change in TEWL during treatment and regression phases expressed as difference from pre-treatment baseline. Regression starts at day 28. *Source*: From Ref. 144.
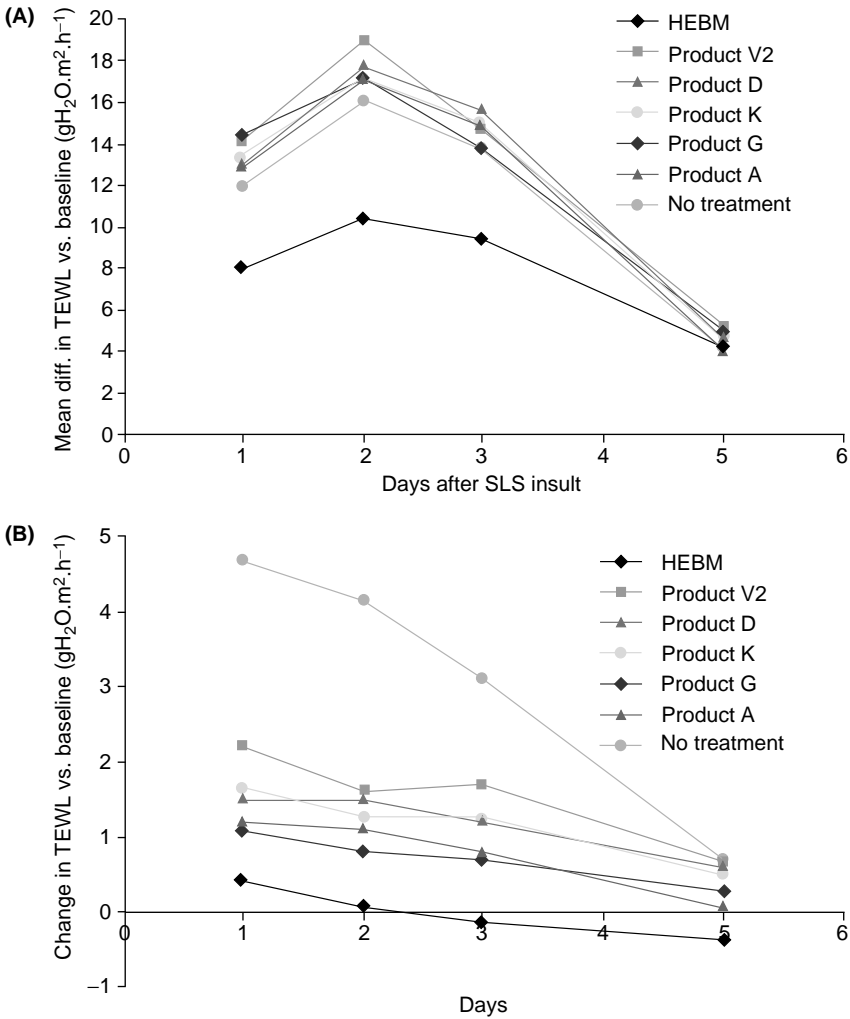
Figure 22 (**A**) Change in TEWL in post-treatment phase after SLS patch chemical insult expressed as difference from pre-treatment baseline. (**B**) Change in TEWL in post-treatment phase after tape stripping mechanical insult expressed as difference from pre-treatment baseline. *Source*: From Ref. 144.

also been proven to be incorporated into CER EOS in vivo (138) which is obviously important for the lipid phase behavior and skin properties. Lipid fractions from unsaponifiable fractions of avocado (furanyl-8-11- cis heptadecadiene) and sunflower oleodistillates (mainly linoleic and oleic acids) also increase ceramide and cholesterol biosynthesis ex vivo (139).

The effects of increasing SC lipid levels by stimulating ceramide biosynthesis have been investigated extensively by Denda et al. (140). Histamine antagonists and certain fragrances stimulate lipid biosynthesis. Mixtures of magnesium and calcium salts have also been shown to accelerate skin barrier recovery and improve surfactant-induced or tape stripping-induced dry skin. Although these studies indicate the importance of these ions for epidermal homeostasis, more work is needed with cosmetic formulations. More recently, it has been demonstrated that gamma-aminobutyric acid (GABA) type A
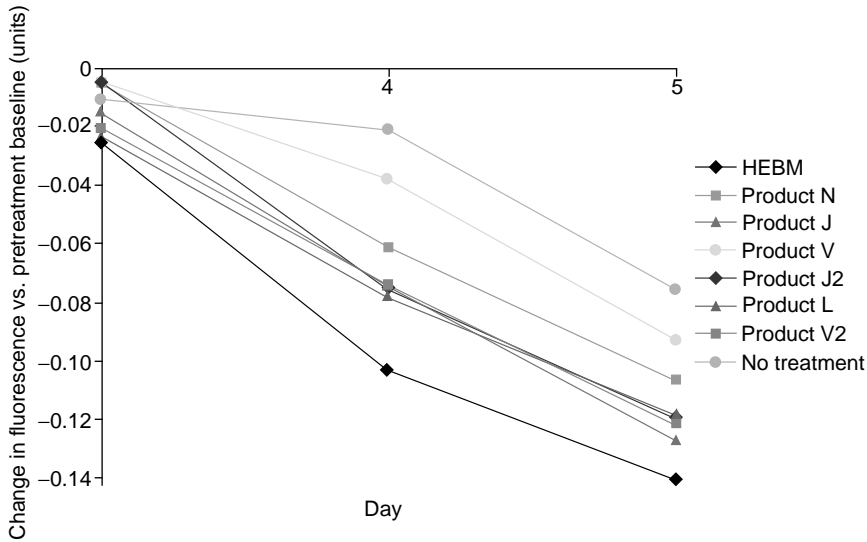
Figure 23   Change in absolute dansyl chloride fluorescence over five days following staining. *Source*: From Ref. 144.

receptor agonists, musimol, and isoguvacine accelerate barrier recovery following barrier disruption. Conversely, ATP (purinergic) receptor (P2X) agonists delay barrier recovery whereas P2Y antagonists accelerate it. These also reduced the epidermal hyperproliferative response induced by acetone treatment under low environmental humidity (Table 2).

Other agents have been shown to stimulate ceramide synthesis in vitro. Lipoic acid and N-acetylcysteine were also reported to increase ceramide synthesis in vitro (141). Recently vitamin C has been shown to activate PKC and increase ceramide synthesis and improve the ceramide subspecies profile in epidermal skin equivalents (142). Yarosh and Brown (143) also demonstrated that Ursolic acid increased ceramides in human skin. For a complete analysis of agents that stimulate lipid biosynthesis see Table 2.

Very recently, exploiting its lipogenesis and differentiation enhancing effects, niacinamide has been introduced into lotions, together with glycerol and other NMF components, that effectively alleviate dry skin and provide a significant improvement in SC barrier function (144). These lotions have been shown to be more effective than traditional emollient and lactic acid-containing moisturisers in relieving dry skin in the treatment phase of a typical Kligman-type regression study (Fig. 19), together with the changes in moisturization (Fig. 20) and barrier function (Fig. 21) as well as improving resistance to SLS and tape stripping-induced barrier perturbation (Fig. 22) (101). The improvement in desquamation was also proven with a dansylchloride exfoliation test (Fig. 23).

SUMMARY AND CONCLUSIONS

New and exciting discoveries have been made in SC biology over the last decade, but more importantly the understanding of the aberration of the normal functioning of the SC in dry, flaky skin conditions has become clearer and a new model of dry skin has been described. On perturbation of SC barrier function, a futile cycle of events begins first with the superficial dehydration of the SC and subsequent release of inflammatory mediators, induction of hyperproliferation of epidermal keratinocytes, and disruption of epidermal
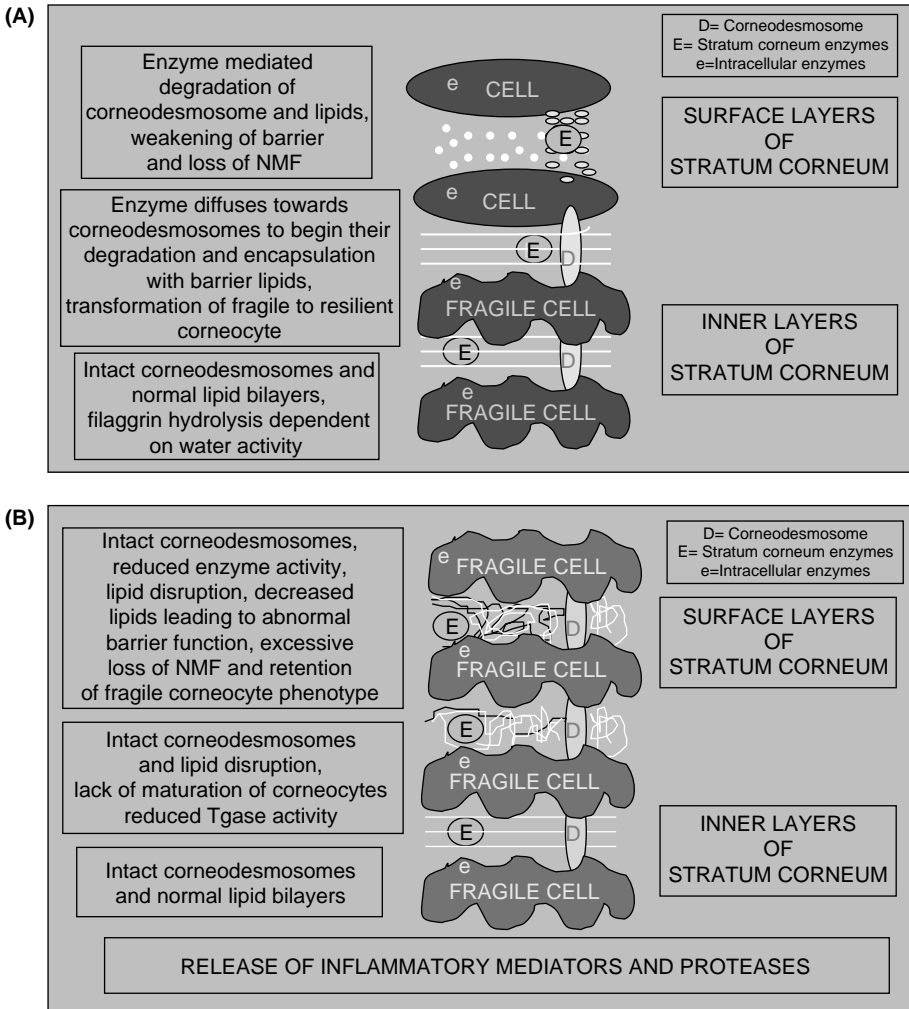
Figure 24 Summary of stratum corneum maturation and corneodesmolysis in (**A**) normal and (**B**) dry skin. *Source*: From Ref. 2.

differentiation, leading to an inferior SC. As has become apparent, reductions in SC water and NMF levels, changes in lipid ultrastructure, and reductions in enzyme activities contribute to the reduced corneodesmolysis known to occur in these conditions. See Figure 24 for a schematic summary of the differences in SC biology in normal and dry skin. As a result, new therapies for the treatment of dry skin have been developed that target all aspects of the aberrant biology described by the "dry skin cycle."

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7

Factors Influencing Optimal Skin Care and Product Selection

James Q. Del Rosso

Department of Dermatology, University of Nevada School of Medicine,
Las Vegas, Nevada, U.S.A.

Due to consistent marketing influences promoting multiple products that claim "removal of fine lines, wrinkles, and age spots," consumer demand for products that provide a "fresh look and a more youthful appearance," television and written advertising media campaigns promoting individual product lines, and the myriad of products available for the consumer to choose from, it is not surprising that patients are confused about which products to use for their skin and how to use them. Despite the high level of confusing "white noise" created by media and advertising promotions, optimal skin care is not rocket science! Based on a few basic principles and knowledge of appropriate product formulation, the dermatologist or designated skin care professional is trained to match a sound skin care regimen with the needs of the individual patient.

Prior to product selection, skin type characteristics, history of previous skin sensitivities or allergies, presence of underlying skin disorders, current skin care regimen, and medication history need to be evaluated. A thorough understanding of skin care product formulations and their differentiating features affords the clinician greater knowledge, confidence, and flexibility when recommending products and designing a skin care regimen for patients.

Unfortunately, the value of basic skin care practices such as cleansing and moisturizer use as a component of the management of dermatologic disorders has taken a back seat due to the strong emphasis on management with pharmacologic agents. Greater attention to basic skin care products and procedures, and maintenance of epidermal barrier function, may provide additive therapeutic benefit for patients. The following chapter emphasizes the core significance of maintaining epidermal barrier integrity. The basic fundamentals of optimal skin care, gentle cleansing and moisturization, and their intimate correlation with product formulation and selection are discussed.

BASIC SKIN CARE PROCESSES

Proper skin cleansing and moisturization are the two basic processes that must work in harmony to maintain overall skin health and epidermal barrier integrity (1,2). The role of

115

skin cleansing is to remove external debris, cutaneous secretions, and microorganisms. In addition, the integrity of the epidermal barrier must be consistently maintained to allow for cutaneous homeostasis as the presence of proper skin water content is mandatory for enzymatic functions required for lipid synthesis and barrier restoration. Therefore, moisturization is a vital component of "routine maintenance" of the outer skin barrier. This is especially true in conditions where epidermal barrier dysfunction and reduced epidermal water content are present. Examples of such conditions include low ambient humidity, xerotic skin disorders such as atopic dermatitis, genedermatoses such as ichthyosis vulgaris, underlying systemic disease states such as hypothyroidism and diabetes mellitus, use of skin care products that produce significant epidermal barrier damage such as harsh soaps and cleansers or astringents, and some topical medications such as topical retinoids (3–5).

The plethora of cleanser and moisturizer products available make it difficult for both professionals and consumers when faced with the question, "Which products should be used?" The bottom line is to maintain a "simplest is best approach," especially as many product claims, special ingredients, and heavily promoted "designer" products are substantiated by little to no scientific evidence supporting their purported benefits and high expense (1,2,5,6).

THE EPIDERMAL BARRIER AND WATER CONTENT

Normal skin appearance, water balance, and continued barrier integrity necessitate an intact epidermal barrier with maintenance of the proper water content required for physiologic and enzymatic functions. As the epidermis is a living dynamic unit, several physiologic functions continue as an ongoing process, with perturbations of barrier integrity requiring necessary adjustments and repairs before the epidermal barrier can return to its normally functioning physiologic state. The epidermal barrier is comprised of two components which work in concert to assure barrier integrity through functions such as maintenance of proper epidermal water balance, physiologic stratum corneum water content (20–35%), optimal lipid synthesis, limitation of transepidermal water loss (TEWL), and orderly corneocyte desquamation (1–4). The first component of the epidermal barrier, the *cellular matrix,* is comprised of a staggered and layered lattice of keratinocytes, referred to as the "bricks." In its uppermost layer, the flattened stratum corneum cells are referred to as corneocytes. The second component of the epidermal barrier, the *intercellular lipid bilayer matrix,* surrounds the keratinocytes, and is referred to as the "mortar" (1–3). Disturbances of these epidermal barrier components, associated with a variety of causes such as use of harsh soaps or underlying "sensitive skin" disorders such as atopic dermatitis or rosacea, enhance TEWL, which can lead to xerotic skin changes. When increased TEWL produces a reduction in stratum corneum water content to below 10%, this marked loss of epidermal barrier integrity is visibly expressed as dryness, scaling, roughness, and fine fissuring, the clinical features of xerosis (2,3,6–8).

The epidermis is in constant flux as keratinocytes traverse from the basal layer, later flattening as they pass upward into the stratum corneum, leading ultimately to surface shedding, or corneocyte desquamation. As referred to above, under normal circumstances, adequate water content allows for enzymatic degradation of the attachments between corneocytes (corneodesmosomes), allowing for the physiologic separation and shedding of superficial corneocytes. Corneocyte moisture content is maintained by a collection of diverse intracellular hygroscopic compounds which have been collectively termed "natural moisturizing factor" (NMF). The components of NMF include filaggrin-derived

amino acids, pyrrolidone carboxylic acid, lactate, sugars, and several electrolytes (1–3,5). Under abnormal conditions associated with xerosis, corneodesmosomes are not readily deagraded, leading to clumping of corneocytes. The visible expressions of clumped corneocytes with impaired desquamation are flaking and scaling (1–3,5,8,9).

EPIDERMAL BARRIER INTEGRITY, FUNCTION, AND REPAIR

A pivotal component of epidermal barrier formation is the synthesis within nucleated keratinocytes of the intercellular lipid bilayer, a functional permeability barrier composed of specific lipids present in proper ratio. Epidermal barrier lipids are autonomous from lipids circulating in the bloodstream and are composed predominantly of equimolar concentrations of free fatty acids, cholesterol, and ceramides (1–3,5,10–12). Within lamellar bodies (Odland bodies) located within keratinocytes of the upper epidermis, precursor epidermal lipids are used to create newly synthesized lipids which are organized into a lipid bilayer referred to as the lamellar unit membrane structure (1,10–17). Ultimately, as cornification occurs in the upper epidermis, a phospholipid-enriched plasma membrane is converted to a ceramide-rich bilayered membrane by weight (1,8,17).

The intercellular lipid bilayer matrix ("the mortar") functions to control intercellular water movement, maintain intracellular water content, and limit TEWL. The major homeostatic signal stimulating epidermal lipid synthesis is an adverse change in epidermal barrier status, sensed as an increase in TEWL. In the presence of exogenous (i.e., use of a harsh soap) or endogenous (i.e., underlying dermatologic disease) insults that cause a loss in barrier lipids which comprise the intercellular matrix, an increased TEWL of as little as 1% produces a physiologic signal that upregulates lipid synthesis (1–3,5). Depending upon the degree of barrier insult and several other factors, normalization of barrier function may occur over a period of hours to days (1,15,17).

IMPACT OF EXOGENOUS MOISTURIZATION ON BARRIER REPAIR

In a state of epidermal barrier disruption characterized by increased TEWL and reduced epidermal water content, a properly formulated moisturizer can act in a manner similar to endogenous epidermal lipids in promoting and restoring epidermal barrier function (1–3,13–24). Lipids applied externally in moisturizer formulations intercalate between corneocytes and have been shown to reduce surfactant-induced skin irritation (15–18). The use of nonphysiologic lipids such as petrolatum initially restores barrier function by producing a diffuse hydrophobic interstitium. Importantly, physiologic lipids applied in moisturizers can be directly incorporated into barrier lipids and lamellar units and do not appear to downregulate physiologic lipid production in skin (16–18). However, it is vital that all three lipid components (ceramide, cholesterol, free fatty acids) be incorporated in moisturizer formulations in optimized concentrations in order to avoid impairment of barrier recovery (16,17).

CLINICAL IMPLICATIONS OF EXOGENOUS MOISTURIZATION

In a clinical study of adult and pediatric patients treated for atopic dermatitis twice daily over a three-week period with a low-potency topical steroid lotion, with or without a moisturizer cream, both regimens exhibited consistent reductions in signs and symptoms

of disease, although greater improvement was noted at treated sites where moisturizer was also used (25). Importantly, patients recognized the therapeutic benefit of moisturizer use as a component of the combination regimen with preference for the combination reported by 96% of patients.

The significance of repeated application of externally applied moisturizers should not be underemphasized. Factors such as the inherent limitations of product substantivity related to formulation characteristics, superficial loss of applied product due to external "wear and tear" effects prior to thorough skin penetration, and the natural consequence of continual corneocyte shedding mandate that repetitive moisturizer application on a daily basis is required for maintenance of barrier function and repair (3,19). In addition, individual moisturizers may vary in the persistence of their moisturizing properties after discontinuation of application based on regression phase analysis studies (20,24).

COMPONENTS OF MOISTURIZER FORMULATIONS

Whether or not a moisturizer formulation "makes it in the real world" is ultimately dependent on recognizable efficacy, cosmetic acceptability, and patient preference. It is important to recognize that the term *moisturizer* does not imply that moisture (water) is being added to the skin. A properly formulated moisturizer contains *occlusive*, *humectant*, and *emollient* ingredients that are ultimately formulated to produce an effective product that is also cosmetically elegant (1–5,8,17,26). Occlusive and humectant ingredients work in a complimentary fashion to maintain epidermal water content and barrier function. Occlusive agents retard water loss via evaporation by forming a hydrophobic film on the skin surface and within the stratum corneum interstitum. Humectant compounds attract water "from the inside out," that is, from the dermis with passage into the upper epidermis (3–5,8,17). Emollients include a wide spectrum of compounds ranging from esters to long-chain alcohols which function to fill "the fine cracks and crevices" between corneocytes in the upper stratum corneum; specific emollients are often incorporated into formulations to enhance efficacy and improve cosmetic elegance by providing a smooth, soft texture to the cutaneous surface (2–5).

BALANCING EFFECTS AND COSMETIC ELEGANCE OF PRODUCT COMPONENTS

The greasiness of occlusive agents such as petrolatum and lanolin can limit their clinical usefulness due to lack of cosmetic elegance (2–5). For example, odor and potential allergenicity may limit the use of lanolin. Although mineral oil demonstrates less capability to reduce TEWL as compared to some other occlusive agents, it is a popular formulation component due to its favorable texture and easy spreadability (5). Silicone derivatives are also popular formulation ingredients as they may serve both occlusive and emollient functions, do not impart a greasy feel to the skin, exhibit a barrier protectant effect that is often incorporated into "hand creams," and are used in combination with petrolatum to achieve greater cosmetic acceptability by reducing the greasiness of the overall product texture (2,5).

Most effective formulations which enhance skin moisturization include humectant agents, such as glycerin, hyaluronic acid, urea, ammonium lactate, and panthenol, which serve to attract water from the dermis into the epidermis, with some humectants also imparting emolliency (1–5). In order to prevent exacerbation of TEWL, a humectant agent

should always be combined with an occlusive ingredient. For example, skin application of glycerin alone without an accompanying occlusive agent results in a significant increase in TEWL (29%) (2,3,5). As referred to above, although emollients may vary in their inherent moisturization and barrier maintenance properties, the elegant characteristics they impart to the overall product may be appreciated by the user after product application and often relate directly to consumer product preference (5).

FORMULATION CHARACTERISTICS

Most moisturizers are formulated as creams (water-in-oil emulsion) or lotions (oil-in-water emulsion) (1,2,8,13). The "heaviness" of the final formulation correlates with the inclusion and relative concentration of heavier occlusive agents such as petrolatum and lanolin derivatives, the inherent qualities of individual emollients and humectants that may be included in some products, and the oil-water ratio (5). Night creams are examples of products that are specifically designed to be heavier formulations. Specific ingredients are often combined in formulations to correlate with use for individual "skin types" such as dry, normal, or oily complexions. This is achieved by altering the heaviness characteristic of the occlusive agent used through selection of specific emollients that may be either protective, fatting, dry, or astringent in their inherent quality, and through adjustment of oil-water ratios. Examples of ingredient adjustments designed to correlate with use in specific skin types include dimethicone, a non-greasy, noncomedogenic emollient agent used in "oil free" facial moisturizers marketed for individuals with "oily skin" or inclusion of oil-absorbent compounds such as kaolin or talc, added to formulations to reduce "facial shine" by absorbing excess sebum (5).

SPECIAL ADDITIVES AND INGREDIENTS

Special ingredients may be added to basic moisturizer formulations to create "targeted moisturizer products" (1–3). Alpha-hydroxy acids, such as glycolic acid and lactic acid, have been added to many formulations to create exfoliant moisturizers, often marketed as anti-aging preparations (2,3,5). In order to reduce associated irritation, reduction in concentration or use of neutralizing additives (buffering) is common. However, as clinical efficacy correlates with availability of free acid, neutralization to a pH > 4.8 results in loss of efficacy (2,3,5). Retinol (vitamin A) and retinyl palmitate are added to some anti-aging moisturizer preparations to improve photodamage by decreasing fine wrinkling and tactile roughness. Both are inactive "precursor retinoids," requiring enzymatic conversions to produce retinoic acid from retinol; it is believed that the extent of retinol conversion to retinoic acid in skin is limited (2,3,5). Niacinamide (nicotinamide) is stable and compatible in moisturizer preparations due to its high water solubility, appears to produce an exfoliant effect, and may have anti-aging characteristics (5). The role of niacinamide in prevention of photocarcinogenesis and promotion of antineoplastic changes in keratinocytes in murine skin models is of considerable interest and is currently a focus of additional research (5,27,28). The addition of effective sunblock or sunscreen agents to moisturizer formulations is significant as photoprotection is important in the maintainance of epidermal integrity, dermal infrastructure and support, avoidance of small vessel damage and formation of telangiectasia, prevention of photocarcinogenesis, and reduction in pigmentation irregularities. Combination moisturizer-sunscreen formulations may

enhance compliance as both are applied together, usually early in the day, in a "one step" process.

THE SIGNIFICANCE OF GENTLE SKIN CLEANSING

The goal of an effective cleanser is to encompass, loosen, and promote easy removal of accumulated surface cutaneous debris, inclusive of natural skin secretions (i.e., sebum, desquamating corneocytes), dirt, microorganisms, and externally applied products (i.e., cosmetics, skin care products, medication residue) (6,29,30). As cleansing is a regular "daily ritual" for many cultures, the choice of an effective and nonirritating cleanser is significant. Cleansers containing irritant or abrasive components may enhance loss of epidermal integrity and barrier function. Improper or aggressve cleansing and overbathing are common causes of epidermal insult, irritation, and xerosis (4,6,29–31).

BASIC CLEANSER FORMULATIONS

Soap is created by a heating process called saponification; an alkali and a long-chain fat compound are combined, producing a fatty acid salt which exhibits detergent properties (6). A surfactant effect from usage of a soap reduces surface tension between water and surface debris, allowing for separation and removal by a lathering effect. A major difficulty with basic soap formulation is a pH of >7 (usually pH 9–10); the normal pH of skin ranges between 4.5–6.5 (6). The use of true soaps commonly leads to unacceptable dryness and irritation.

The development of soap-free synthetic detergent ("syndet") bars and non-lipid liquid cleansers has significantly improved the cosmetic acceptability and tolerability of skin cleanser formulations (6,29). Syndet bars are efficacious cleansers formulations, effectively limit damage to the epidermal barrier, and are widely accepted and very popular in the marketplace (6,30). These formulations are comprised of $<10\%$ soap and sustain an adjusted pH of 5.5–7 by utilizing synthetic detergents ("syndets") and filler substances that are associated with effective cleansing and little to no irritation (6). Lipid-free liquid formulations are also effective cleansers which may create a thin moisturizing film and produce little to no irritation in patients with normal, sensitive, photoaged, or diseased skin (6). They are also effective in the removal of cosmetics and makeup. Major components of non-lipid liquid cleansers include water, cetyl alcohol, stearyl alcohol, and glycerin (6).

The terms *gentle* or *mild* do imply that irritation is significantly minimized or absent due to the combination of ingredients and adjusted pH of the formulation, and do not imply a lack of efficacy. Several studies support the efficacy, high degree of patient preference, and lack of irritation associated with use of syndet bars and non-lipid liquid cleansers (6,31). Some combination bars ("combars") utilize additives to improve the "feel" of the formulation and reduce dryness through creation of a superfatted soap or by addition of humectants (i.e., glycerin). However, these formulations usually sustain an alkaline pH > 9, and some tend to dissolve rapidly during usage (6).

CONCLUSION

The primary goals of skin cleansing and moisturization are to sustain overall skin health and appearance by maintaining epidermal barrier integrity. This is achieved by selecting

products that are formulated to preserve retention of water content, limit damage to epidermal lipids and proteins, minimize TEWL, and contribute to barrier repair during episodes of compromise. Optimal product selection is based primarily upon the inherent qualities of the formulation, correlated with the needs and skin type characteristics of the individual patient. Ultimately, effective products are well designed with regard to their fundamental skin care characteristics and not dependent on multiple special additives that are included based on marketing trends rather than scientific validity.

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8
Antiperspirants

John E. Wild
Hill Top Research, Miamiville, Ohio, U.S.A.

A. C. Lanzalaco and D. F. Swaile
P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

INTRODUCTION

Personal care has been a concern of both men and especially women since the beginning of recorded history and most likely prior to those times as well. The ancient Egyptians used perfumes while bathing and for their hair and clothing (1).

The art of making the body smell better was evident in the early civilizations of Babylon, Assyria, Persia, China, Greece, and Rome (2). Although this chapter topic is related to antiperspirants it is difficult to separate the fact that the antiperspirant market has grown to its sales level in the market place because an antiperspirant delivers not only wetness control but, as a secondary benefit, imparts deodorant efficacy as well.

History

While deodorizing or masking of unpleasant body odor has been in practice for much of recorded history, controlling underarm wetness has only become a personal care practice in the past 100 or so years. Underarm products began to appear in the market place in the United States in the late 19th century with the introduction of a product called MUM in 1888. At the dawn of the 20th century the first brand name antiperspirant appeared on the U.S. market as EverDry. It was followed in a few years by a product called Odo-RO-No (3). These early products lacked the aesthetic qualities of today's brands. Aluminum chloride solutions were wet and runny and had very little cosmetic appeal but managed to sell at a reasonable rate and therefore had enough potential for their manufacturers to keep them in the market. The greatest shortcomings of these products were their irritating effects on the skin and the damage they caused to clothing materials (3).

During the early part of the 20th century the antiperspirant market progressed slowly. Following World War II the antiperspirant market expanded very rapidly. The

technology advancements that occurred because of the war could now be applied to non-war related applications. The ball point pen led to the idea for roll-on applicators. Aerosolized packaging led to aerosol antiperspirants and deodorants.

Radio and, the most impactful communication system of our time, television provided a medium for commercial advertising that captured the attention of millions of consumers with both verbal and visual displays.

Manufacturers of antiperspirants and deodorants were quick to buy into TV advertising to extol the virtues of their new products. TV watchers were provided a daily barrage of how to control offensive body odor and underarm wetness. The fact that people themselves can experience their own odor and wetness, as well as notice these attributes in others, reinforced the commercial appeal of these products.

Antiperspirants and deodorants, which in earlier days had been formulated as creams and solutions, now became available in all types of product forms. There were pads, daubers, pump sprays, squeeze bottles, powders, stick creams, solids, roll-ons, and aerosols.

The aerosol market grew rapidly and created "family use" products that were an aesthetically as well as hygienically pleasing way of delivering the product. The aerosol market captured the greatest market share until late in the 1970s when the use of aerosols became severely impacted by the concerns for the atmospheric ozone layer depletion and the ultimate ban on chloroflurocarbon propellants for aerosols. New propellant technology has preserved the aerosol but the solid cream and gel sticks came to the forefront of the United States market in the 1980s and remain as a large market share of the current formulation market place.

ANTIPERSPIRANTS

Definition

An antiperspirant, as defined by the Department of Health and Human Services in the final antiperspirant monograph published in 2003, reads as follows:

"A drug product applied topically that reduces the production of perspiration (sweat) at that site" (4).

There has always been some confusion in the industry that consumers do not always relate to the basic difference between antiperspirant and deodorant products. Antiperspirants, because of their ability to reduce perspiration and thus diminish the medium that is a factor in the development of axillary odor, can also claim to be a deodorant. However, because a deodorant product only reduces the body odor and does not reduce perspiration it can only be labeled as a deodorant.

Delivering that message to the consumer has been difficult because of that dual capability of the antiperspirant product. This problem may have been more prevalent during the earlier history of these products than now. In the European market the problem continues as labeling allows products containing antiperspirant actives to be labeled as deodorants. More recently some manufacturers have begun marketing these products as antiperspirants within Europe and these have started to reduce deodorant market share. The United Kingdom was the only one of the European markets that was always open to the use of antiperspirants and now the remaining countries in the common market are showing greater market share with antiperspirants. Japan seems to categorize antiperspirants with deodorants and suggests that their mode of action is the reduction of body odor by way of suppression of perspiration.

Regulatory Status

The regulatory status of antiperspirants is somewhat different in various regions of the world market place.

United States

In the United States an antiperspirant is categorized as an over-the-counter (OTC) drug product and therefore subject to regulations by the Food and Drug Administration (FDA). In 1972 the FDA announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by an independent advisory panel. In 1978 the FDA announced the establishment of a monograph and notice of proposed rulemaking that would establish conditions under which OTC antiperspirants are generally recognized as safe and effective and not misbranded.

In 1982 the FDA issued a tentative final monograph for antiperspirants. In 1990 the FDA issued a rule that certain active ingredients which were used in antiperspirants are not generally recognized as safe and effective and are misbranded. Then in 2003 the FDA issued the final monograph for antiperspirant products. The final antiperspirant monograph became effective in December of 2004 and did not address foot antiperspirancy claims. In addition the monograph did not identify any OTC antiperspirant products to be effective in reducing problem or especially troublesome perspiration. However, there was no data submitted to support those claims. The agency remains open to those potential claims if data are submitted with individuals who perceive themselves to have problem perspiration (4).

European Union

In the European Common Market antiperspirants are considered to be cosmetic products and are therefore subject to the European Cosmetic Directive. The definition of a cosmetic product is "any substance or preparation intended to come in contact with the various surface areas of the body (epidermis, hair, and capillaries, nails, lips, and external genital organs) or with the teeth and buccal mucosae, solely or principally for cleansing, perfuming, or protective purposes in order to maintain them in good condition, modify their appearance, and/or improve body odor, and/or protect or maintain them in good order" (5).

The European Cosmetic Directive has three essential objectives: (i) to ensure consumer safety, (ii) to harmonize legislation between the different Member States of the European Union, and (iii) to respond to the consumer's need for information (5).

The overall impact of the Cosmetics Directive is to deliver safe products to the consumer. There is also the implication that the manufacturers should possess data that supports the product's efficacy. However, unlike the OTC monograph for antiperspirants which sets a minimum standard of 20% reduction in axillary perspiration for an antiperspirant, there is no minimum level of efficacy stipulated.

Japan

In Japan antiperspirant products are controlled under the system of the Ministry of Health and Welfare (MHW). The regulation governing them is Japan's Pharmaceutical Affairs Law (PAL). Antiperspirant products in Japan are regulated and classified as quasi-drugs. A quasi-drug is an article used only for certain purposes that are specifically designated by the MHW. Antiperspirants are categorized under body deodorant quasi-drugs based upon their indication of effects against body odor, perspiration odor, and suppression of

Table 1 Data Required in Applications for Approval of Cosmetics and Quasi-Drugs

Data required	Scope	Quasi-drug	Cosmetic
Origin, background of discovery; use in foreign countries	Origin and details of discovery	X	X
	Use in foreign countries	X	X
	Characteristics and comparison with other quasi-drugs or cosmetics	X	X
Physical and chemical properties, specifications, testing methods, etc.	Determination of structure	X	X
	Physical and chemical properties	X	X
	Specification and testing methods	X	X
Stability	Long term storage	X	
	Severe test	X	X
	Acceleration test	X	
Safety	Acute toxicity	X	X
	Subacute toxicity	X	[a]
	Chronic toxicity	[a]	NA
	Reproductive effects	[a]	NA
	Skin sensitization, photosensitization, etc.	X	X
	Mutagenicity	X	X
	Carcinogenicity	[a]	NA
	Skin irritation, mucosa irritation, etc.	X	X
	Absorption, distribution, metabolism, and excretion	X	X
Indications or effects	Laboratory tests supporting indications or effects	X	NA
	Use test in humans	X	NA

[a] May not be required under certain conditions.
Abbreviations: X, required; NA, not applicable.

perspiration (6). Quasi-drugs and cosmetics are clearly stipulated to be articles whose biological activities are gentle and mild. Table 1 presents a tabular summary of the data required in an application for approval of cosmetics and quasi-drugs.

The practical result of the U.S., EU, and Japanese regulatory control of antiperspirants is that to be in a global market place, such products require a high level of formulation and manufacturing expertise to ensure safety and efficacy.

ANTIPERSPIRANT EFFICACY

In the U.S. the FDA has included in the OTC Antiperspirant Final Monograph guidelines that the manufacturer may use in testing for effectiveness. The agency does not require that these guidelines be used but requests that alternate methods and statistical evaluations are subject to FDA approval (4).

The FDA has established in the monograph the minimum standard for effectiveness at 20% sweat reduction to allow a product to be labeled as an antiperspirant. There are no guidelines suggested in the European Cosmetics Directive, however, because there are

many publications on this topic concerning antiperspirant efficacy, and techniques for proving efficacy are well known and readily available in the testing market place.

In Japan, Tagami indicates that the MHW does not specify in the PAL any specific standard test methodology for evaluating the clinical effects of quasi-drugs. It only makes reference to the use of a clinical use test in humans, under conditions simulating actual daily usage, for supplying data to assess the effects and safety of such products (6).

Recommended and Approved Uses

The antiperspirant monograph provides very specific labeling requirements for an antiperspirant drug product as follows:

1. A statement that the product be identified as an antiperspirant and that the product contains a drug identified by its established name, if a drug is present.
2. Under a heading titled "uses" the following language may be used by selecting one of the following phrases: "decreases," "lessens," or reduces underarm: "dampness," "perspiration," "sweat," "sweating," or "wetness." Other language can be appended to the phrase if it is truthful and not a misleading statement describing an established use as follows: "decreases, lessens or reduces" underarm "dampness, perspiration, sweat, sweating or wetness due to stress." For products that demonstrate the minimum standard of 20% sweat reduction over a 24-hour period the label may state either "all day protection," "lasts all day," "lasts 24 hours," or "24-hour protection."

For products that demonstrate extra effectiveness of 30% sweat reduction the label may state "extra effective." In addition for products that demonstrate the extra effective reduction over a 24-hour period the language for the standard reduction may be used or combined with any one of these statements: "24-hour extra effective protection," "all day extra effective protection," "extra effective protection lasts 24 hours," or "extra effective protection lasts all day."

The product label must also contain the following items listed under "Warnings:"
"Do not use on broken skin."
"Stop use if rash or irritation occurs."
"Ask a doctor before use if you have kidney disease."
If the product is aerosolized:
"When using this product keep away from face and mouth to avoid breathing it."
The label must also contain the following under the heading of "Directions:"
"Apply to underarms only" (4).

The regulatory agencies in other countries have not been as specific in as many details as the FDA.

Function of Antiperspirants

Antiperspirant products are relatively unusual drug formulations. Unlike most drugs, their mechanism of action is physical rather than pharmacological. Figure 1 illustrates how the antiperspirant actives form a shallow plug near the opening of an eccrine sweat duct on the skin surface (7). These blockages prevent the eccrine excretion from reaching the skin surface in the axilla without creating a significant systemic effect on the thermal regulatory system. These blockages can remain within the sweat duct for seven to 14 days depending on the rate of skin desquamation, consumer's hygiene regime, activity type, and quality.
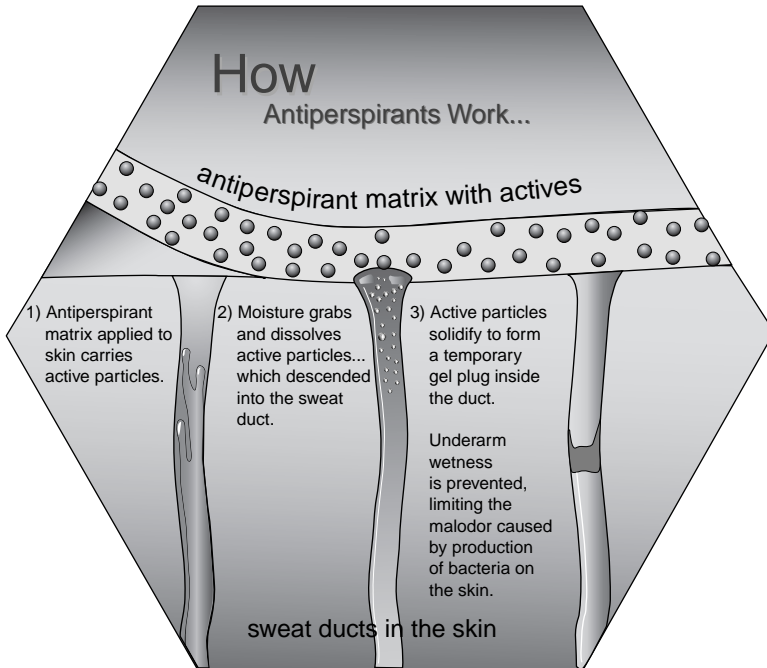
Figure 1 Graphic showing the formation of the shallow plug in the sweat duct demonstrating the mechanism of action for current antiperspirant products.

Function of Deodorants

Historically, there has been some confusion among the public when distinguishing between the benefits provided by commercial antiperspirant and deodorant products (8). While antiperspirants are designed to reduce both axillary sweating and malodor, deodorants provide only malodor control. The most effective deodorants are typically glycol-based products containing odor-masking fragrances. The use of a glycol base is especially effective as it augments the masking fragrance by providing microbial control of the odor causing bacteria (9). However, these products do not impact axillary sweating in any way.

In contrast, OTC antiperspirant products provide the dual benefits of axillary wetness and malodor control. Antiperspirants reduce malodor through a combinatorial effect that includes the microbial inhibition of the aluminum and zirconium salts; the deleterious effect on the odor causing bacterial ecosystem of a drier axillary vault and the ability of skin substantive antiperspirant products to extend the residence time of masking fragrances (10). For perspective, in a head-to-head clinical comparison, a fragrance-free aluminum zirconium tetrachlorohydrex glycine-containing antiperspirant was shown to be superior to a fragrance-free glycol-based deodorant at reducing axillary malodor (11).

FORMULATION

Approved Active Ingredients

The final OTC antiperspirant monograph itemized the 18 active ingredients that are approved for use in antiperspirant products in the U.S. Table 2 shows each of the approved

Table 2 Antiperspirant Active Ingredients

Active ingredient	Concentration	Dosage form
Aluminum chloride	Up to 15% (calculated on hexahydrate form)	Only aqueous solution (must be nonaerosol)
Aluminum chlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum chlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum chlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum dichlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrate	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrex polyethylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum sesquichlorohydrex propylene glycol	Up to 25%	Aerosol or nonaerosol
Aluminum zirconium octachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium octachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium pentachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium pentachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium tetrachlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium tetrachlorohydrex gly	Up to 20%	Nonaerosol
Aluminum zirconium trichlorohydrate	Up to 20%	Nonaerosol
Aluminum zirconium trichlorohydrex gly	Up to 20%	Nonaerosol

ingredients, concentration limits, and dosage forms/types in which the approved active can be formulated.

There are no specific active ingredient lists specified by the EU or Japan.

Formulation Variations

As with all treatment programs, the key to achieving maximum benefit is compliance. Antiperspirant products can require up to 10 consecutive days to reach maximum efficacy and benefits can be completely eliminated within 14 days of treatment termination. Barriers to compliance are typically associated with products' aesthetics rather than skin irritation. Refer to Table 3 for details on formulation and compliance. Erythema and

Table 3 Formulation and Compliance

Product types	Active types	Carrier system	Barriers to compliance	Comments
Water-based roll-on	Aluminum chloride Aluminum chlorohydrate Aluminum zirconium tetrachlorohydrate gly	Water Oil in water Emulsion	Skin irritation (aluminum chloride) Wet sticky skin feel	Only form available with aluminum chloride in mass market
Powder-based roll-on	Aluminum zirconium tetrachlorohydrate gly	Anhydrous emollients	Wet skin feel at application	
Gels	Aluminum zirconium tetrachlorohydrate gly	Water in silicone emollient emulsion	Sticky skin feel	
Stick	Aluminum chlorohydrate Aluminum zirconium trichlorohydrate gly Aluminum zirconium tetrachlorohydrate gly	Silicone emollient system solidified with wax	White residue on skin and clothes	Most common product form in mass market
Creams	Aluminum zirconium trichlorohydrate gly Aluminum zirconium tetrachlorohydrate gly	Silicone emollient system thickened with wax	Skin feel at application	Generally the most efficacious form in mass market

stinging can still be common for products containing Aluminum Chloride and/or high levels of glycol or fragrance but are not common on most commercial antiperspirants. Unscented products based on the emollients cyclopentasiloxane and dimethicone have very good skin compatibility.

Most common barriers to compliance are associated with the skin feel of product, product appearance on skin, product transfer to clothes, and fragrance. Typically, consumers view antiperspirant application as part of their total grooming process and often create application behaviors that reduce product efficacy. Behaviors such as removing the product shortly after application, not applying the dose of product recommended by the manufacturer, or only applying it to a portion of the axilla will reduce efficacy. Encouraging consumers to identify a product form that allows them to comply with a daily application routine will maximize their observed benefit. Efficacy can further be improved by placing the user on a nighttime application to remove issues with the user's morning grooming routine. Night time application allows the active to enter the duct during a time of low sweating rates and allows for more efficient plug formation.

FORMULATING FOR THE CONSUMER

The approach taken by manufacturers to encourage compliance has been to offer a wide choice in product form and aesthetics. Today's consumers are accustomed to a variety of choices in their antiperspirant selection. It is clear, from even a cursory glance at the antiperspirant/deodorant shelves in any supermarket or pharmacy, that there is a wide range of aesthetic experiences acceptable to people. The desired experiences are delivered through a multitude of packaging presentations, both in size variation and product type. These include aerosol sprays, silicone/wax sticks, aqueous clear gels, and lotion-like creams. In addition, most antiperspirant brands provide a variety of fragrance options for their consumers. All of these variations cater to the consumer's demands for both gender and ethnic preferences. Manufacturers long ago discovered that people tend to gravitate to the form that they are most comfortable with, which in turn ensures compliance leading to effective axillary wetness control. Importantly, the drive to meet the consumer's demand for aesthetically appealing products applies globally to the antiperspirant market place.

INTRODUCING NEW ANTIPERSPIRANT ACTIVE FORMULATIONS

In the U.S. the introduction of any new antiperspirant actives into the market will require a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA). These procedures will no doubt inhibit bringing new actives into the market place unless there is a strong inclination by the manufacturer to believe their new active will bring a large return from the market place. The submission of an NDA or ANDA requires a major commitment of time and capital by the manufacturer. When consumers demand new and more effective products, industry will usually respond as long as there will be the hope for a return on its investment.

MEDICAL APPROACHES TO HYPERHIDROSIS

Hyperhidrosis is defined as excessive sweating. The profusion of sweat may be in the axillae, the palms, the feet, the face, on the trunk, or a combination of any or all of the above body parts. The excessive sweat is beyond the person's physiological requirement to regulate the body's temperature and is largely under emotional control (12).

In a culture where the personal hygiene and social standards are established to not emit unpleasant odors and/or exhibit underarm wetness, clammy skin, etc., a hyperhidrodic condition can be devastating in social environments. The condition can adversely affect the person's ability to attain a normal and healthy quality of life. Persons suffering with hyperhidrosis have reported both physical and emotional impairment and difficulty in their professional and social lives. Approximately 0.5% of the U.S. population suffers from axillary hyperhidrosis and report that their excessive sweating is barely tolerable to intolerable and interferes in some way with their daily activity (12,13).

Treatment

Antiperspirants

The treatment of hyperhidrosis with OTC antiperspirant products is usually the first method employed by those who suffer with this condition. There are no currently marketed

antiperspirants that are explicitly designed or claim to have a beneficial effect on excessive sweating. As stated earlier the FDA has not approved any marketed OTC antiperspirant product for an excessive sweating condition. In addition, all the currently marketed OTC antiperspirant products are explicitly labeled to be used only in the axilla and are not approved for any other body location. The FDA has, however, remained open to a claim for the treatment of excessive sweating if data are submitted for their review for this claim (12).

The currently marketed OTC antiperspirant products most likely offer only marginal effectiveness to those who suffer from hyperhidrosis. Because this condition is so socially devastating, a large number of those who suffer with hyperhidrosis seek the advice of a health professional (12,14).

There are prescription drug solutions available for those who seek medical treatment for their condition. These prescription products usually contain aluminum chloride concentrations greater than those which have been established as safe and effective in the final OTC antiperspirant monograph. These higher concentration products are usually recommended to be used at bedtime to allow for maximum absorption at a time when sweating may be at a minimum for the day. They are typically applied nightly for three nights under the occlusion of plastic wrap. The plastic wrap occlusion traps perspiration in the armpit and hydrates the skin enhancing penetration of the aluminum chloride solution, which increases efficacy. After this initial treatment period, the plastic wrap occlusion is discontinued and the aluminum chloride solution is only applied every other night for a week and then twice weekly for a week. Patients are advised to keep decreasing the frequency of aluminum chloride application until the minimum application frequency to maintain sweating control has been determined. Applications at this frequency are continued indefinitely as the aluminum chloride only decreases axillary sweating temporarily.

The higher concentrations of aluminum chloride can be more irritating to the skin than OTC antiperspirant products. These higher concentrations have also been known to be harmful to fabrics, and therefore caution should be used about clothing worn during treatment (12).

Other treatment options are also available to those who suffer with hyperhidrosis. These treatments include some of the following.

Iontophoresis

This procedure employs the use of weak electric current to slow down sweat production. It requires the purchase of a battery-operated device with a removal pad. The pad is soaked either with tap water or a dilute solution of aluminum chloride in tap water. The device is placed in the armpit and turned on for approximately 20–30 minutes. During this time, the low voltage electric current is used to drive the tap water with or without aluminum chloride into the duct of the eccrine sweat gland to create a plug. This plug prevents the release of the sweat into the armpit. Devices are also available for the palms of the hands and the soles of the feet.

The primary drawback to this technique is the time required to administer the treatments. With continued use, it is possible to cut back on the frequency or sessions from daily, to twice weekly, to once weekly. It is key to maintain the plug in the sweat duct for efficacy. Once the plug is gone, the previous rate of sweating will return. Unfortunately, iontophoresis can only decrease the amount of sweating, not stop it completely (12).

Endoscopic Thoracic Sympathectomy Surgery

Early surgical techniques that were used to treat hyperhidrosis were invasive, risky, scarring, and sometimes unsuccessful. Endoscopic thoracic sympathectomy (ETS) surgery

is less invasive, since it is performed with the aid of a small endoscope that is introduced into the body. This surgery is designed to interrupt the transmission of nerve signals to the sweat glands. This procedure carries with it the usual risks that can be encountered during surgery, such as nerve damage, as well as other side effects, such as chronic pain syndrome. The most notable of these side effects may be compensatory sweating, that is, increased sweating may occur at a new body location. In addition, the cut nerves may reconnect, rendering the procedure completely unsuccessful (12).

Prescription Medications

Anticholinergic drugs, such as Robinal, may help prevent the stimulation of the sweat glands and thus inhibit sweat output. The FDA has not approved any drug for the treatment of hyperhidrosis. Although these drugs may be effective in inhibiting excessive sweat, there are significant side effect risks with these medications. These include such effects as dry mouth, blurred vision, urine retention, constipation, impaired swallowing, taste, etc. Medications such as these are usually taken only for special occasions when sweat control is important. Most persons cannot tolerate the side effects on a daily basis (12).

Botulinum Toxin A Injections (Contributed by Zoe Diana Draelos, M.D.)

Botulinum toxin A (Botox, Allergan) is the most effective method of reducing axillary hyperhidrosis. It is classified as a method of chemodenervation, since it interrupts the nerve signal to sweat. As mentioned previously, axillary hyperhidrosis is largely under central control. The brain must send a signal to the nerves in the armpit to initiate sweating. If the nerve signal is never received by the sweat gland, sweating does not occur. This is how botulinum toxin works. Unfortunately, it cannot be applied to the skin surface, but must be injected with a small insulin syringe just beneath the skin surface where the sweat glands lie.

Botulinum toxin A treatment for hyperhidrosis is typically administered as a medical procedure in the office of a dermatologist. The armpit is first cleaned thoroughly to remove all sweat and antiperspirants. It is then painted with an iodine solution and dusted with cornstarch. The reaction between the sweat and iodine will turn the cornstarch black once perspiration has begun. An indelible marker is then used to draw a line around the area of maximum sweating. This is the location for the botulinum toxin A injections.

Once the area of maximum sweating has been determined, the botulinum toxin A is removed from the freezer, where it must be keep until just before use. The freeze-dried botulinum toxin bottle containing 100 units is then reconstituted with 2 cc of unpreserved sterile saline. Approximately 10 units are drawn up into 20 insulin syringes for injection with 10 syringes used in each armpit. The injections are made just under the skin surface to raise a tiny wheal at 2 cm intervals in a whirl configuration from the central armpit outward until the entire area outlined by the indelible marker has been injected. As might be imagined, this is a painful and tedious procedure.

Fortunately, the sweat reduction induced by the botulinum toxin A lasts for approximately six months, or longer in some individuals. The treatment does not completely eradicate axillary sweating, but significantly diminishes its amount. Any remaining sweating can usually be controlled with traditional nonprescription antiperspirants. Botulinum toxin A can also be injected into the hands and feet for purposes of sweat reduction.

Other Surgical Treatment Options

There are a variety of other treatment options that have been tried with limited documented success. These treatments include such surgeries as excision of sweat glands

and liposuction. It is very difficult to excise the sweat glands without creating movement problems in the armpit. The hair bearing skin typically denotes the location of the sweat glands in the armpit, but removal of this quantity of skin is both scarring and restrictive. A better alternative is liposuction. Liposuction can be performed under a form of local lidocaine anesthesia known as tumescent anesthesia. Here a dilute solution of water and lidocaine is introduced into the fat just below the armpit skin. The lidocaine provides pain relief and raises the armpit skin away from the underlying nerves and vessels that must not be damaged during surgery. A 2 mm opening is made in the armpit and a metal tube, known as a cannula, is inserted. The cannula has a cutting edge just below the tip and is vigorously pulled against the undersurface of the skin to intentionally damage and scar the sweat glands. The cannula is attached to a negative pressure vacuum suction device that collects the removed tissue and anesthesia. Tumescent liposuction of sweat glands is effective at reducing axillary sweat in some individuals.

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9

Sunscreens

J. F. Nash and Paul R. Tanner
*P&G Beauty, Sharon Woods Technical Center, Cincinnati,
Ohio, U.S.A.*

INTRODUCTION

There is consensus among the scientific and medical communities that exposure to sunlight is a major factor in the etiology of the progressive unwanted changes in the appearance of skin, i.e., photoaging, and in the risk of skin cancers (1–3). The evidence supportive of this view comes from epidemiology, clinical studies, and experimental studies in humans, laboratory animals, and in vitro systems. It is well established that acute exposure of unprotected skin to ultraviolet (UV) radiation in sunlight produces numerous physiological effects beyond the most obvious which is sunburn (4). Such insults or damage following repeated, lifetime exposure to solar UV lead to skin cancers (5–8), and as presented in Table 1, a myriad of degenerative events responsible for the visible signs of skin aging (10,11). Recent years have seen a very rapid increase in knowledge concerning the etiology and prevention of solar damage (12–14). Since exposure to UV radiation in sunlight is associated with deleterious dermatological events, it is logical that reducing solar UV exposure will diminish such damage to the skin.

Arguably, the complete avoidance of solar UV is neither achievable nor entirely healthy. For example, it is known that exposure to sunlight has health benefits including production of vitamin D (15). As such, moderation seems prudent when considering the balance between the established damage and benefits of solar exposure. To this end, a "safe sun" strategy has been developed and promoted by healthcare professionals worldwide (16–18). An important part of this "safe sun" strategy is the use of sunscreens.

Once the energy from UV is absorbed in the skin, it may produce new chemical entities, e.g., $6',4'$-DNA photoproducts, free radicals, etc., or dissipate the excess energy as heat or phosphorescence. This absorption and subsequent conversion of energy contribute to the processes involved in the etiology of skin cancer and photoaging. Preventing solar UV from interacting with skin chromophores is the primary function of sunscreens. To this end, sunscreen products are quite simple; they absorb/reflect/scatter UV radiation from sunlight before this energy can be absorbed by chromophores residing in the skin. As it turns out, sunscreen products are technically complex. Moreover, such products must be applied to be effective, and as with any other preventative measure, compliance is the key to achieving health benefits.

Table 1 Features of Chronological (Intrinsic) and Photo-Induced Skin Aging

Chronological		Photo-induced	
Clinical	Physiological/histological	Clinical	Physiological/histological
Fine wrinkles	Increase variability in epidermal thickness	Varying degrees of thickness	Epidermal acanthosis
Skin laxity	Decrease in epidermal filaggrin	Coarse wrinkles	Thickened stratum corneum
Dry skin	Reduction in the number of melanocytes	Marked dryness and scaliness	Marked cellular dysplasia
Even skin tone	Reduction in number of Langerhans cells	Uneven pigmentation and lentigines	Variability in size and shape of keratinocytes
Impaired wound healing	Decrease in dermal thickness	Benign, premalignant, and malignant skin lesions	Pronounced flattening of epidermal-dermal junction
	Increase in cross-linkage and disorganization of collagen fibers		Reduction in number of Langerhans cells
	Decrease in number of eccrine, apocrine, and sebaceous glands		Solar elastosis resulting from hyperplasia of abnormal elastic tissue
	Flattened dermoepidermal junction		Blood vessels dilated and on the face called telangiectasias
			Sebaceous gland hyperplasia and pore size

Source: Modified from Ref. 9.

SUNSCREENS

Unquestionably, the safety and efficacy of sunscreen products is of paramount importance. To this end, the function, UV filters, and product design will be discussed.

Function

As stated, the function of sunscreen products is to absorb/scatter/reflect solar UV, thereby reducing the dose of such harmful radiation to the skin. This is accomplished through the use of a combination of UV filters (Table 2) and an appropriate film-forming vehicle. Whereas for most products, such as cosmetics or over-the-counter (OTC) drugs, it might be enough to simply include ingredients that have an established effect, i.e., cough/cold preparations with antihistamines, decongestants, etc., for sunscreens, the protective effectiveness is communicated directly to consumers as the sun protection factor (SPF). Recently, it has been recognized that SPF is incomplete and some additional measure of protection against long wavelength UV, i.e., UVA-I (340–400 nm), is needed. Nonetheless, the SPF is meaningful to consumers and the single most important in vivo measure of sunscreen product efficacy.

    For consumers, the most recognized and understood skin response to sunlight exposure is erythema or "sunburn." This can occur in most Fitzpatrick Skin Types and can

Table 2 Approved UV Filters

UV filter	Up to % concentration
Aminobenzoic acid or PABA	15
Avobenzone or butyl methoxydibenzoylmethane	3
Cinoxate	3
Dioxybenzone	3
Homosalate	15
Menthyl anthranilate or meradimate	5
Octocrylene	10
Octyl methoxycinnamate or octinoxate	7.5
Octyl salicylate or octisalate	5
Oxybenzone or benzophenone-3	6
Octyl dimethyl PABA or padimate O	8
Phenylbenzimidazole sulfonic acid or ensulizole	4
Sulisobenzone	10
Titanium dioxide or TiO_2	25
Trolamine salicylate	12
Zinc oxide or ZnO	25

Source: From Ref. 19.

be produced in a clinical setting following exposure to an artificial light source. Most important, the erythema action spectrum, i.e., erythemal response as a function of UV wavelength, is nearly identical to the action spectrum for DNA damage (20–22) and nonmelanoma skin cancer as evaluated in hairless mice and predicted for humans (23). Thus, the current in vivo test used to evaluate the functional efficacy of sunscreens is based on an endpoint that is meaningful to consumers, e.g., sunburn protection, and a surrogate for clinically relevant acute and longer term skin damage.

The SPF is a ratio of the response to solar-simulated UV exposure in protected skin versus unprotected skin. Specifically, the minimum erythema dose (MED) is determined for each panelist in an SPF test. This is the time/dose of solar-simulated UV needed to produce a uniform, barely perceptible redness in the skin. The MED will vary depending on Fitzpatrick Skin Type (24,25). To determine the SPF, a product is applied at a fixed dose of 2 mg/cm^2 over a 50–100 cm^2 area of the lower back. Five to seven "spots" are exposed to varying doses of solar-simulated UV, two/three above, two/three below, and one at the "expected" product SPF. The "expected" SPF is a predicted value from in vitro estimates or the experience of the sunscreen product formulator. At 16–24 hours after UV exposure, the sites are evaluated and the one receiving the lowest UV dose in which a uniform, barely perceptible redness was produced is recorded (26). The "UV-dose/time" is used to calculate the SPF using the following equation: SPF = MED protected skin/MED unprotected skin. According to the methods stipulated by FDA, the SPF is determined in 20 panelists.

There has been much effort to make the SPF test reproducible and reliable, most recently with the introduction of an International SPF Test coordinated by the European Cosmetic Toiletry and Perfumery Association (COLIPA). However, there are several shortcomings of the SPF test and resulting label which should be pointed out. First, it must be clearly understood that the SPF test measures a biological effect using an artificial light source, fixed dose, and an endpoint, i.e., erythema, that is weighted for short wavelengths of UV, namely 290–340 nm (27). Unfortunately, it is overly convenient to refer to SPF as a measure of UVB protection even though it is determined using full spectrum, 290–400 nm, solar-simulated UV and that the UVA-II region (320–340 nm) contributes significantly to high SPF

values. Moreover, because it is a "number," even knowledgeable individuals overemphasize this quantitative index of what is most certainly a qualitative response. For example, an SPF 12 is quantitatively different than an SPF 17, yet from a biological standpoint, the protection afforded by proper use of an SPF 12 or 17 is indistinguishable. As well, the SPF determined under controlled laboratory conditions is dependent on the light source and may be different if the light source changes, e.g., solar-simulated light versus natural sunlight. Finally, the SPF ratio is "nonlinear" since an SPF 15 is not half of an SPF 30 based on the ability to reduce erythemally-weighted UV. That is, the SPF is determined by the erythema action spectrum which, as stated previously, is weighted for short wavelengths of UV. The SPF can be represented as a percent of erythemally-weighted UV transmitted, i.e., $1/SPF \times 100$, or blocked, i.e., $[1-(1/SPF) \times 100]$. Thus, an SPF 15 blocks 93.3% and SPF 30, 96.7% of the erythemally-weighted UV or a mere 3% difference. Finally and perhaps the most significant limitation of SPF is the failure to provide assurance of protection against long wavelengths of UV, 340–400 nm, or the so-called UVA-I.

Whereas it is now established that protection of long wavelength UVA is essential (28–30), as of December 2005 there is no agreed to, regulatory-mandated means of measuring or communicating UVA protection of sunscreen products to consumers in the United States. To further complicate the situation, there are currently no known surrogates for long wavelength UVA damage that can be measured in the skin following acute exposure to filtered solar-simulated UV. This fact has profound implications for any in vivo human study measuring a UVA protection factor, i.e., the ratio of response to a filtered, artificial light source at a fixed dose in protected versus unprotected skin. The most prominent concern is that any such UVA protection factor based on a response which has no direct relationship to a human health concern, e.g., photoaging or skin cancer, is nothing more than misleading at best. Further, the resulting UVA protection factor is meaningless to consumers since the skin response, e.g., persistent pigment darkening or "color change," is not a response to which protection is considered when purchasing a sunscreen product. Finally, it is possible to measure a UVA protection factor without protecting against the breadth of UVA. Nonetheless, there are numerous proponents of such an approach and tests including persistent pigment darkening (PPD) (31) and protection factor UVA (PFA) (32,33).

Since any in vivo test is without merit, there have been several in vitro methods proposed (34,35). In general, the in vitro approach is based on measurement of absorbance/transmittance of UV through a sunscreen product applied to a substrate (36). The resulting data can be used to calculate a "metric" from which some labeling designation can be derived (37–39). This general approach has been used successfully in several countries including Australia (AS/NZS 2604 Sunscreen products, evaluation, and classification), U.K. (Boots Star Rating), and Germany (DIN draft standard 67502 whereas the UVA-protection is now calculated as UVA-balance). The stated objection to such in vitro approaches is that they are not done on human skin and, as such, cannot provide quantitative information regarding "protection." Despite this concern, substrate spectrophotometric measures of absorption have several advantages including cost, reproducibility, and human subjects are not intentionally exposed to an artificial filtered light source the health consequences of which are unknown. Moreover, the results from in vitro substrate spectrophotometric studies can provide complimentary information to the in vivo derived SPF.

In sum, the function of sunscreen products is to reduce the dose of solar UV thereby mitigating or reducing damage to the skin. The SPF test provides meaningful, in vivo information regarding the protection against solar UV which is weighted for short wavelengths based on the erythema action spectrum. The SPF "number" is recognized by consumers as the measure of sunscreen product efficacy. In vitro substrate

spectrophotometric measures of sunscreen product absorbance and calculation of a metric such as Critical Wavelength can serve as an independent, complementary measure of long wavelength, UVA, sunscreen product efficacy. The American Academy of Dermatology has provided a recommendation (40) which may serve as the basis for a regulatory-mandated testing and labeling for UVA efficacy of sunscreen products.

Active Ingredients: UV Filters

In the U.S., there are 16 UV filters which are approved for use in sunscreen products and are listed in Table 2. Of these 16, there are nine which appear in most currently marketed sunscreen products in the U.S. (41). There is much overlap in the use of such ingredients between U.S. and other regions throughout the world such as Europe (42), the latter having a larger number of UV filters available for use. The human safety of UV filters has been reviewed (39,43–45). In general, the human safety profile of UV filters used in U.S. sunscreen products is favorable based on extensive toxicological data and marketing history. This view is reflected in the appearance of these ingredients on either positive lists in various regions of the world such as Europe and Australia or as Category I ingredients, i.e., safe, and effective, according to the U.S. FDA. Detailed information regarding the human safety of individual UV filters can be found in the review by Nash (39).

The UV filters in sunscreen products are primarily, if not solely, responsible for the absorption/reflection/scattering of solar UV. To achieve the SPF and breadth of UV protection, a combination of UV filters is selected based on their individual absorption profiles and other physiochemical characteristics. For example, to create a sunscreen product with an SPF 15, nearly any combination of UV filters listed in Table 2 can be used. The selection of filters must absorb wavelengths from 290–340 nm to achieve the desired SPF 15. If protection against long wavelength UV is to be achieved, then in the U.S. the options are much more limited. Specifically, one must select either avobenzone or zinc oxide, both of which absorb long wavelength UVA-I (340–400 nm). As the SPF of the product increases so too does the concentration and number of UV filters. This is represented in Figure 1. The percent concentration of UV filters in a hypothetical SPF 15 product ranges from 10–15% and for an SPF 45, up to 30% and beyond. Net, the higher the SPF, the higher the concentration of UV filters.

Products

UV filters are the functional component of sunscreens while the formulation is the "art." The general goal in formulating modern sunscreens is to design the best product that meets the desired UV efficacy targets of SPF, UVA/broad spectrum protection, and substantivity, i.e., water/wear resistance. Typically, the best product is the one that most effectively manages factors such as cost, skin compatibility, and aesthetics/skin feel (46).

From an ingredient standpoint, most sunscreen products are typically very similar to conventional lotions or creams, with the key difference being the addition of 4% to 40% sunscreen actives (Fig. 1). From a formulation perspective, the current list of UV filters (Table 2) can be categorized into one of four groups based on the physical properties of the active:

- Polar oils, e.g., octinoxate, octisalate, homosalate, and octocrylene
- Oil soluble crystalline solids, e.g., avobenzone, and the benzophenones
- Water soluble salts, e.g., ensulizole
- Insoluble powders/particulates, e.g., zinc oxide and titanium dioxide
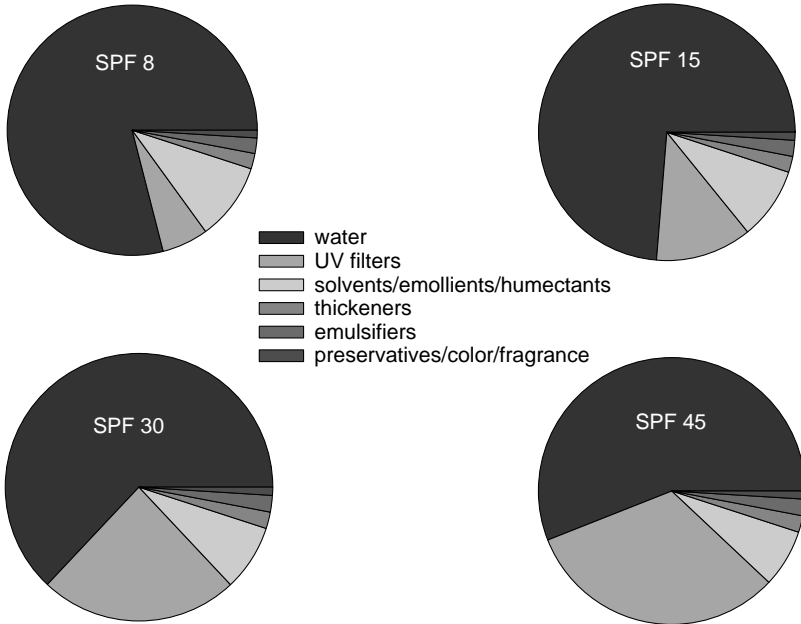
Figure 1 Hypothetical sunscreen products ranging from SPF 8–45. As the SPF increases the percent of UV filters increases.

Importantly, given the concentration of UV filters used in sunscreen products, i.e., up to 40% for high SPF products, and their physical properties, by far the greatest factor involved in managing cost, skin compatibility, and aesthetics/skin feel in formulating new sunscreen products is the selection and combination of these sunscreen actives.

Cost

Current sunscreen actives are expensive relative to the key ingredients utilized in most lotion and cream vehicles, typically ranging from $10 to $100 per kilogram. Thus, the higher the level of sunscreen actives in a formulation, the greater the formula cost, and hence the more marketers charge for the product. In turn, and perhaps as a direct consequence, one might expect that the more expensive the sunscreen product the more sparingly, i.e., lower dose and reduced frequency, it will be used by consumers (47).

Skin Compatibility

Along with fragrances and dyes, UV filters, particularly organic moieties, are known to elicit irritant responses in subjects predisposed to such skin reactions (48,49). It is generally desirable, therefore, to reduce to a minimum the concentration and number of UV filters present in a sunscreen product formulation to minimize risk of these types of incompatibilities.

Aesthetics/Skin Feel

Each type of sunscreen active described above can have a negative impact on sunscreen product skin feel, with higher levels having a corresponding larger effect. Specifically, the general skin-feel tradeoffs of the various types of sunscreen actives are:

- Polar oils tend to make the product feel greasy and oily, especially at high concentrations.
- Oil soluble crystalline solids require high levels of oily solvents/emollients to dissolve them and keep them from crystallizing in the product over time, and hence make the product feel greasy and oily.
- Water soluble salts tend to reduce the capability of most aqueous polymeric thickeners. This, in turn, leads to the use of much higher polymer levels to achieve a target product thickness, and these high polymer levels make the product feel sticky and heavy on the skin.
- Insoluble powders/particulates can make the product feel dry and draggy, and often can lead to an undesirable white appearance on the skin.

Additionally, even beyond the specific aesthetic effects above, there is a further general effect that comes from putting significant levels of sunscreen actives into a product—higher "coated" feel on the skin. Specifically, the single largest component of most non-sunscreen lotions and creams is a volatile carrier, typically water. Thus, when a layer of non-sunscreen lotion or cream is applied to the skin, most of the product evaporates, leaving behind a thin layer of non-volatile material consisting of moisturizers, emollients, thickeners, preservatives, and similar materials. By adding UV filters to a formula to achieve SPF 15 or SPF 30, for example, the level of volatile carrier in the product is significantly reduced. As a result, much more of the applied product is left behind on the skin, and the skin feels "coated." Thus, even if the greasy, draggy, or sticky effects of the sunscreen actives are reduced by other technologies, the skin will still be left with an unpleasant coated feeling given the high level of non-volatile materials left behind from the sunscreen product. To compensate for this, many consumers apply product at a lower dose or less frequently, which will likely reduce the efficacy (50,51).

As stated, all of these factors—cost, skin compatibility, and aesthetics/skin feel—will influence patient compliance, either directly, viz amount of product applied and frequency of application/reapplication, or indirectly in decisions related to repurchasing the product. Thus, by developing more efficient sunscreens, manufacturers can minimize the amount of sunscreen actives needed to achieve a given efficacy target, and hence deliver lower cost, less irritating, and better-feeling sunscreen products. Sunscreen products consumers will use more regularly will provide a significantly greater degree of protection.

SELF-TANNING PRODUCTS

The health and beauty of a "tan" has been ingrained in a generation of westerners (52). Unfortunately, this fashion image is diametrically opposed to the message being promoted by healthcare professions, namely to avoid sunlight or other artificial UV light sources, e.g., tanning salons, which is primarily responsible for the beautiful tan. Attempts have been made to provide "color" or artificial tans without intentional exposure to solar or solar-simulated UV. The most successful of these self-tanning products are the ones which containing dihydroxyacetone (DHA). These self-tanning products impart color to the skin which is temporary and may be a safer approach toward achieving a "tan" (53).

Function

As stated, the function of self-tanning products is to temporarily impart color to the skin. Darkening of the skin occurs in response to solar or solar-simulated UV exposure which is

the body's natural response to UV exposure. Melanogenesis is a very complex process that is still not fully understood (54,55). It is the image of beauty and health to sport a "tan," and whereas the public health message to avoid intentional solar exposure has had some small impact, there has been an increase in the use of tanning parlors (56,57). Importantly, there are individuals who will engage in risky behavior regardless of the costs/consequences. As such, the use of sunless tanning products may provide an important alternative for some.

An artificial "tan" resulting from the application of a DHA-containing product does provide some limited, short-lived protection against UV (58–60). More recently, it has been reported that topical application of DHA to hairless mice will delay UV-induced photocarcinogenesis (61). These protective benefits are promising as sunless tanning gains in popularity.

Ingredients

Most, if not all, commercial sunless tanning products utilize DHA to deliver a tanned appearance to the skin. Dihydroxyacetone is a three-carbon sugar that reacts nonenzymatically with amino acids in the outer layers of skin to produce brown/tan colored polymers (62). This color-forming reaction, i.e., the Maillard Reaction, is not immediate, and hence visible tanning is not noticeable until a few hours after application. Further, the tanned color produced by DHA is substantive, lasting several days before it gradually fades away as the outer layers of skin cells slough away. This is in contrast with common bronzing products that provide immediate color to the skin through the use of dyes and colored pigments that can be easily washed off. In addition to DHA, several sunless tanning products also contain erythrulose (63), another sugar capable of reacting with skin proteins to generate a more even and longer lasting sunless tan.

Products

The goal of a sunless tanning product is to deliver DHA to the skin in a way that provides an even, natural looking tan color (64). To achieve this, there are three important considerations. First, the formulation must ensure that the DHA itself remains stable; otherwise, the product will develop an unpleasant brown color and burnt caramel off-odor in the package, and the sunless tan provided by the product will be compromised. Stability is achieved, for example, by a combination of an optimal product pH and avoiding materials in the formula that react with DHA, such as amine functional materials and certain pigments.

Second, the product needs to spread the DHA very uniformly on the skin to provide an even, streak-free tanned color. To achieve good spreading, a number of new product forms beyond traditional sunless tanning lotions have been introduced, including sunless tanning sprays, foams (mousses), and wipes. Finally, the sunless tanning product needs to absorb into the skin and dry quickly, to make it easier and more convenient to achieve a good tan. Getting dressed or going to bed while a sunless tanning product has not fully absorbed into the skin can lead to uneven color as well as stained fabrics. Thus, creating faster absorbing/drying sunless tanning formulas, like the sprays and foams mentioned above, ensures best results.

Importantly, while all of this sunless tanning product technology has yielded significantly improved sunless tanning products over the early sunless tanning products of 20-plus years ago, the reality is that achieving a good, even sunless tan still depends a great deal on factors other than the product. For example, proper skin preparation via cleansing

and exfoliation is critical to achieving an even, lasting sunless tan. Also the reaction between DHA and the skin takes several hours. Avoiding sweating, swimming, or showering for several hours after product application is also important to ensure best results. Finally, since DHA tends to more intensely color skin that has thicker, more compact outer layers, it is important to wash the hands after applying product to avoid dark brown stained palms.

FORMULATION CHALLENGES

Given the potential cost, compatibility, and skin feel benefits of increased sunscreen efficiency, there have been a number of technologies developed in the past 10-plus years to improve sunscreen products. For example, the use of film formers, better wetting/spreading emollients, and shear-thinning rheology modifiers allow sunscreen products to spread more evenly and form a uniform film on the skin. A more uniform film leads to increased UV efficacy/efficiency by effectively reducing and/or eliminating "holes" in the product film. The use of combinations of UV filters in both the water and oil phases of emulsions provide increased efficacy/efficiency by ensuring that there are no unprotected areas in the product film. Another example is the identification/development of photostable sunscreen active combinations which allows lower concentrations of UV filters to be used to achieve a UV efficacy target. For systems that are not photostable, much higher concentrations of UV filters are needed to compensate for the loss of UV efficacy that occurs during product exposure to UV on the skin. Finally, the development of newer, more efficient and more photostable UV filters allows formulators to achieve a target UV efficacy with less sunscreen active. Reducing the concentration of UV filters may improve the product aesthetics with the potential for increasing compliance.

Improving Sunscreen Product Aesthetics

Based on the above discussion, the first and simplest strategy for modern sunscreen formulation must be to use a lower concentration and number of UV filters to achieve the target UV efficacy level or, in other words, identify the most efficient sunscreen systems. Beyond this, there are other approaches that are often utilized to manage the trade-offs of the various sunscreen actives. These include:

- The use of cosmetic powders to reduce the greasiness of the oily UV filters or solvents. These powders can absorb oily materials and give the product a drier skin feel.
- Adding oil-soluble film-forming polymers to thicken the oily sunscreen actives and solvents/emollients, thus reducing slick/oily/greasy feel on the skin. Such polymers are also important as they increase the efficiency/efficacy of the sunscreen product by improving uniform skin coverage or film.
- Incorporating silicone emollients to reduce the draggy, dry skin feel of zinc oxide and titanium dioxide sunscreen actives.
- Utilizing alternative product forms to minimize product skin feel negatives, such as using rub-free sprays.

It is these types of technologies, driving efficiency and promoting aesthetics, which have given birth to the new generation of sunscreens, allowing even products with SPF greater than 15 to be formulated as recreational as well as daily use products such as

moisturizers. Importantly, these optimized sunscreen products can have excellent aesthetics that improve compliance and afford greater protection.

REGULATORY ISSUES

In the U.S., sunscreen products are regulated by the Food and Drug Administration (FDA). Specifically, sunscreens are considered OTC drug products, required to abide by the monograph regulating such products. The OTC Drug Monographs establish conditions for safe and effective self-treatments. These are regulatory standards for marketing of non-prescription drug products not covered by New Drug Applications (NDAs). Products marketed in accordance with the monograph do not require FDA approval. An abbreviated chronology of the Sunscreen Monograph is presented in Table 3.

That sunscreens are considered drugs in the U.S. sets it apart form other regions of the world. The FDA considers cosmetics as "… articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance." In 1978, the FDA recognized that products intended to be used for prevention of sunburn or any other similar condition should be regarded as drugs. As such, in the Advanced Notice of Public Rule Making (ANPRM) it states that "[sunscreens] reduce by varying amounts the solar radiation absorbed by the skin and thereby affect the physiological response and extent of the erythemal reaction (redness) produced …" and as such fit the definition of a drug: "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

Since the publication of the ANPRM in 1978 up to the publication of the Final Rule in 1999 (19) and beyond for a total of 27-plus years, the Sunscreen Monograph has been discussed and commented on by interested parties including industry, academicians, practicing dermatologists and various trade associations (65). There has been extraordinary criticism of the agency ranging from being too slow to completely unresponsive. Perhaps the critics are right. However, it should be noted that there are diverse opinions on many key aspects of sunscreens including product testing and labeling, the knowledge that consumers don't apply enough product to achieve the labeled SPF, the absence of any meaningful and relevant acute endpoint for UVA protection, the need for sunscreens with unlimited SPF, i.e., beyond 100-plus, and what exactly such products are protecting against. This is compounded by the fact that there are sharp disagreements regarding how best to measure and label sunscreen products (see Sept. 2000 submissions to the FDA Sunscreen Docket 78N-0038). As such, it may not be surprising that the monograph has not been completed.

Beyond the monograph, there are other regulatory processes that can be followed in order to market a sunscreen product in the U.S. Options for marketing an OTC drug product besides the monograph include NDAs and the Abbreviated NDA (ANDA). An NDA is the same process that prescription drugs follow including the comprehensive safety and clinical testing. Approval is generally for a specific product including the 10–20 or so ingredients used to formulate a topically applied product. As such this approach is time consuming and costly and does not allow for minor reformulations of the product for marketing or other reasons. There are few sunscreen products which follow this process given the high cost in time and resources and the inflexible nature of this process.

Currently, there are several suppliers attempting to have specific UV filters added to the list of approved ingredients (Table 2). The Time and Extent Application (TEA) is being used. The purpose of TEA is to request that applicable conditions be considered for

Table 3 Abridged Chronology of FDA Sunscreen Monograph

Federal register (FR) notification	Date
Pursuant to the notice published in the FR requesting the submission of data and information on OTC topical sunscreen drugs	Dec 1972
Advisory review panel reviewed ingredients, claims, labeling, dosage, and warnings	
Advanced notice of proposed rule making (ANPRM)	Aug 1978
Establish conditions for the safety, effectiveness, and labeling of the OTC sunscreen drug products	
ANPRM—Extension of comment period (FR) to Dec 15, 1978	Dec 1978
Docket officially closed Dec 26, 1978	
Administrative record reopened	March 1980
FR announcement of public meeting held on Jan 26, 1988	Sept 1987
FR extended comment period for test procedures and related claims	May 1988
Tentative final monograph (TFM)	May 1993
Reflects tentative adoption of the ANPRM on the basis of the comments received and agency's independent evaluation	
FR announced public meeting to discuss UVA claims and testing	April 1994
FR amend TFM and reopen comment period	June 1994
FR announced a public meeting to discuss the photochemistry and photobiology of sunscreens	Aug 1996
FR amendment to TFM to include avobenzone	Sept 1996
Interim marketing was allow according to FR, April 1997	
FR amendment to TFM to include zinc oxide	Oct 1998
Final rule—sunscreen products monograph	May 1999
Completes the TFM except for certain testing issues such as UVA testing and labeling, which will be addressed later. UVA labeling may continue in accord with the TFM and its amendments	
FR extended effective date to Dec 2002 and reopened administrative record for public comment until Sept 2000	June 2000
FR suspended final rule indefinitely until comprehensive monograph developed	Dec 2001
FR technical amendment updates to incorporate USP names for four active ingredients, effective Sept 2002	June 2002

inclusion in the monograph. This is a two-step process: first is the submission followed by demonstration of general safety and effectiveness. The demonstration of general safety and effectiveness has, to date, been the limiting factor for TEAs.

Whereas the debate regarding sunscreens being cosmetics or drugs and the criticism of the Sunscreen Monograph and FDA will continue, it again is worthwhile pointing out that in the U.S. such a process works by necessity if nothing else.

SAFE SUN STRATEGY

Skin cancers and photoaging/chronic skin damage are recognized as consequences of solar UV exposure by government agencies and numerous professional organizations. These groups recommend strategies to reduce solar UV exposure (Table 4). Chief among the recommendations of any safe sun strategy is the use of sunscreen products.

American Academy of Dermatology (http://www.aad.org/)

The American Academy of Dermatology's Guidelines/Outcomes Committee has developed "Guidelines of Care for Photoaging/Photodamage." In these guidelines the committee states, "No credible scientific evidence contradicts the relation of sun exposure to the development of skin cancer and the undesirable results of photoaging and photodamage." The committee contends that a significant portion of the approximately $14 billion spent on cosmetics in the U.S. in 1996 was specifically spent to conceal the effects of photoaging and photodamage. An additional significant amount of money is spent on surgical and medical procedures. The committee believes that early recognition and treatment of photodamaged and photoaged skin will lead to a decrease in the incidence of premalignant and malignant skin lesions.

- Photodamage and photoaging are at least partially reversible with photoprotection, and the use of sunscreens that protect against solar UV is encouraged.

American Cancer Society (http://www.cancer.org)

In its efforts to educate the American public about the importance of prevention and early detection of nonmelanoma and melanoma skin cancers, the American Cancer Society discusses on its Web site the damage that UV can cause to skin and eyes, including the effects of photoaging.

The short-term results of unprotected exposure to UV rays are sunburn and tanning. The long-term effect of such damage is more serious. UV exposure that is intense enough to cause sunburn clearly increases the risk of developing skin cancers. And UV exposure can increase skin cancer risk even without causing sunburn. Long-term exposure can also cause premature changes in skin including:

- Aging
- Wrinkles
- Loss of elasticity
- Dark patches (lentigos, that are sometimes called "age spots" or "liver spots"
- Actinic keratoses.

Skin Cancer Foundation (http://www.skincancer.org/)

The Skin Cancer Foundation recently updated its brochure, "Simple Steps to Sun Safety," which states:

- Your skin is an excellent record keeper. Every moment in the sun adds up, accumulating like money in the bank. The payoff, however, is damage to the skin

Table 4 Safe Sun Guideline Practices

Minimize exposure to solar UV radiation, especially between the hours of 10:00 am and 3:00 pm DST

Wear protective clothing (e.g., wide-brimmed hats, sunglasses, long-sleeved shirts, and pants)

Always use sun protection while outdoors, including when near snow, water, sand, and at high elevations

Avoid artificial tanning devices, such as tanning booths and sunlamps

Use the UV index when planning outdoor activities

Apply sunscreens with an SPF greater than or equal to 15 daily

and possibly skin cancer. … Sunlight also causes wrinkling, blotching, drying, and leathering of the skin, making you look old before your time. The best defense, now, and for the future, is to limit time in the sun and protect yourself whenever you go outdoors.

American Society for Photobiology and European Society for Photobiology (http://www.pol-us.net/)

The American Society for Photobiology (ASP) is also "concerned with the interaction of light and living things" including the harmful effects of UV on humans. In its publication the *Light and Life* brochure, published "to inform government officials, students, and the general public about the science of photobiology," the ASP states:

- *Harmful effects of light*. Sunlight is implicated in several skin diseases, including premature aging of the skin and skin cancer. Skin sensitivity to sunlight is controlled by the genetic ability of an individual to produce melanin, the pigment that helps protect the skin from light-induced injury.
- *Photoprotection*. Both topical and systemic sunscreen agents prevent the acute and chronic effects of sunlight. They enable people to work outdoors and enjoy outdoor activities with reduced risk of sun-induced injury. The damage that absorbed light creates in the skin, such as the changes recognized as aging of the skin, is preventable by using new types of water- and sweat- resistant sunscreens.

Centers for Disease Control and Prevention (http://www.cdc.gov/)

The Centers for Disease Control and Prevention (CDC) has educational programs and recommendations that are targeted to apply "disease prevention and control, environmental health, and health promotion and education activities designed to improve the health of the people of the United States." On its Web site "Choose Your Cover," it specifically states:

- …excessive and unprotected exposure to the sun can result in premature aging and undesirable changes in skin texture. Such exposure has been associated with various types of skin cancer, including melanoma, one of the most serious and deadly forms.

National Institutes of Health/Environmental Protection Agency (http://www.nih.gov/)

In addition to the CDC, other government agencies including the National Institutes of Health (NIH) and the Environmental Protection Agency (EPA) have reiterated concern about the effect of UVA on the skin. The "MEDLINEplus Health Information" service of the U.S. National Library of Medicine and the National Institutes of Health states that

- …[s]unscreens help to prevent sunburn and reduce the harmful effects of the sun such as premature skin aging and skin cancer.

The EPA has related materials on its Web site to promote greater public awareness of the impact of UV exposure:

- Exposure to UV radiation from the sun can seriously harm human health. Mild exposure can lead to sunburn. More extended exposure to the sun may result in premature aging and discoloration of the skin and, ultimately, skin cancer. These

health effects have only been made more acute by the destruction of the ozone layer which protects the earth from the sun's UV radiation. … The EPA and other agencies also promote awareness of the dangers of sun exposure and the safety precautions such as minimizing exposure and using sunscreen.

CONCLUSIONS

Given the potential health benefits of sunscreens, it is perhaps not surprising that they have been referred to as the "ultimate cosmetic" (66). It is clear that exposure to solar UV damages human skin. This can be in the form of acute over-exposure resulting in sunburn or more subtle subclinical damage. In either case, repeated exposure to solar UV manifests as photoaging and skin cancers after many years. The molecular mechanisms of skin cancers and photoaging have been studied using human and animal models. More important, use of sunscreens protects against short-term markers of UV-induced skin damage and the molecular events believed to be responsible for skin cancers and photoaging. That is, based on experimental investigations, sunscreens or UV filters reduced molecular, biochemical, and clinical events associated with skin cancer and photoaging.

An international meeting with experts from around the world concluded that sunscreens were probably of benefit in reducing squamous cell carcinoma but there was not enough evidence supportive of protection against basal cell or melanoma skin cancers (67,68). Prospective clinical studies in areas of high incidence such as Australia (69,70) and Texas (71) clearly show the benefits of regular application of sunscreens. Demonstration of such effects in these relatively short duration studies, i.e., less than five years, are if nothing else encouraging.

The formulation of sunscreen products should be focused on improving compliance rather than increasing the Protection Factor of products. It is easy for sunscreen manufacturers to get caught up in the SPF horsepower race since consumers may purchase product based on the SPF number and physicians may recommend/prescribe products thinking that sunscreens are not applied at the proper dose and, as such, a higher SPF will compensate for this underdosing. However, as with any preventive therapy, compliance is the key and making products which are applied at the proper dose and reapplied should be the goal of manufacturers.

Also, sunscreen products need to protect against the breadth of solar UV and not simply short wavelengths. Presently, consumers purchase products which infer protection against harmful rays of the sun, i.e., SPF. As discussed, this does not ensure any protection against long wavelength UVA-I. Arguably, sunscreen manufacturers should *only* market products which protect against the breadth of solar UV. In the U.S., the FDA could ensure all products sold meet or exceed a single criteria to achieve a "broad spectrum" label such as recommended by the AAD (40) thereby ensuring consumers are fully protected by the sunscreen products purchased.

The public health message endorsed by numerous governmental and academic groups is that of a "safe sun strategy," which includes the daily use of a sunscreen at least SPF 15. It will be important to maintain this basic message and expand it to include sunscreen products that provide "broad spectrum" protection. This could be achieved by regulatory adoption of, and in vitro substrate spectrophotometric measure of UVA efficacy and a simple pass/fail label. As such, consumers could choose products which protect against the solar UV spectrum.

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10

Photoprotection and the Prevention of Photocarcinogenesis

Nathalie Nguyen and Darrell S. Rigel
*Department of Dermatology, New York University School of Medicine,
New York, New York, U.S.A.*

OVERVIEW

Exposure to ultraviolet (UV) energy leads to two significant types of skin problems—increased risk for the development of skin cancer and accelerated photoaging changes. At current rates, one in five Americans will develop a skin cancer of some sort during their lifetime, with over 1,000,000 new cases appearing this year alone in the U.S. The incidence of malignant melanoma is increasing faster than any other cancer in the United States. In 1935, the lifetime risk for an American developing invasive melanoma was one in 1500. In 2005, this risk was one in 62 for invasive melanomas and one in 34 if in situ melanomas are included. In addition, according to the World Health Organization, melanoma is increasing faster than any other malignancy worldwide. The economic magnitude of this public health problem is illustrated by the fact that costs associated with the treatment of skin cancers are over 500 million dollars annually in the U.S. alone (1). Therefore, the development and implementation of effective mechanisms that protect the skin from cancer-causing UV rays is critical.

Photoprotection is therefore focused on protecting the skin from the damage that occurs as a result of UV exposure. The approach to photoprotection focuses on a reduction in the overall exposure to sunlight, not to just a single component of it. To put the importance of photoprotection and skin cancer into perspective and to better understand the key associated issues, one needs to appreciate:

- The relationship of skin cancer and UV exposure
- Why recent changes have made this issue even more important,
- Current available agents and approaches,
- How effective these approaches are and can be,
- What can be done in the future to improve photoprotection effectiveness, and,
- What clinical recommendations can be made to patients to lower their future risks for photoaging and skin cancer.

Increasing awareness of the damaging effects of sunlight has led to an increased need for adequate photoprotection. Primary prevention to reduce the incidence of skin

cancer therefore includes a regimen consisting of effective sunscreen, protective clothing, and behavior modification.

RELATIONSHIP OF UV EXPOSURE TO SKIN CANCER DEVELOPMENT

The skin is the most exposed organ to environmental UV and to the associated sequellae (2). Exposure to UV radiation on the skin results in clearly demonstrable mutagenic effects. The p53 suppressor gene, which is frequently mutated in skin cancers, is believed to be an early target of UV radiation-induced neoplasm (3). Although there is no direct way that the active wavelengths for the development of skin cancer in humans can be determined, there is ample indirect evidence demonstrating probable ranges. In terms of SCC in albino hairless mice, the action spectrum has been determined to have a strong peak at 293 nm with secondary peaks at 354 and 380 (4). The primary wavelength influencing melanoma risk appears to be in the Ultraviolet B (UVB) (290–320 nm) range. However, studies in fish and opossums have also shown an increase in melanoma development when exposed to UVA wavelengths (5,6). Fair skinned individuals who are more sensitive to the effects of exposure at these wavelengths are at higher risk for the development of skin cancer (7). In addition, skin cancer rates are also elevated in persons with increased artificial UV exposure through tanning salons (8).

The amount of average annual UV radiation correlates with the incidence of skin cancer (9). There is a direct correlation with BCC and SCC incidence and latitude (10). Scotto et al. (11) demonstrated a strong inverse correlation between latitude and incidence of BCC and SCC for both men and women.

In terms of melanoma, the relationship is not as clear-cut. Incidence rates for melanoma correlate in a lesser way with latitude as that for NMSC but other factors may also be involved (12). Melanoma mortality rates in the U.S. and Canada have also been shown to directly correlate with ambient UV exposure (13). The correlation of melanoma incidence to UV radiation exposure is greater when ambient UVA (320–400 nm) radiation is also included (14). High-altitude regions tend to have a higher melanoma rate that may be related to the higher UV fluences noted at these sites (15). Melanoma risk has also been noted to be directly related to annual UV flux. Fears et al. (16) demonstrated that when lifetime residential history was coupled with levels of midrange UV radiation (UVB flux) to provide a measure of individual exposure to sunlight a 10% increase in annual UVB flux was associated with a 19% increased risk of melanoma. Even in women who could develop a deep tan, a 10% increase in hours spent outdoors was associated with 5.8% increase in melanoma incidence. The association between melanoma risk and average annual UVB flux was strong and consistent for men and women. However, some of the studies examining a latitudinal gradient for melanoma risk have been somewhat inconclusive (17). Although worldwide studies have only shown a weak correlation, the association of melanoma mortality in 1950–1967 with estimates of annual erythemal solar UVB dose across the U.S. and Canada demonstrated a stronger relationship (18).

The anatomic areas that skin cancer develops on appear to be somewhat related to the average amount of UV exposure to those sites (19). The density of skin cancer is highest on the sites that are virtually constantly exposed to UV, namely, the head and neck. Skin cancer rates are low in rarely UV-exposed areas such as the scalp in women and the buttocks in both sexes (20). Melanoma tends to be found more frequently in women on the legs where more average UV exposure may occur than in men (21).

The timing and periodicity of the UV exposure appears to be important in its effect on subsequent skin cancer risk. In terms of NMSC, the long-term chronic UV exposure

appears to increase the chance of developing this cancer. Acute intermittent UV exposure elevates subsequent melanoma risk (22). Migration studies have demonstrated sun exposure early in life appears to have a greater influence on subsequent skin cancer risk than does that at a later age. Persons born in the high-UV insolation environment of Australia have a increased risk for developing skin cancer compared to those born in Northern Europe who migrated at age 10 or older (23). Several additional studies from other countries have also found that risk of developing melanoma was less in those who migrated to the country 10 or more years after birth than were those who were born there (24,25). However, a recent study has now demonstrated that excessive UV exposure later in life may be equally important to that acquired earlier. Pfahlberg et al. (26) found a very similar upward gradient of melanoma risk in exposure categories related to the frequency of sunburns comparing UV exposure occurring before and after age 15. More than five sunburns doubled the melanoma risk, irrespective of their timing in life. This study did not provide supporting evidence for the existence of a critical age interval but rather suggested that the hazardous impact of UV exposure seems to persist lifelong.

SPECTRAL DIFFERENCES RELATED TO UV PHOTOCARCINOGENESIS

Most of the cutaneous damage resulting from radiation exposure occurs from the UV band. The shortest of the UV rays, UVC (100–280 nm), fail to penetrate the earth's ozone layer and thus exert little damage. UVB (290–320 nm) is responsible for most of the cutaneous changes induced by exposure to the sun. Known biochemical changes induced by UVB include alterations in DNA, RNA, and protein synthesis, induction of cyclobutyl pyrimidine dimers, and production of various cytokines (27,28).

In the past, UVA was believed to play less of a role in the pathogenesis of skin cancer and sun damage. The longer wavelengths of UVA (320–400 nm) allow deeper penetration into the skin. UVA induces an immediate pigment-darkening reaction and new melanin pigment formation (29). Earlier sun protection focused primarily on eliminating UVB exposure to the skin. UVA is now known to contribute to skin cancers by inducting DNA mutations directly as well as by augmenting damage incurred by UVB (30). Human skin exposed to UVA has altered expression of the p53 tumor suppressor protein (31). These mutations can be reduced by using UVA sunscreens, demonstrating that there is less p53 accumulation with better UVA protection (32).

PHOTOCARCINOGENESIS-DECREASING PHOTOPROTECTION MODALITIES

Protection from exposure to UV radiation leads to decreased risk for developing skin cancer. The use of multiple modalities leads to overlapping and more comprehensive spectral coverage. Therefore, optimal photoprotection includes regularly using sunscreen, wearing protective clothing, and avoiding UV exposure where possible. Recommendations for photoprotection which include all three of these approaches should be most effective in reducing skin cancer risk.

SUNSCREENS

Sunscreens work primarily through two mechanisms: (i) scattering and reflection of UV energy, and (ii) absorption of UV energy. Many current sunscreens contain ingredients that work through both mechanisms in terms of UV protection.

The most important assay for determining the effectiveness of a sunscreen is the sun protection factor (SPF). The SPF measures a sunscreen's ability to prevent development of erythema upon exposure to UV radiation, primarily UVB. The SPF value is defined as the ratio of the UV energy required to produce minimal erythema on protected skin to that required to produce the same erythema on unprotected skin in the same individual. For example, an individual using a sunscreen SPF 4 will take four times as long to develop cutaneous erythema when exposed to UVB radiation, as compared to when that individual has no protection. The Food and Drug Administration (FDA), which oversees the marketing and distribution of sunscreen products in the United States, mandates that a sunscreen agent must provide at least an SPF value of 2. Most commercially available sunscreen products have SPF values that exceed the minimum protection.

Despite attempts by the FDA to educate consumers and promote appropriate branding by manufacturers, sunscreen labeling has its limitations. The complicated names, as well as the variations in names for any given agent, may be overwhelming for the average consumer. The photostability of sunscreens is not quantified or labeled, and varies according to the chemical agent. The SPF value primarily measures a sunscreen's ability to protect against UVB radiation and does not adequately address the effects of UVA. In addition, SPF readings may also vary for a given agent depending on the light source (33).

Nonetheless, concerted efforts to educate consumers have been the goal of the FDA. Confusing terminology such as "sunblock" and "all-day protection" is prohibited. The term "waterproof" should be replaced with "water resistant." The FDA discourages the branding of a sunscreen product as having an SPF of greater than 30. Although values greater than 30 offer increased protection, the risks of providing consumers with a false of security encouraged the labeling to restrict labeling to 30-plus. For sunscreen products making the claim of "water resistant," the label SPF is the SPF value determined after forty minutes of water immersion, as determined by FDA guidelines.

TYPES OF SUNSCREENS AND MECHANISMS OF ACTION

Sunscreen use began in the early 20th century. Salicylates were the first agents used in sunscreen preparations, with the first reported sunscreen containing benzyl salicylate and benzyl cinnamate (34). In the 1940s, p-Aminobenzoic acid (PABA) was patented and incorporated into sunscreen formulations (35). Since its debut, various formulations and derivates of PABA have been introduced into the sunscreen market. Today, the FDA approves the use of 16 chemicals as defined sunscreen agents (Table 1).

Since no single agent effectively provides adequate protection from both UVA and UVB radiation, nearly all commercially available sunscreen products contain agents from both groups. Two or more sunscreen active ingredients may be combined with each other in a single product when used in the concentrations approved by the FDA for each agent. Each individual active ingredient must contribute a minimum SPF of at least 2 to the finished product, with the finished product having a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by two. Sunscreen agents are classified based on their method of protection. Chemical sunscreens

Table 1 FDA-Approved Active Ingredients for Sunscreens

Ingredient	UV absorbance
Aminobenzoic acid	UVB
Avobenzone	UVA
Cinoxate	UVB
Dioxybenzone	UVA, UVB
Homosalate	UVB
Methyl anthranilate	UVA
Octocrylene	UVB
Octyl methoxycinnamate	UVB
Octyl salicylate	UVB
Oxybenzone	UVA, UVB
Padimate O	UVB
Phenylbenzimidazole sulfonic acid	UVB
Sulisobenzone	UVA, UVB
Titanium dioxide	Inorganic
Trolamine salicylate	UVB
Zinc oxide	Inorganic

Source: From Ref. 36.

absorb UV radiation while physical blockers act as particulate matters that reflect and scatter incident light.

CHEMICAL SUNSCREENS

Chemical sunscreen agents protect the skin by absorbing UV energy and transforming it into heat energy. These compounds absorb UV radiation and convert the energy into longer wave radiation. The sunscreen chemical is excited to a higher energy state from its ground state. As the excited molecule returns to the ground state, energy is emitted that is lower in magnitude than the energy initially absorbed. This energy is emitted in the form of longer wavelengths, typically mild heat radiation.

These synthetically derived compounds can be broadly categorized into two groups: UVB (290–320 nm) and UVA (320–400 nm) absorbing chemicals. Sunscreen chemicals are generally aromatic compounds conjugated with a carbonyl group (37). Chemical sunscreens can be classified based on their chemical properties, and each class has its own characteristic absorption spectra (Table 2).

PABA was a widely used sunscreen in the 1950s and 1960s. Several of the properties pertaining to the limitations of PABA can be attributed to its chemical structure: amino and carboxylic acid groups in a *para*-orientation on a benzene nucleus. The highly polar nature of PABA made this agent extremely water soluble, but the increased hydrogen bonding between molecules also promoted a crystalline physical state (39). This led to some difficulty in manufacturing a solvent that ensured continuous dissolution of PABA. The amine and carboxyl groups also made the PABA molecule sensitive to pH changes, and therefore somewhat labile in its effectiveness as a UV chemical absorbing agent. The molecule's lack of stability also led to changes in the color of the product when exposed to air.

Glycerol PABA was subsequently developed to protect the carboxylic acid group from pH changes and therefore was slightly more stable than the original PABA formulation. Other preparations attempted to protect both the carboxyl and the amine

Table 2 Sunscreen Agents and Their UV Protective Wavelengths

Sunscreen	Range of protection (nm)	Maximal effect of protection (nm)
PABA and PABA esters		
PABA	260–313	283
Padimate O	290–315	311
Padimate A	290–315	309
Glycerol aminobenzoate	260–313	297
Cinnamates		
Octyl methoxycinnamate	280–310	311
Cinoxate	270–328	290
Salicylates		
Homosalicylate	290–315	306
Octyl salicylate	260–310	307
Triethanolamine salicylate	269–320	298
Octocrylene	287–323	303
Etocrylene	296–383	303
Benzophenones		
Oxybenzone	270–350	290,325
Dioxybenzone	206–380	284,327
Sulisobenzone	250–380	286–324
Menthylanthranilate	200–380	336
Dibenzoylmethanes		
Tert-butylmethoxydibenzoylmethane (Parsol)	310–400	358
4-isopropyldibenzoylmethane (Eusolex)	310–400	345
Trometrizole trisiloxane, terephthalylidene dicamphor sulfonic acid (Mexoryl XL)	300–400	328

Source: Adapted from Ref. 38.

group. Padimate O (N, N-dimethyl PABA octyl ester), addressed many of the original structure's limitations and became a widely used sunscreen agent. Both the amino and the carboxyl groups are protected, making Padimate O less sensitive to pH changes. This new chemical structure also resulted in decreased intermolecular hydrogen bonding, resulting in a sunscreen agent that is a liquid instead of a crystalline solid.

The original PABA fell out of favor largely because of staining and allergic contact reactions. There is a much higher presence of contact and photocontact allergy to PABA than to other sunscreening agents (40). The PABA derivates also were reported to induce contact sensitization. Sensitization to PABA showed strong reactions to benzocaine, suggesting that reports of glycerol PABA allergy may in fact have been due to impurities in glyceryl PABA preparations (41). Other PABA derivates such as Padimate A, and to a lesser extent, Padimate O, have also been reported to cause sensitization or photocontact sensitization. Padimate A was also found to cause phototoxicity and is no longer used in the United States (42).

Salicylates were the first UV chemical absorbers used in commercially available sunscreen preparations. In contrast to the *para*-distribution of the carboxyl and amine groups, the salicylates are *ortho*-distributed (the carboxyl and amine groups are on neighboring carbon atoms on the benzene ring). This spatial arrangement allows hydrogen bonding within the molecule itself, leading to a UV absorbance of about 300 nm (43). This intramolecular hydrogen bonding results in increased molecule stability, less interaction

with other compounds, and good overall safety record. The salicylate group of sunscreen agents include octyl salicylate and homomenthyl salicylate.

Cinnamates are effective sunscreen agents with a peak absorption wavelength of about 305 nm. They are chemically related to balsam of Peru, coca leaves, cinnamic aldehyde, and cinnamic oil. The chemical structure of the cinnamates, as a group, makes the molecule insoluble to water, requiring more frequent reapplication of the preparation. Contact dermatitis to the cinnamates and cross-sensitization to structurally related products have been reported.

Benzophenone derivates and anthranilates are effective at absorbing UVA radiation. Although the primary protective range for benzophenone is in the UVA range, a secondary protective band is also noted in the UVB range. The most commonly used benzophenone agents are oxybenzone and dioxybenzone. Although these ingredients are much less allergenic than PABA, they do nonetheless still carry a risk of photocontact and contact allergy. Anthranilates, such as menthylanthranilate, provide low-level, yet broad-spectrum coverage. They are commonly added to sunscreens to augment protection. Camphor is an agent widely used in Europe, but not approved for use in the United States. They are effective UVB-absorbing agents.

Dibenzoylmenthanes are a relatively new group of sunscreen agents and are especially effective at offering protection against UVA radiation. Tert-butylmethoxy-dibenzoylmethane (Avobenzone, Parsol 1789) is approved for use in the United States, while isopropyldebenzoylmethane (Eusolex 8020) has been widely used in Europe. The latter has been associated with a high incidence of contact dermatitis, and has not been approved in the United States. In a study of 19 patients with positive photopatch tests to sunscreens, eight showed positive reactions to butyl methoxy dibenzoylmethane (44).

PHYSICAL SUNSCREENS

Physical sunscreens are particles that scatter and reflect UV energy back into the environment. In sufficient quantities, they will serve as a physical barrier to incident UV and visible light. Their popularity has grown in recent years due primarily to their low toxicity profile. These agents are fairly photostable and have not been shown to induce phototoxic or photoallergic reactions. They are also extremely effective in protecting against both UVA and UVB. The most common particulate sunscreen agents are titanium dioxide and zinc oxide.

Early formulations of physical sunscreen agents were not widely accepted because the particulate matters had to be incorporated in high concentrations, resulting in an opaque film on the skin in order to achieve adequate protection. This was often not cosmetically acceptable. Newer formulations which provide "micronized" formulations give rise to a more translucent appearance, and allow for adequate protection with improved cosmetic results. Comparison between zinc oxide and titanium dioxide showed that zinc oxide is superior for UVA protection in the 340–380 nm range and tends to be less pasty on the skin (45).

PHOTOCARCINOGENESIS REDUCTION BY WEARING CLOTHING

Clothing specifically designed to avoid sun exposure should be incorporated into a comprehensive sun-protection program. Transmission of UV radiation through fibers depends on the radiation that is absorbed by the fiber and scattered by the fiber. Polyester

provides more protection than cotton. The cover factor, defined as the ratio of closed spaces to open spaces in the fabric, is the most important factor in determining the photoprotection of the fabric (46). Darker colors provide better protection than lighter colors. To enhance the ultraviolet protection factor (UPF) of clothes, UV-absorbing laundry detergents have been shown to increase the UPF of a cotton T-shirt by 400% (47).

BEHAVIOR MODIFICATION

Sunscreens should be used in conjunction with daily sun-safety behavior in order to achieve maximal photoprotection. Avoidance of UV radiation to the skin is the ultimate goal. Hats, umbrellas, and protective clothing are easy ways to protect the skin. Daily use of sunscreens with frequent reapplication should be a part of the daily routine. Sunbathing and tanning salons should be strictly avoided.

Sun avoidance is easy to advocate, but in reality, difficult to practice. Sunscreen is the most common sun-protection behavior practiced, yet only about 40% of British colleges students admitted to daily sunscreen use (48). Within the adult age range, women and people with sensitive skin were most likely to be using skin protection (49). However, women were also more likely than men to sunbathe deliberately and to use sun-tanning booths. Adolescents have the lowest skin protection rates of all age groups. Less than one-third of U.S. youths, ages 11–18, practice routine sun protection on sunny days during the summer (50). Furthermore, adolescents are increasingly using tanning salons. In a study of 1274 U.S. adolescents, 12% of boys and 42% of girls had tanned indoors (51).

EFFECTIVENESS OF PHOTOPROTECTION

Primary prevention programs for skin cancer that are focused on lowering UV exposure appear to be having a positive effect in lowering skin cancer incidence (52). Persons with a prior history of BCC had fewer subsequent BCCs develop if they protected themselves from UV exposure (53).

Reduction in sun exposure by daily use of a sunscreen may reduce risk of SCC (54). A meta-analysis of 11 studies of melanoma risk and sunscreen usage showed only a small protective advantage (55). However, when evaluating only the more recent studies where high-SPF sunscreens were available, there appeared to be a protective effect and other inherent flaws associated with retrospective studies which may be responsible for protection not being noted (Table 3) (70).

PHOTOPROTECTION AND VITAMIN D

Sunlight is important in the generation of Vitamin D in the skin. In addition to eating foods containing vitamin D, an essential hormone for normal bone development, sunlight exposure also plays a critical role in supplying the human body with its necessary dose of vitamin D (71). Sunlight converts cutaneous stores of 7-dehydrocholesterol (provitamin D3) to previtamin D3 (precholecalciferol) and then to vitamin D3 (cholecalciferol). Vitamin D3 is also the form obtained though ingestion of foods. Once in the body, vitamin D3 is hydroxylated first in the liver to 25-hydroxyvitamin D (25-OHD), and then subsequently hydroxylated again to the active form, 1,25-dihydroxdyvitamin D [1,25-(OH)2D], by the kidneys. It should be noted that 25-OHD is a measure of body stores of Vitamin D.

Table 3 Studies Evaluating Protective Effects of Sunscreens on Melanoma

Study	Interval of sunscreen use examined	Findings
Klepp 1979 (56)	1974–75	Increased MM in users
Graham 1985 (57)	1974–80	NS
Herzfeld 1993 (58)	1977–79	NS
Beitner 1990 (59)	1978–83	Increased MM in a subset of users
Green 1986 (60)	1979–80	Protective for MM
Holman 1986 (61)	1980–82	NS
Osterlind 1988 (62)	1981–85	NS
Holly 1995 (63)	1981–86	Protective for MM
Westerdahl 1995 (64)	1988–90	Increased MM in users
Rodenas 1996 (65)	1989–93	Protective for MM
Autier 1995 (66)	1991–92	Increased MM in users
Espinosa 1999 (67)	1994–97	Protective for MM
Naldi 2000 (68)	1994–98	NS
Westerdahl 2000 (69)	1995–97	Increased MM in a subset of users

Abbreviation: NS, not significant.

Because sunlight is considered to be the most important source of vitamin D, there has been concern that photoprotection may, in fact, be contributing to its deficiency. Vitamin D deficiency increases the risk of bone disease, muscle weakness, and possibly certain types of cancer (72,73). In one study, the application of a sunscreen was shown to reduce the skin's ability to synthesize vitamin D3 (74). 25-hydroxy vitamin D levels have also been shown to be reduced with chronic sunscreen use (75). The active form of vitamin D, 1,25-dihydroxyvitamin D, was shown to be lower in patients using sunscreen compared to a placebo group who did not use sunscreen (76). Although values were lower for the sunscreen group, they still remained within the normal range. However, other studies have reported conflicting findings (77).

Studies of individuals who consistently sustain a lifestyle involving photoprotection have failed to show clinical evidence of vitamin D deficiency. A study of eight xeroderma pigmentosum patients showed that, although 25-OHD levels were low normal, the 1,25(OH)2D levels were normal (78). The lack of seasonal variation in 25-OHD levels showed that the patients received the same amount sunlight (or lack thereof) throughout the year. The evidence provided in this study is supported by epidemiologic studies of sunscreen use, which failed to show that regular sunscreen use led to vitamin D deficiency (79).

Recent media attention to the issue of vitamin D and sunlight reinforces the need for patient education. Although sunlight exposure is important as a source of vitamin D, photoprotection does not result in vitamin D deficiency. Furthermore, the use of tanning beds should not be used as a source of vitamin D. Patients concerned about their vitamin D levels should be encouraged to eat foods rich in vitamin D, such as fish liver oils, egg yolks, and milk fortified with vitamin D or take oral vitamin D supplements.

PATIENT RECOMMENDATIONS AND FUTURE DIRECTIONS

There appears to be a direct relationship between UV exposure and the development of photocarcinogenesis. Based upon the best current information available, a regimen of overall photoprotection which includes protective clothing, avoiding midday sun, and

regular use of broad-spectrum high SPF sunscreen should provide significant protection and appears to be reducing melanoma incidence rates. This is the current recommendation of the American Academy of Dermatology, Skin Cancer Foundation, and other major international organizations, and it is also the recommendation that is best supported by the existing data. There is no reason to recommend intentional sun exposure or decreased photoprotection to increase vitamin D levels as adequate incidental UV exposure occurs in day-to-day activities. Hopefully, we will have even more definitive answers to questions related to the optimization of effectiveness of sunscreens and other forms of photoprotection and for reducing the risk from exposure to UV radiation as improved photoprotective agents, strategies, and methods are developed in the future.

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11
Anti-aging Skin Care Formulations

Donald L. Bissett
P&G Beauty, Miami Valley Innovation Center, Cincinnati, Ohio, U.S.A.

INTRODUCTION

There are many cosmetic materials that are claimed to have anti-aging effects when used topically. Since there are so many of these materials and since the term anti-aging is very broad (in terms of prevention vs. improvement and the wide array of possible benefit areas such as wrinkling, sagging, texture, sallowness, hyperpigmentation, etc.), this relatively short chapter must necessarily be selective in its scope. Thus, this discussion will focus on only a few classes of cosmetic agents which are reported to have bio-activity to provide wrinkling and/or sagging improvement (i.e., repair or reversal). Particular attention will be directed to those materials within these classes for which there are readily available or published clinical data to support their reported skin appearance improvement benefits.

VITAMIN A

Forms

There are several forms of vitamin A that are used cosmetically. The most widely utilized ones include retinol, retinyl esters (e.g., retinyl acetate, retinyl propionate, and retinyl palmitate), and retinaldehyde. Through endogenous enzymatic reactions, all of these are converted ultimately to trans-retinoic acid (trans-RA), which is the active form of vitamin A in skin. Specifically, retinyl esters are converted to retinol via esterases. Retinol is then converted to retinaldehyde by retinol dehydrogenase. And finally retinaldehyde is oxidized to RA by retinaldehyde oxidase.

Mechanisms

Since trans-RA is the active form of vitamin A in skin, the abundant published literature on the former is applicable to this discussion. Trans-RA interacts with nuclear receptor proteins described as RA receptors and retinoid X receptors, which can form heterodimer complexes. These complexes then interact with specific DNA sequences to affect transcription, to either increase or decrease expression of specific proteins/enzymes (1). Using genomic methodology, we have observed that the expression of over 1200 genes is

significantly affected by topical retinoid treatment of photoaged human skin (unpublished observations). Many of these changes can be ascribed, at least on some level, as being normalization of the altered skin conditions that occur with aging (induced by both chronological and environmental influences such as chronic sun exposure). Some specific changes induced by retinoid that are likely relevant to skin anti-wrinkle benefits are those that result in thicker skin to diminish the appearance of fine lines and wrinkles, e.g., increased epidermal proliferation and differentiation (increased epidermal thickness), increased production of epidermal ground substance [glycosaminoglycans (GAGs) which bind water, increasing epidermal hydration and thickness], and increased dermal production of extracellular matrix components such as collagen (increase dermal thickness) (2).

In addition to stimulation of events in skin such as those mentioned above, retinoids can also have an inhibitory effect on other tissue components. For example, retinoids are reported to inhibit production of collagenase (3). And while retinoid will stimulate production of ground substance (GAGs) in epidermis, it will inhibit production of excess ground substance in photoaged dermis (Fig. 1). While a low level of GAGs are required in the dermis for normal collagen structure and function, excess dermal GAGs are associated with altered dermal collagen structure and wrinkled skin appearance in photoaged skin (4) and in the Shar Pei dog (5). Reduction in this excess is associated with reduced skin wrinkling (6,7).

Since at least some of the epidermal effects of topical retinoid (e.g., epidermal thickening) (8) occur relatively rapidly (days) after initiation of treatment, some skin benefits (e.g., diminution of fine lines) can be realized quickly. The dermal effects likely occur on a much longer time frame (weeks to months) such that reduction in skin problems like wrinkles require much longer time frames (weeks to months) (2).

Efficacy

While much of the substantial literature on the improvement of skin wrinkles by topical retinoids is focused on trans-RA, there are also data available on the vitamin A compounds which are used cosmetically. Since retinoids are irritating to skin, defining skin-tolerated doses clinically is a key step in working effectively with these materials. Retinol is better
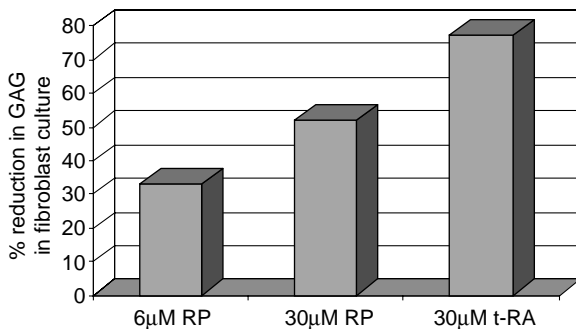
Figure 1 Retinoids reduce excess dermal GAGs. In cell culture, using fibroblasts from an old donor (57 years old), there was a two- to three-fold increase in GAGs (measured as hyaluronic acid) versus from a young donor (neonatal). The treatments were effective in reducing the excess GAG level. *Abbreviations*: RP, retinyl propionate; t-RA, trans-retinoic acid.
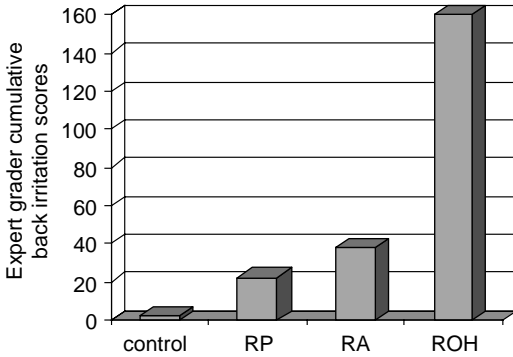
Figure 2 Retinoid irritation in cumulative human back irritation testing (double-blind, vehicle-controlled, randomized study; daily patching for 20 days, under semi-occluded patch, n=45; 0–3 irritation grading). Doses and abbreviations used are: 0.09% RP (retinyl propionate), 0.086% RA (retinyl acetate), and 0.075% ROH (retinol). RP and RA were significantly less irritating than ROH, and RP was less irritating than RA.

tolerated by the skin than trans-RA (2). In our testing we noted that retinyl propionate is milder to skin than retinol and retinyl acetate (Fig. 2).

Since retinoids in general tend to be fairly potent, topical doses of less than 1% are generally sufficient to obtain significant effects. At low doses, in double-blind, split-face, placebo-controlled facial testing (12-week duration), both retinol and retinyl propionate have been shown to be significantly effective in reducing facial hyperpigmentation and wrinkles across the study (Fig. 3). Determination of treatment effects was based on quantitative computer image analysis and blinded expert grading of high resolution digital images.
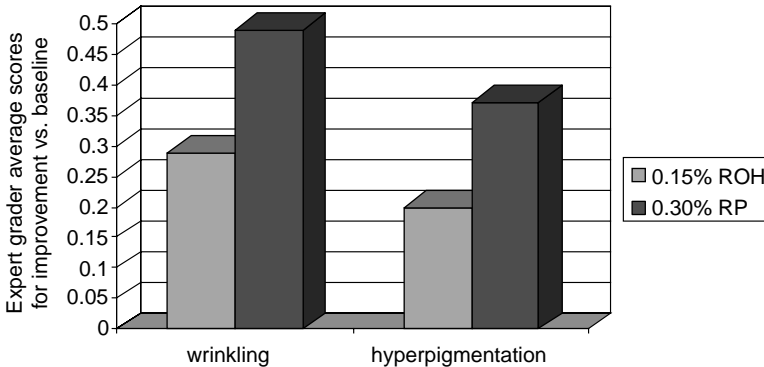
Figure 3 Reduction in wrinkles and hyperpigmentation in a 12-week clinical study (double-blind, left-right randomized, split-face, placebo vehicle-controlled study with once daily application, n=52–56 per product). Evaluation for reduction versus baseline in wrinkling and hyperpigmentation was done by three independent expert graders (0–4 grading scale) on blind-coded images after four, eight, and 12 weeks of treatment. The grader scores at each time point were averaged. There were significant effects for both treatments across the study. The data presented here are averages for all three time points. The low irritation of RP permits use of higher levels to achieve greater effects without significant negative aesthetic issues.

There are also clinical studies published on other retinoids. Retinyl palmitate has very low irritation potential and is effective if tested at a very high dose such as 2% (9). There are also several references describing the clinical efficacy of retinaldehyde, typically at a dose of 0.05% (10–12). However, retinaldehyde has irritation potential similar to retinol (13).

Product/Formulation Challenges

There are two primary challenges in working with retinoids. One is their tendency to induce skin irritation (as noted above) which negatively affects skin barrier properties. While high doses will provide ever greater skin aging improvement, the associated irritation tends to define an upper concentration limit where they can be used practically. While the skin may have some capacity to accommodate to retinoid treatment to yield less irritation, it is not completely eliminated even with long-term use, as demonstrated by evaluation of skin barrier function (Fig. 4). Mitigation of the irritation may be managed to some extent with appropriate formulation to meter delivery into the skin, use of retinyl esters which are less irritating than retinol (as noted above), or inclusion of other ingredients (e.g., those with anti-inflammatory activity) to counter this issue.

The second key issue is instability, especially to oxygen and light. Thus, to ensure stability of retinoid in the finished product, formulation and packaging must be done in an environment that minimizes exposure to oxygen and light. The final product packaging also ideally needs to be opaque and oxygen impermeable, including use of a small package orifice to reduce oxygen exposure once the container is opened. In addition, a variety of other strategies can be employed, e.g., encapsulation of the retinoid and inclusion of stabilizing antioxidants.

VITAMIN B3

Forms

There are three primary forms of vitamin B3 that have found utility in skin care products: niacinamide (*aka* nicotinamide), nicotinic acid, and nicotinate esters (e.g., myristoyl nicotinate, benzyl nicotinate).
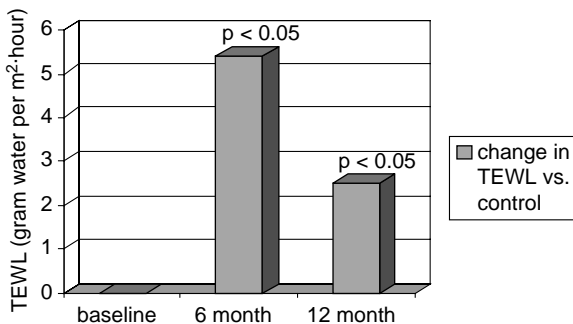
Figure 4 Effect of topical 0.05% trans-retinoic acid on skin barrier as determined by transepidermal water loss (TEWL). Although the skin becomes more tolerant of topical retinoic acid, even after 12 months of treatment there is still significant elevation of TEWL above baseline.

Mechanisms

Vitamin B3 serves as a precursor to a family of endogenous enzyme co-factors, specifically nicotinamide adenine dinucleotide (NAD), its phosphorylated derivative (NADP), and their reduced forms (NADH, NADPH), which have antioxidant properties. These co-factors are involved in many enzymatic reactions in the skin, and thus have potential to influence many skin processes (14). This precursor role of vitamin B3 may thus be the mechanistic basis for the diversity of clinical effects observed for a material such as niacinamide. While precisely how the dinucleotide co-factors might contribute to all these effects has not been elucidated, several specific actions of niacinamide have been described (14–19). For example, topical niacinamide has the following effects:

- Niacinamide inhibits sebum production, specifically affecting the content of triglycerides and fatty acids. This may contribute to the observed reduction in skin pore size and thus improved skin texture (a component of texture being enlarged pores).
- Niacinamide increases epidermal production of skin barrier lipids (e.g., ceramides) and also skin barrier layer proteins and their precursors (keratin, involucrin, filaggrin), leading to the observed enhancement of barrier function as determined by reduced transepidermal water loss (TEWL). This improved barrier also increases skin resistance to environmental insult from damaging agents such as surfactant and solvent, leading to less irritation, inflammation, and skin redness (e.g., facial red blotchiness). Since inflammation is involved in development of skin aging problems, the barrier improvement may contribute to the anti-aging effects of topical niacinamide. The anti-inflammatory and sebum reduction effects of niacinamide likely contribute to the anti-acne effect reported for this material (20).
- Niacinamide and its metabolite 1-methyl nicotinate have been reported (21,22) to have anti-inflammatory properties (e.g., inhibition of inflammatory cytokines).
- Niacinamide increases production of collagen which may contribute to the observed reduction in the appearance of skin wrinkling.
- Niacinamide reduces the production of excess dermal GAGs (glycosaminoglycans). In cell culture testing, as noted above for retinyl propionate, 0.5 mM niacinamide reduced excess GAG production by 15%.
- Niacinamide inhibits melanosome transfer from melanocytes to keratinocytes, leading to reduction in skin hyperpigmentation (e.g., hyperpigmented spots).
- Niacinamide inhibits skin yellowing. A contributing factor to yellowing is protein oxidation (glycation; Maillard reaction), which is a spontaneous oxidative reaction between protein and sugar (23–25), resulting in cross-linked proteins (Amedori products) that are yellow-brown in color. These products accumulate in matrix components such as collagen that have long biological half-lives (26,27). Niacinamide has been separately reported (28,29) to have anti-glycation effects.

Since nicotinic acid and its esters are also precursors to NAD(P), they would be expected to provide these same benefits to skin. Nicotinic acid and many (if not all) of its esters (following in-skin hydrolysis to free nicotinic acid) also stimulate blood flow, leading to increased skin redness or a flush response (30).

Efficacy

As representative for the vitamin B3 family of compounds, there are several published reports on the diversity of clinical effects of topical niacinamide (14–18). These data
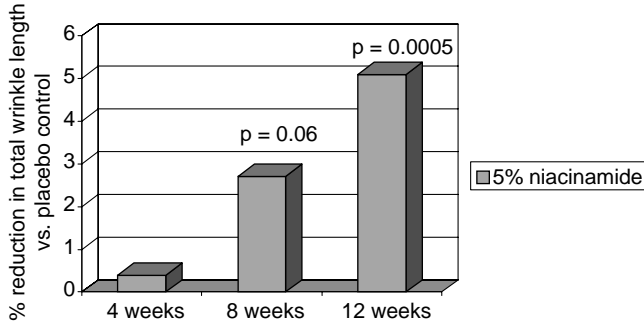
Figure 5 Topical 5% niacinamide reduces fine lines/wrinkling in facial skin. Subjects were female Caucasians (n=50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

were obtained from double-blind, placebo-controlled, left-right randomized studies. For example, topical niacinamide has been shown to reduce skin fine lines/wrinkling (Fig. 5). The effect increases over time and is significant after eight to 12 weeks of treatment. Topical niacinamide also improves other aspects of aging skin, such as reduction in sebaceous lipids (oil control) and pore size, which likely contribute at least in part to improved skin texture (Fig. 6). Additionally, niacinamide improves skin elastic properties as demonstrated for two parameters of skin elasticity (Fig. 7). Beyond these effects, there is also improvement in appearance of skin color (reduction in hyperpigmented spots and reduced skin yellowing) as noted above. Fairly high doses (2–5%) of vitamin B3 have been used to achieve desired benefits. However, since there is very high tolerance of the skin to niacinamide even with chronic usage, high doses can be used acceptably. In fact, as noted above, since topical niacinamide improves skin barrier, it actually increases the skin's resistance to environmental insult (e.g., from surfactant) and reduces red blotchiness (Fig. 8).

Some data on myristoyl-nicotinate have been presented (31) to suggest that a similar broad array of benefits occurs with this agent when used topically (1–5% doses). Clinical data for topical nicotinic acid and other esters are not available.
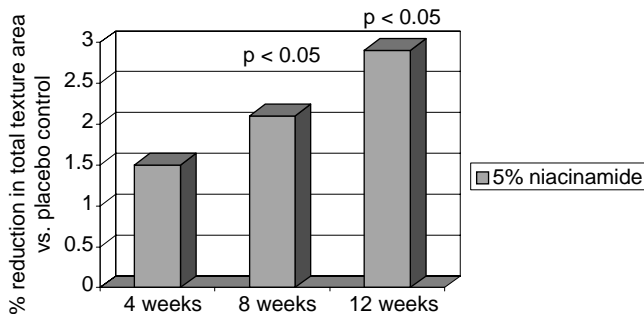
Figure 6 Topical niacinamide improves skin surface texture. Subjects were female Caucasians (n=50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

(A)

(B)
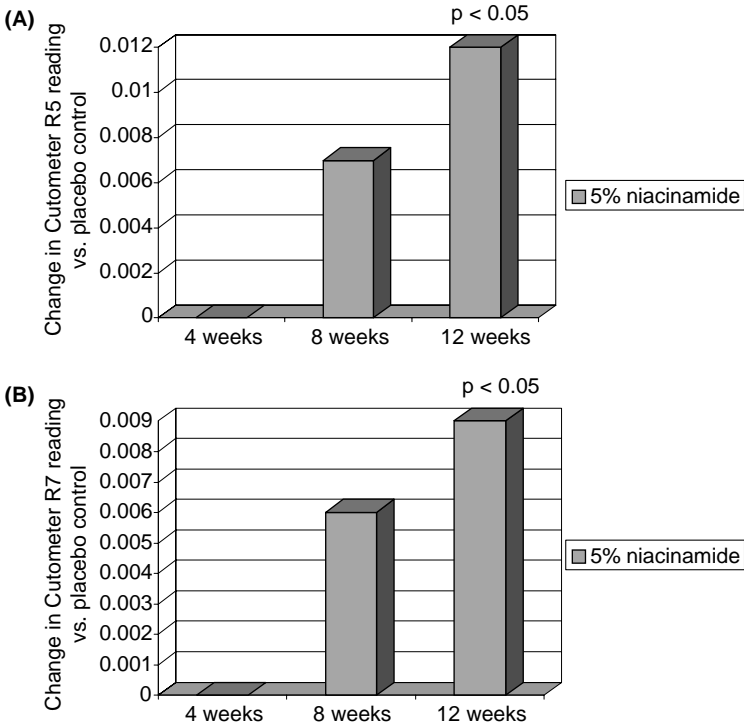
Figure 7 Topical 5% niacinamide improves skin elasticity. Subjects were female Caucasians (n=50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial). (**A**) Effect on R5 parameter (measure of viscoelastic properties). (**B**) Effect on R7 parameter (measure of elastic recovery).

Product/Formulation Challenges

The key challenge for working with niacinamide and nicotinate esters is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing) response (30). While a little skin redness (increased skin "pinkness") may be a
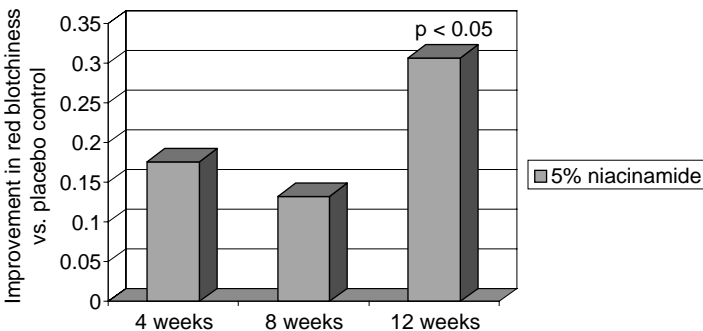
Figure 8 Niacinamide is well tolerated by the skin and even reduces facial skin red blotchiness. Subjects were female Caucasians (n=50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

desired effect, the flushing response among individuals is highly variable in terms of dose to induce it, time to onset of the response, and duration of response. Additionally, the flushing can also have associated issues such as burn, sting, and itch, particularly under cold and/or dry conditions. To avoid hydrolysis, formulating in the pH range of 5 to 7 is preferred. This flushing issue also requires that the purity of the raw material (e.g., niacinamide) be very high to minimize any contaminating free acid.

For the nicotinate esters, there are many commercial options. Many of them unfortunately are readily hydrolyzed to nicotinic acid on or in the skin such that flushing responses occur rapidly (within seconds/minutes) even at very low concentrations (<1%). The longer chain esters (e.g., myristoyl-nicotinate) apparently are more resistant to this hydrolysis and thus appear to be more suitable for use topically.

VITAMIN C

Forms

Of the many forms of this vitamin, some of the more commonly used are ascorbic acid, ascorbyl phosphate (typically as the magnesium and sodium salts), and other ascorbate derivatives (e.g., ascorbyl palmitate, ascorbyl glucoside).

Mechanisms

Vitamin C is well known as an antioxidant and has been utilized as a skin lightener (e.g., via tyrosinase inhibition and/or its antioxidant effect). It also has been reported to have anti-inflammatory properties since it reduces the erythema associated with post-operative laser resurfacing (32). In addition, ascorbic acid also serves as an essential co-factor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for post-translational processing in collagen (Types I and III) biosynthesis (33–36). Thus, by stimulating these biosynthetic steps, ascorbic acid will increase the production of collagen which will lead to wrinkle reduction as discussed above.

While the ascorbic acid derivatives may possess some properties of the free acid (e.g., antioxidant), hydrolysis of the derivatives would be required for the increased collagen production effect since the acid is the active co-factor. Demonstration of the hydrolysis of all these derivatives in skin has not been well documented.

Efficacy

There are several published studies discussing the anti-aging benefit of ascorbic acid. The reported doses of vitamin C tested are fairly high, and the base sizes are relatively small (n≤23). Some of the studies address ingredient oxidative stability, a particular challenge with this form of vitamin C. In oil-in-water emulsion, loss of nearly half of the ascorbic acid in a month is typical (37). To achieve stability, these authors used oxygen impermeable aluminum tube packaging which reduced ascorbic acid loss to less than 10%. After one week of topical treatment of human skin, there was significant reduction of UVA-induced oxidation by 3% ascorbic (41% reduction), whereas the reduction by 3% sodium ascorbyl phosphate was smaller (16%) and not significant. In a double-blind, placebo-controlled, split-face 12-week study (37), stabilized 3% ascorbic acid applied topically (n=23) was found to be well tolerated by the skin and reduced facial wrinkles as determined by skin replica analysis (Fig. 9).
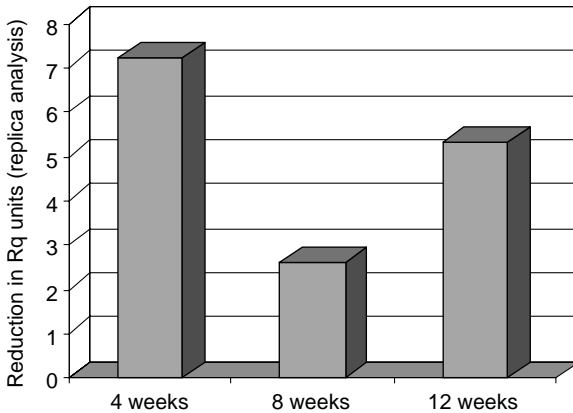
Figure 9 Facial wrinkle reduction (skin replica analysis) by topical 3% ascorbic acid.

In another double-blind, placebo-controlled, split-face 12-week study (38), 17% vitamin C (10% as ascorbic acid and 7% as tetrahexyldecyl ascorbate; n=10) in an anhydrous gel was applied topically. Based on dermatologist grading, there was reduced facial photoaging. From histological assessment of biopsy specimens, there was improvement in the collagen (increased Grenz zone). In a third study (39), topical 5% ascorbic acid (n=20, 6 months) improved photodamaged forearm and upper chest skin based on dermatologist scores, skin surface replicas, and biopsy specimen analysis (improvements in elastin and collagen fiber appearance). And lastly, a three-month study (40) of a stabilized ascorbic acid formulation (specific concentration and pH not specified, but likely approximately 10% ascorbic acid at low pH) revealed improvement in facial skin based on dermatologist grading and facial image analysis. However, this formulation led to instances of aesthetic issues for test subjects (sting, erythema, dryness) which may have contributed to the very high drop-out rate in this study (started with n=28, with n=19 finishing the study).

Product/Formulation Challenges

The key challenge with vitamin C compounds in general is stability (oxygen sensitivity), particularly with ascorbic acid. Not only does oxidation lead to loss of the active material, there is also rapid product yellowing (an aesthetic negative for the consumer). Various stabilization strategies can be attempted to address the issue, such as exclusion of oxygen during formulation, oxygen impermeable packaging, encapsulation, low pH, minimization of water, and inclusion of other antioxidants. In spite of all those approaches, in general ascorbate stability remains a challenge, and some of these approaches (e.g., very low pH) can lead to unwanted aesthetic skin effects as noted above.

For the ascorbyl phosphates (Mg and Na salts), the resulting high content of salt in product can dramatically impact the thickener system, requiring increased use of thickener ingredients. These ascorbate derivatives are also considerably more expensive than other ascorbate compounds.

Another challenge is skin delivery. Ascorbic acid's penetration across skin is in general poor (typically less than 1% of the topical dose entering skin). For the phosphate derivates of ascorbate, skin penetration can be an even greater challenge due to the

negative charges on the phosphate moiety. Thus, the use of skin penetration enhancement approaches is desired.

PEPTIDES

Forms

There is a limitless array of possible peptides, based on amino acid sequence, number of amino acid residues, and use of derivatives/isomers of these residues. A few peptides with well-characterized sequences that have received particular focus in the cosmetic industry are palmitoyl-lysine-threonine-threonine-lysine-serine (pal-KTTKS; Matrixyl®), acetyl-glutamate-glutamate-methionine-glutamine-arginine-arginine (Ac-EEMQRR; Argireline®), and the tripeptide copper glycine-histidine-lysine (Cu-GHK).

Mechanisms

KTTKS is a fragment of dermal collagen and has been shown to stimulate production of collagen and thus has been discussed in regard to wound healing (41). Incorporation of long-chain lipophilic residues such as palmitoyl onto peptides can dramatically improve their delivery into skin, e.g., the observed five- to six-fold increase in delivery of palmitoyl peptides versus their underivatized versions (42). Thus, pal-KTTKS was synthesized specifically for topical use of this peptide. Like the underivatized peptide, the palmitate derivative (pal-KTTKS) is also active in stimulating collagen production (43–45). In addition, at extremely low levels (ppb) in culture, pal-KTTKS reduces excess dermal GAGs (Fig. 10). As discussed above, this effect may also contribute to an anti-wrinkle effect.

Like KTTKS, GHK is also a fragment of dermal collagen (46). Copper is a required factor for activity of lysyl oxidase, an enzyme involved in collagen synthesis (47). The complex of these two (Cu-GHK) has been shown to stimulate wound healing processes
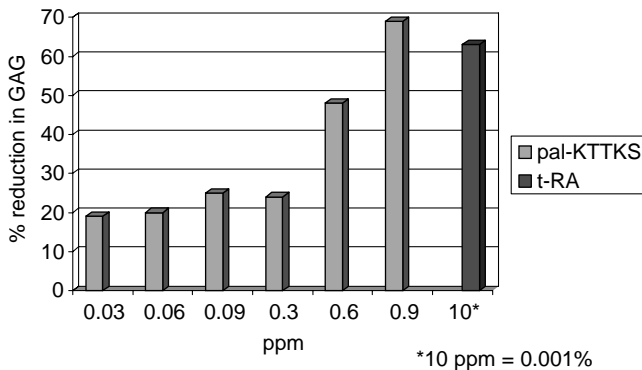
Figure 10   Pal-KTTKS reduces excess dermal GAGs. In cell culture, using fibroblasts from an old donor (57 years old), there was a two- to three-fold increase in GAGs (measured as hyaluronic acid) versus from a young donor (neonatal). Pal-KTTKS was effective in reducing the excess GAG level in old fibroblasts. *Abbreviation*: t-RA, trans-retinoic acid.

in laboratory model systems by increasing production of dermal matrix components such as collagen and specific matrix remodeling matrix metalloproteinases (MMPs) (48–52).

Ac-EEMQRR is described as a mimic of botulinum neurotoxin (Botox®) which functions by inhibiting neurotransmitter release, thus "relaxing" the muscles involved in defining facial wrinkles (53).

Since the reported mechanisms of pal-KTTKS and Cu-GHK involve matrix production and remodeling, their appearance benefits would be expected to require chronic treatment. In contrast, Ac-EEMQRR should have acute benefit effects based on its reported Botox®-like mechanism.

Efficacy

The peptide pal-KTTKS has been shown to be quite potent clinically, providing effects from very low topical doses. This low dose for clinical activity is consistent with the very low concentration (as low as ppb) required to obtain effects in vitro as noted above. In small-base human clinical testing (54), topical pal-KTTKS at 3 ppm was described as providing improvement in appearance of wrinkled skin. To confirm this observation, a larger base size 12-week, double-blind, placebo-controlled, split-face, left-right randomized study (n=94) was conducted (43), again testing the effect of topical 3 ppm pal-KTTKS. This topical peptide is extremely well tolerated by test subjects, i.e., it does not induce skin irritation responses (no redness, dryness, burn, sting, or itch responses). Based on quantitative computer image analysis, it reduced fine lines/wrinkles versus the placebo control (Fig. 11). While the effect was small, it was significant at weeks 8 and 12. Expert graders evaluating blind-coded images also identified an improvement in fine lines/ wrinkles, with directional and significant effects noted at weeks 8 and 12, respectively (Fig. 12). Consistent with the good skin tolerance of the peptide, there was no impact on skin barrier function, as assessed by TEWL (Table 1), indicating lack of irritation.

In contrast to the potency of pal-KTTKS, the reported effects of other peptides require much higher doses, such as 2% for Cu-GHK and as high as 10% for Ac-EEMQRR. There is also limited published information available on the clinical effects of these peptides. One study (55) describes increases in skin thickness, hydration, and smoothness from topical use of a commercial product containing Cu-GHK (peptide dose not indicated) in an open-label study involving 40 subjects. A series of clinical studies of eight to 12 weeks, duration (up to n=71) describing skin improvements such as reduced
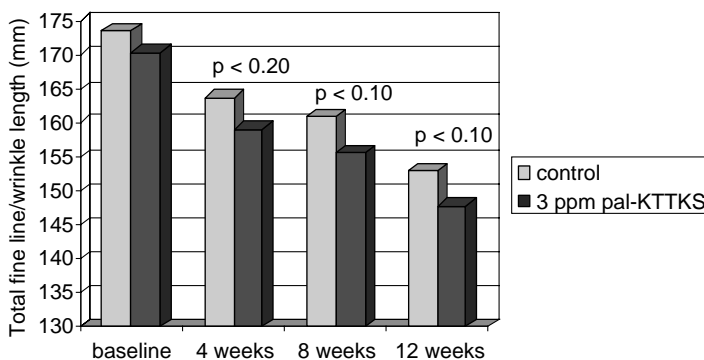
Figure 11 Topical pal-KTTKS improves the appearance of facial skin wrinkles (quantitative computer image analysis). Smaller numbers indicate fewer fine lines/wrinkles.
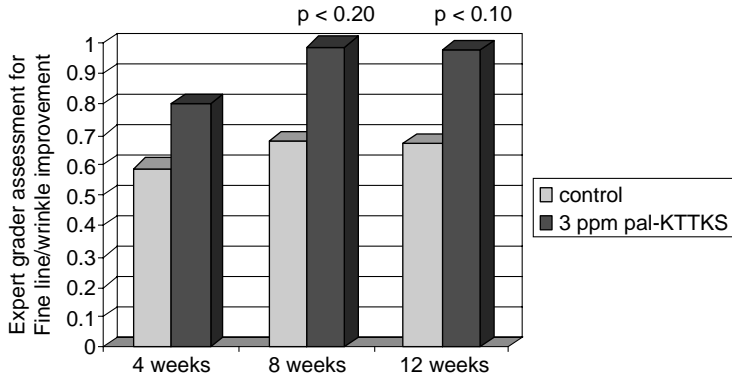
Figure 12 Topical pal-KTTKS improves the appearance of facial skin wrinkles (blinded expert grader image analysis). Grading was on a 0–4 grading scale. Larger numbers indicate fewer fine lines/wrinkles.

wrinkling, apparently using topical 2% Cu-GHK, have been presented as meeting posters (56–59). For Ac-EEMQRR, a conference platform presentation (53) describes 30% reduction in wrinkle depth with 10% of this peptide used topically in a 30-day study.

Product/Formulation Challenges

An important challenge is delivery into skin since peptides are poorly penetrating, especially as the number of amino acid residues increases. An approach to that problem is addition of a lipophilic chain (e.g., palmitate), which in the case of KTTKS increased skin penetration several-fold over the underivatized peptide.

An additional challenge is the cost. As the number of amino acid residues increases, the cost of peptide can increase dramatically. The consequences are that only low levels of peptide can be used in product (which is acceptable if the peptide is potent as in the case of pal-KTTKS) or the finished product cost to the consumer must be very high.

DIMETHYLAMINOETHANOL (DMAE)

Mechanism

DMAE (also known as deanol) is a precursor to acetylcholine, a neurotransmitter involved in increased muscle tone. There thus could be firming of the skin via effects on the facial

Table 1 Lack of Effect of Pal-KTTKS on Skin Barrier Properties as Assessed by Transepidermal Water Loss

Time point	Transepidermal water loss (g water/m^2/hr)		p value
	Placebo formulation	Pal-KTTKS formulation	
Baseline	11.15	11.40	$p > 0.38$
4 weeks	8.10	8.24	$p > 0.60$
8 weeks	8.56	8.41	$p > 0.60$
12 weeks	7.89	8.15	$p > 0.35$

musculature. In addition, acetylcholine may affect the keratinocytes (specifically their proliferation, adhesion, and motility) leading to "epidermal contractility," leading to a firming/tightening effect on the skin (60). DMAE also has antioxidant properties, which may contribute to its anti-aging effects (61,62).

Efficacy

Several studies have been discussed and overviewed (60). For example, in an open-label, one-month study with a DMAE-containing formulation (DMAE dose not specified), the skin of 50 subjects was compared at the end of the treatment period versus baseline by dermatologist grading and subject self-assessment. Significant improvements were reported in several measures, particularly in the area of skin firming and lifting. The topical treatment was well tolerated by the subjects. As a further example, in a double-blind, placebo-controlled, 16-week, full-face study (n=156), 75% of the subjects used a DMAE-containing formulation (DMAE dose not specified), and 25% of the subjects used a placebo formulation (60). Effects were determined based on dermatologist grading and image analysis. The statistical p value presentation indicates several facial benefits related to skin firming (e.g., under-eye firming, cheek area firming, jaw line lifting and firming, increased elasticity, etc.). Again, the skin tolerated the DMAE formulation well. These reported observations are consistent with other small-base (n=8) clinical testing showing improved skin firmness instrumentally from topical use of 3% DMAE in a one-day study (63).

The interesting aspect of the clinical effects is that while some testing has been weeks/months in duration, the onset of the benefit was reported to be very rapid, within minutes of topical application (60,63). This seems consistent with the suggested mechanism if sufficient DMAE can penetrate into skin and be converted to acetylcholine in such a short time period.

Product/Formulation Challenge

DMAE, a base, has historically been used as a formula pH adjusting agent. In the un-neutralized state, its pH is approximately 10. Thus, pH adjustment to the desired value appears to be sufficient.

KINETIN (N_6-FURFURYLADENINE)

Mechanisms

Kinetin is a plant hormone. While its specific mechanisms have not been elucidated, it has been observed to promote growth and have anti-senescence effects in plants. It is a powerful natural antioxidant with effects in protecting DNA and protein from oxidative damage. In human fibroblast cell culture, even very low levels (ppm) delay the onset of changes associated with cell aging, e.g., appearance of lipofuscin, appearance of multinucleate cells, and microtubule disorganization (64).

Efficacy

In three reported clinical tests (10–24-week duration, n=30–98), topical 0.1% kinetin was reported to improve several aging skin problems, such as wrinkling, poor texture, and hyperpigmentation (64). All of these studies apparently did not involve a placebo control,

but rather were comparisons (dermatologist grading and self-assessment) of treatment effects versus baseline. The 0.1% dose is well tolerated by the skin, with no significant irritation issues described.

Product/Formulation Challenge

The limitation with kinetin is its fairly low solubility in formulation. This restricts the upper dose to approximately 0.1% for an aesthetically elegant formulation. This also impacts delivery into skin, although even from this relatively low dose sufficient material does enter skin to provide clinical effects.

TRITERPENOIDS

Forms

There are numerous plant-derived triterpenoid compounds and derivatives of them, with a few receiving attention in the cosmetic area, e.g., asiatic acid, ursolic acid, medacassic acid, oleanolic acid, betulinic acid, and boswellic acid. There are also naturally occurring saccharide esters of these, such as asiaticoside, which is the ester of asiatic acid.

Mechanisms

There are many reported mechanisms for triterpenoids, for example, antioxidant, anti-inflammatory, elastase inhibition, wound healing, and promotion of collagen and ceramide production (65,66). Since triterpenoids share some structural similarity to steroidal compounds such as hydrocortisone, they may also share some of the mechanistic properties and potency of such compounds (e.g., anti-inflammatory effects).

Efficacy

There is little published information to illustrate the clinical effects of triterpenoids. Topical ursolic acid in liposomes (final concentration of ursolic acid <0.002%) resulted in increased skin ceramides in small-base forearm testing (n=3; 11 days of treatment). The increased ceramides were suggested to indicate improved skin barrier (66). In a double-blind, placebo-controlled, left-right randomized forearm clinical study of 20 subjects (67), treatment with topical liposomal triterpenoid (specific content not indicated) was done for one month. Improvements in skin extensibility and firmness (instrumentally determined) were reported. While the dose of triterpenoid was not specified, it was probably low and apparently consisted of a blend of boswellic acid, asiatic acid, and possibly others since the content may have included extracts.

Product/Formulation Challenge

The key issue with triterpenoids is poor solubility which also results in limited skin delivery. Formulation in liposomes has been employed to improve both delivery and formula solubility, although the resulting increase in oil content of the formulations may negatively impact the aesthetics.

UBIQUINONE (CO-ENZYME Q10)

Mechanism

Ubiquinone is an endogenous antioxidant present throughout the body, including the skin. The levels decrease with age. Topical ubiquinone replenishes the skin (68).

Efficacy

While much has been discussed regarding the skin care benefits of topical ubiquinone, the available data address only the antioxidant properties of this ingredient (69).

Product/Formulation Challenge

Ubiquinone is yellow-orange in color. Thus, only low doses ($<1\%$) can be used in topical cosmetic skin care products to avoid aesthetic color concerns. This low dose likely limits the benefit potential of this ingredient.

OTHER TECHNOLOGIES

Hydroxy and Keto Acids

There are many compounds within this group: alpha-hydroxy acids such as glycolic acid and lactic acid, alpha-keto acids such as pyruvic acid, and beta-hydroxy acids such as salicylic acid. Their mechanism involves accelerated exfoliation of stratum corneum, leading to a variety of skin surface texture and color appearance improvement effects. These materials are the subject of another chapter in this volume.

Moisturizers

Topical materials such as glycerol and hyaluronic acid will readily hydrate the skin surface and will diminish the appearance of fine lines simply by plumping the skin. Moisturizers are the subject of another chapter in this volume.

Flavonoids

This family of plant-derived and synthetically prepared chemicals encompasses a huge variety of compounds. They are beginning to appear in cosmetic products and are a fertile area for identification of materials active in improving aging skin.

Plant Extract Components

In addition to flavonoids, plant extracts are a rich source of diverse compounds that are being explored to identify skin care bioactives.

DISCUSSION

It is clear that many anti-aging ingredients that are used cosmetically do provide appearance improvement benefits to the skin, but for others data supporting their claimed effects are not readily available for assessment. For the active ones, while the benefits

RP = retinyl propionate; N = niacinamide
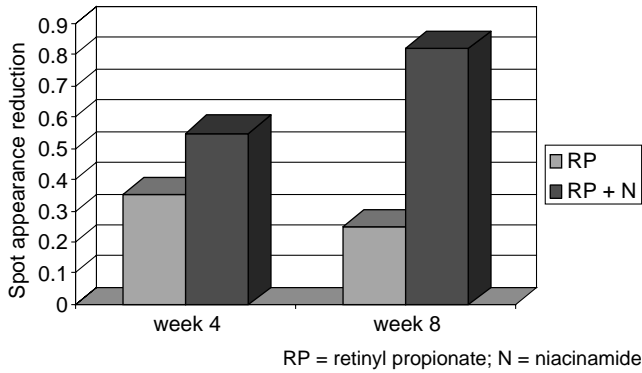
Figure 13 Combining niacinamide with retinyl propionate increases the skin appearance improvement effect.

may be small, they are significant and do meaningfully improve skin appearance with continued use of the materials. It is difficult to quantitatively compare the magnitude of the effects among the various technologies since there are many variables across studies: the specific end points measured are often different (e.g., surface replicas vs. facial image analysis), equipment and method sensitivities vary, formulation types vary which can impact active delivery into skin, different body sites were used (e.g., forearm vs. face), clinical base sizes ranged from very small to large, etc. But it is reasonable to state that they are all less effective than a technology such as trans-RA. This simply presents an opportunity to identify more potent cosmetic materials.

While the benefits of current technology may be small, the magnitude can increase by combining materials, especially those with different mechanisms of action. For example, combining a vitamin B3 with a vitamin A (Fig. 13) or with a peptide (Fig. 14) leads to greater benefits than the individual materials. There is certainly opportunity to continue to explore this avenue.

There is ample room for exploration of new materials within the current classes of compounds (e.g., peptides) and in newer classes of compounds (e.g., flavonoids).
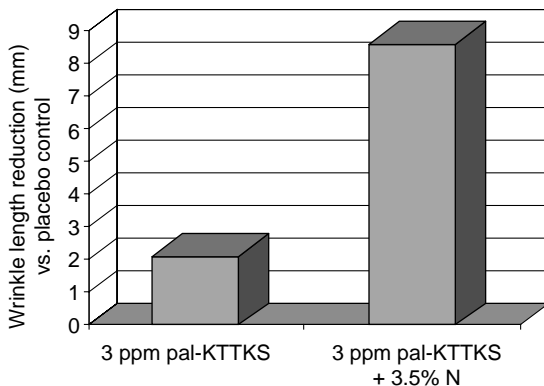
Figure 14 Combining niacinamide (N) with pal-KTTKS increases the skin appearance improvement effect.

Considering the enormous diversity of compounds to be found in natural extracts, for example, the future possibilities seem limitless for identifying new active materials and mechanisms to improve the appearance of aging skin.

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12

The Role of Cosmeceuticals in Dermatology

David H. McDaniel
The Institute of Anti-Aging Research, Virginia Beach, Virginia, U.S.A.

Joseph DiNardo and Joseph Lewis
Pharma Cosmetix Research, LLC, Richmond, Virginia, U.S.A.

WHAT ARE "COSMECEUTICALS"—COSMETICS VS. RX DRUGS

History and Background

The term "cosmeceuticals" was first popularized about twenty-five years ago by Albert Kligman, MD, PhD, to bridge the gap between cosmetics and drugs or pharmaceuticals. Historically, after the Food, Drug, and Cosmetic Act of 1938, the world of topical skin care products was divided into two groups: cosmetics and drugs. Drugs were for the treatment or prevention of diseases, and it was required that safety and efficacy be established before sales and marketing could proceed. In contrast, cosmetics were viewed as agents to enhance the beauty of the skin or improve the appearance of the skin, and safety and efficacy were not required to be demonstrated before sales and marketing of these products (1).

Another organization, the Cosmetic, Toiletry, and Fragrance Association (CFTA), in the United States was formed in 1894 and today serves as a valuable liaison among suppliers, manufacturers, and distributors of cosmetic products for the personal care industry. No formal organization exists at this time specifically for the cosmeceutical realm.

At a fundamental level cosmetics are products which affect the appearance of the skin, while drugs affect the structure and function of the skin. Thus the term "cosmeceutical" is intended to describe skin care products that fall in between these categories. Increasingly though products which are considered cosmeceuticals actually do affect the structure or function of the skin and thus have drug-like effects but are marketed using appearance-based claims. This has given rise to much confusion and ironically may provide some disincentive for manufacturers to conduct or publicize clinical testing since the data generated may support the drug-like effects. For example, a drug may be marketed as a product that "reduces wrinkles by stimulating collagen production," but a cosmetic which could potentially have essentially the same mechanism of action and clinical effects would be marketed as a product that "reduces the appearance of wrinkles." While some

cosmeceuticals are "drugs in disguise" as cosmetics, if marketing claims push the edge of the claims envelope too hard, then the Food and Drug Administration (FDA) may intervene with various warnings or actions; thus, the issue of "when" does a cosmeceutical become a drug is likely to become more significant in the future (2,3).

If one looks at sunscreens and antiperspirants, these are regulated as over-the-counter (OTC) drugs in the United States but not in Europe. One need only look at the delays in availability in the United States of some of the new and highly effective sunscreens to appreciate some of the archaic aspects of the 1938 legislation. Thus the term "cosmeceutical" encompasses a broad range of the ill-defined territory which lies between cosmetics and drugs. It is a very useful concept scientifically and has been accordingly embraced on a broad global scale. The years ahead will see a struggle to define and refine this cosmeceutical concept. Some exemplary efforts towards this have been made in Japan, but a global uniform concept is yet to emerge (4).

The Skin's Response to Environmental Damage and Chronologic Aging

The skin is the body's first line of defense for environmental exposure. Much of the "premature" aging (in contrast to intrinsic or chronologic aging) occurs as a direct or indirect result of the skin's interaction with its environment. While photoaging is properly recognized as one of the principal causes of aging in lighter skin types, many other factors are also significant. For example, tobacco smoke produces a host of problems and in some darker skinned ethnic populations may be the primary cause of wrinkles rather than ultraviolet (UV) light. Ozone, air pollution, industrial, occupational, or recreational exposures bring contact with a diverse array of potential toxins. Personal skin care habits and excessive or improper use of products can also cause problems. Disease and drugs and therapies for diseases may produce many challenges to the skin as well.

Traditionally the sun protection factor (SPF) has been the primary focus of protection from the environment for UV light. Various moisturizer products have some function for barrier protection (5–7). However, there is a growing realization that the issues are more complex than this. As a result, discussion is growing about SPF to include a broader range of UV exposure including UVA-1 wavelengths. You will be reading more about immune protection factor (IPF) and also environmental protection factor (EPF) in the years ahead as our understanding of the full spectrum of environmental insults to the skin is explored.

The common pathways of much of the environmental damage to the skin are twofold: free radical generation and DNA damage. The concept of repetitive small "injuries" to the skin resulting in cumulative long term chronic alteration of the optimal structure and function of the skin resulting in "scars" is a good one. In this scenario wrinkles might be considered "solar scars" … or "tobacco scars" … or "environmental injury scars." The latter is more comprehensive, but the former are useful teaching tools for educating our patients. The growing evidence that environmental damage reduces the efficiency of mitochondrial ATP production provides a unique area of future research. The ability to "re-energize" skin cells as one ages using cosmeceuticals is another very exciting area for the future (8,9).

If one considers environmental damage then the first goal of therapy is avoidance … followed by protection … then minimizing or neutralizing free radical damage … and finally repair or restorative treatments. As clinicians we try to focus on all of these factors and develop practical, useful, and affordable treatment plans that adapt to our patient's

lifestyle so that compliance is maximized. One of the great challenges with the proliferation of cosmeceuticals is finding good scientific and clinical data like we are accustomed to having for our pharmaceutical drug therapies. Such information is often absent or studies are poorly designed and physicians are often left sorting through marketing claims instead of scientific data.

This scenario has led to the increasingly popular practice of dispensing cosmeceuticals within the physician's office. This provides the physician with the ability to control and select products that are scientifically based, but it also opens the door for misuse of the privilege and trust that our patients place in us. The American Academy of Dermatology has a formal policy and guidelines for this practice which is useful to review (Fig. 1) (10).

Properly used, office dispensing can be a very valuable tool for the optimal use of cosmeceuticals (11). Dispensing "private label" products to "control" patient purchase habits or using products which have no scientific or clinical basis established is a good example of practices which do not enhance the physician's professional stature nor benefit the consumer. Since nearly half of dermatologists currently dispense products, the need for better educational resources for physicians is growing and the availability of textbooks such as this are one part of the effort to put cosmeceutical skin care on a solid scientific and academic basis.

The sales growth of cosmeceuticals is dramatically increasing relative to skin care products in general with special interest for the anti-aging category of products. This trend is likely to continue. The consumers have a need for reliable information, not just marketing claims. Physicians are the traditional source of such information; however, many are poorly informed and their patients are increasingly seeking this expertise and advice elsewhere at non-traditional and often non-medical sources. With the proliferation of products and marketing claims that are ahead of or unsupported by clinical data, it is truly an information wilderness for many products.

RX vs. Cosmetics—the Response of the Skin's Structure and Function to Cosmeceuticals

The skin plays many roles ranging from barrier function to highly complex biochemical and photobiochemical processes. If we follow the definition above then cosmeceuticals are inherently not simply cosmetics to beautify the appearance of the skin.

American Academy of Dermatology Office Dispensing Guidelines for Prescription and Non-prescription Products
* DO NOT place your own financial interests above the well-being of patients
* DO NOT price products at an excessive mark-up
* DO NOT create an atmosphere of coercive selling
* DO NOT sell products whose claims of benefit lack validity
* DO NOT represent products as "special formulations" not available elsewhere if this is not the case
* DO clearly list all ingredients, including generic names of drugs
* DO advise patients of alternative purchase options if products are available elsewhere
* DO provide prescription refills that can be filled outside the office if patients so choose

Figure 1 American Academy of Dermatology Office Dispensing Guidelines for Prescription and Non-prescription Products. *Source*: American Academy of Dermatology, 2003.

Cosmeceuticals then affect either the structure or the function (or both) of the skin. Unlike drugs, cosmeceuticals typically are very safe and have few significant serious adverse events. However, like drugs, these active agents can impact many diverse functions of the skin and we do not fully comprehend the implications of these actions in many cases.

For example, take botanical-based actives in cosmeceuticals. These plant-derived substances have the potential for contact dermatitis like reactions similar to poison ivy dermatitis. Irritant reactions are also possible as are phytophotodermatoses. Typically products are selected which do not pose these concerns and also the concentrations used in the formulations are below the threshold of reaction (12).

There are also issues of bioequivalency. Most physicians recall the use of digitalis in past for cardiac treatments—before standardized digoxin became available. An example with cosmeceuticals is that the polyphenol content of a particular botanical may vary from brand to brand; even though the percentage concentration of that active seems equal among brands, the difference in polyphenol content may make one product less efficacious than the other brand, which has a higher content of polyphenols (13).

Another example of an issue is with one of the very popular alpha-hydroxy acid (AHA) actives, glycolic acid, where the pH and pKa values impact the clinical effects and side effects. For these products, simply comparing the percentage of glycolic acid did not provide the physician, esthetician, or consumer with an accurate assessment of the effects on the skin. In fact, a lower percent glycolic acid product could potentially be more irritating than a higher percentage glycolic acid product depending on the pH (14,15).

An issue infrequently discussed is that of pesticide residues or other contaminants for botanicals. So bioequivalency and bioavailability and purity are all issues for these types of active ingredients. Also, while we are thinking in the "drug" pattern, the "dose" is important. So the percentage of actual active ingredient also determines to some extent the effects of cosmeceuticals compared to Rx drugs. Also, physician-dispensed products often have a higher "dose" or concentration of actives than the OTC products.

Other factors are synergistic reactions and stability. Many cosmeceutical formulations have complex mixtures of actives the interactions of which are not all well defined. Some antioxidants are not that stable and others may be unstable after they are opened. Novel new "airless" pump delivery systems or mixing as pumped onto skin from applicator provide ways to combat these problems.

Data on the relative potency is often lacking on active ingredients within the same category. Antioxidants are a good example, and this data has only recently begun to be published. Much of the data about the drug-like effects on the skin's structure and function are considered proprietary and not available for physicians or the consumer to review. Additionally many products are sold widely with minimal scientific or clinical data whatsoever. Thus, while cosmeceuticals increasingly affect the skin's structure and function like drugs, the data that is traditionally available for drug evaluation is often incomplete or nonexistent. The great safety of most cosmeceutical actives is one of the mitigating factors in this scenario. We will see antioxidants grow dramatically in their role with the cosmeceutical armamentarium to protect and also in some cases repair environmental damage and aging in general.

In summary, cosmeceuticals may have profound effects on the structure and/or function of the skin—or they may have little or no effect and behave like cosmetics. A comprehensive discussion of this is beyond the scope of this section, but the use of cosmeceuticals to improve the appearance and health of the skin is a fascinating area of science and one which we will see explored and mapped in the years ahead.

DOMESTIC AND INTERNATIONAL REGULATORY GUIDELINES IMPACTING COSMETICS

Domestic Regulations

There have been many misunderstandings relating to the regulation of cosmetic products and OTC drugs in the United States. For the most part, the cosmetic industry has never been directly regulated by any government agency and does not require the FDA to approve a cosmetic/cosmeceutical product prior to marketing. Additionally, in 1972 the FDA initiated a monograph process for OTC drugs which eliminated the need to have pre-market approval for certain product categories (sunscreens, antiperspirants, anti-acne, etc.) by companies prior to being sold to consumers. The process of regulation for cosmetics and OTC drugs would appear to be better described as "self-regulated" and, therefore, impacted by various guidelines, legislation, and regulatory bodies as opposed to governed by these entities. Outlined below is a brief review of the laws that are currently in place. A more detailed review can be obtained through other references and/or review of the various regulatory agency Web sites (FDA.gov, FTC.gov, EPA.gov, etc.) (16).

The most important regulations to note are the Food, Drug, and Cosmetic Act of 1938 and the 1960 amendment, the Fair Packaging and Trade Act of 1966 and 1973, the OTC Drug Monograph Process introduced in 1972, and the 1916 Federal Trade Commission Act. With the exception of the latter, which is governed by the FTC, the others are the responsibility of the FDA. Additionally, there have been laws brought about by individual members of the government (Delaney Amendment in 1958—anti-cancer act) as well as by individual state legislatures (California, New York, New Jersey, and Massachusetts, to name a few) which relate to areas such as the Volatile Organic Compounds (VOCs) and the Safe Drinking Water and Toxic Enforcement Act (Proposition 65). Lastly, it should be noted that cosmetic manufacturers are allowed to use any ingredient in a product, as long as the product has been tested and shown to be safe for its intended use, with the exception of hexachlorophene, mercury compounds, chlorofluorocarbon propellants, bithionol, halogenated salicylanilides, chloroform, vinyl chloride (aerosol products), zirconium (aerosol products), methylene chloride, acetylethyltetramethyltetralin, musk ambrette, 6-methylcoumarin, nitrosamines, dioxane, and estrogen.

International Regulations

Numerous countries all around the world have recently instituted some form of cosmetic regulation, other than product registration with their ministries of health, with respect to protecting the consumers of their respective countries. The amount of information is massive and to simply list current activities would go far beyond the scope of this chapter. However, it should be noted that Australia (http://www.nicnas.gov.au/) as well as Canada (http://www.hc-sc.gc.ca/english/media/releases/2004/cosmetic_labelling.htm) have taken very proactive approaches to cosmetic regulation, and the Web sites noted above can be accessed for additional information if so desired. The European Union (EU) has probably been the most proactive globally in attempting to regulate cosmetics. New provisions made in the seventh amendment to the EU cosmetic directives are outlined below identifying some of the significant changes in how cosmetic manufacturers will need to do business in the EU as well as what information will need to be provided to consumers in order for the product to be sold in the various EU countries. These regulations are all in effect as of March 11, 2005.

- A product information dossier on qualitative and quantitative composition of the product and existing data on undesirable effects must be made "easily accessible to the public by means including electronic means." Companies can list themselves and this information in the European Cosmetic Toiletry and Perfumery Association (COLIPA) database (www.European-Cosmetics.info). Additionally, the dossier must include information on any animal testing relating to development or safety evaluation of a product or ingredient.
- A Quantitative Declaration of Ingredients containing any ingredient(s) listed in the Dangerous Substances Directive (67/548/EEC) must list the concentration or concentration range of the substance(s) in question.
- Information on Undesirable Effects on Human Health Resulting from Use of the Cosmetic Product. Undesirable effects are, essentially, irritant or allergic reactions that can in rare cases affect skin or eyes. It is also recommended that companies present the number of undesirable effects in context of the number of units placed in the marketplace (i.e., to date there have been zero undesirable effects per one million units placed in the EU market).
- A ban on animal testing went into effect immediately for finished products and for ingredients.
- Need exclusive exposure assessments for products intended for children under 3 years of age and for intimate hygiene products.
- Color additives for the entire range of decorative cosmetics may be listed at the end of the ingredient list after the term "may contain" or the symbol "$+/-$."
- Any ingredient identified as carcinogenic, mutagenic, and/or a reproductive hazard (CMR) Category 1 and 2 must not be intentionally added to cosmetic products. Any ingredient identified as CMR Category 3 must not be intentionally added unless evaluated by SCCNFP and found acceptable for use in cosmetic products.
- Products that have a durability (shelf life) over thirty months must have the a "Period After Opening" (PAO) symbolized by an open jar with the number of months which indicates how long after a product is opened it can be used without harm to the consumer (see example below under "How to Select the 'Best' Formulation of a Cosmeceutical."
- Problem fragrance ingredients (26 fragrances ingredients with a history for contact dermatitis) need to be labeled by INCI name in the ingredient label if they are used in the formula at 0.001% in leave-on and 0.01% in rinse-off products.

CATEGORIES OF CURRENTLY POPULAR COSMECEUTICALS IN DERMATOLOGY

Amino Filaggrin Acids—Filaggrin Protein/Fruit Acids

1. *Science and clinical studies*: Although no peer review articles were found, studies outlined by the manufacturer of the product claim that the product has been tested over the last three years and is effective in reducing the appearance of visible lines and improving tone and texture of the skin.
2. *Key benefits*: Amino Filaggrin Acids (AFAs) are amino acids that are naturally found in skin and are associated with increasing moisture retention in skin. They claim to be able to penetrate through the keratinized epidermis.

3. *Primary adverse effects*: None found. Considered to be milder than AHA or BHA preparations.
4. *Practical applications in dermatology*: AFA in-office peels may be used on an alternating basis with AHA peels, or may be helpful in patients having problems with long term use of various peeling agents. Can be used with microdermabrasion or other minimally invasive procedures.

Vitamins: C and E

1. *Science and clinical studies*: Numerous studies have been published on both of these ingredients relating to antioxidant function and protection against UV damage. Additionally, vitamin C has been shown to enhance collagen and elastin production. Both ingredients are essential in a formula if any antioxidant and/or anti-aging claims are to be made. The two ingredients work together to a redox manner to neutralize free radicals by converting to both a pro-oxidative and natural state.
2. *Key benefits*: Vitamin E is an effective antioxidant which can act synergistically with vitamin C to help fight against free radical damage associated with premature aging.
3. *Primary adverse effects*: Although uncommon, some contact dermatitis reactions have been reported to vitamin E over the years as well as irritant reactions caused by vitamin C due to some products low pH.
4. *Practical applications in dermatology*: Used alone or in combination these antioxidants have a variety of applications for anti-aging.

Vitamins: K

1. *Science and clinical studies*: Two studies have been published whereby vitamin K has been used to minimize purpura production after pulse dye laser treatments (17). Both studies employed approximately 20 subjects, with one evaluating the effects of the ingredient alone and the other with the use of retinol BID weeks before and two weeks after laser treatment. The side of the face treated with topical vitamin K with or without retinol demonstrated significantly lower scores of bruising severity when compared with the side treated with placebo (18).
2. *Key benefits*: Reduces bruising and can minimize damage associated with pulse dye lasers.
3. *Primary adverse effects*: None noted.
4. *Practical applications in dermatology*: Using vitamin K, two weeks before and after pulse dye laser treatments may reduce adverse cutaneous reactions. Efficacy for bruising from other etiologies is unknown.

Vitamins: B3 (Niacinamide)

1. *Science and clinical studies*: Niacinamide was evaluated clinically in Japanese women for the inhibition of pigmentation. Eighteen subjects with hyperpigmentation received either a 5% Niacinamide containing product or a placebo. Additionally, 120 subjects with facial tanning were given either a 2%

Niacinamide cream containing a sunscreen, a sunscreen, or a vehicle. Changes in facial pigmentation were evaluated via computer analysis and visual grading of high-resolution digital images of the face. Niacinamide significantly decreased hyperpigmentation and increased skin lightness compared to vehicle alone after four weeks of use. Other studies have been reported whereby topical Niacinamide application demonstrates improvement of barrier function via decreased transepidermal water loss (TEWL) and skin appeared to be more resistant to irritation produced by topical irritants such as detergents (19,20).

2. *Key benefits*: Decreases hyperpigmentation and may improve barrier function and resiliency to environmental insults.
3. *Primary adverse effects*: Well tolerated.
4. *Practical applications in dermatology*: Niacinamide may be a suitable replacement for treating hyperpigmentation when results are not obtainable with hydroquinone and/or other conventional forms of treatment.

Vitamins: B5 (Panthenol)

1. *Science and clinical studies*: Topical application of Pantothenic Acid has been shown to provide moisturizer-like benefits, improving stratum corneum hydration, reducing transepidermal water loss, and maintaining skin softness and elasticity. Activation of fibroblast proliferation, which is of relevance in wound healing, has been observed both in vitro and in vivo, and accelerated re-epithelization in wound healing has been demonstrated via transepidermal water loss. Pantothenic Acid has also been shown to have an anti-inflammatory effect reducing UV-induced erythema. In double-blind, placebo-controlled clinical trials, a Pantothenic Acid-containing cream resulted in significantly less damage to the stratum corneum barrier, compared with no pretreatment over three to four weeks.
2. *Key benefits*: Moisturizer-like benefits, reduction in TEWL, fibroblast activation, and anti-inflammatory potential.
3. *Primary adverse effects*: Topical administration of Pantothenic Acid preparations are generally well tolerated, with minimal risk of skin irritancy or sensitization.
4. *Practical applications in dermatology*: Pantothenic Acid may be beneficial in patients who have undergone skin transplantation or scar treatment, or therapy for burn injuries and different dermatoses.

Enzymes: SOD

1. *Science and clinical studies*: Superoxide Dismutase (SOD) is the most effective internal antioxidant found in humans. Superoxide radials are reduced to hydrogen peroxides by SOD and then further reduced by catalase to water. Data from the literature indicate a protective effect of SOD in topical application against UV-induced cutaneous damage (21). When an SOD cream containing 0.6 mg/ml of bovine SOD was applied locally onto the skin and mucosal lesions caused by progressive systemic sclerosis, systemic lupus erythematosus, Behcet's disease, herpes simplex, and burns, the lesions and symptoms were rapidly improved in many cases after its administration, even when the

symptoms were stabilized for several weeks before the treatment (22). SOD was concluded to be effective for these conditions. In another study, topical application of free Mn-SOD or Cu, Zn-SOD showed complete healing in a burn patient who was advised to undergo skin transplantation (23). However, the later study noted that SOD dissolved in a white petrolatum vehicle rapidly lost its activity (within three months) and commented that SOD should be dissolved in the vehicle before use (24–26).

2. *Key benefits*: Suppression of UV-induced cutaneous damage and possible reversal of free radical-mediated disease states.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be effective in treating progressive systemic sclerosis, systemic lupus erythematosus, Behcet's disease, herpes simplex, and burns.

Growth Factors: EGF/TGF

1. *Science and clinical studies*: No peer review clinical data was found on the effects associated with epidermal growth factor (EGF/TGF). However, several in vitro studies are obtainable. A bioassay for EGF reported by Carpenter and Zendegui was described as rapid, specific, and extremely sensitive (27). The bioassay detects as little as 25 pg of EGF and was considered more sensitive than commonly used radioreceptor assays and nearly as sensitive as radioimmuno assays. The bioassay involved measurement of the proliferation of cultures of an EGF-requiring cell line and can be carried out in a quantitative manner over a 40-fold range of EGF concentrations. One in vivo study in rabbits evaluated wound healing with a placebo ointment and one containing EGF (28). Less wound contracture occurred in the EGF-treated wounds, and wound maturation occurred earlier. The healed wounds that had been treated with EGF more closely resembled the surrounding normal tissue, producing less local deformity than in the controls. A study evaluating the epidemiological and experimental evidence that dietary poly-phenolic plant-derived compounds have anticancer activity is also note worthy (29). The investigators found that green tea components induce apoptosis via a TGF-beta superfamily protein, non-steroidal anti-inflammatory drug activated gene (NAG-1) and showed that ECG is the strongest NAG-1 inducer among the tested catechins and that treatment of HCT-116 cells results in an increasing G(1) sub-population, and cleavage of poly (ADP-ribose) polymerase (PARP), consistent with apoptosis. The data generated by this study elucidate mechanisms of action for components in green tea and was hopeful in leading to the design of more effective anticancer agents and informed clinical trials (30).
2. *Key benefits*: May facilitate wound healing.
3. *Primary adverse effects*: None reported.
4. *Practical applications in dermatology*: May accelerate normal wound healing in patients under going evasive cosmetic procedures.

Growth Factors: Kinetin (Plant Growth Factor)

1. *Science and clinical studies*: Kinetin is a plant-derived nucleotide (growth factor) known to delay senescence (aging) in plants. Two one-year long clinical

studies have been completed on Kinetin. Study results report that Kinetin can reverse the signs of photodamaged skin and improve the overall appearance of the skin, making it smoother and more even in color and visibly diminishing the appearance of fine lines and wrinkles. These studies also demonstrated that Kinetin can significantly improve the skin barrier function and help the skin to retain more moisture, making the skin softer and smoother. Additionally, Kinetin is also thought to process some antioxidant capabilities; however, this activity is not considered to be the mechanism of action for the reversal of photoaging observed in the clinical studies noted.

2. *Key benefits*: It demonstrates antioxidant and barrier function benefits.
3. *Primary adverse effects*: None reported.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Alpha-Lipoic Acid

1. *Science and clinical studies*: Topical application of 3% Alpha-Lipoic Acid has been shown to decrease UVB-induced erythema. These observations are thought to reflect the ingredient's ability to function as an antioxidant blocking the transcription factor of nuclear factor-kappa B (NF-kappa B) (31). Clinical testing in 33 women with photodamage indicated that 12 weeks of treatment with a cream containing 5% Lipoic Acid improved clinical characteristics related to photoaging of facial skin (32).
2. *Key benefits*: Antioxidant functions, inhibition of NF-kappa B and secondary oxidative products.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Co-Q10 (Ubiquinone)

1. *Science and clinical studies*: Co-Q10 plays a vital role in mitochondrial enzymes of the oxidative phosphorylation pathway and is essential for the production of the high-energy phosphate, adenosine triphosphate (ATP), upon which all cellular functions depend. Numerous in vitro studies have been reported demonstrating the antioxidant efficacy of Co-Q10. However, limited clinical studies are available reporting on the benefits of topical administration. One study was found which noted that Co-Q10 penetrates into the viable layers of the epidermis and reduces the level of oxidation measured by weak photon emission and a reduction in wrinkle depth was also shown (33). Co-Q10 also protected against UVA-mediated oxidative stress in human keratinocytes in terms of thiol depletion, activation of specific phosphotyrosine kinases, and prevention of oxidative DNA damage.
2. *Key benefits*: Antioxidant functions which mediate UVA oxidative stress in human keratinocytes minimizing DNA damage.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Idebenone (Hydroxydecyl Ubiquinone)

1. *Science and clinical studies*: Idebenone is a synthetic version of Co-Q10 with a molecular weight approximately 60% smaller. A multi-step in vitro process utilizing a variety of biochemical and cell-biological methods combined with in vivo studies was designed to compare the oxidative stress protective capacity of commonly used antioxidants. Summarizing and totaling the data equally weighted for each oxidative stress study, the overall oxidative protection capacity score of 95, 80, 68, 55, 52, and 41 was obtained for idebenone, DL-a-tocopherol, kinetin, ubiquinone, L-ascorbic acid, and DL-a-lipoic acid, respectively. The higher the score the better the overall oxidative stress protection capacity of the antioxidant. This multi-step protocol was thought to serve as a standard when investigating and comparing new putative antioxidants for topical use (34). In a non-vehicle control study, 0.5%, and 1.0% idebenone commercial formulations were evaluated in a clinical trial. Forty-one female subjects, age 30–65, with moderate photodamaged skin completed the study. After six weeks of BID use, the 1.0% idebenone formula produced a 26% reduction in skin roughness/dryness, a 37% increase in skin hydration, a 29% reduction in fine lines/wrinkles, and a 33% improvement in overall global assessment of photodamaged skin. The 0.5% idebenone formulation demonstrated a 23% reduction in skin roughness/dryness, a 37% increase in skin hydration, a 27% reduction in fine lines/wrinkles, and a 30% improvement in overall global assessment of photodamaged skin. Additionally, punch biopsies were taken from random select subjects, baseline at and after six weeks, and stained for certain antibodies Interleukin [(IL)-6, IL-1b, Matrixmetalloproteinase (MMP)-1, Collagen I] using immunofluorescence microscopy. The immunofluorescence staining revealed a decrease in IL-1b, IL-6, and MMP-1 and an increase in Collagen I for both concentrations (35).
2. *Key benefits*: Antioxidant protection against multiple free radical pathways, modulation, and regulation of inflammatory markers, and treatment of photodamaged skin.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: Amino Peptides

1. *Science and clinical studies*: Amino peptides are chemically linked to Palmitic Acid to enhance solubility allowing the peptide to become non-polar to cross lipids bilayers. Palmitoyl Pentapeptide-3, tested in a six-month clinical study, demonstrated improvement in the visual appearance of wrinkles by possibly stimulating fibroblast to rebuild the extra-cellular matrix and induce collagen synthesis. Palmitoyl Tetrapeptide-3 is said to control the secretion of cytokine (IL-6), delaying the effects of premature aging. Recent studies have shown that Palmitoyl Tetrapeptide-3 can make a substantial difference in the appearance of stretch marks. In one study, 93% of subjects showed a marked improvement in the length and depth of stretch marks and wrinkles. In addition, there was a substantial improvement in the skin smoothness and tone. Similarly, Acetyl Hexapeptide-3 is thought to reduce wrinkles by disrupting the nerve signals sent

to tense muscle beneath the dermis—functionally relaxing them and smoothing the overlying skin.

2. *Key benefits*: Collagen and glycosaminoglycan stimulation, inhibition of cytokines, disruption of nerve signaling.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: Copper Peptides

1. *Science and clinical studies*: Benefits of copper peptides for tissue regeneration were discovered in the 1970s. Copper peptides have been shown to be effective in healing wounds and skin lesions as well as some gastrointestinal conditions (36). A double-blind, placebo-controlled study demonstrated that topical application of a copper peptide cream accelerated the rate of skin healing and reduced irritation after both irritant and allergic contact dermatitis. Although the primary area of studying copper peptides relates to wound healing, there has been some research implying that the complex has anti-inflammatory and antioxidant functions.
2. *Key benefits*: Cell signaling, wound healing, may have anti-inflammatory and antioxidant activity.
3. *Primary adverse effects*: None known, well tolerated.
4. *Practical applications in dermatology*: Acceleration of wound healing and may serve as an alternative to patients who are cannot tolerate retinoids.

Cell Signaling: DHEA

1. *Science and clinical studies*: DHAE and the sulfated conjugate (DHAE-S) are abundantly produced human adrenal steroids which become minimized with age. These materials relate to skin aging through the regulation of and degradation of extra cellular protein. DHEA has been shown to increase procollagen synthesis and inhibit collagen degradation by inhibiting metallo-proteinase (MMP-1) and increase tissue inhibition of MMP (TIMP-1) in dermal fibroblasts. Inhibition of cellular damage caused by UV exposure is thought to be due to inhibition of AP-1 activity. DHAE was also found to induce growth factor-beta 1 and connective tissue growth factor mRNA in cultured fibroblast. In a four-week study, a 5% DHAE mixture was applied to buttock skin three times a week to volunteers and produced a significant increase in the expression of procollagen alpha 1 mRNA and protein in both young and old skin and significant reduced basal expression of MMP-1 mRNA and protein, but increased TIMP-1 protein in aged skin.
2. *Key benefits*: Increase collagen synthesis, decrease MMP-1, and increase TIMP-1 to enhance collagen production and minimize collagen breakdown.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: DMAE

1. *Science and clinical studies*: DMAE is considered a tertiary amine and a precursor of choline. At concentration of 1% to 5% when applied to facial skin, DMAE have been shown to produce and increase tone in about 20 to 30 minutes. Half-and full-face studies applied over 16 weeks to one year have been shown to produce periorbital tightening as well as tightening in the molar and mandible regions. These results appear to reverse when product application is stopped after eight weeks (36).
2. *Key benefits*: Enhances muscle tonality and can act as a penetration enhancer.
3. *Primary adverse effects*: Low toxicity and no side effects.
4. *Practical applications in dermatology*: Non-surgical treatment to correct loss facial anatomic positions.

HOW TO SELECT THE "BEST" FORMULATION OF A COSMECEUTICAL

Stability

Most companies do not state if a product is stable or how long it will last either opened or unopened, with the exception of OTC products, which are expiration dated if they do not last more than three years. However, international cosmetic and/or cosmeceutical companies marketing in the EU are required to put an expiration date on products if they do not last for at least 30 months. Most recently, the EU has instituted in law that companies must now include an icon of an open jar with the number of months that the product is good for after it has been opened (Fig. 2). The latter is the best way for the consumer and skin care professionals to determine how stable a product may be. Although this regulation has become effective as of March 2005, it will eventually appear on domestic products manufactured by international marketing companies. With the exception of waiting for this system to come into practice in the U.S., the only other way to determine the stability of a product not expiration dated would be to call the manufacturer directly and ask.

36M on or near the open jar icon (below) would represent the number of months that a product is stable (in this case, 36 months or three years) after it has been opened. This number and icon must be present on both the product container as well as the box (if applicable) that it is sold in. At this time there is no standard for testing or minimal
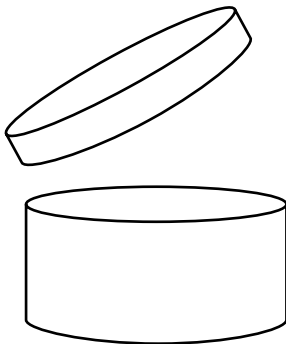
Figure 2 Example of period after opening (PAO) icon.

requirements that a product most be stable for in order to be marketed; however, it is expected that guidelines will follow shortly.

Efficacy

With the age of computers and Internet access, the best and easiest way to evaluate the efficacy of a product is to run a simple Internet search using an engine similar to Google (http://www.google.com). More advance searches may be conducted using various databases like PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed). The latter will be more specific; however, remember that not all manufacturers publish data in peer-reviewed scientific journals. Short of running your own database searches, the only other way to obtain this information is to call manufacturers directly and request copies of any data they have on file.

Science vs. Science Fiction

Although it would be great to be able to find all the information you want in a straight-forward peer-reviewed journal search, it is highly unlikely. The basic information that is obtained from an on-line database like Google will have a great deal of marketing hype with little to no science. However, it may not be a bad place to at least start to learn some basic information prior to contacting a manufacturer for additional information.

Value

With the cost of cosmeceuticals escalating to as much as $500 per ounce, it is extremely difficult to determine how to advise patients. First and foremost are questions of efficiency and safety. Is the product effective at all? Is it effective for each of the claims? Is there well-controlled statistically significant claimed data to substantiate these claims? How effective is the product relative to other effective products (OTC or Rx)? What is the relative cost to the patient compared to other available and effective products? Would you purchase this product using your own money for use on your own family?

THE FUTURE OF COSMECEUTICALS

Our knowledge of the cellular signaling pathways is growing by leaps and bounds due to advances in gene microarray analysis and other genomics and proteinomic discoveries. These are being rapidly translated into practical applications for skin care. The ability to understand the molecular biology associated with the development and maintenance of the skin's structure and function is vital to the future of scientifically sound skin care.

As we learn more about how the skin interacts with the environment around it and how it responds to injuries, we will see significant advances in therapies. There are vast numbers of botanical products available to evaluate which produce many unique molecules. Some of these are part of the plant's defenses against their environment and have applications for our skin as well. The ability to synthetically manufacture some of these complex compounds has expanded greatly in recent years, and the future is bright for our ability to not only copy but also to create new analogs and derivatives of such compounds.

The impact of free radicals/ROS on the skin and how to neutralize or control this at an early stage as ROS are initially generated will lead to more "preventive/defensive"

products and, with proper public education, hopefully a more proactive approach to skin care. This is the true "anti-aging"—much of current therapies are still focused on "age reversal" or repair rather than preventive therapies. The cascade of cellular events and damage triggered by free radicals and the negative impact of chronic upregulation/activation of degrading enzymes and chronic inflammation in the skin contribute greatly to "premature" aging. The years ahead will see more emphasis on "beauty maintenance" or "skin fitness for life" as products and actives and delivery systems become more scientifically sound.

The large pharmaceutical companies may begin to play a more significant role in cosmeceutical development as the ability to use cosmeceuticals for drug-like effects allows them to utilize their resources to develop effective new skin care products without some of the regulatory burdens and costs associated with drugs. The time delay from new discoveries to actual products available for consumer use can potentially be dramatically reduced by this pathway.

Single Nucleotide Polymorphism (SNP) testing via a mouth swab may well play a role in determining long-term skin care plans/needs for people in the near future as this testing becomes more available. Correlations of testing results with actual clinical needs based on solid science and clinical studies will be a challenge since this database will need to be developed. However, the ability to look at one's "variation" from the "normal" population in SNP could provide very useful insights into skin care.

Major breakthroughs in photoaging and repair of DNA damage and telomere repair appear to be imminent. Genetic engineering is still a struggling infant but can become a giant in skin care in the future. Hormonal regulation and immune function issues with the skin will be more important in the future. Much of what we were taught was "intrinsic aging" and thus not alterable by medicine and science will soon be able to be manipulated at some level—only time and some core genetic issues will be immutable. Treatments that were unthinkable a few decades ago will become a reality, and cosmeceuticals or their derivatives may well play a role in this area of medicine. The use of low intensity light to photomodulate skin cells and/or to activate or interact with topical cosmeceutical agents may also enter the market place.

Marketing claims will likely continue to push the edge of the envelope. It is unclear if or when (and at what point) the FDA may intervene in this arena, but this too bears watching closely. The science needed to support the claims is sadly absent in many cases, but there are also some stellar examples of great science and clinical studies for cosmeceuticals and this trend is growing. Hopefully we will see some new standards set in this industry for science and data that will allow us to discern what benefits are real and which products deliver them. However, in the short term it is likely that the current confusion in the marketplace will continue or perhaps worsen so education will be the key. Dermatology residency programs need to increase their training related to cosmeceuticals so that dermatologists are not left behind and maintain their tradition of being the true "skin care experts" and the best resource for consumers who need guidance in planning their skin care regimen. Dermatology needs to take a strong leadership position in cosmeceutical research and development as well.

Hopefully the near future will see more science and less "science fiction" in research and marketing claims for cosmeceuticals. The issue of hype versus hope versus reality is a very real one for contemporary advertising. The ability to harness the power of natural products and their derivatives for treating skin diseases and for anti-aging purposes is about to undergo giant leaps forward as genomic research gives us new understanding of the structure and function of the skin—and also provides much more accurate ways to

screen for active compounds and produce optimal formulations. Cosmeceuticals are the wave of the future in science-based skin care.

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13
Skin Lightening Agents

Wen-Yuan Zhu
Department of Dermatology, The First Affiliated Hospital, Nanjing Medical University, Nanjing, P.R. China

Ru-Zhi Zhang
Department of Dermatology, The Affiliated Hospital, BangBu Medical College, BangBu, P.R. China

The ideal depigmentating compound should have a potent, rapid, and selective bleaching effect on hyperactivated melanocytes, carry no short- or long-term side effects, and lead to a permanent removal of undesired pigment. Depigmentation can be achieved by regulating (i) the transcription and activity of tyrosinase, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), and/or peroxidase, (ii) the uptake and distribution of melanosomes in recipient keratinocytes, and (iii) melanin and melanosome degradation and turnover of "pigmented keratinocytes" (1).

TYROSINASE INHIBITION

Tyrosinase is a copper enzyme, which catalyses both the hydroxylation of monophenols to o-diphenols and the oxidation of o-diquinones to o-quinones. Most whitening agents act specifically to reduce the function of this enzyme by means of the following mechanisms (2): (i) interference with its transcription and/or glycosylation, (ii) inhibition by different modalities, (iii) reduction of by-products, and (iv) post-transcriptional control.

Hydroquinone

Hydroquinone (HQ), which is a hydroxyphenolic chemical, has been the gold standard for treatment of hyperpigmentation for over 50 years. Its therapeutic efficacy alone or in association with other compounds (3) seems to exert mainly in melanocytes with active tyrosinase activity. HQ may interfere with pigmentation even through: (i) the covalent binding to histidine or interaction with coppers at the active site of tyrosinase, (ii) the inhibition of DNA and RNA synthesis, (iii) the alteration of melanosome formation and melanization extent, and (iv) selectively damaging melanosomes and melanocytes.

The effectiveness of HQ is related directly to the concentration of the preparation. Concentrations of HQ vary from 2% (over the counter) to as high as 10% that are prescribed extemporaneously for resistant cases. It was known that the higher concentrations of HQ were more effective, but the irritating and toxin for melanocytes sign were obvious. There was a reduction in the effectiveness of HQ preparation due to oxidation so that stabilizing agents like sodium bisulphate and ascorbic acid were used as antioxidants. The most suitable vehicle for the formulation is a hydroalcoholic solution (equal parts of propylene glycol and absolute ethanol) or an hydrophilic ointment, or a gel containing 10% alpha-hydroxy acids (AHAs), taking into consideration the desired 3% to 5% HQ concentration in ethanol and propylene glycol 1:1 (or in a cream base or an AHA 10% gel).

The skin lightening effect of HQ can be enhanced by adding various topical agents such as tretinoin and corticosteroids. The following combination has been proposed by Kligman and Willis (5): HQ 5%, tretinoin 0.1%, dexamethasone 0.1%, in ethanol and propylene glycol 1:1 or in hydrophilic ointment. In this formula, tretinoin stimulates the cell turnover promoting the rapid loss of pigment via epidermopoieses, and acts as a mild irritant facilitating the epidermal penetration of HQ and as an antioxidant preventing the oxidation of HQ. Corticosteroids can eliminate the irritation caused by HQ and/or tretinoin (6).

Depigmentation of HQ preparation begins within three weeks after twice-daily application and it is used for a maximum of five to seven weeks. The formulation without antioxidants should never be more than 30 days old. A slight modification of the Kligman and Willis formula is the following: HQ 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% (or hydrocortisone 1%), in ethanol and propylene glycol 1:1 or in hydrophilic ointment. In this formulation the concentration of tretinoin is lowered to 0.05%, and the aim is to minimize the irritation caused by tretinoin and eliminates local steroid side effects (7). The improvement rate of melasma was ranging from 40% to 87.5% in two to four months.

The side effects of HQ include allergic contact dermatitis, irritant contact dermatitis (more probable with the higher concentrations), and post-inflammatory hyperpigmentation and nail discoloration. Irritation, stinging, and/or burning were observed transiently during the first day of application and disappeared with use of the medication after a few days.

Kojic Acid

Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyrane-4-one, KA) (8), a naturally occurring hydrophilic fungal derivative evolved from certain species of Acetobacter, *Asperigillus* and *Penicillium*, is used in the treatment of hyperpigmentation disorders (9). Its molecular formula is $C_6H_6O_{4,5}$, and its molecular weight is 142.1. It also eliminates free radicals, strengthens the activity of cells and keeps the food fresh.

The depigmetation action of kojic acid is attributed to the chelating ability (10), even if an interference with different steps of melanin synthesis (11) and inhibition of nuclear factor-kappa B (NF-kappa B) activation in keratinocytes, contrasting with the hyperpigmentation associated with inflammatory response (12). It is a kind of specialized inhibitor for melanin for preventing the tyrosinase activity through synthesizing with copper ion in the cells after it enters skin cells. KA and its derivative have better inhibitory effect on tyrosinase than any other skin whitening agents. At present it is assigned into various kinds of cosmetics for curing freckles, age spots, pigmentation, and acne. It has been used alone in concentration 2–4% and it has also been combined with HQ 2% in an AHA gel base (13).

KA dipalmitate is a modified kojic acid derivative, which not only overcomes the instability to light, heat, and metallic ion, but also keeps the inhibitory tyrosinase activity

and prevents the forming of melanin. As fat-soluble skin whitening agent, it is more easily absorbed by skin. Kojic acid has the potential for causing contact dermatitis and erythema (14). The heterozygous p53-deficient CBA mice were fed a diet containing 0%, 1.5%, and 3% KA for 26 weeks. KA induced diffuse hypertrophy and hyperplasia of the thyroid follicular epithelial cells and tumorigenic potential in the liver (15).

Azelaic Acid

Azelaic acid (AZA) is a naturally occurring 9-carbon dicarboxylic acid compound isolated from cultures of *Pityrosporum Ovale*. It inhibits tyrosinase activity in vitro ($K_i = 2.73 \times 10^{-3}$M) and may also interfere with DNA synthesis and mitochondria activity in hyperactive and abnormal melanocytes. AZA has been used to treat melasma and post-inflammatory hyperpigmentation and to arrest the progression of the lentigo maligna to melanoma. This specificity may be attributed to its selective effects on abnormal melanocytes (16). AZA produced ultra structural damage to normal melanocytes (17).

AZA cream has been reported to be of benefit in the treatment of melasma. The cream is applied twice daily and most patients report a mild but transient irritation and dryness of the skin at the beginning of the treatment. In the treatment of melasma, a 24-week study in South America found that a 20% concentration of AZA was equivalent to 2% HQ (18). In the Philippines, a study found that 20% AZA was better than 2% HQ. Three hundred and twenty nine patients with melasma were treated with 20% AZA and 4% HQ. Fifty six percent of the AZA group had good or excellent results while 73% HQ had a similar result (19).

Topical potent steroids and 20% AZA cream combines the beneficial effects of both besides perhaps increasing the compliance of the patients (20). AZA with tretinoin caused more skin lightening after three months than AZA alone, and a higher proportion of excellent responders at the end of treatment (16). The combination of AZA 20% cream and glycolic acid 15% or 20% lotion was as effective as HQ 4% cream in the treatment of hyperpigmentation in darker skinned patients, with only a slightly higher rate of mild local irritation (21).

Particular advantages of AZA therapy include its favorable safety and side effect profile. It is non-teratogenic, is not associated with systemic adverse events or photodynamic reactions, exhibits excellent local tolerability, and does not induce resistance in *Propionibacterium acnes* (22). Adverse effects from the AZA included irritant contact dermatitis that was usually mild and transient, but occasionally was pronounced.

Paper Mulberry Extract

Mulberry (*Morus alba* L.) leaves containing many nutritional components are the best food for silkworms. The extracts from mulberry leaves have a potent antihyperglycemic activity in diabetic mice. Many phenolic compounds have been identified from the root bark of mulberry tree. *Morus alba* L. also contains rutin, isoquercitrin, and astragalin. The root bark of *Morus alba* has been shown to have a skin whitening effect.

Lee et al. (23) investigated the in vitro effects of an 85% methanol extract of dried *Morus alba* leaves on melanin biosynthesis. These extracts inhibited the tyrosinase activity that converts dopa to dopachrome in the biosynthetic process of melanin. Mulberroside F (moracin M-6, 3′-di-O-beta-D-glucopyranoside), which was obtained after the bioactivity-guided fractionation of the extracts, showed inhibitory effects on tyrosinase activity and on the melanin formation of melan-a cells. But its activity was low and weaker than that of KA.

Aloesin

Aloesin, a natural hydroxymethylchromone derivative isolated from aloe vera, acts by two different mechanisms of action on tyrosinase activity, e.g., aloesin inhibits the formation of DOPA quinone by competitive inhibition at the DOPA oxidation site, reduction of copper ions at the hydroxylase site, and consequently tyrosine hydroxylation by non-competitive inhibition (24). In comparison with other depigmenting agents, aloesin shows no cytotoxicity in cell-based assays, no skin irritation in preliminary human studies and any genotoxicity or mutagenicity in the Ames assay. Cultured cells used in tyrosinase activity assays show no morphologic abnormalities when treated with aloesin, and human melanocytes appear normal with multiple dendrites (24).

Thus aloesin is a potent inhibitor of human tyrosinase. However, because of the hydrophilic nature of the compound and moderately high molecular weight, penetration of human skin was poor. Jones et al. (24) demonstrated aloesin dissolved in ethanol penetrates the skin slowly with approximately 1.59% of a finite dose penetrating the skin over a 32-hour period. At non-cytotoxic concentration aloesin probably acting as a competitive inhibitor on DOPA oxidation and as a non-competitive on tyrosine hydroxylase activity. Aloesin treatment showed pigmentation suppression in a dose-dependent manner; thus, aloesin might be used as an agent that inhibits melanin formation induced by UV radiation (25). In vivo, aloesin and arbutin co-treatment inhibits UV-induced melanogenesis in a synergistic manner.

The mixture of aloesin and arbutin showed a significant inhibition on tyrosinase activity of human melanocytes and reduced significantly melanin content, and had little influence on melanocytes viability (26).

Arbutin

Arbutin was first discovered in Arctostapylos uva-ursi (L.) Spreng and then in the leaves of Vaccinicum vitis-idaca L., Pyrus pyrifolia (Burm.f.) Kakai. and Saxifraga stolonifera (L.) Meerb. It is a naturally occurring HQ beta-D-gluconopyranoside, which causes depigmentation at non-cytotoxic concentrations. In both normal human melanocytes and melanoma, arbutin induces a decrease of tyrosinase activity without affecting messenger RNA (mRNA) expression, inhibits the 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase activity (pmel 17/*silver* protein) (27), and exerts an inhibitory effect on melanosome maturation. It was found to inhibit the oxidation of l-tyrosine catalyzed by mushroom tyrosinase (28). The kinetics and mechanism for inhibition of tyrosinase confirms the reversibility of arbutin as a competitive inhibitor of this enzyme (29). Arbutin was much less cytotoxic than HQ to cultured human melanocytes.

A clinical trial performed with Japanese women with melasma found a 3% arbutin-containing skin lotion, milky lotion and cream, applied twice daily for three months, to be effective in reducing melasma intensity and lesion size (good-to-excellent clinical response in 71.4% of patients) (30). Higher concentrations are more efficacious than lower concentrations, but they may also result in a paradoxical hyperpigmentation.

Licorice Extract

The licorice extract includes liquiritin, isoliquertin (a chalcone) that occurs as a glycoside and during drying is partly converted into liquiritin, liquiritigenin, isoliquiritigenin, and other compounds. Liquiritin causes depigmentation by two mechanism: (i) via melanin dispersibility by means of the pyran ring of the color dispersing flavonoidal nucleus of

liquiritin, and (ii) via amelanodermic and epidermal stain removing property. Acute and chronic toxicity studies have been carried out with no adverse effects. Glabrene and isoliquiritigenin ($2'$, $4'$, 4-trihydroxychalcone) in the licorice extract can inhibit both mono- and diphenolase tyrosinase activities. The IC_{50} values for glabrene and isoliquiritigenin were 3.5 and 8.1 μM, respectively, when tyrosine was used as substrate. The effects of glabrene and isoliquiritigenin on tyrosinase activity were dose-dependent and correlated to their ability to inhibit melanin formation in melanocytes (31).

Liquiritin cream is a new bleaching agent. Amer et al. (32) described that topical liquiritin cream applied at 1 g/day for four weeks is therapeutically effective in melasma. Good to excellent results with complete disappearance of melasma were observed in 18 (90%) out of 20 patients. Yasuaki (33) described the formulation of a liquiritin cream containing 20% liquorice. The cream was applied at 1 g/day to patients with melasma for one to four months and showed good efficacy. Side effects were minimal with mild irritation, which disappeared with continuation of treatment.

Ellagic Acid (Copper Chelation)

A polyphenol widely distributed in plants, is capable of preventing pigmentation caused by sunburn (34). Ellagic acid inhibits tyrosinase non-competitively in a dose-dependent manner, through its capacity to chelate copper, even if other mechanisms, such as a scavenger effect have been suggested. Interestingly, in brownish guinea pigs (34), ellagic acid induced a reversible inhibition of melanin synthesis only in UV-activated melanocytes (34).

PRODUCT REDUCTION AND REACTIVE OXYGEN SPECIES

Compounds with redox properties can have depigmenting effects by interacting with o-quinones, thus avoiding the oxidative polymerization of melanin intermediates, or with copper at the active site. Therefore, that melanin cannot be formed by the action of tyrosinase until all ascorbic acid is oxidized.

Ascorbic Acid

Ascorbic acid (AsA) interferes with the different steps of melanization, by interacting with copper ions at the tyrosinase active site and reducing dopaquinone and DHICA oxidation. Melanin can be changed from jet black to light tan by the reduction of oxidized melanin (35).

AsA is an effective reducing agent, which, at high concentrations, can momentarily retard the melanin-biosynthesis pathway, but never eliminate it. On the contrary, the resultant accumulation of diphenol produces an indirect activation on this pathway when the reductant is completely depleted (36). However, AsA is highly instable, being quickly oxidized and decomposed in aqueous solution and, because of its prevalent hydrophilic nature, has a low degree of penetration into the skin. Vitamin C iontophoresis may be an effective treatment modality for melasma (37).

Sixteen women with idiopathic melasma were instructed to use, at night, 5% ascorbic acid cream on one side of the face and 4% HQ cream on the other side, for 16 weeks. The improvement was observed on the HQ side with 93% good and excellent results, compared with 62.5% on the ascorbic acid side. Side effects were present in 68.7% with HQ versus 6.2% with ascorbic acid (38).

The numbers of DOPA-positive melanocytes of guinea pigs treated with VC, VE, and cystine were significantly decreased compared with those in VC group. In B16 melanoma cells, simultaneous treatment of VC, VE, and N-acetyl-cysteine was the most effective to decrease the melanin contents and to inhibit tyrosinase activity (39).

A multi-clinical, double-blind study on therapeutic effect of combination preparation of vitamins E and C was undertaken in comparison with single preparation of vitamin E and vitamin C in the treatment of chloasma or pigmented contact dermatitis (PCD). Objective data revealed significantly better results with combination treatment in chloasma than vitamin C alone and, in PCD, than vitamin E or C alone. The total serum lipoperoxide level and its ratio to total serum lipids tended to decline in the combination group and decreased significantly in vitamin E group. The sebum lipoperoxide level decreased significantly only in the combination group (40).

Magnesium-L-Ascorbyl-2-Phosphate (VC-PMG)

AsA is quickly oxidized and decomposed in aqueous solution and thus is not generally useful as a depigmenting agent. To resolve that problem, Magnesium-L-ascorbyl-2-phosphate (VC-PMG) was synthesized. VC-PMG is stable in water, especially in neutral or alkaline solution containing boric acid or its salt. VC-PMG is hydrolyzed by phosphatases of liver or skin to AsA and thus exhibits vitamin C-reducing activity (41). VC-PMG significantly suppressed melanin formation on purified tyrosinase or cultured cells and inhibited melanin formation without cell growth suppression on cultured human melanoma cells. Inhibition of melanogenesis was stronger when the activity of melanogenic enzymes was relatively high.

VC-PMG is absorbed percutaneously, stays in the skin, and inhibits tyrosinase activity of melanocytes. The addition of 1% to 3% 1,1-methyleneglycol-bis increases the absorption of VC-PMG. In situ experiments demonstrated that 10% VC-PMG cream was absorbed into the epidermis and that 1.6% remained 48 hours after application. When the 10% VC-PMGcream was topically applied to the patients, the lightening effect was significant in 19 of 34 patients with chloasma or senile freckles and in three of 25 patients with normal skin (42).

Thioctic Acid (Alpha-Lipoic Acid)

A disulfide derivative of octanoic acid, it exhibits several biologic effects, which include the quenching of ROS, metal chelation, interaction, and the regeneration of other antioxidants, redox regulation of protein thiol groups, and effects on gene expression and apoptosis (43). Thioctic acid has been reported to prevent UV-induced photo-oxidative damage, mainly through the down-modulation of NF-kappa B activation and to inhibit tyrosinase activity probably by chelating the copper ions (44).

Dihydrolipoic acid, lipoid acid, and resveratrol reduced microphthalmia-associated transcription factor and tyrosinase promoter activities. Dark skinned Yucatan swine treated with these agents showed visible skin lightening, which was confirmed histological, whereas ultraviolet B-induced tanning of light skinned swine was inhibited using these agents (45).

Alpha-Tocopherol (α-Toc)

Alpha-Tocopherol (alpha-Toc) and its derivatives inhibit tyrosinase in vitro and melanogenesis in epidermal melanocytes. The antioxidant properties of alpha-Toc,

which interferes with lipid peroxidation of melanocyte membranes and increases the intracellular glutathione content, could explain its depigmenting effect. Alpha-Toc has a more effective and long-lasting antioxidant response. Topical application of alpha-Toc and AsA, in vivo, decreases the tanning response inhibiting the UV-induced melanogenesis and proliferation of melanocytes. An alternative compound is alpha-Tocopherol ferulate (alpha-Toc-F), a derivative of alpha-Toc linked by an ester bond to ferulic acid, an antioxidant, which provides stabilization to alpha-Toc, similar to AsA. Alpha-Toc inhibited melanogenesis in cultured normal human melanocytes, although it did not influence melanin synthesis in enzyme solution prepared as cell homogenates. In addition, alpha-Toc stimulated intracellular glutathione (GSH) synthesis (46).

Thirty μ/ml of alpha-TF dissolved in 150 μg/ml of lecithin inhibited melanization significantly without inhibiting cell growth. No significant effect on DOPA chrome tautomerase (DT) activity was observed (47).

INHIBITION OF MELANOSOME TRANSFER

The activation of protease-activated receptor-2 (PAR-2), a seven *trans*-membrane G-protein coupled receptor, which is expressed in keratinocytes and not in melanocytes, was found to activate keratinocyte phagocytosis, enhancing the melanosome transfer (48). Inhibition of PAR-2 cleavage by serine protease inhibitor, such as RWJ-50353, completely avoids the UVB-induced pigmentation of epidermal analogs (49,50).

Niacinamide

Niacinamide or nicotinamide is a biologically active form of niacin (vitamin B_3) involved in over 200 enzyme reactions in the form of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate.

Hakozaki et al. (51) suggested that niacinamide has no effect on tyrosinase activity, melanin synthesis, or cell number in melanocyte monoculture system, and no effect on the proliferation of keratinocytes. The research results showed that niacinamide downregulated the amount of melanosomes transferred from melanocytes to surrounding keratinocytes in a coculture system by approximately 35–68%.

Daily use of a niacinamide moisturizer was effective in reducing hyperpigmentation and in increasing lightness of basal skin color compared with control moisturizer. The efficacy of topical niacinamide for decreasing facial hyperpigmentation and lightening skin color in vehicle-controlled protocols was evaluated (51).

RWJ-50353

RWJ-50353, a serine protease inhibitor that reduced melanosome uptake in culture, is shown to have a dose-dependent depigmenting activity in vivo with no irritation or other side effects. Treatment with increasing concentrations of RWJ-50353 did not affect tyrosinase mRNA levels. Interestingly, this treatment led to decreased levels of TRP-1 and increased levels of TRP-2 mRNAs (49). The downregulation of TRP-1 by RWJ-50353 should lead to reduced tyrosinase activity and reduced pigment production.

RWJ-50353 inhibits melanosome transfer from melanocytes to keratinocytes by its inhibitory effect on the keratinocyte PAR-2 signaling pathway. RWJ-50353-treated keratinocytes are unable to actively take or receive melanosomes from the presenting dendrites. Electron microscopy studies illustrated an accumulation of immature

melanosomes inside melanocytes and abnormal dendrite dynamics in RWJ-50353-treated epidermal equivalents.

In vivo RWJ-50353 (up to 10mM, twice-daily treatment to swine skin) could not completely inhibit melanogenesis or pigment transfer, and the transferred melanosomes are of poor quality (50). Treatment of dark skinned Yucatan swine for eight weeks with RWJ-50353 induced visible skin lightening. Histological analysis of treated sites at eight weeks shown only minimally stained melanin granules dispersed in the basal layer of epidermis (50).

Soybean Trypsin Inhibitor

Soybean trypsin inhibitor (STI) inhibited PAR-2 cleavage, and completely inhibited the UVB-induced pigmentation of the epidermal equivalents containing melanocytes (50). Treatment with STI resulted in significant depigmentation, and reduced pigment deposition within the swine epidermis and prevented UVB-induced pigmentation in vivo. STI reduced keratinocyte ingestion of microspheres or *E.coli* particles (48). STI-treated cells showed reduced number and shorter length podia.

STI-treated melanocytes within epidermal increased the number of less mature melanosome and dendrites with mature melanosomes. UV-induced tanning of Yucatan swine was prevented with topical treatments of STI-containing compositions (52).

SKIN TURNOVER ACCELERATION

The capacity of several compounds to disperse melanin pigment and/or accelerate epidermal turnover can result in skin lightening. Chemical substances used as exfoliates, such AHAs, free fatty acids, and retinoic acid, stimulate cell renewal facilitating the removal of melanized keratinocyte, leading to melanin granules loss (53). Topical application has been shown to reduce the visibility of age spots without reducing their size or number (54), and can be useful in the treatment of melasma (55).

Unsaturated fatty acid, such as oleic acid, linoleicacid, or alpha-linolenic acid, suppress pigmentation, in vitro, whereas saturated fatty acids, such as palmitic acid, increase the rate of melanogenesis (56).

Alpha Hydroxy Acids

The benefits of AHAs have long been recognized. Sour milk [contains lactic acid (LA)] and sugarcane juice [contains glycolic acid (GA)] were applied to the face. In low concentrations, AHAs decreased corneocyte cohesion, leading to sloughing of dead cells and stimulation of new cell growth in the basal layer. In higher concentrations, they cause epidermilysis. AHAs have been reported to be effective in treating pigmentary lesions such as melasma, solar lentigines, and post-inflammatory hyperpigmentation. The mechanism of this effect might be due to epidermal remodeling and accelerated desquamation, which would result in quick pigment dispersion. GA and LA might work on pigmentary lesions not only by accelerating the turnover of the epidermis but also by directly inhibiting melanin formation by inhibiting tyrosinase in melanocytes (57). GA or LA (at doses of 300 or 500 µg/ml) inhibited melanin formation in similar dose-dependent manner, without affecting cell growth. The bioavailability of AHAs increases as the pH decreases (desirable pH 2.8–4.8), and they are the only peels that are time-dependent and can be neutralized easily.

A cream containing 4% HQ, 10% buffered GA, vitamins C and E, and sunscreen is safe and effective in the treatment of melasma (58). The addition of kojic acid to a gel containing 10% GA and 2% HQ further improves melasma (59). Javaheri et al. (55) concluded that a prepeel program of daily application of topical sunscreen (SPF-15) and 10% GA lotion at night for two weeks, followed by 50% GA facial peel with a duration of two, four and five minutes once every month for three consecutive months proved to be an effective treatment modality for melasma in Indian patients. The beneficial results achieved can be maintained with topical application of 10% GA and 2% HQ. There are hardly any side effects.

Linoleic Acid

Linoleic acid in vivo showed the greatest lightening effect in UVB-induced pigmentation, without toxic effects on melanocytes (53). Several protease inhibitors caused the accumulation of an approximately 60 kDa tyrosinase doublet promoted the translation of the enzyme to melanosomes (60). The evidence suggests that tyrosinase in selectively targeted by fatty acids, which seem to act on the degradation of the enzyme during the physiologic proteasome-dependent mechanism (61). Linoleic acid accelerates the process whereas palmitic acid works in an antagonistic manner mimicking protease inhibitors (61).

In vitro experiments using cultured murine melanoma cells showed that melanin production was inhibited most effectively by alpha-linolenin acid, followed by linoleic acid and then by oleic acid. Furthermore, the turnover of the stratum corneum, which plays an important role in the removal of melanin pigment from the epidermis, was accelerated by linoleic acid and by alpha-linolenic acid (62). Topical application of linoleic acid is considered to be effective in the treatment of melasma patients (63).

TRADITIONAL CHINESE MEDICINE

Traditional Chinese herbs are a very popular mode for the treatment of hyperpigmentation disorders. Two hundred nineteen kinds of herbs have been screened; among them 19 kinds have been shown to inhibit tyrosinase in vitro (64). The inhibitory effects of tyrosinase activity of *Atractylodes macrocephala, Bombyx mori, Ligusticum sinense, Bletilla striata, Typhonium giganteum, Astragalus complanatus, Serissa erissoides*, and *Diospyros kaki* were either superior or similar to that of arbutin (64).

Cinnamic Acid

Cinnamic acid, a naturally occurring aromatic fatty acid of low toxicity, has a long history of human exposure. The cinnamic acid induces cytostasis and a reversal of malignant properties of human tumor cells in vitro. The cinnamic acid was found to induce cell differentiation as evidenced by morphological changes and increased melanin production in melanoma cells (65). Cinnamic acid does not influence the fungal growth but decreases the yield of the pigment from the mycelium (66).

Sophorcarpidine

Tyrosinase activity can be greatly inhibited by cinnamic acid, aloin, and sophorcarpidine, of which sophorcarpidine functions as an uncompetitive inhibitor, compared to aloin and cinnamic acid, which are mixed-type inhibitors (67). Tan et al. (67) demonstrated that

sophorcarpidine, aloin, and cinnamic acid can not only bind to the enzyme, but also to the enzyme-substrate complex as well, leading to the inactivation of tyrosinase.

Chemical structures of some depigmenting agents. Most of the compounds are modulators of melanogenic enzyme activity, their structures show chemical analogy with L-tyrosinase the natural substrate of tyrosinase.

1. Structure of hydroquinone
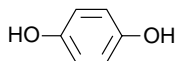
2. Structure of kojic acid
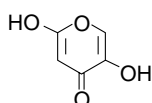
3. Structure of ellagic acid
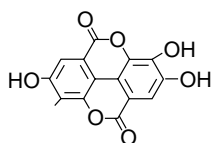
4. Structure of aloesin
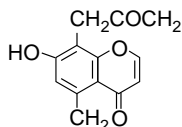
5. Structure of arbutin
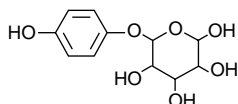
6. Structures of liquiritin and liquirigenin
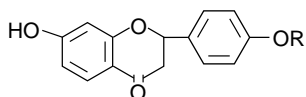
Liquiritin, R=Glucosyl liquirigenin, R=H.

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14

Medical and Surgical Approaches to Skin Lightening

Marta I. Rendon

Dermatology and Aesthetic Center and University of Miami, Miami, and Florida Atlantic University, Boca Raton, Florida, U.S.A.

Jorge I. Gaviria

Medical Hair Research Group, Inc. and Clinical Research, Skin Care Research, Inc., Boca Raton, Florida, U.S.A.

INTRODUCTION

When approaching a patient with a pigmentary disorder, four issues must be taken into consideration: the patient's skin type and ethnic background, type of disorder, history of reaction to prior surgical treatments, and post-inflammatory hyperpigmentation (PIH). This information is necessary to determine the most appropriate treatment option. Hyperpigmentation is caused by a wide variety of conditions, diseases, and entities, most of which are acquired. Pigmentary disorders have a tremendous impact on patients' self-esteem and social interactions; therefore, improving patients' quality of life is essential.

Treatments for these disorders can be difficult and lengthy, often resulting in a high degree of patient dissatisfaction and causing some patients to seek care from another dermatologist. Therefore, educating patients to have realistic expectations is an important aspect of the therapeutic process. This chapter will discuss the factors essential to choosing the optimal therapeutic approach, and includes a discussion of first-line therapies, when botanicals should be incorporated, and at what point surgical or other procedures should be used.

The treatment of pigmentary disorders is one of the greatest challenges in dermatology (Table 1). The therapeutic armamentarium has been reduced due to the lack of efficacy of most depigmenting agents available on the market. Relapses, as well as lack of permanent remissions, are the norm rather than the exception.

Hyperpigmentation is caused by a wide variety of factors (Tables 1 and 2). The mechanisms inducing hyperpigmentation have not been completely elucidated. Pigmentation is a complex metabolic process that includes tyrosinase activity, melanosome formation, and a cascade of intermediate metabolites that result in the formation of melanin. A rational therapeutic approach should be medications or

Table 1   Causes of Hyperpigmentation

Acanthosis nigricans
Addison's disease
Argyria
Becker's nevus
Café au lait macules
Drug-induced hyperpigmentation (Table 2)
Dyschromatosis symetrica hereditaria
Dyschromia of photoaging
Ephelides
Erythema dyschromicum persistans
Erythromelanosis follicularis
Exogenous ochronosis
Familial periorbital hyperpigmention
Hemochromatosis
Hyperthyroidism
Lentigines
Linea fusca
Liver disease
McCun-Albright syndrome
Melasma
Nevi
Nevus de ota
Photoallergic reaction
Pituitary tumors
Poikiloderma of civatte
Post-inflammatory hyperpigmentation
Polycistic ovarian syndrome
Pregnancy
Scleroderma
Riehl's melanosis
Solar lentigines
Sun exposure
Tinea versicolor
Causes of acquired hyperpigmentation
Skin diseases and conditions
Erythromelanosis follicularis
Linea fusca
Melasma
Poikiloderma of civatte
Postinflammatory hyperpigmentation
Riehl's melanosis
Exogenous causes of acquired hyperpigmentation
Cosmetics
Drugs (Table 2)
Photosensitizing agents (e.g., berloque dermatitis due to bergamot oil, furocoumarins)
Ultraviolet exposure (e.g., melasma, solar lentigines, ephelides)
Ultraviolet tanning beds

compounds acting at different levels of the melanogenesis cascade to produce better aesthetic and clinical results.

Treatment of hyperpigmentation induced by medications should be individualized. In some cases, discontinuation of the drug is impossible, and treatment must be delayed

Table 2   Drugs Known to Induce Hyperpigmentation

Amiodarone
Amitriptyline
Arsenic
Bismuth
Bleomycin
Busulfan
Clofazimine
Cyclophosphamide
Daunorubicin
Dibromomannitol
Doxorubicin
Gold
Mercury
Minocycline
Nitrogen mustard
Phenothiazines
Phenytoin
Silver
Sulfonamides
Tetracyclines
Zodovudine

until that medication is no longer in use. In other cases, progressive discontinuation of the medication is the answer. Use of an alternative medication can solve the pigmentation phenomenon in other patients (1).

No standard therapeutic guidelines exist for treating the most common hyperpigmentation disorders, including lentigines, melasma, pigmentation of aging, and PIH. Due to variations in therapeutic regimes, the different population groups studied, and the limited number of comprehensive studies performed to date, comparison of results is very difficult. This chapter is an overview of topical depigmenting agents and a discussion of physical and combination therapies currently available to treat hyperpigmentation (2).

TOPICAL DEPIGMENTING AGENTS

See Tables 3, 4, and 5.

PHENOLIC DEPIGMENTING AGENTS

Hydroquinone

Hydroquinone, a phenolic compound, is considered the gold standard depigmenting agent. Multiple studies have shown its efficacy in the treatment of many different types of hyperpigmented lesions (3).

Monomethyl of Hydroquinone

Monomethyl of hydroquinone, also known as 4-hydroxyanisole, mequinol, 4-methoxyphenol, hydroquinone monomethyl ether, and p-hydroxyanisole, is a substance widely used in France

Table 3 Cosmeceutical Skin Lightening Agents

Aloesin
Alpha-lipoic acid
Arbutin and bearberry
Ascorbic acid
Azelaic acid
Emblica
Glycolic acid
Helix aspersa müller
Hydroquinone
Idebenone
Kojic acid
Licorice extract—glabridin
Linoleic acid
Liquiritin
Melatonin
Niacinamide-niacin
Oleic acid
Paper mulberry
Retinoids
Soy extract
Tyrostat
Unsaturated fatty acids, oleic acid, linoleic acid, and alpha-linolenic acid
Vitamin C

for melasma and PIH, and throughout the European Union as an alternative to hydroquinone. It was recently approved in the United States for the treatment of lentigines. Reported side effects include contact dermatitis, hypomelanosis at distant sites, leukoderma, and PIH. In a recent study of mequinol in the treatment of solar lentigines, two women diagnosed with solare lentigines were successfully treated with a combined regimen of mequinol 2% and tretinoin 0.01% (4).

Table 4 Prescription Skin Lightening Agents

Hydroquinone
Mequinol
Retinoid monotherapy, tretinoin (all-trans-retinoic acid), tazarotene
Azelic acid
Combination products
Hydroquinone, retinoic acid and steroids
Hydroquinone, retinol
Hydroquinone, retinol and vitamins
Other depigmenting agents
4-N-butylresorcinol
4-Isopropylcatechol
Kojic acid
Monomethyl of hydroquinone
N-acetyl-4-S-cystalminylphenol
Polipodium leucotomos

Table 5 Therapeutic Approaches to Hyperpigmentation

Mild	Moderate	Severe	Sunscreen	Sunscreens	Sunscreens
	Azelaic acid Glycolic acid	Hydroquinone 3%–4% Hydroquinone 4%	Hydroquinone 3%–4% Tretinoin 0.05% and Fluocinolone acetonide 0.01%		Tretinoin 0.05% and Fluocinolone aceto-nide 0.01%
Hydroquinone 4%, Tretinoin 0.05% and Fluocinolone acetonide 0.01%	Hydroquinone 2%–4%	Kojic acid Hydroquino-ne/Retinol Kojic acid	Hydroquinone/Retinol	Hydroquinone 4%	
Retinol / Tretinoin	Retinol / Tretinoin Chemical Peels	Hydroquinone +G.A. Hydroquinone + Retinol	Retinol / Tretinoin Microdermabrasion	Kojic acid	
Maintenance: Tretinoin Azelaic acid Kojic acid Cosmeceuticals					

4-Isopropylcatechol

4-isopropylcatechol has been known as a potent depigmenting agent for more than 35 years. Like other phenolic compounds, it is a tyrosinase inhibitor. In a study done in the early 1970s, most of the melasma patients treated showed skin irritation, and atopic dermatitis. Yet two-thirds also showed significant improvement (5). Due to its specific mechanism of action targeting melanocytes, it has promise for use in melanoma and melasma patients (6–8).

N-Acetyl-4-S-Cystalminylphenol (NA-CAP)

N-acetyl-4-S-cystalminylphenol (NA-CAP) is one of the four known synthesized phenolic thioether amines that are tyrosine-amine derivative analogues. Their toxicity is tyrosinase dependent and targets only melanocytes. This makes NA-CAP, a promising anti-melanoma and anti-melasma medication (9). In vitro and in vivo studies of NA-CAP have demonstrated its selective melanocytotoxic and antimelanoma effects (10,11), particularly in the selective disintegration of melanocytes in black hair and skin. NA-CAP is more stable than catechols, and its toxicity appears after oxidation by tyrosinase. A small study showed its efficacy in melasma patients (12). Due to the fact that it is less irritating than hydroquinone, this phenolic thioether known for 20 years is a promising stable molecule for use in melasma patients.

4-N-Butylresorcinol

4-N-butylresorcinol has been approved in Japan, where it is used to treat melasma. This compound decreases PIH following laser therapy in melasma patients.

Aloesin

Aloesin a low-molecular-weight ingredient of latex exudates and glycoproteins from aloe vera gel. Aloesin is a hydroxychromone that inhibits tyrosinase at non-toxic concentrations. In vivo, aloesin inhibits UV-induced melanogenesis (13,14).

NON-PHENOLIC AGENTS

Azelaic Acid

Azelaic acid is a 9-carbon dicarboxylic acid used in melasma and PIH. Azelaic acid is often better tolerated in individuals sensitive to hydroquinone. Although its lightening effects are mild, several large studies done with a diverse ethnic background population have compared its efficacy to that of hydroquinone. This has led to the conclusion that although skin irritation is greater, the efficacy of azelaic acid is similar to that of hydroquinone (15–18).

Kojic Acid

Kojic acid is a fungal metabolic product used for the treatment of hyperpigmentation. Kojic acid has been used as an agent to treat melasma (19). When combined with hydroquinone, kojic acid improves the melasma outcome treatment (20). Studies comparing the product to hydroquinone shows kojic acid has the same efficacy (21).

Ascorbic Acid

Ascorbic acid. The stable ester of ascorbic acid (ascorbyl) is used in treating hyperpigmentation. It acts on the melanogenesis cascade, interacting with copper ions to reduce dopaquinone and block dihydrochinindol-2-carboxyl acid oxidation (22). When objective measures were used in a double-blind, randomized trial study to determine efficacy, ascorbic acid (Mg L-ascorbyl-2 phosphate) in a 10% cream base had an efficacy similar to that of hydroquinone in melasma patients (23). Subjective measurements favored hydroquinone. However, these data are limited, and larger studies should be done to verify its efficacy.

Retinoid

Retinoid monotherapy is conducted with tretinoin (all-trans-retinoic acid), which is formed from the oxidation of the aldehyde group of retinene to a carboxyl group. Tretinoin reduces epidermal pigment in a variety of pigmentary disorders (lentigines, melasma, pigmentation of aging, and PIH) in dark skinned people (24). Results are encouraging, but improvement can take from several months to one year (25).

Tazarotene

Tazarotene, an acetylenic topical retinoid, produces good results in pigmented aging spots. Moderate to marked depigmenting effect occurs when used as a gel in a concentration of 0.1%.

TOPICAL COSMECEUTICALS

Topical skin lightening cosmeceuticals are becoming more popular. They have been used alone and in combination therapy. In medical practice they are sometimes used as maintenance agents, and very seldom used in patients who are unable to tolerate various prescription medications or in place of other properties such as antioxidants, anti-aging products, or moisturizers.

Commonly used depigmenting agents include arbutin, ascorbic acid, bearberry extract, idebenone, indomethacin, licorice extract, melawhite, mercury, and mulberry plant extract (Table 3). No controlled studies investigating the efficacy and safety of these compounds have been conducted, and although insufficient data exist to conclude their efficacy, successful results have been published (26).

Thioactic Acid

Thioactic acid (alpha-lipoic acid) is a disulfide derivative of octanoic acid that inhibits tyrosinase activity and prevents UV-induced photodamage. Clinical data proving its efficacy are minimal (27).

Unsaturated Fatty Acids

Unsaturated fatty acids [oleic acid (C18:1), linoleic acid (C18:2), and alpha-linolenic acid (C18:3)], suppress pigmentation in vitro. A clinical study done with Korean women using topical linoleic acid showed significant improvement in melasma (28).

Idebenone

Idebenone, a potent antioxidant, is a benzoquinone that has shown depigmenting properties in pilot studies of patients with melasma and facial hyperpigmentation. Idebenone has been recently introduced to the U.S. market as Prevage.

Licorice Extracts

Licorice extracts (Glycyrrhiza Glabra and Glycyrrhiza Uralensis), marketed as liquiritin, contains flavanoids and a glycoside called glycyrrhizin, and have shown utility in treating melasma (29).

BOTANICALS

In the early 20th century, cosmetics and skin care treatments were made at home from fruits, herbs, and vegetables. A century later, manufacturers and consumers are returning to the notion that natural is healthier, and the holistic approach to skin care is in demand. A 47.3% increase in the demand for alternative remedies occurred between 1990 and 1997, and an estimated 60% of doctors recommend alternative therapies; 47% use alternative therapies themselves (30).

The search for alternatives to hydroquinone led to the discovery of a wide variety of natural depigmenting agents that are now available commercially and are found in cosmetics and in various skin lightening agents sold over the counter.

In addition to their lightening effects, these products can have antiseptic, antioxidant, and moisturizing properties. In many cases, synthetic ingredients are added to enhance results. However, there is a rising tide of patients demanding that all components of skin care products and cosmetics be natural, including preservatives. The challenge is to find naturally derived preservatives that interact with advanced formulations for today's skin care demands. Manufacturers are using all-natural preservatives, such as essential oils, herbs, and fruit extracts that when processed can be 75 to 100 times more potent that their original source.

The research and development departments of cosmeceutical skin companies continually search for new avenues in the treatment of skin pigmentation, new ingredients, and alternate delivery systems.

The use of botanicals should be considered in patients with hypersensitivity to multiple prescription products, patients with contraindications to the use of laser or pulse light therapies, and patients seeking alternative therapies without invasive procedures.

PHYSICAL THERAPIES

This section will focus on physical therapies and lasers, concentrating on the most common hyperpigmenting disorders seen in our daily dermatology practice: lentigines, melasma, pigmentation of aging, and PIH. We will also discuss the use of combination therapies in managing these disorders.

Most authors believe that physical therapies have a place in the treatment of pigmentary disorders. This is also our personal experience. Medium and deep chemical peels with trichloroacetic acid, dermabrasion, and laser therapy may be used in the treatment of hyperpigmentation. However, their success and clinical efficacy are limited.

Medium-depth peels and dermabrasion are rarely used when treating types IV-VI skin phototypes, as these approaches often result in hypopigmentation or hyperpigmentation in this population (31).

CHEMICAL PEELS

Chemical peels with glycolic acid, trichloroacetic acid, Jessner's solution, kojic acid, salicylic acid, and tretinoin are used in the treatment of melasma. Peels are usually done as adjunctive therapy or when faster results are desired. Glycolic acid peels in concentrations ranging from 10% to 70% can produce excellent results in dark skinned patients, as well as in Asians and Latinos. In one study involving 25 non-pregnant women with melasma who were treated with 50% glycolic acid once a month for three consecutive months, a 91% improvement was seen (32).

Serial glycolic acid peels have been shown to provide additional benefit when added to triple-combination therapy (5% hydroquinone, 0.05% tretinoin, and 1% hydrocortisone acetate) in epidermal melasma. In a study done in 40 dark skinned Indian patients, 20 were given triple combination therapy plus serial glycolic acid peels and 20 received triple therapy alone. Both groups showed statistically significant improvement from baseline. However, there was a trend toward more rapid and greater improvement in the group receiving serial peels (33,34). Further success has been achieved through the combination of glycolic acid peels and hydroquinone with kojic acid (20).

In dark skinned patients, 1% tretinoin peels have shown similar efficacy and tolerance to 70% glycolic acid peels. In a study of Asian women, clinical, and histological improvement was achieved with twice-weekly topical 1% tretinoin peels for two-and-a-half weeks. Minimal skin reactions were noted (35).

The combination of glycolic acid peels with hydroquinone has proven no more effective than hydroquinone alone. However, the combination subjectively improves melasma. In one study, 10 Asian women were treated with a 10% glycolic acid and 2% hydroquinone combination product applied to the entire face twice daily. The patients also received a 20–70% glycolic acid peel every three weeks to one side of the face (eight peels total). All participants were evaluated by an independent dermatologist. Munsell color chart and photographs showed improvement in pigmentation and fine wrinkling on both sides of face. The side receiving glycolic acid peel showed slightly better improvement, but it did not reach statistical significance (25).

Another study of combination therapy involving hydroquinone and glycolic acid peels produced no difference in 21 Latin women with epidermal and mixed melasma. In this split-faced study lasting eight weeks, patients applied 4% hydroquinone to the entire face twice daily and 20%–30% glycolic acid peels hemifacially every two weeks (four peels total). Objective evaluation showed that both treatments significantly reduced skin pigmentation, although no significant difference between the combination therapy and hydroquinone alone were seen (37).

Superficial peels have been shown to hasten the effect of topical treatments. Sixteen women with Fitzpatrick skin types II-VI received pre-treatment peels with 0.05% tretinoin for one to two weeks. They were then given three peels one month apart in which half the face was treated with 70% glycolic acid and half with Jessner's solution. Post-treatment was done with 4% hydroquinone and 0.05% tretinoin. Objective evaluation showed average lightening on both sides of the face (38). Similar improvement was seen in a similar study where topical tretinoin alone was used for 10 months (24).

Topical therapies can also enhance the results of resurfacing techniques. Hevia showed that 0.1% tretinoin accelerates healing after 35% trichloroacetic acid peels in a split-face, placebo-controlled study of 16 male patients. In this cohort, 75% of tretinoin-pretreated hemifaces were completely healed at day 7, as compared with 31% of the placebo-treated hemifaces (39).

Alpha-hydroxy acid peels have been shown to increase efficacy when combined with topical treatments containing bleaching agents on patients with melasma. They have also shown efficacy in patients with pigmentation due to photodamage. Alpha-hydroxy acid peels have proven safe and effective on all skin phototypes (40).

MICRODERMABRASION

Aluminum oxide crystal microdermabrasion was developed in 1995 (41). This process produces superficial epidermal abrasion, and has been used primarily for facial scarring and photodamage. No clinical studies have been done in melasma or any other hyperpigmentation disorder. Although data are lacking in this regard, the effect of microdermabrasion on accelerating the epidermal barrier function makes it a valuable adjuvant therapy (42).

Microdermabrasion is a "feel-good" procedure that can be used to complement topical regimens. We usually alternate the procedure with a series of glycolic acid peels, since their mechanisms of action are different.

DERMABRASION

Dermabrasion is rarely used in pigmentary disorders. One Asian study involving 410 patients with recalcitrant melasma treated with dermabrasion reported 97% clearing. Erythema and PIH was seen following dermabrasion, and partial recurrence of pigmentation can occur following initial clearance of melasma (43).

No clinical trials of combination therapy with dermabrasion and other physical therapies or topical depigmenting agents for melasma or PIH have been performed.

LASERS

CO2 and Erbium

CO2 and erbium resurfacing lasers are commonly used in the treatment of photoaging and acne scarring. They are seldom used for treating pigmentary disorders. Although no general consensus exists on the value of CO2 laser treatment for hyperpigmentation disorders, some authors have reported its use in recalcitrant melasma.

The Combination of CO2 and Q-Switched Alexandrite Lasers

The combination of CO2 and Q-switched alexandrite lasers has produced better results than the Q-switched alexandrite laser alone. In a study done in Thailand, six women were treated on one side of the face with combined ultrapulse CO2 laser and Q-switched alexandrite laser, and on the other side with the Q-switched alexandrite laser alone. The combination of lasers produced a superior and significant reduction in pigmentation, as compared with the single laser (45,46). However, an increase in undesirable side effects,

including PIH, was also seen. Some authors believe that treatment with hydroquinone and retinoic acid prevents PIH after treatment with CO2 laser (47,48).

Pigment-Specific Lasers (Pulse-Dye Pigment, Q-Switched Alexandrite CO2, Q-Switched Ruby, and Q-Switched Nd-Yag)

Pigment-specific lasers (pulse-dye pigment, Q-switched alexandrite CO2, Q-switched ruby, and Q-switched Nd-Yag) are generally recommended only for recalcitrant melasma following the failure of all other therapies. On the other hand, these lasers are the treatment of choice for isolated pigmented lesions, such as lentigos (49).

Q-Switched Ruby Lasers

Q-switched ruby lasers have been successfully used treating specific pigmented lesions such as benign melanosis, labial melanotic macules, mucocutaneous melanosis associated with Peutz-Jeghers syndrome, and phacomatosis pigmentovascularis. Efforts to treat melasma and solar lentigines with the Q-switched ruby laser have not been successful (50–54).

Q-Switched Alexandrite Lasers

Q-switched alexandrite lasers combined with chemical peels have been used to successfully treat acquired bilateral nevus of Ota, freckles, PIH, and recalcitrant dermal melasma in Korean patients with Fitzpatrick skin types IV–VI. The combination is effective and safe (55). Statistically significant results were achieved in a study group of Koreans with Fitzpatrick skin types II–IV and solar lentigines using an alexandrite laser for hair removal (56). When used in combination with CO2 laser, the results in the treatment of refractory melasma were superior to the use of the alexandrite laser alone (45).

Q-Switched Nd-Yag

Q-switched Nd-Yag lasers have proven useful for treating deep-pigmented lesions, such as nevi of Ota and tattoos in dark skinned persons, with a reduction in the risk of epidermal injury (57). Freckles and lentigines in Fitzpatrick prototypes IV or prototypes IV-IV can also be successfully treated with the Q-Switched Nd-Yag laser. Minimum adverse reactions and good cosmetic results can be expected (58).

Tattoos also can be effectively treated and removed with several Q-switched lasers, resulting in minimal scarring (59).

In our clinical practice, a thorough and detailed medical history is performed on each patient seeking treatment for a pigmentary disorder before using any kind of laser. This is done to identify high-risk patients, such as dark skinned patients with Fitzpatrick IV–VI, since post-laser repigmentation and PIH are common occurrences (Table 6).

Erbium:YAG Lasers

Erbium:YAG lasers have been shown to improve melasma, but the nearly universal appearance of PIH necessitates prophylactic skin preparation with tretinoin, hydro-quinone, and desonide nightly for two to four weeks prior to laser treatment (60).

Intense Pulsed Light (IPL)

Intense pulsed light (IPL) has been successfully used in refractory melasma in Asians, and has been found to be more useful than pigment-specific lasers in severe cases of melasma. It is also an excellent laser for treating lentigenes associated with photoaging (61). In a study of 33 Asian women with refractory dermal or refractory mixed melasma, the combination of IPL with 4% hydroquinone for one month was more effective than hydroquinone alone. Objective measurements were used to evaluate the skin lightening effect. A 39.8% improvement in relative melanin index was seen in the combination treatment group, versus 11.6% in the hydroquinone group at week 16 ($p < 0.05$). Four treatments were done at one-month intervals. Two patients in the IPL group experienced PIH. Partial transient repigmentation was noted 24 weeks after the last treatment session in two patients (62). IPL has also proven effective in the treatment of freckles in Asian patients (61) and in disfiguring lentigines associated with Peutz-Jeghers syndrome (63,64).

Intense pulse light can be safely used in dark skinned people with dermal hyperpigmentation.

Pigment Dye Lasers

Pigment dye lasers have been used with success in café-au-lait macules, ephelides, lentigines, and orange, red, and yellow tattoos. However, they are no longer recommended due to serious secondary reactions reported, including skin discoloration and purpura (66). When topical 0.05% retinaldehyde is used with the 1540 nm erbium:glass laser, the effects of the increasing dermal thickness is potentiated. In one study, half the subjects applied 0.05% retinaldehyde daily after laser treatment and for up to three months after the fifth treatment, and half applied it daily for seven months. Dermal thickness increased in all patients, with a larger increase seen in the retinaldehyde group. A statistically significant increase in forehead dermal thickness was noted in the retinaldehyde group (67).

Although laser treatment has been used in pigmentary disorders in dark skinned patients, their cautious use is warranted. Prospective studies with larger populations of Fitzpatrick phototypes IV–VI are needed to determined their safety and efficacy (68).

OUR THERAPEUTIC APPROACH

As the pigmentary system yields its secrets, and pathogenic disease mechanisms are more intensely investigated and studied, therapeutic options for pigmentary disorders expand.

Once a pigmentary disorder has been diagnosed, the first step is to educate the patient about the condition. This is particularly important if the condition has a chronic nature that will require long-term follow-up, such as melasma.

Table 6   Clinical Parameters to Be Considered Before Using Lasers in the Hyperpigmented Patient

Ethnicity
Medical and surgical history
History of hypertrophic scarring and keloid formation
History of post-inflammatory hyperpigmentation
Skin type (Fitzpatrick phototype)
Use of isotretinoin
Results of previous cosmetic procedures

Sun protection must be the primary preventive measure for all patients. In order for therapy to be successful, counseling patients on sun safety is crucial. A broad-spectrum sunscreen with sun protection factor (SPF) 30 and physical blockers containing titanium dioxide or zinc oxide are preferred. Sunscreens block the stimulatory effect of the sun on melanocytes, as well as the transfer of existing melanosomes to keratynocytes.

In general, therapy for pigmentary disorders must be disease-specific and designed for the individual patient. Due to the complexity of the pigmentary system and the many pathogenic mechanisms involved in most acquired pigmentary disorders, it is only logical to assume that attacking the pigmentary cascade at different levels with different compounds would be the most reasonable approach.

First-line treatment for conditions such as melasma and PIH is topical therapy with a dual- or triple-combination product. Triple combinations contain hydroquinone with a retinoid and a mild corticosteroid; dual combination products contain hydroquinone and a retinoid. In the presence of sensitivity to any of these ingredients, alternative bleaching agents such as kojic acid, azelaic acid, or a cosmeceutical herbal compound can be considered.

Physical therapies are also introduced early in the treatment program. These therapies might include chemical peels, dermabrasion, microdermabrasion, laser, or pulsed light (Table 5). While there is insufficient evidence to conclude that these therapies are indispensable, we feel they are synergistic and help with maintenance control. Their help with the prevention of PIH is an added benefit.

The most commonly used physical therapies are salicylic acid peels, glycolic acid peels, and Jessner's solution. These are primarily superficial peels. Our success rate with these mild procedures used in combination with topical therapies and sunscreen is quite high.

We put all our patients on pre-procedure protocols with skin care products ranging from mild cleansers and moisturizers to products containing active ingredients such as glycolic acid, retinol, Kinerase, or one of the new growth factors (TNS vs. e.g.,). After the procedure, patients are followed closely, and skin care regimens are restarted about a week later.

Light therapies have recently been introduced. We use IPL for treating lentigos. We have not tried IPL on melasma, although several studies have reported success, particularly in Asian patients. IPL provides a more acceptable modality than lasers, as that there is less photothermal injury and, therefore, less risk of PIH in patients with melasma.

Pigment-specific lasers such as Q-switched Nd-Yag are used for isolated lesions such as lentigos, and are only used as a last resort in cases of recalcitrant melasma.

When all other measures have failed, combining topical therapies with procedures is a reasonable approach, especially in recalcitrant conditions. The wisdom of this approach is supported by a handful of trials, although solid evidence is lacking. It is possible that the combination of all available therapies could lead to more rapid and greater improvement and accelerated healing times while reducing the occurrence of PIH.Once their disease has been cleared, patients are always placed on maintenance therapy with a retinoid, a mild lightening agent such as azelaic acid, or a cosmeceutical agent (4,33,56).

CONCLUSIONS

The treatment of pigmentary disorders remains a challenge, as there are no standardized treatments for melasma, PIH, or pigmentation due to photoaging.

The clinical response to pharmacological monotherapy is frequently slow and, in some cases, suboptimal. Whenever possible, the use of a dual- or triple-combination product as a first approach is recommended. The combination of various pharmacologic agents with chemical peels, microdermabrasion, and/or pigment-specific lasers can lead to accelerated healing times and a more rapid and greater improvement, and can reduce the occurrence of PIH. These advantages may enhance compliance.

Scientific evidence exists for a few of the pharmacologic agents, but evidence supporting the use of chemical peels and microdermabrasion for pigmentation disorders is scarce. Lasers have specific uses in the treatment of isolated lesions such as lentigos. Some reports have shown success with light sources including IPL for the treatment of melasma in Asians, specifically dark skinned ones. Pigment-specific lasers should only be reserved for refractory cases.

In general, combining procedural therapy with pharmacologic therapy is logical, although scientific evidence is lacking. Where trials do exist, evidence supports the combination of modalities. The procedures can also improve or hasten the cosmetic results obtained from other conventional therapies.

The choice of therapeutic agents involves assessment of the risk-benefit profile, and regimens should be individualized to specific disease and patient characteristics, as mentioned in Table 6.

Our success rate in the treatment of pigmentary disorders is quite high with the above approaches. However, due to the chronicity of some of these disorders, constant follow-up, patient counseling, and use of sunscreens are critical for long-term improvement and maintenance of results.

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15

Topical Exfoliation—Clinical Effects and Formulating Considerations

M. Elizabeth Briden
Advanced Dermatology and Cosmetic Institute, Edina, Minnesota, U.S.A.

Barbara A. Green
NeoStrata Company, Inc., Princeton, New Jersey, U.S.A.

EXFOLIATION

By definition, to exfoliate is to remove the surface in scales or laminae. Therefore, classical exfoliants are those agents that work at the skin's surface causing the removal of skin in layers. Exfoliation is characterized, based on its mechanism of action, into 3 categories:

1. physical/manual (loofah or microdermabrasion)
2. chemical/keratolytic agents (e.g., salicylic acid)
3. natural/exuviation (e.g., alpha-hydroxy acids)

Manual or physical exfoliation involves the use of physically abrasive devices such as loofahs and could also include instrumental techniques such as microdermabrasion. Manual exfoliants physically scrape and remove surface skin cells.

Salicylic acid represents the *chemical/keratolytic* class of exfoliants. Recent reviews of salicylic acid propose a change to the term "desmolytics" to more accurately reflect the action of these materials on skin (1,2); these agents dissolve the desmosomal bonds between cells beginning at the uppermost skin layers providing exfoliative effects from the top of the skin downward in a non-specific manner (1–5).

Natural exfoliation, also known as exuviation, is the naturally occurring process of epidermal turnover, which occurs approximately every 28 days. Compounds that enhance the natural process of exuviation include, the alpha-hydroxy acids (AHAs), polyhydroxy acids (PHAs), and bionic acids. These agents are frequently considered exfoliants; however, their effects differ from those of conventional keratolytics or desmolytics (6,7). They target the base of the stratum corneum, the layer identified as the stratum dysjunctum, and function by diminishing bonding strength between cells in a specific manner leading to normalization of cell turnover and, thus, exfoliation (6,8).

This chapter discusses the mechanisms, effects and formulating considerations of exfoliants, including physical implements, microdermabrasion, exuviating compounds (AHAs, PHAs, bionic acids), the keratololytic/desmolytic salicylic acid, and finally a newly emerging, non-acid, acetyl amino sugar known as N-acetylglucosamine.

PHYSICAL EXFOLIANTS: SCRATCHING THE SURFACE

Physical exfoliants involve the use of manual implements to erode away surface skin cells. Presumably, as rubbing is continued and additional force is exerted, skin cells will continue to forcibly desquamate in a non-specific manner. This can continue until the stratum corneum is removed and the "glistening" layer of the live epidermis is reached. A similar effect can be observed following repeated tape stripping, which could be thought of as a process of forced physical exfoliation.

Common methods of manual exfoliation include use of physically abrasive materials such as pumice, loofahs, and buff puffs. The repetitive action of shaving with a razor also serves to physically remove or exfoliate the stratum corneum (9). Newer methods of physical exfoliation, such as microdermabrasion, involve the use of sophisticated equipment which "sandblasts" the skin surface with particles.

Bathing Devices

Buff puffs, loofahs, mesh poofs, and, to a certain extent, washcloths are used by many people on a daily basis to provide varying degrees of exfoliation to the face and body. The amount of exfoliation is dependent on the force of application, the number of passes over the skin, and abrasiveness of the material being used. There is little information in the published literature discussing the effects of washing devices on skin physiology and function. A study by Grove showed that use of abrasive fiber sponges stimulates epidermal cell turnover and reduces the size of corneocytes, indicating an exfoliation effect on skin (10).

Another study by Bergfeld et al. directly compared the relative effectiveness of manual exfoliation with a loofah (controlled application twice daily) in comparison to topical application of the AHA, glycolic acid (10% lotion twice daily to one hand plus weekly, 3-minute 50% peels), in improving the quality of photoaged skin on the back of hands. Results on 21 women (mean age 44 years) indicated that glycolic acid treatment was superior to mechanical exfoliation in improving the quality of photodamaged skin. There was a greater than four-fold improvement in overall photodamage severity compared to the loofah treatment, and significant improvements (p < 0.05) in texture and wrinkling were also observed for the glycolic acid treatment. There were no significant changes to these characteristics on the loofah treated sites; however, loofah use resulted in significantly less irritation (11).

Shaving

Shaving with a razor blade removes hair as well as stratum corneum. As a result, there are many potential detrimental effects to skin including increased risk of irritation from other topically applied products, such as antiperspirants (9). Moreover, while shaving seems at first to make the skin smoother, this process actually generates uplifting scales and increased dryness, as well as diminished barrier function in the stratum corneum

and a pro-inflammatory environment in the epidermis (12). The amount of surface trauma and corresponding potential for irritation is increased with use of new razors, a non-optimal shaving angle, and insufficient use of lubricating products (9). Optimal shaving and minimal skin irritation can be achieved by following a few key steps including: (i) having clean skin, (ii) allowing warm water to soften hair, (iii) liberal use of shaving cream applied for two to three minutes to soften hair, and (iv) use of a wet, warm, sharp razor (13).

Microdermabrasion

The closed, self-contained procedure known as microdermabrasion was first developed in the mid-1980s by researchers in Italy to eliminate the risk of airborne blood generated during conventional dermabrasion treatments (14). Microdermabrasion was approved for use in the United States by the Food and Drug Administration (FDA) in 1997 and has become one of the most popular procedures used for aesthetic skin care (15).

This novel exfoliation technique utilizes a stream of aluminium oxide, sodium bicarbonate, or sodium chloride crystals that functions by "sandblasting" skin under mild suction, which serves to collect the aerosolized crystals and skin particulates for disposal (15,16). Depending on the power of the machine, the number of passes of the hand piece over the skin and/or the speed of the hand piece over the skin, micro-dermabrasion can cause superficial exfoliation of the uppermost layers of the epidermis or reach the dermis, as indicated by signs of bleeding (14). One study reported complete ablation of the stratum corneum after two passes with microdermabrasion and a resulting increase in vitamin C penetration by a factor of 20 compared to non-abraded skin, demonstrating the potential for significant exfoliation effects from microdermabrasion (17).

Microdermabrasion has been used to treat a variety of skin conditions including photoaged skin, acne, hyperpigmentation, striae distensa, actinic keratosis, and keratosis pilaris. Adverse events are infrequent and include pigmentation irregularities, which occur mainly in darker skin (Fitzpatrick skin types V and VI) and prolonged erythema lasting beyond 24 hours (15). Many microdermabrasion protocols suggest a series of superficial procedures on a monthly or half-monthly basis in order to achieve skin benefits while minimizing the likelihood for adverse events (15). Several publications support the safe and effective use of microdermabrasion, with both dermal and epidermal benefits, and corresponding patient satisfaction (18–21).

Due to the perceived benefits of microdermabrasion by patients and its success in dermatologist offices and spas/salons, a home care market is emerging. Accordingly, several cosmetic companies have tested and introduced home "microdermabrasion" kits; many of these kits incorporate use of scrubs or exfoliating moisturizers made by suspending physical particles, such as polyethylene beads or apricot kernels, in a cream emulsion or gel, rather than providing actual exfoliating devices (22,23).

CHEMICAL EXFOLIATION

Chemical exfoliants are substances that cause superficial skin cells to desquamate at an increased rate as a result of their ability to disrupt intercellular bonding within the stratum corneum. This effect on skin occurs through several different mechanisms as described below.

Glycolic Acid   Lactic Acid   Mandelic Acid
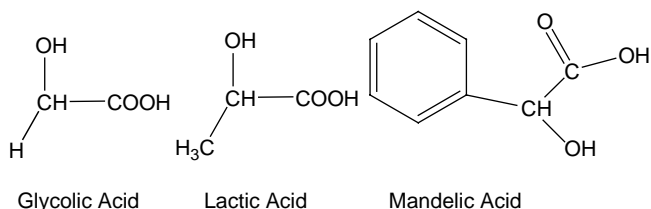
Figure 1   Alpha-hydroxy acids.

Exuviating Compounds: Alpha-Hydroxy Acids—Polyhydroxy Acids, and Bionic Acids

The alpha-hydroxy acid (AHAs), polyhydroxy acids (PHAs) and bionic acids are exvuviating compounds that enhance desquamation and cell turnover. Because of the differences in their molecular structures, these compounds provide some additional benefits to skin as described below.

Alpha-Hydroxy Acids—Anti-aging Plus Exfoliation

AHAs, such as glycolic acid, lactic acid, and mandelic acid (Fig. 1), have many beneficial effects on skin including enhanced exfoliation as well as reversal of photoaging (24–27). Upon topical application, AHAs have been shown to have a profound effect on desquamation and exuviation, the natural process of epidermal cell turnover (Fig. 2). When applied to severely hyperkeratotic skin, such as ichthyosis, AHAs at cosmetic strengths [defined by the Cosmetic Ingredient Review panel as a concentration of 10% or less with a minimum pH of 3.5 (28)] cause separation of abnormally thick stratum corneum at the base of the stratum corneum, the layer known as the stratum compactum (6,29). In severely hyperkeratotic skin, the thickened stratum corneum lifts off as a sheet (6). This observation distinguishes the effects of AHAs from traditional, non-specific exfoliating agents, such as salicylic acid, which diminish corneocyte cohesion thoughout the entire thickness of the stratum corneum (2).
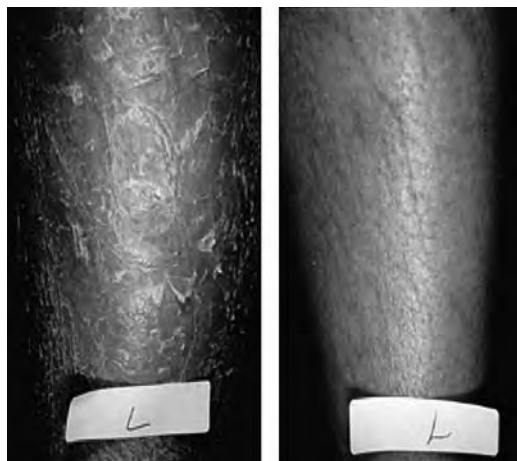
Figure 2   Lamellar ichthyosis before and after four weeks, with twice-daily topical application of an occlusive 10% AHA cream formulation containing glycolic acid, gluconolactone, tartaric acid, citric acid, and mandelic acid at pH 3.1.

AHAs have been shown to normalize the process of exuviation. As a result, continued use of AHAs results in a normalized rate of desquamation, and skin shedding becomes clinically lessened or non-apparent to the product user after two to three weeks (8). Effects of cosmetic strength AHA formulations on skin barrier function have been studied; Berardesca reported that twice-daily application of AHAs (8% lactic acid or 8% glycolic acid) over a period of four weeks resulted in maintenance of normal stratum corneum barrier function as measured by trans epidermal water loss (TEWL) and, therefore, excessive exfoliation of the stratum corneum was not apparent (30).

The mechanism of action of AHAs in promoting desquamation is postulated to be due to activation of the naturally-occurring enzyme steroid sulfatase to facilitate conversion of cholesterol-3-sulfate to cholesterol at the level of the stratum compactum. Exfoliation of normal, healthy skin requires the biochemical conversion of cholesterol-3-sulfate to free cholesterol in skin (31). When present at elevated levels, the more ionic molecule, cholesterol-3-sulfate, increases desmosomal bonding strength between corneocytes, thus prolonging the desquamation process. X-linked ichthyosis is known to be deficient in this critical enzyme (32).

AHAs also have stimulatory effects on dermal components. This, in conjunction with normalization of epidermal thickness and morphology, produces the anti-aging benefits of AHAs (26,33,34). Skin effects of AHAs include:

- *reduced* corneocyte cohesion at the stratum compactum (base of the stratum corneum) corresponding to fewer desmosomal attachments between cells
- *reduced* epidermal thickness especially in the case of abnormally thickened epidermis, e.g., lamellar ichthyosis
- *more even* distribution of melanin
- *increased* epidermal thickness of atrophic, photoaged skin
- *increased* synthesis of glycosaminoglycans (GAGs) and collagen fibers
- *normalization* of elastic tissue distribution and alignment
- *increased* dermal dendrocyte activity (8,33–37)

These effects together with their effects on exfoliation and cell turnover enable the AHAs to contribute significantly to the dermatologist's armamentarium in treating hyperkeratotic and photodamaged skin.

Polyhydroxy Acids and Bionic Acids—Gentler AHAs
with Exfoliation Effects

PHAs are organic carboxylic acids that possess two or more hydroxyl groups on an aliphatic or alicyclic molecular structure. When one of the hydroxyl groups occurs in the alpha position, the PHA is a polyhydroxy AHA. In addition to the anti-aging and cell turnover benefits afforded by the alpha-hydroxy structure, the multiple hydroxyl groups of the PHAs, such as gluconolactone (gluconic acid), (Fig. 3) (29,38) and glucoheptonolactone, and polyhydroxy bionic acids, such as lactobionic and maltobionic acid (Fig. 4), impart humectant properties to these molecules. Studies indicate that PHA compounds can attract and bind water (38), which, on a practical level, provides moisturization to skin.

Aside from their moisturizing effects, PHAs have also been shown to strengthen the skin's natural barrier against a chemical irritant (30), and provide non-irritating and non-stinging anti-aging skin benefits to clinically sensitive skin including rosacea and atopic dermatitis (39–41). Previous studies of gluconolactone and lactobionic acid have documented their ability to provide measurable anti-aging effects including skin smoothing, reduced appearance of fine lines and wrinkles, and improved clarity, without
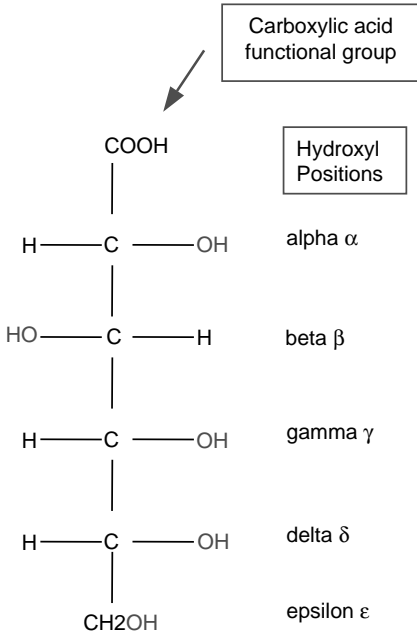
Figure 3 Gluconolactone hydrolyzes to gluconic acid in the presence of water in water-based formulations and skin. Gluconic acid is an alpha-hydroxy acid with additional hydroxyl groups (β, γ, δ, ε), thereby being a polyhydroxy acid (PHA).

causing irritation (42–44). These agents have also been shown to increase skin exfoliation and enhance cell turnover as demonstrated in dansyl chloride cell turnover studies (45).

AHA, PHA, and Bionic Acid Use in Dermatology

AHAs are used extensively as adjunctive agents in the treatment of hyperkeratotic disorders including psoriasis, callouses, acne, keratosis pilaris, and keratoses (6,8,27). They are considered among the best therapeutic options for the treatment of most forms of ichthyosis (24,25). These compounds are also used ubiquitously for the treatment of aging-related skin changes. AHAs are marketed in a variety of forms that are readily available to physicians including superficial peel reagents, cleansers, creams, lotions, and gels.
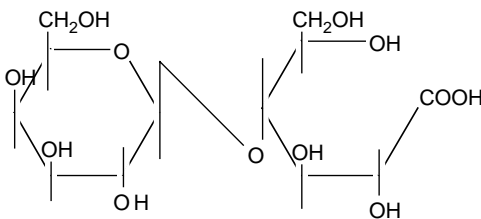
Figure 4 Lactobionic acid, a polyhydroxy bionic acid, is chemically defined as a bionic acid because it is comprised of two units: one gluconic acid molecule (*right*) and one galactose molecule (*left*).

Table 1 Chemical Exfoliants

Exfoliation class	Ingredient	Regulatory status	Solubility	pKa	Bioavailable (non-ionized) % at a selected formulation pH of 3.5[a]	Common concentration range in topical formulations, %
Alpha-hydroxy acid (AHA)	Glycolic acid	Cosmetic	Water-soluble	3.83	68%	Up to 10%
Alpha-hydroxy acid (AHA)	Lactic acid	Cosmetic or Rx (12% ammonium lactate form)	Water-soluble	3.86	70%	Up to 10%
Alpha- (and beta-) hydroxy acid (AHA)	Citric acid	Cosmetic	Water-soluble	3.13	30%	Up to 10%
Alpha-hydroxy acid (AHA)	Mandelic acid	Cosmetic	Water-/alcohol-soluble	3.4	44%	Up to 10%
Alpha-hydroxy acid (AHA)	Benzilic acid	Cosmetic	Slightly soluble in water, freely soluble in alcohol, ether	3.0	24%	Up to 10%
Polyhydroxy acid (PHA)	Gluconolactone/ gluconic acid	Cosmetic	Water-soluble	3.6	56%	Up to 15%
Bionic acid	Lactobionic acid	Cosmetic	Water-soluble	3.8	68%	Up to 15%
Salicylic acid	Salicylic acid	OTC drug or cosmetic depending on claims	Slightly soluble in water, freely soluble in alcohol, ether	2.97	23%	0.5–2.0% (OTC monograph)
Acetyl amino sugars	N-Acetylglucosamine	Cosmetic	Water-soluble	Neutral	N/A	Up to 10%

[a] Calculation based on Henderson-Hasselbalch equation: pKa = pH + log [Acid]/[Base].

The PHAs and bionic acids are gaining use in dermatology due to their significant skin normalizing effects and anti-aging benefits in conjunction with their non-irritating characteristics. These non-irritating agents are especially useful on the sensitive skin of rosacea, atopic dermatitis, and post-procedure (microdermabrasion, peels, non-ablative laser, etc.) when the skin barrier has been disrupted and irritation or stinging is likely to occur due to the increased potential for rapid absorption of skin care ingredients (38,44).

Formulating Factors for the Hydroxyacids

There are several factors to consider in the formulation process to optimally and safely deliver hydroxy acids to skin. The AHAs, PHAs, and bionic acids are mild, organic acids that are optimally absorbed into skin when present in the free acid, non-ionized form (46). As a result, formulation pH is extremely important. At a defined pH, the concentration of the acid and its pKa determine the amount of free acid and, thus, bioavailability, provided by a formulation (Table 1). As the pH of a formulation is reduced below the pKa of the acid, there is a significant increase in the amount of free acid that is available for penetration. As a result, the potential to cause sensory irritation and erythema increases and must be considered in the formulation process. Formulation technologies exist to facilitate the gradual penetration of free acid into skin, thereby diminishing irritation potential and stinging without reducing skin benefits (46). One such technology utilizes amphoteric amino acids during formulation pH adjustment to temporarily complex free AHA molecules and allow a more gentle delivery of the AHA with reduced irritation and stinging.

Another important factor in the hydroxy acid formulation process involves selection of the specific AHA ingredient. The relatively broad selection of ingredient options provides the formulator with the ability to customize AHA solubility parameters and modify potential skin benefits. For example, the more common AHAs, including glycolic acid and lactic acid, are readily soluble in water. In comparison, those with lipophilic side chains have increased oil solubility and the resultant increased potential to absorb into oily skin and pores. Examples include mandelic acid (phenyl glycolic acid) and benzilic acid (diphenyl glycolic acid) (Fig. 1).

Salicylic Acid—A Topical Desmolytic

Salicylic acid (orthohydroxybenzoic acid) (Fig. 5) is an aromatic hydroxyacid with the hydroxyl and carboxyl groups attached directly to a benzene ring (47,48). It is frequently referred to as a beta-hydroxy acid, but a more accurate description is a phenolic aromatic acid because the carboxyl and hydroxyl groups are present on the benzene ring; in this position, the hydroxyl group is acidic (2,47,48). This is to be compared to the hydroxyl group of conventional alpha- or beta- hydroxy acids, which have their attachment on an
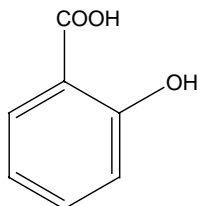
Figure 5 Salicylic acid, orthohydroxybenzoic acid.
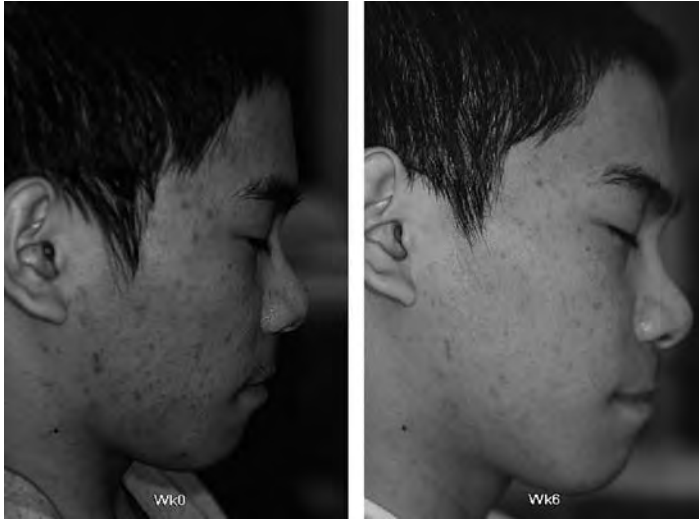
Figure 6 Mild acne: baseline and after six weeks. Twice-daily application of a topical solution containing 2% salicylic acid in combination with 4% alpha-hydroxy acids (benzilic acid, citric acid, tartaric acid, and O-acetylmandelic acid).

aliphatic or alicyclic structure, rendering the hydroxyl group chemically neutral (48). This chemical difference appears to differentiate the activity of salicylic acid from AHAs on the skin (8).

Salicylic acid has been used as a keratolytic since the 1800s, when it was first derived from the bark of the willow tree (49,50). Its effects on skin have been studied and determined to be primarily limited to enhanced shedding of the stratum corneum, with no increase in mitotic activity of the epidermis (3–5). Salicylic acid reportedly functions by decreasing corneocyte cohesiveness over the entire thickness of the stratum corneum via disruption of desmosomal attachments and denaturing glycoproteins, thus the term "desmolytic" (1,3–5).

The effects of salicylic acid are reported to be more extensive and clinically relevant on skin exhibiting conditions of increased corneocyte cohesiveness (3–5). As a result, dermatologists have used salicylic acid to treat various conditions of hyperkeratosis, including corns, warts, seborrheic dermatitis, psoriasis, and dandruff (2,51). Topical salicylic acid is also a mainstay in home care for acne; this is due to the comedolytic effect of salicylic acid (Fig. 6) (7,52). Aside from OTC formulations, there are products designed for use in dermatologists' offices including topical peels with concentrations of salicylic acid up to 30%. These products are primarily targeted for the adjunctive treatment of acne, and are also used in photoaging (53–55). Salicylic acid is frequently also used adjunctively in the treatment of psoriasis as a result of its keratolytic effects and its ability to enhance penetration of topical medications (56,57).

The anti-aging benefits of salicylic acid may be limited to the epidermis. Whereas alpha-hydroxy acids have been shown to stimulate biosynthesis of dermal components and increase dermal skin thickness upon topical application, salicylic acid has been shown to decrease dermal skin thicknness (8). Nonetheless, salicylic acid has been used extensively in anti-aging formulations (7), presumably due to its exfoliation effects.

Formulating Factors for Salicylic Acid

Salicylic acid is a somewhat stronger acid with a lower pKa compared to most AHAs due to the electron-withdrawing properties of the benzene ring. As a result, a lower pH should be considered to optimally formulate bioavailable products (Table 1). However, as pH is reduced, and penetration is increased, there is an increased likelihood to cause irritation. The concentration of use of salicylic acid in over-the-counter (OTC) treatments of acne, dandruff, seborrheic dermatitis, psoriasis, and wart formulations is governed by the FDA OTC monographs. These regulatory documents dictate product form, concentration, uses, directions, and warnings. Since these formulations are regulated as OTC drugs, chemical stability of salicylic acid must be proven over the shelf-life of the formulation. Cosmetic formulations that make cosmetic claims, on the other hand, are free to use varying strengths of salicylic acid; however, the upper concentration may be limited by irritation potential.

N-Acetylglucosamine—A Non-Acid Chemical Exfoliant for Aging Skin

N-acetylglucosamine (NAG) (Fig. 7) is a water-soluble, neutral compound that can easily be incorporated into skin care formulations. It is found naturally occurring as a repeating unit of the abundantly available material known as chitin (e.g., shrimp shells). In human skin, it is a natural component of GAGs, glycolipids, and membrane glycoproteins. Along with glucuronic acid (a polyhydroxy acid), NAG is a one of the repeating, alternating units in hyaluronic acid, the prominent GAG of skin (29).

   NAG represents a new class of anti-aging and exfoliation compounds. Its reported beneficial effects on exfoliation occur as a result of its interaction with CD44 receptors on corneocytes, which prevents cross-linking between cells (58,59). Topical application of NAG has been shown to induce desquamation and epidermal cell turnover, as well as increase epidermal differentiation. In a pilot (n=9) dansyl chloride exfoliation study of NAG (8% cream, native pH 4.9) in comparison to glycolic acid (8%, pH 3.7) and an untreated control, NAG significantly reduced mean fluorescence scores significantly compared to the untreated control (82% and 62%, respectively), but not as effectively as the tested glycolic acid formulation (92%), $p < 0.05$ (60).

   NAG also provides moisturizing and anti-aging benefits to skin. As a component molecule in hyaluronic acid and a potential precursor to its synthesis, NAG has been shown to stimulate synthesis of hyaluronan in fibroblasts and keratinocytes (61–62).
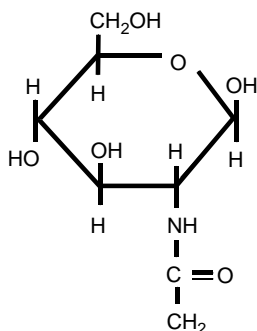
Figure 7   N-acetylglucosamine.

Oral supplementation of NAG (1 g orally per day vs. placebo for 60 days) reportedly reduced skin dryness and roughness, and increased moisturization (63).

Topical evaluation of 8% NAG was shown to provide significant, clinically-assessed improvements on mild to moderate photodamage with substantial improvements in skin firmness and skin thickness. The latter effect is thought to be due to an increase in the production of GAGs, which increases skin volume through water binding and plumping (64). In addition to its desirable cosmetic effects, NAG was shown to be well tolerated on skin (64), and therefore represents a desirable new class of compounds in the growing exfoliation and anti-aging ingredient technology market.

CONCLUSION

Dermatologists and patients are inundated with products and devices to assist the skin in its natural exfoliation process. The purest form of exfoliation is achieved through use of physically abrasive implements on skin. These devices, such as loofahs, buff puffs, and mesh poofs, can provide light exfoliation on a daily basis to slough away excess layers of stratum corneum, helping to keep the skin smooth and luminous. Additional clinical benefits to skin are few, if any, and have not been well documented. Microdermabrasion elevates the physical exfoliation process to the next level. Depending on how it is used, this procedure can simply provide mild exfoliation or, when used as part of a comprehensive skin care regimen, it can help the clinician to achieve meaningful cosmetic outcomes.

Chemical exfoliants have more to offer the dermatologist and patient in terms of flexibility and patient outcomes. When properly formulated for optimal bioavailability and safety, these agents penetrate the skin and disrupt binding between stratum corneum cells to facilitate exfoliation. This effect is beneficial in the treatment of various hyperkeratotic disorders including acne and dry skin. Some chemical exfoliants also provide significant anti-aging effects leading to smoother skin with the reduced appearance of fine lines and wrinkles and an increase in skin firmness. Careful selection of a chemical exfoliant facilitates customization of the formulation to skin condition including oily, dry, and sensitive skin. Furthermore, the chemical exfoliants can be readily formulated into products that can be used at home or in physicians' offices and spas/salons. The use of exfoliating procedures, including topical peels and microdermabrasion, is frequently combined with home application of skin benefit ingredients to achieve significant therapeutic outcomes.

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16
Over-the-Counter Acne Medications

Theresa Chen and Yohini Appa
Neutrogena Skincare Institute, Los Angeles, California, U.S.A.

INTRODUCTION

Acne vulgaris is an extremely common condition affecting more than 80–90% of adolescents and young adults (1,2). It typically starts in late childhood or early teens, but onset may be delayed in some people well into their 20s and 30s (3). The incidence rate of acne is roughly the same in males and females but, males tend to have more serious conditions (4). Even later in adulthood, roughly 25% of adult men and 50% of adult women can have acne at some time in their adult lives.

Acne can be difficult to cope with no matter what age, and can cause depression and social anxiety in an adult the same way it can in a teen. Kellett and Gawkrodger (5) found that acne patients reported levels of social, psychological, and emotional problems as great as those reported by patients with chronic disabling asthma, epilepsy, diabetes, back pain, or arthritis. This study also reported that the impact on quality of life did not correlate with acne severity. To a teenager, acne can be one of the worse things that ever happened. Acne frequently makes teens feel embarrassed and lowers their self-esteem. A recent survey of British teenagers found that the emotional toll could be significant (6). This survey found:

- About two out of five teenagers with acne claimed to have skipped school because of embarrassment.

- Between 11- to 18-year-olds, over half said acne prevented them from having a boyfriend or a girlfriend.

- One-third indicated acne hurt their ability to make friends.

Proper care and intervention help improve the life quality by alleviating the negative emotional impacts and building up self-esteem. Treatment can also prevent acne from getting worse and deter scarring.

When it comes to treatment, one study conducted in 2000 indicated that 75% of patients waited about one year before seeking professional help for acne (7). Another survey estimates that only a third of acne sufferers consult their physicians at all. Thus, the majority of acne sufferers apparently opt for the over-the-counter (OTC) acne products to treat their acne. This is most likely due to the fact that most acne cases are mild to moderate in severity for which OTC acne products—readily available and not requiring a prescription and an appointment to the doctor's office—are perfectly suited. And many of today's new OTC acne products are not only clinically effective and safe but also aesthetically elegant and pleasant to use. Non-prescription products tried most frequently were medicated cleansers, washes, pads, gels, and lotions (8). A 2001 report estimates that consumers of all ages spend approximately $100 million per year on OTC remedies for acne (9). The actual market figure today is probably much higher than that as evidenced by the sheer number of OTC acne products that have since come on the market in the recent years. Given the large variety of acne OTC products, this chapter attempts to provide a comprehensive overview while focusing on the recent OTC advances of the two most-widely used acne OTC medications, salicylic acid (SA) and benzoyl peroxide (BPO).

CLINICAL CONSIDERATIONS

Acne affects mainly the face, although other regions rich in sebaceous glands can also be affected (chest, back, upper arms). The lesions can be distinguished into non-inflammatory (open and closed comedones or blackheads and whiteheads) and inflammatory lesions (papules, pustules and nodules).

Four main factors are known to influence the development of acne, namely: (i) sebaceous gland hyperplasia with excess sebum production (seborrhea); (ii) follicular epidermal hyperproliferation and altered differentiation; (iii) follicular colonization by *Propionibacterium acnes* (*P. acnes*); and (iv) inflammation and immune response. Altered epidermal growth and differentiation, combined with seborrhea, is responsible for the formation of the primary lesion in acne: The microcomedo. The development of inflammatory lesions, instead, is often triggered by the effects of *P. acnes* with release of inflammatory mediators.

The first entity in the development of an acne lesion is a tiny invisible plug (microcomedone) of the pilosebaceous duct; skin that is at one time apparently unaffected may subsequently develop lesions if not treated. Generally speaking, it may take up to four weeks for an untreated papule or pustule to complete its life cycle from start to end. Therefore, an acne therapy that significantly reduces lesion counts during the first four weeks is recognized as having treated existing lesions, while therapies effective in reducing acne lesions count during the following four weeks are considered also effective in preventing the appearance of new lesions.

Because of the multiple pathogenetic factors, dermatologists recommend treating acne with combinations of agents that act at different levels. It is widely recognized that an effective acne treatment should not only clear current acne lesions but also prevent the appearance of new ones.

HIGHLIGHTS OF OVER-THE-COUNTER ACNE MONOGRAPH

The Food and Drug Administration (FDA) is the regulatory agency that oversees the marketing of non-prescription acne products. In the Final Acne Monograph, an "acne drug product" is defined as: "A drug product used to reduce the number of acne blemishes, acne pimples, blackheads and whiteheads" (10).

The following ingredients and concentrations are currently allowed in OTC acne products.

- Salicylic acid 0.5–2%

- Sulfur 3–10% alone, or 3–8% in combination with resorcinol

- Resorcinol 2% or resorcinol monoacetate 3% in combination with sulfur 3–8%

- Benzoyl peroxide 2.5–10%

Salicylic acid, sulfur alone, or sulfur in combination with resorcinol are included in the Final Monograph for meeting the monograph conditions of being "generally recognized as safe and effective and not misbranded (Category I)" for the treatment of acne. Although the final rule on benzoyl peroxide is still pending, FDA has allowed its continued use in OTC acne products (11).

In the Final Acne Monograph, it also lays down the requirements for the labeling of OTC acne products. The labeling requirements include a statement of identity that contains the established name of the drug and identifies the product as an acne medication or treatment and the dosage form, a statement for the indications that the drug product is intended to treat; additional statements of treatment benefits; appropriate warnings; and directions of product usage. In the absence of a final ruling on the use of benzoyl peroxide in OTC acne products, manufacturers are referred to the proposed rules (12,13).

FORMULATION OF OVER-THE-COUNTER ACNE PRODUCTS

Manufacturing of OTC acne products is both a science and an art. An OTC acne product must abide by the rules and regulations set in the Acne Monograph in the choice of an allowed active ingredient or combination of active ingredients and the allowable concentration ranges.

Amongst the approved OTC acne ingredients, BPO and SA are the most widely used. Both are topical comedolytics that help dry excess sebum and make the excreted sebum less sticky. This prevents occlusion of the pores and consequent formation of comedones. Topical comedolytics also cause sloughing of the stratum corneum and help remove existing sebum plugs along with loose keratinocytes. They also help normalize keratin turnover in the follicle (14). Interestingly, in the Final Acne Monograph, the agency notes that only BPO has known comedolytic activity and considers the other monograph ingredients as exfoliating agents that can evoke superficial peeling, thereby "aiding in unroofing superficial pustular lesions and causing spontaneous drainage" (15).

Benzoyl peroxide and SA come in a variety of products and in several different delivery systems, such as creams, washes, gels, and cleansing pads (16). Skin reactions to topical treatments may vary depending on the skin types. Thus, formulating the right OTC product that can work best for the majority of acne population is a formidable task. The main concern should be minimization of irritation on all skin types. The formulator should also take into account the time an individual has to care for the skin, the lifestyles of consumers, and the cost of individual products.

Another important consideration for formulation is the effects of the vehicle on the skin. Gels and solutions such as astringents can have higher alcohol contents and may increase the drying effect, while creams and lotions delivered in an emollient base tend to be moisturizing to the skin. "A proper vehicle is one that will deliver the drug to the site of action at a rate that will allow maximum benefit without causing or allowing toxic effects" (17). Given that all OTC acne drugs are keratolytics and can be somewhat drying and irritating, the ability of a vehicle that can mitigate the irritancy potential and allow delivery of the maximum drug benefits is all the more important.

What this also translates into is that in order to provide sustainable treatment benefits, OTC acne treatment should be developed in such a way that the consumers can and will like to use on a consistent, long-term basis. In other words, OTC acne products should be effective in delivering the clinical improvements as indicated, cause little or no irritation, be aesthetically pleasant, and be easy to use.

TRENDS IN OVER-THE-COUNTER ACNE FORMULATIONS

In the last decade, no new OTC ingredient has been approved for the treatment of acne. However, much research effort has led to the development of better vehicles and delivery forms designed to reduce skin irritation and improve efficacy. The common product forms are gel, lotion, cream, and cleanser.

In addition, other delivery methods have appeared, which include masks, scrubs, pads and even makeup foundation and concealing sticks. Body acne has also been gaining notices: Body washes and leave-on sprays have been developed to address delivery to hard-to-reach areas such as the back. The varieties in forms and delivery systems make it possible to design OTC treatment programs that are tailored to an individual's needs.

At the same time, there is an increasing desire to provide patients with a comprehensive product system or regimen that is easy to follow on a daily basis. This approach has two potential advantages: Encouraging usage compliance by consumers, and ensuring a product system that has been tested and proven to be compatible and may even be synergistic to deliver optimal efficacy and safety profiles. Multi-step systems that consist of combinations of products from cleanser to lotion or cream have been designed to provide a full range of products to use in daily routines. Typically one or two of the products in the system contain an OTC active ingredient. Cleansers, toners, masks, cosmoceuticals, emollients and sunscreens can be incorporated as adjunctives in the system. Some products even go beyond acne to try to address both acne and aging, targeting those adults who are concerned about both conditions on their skin.

ADVANCES IN OVER-THE-COUNTER ACNE FORMULATIONS

Salicylic Acid

SA is a keratolytic agent. It is used to treat a variety of hyperkeratotic skin disorders such as psoriasis, ichthyoses, seborrheic dermatitis, palmoplantar keratosis, keratosis pilaris, and pityriasis rubra pilaris (18). In acne, SA may reduce comedones (comedolytic) and prevent the formation of new ones by breaking down the comedonal follicular plug and by reducing follicular desquamation. It is an effective alternative for patients who do not tolerate topical retinoids. SA is approved for use in pediatric acne.

Concentrations of SA ranging from 0.5–10% from various manufacturers have been recommended for acne, but 2% is the maximum strength allowed in non-prescription acne products in the U.S. It is commonly found in acne cleansers.

The effectiveness of 0.5–2% SA as an acne treatment was originally demonstrated in two studies submitted to the FDA during the OTC approval phase (50 FR 2174, 1/15/85). The first study was a 12-week, double-blind investigation on 180 subjects comparing the efficacy of 2% SA solution versus vehicle solution and active control (5% benzoyl peroxide) in the treatment of acne. Forty percent of the subjects treated with 2% SA showed a good or excellent decrease in total lesions compared to 5% of the subjects in the vehicle group and 2% of the subjects in the benzoyl peroxide group. The study reported that SA was significantly more effective than vehicle and benzoyl peroxide in the reduction of total lesions, inflammatory lesions, and open comedones (but not closed comedones) (19). The second study was conducted on 187 subjects. Two SA formulations at 0.5% and 2% were tested against the vehicle. The results showed that both 0.5% SA and 2% SA were superior to the vehicle in reducing inflammatory lesions, open and closed comedones, and total lesions (20).

The efficacy of the cleanser form was investigated by Shalita in a cross-over study. He compared a 2% SA cleanser and a 10% benzoyl peroxide wash in 30 acne subjects. Subjects were randomly treated for two weeks with either SA or benzoyl peroxide. At the end of the first two weeks they switched treatment. The study concluded that only SA cleanser induced a significant reduction in comedones (21). More recently, a study by Pagnoni et al. (22) showed a significant reduction from baseline in open comedones count after four weeks of treatment using a 2% SA scrub or a 0.5% SA toner with 1% glycolic acid. The scrub induced a significant improvement as early as two weeks after treatment.

SA pads were investigated by Eady et al. (23). They compared 2% SA lotion versus placebo impregnated into pads. They found that the SA pads were significantly better than the control in reducing the total lesion count, starting at the fourth week of treatment. The superiority in improving comedones was also noted. Zander and Weisman reviewed three placebo-controlled studies and reported that SA pads were effective in reducing the number of primary lesions and thereby the number and severity of all lesions associated with acne (24). They also reported that SA was superior to benzoyl peroxide in reducing the total number of acne lesions.

Based on these previous studies, SA is generally considered less effective than benzoyl peroxide in the treatment of inflammatory acne but more effective in the treatment of comedonal acne.

Recently a new paradigm on SA has been ushered in when an acne treatment gel containing 2% SA was shown to be as effective as a 10% benzoyl peroxide lotion in all acne-related parameters. Because of the drying and irritating potentials of acne active

Table 1 Anti-acne Efficacy Comparison of a 2% Salicylic Acid Treatment Gel Containing Skin Soothing Naturals with a 10% Benzoyl Peroxide Lotion

	Mean change from baseline (%)			
	2% Salicylic acid gel (N=44)		10% Benzoyl peroxide lotion (N=46)	
Acne lesion type	Week 2	Week 4	Week 2	Week 4
Open comedones	−31	−43	−34	−56
Closed comedones	−30[a]	−26[a]	−13	−6
Inflammatory (papule + pustules)	−26[a]	−23	−15	−6
Total lesions	−28[a]	−27	−17	−15

Shading indicates a significant change from baseline (p < 0.05).
[a] Significantly higher improvement compared to the other treatment (p < 0.05).

ingredients, some of today's acne treatment products are formulated with cosmetic ingredients or cosmoceuticals that can help soothe the skin and reduce irritation. This approach has proven very effective in optimizing efficacy for OTC acne products containing SA.

A SA gel formulated with a proprietary soothing blend of naturals was compared to a 10% benzoyl peroxide treatment lotion, to the vehicle and also to no treatment control in double-blind and randomized clinical studies (25,26). The 2% SA treatment gel was found to be at parity to 10% benzoyl peroxide in target lesion resolution and on par or even superior in reducing closed comedones and inflammatory lesions (Table 1).

The effects on the target lesion resolution was evaluated by assessing lesion erythema, size and elevation and surrounding erythema. Significantly faster resolution was observed with the active treated group versus the vehicle group and the untreated group in blinded and randomized clinical evaluation (Fig. 1).

When it comes to irritancy, the 2% SA gel was superior to the 10% benzoyl peroxide lotion in mildness. Skin soothing benefits were evidenced in the reduction of pimple associated discomfort and the lessening of global erythema. These effects were observed in the majority (70–90%) of the study subjects. Similar gentle yet effective treatment benefits were also noted with another SA treatment in a lotion base (27).

Yamamoto et al. (28) have reported diminished water barrier function in acne patients. The strong vehicle effects often observed in acne clinical studies might be due to the vehicles being less drying. Thus, having a delivery vehicle that helps improve skin moisturization can have a positive impact in the treatment.

Recently, Chantalat et al. (29) reported the use of a microgel complex to optimize SA's anti-acne efficacy through solubilizing sebum and enhancing the delivery of SA. This microgel complex is a multiple-phase system consisting of micro-droplets in an aqueous phase. High-performance liquid chromatography (HPLC) analysis of

(A)

Surrounding Erythema of Acne Lesions

(B)
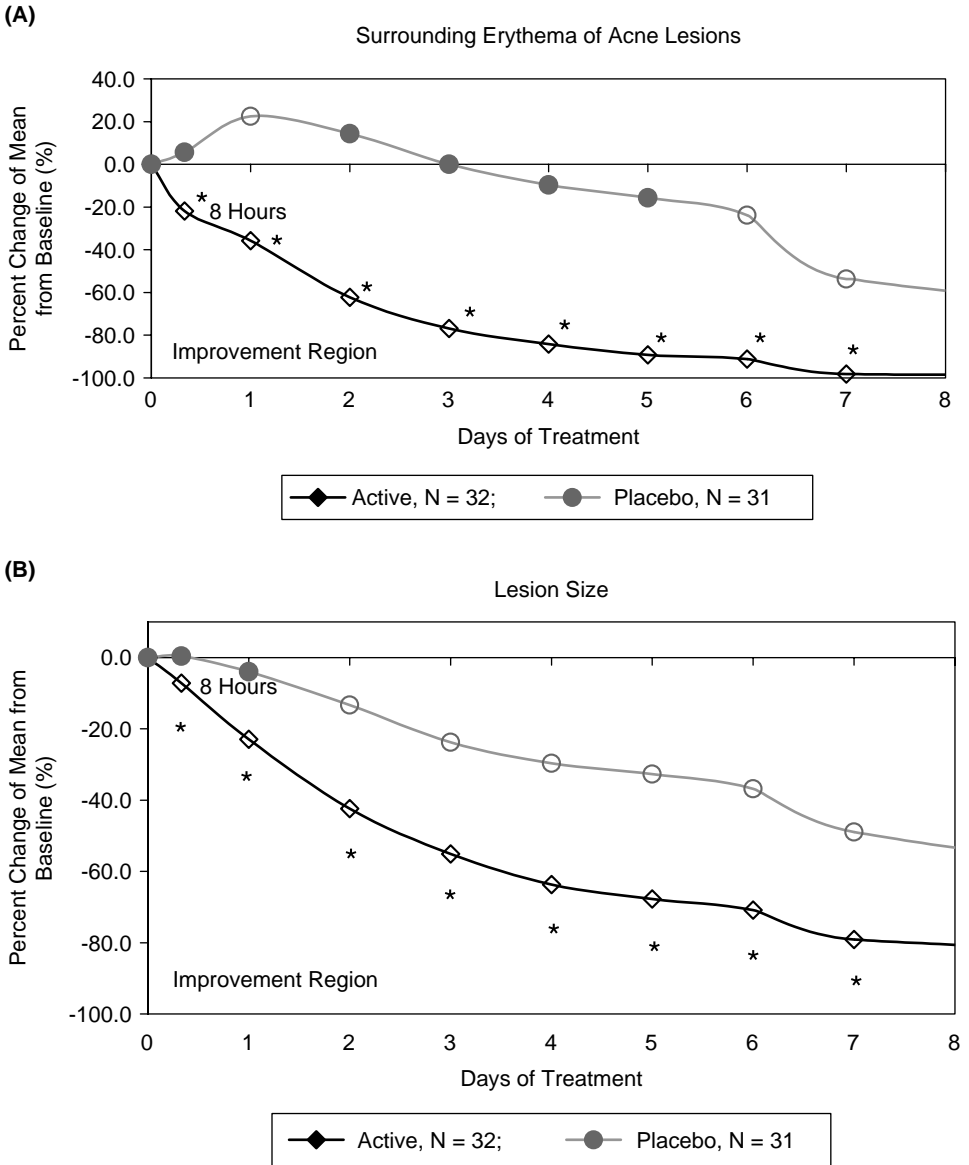
Lesion Size

Figure 1 Blinded clinical expert grading of (**A**) surrounding erythema and (**B**) lesion size comparing a salicylic acid gel with a synergistic blend of skin soothing naturals (active) and its vehicle control (placebo). Note: open symbols denote mean values that are significantly different from baseline (p <0.025). Asterisks next to the data points denote between treatments difference in favor of the labeled treatment (p <0.01).

microgel complex formulations with SA shows that the distribution of SA is significantly higher in the hydrophobic phase than the aqueous phase. In vitro investigations with model sebum compositions showed that certain components of the microgel complex solubilize sebum. Using fluorescence spectroscopy, ultraviolet (UV) light imaging, and confocal microscopy, they demonstrated in vivo that the depth of SA penetration in the skin was increased, as was the extent of deposition. Furthermore, skin conductance and transepidermal water loss (TEWL) measurements showed that formulations with the microgel complex delivered greater moisturization benefits versus placebo. This microgel formulation containing SA was shown to be highly effective not only at treating existing acne lesions but also at ameliorating emerging acne pimples—the sub-surface acne lesions that are not yet visible on the skin surface (30).

Benzoyl Peroxide

Benzoyl peroxide has been one of the most important topical acne agents for a long time. It has a combination of antibacterial, anti-inflammatory and comedolytic properties. Benzoyl peroxide can penetrate through the follicular duct deeply into the infundibulum where it then releases oxygen to inactivate anaerobic bacteria that cannot live in its presence, *P. acnes* being one of those bacteria. A study by Bojar et al. (31) reported an almost 2-$\log_{10}$ decrease in the density of *P acnes* after two days of 5% benzoyl peroxide treatment. Pagnoni et al. (32) confirmed this rapid effect in their investigation that showed *P. acnes* count decreased by an average of 2-log after a three-day treatment with a 10% benzoyl peroxide cream, without any further decline by day 7. In contrast to the bacterial resistance known to be associated with the use of oral and topical antibiotics, the antibacterial activity of benzoyl peroxide occurs without the induction of bacterial resistance.

The anti-inflammatory effect of benzoyl peroxide is probably directly related to the decrease of *P. acnes* density in the sebaceous follicles. It is known that *P. acnes* induces monocytes to secrete pro-inflammatory cytokines such as tumour necrosis factor α (TNF-alpha), interleukin-1β (IL-1β), and IL-8 through a Toll-like receptor 2-dependent pathway (33,34).

Benzoyl peroxide is commonly available as a liquid cleanser (2.5–10%), bar cleanser (5–10%), pads (3–9%), mask (2.5–5%), lotion (5–10%), cream (5–10%), and gel (2.5–20%). A report from the Global Alliance to Improve Outcomes in Acne (35) indicates that gel formulations may be more stable and may release benzoyl peroxide more consistently than creams and lotions.

Specific cleanser forms of benzoyl peroxide (5% and 10%) have been shown to reduce *P. acnes* density and inflammatory lesion counts. To increase the cleanser's benefits, patients should be instructed to gently massage the cleanser into moistened skin and allow a 20-second contact time followed by a 10-second gentle rinse (36). Recently a benzoyl peroxide cleanser mask takes this one step further by allowing the patients to use the product either as a cleanser or as a mask that allows for even longer contact time (37).

Benzoyl peroxide can enhance the efficacy of concomitant antibiotic therapy and reduces the development of antibiotic-resistant *P. acnes*. When used in combination with oral antibiotics, it has been shown to reduce the resistance of bacteria to the systemic drug. Recently, new drugs have combined benzoyl peroxide with other topical antibiotics. These

formulations are available only by prescriptions and include erythromycin 3%–benzoyl peroxide 5% and clindamycin 1%—benzoyl peroxide 5% combinations. These products have been shown to have some additive effect compared to either drug alone and to reduce the resistance to the antibiotic.

Once absorbed by the skin, benzoyl peroxide is metabolized to benzoic acid and excreted in the urine as benzoate. There is no evidence of systemic toxicity caused by benzoyl peroxide in humans (38). Side effects of benzoyl peroxide may include mild to moderate irritation and skin dryness. Contact allergy has been reported in approximately 1% of patients. Additionally, benzoyl peroxide formulations may bleach fabrics and hair. It is the controversy over tumor-promoting reports from animal studies on benzoyl peroxide that caused the FDA to delay ruling on its monograph status. In the interim, the agency has issued proposed rules that recommend sun avoidance and the use of a sunscreen when using a benzoyl peroxide product to treat acne (39).

Many peer-reviewed studies have been published supporting the efficacy and safety of benzoyl peroxide in acne. This ingredient is the main OTC treatment suggested by dermatologists because of its undisputed efficacy in inflammatory lesions. In fact, a review of the literature by Eady et al. (40) showed that none of the topical antibiotics used in various studies was clinically better than benzoyl peroxide. A direct comparison between a 10% benzoyl peroxide gel, a 1% clindamycin lotion, and a 20% azelaic acid cream found that the 10% benzoyl peroxide gel was significantly superior in reducing *P. acnes* at two and four weeks of treatment (41). Clinically, benzoyl peroxide has also additive benefits when combined with other topical antibiotics (such as clindamycin or erythromycin) (42,43).

Several previous studies have originally documented the efficacy of 2.5–10% benzoyl peroxide, which were reported in the Advance Notice of Proposed Rulemaking for Topical OTC Acne Drugs and accepted as support for the efficacy of benzoyl peroxide in acne (44). It is interesting to note that higher concentrations of benzoyl peroxide have not been shown to be more effective in acne, but may actually increase the risk of irritation. An eight-week study (45) compared the efficacy of 2.5% benzoyl peroxide versus 10% benzoyl peroxide in 50 acne subjects. The results showed that both treatments significantly decreased the total number of papules and pustules, with no difference in effectiveness between the two concentrations. There was also basically no difference in the reduction of total lesions between the two concentrations, while the incidence and severity of adverse events was much higher in the 10% benzoyl peroxide group. Similar findings were reported by Mills et al. (46), in which they compared a 2.5% benzoyl peroxide against its vehicle, and against a 5% and a 10% benzoyl peroxide gel in three double-blind studies involving 153 patients with mild to moderately severe acne vulgaris. The 2.5% benzoyl peroxide formulation was more effective than its vehicle and equivalent to the 5% and 10% concentrations in reducing the number of inflammatory lesions.

Orth et al. (47) investigated the penetration of a 2.5% and a 10% benzoyl peroxide formulation into the sebaceous follicles using cyanoacrylate follicular biopsy. The results showed that benzoyl peroxide penetrated into the follicles within a few hours and that the 2.5% formulation delivered a similar amount of benzoyl peroxide as the 10% product. The authors suggested that the vehicle of the 2.5% formulation played a significant role in enhancing the delivery of benzoyl peroxide.

One of the few studies comparing benzoyl peroxide to topical retinoids was conducted by Belknap (48). He compared 5% benzoyl peroxide twice daily versus 0.05%

retinoic acid once daily in an eight-week study. Both treatments were "extremely effective" for all types of lesions and significantly reduced open and closed comedones after two weeks of treatment. Somewhat higher number of patients in the benzoyl peroxide group showed excellent results.

A study by Shalita et al. showed the additive effect of the cleanser in acne treatment (49). They compared the efficacy of a combination of benzoyl peroxide 6% cleanser and tretinoin 0.1% microsphere gel versus tretinoin alone during a 12-week study. Fifty-six subjects with moderate acne completed the study. Both treatments showed a significant reduction in inflammatory and non-inflammatory lesions from baseline. However, the combination regimen produced a greater reduction of inflammatory acne lesions than the monotherapy without increasing local irritation.

Recently, a British study compared the efficacy and treatment costs of benzoyl peroxide versus oral antibiotics (50). This 18-week study evaluated five antimicrobial acne treatments in approximately 650 participants: oral oxytetracycline; oral minocycline; benzoyl peroxide; separate administration of topical erythromycin and benzoyl peroxide; and a combination of topical erythromycin and benzoyl peroxide. The authors found that topical 5% benzoyl peroxide used twice daily as single active agent was similar in efficacy to 100 mg minocycline once daily. The analysis of cost-effectiveness found that the cheapest treatment (benzoyl peroxide) was 12 times more cost-effective than minocycline. Additionally, the authors noted that pre-existing propionibacterial resistance compromised the clinical efficacy of oral tetracyclines. In contrast, regimens combining benzoyl peroxide with erythromycin were unaffected by resistance. The authors concluded that topical benzoyl peroxide and benzoyl peroxide/erythromycin combinations are similar in efficacy to oral antibiotics (oxytetracycline and minocycline). The more significant message is that the clinical equivalence comes without being affected by propionibacterial antibiotic resistance.

Sulfur and Sulfur/Resorcinol Combinations

Sulfur has been used to treat acne for hundreds of years for its peeling and drying actions, and it is found in various washes, soaps, and creams. It is an antifungal and antibacterial agent. Its keratolytic activity is somewhat controversial, with some authors showing even a comedogenic effect (51). It is not fully understood how sulfur works in the treatment of acne lesions. The claimed keratolytic properties may derive from the interaction between sulfur and keratinocytes, producing hydrogen sulfide. Smaller sulfur particles could allow greater interaction with keratinocytes and, therefore, produce greater therapeutic efficacy (52). Because of its unpleasant odor, sulfur is rarely used alone. As an OTC ingredient, it is most frequently found in combination with resorcinol. Sulfur is also present in prescription acne products in combination with sodium sulfacetamide.

Resorcinol has antibacterial, antifungal and mild keratolytic activity. When used as resorcinol monoacetate, this slowly liberates resorcinol, generating a milder but longer lasting effect. In the Acne Monograph, the OTC panel concluded that resorcinol is safe for human applications but did not find it efficacious in acne as a single ingredient (53). Therefore, resorcinol and resorcinol monoacetate are currently approved as OTC acne ingredients only in combination with sulfur. Side effects of sulfur and of resorcinol include

mostly mild irritation. Unpleasant odor (sulfur) of the formulation may also be a problem for patients.

Sulfur preparations for acne treatments are not as popular as they were in the past decades. Although sulfur is found in the forms of cream, lotion, ointment, spot-treatment mask, and bar soap, the more common use is in its prescription combination with sodium sulfacetamide.

Published peer-reviewed studies on the efficacy of sulfur, alone or in combination with resorcinol, are basically non-existent. Few controlled efficacy studies are, however, described in the OTC Acne Monograph and were presented to the OTC panel as substantiating material for the approval of these ingredients (54). Based on these studies, sulfur was approved as an acne ingredient in the concentrations of 3–8%. Resorcinol (2%) and resorcinol monoacetate (3%), however, were not found to be effective as single ingredients, and they were approved only in combination with sulfur 3–8% (55). The Acne Monograph reports that in a 12-week study (56), more subjects treated with 3% sulfur showed a good to excellent response, compared to the vehicle group, although no statistical analysis was conducted. A series of split-face, vehicle-controlled studies (57) showed a better reduction in lesion count in the subjects treated with a 5% sulfur product compared to vehicle.

Another study compared an 8% sulfur-2% resorcinol cream against placebo cream in 25 subjects using a split-face design (58). After eight weeks of treatment sulfur-resorcinol was significantly better in reducing open comedones, papules and pustules compared to placebo. A third study compared four treatment cells of 60 acne subjects each. The treatments were applied three times daily for eight weeks and consisted of: (i) 2.66% sulfur–1% resorcinol; (ii) 8% sulfur–2% resorcinol; (iii) 2.66% sulfur; and (iv) placebo. The two combinations of sulfur-resorcinol were found equivalent and were superior to both the placebo and the sulfur alone in the reduction of papules and "whiteheads" (59).

While the effect of sulfur on non-inflammatory lesions is not clear, its combination with resorcinol seems to increase its efficacy in both inflammatory and comedonal lesions.

Adjunctive Acne Products

A few adjunctive products have been promoted for the treatment of acne. Since these are not sold as OTC drugs, well-controlled studies are usually missing and it is difficult to interpret their true benefit as acne treatments.

Tea Tree Oil

Tea tree oil (TTO) is extracted from the Melaleuca alternifolia and in the past decade has become a popular topical antimicrobial for skin conditions such as tinea pedis and acne. The three major components of TTO responsible for anti-*P. acnes* activity have been found to be alpha-terpineol $<$ terpinen-4-ol $<$ alpha-pinene (listed in order or increased minimum inhibitory concentration (MIC) values) (60). Besides its anti-*P. acnes* properties, TTO has been found to have a significant and rapid (within 10 minutes) anti-inflammatory activity when applied to histamine-induced weals (61). This could be an additional pathway through which TTO improves inflammatory acne.

One of the few clinical studies conducted in acne compared a 5% TTO gel with a 5% benzoyl peroxide lotion in 124 acne patients. Both treatments had a significant effect in improving both inflamed and non-inflamed acne lesions, although benzoyl peroxide produced faster results. Fewer side effects, though, were experienced in the TTO group (62).

Botanicals

Although products cannot be sold bearing an anti-acne label unless they contain an OTC approved ingredient, many botanical formulations are marketed towards the acne-prone consumer claiming to "heal," "purify," or "cleanse" the skin and pores. Companies promote their proprietary formula of herb extracts, but well-conducted clinical studies are lacking, and therefore it is difficult to understand the true efficacy of these products. The formulation may include different herb extracts with various activities (antimicrobial, anti-oxidant, anti-inflammatory, soothing, etc.).

Retinaldehydes

A novel European acne formulation combines 6% glycolic acid and 0.1% retinaldehyde. In a study on mild to moderate acne patients, the combination led to "important/very important" global improvement at two months (63). This formulation has been also suggested to prevent post-inflammatory pigmentation (64).

Capryloyl Salicylic Acid

A lipophilic derivative of SA (capryloyl SA or LHA) has been proposed as a new anti-acne agent by a European firm. In a recent study, they showed that the LHA cream was well tolerated and significantly more effective than a control moisturizing cream throughout the 87-day period as per the global evaluation scale (65). However, no comparison with its vehicle cream or with any approved SA drug was presented.

Oral Supplements (Nutraceuticals)

Oral supplements have recently become more popular as a way of promoting total well-being. Some supplements are marketed as part of a multi-step aging or acne treatment. Nutraceuticals marketed for acne typically contain either herb extracts or specific vitamins (especially vitamin A and vitamin B-complex).

Alpha-Hydroxyl Acids

Alpha-hydroxy acids (AHAs) such as glycolic acid and lactic acid have been used for many years by dermatologists at concentrations of 20% to 30% for facial peel procedures. More recently, AHAs have been added to OTC washes and moisturizers at concentrations of 4% to 6%. AHAs have been found to soften the stratum corneum, remove dead cells, and change free radicals on the skin. These products combine well with both topical comedolytics and topical antibiotics. They can be used as the daily facial cleanser or moisturizer before application of prescription medication. AHAs in the 20% to 30% strength help to improve discoloration and scarring. Mild benefit can also be seen at the 4% to 6% strength. As with all other topical products, irritation may be a problem, especially during the initial few weeks of usage. AHAs are sometimes used

alone in mild acne. Various products, though, add glycolic acid to SA formulations claiming an increase in the exfoliation benefits. A 2% lactic acid cream gel preparation has been reported to be effective in both inflammatory and non-inflammatory acne lesions compared to placebo (66).

Over-the-Counter Combination Therapy

Since acne is a multi-factorial disorder, dermatologists recommend the use of combination therapy. In analogy, an OTC combination therapy was recently developed to treat multiple pathogenic factors of acne. This system combines a 2.5% benzoyl peroxide lotion with an SA cleaner that also contains glycolic acid. A daytime broad-spectrum sunscreen containing a proprietary blend of skin soothing naturals is included in the system as per FDA recommendation (67).

This OTC combination therapy system was compared to a benzoyl peroxide only system in a double-blind, randomized, placebo-controlled clinical study on 90 subjects with mild to moderate acne. Both systems were well tolerated, although the benzoyl peroxide–only system had slightly higher irritation. The clinical results showed that the OTC combination therapy system with both SA and benzoyl peroxide treatment products rapidly improved acne within one week and continued to further ameliorate over the course of treatment. Target pimple size, edema and erythema were significantly reduced within two days (first time point). Significant reduction of full-face total acne lesion counts was seen as early as day 4. In contrast, the benzoyl peroxide only system did not show significant reduction of full face acne lesions until week 2 and global acne severity until week 4 (68). The time course kinetics of the treatments (charts in Fig. 2) show that the main difference clinically appeared to be in the superior reduction of the closed comedones or the primary lesions by the SA + BPO OTC combination therapy system.

These results demonstrate the value of using the combination therapy approach in OTC acne treatments as in Rx.

Clinical Imaging in the Development and Evaluation of Over-the-Counter Acne Products

Photography has been a useful tool for evaluating and documenting treatment benefits (Fig. 3 for example). Several acne-grading methods have even been proposed based on photographs. Recent advancement in digital imaging has made image capture and evaluation much more convenient. The techniques that have been applied to clinical imaging go beyond just regular photography that mainly utilizes the visible light spectrum. Photographers have used polarized filters to either cut through the surface specula for a matted appearance with cross-polarized light (Fig. 4 for example), or to enhance the surface specula to make the shine shinier or the surface texture more 3-dimensional–like with the help of parallel-polarized light. Skin redness and pigmentation are highlighted in cross-polarized light images, while parallel-polarized light images bring out the surface luminosity and make the height of a pimple or the depth of a wrinkle more distinctive.

(A)

Whole Face Inflammatory Lesion Counts

(B)

Closed Comedone Counts
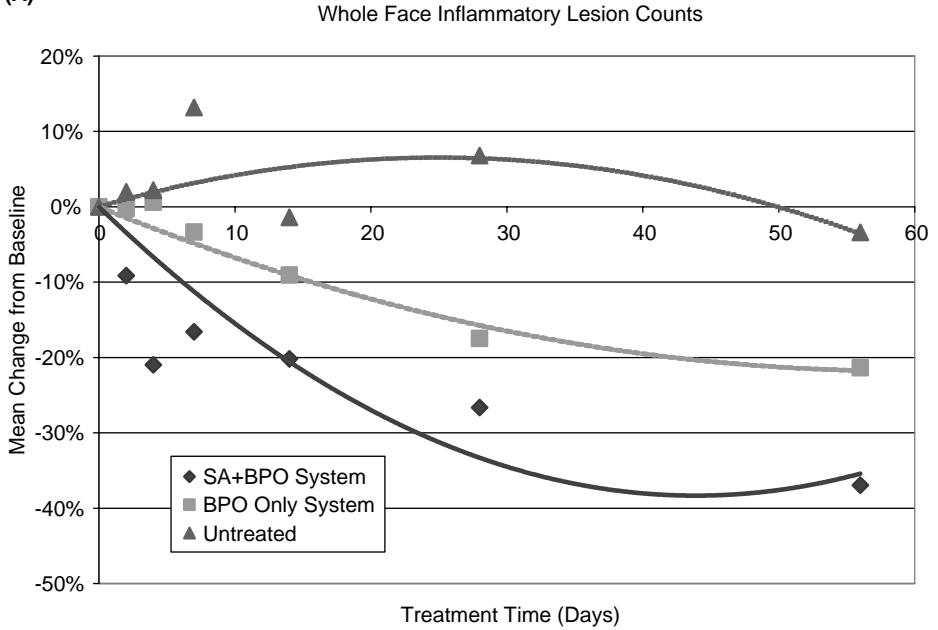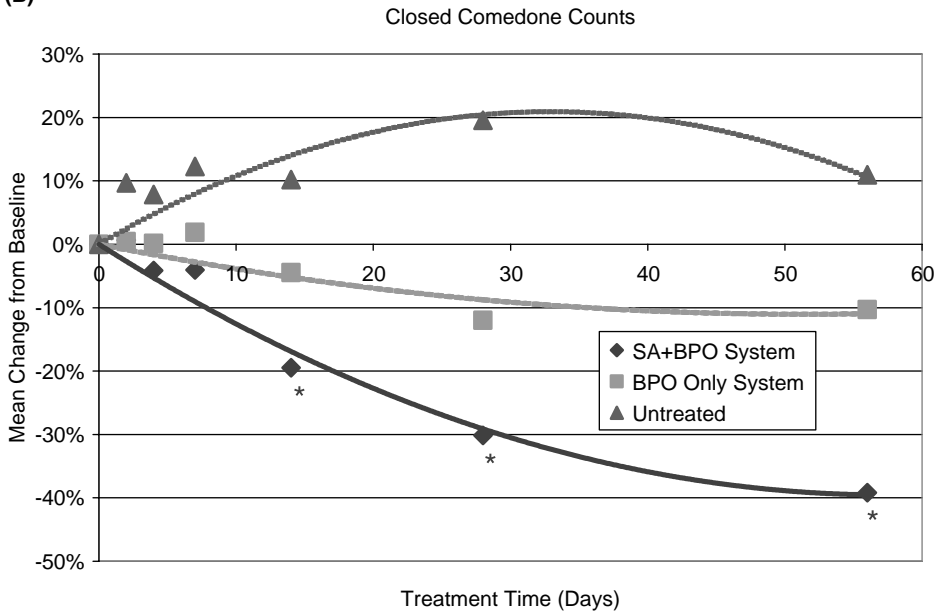
Figure 2 Treatment effects of an over-the-counter regimen containing salicylic acid and benzoyl peroxide versus a regimen containing only benzoyl peroxide. Upper chart (**A**) shows the changes in the total inflammatory lesion counts and the lower chart (**B**) shows the changes in closed comedone counts. Asterisks denote significantly greater reduction among treatments in favor of the labeled treatment.

Figure 3 Acne skin images from visible light photography comparing the skin conditions before, during and after treatment with an over-the-counter combination therapy system (salicylic acid + benzoyl peroxide). Note the marked improvements in skin texture, bumpiness and clarity. Skin redness was also reduced (data not shown).
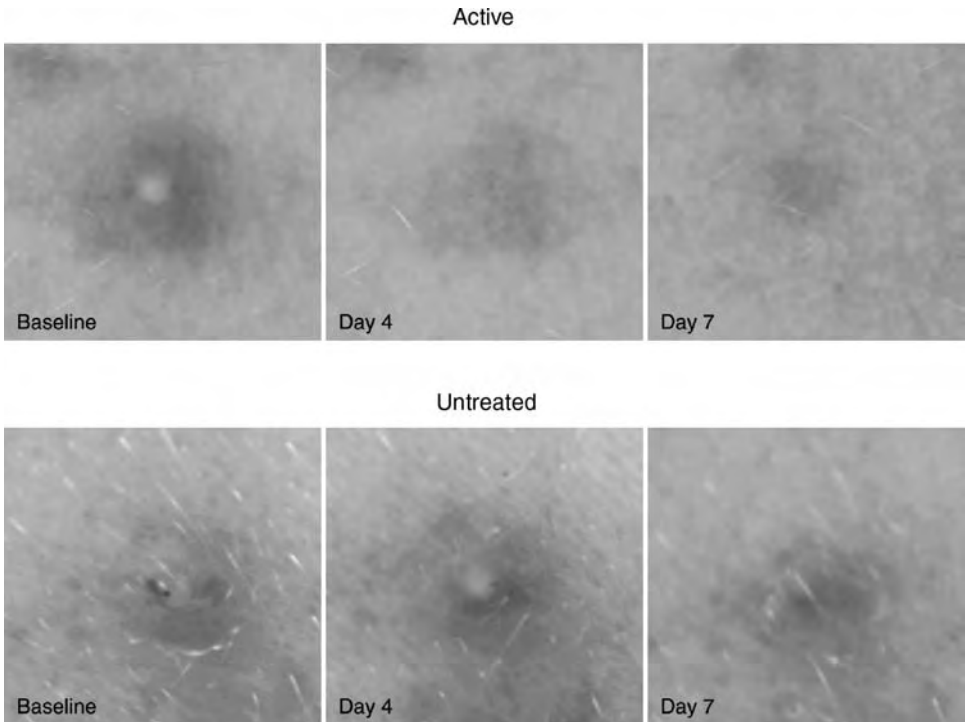
Figure 4 Cross-polarized light images tracking pimple resolution and redness reduction of a pimple treated with a 2% SA gel (active) and of an untreated pimple. Blinded analysis of individual pimple images showed pimple resolution by the 2% SA gel was faster than by the placebo (the vehicle gel) and the untreated control, and similar to that of a 10% benzoyl peroxide lotion. *Abbreviation*: SA, salicylic acid.

(A)
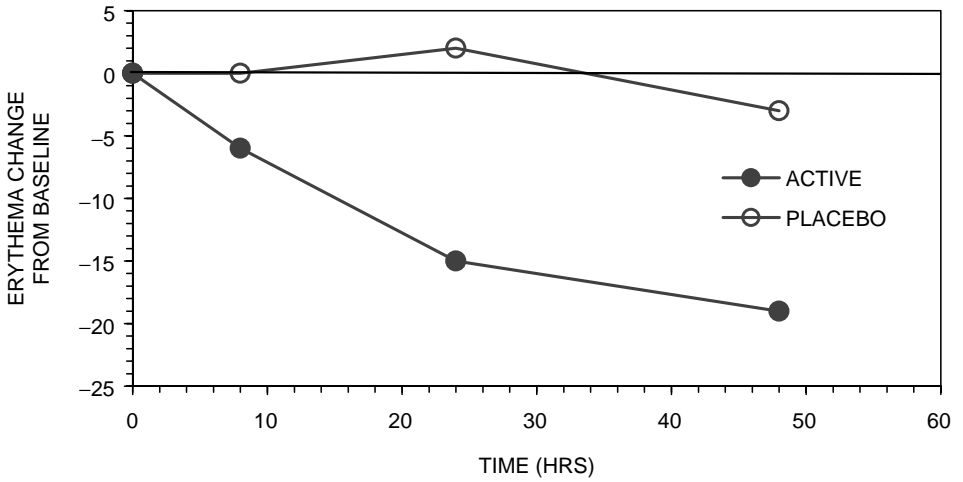
(B)
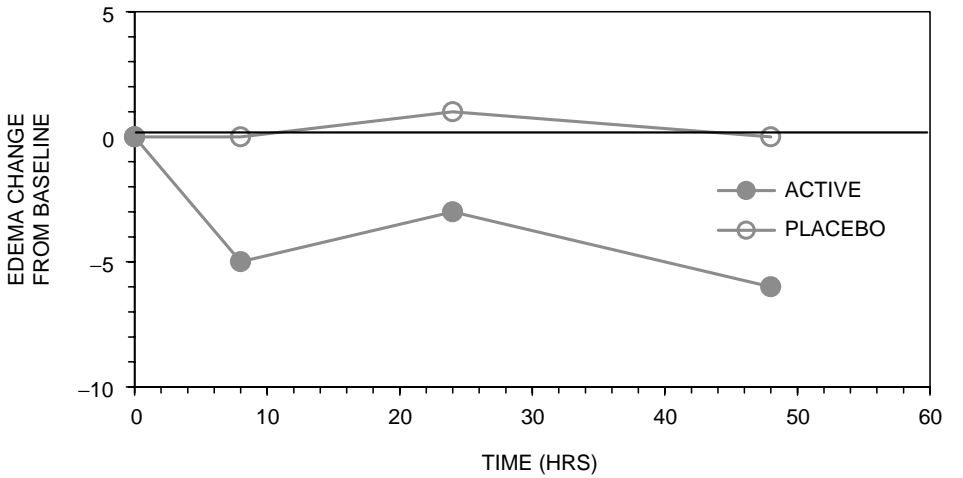
Figure 5 Time Course of target Lesion resolution as measured by hyper-spectral image analysis quantifying (**A**) Erythema, and (**B**) Edema (water).

Another imaging technique involves the use of UV-enriched lamp or blue light. When the skin is illuminated in this manner, the pilosebaceous glands glow as intensely yellow-green or orange-red fluorescent spots (69). Partially or totally clogged pilosebaceous glands all show particularly intense fluorescence of different sizes and brightness, reflecting the degrees to which they are blocked. While the yellow-green fluorescence is associated with the pore plug materials, the orange-red fluorescence is shown to be the emission at wavelengths of 620 and 680 nm by the *P. acnes* under

385–415 nm light (70–73). The intensity of this orange-red fluorescence is proportional to the density of *P. acnes* and declines under effective antibiotic treatment (74,75). Fluorescence photography is thus a quick way to assess the antibacterial efficacy of benzoyl peroxide formulations (76).

A powerful method has recently been developed that incorporates all of the above imaging techniques to enable concurrent evaluation of clinical and sub-clinical conditions in the skin (77,78).

The most recent advancement in the clinical digital imaging field is the hyper-spectral imaging technique (79). This technique uses narrow-band filters in front of the camera to acquire a series of images (called a hyper-spectral cube). The narrow band filters are selected to detect different chromophores in the skin, the distribution of which is captured in the corresponding images. Each pixel in an image, thus, contains spectral information of the corresponding imaged site on the skin. Reflectance data can be analyzed on a pixel-by-pixel basis to yield chromophore concentrations (oxy-hemoglobin, deoxy-hemoglobin, melanin, water, and light scattering). Increased local oxy-hemoglobin concentrations are manifested as erythema. Increased local water concentrations are related to interstitial fluid accumulation due to edema. Chen et al. (80) studied the progression of acne lesion maturation by monitoring lesion erythema and edema with hyperspectral imaging. An example of the results that can be obtained is shown in Fig. 5. Chantalat et al. (81) applied hyperspectral imaging to detect sub-clinical acne lesions that were not yet visible on the skin surface, and tracked the effects of treatments on resolving inflammation associated with the sub-clinical lesions. These studies demonstrate the unique potential of hyperspectral imaging in the evaluation of clinical and sub-clinical acne non-invasively.

SUMMARY

Majority of acne sufferers rely upon OTC acne medication to treat their acne. Therefore it is incumbent upon the OTC manufacturers to improve OTC formulations in response to the unmet needs of the average acne patients. While no new OTC acne ingredients have emerged since FDA issued the Final Acne Monograph in 1991, step change has taken place in terms of improved delivery of actives, the choices of vehicles, and the forms of treatments. This is particularly true with daily regimen. It has changed the paradigm of OTC acne therapy from reactive, occasional and irregular usage to routine daily treatment providing the ultimate acne control.

The body of works mentioned in this chapter clearly demonstrates that both benzoyl peroxide and SA are two powerful acne-fighting ingredients. Even though benzoyl peroxide has been the mainstay in OTC acne therapy, our recent work indicates that SA has been under-appreciated. With proper formulation, SA can provide rapid acne clearance with overall efficacy comparable to a 10% benozyl peroxide treatment, while providing high degree of skin compatibility.

In parallel, we have developed powerful, non-invasive imaging and spectral techniques to track acne clinically and sub-clinically at the follicular level. These advanced acne diagnostic methods will enable dermatologists and scientists to develop a much clearer understanding of the acne life cycle in vivo and control its emergence.

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17

Acne Treatment Methodologies

Emmy M. Fernandez, Andrea L. Zaenglein, and Diane M. Thiboutot
Department of Dermatology, Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania, U.S.A.

INTRODUCTION

Acne is an exceedingly common condition affecting millions of adolescents and young adults. Not surprisingly, the psychological and economic impact of acne is reflected in these vast numbers. The prevalence in teenage girls ranges from 16–80%, while teenage boys are even more likely to be affected with prevalence ranging from 29–90% (1–4). These large variations in prevalence are due to differences in acne grading scales used in the various studies. Adult acne, although less common than adolescent acne, continues to be a significant problem for 3–6% of adult men, and 5–12% of adult women well into their thirties and forties (5,6). With so many persons affected, the economic impact of acne is immense. In 1999 there were approximately 35 million Americans with acne generating 7.9 million physician visits. That same year approximately 1.2 billion dollars was spent on prescription acne medications (7).

In addition to the economic impact, acne also has a significant psychological impact in both adolescents and adults.Thirty to fifty percent of adolescents experience psychiatric disturbances due to acne (8). Studies have shown that acne causes similar levels of social, psychological, and emotional impairment as asthma and epilepsy (9). Studies have also shown that unemployment is higher among adults with acne than among adults without acne (10).

In order to implement effective treatment strategies for patients with acne, a solid understanding of the physiology of the pilosebaceous unit and the pathological events that lead to acne are essential. The pathogenesis of acne is very complex, but four basic steps have been identified. These key elements (Fig. 1) are: (i) follicular epidermal hyper-proliferation, (ii) excess sebum production, (iii) inflammation, and (iv) the presence and activity of *Propionibacterium acnes* (P. acnes).

Follicular Epidermal Hyperproliferation

Follicular epidermal hyperproliferation results in the formation of the primary lesion of acne, the microcomedo. The epithelium of the upper hair follicle, the infundibulum, becomes hyperkeratotic with increased cohesion of the keratinocytes. The excess cells and their tackiness result in a plug in the follicular ostium. This plug then causes downstream concretions of keratin, sebum, and bacteria to accumulate in the follicle. These packed concretions cause dilation of the upper hair follicle producing a microcomedo. The stimulus for keratinocyte hyperproliferation and increased adhesion is unknown. However,
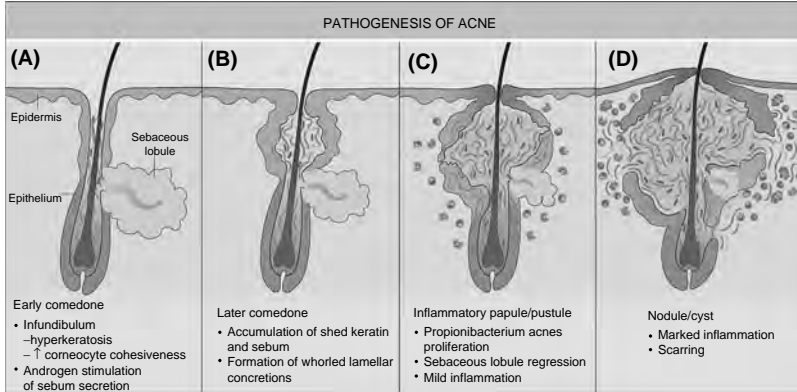
Figure 1   Acto Pathogenesis. The four key steps in acne pathogenesis: (**A**) follicular epidermal hyperproliferation, (**B**) excess sebum production, (**C**) inflammation, and (**D**) the presence and activity of *Propionibacterium acnes*. *Source*: Adapted from Ref. 11.

several proposed factors in keratinocyte hyperproliferation include: androgen stimulation, decreased linoleic acid, and increased interleukin-1 alpha (IL-1 alpha) activity.

Androgenic hormones may act on the follicular keratinocytes stimulating hyperproliferation. Dihydrotestosterone (DHT) is a potent androgen that may play a role in acne. Figure 2 demonstrates the physiologic pathway for dehydroepiandrosterone sulfate (DHEA-S) conversion to the androgen DHT. 17-beta HSD and 5-alpha reductase, are enzymes responsible for converting DHEA-S to DHT. When compared to epidermal keratinocytes, follicular keratinocytes have increased 17-beta HSD, and 5-alpha reductase thus enhancing DHT production (12,13). DHT may stimulate follicular keratinocyte proliferation. Also supporting the role of androgens in acne pathogenesis is the evidence that the individuals with complete androgen insensitivity do not get acne (14).

Follicular keratinocyte proliferation may also be regulated by linoleic acid. Linoleic acid is an essential fatty acid in the skin that is decreased in subjects with acne. The quantity of linoleic acid normalizes after successful treatment with isotretinoin. Subnormal levels of linoleic acid may induce follicular keratinocyte hyperproliferation, and produce pro-inflammatory cytokines. It has also been suggested that regular quantities of linoleic acid are actually produced but are simply diluted by increased sebum production (15).

In addition to androgens and linoleic acid, IL-1 may also contribute to keratinocyte hyperproliferation. Human follicular keratinocytes demonstrate hyperproliferation and microcodemo formation when IL-1 is added. IL-1 receptor antagonists inhibit
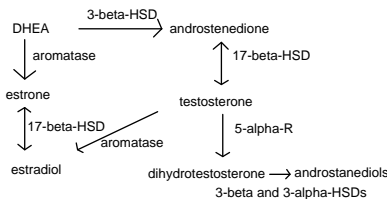
Figure 2   Steroid metabolic pathway. DHEA is a weak androgen that is converted to the more potent testosterone by 3-beta-HSD and 17-beta-HSD. Five-alpha-reductase then converts testosterone to dihydrotestosterone, the predominant hormonal effector on the sebaceous gland. Both DHEA and testosterone can be metabolized to estrogens by the enzyme aromatase. The sebaceous gland expresses each of these enzymes. *Source*: Adapted from Ref. 11.

microcodemo formation providing additional support for the cytokine's role in acne pathogenesis (16,17).

Excess Sebum Production

The second key feature in the pathogenesis of acne is excess sebum production from the sebaceous gland. Patients with acne produce more sebum than those without acne although the quality of sebum is the same between the two groups (18). One of the components of sebum, triglycerides, may play a role in acne pathogenesis. Triglycerides are broken down into free fatty acids by *P. acnes*, normal flora of the pilosebaceous unit. These free fatty acids promote further bacterial clumping and colonization of *P. acnes*, incite inflammation, and may be comedogenic (19).

Androgenic hormones also influence sebum production. Similar to their action on the follicular infundibular keratinocytes, androgen hormones bind to and influence sebocyte activity (20). Those with acne have higher average serum androgen levels (although still within normal range) than unaffected controls (21,22). 5-alpha reductase, the enzyme responsible for converting testosterone to the potent DHT, has greatest activity in areas of skin prone to acne, the face, chest, and back (23).

The role of estrogen on sebum production is not well defined. The dose of estrogen required to decrease sebum production is greater than the dose required to inhibit ovulation (24). The mechanisms by which estrogens may work include: (i) directly opposing the effects of androgens within the sebaceous gland; (ii) inhibiting the production of androgens by gonadal tissue via a negative feedback loop on pituitary gonadotrophin release; and (iii) regulating genes that suppress sebaceous gland growth or lipid production (25).

Inflammation

The microcomedo will continue to expand with densely packed keratin, sebum, and bacteria. Eventually this distension will cause follicular wall rupture. The extrusion of the keratin, sebum, and bacteria into the dermis results in a brisk inflammatory response. The predominant cell type within 24 hours of comedo rupture is the lymphocyte. CD4+ lymphocytes are found around the pilosebaceous unit while CD8+ cells are found perivascularly. One to two days after comedo rupture, the neutrophil becomes the predominant cell type surrounding the burst microcomedo (26).

Propionibacterium Acnes

As mentioned above, *P. acnes* also plays an active role in the process of inflammation. *P. acnes* is a gram-positive, anaerobic, and microaerobic bacterium found in the sebaceous follicle. Adolescents with acne have higher concentrations of *P. acnes* compared to non-acne controls. However, there is no correlation between the raw number of *P. acnes* organisms present in a sebaceous follicle and the severity of the acne (27).

The cell wall of *P. acnes* contains a carbohydrate antigen that stimulates antibody development. Those patients with the most severe acne have the highest titers of antibodies (28). The anti-*P. acnes* antibody enhances the inflammatory response by activating the complement cascade and thus initiating pro-inflammatory events (29). *P. acnes* also facilitates inflammation by eliciting a delayed type hypersensitivity response (30) and by producing lipases, proteases, hyaluronidases, and chemotactic factors (31). Additionally, *P. acnes* has been shown to stimulate an upregulation of cytokines by binding to toll-like receptor 2 (TLR-2) on monocytes and polymorphonuclear cells surrounding the sebaceous follicle (32). After binding TLR-2, pro-inflammatory cytokines such as IL-1, IL-8, IL-12, and TNF-alpha are released (33,34).

The four elements of acne pathogenesis—follicular keratinocyte hyperproliferation, seborrhea, inflammation, and *P. acnes*—are intertwined steps in the formation of acne. Various acne treatments target different elements in acne pathogenesis. Understanding the mechanisms of action of the multitude of therapeutic options in treating acne will help assure better therapeutic results.

MORPHOLOGY

Clinically, acne can present as non-inflammatory or inflammatory lesions or both. Non-inflammatory acne is marked by the presence of codemos. Codemos are follicular-based papules that may be either open or closed. Open codemos, commonly called blackheads, are papules with prominent dilated follicular ostia. Closed codemos, or whiteheads, are flesh colored papules without an evident follicular opening. Inflammatory acne can include lesions such as erythematous papules, pustules, nodules, cysts, or plaques. Post-inflammatory hyper- or hypopigmentation are common sequelae of inflammatory acne. However, scarring can be a complication of both inflammatory and non-inflammatory acne.

TOPICAL RETINOID

All acne lesions begin as non-inflammatory lesions, either open or closed codemos. Topical retinoids are a mainstay of acne treatment due to their ability to hamper the primary acne lesion, the microcodemo. Additionally, retinoids have fairly potent anti-inflammatory effects. Retinoids are structural and functional analogs of vitamin A that exist in both topical and systemic forms. They act by binding to two nuclear receptor families within keratinocytes: the retinoic acid receptors (RAR), and the retinoid X receptors (RXR). Each of the receptor families contains three receptor isotypes: alpha, beta, and gamma. In the human epidermis RXR receptors are by and large the alpha isotype and RAR are generally the gamma isotype (35). Both families of receptors act as ligand-activated transcription factors. The RAR receptors function as a heterodimer by binding to RXR. The RXR receptors may act as homodimers or may bind to other nuclear receptors such as: vitamin D3, thyroid hormone, and peroxisome proliferator-activated receptors. The retinoid receptors bind to specific regulatory DNA sequences called retinoid hormone response elements (HREs) where transcription is activated. The retinoid HREs activate the transcription of genes that normalize follicular keratinization, and decrease cohesiveness of keratinocytes. This prevents the formation of microcodemos. The retinoid-receptor complex also antagonizes genes that do not contain retinoid HRE. AP-1 and NF-IL6 are key transcription factors in inflammatory responses. The retinoids suppress these transcription factors by competing for the co-activator proteins needed to activate AP-1 and NF-IL6 (36). These combined anti-comedogenic and anti-inflammatory properties make retinoids beneficial for patients with either non-inflammatory or inflammatory acne.

Tretinoin

Tretinoin, the original topical retinoid, has been formulated in different vehicles in an attempt to decrease the irritation associated with the original formulations (Table 1). One delivery system involves the use of inert microspheres impregnated with tretinoin to allow for a slower delivery of tretinoin (Retin-A Micro® 0.04%, and 0.1% gel). Another formulation involves the combination of tretinoin with polyolprepolymer-2 (Avita®). Polyolprepolymer-2 prevents rapid percutaneous absorption of tretinoin, thus lessening some of the early irritation experienced with pure tretinoin products (37). Less peeling and

Table 1 Topical Retinoid Preparations Used for Treatment of Acne Vulgaris

Drug	Trade	Vehicle	Concentration
Tretinoin	Retin-A	Cream	0.025%, 0.05%, 0.1%
		Gel	0.01%, 0.025%
		Solution	0.05%
	Retin-A Micro	Gel with microsponge system	0.04%, 0.1%
	Avita	Cream	0.025%
		Gel	0.025%
	Altinac	Cream	0.025%, 0.05%, 0.1%
	Renova	Cream	
	Generic	Cream	0.025%, 0.05%, 0.1%
		Gel	0.025%
Adapalene	Differin	Cream	0.1%
		Gel	0.1%
		Solution	0.1%
Tazarotene	Tazorac	Gel	0.05%, 0.1%
		Cream	0.05%, 0.1%

Many topical retinoids are available in different vehicles and varying concentrations.
Source: Adapted from Ref. 11.

drying can be seen in patients using Avita® (37,38). A multi-center, double-bind, parallel study demonstrated comparable efficacy between Avita® and tretinoin 0.025% cream in 215 patients after 12 weeks of treatment (38).

Adapalene

Adapalene and tazarotene are topical medications that are formulated to bind the to the RAR without affinity for the RXR. Adapalene is a naphthoic acid derivative that was manufactured to be structurally similar to a naturally occurring hormone, retinoic acid. It works by directly binding to the RAR gamma and beta. A multi-center trial comparing adapalene 0.1% gel to tretinoin 0.025% gel found adapalene to produce a greater decrease in inflammatory and non-inflammatory lesions over a 12-week period. The adapalene group also had significantly less side effects of erythema, scaling, dryness, and burning (39). Adapalene is light stable allowing for daytime use. Adapalene is also resistant to oxidation by benzoyl peroxide. It is available in 0.1% concentration in a cream, solution, pledget, and propylene glycol-based gel.

Tazarotene

Tazarotene, a synthetic retinoid, exerts it action through its metabolite tazarotenic acid that binds RAR-beta and gamma. Studies have shown that tazarotene 0.1% gel is more effective than tretinoin 0.025% gel (40) or tretinoin 0.1% microspheres (41). Tazarotene can be used once daily overnight similarly to tretinoin or it can be applied for a brief period, and then washed off. This latter method minimizes irritation but maintains efficacy by exposing the skin to the retinoid for only five minutes once a day (42). It is available in 0.05% or 0.1% cream or gel formulations.

While the other topical retinoids are classified as pregnancy category "C," tazarotene is category "X" (Table 2). In two surveys of patients with first trimester exposures to tretinoin, there was no increased incidence of congenital malformations

Table 2 Comparison of Topical Retinoids

Generic	Required nighttime use?	Inactivated by benzoyl peroxide?	Pregnancy category
Tretinoin	Yes	Yes	C
Adapalene	No	No	C
Tazarotene	No	Yes	X

Comparison of topical retinoids with regards to inactivated by sunlight and benzoyl peroxide and their pregnancy categories.

(43,44). In one study, six patients who inadvertently became pregnant while on tazarotene had no babies with congenital malformations (45). This difference in categorization is due to the dual indication for tazarotene for both acne vulgaris and psoriasis. In psoriasis patients, larger amounts of tazarotene are used thus raising plasma levels of the retinoid to teratogenic potential. Only one pregnancy class can be assigned to a drug, therefore category "X" was designated given thus drug's potential to be used on a large surface area (46). Therefore, female patients must undergo contraceptive counseling while on tazarotene. For women who intend to become pregnant, there is no specific recommended wash-out period after tazarotene use (45).

Adverse Effects

Although effective for different types of acne, topical retinoids commonly cause adverse effects. These are generally mild in severity and usually during the start of therapy. Within the first month of treatment many patients experience a "retinoid dermatitis." This may consist of erythema, burning, scaling, pruritus, and dryness. These effects tend to decrease with continued use. Detailed instructions on appropriate use of retinoids can help limit any adverse side effects and enhance tolerability (Table 3). In general, a pea-sized amount should be applied evenly over the entire face. If any medicine is visible on the skin after application too much was applied and additional irritation may ensue. Instructing patients to apply their retinoid to dry skin can also minimize retinoid dermatitis. Patients should be advised to wait 15 minutes after washing the face to apply a topical retinoid. Wet skin enhances the penetration of the retinoid into the dermis, thus exacerbating irritation. A gradual increase in application frequency can also help to minimize irritation. The patient should apply the retinoid starting every other night or every third evening for the

Table 3 Patient Information About Topical Retinoids

When initiating treatment, apply topical retinoids every second or third day for the first couple weeks and gradually increase to once-daily application

Tretinoin must be applied at night

Wait 15 minutes after washing face to apply the retinoid

Apply a pea-sized amount to cover the entire face

Do not use a benzoyl peroxide product at the same time of day as retinoid application (concomitant use all right with adapalene)

Redness, burning, scaling, pruritus, and dryness may occur, especially during the first month of treatment. These side effects generally decrease with use

A non-comedogenic moisturizer may be used to prevent dryness

Photosensitivity may occur with all retinoids

Some patients experience a flare of their acne during the first few weeks of treatment

The above patient information regarding topical retinoid use can improve compliance and efficacy.

first one to two weeks of treatment. The patient can then gradually increase the frequency to nightly use as tolerated. Tolerance is often achieved in three to four weeks. It is important that the topical retinoid be applied at night-time for two reasons. Firstly, patients who use topical retinoids during the daytime notice increased sensitivity to ultraviolet (UV) light. Secondly, tretinoin is unstable when exposed to sunlight. When exposed to light, 50% of tretinoin is degraded in two hours (47). The synthetic formulations adapalene (47) and tazarotene (48) remain chemically stable when exposed to sunlight, and may be applied morning or evening. To combat irritation it is recommended that a non-comedogenic facial moisturizer be applied during the daytime. Some patients experience a pustular acne flare during the initial weeks of retinoid treatment that subsides with use. Patients should be warned of this possibility and encouraged to continue treatment through the exacerbation.

CLEANSERS

Treatment with retinoids, and acne itself, will cause dysfunction of the skin barrier. Facial cleansers also interact with proteins and lipids on the stratum corneum, and may further disrupt the skin barrier. However, acne patients need to use cleansers to control the level of skin oils and microbial levels. It is important to utilize facial cleansers that minimally disrupt the stratum corneum so that the barrier can be preserved. Soaps are alkaline cleansers that increase the skin's normal pH causing a decrease in the cutaneous lipid content (49). Soaps that contain antibacterial agents (such as triclosan) can inhibit gram-positive cocci but increase gram-negative rods (50). The irritant effects of soaps is worsened by hard water (51). Rather than using a soap, patients should cleanse their face with a syndet (synthetic detergent) cleanser. Rather than being alkaline, syndets have a pH close to the skin's pH of 5.5 (Table 4). Syndets used with hard water do not produce a scum on the skin, as do soaps. Syndets are minimally irritating, and compatible with other acne treatment regimens (52,53). Patients using syndets report more improvement in their acne than those using soaps. Syndets will also aid in minimizing irritation from other acne treatments such as tretinoin (53).

There are cleansers other than syndets may be more irritating but contain superior anti-acne properties. These other products, such as hydroxy acids and benzoyl peroxide, may exist as washes, and also as creams, gels, scrubs, and peels.

HYDROXY ACIDS

Hydroxy acids are present in over-the-counter and prescription formulations (Table 5). Alpha-hydroxy acids, such as glycolic acid and lactic acid, are water-soluble, and therefore penetrate to the dermis. Glycolic and lactic acids are derived from sugar cane and sour milk, respectively. Beta-hydroxy acids, such as salicylic acid, are lipid-soluble, and penetrate into the upper epidermis and into the pilosebaceous unit. Salicylic acid is derived from willow bark, wintergreen leaves, and sweet birch, and is also available in synthetic forms (54,55). Both alpha- and beta-hydroxy acids decrease cohesion among the keratinocytes in the stratum corneum, causing exfoliation (56,57). Due to their ability to penetrate the pilosebaceous unit, beta-hydroxy acids such as salicylic acid have a stronger comedolytic effect than alpha-hydroxy acids (58). However, in comparison with tretinoin and isotretinoin, salicylic acid is a mild comedolytic agent. Salicylic acid is available in both over-the-counter and prescription preparations ranging from 0.5 to 5% (59). Over-the-counter products are listed in Table 6.

Table 4 Cleansers

Brand name	pH	Composition
Aderm	6.44	Syndet
Avecyde	3.61	Syndet
Avéne	6.94	Syndet
Cetaphil	7.72	Syndet
Dove white	7.53	Syndet
Dove baby	7.0	Syndet
Dove (liquid)	5.16	Syndet
Dove pink	7.23	Syndet
Johnson's baby	11.9	Soap
Johnson's baby oat	12.35	Soap
Lux with glycerin	12.38	Soap
Nivea baby creamy	12.35	Syndet[a]
Nivea bath care	12.21	Syndet[a]
Nivea bath c. Almond	12.22	Syndet[a]
Nivea bath c. Oat	12.30	Syndet[a]
Oilatum	10.26	Syndet[a]
Natural oilatum	10.01	Syndet[a]
Zest neutral	9.85	Soap
Zest citrus sport	9.75	Soap
Zest herbal	9.97	Soap
Zest aqua	9.89	Soap
Palmolive green	10.18	Soap
Palmolive (white)	10.23	Soap
Palmolive botanicals	10.38	Soap
Camay classic	10.38	Soap
Camay gala	10.36	Soap
Camay soft	10.26	Soap
Rosa venus	10.65	Soap

pH and composition of some commercially available cleansers. The pH of each emulsion or liquid cleanser was recorded by using the Chemcadet pH meter (Cole-Parmer Instrument Co.).
[a] Plus mineral oil.
Source: Adapted from Ref. 60.

Table 5 Properties of Hydroxy Acids

Hydroxy acid	Solubility	Derived from	Penetration	Action
Alpha-hydroxy acids	Water-soluble		Dermis	Exfoliative
Glycolic acid		Sugar cane		
Lactic acid		Sour milk		
Beta-hydroxy acid	Lipid-soluble		Epidermis & pilose baceous unit	Exfoliative & comedolytic
Salicylic acid		Willow bark, wintergreen leaves, sweet birch		

Solubility, derivation, penetration, and action of alpha- and beta-hydroxy acids.

BENZOYL PEROXIDE

Benzoyl peroxide is a topical medication that has bactericidal effects to reduce *P. acnes*. It is available in both over-the-counter (Table 7) and prescription formulations as a bar soap, wash, gel or lotion in varying concentrations. The stay-on formulations of benzoyl peroxide will decrease *P. acnes* counts more so than the washes although both significantly decrease *P. acnes*. The concomitant use of benzoyl peroxide with antibiotics will lessen *P. acnes* resistance to antibiotics and increase the bactericidal effect of the antibiotic (61). None of the topical antibiotics alone is more effective against *P. acnes* than benzoyl peroxide (27). Benzoyl peroxide products need to be used at different times of the day than tretinoin or tazarotene. Oxidation of these retinoids, and thus decreased efficacy, can occur when in contact with benzoyl peroxide. A benzoyl peroxide product may be utilized in the morning with night-time application of a retinoid. Caution should be given to the patient that benzoyl peroxide products can bleach linens and clothing. Benzoyl peroxide allergic contact dermatitis may happen but is rare with a 1:500 incidence (62).

There are several topical products that combine benzoyl peroxide with either erythromycin or clindamycin. These combination topical products treat inflammatory acne better than either product alone (63,64). The shelf-life for these combination products is limited; therefore, some formulations of erythromycin, and benzoyl peroxide need to be refrigerated. Diarrhea and pseudomembranous colitis are rare but have been associated with topical clindamycin.

OTHER TOPICAL TREATMENTS

Other topical products with antimicrobial effects include azelaic acid and sodium sulfacetamide. Azelaic acid is a naturally occuring nine-carbon dicarboxylic acid. It is available for the treatment of acne in a 20% cream preparation. Azelaic acid has antimicrobial and weak anti-comedogenic effects. It reduces the production of keratohyalin granules in the pilosebaceous epithelium, thus normalizing ductal keratinocyte proliferation (62). Its anti-microbial effect is inferior to that of antibiotics or benzoyl peroxide (65). Azelaic acid can also decrease pigmentation by competing with tyrosinase (66). It may therefore be helpful for acne patients with post-inflammatory hyperpigmentation. It causes minimal erythema and does not produce the same degree of irritation as topical retinoids (62). Additionally, azelaic acid is safe for use in pregnancy.

Sulfur–sodium sulfacetamide is another well-tolerated topical antimicrobial. It is available as washes, bars, and creams. Sulfur presumably inhibits the growth of *P. acnes* by inhibiting its sustenance, para-aminobenzoic acid (PABA). The irritant effect on the skin causes keratolysis. The addition of sodium sulfacetamide lotion to sulfur has made its use more cosmetically acceptable.

ORAL ANTIBIOTICS

Oral antibiotics are often administered to patients with moderate to severe acne or in patients in whom topical therapy has failed. Patients with moderate acne with scarring or those whose acne covers a large surface area making topical application difficult may also be candidates for oral antibiotics. Oral antibiotics used in acne are typically of the tetracycline or macrolide family (Table 8).

Tetracyclines

The tetracyclines work by interacting with the 30S ribosomal subunit of bacteria, and thus inhibiting protein synthesis. Included in the tetracycline family are tetracycline,

Table 6 Over-the-Counter Salicylic Acid Products

Product	Strength (% salicylic acid)
Aveeno Clear Complexion Cleansing Bar	1%
Aveeno Clear Complexion Correcting Treatment	1%
Aveeno Clear Complexion Daily Cleansing Pads	0.5%
Biore Pore Perfect Blemish Fighting Cleansing Cloths	0.5%
Biore Pore Perfect Unclogging Scrub	2%
Biore Pore Perfect Warming Anti-blackhead Cream Cleanser	2%
Bye Bye Blemish Anti-acne Serum	1%
Bye Bye Bleamish Anti-acne Cleanser	0.5%
Clean and Clear Acne Wash Oil-free	2%
Clean and Clear Advantage Acne Spot Treatment	
Clean and Clear Advantage Acne Cleanser	2%
Clean and Clear Advantage Daily Cleansing Pads	2%
Clean and Clear Blackhead Clearing Scrub	2%
Clearasil 3 in 1 Acne Defense Cleanser	2%
Clearasil Icewash Gel Cleanser	2%
Clearasil Pore Cleansing Pads	2%
Clearasil Wipes	2%
Cuticura Acne Treatment Foaming Face Wash	
Eucerin Clear Skin Formular Concealer Pencil	
Neutrogena Acne Wash Foam Cleanser	2%
Neutrogena Acne Wash Cloths	2%
Neutrogena Acne Wash Cream Cleanser	2%
Neutrogena Blackhead Eliminating Daily Scrub	2%
Neutrogena Body Clear Body Wash	2%
Neutrogena Oil-free Acne Wash	2%
Neutrogena Oil-free Acne Wash Cream Cleanser	2%
Neutrogena Oil-controlling Cleansing Pads	2%
Neutrogena Healthy Skin Anti-wrinkle Anti-blemish Cleanser	0.5%
Neutrogena Advanced Solutions Acne Mark Fading Peel	2%
Neutrogena Deep Clean Cream Cleanser	
Neutrogena Clear Pore Treatment	2%
Olay Daily Facials Clarity Foaming Cleanser	2%
pH Isoderm Facial Wash Clear Confidence	2%
Stridex Face Wipes to Go	0.5%
Stridex Triple Action Acne Pads	2.0%
Stridex Sensitive Skin Pads	0.5%

Some commercially available over-the-counter salicylic acid products and the percent of salicylic acid they contain.

minocycline, and doxycycline. In addition to their antimicrobial effect, all of the tetracyclines are anti-inflammatory agents. They inhibit white blood cell chemotaxis, decrease lipase production by *P. acnes,* and decrease cytokine production. They also offer anti-inflammatory effects by decreasing the activity of matrix metalloproteinases (MMPs) (67). MMPs degrade several components of the extracellular matrix.

Tetracycline is a first-generation tetracycline. It is often administered at 500 mg twice daily for acne. Tetracycline should not be taken with milk as calcium blocks its absorption in the gut. It therefore must be taken on an empty stomach, one hour prior to or two hours after meals. Tetracycline may also cause gastrointestinal upset in some patients. Patients should also be warned of increased photosensitivity while on tetracycline. Other

Table 7 Over-the-Counter Benzoyl Peroxide Products

Product	Strength (% benzoyl peroxide)
Clean and Clear Continuous Control Acne Cleanser	10%
Clean and Clear Persa-gel Maximum Strength	10%
Clearasil Cream	10%
Clearasil Ultra Acne Treatment Cream	10%
Neutrogena Clear Pore Cleanser/Mask	3.5%
Neutrogena On-the-Spot Acne Treatment Vanishing Formula	2.5%
Oxy Acne Wash	10%
Oxy Acne Treatment Vanishing	10%
Panoxyl Bar	10%
Panoxyl Aqua Gel	10%
Stridex Power Pads	2.5%
Zapzyt Bar	10%
Zapzyt Treatment Gel	10%

Some commercially available over-the-counter benzoyl peroxide products and the percent of benzoyl peroxide they contain.

photosensitive side effects that may occur while on tetracycline include painful photo-onycholysis and pseudoporphyria. Tetracycline is deposited in areas of calcification. As a result, hyperpigmentation of deciduous and permanent teeth and bone may occur. For this reason, tetracycline should not be used in children under the age of 10 as deposition in the bone epiphyses may halt bone growth. Tetracycline is pregnancy category D since it can be deposited in the fetal bones. Nursing mothers should not be given tetracyclines due to the potential for drug excretion through the breast milk.

Doxycycline is a second generation tetracycline administered at 100 mg twice daily for acne. It is better absorbed from the gastrointestinal tract than tetracycline, and can be taken with food, although maximum absorption occurs when taken 30 minutes prior to a meal. Like tetracycline, it can be deposited in areas of calcification such as the teeth and bones, and therefore cannot be used in children under the age of 10, and is pregnancy category D. Photosensitivity is most common with doxycycline and is dose-dependent. 42% of patients taking a total of 200 mg a day will develop photosensitivity (68).

Doxycycline can also be administered for acne at subantimicrobial doses of 20 mg twice a day. In this manner the doxycycline is given at a low dose so that it has only anti-inflammatory effect, and not an antimicrobial effect. Without an antimicrobial action, there

Table 8 Comparing the Oral Tetracylines

Antibiotic	Dosing	Advantages	Disadvantages
Tetracycline	Taken on an empty stomach without milk	Inexpensive	Gastrointestinal upset
Minocycline	May be taken with food	Rapid onset of action	Risk of pigmentation, dizziness, autoimmune disorders
Doxycycline	May be taken with food	May be used at subantimicrobial doses	Photosensitivity

Comparing tetracycline, minocycline, and doxycycline with regards to dosing and the unique advantages and disadvantages of each.

is no opportunity for antibiotic resistance to arise. Doxycycline is the almost effective of the tetracyclines used at subantimicrobial doses because it is the most potent inhibitor of MMP (69). In a study of 40 acne patients who received doxycycline 20 mg po bid for 6 months, no adverse events such as nausea, vomiting, phototoxicity, or vaginitis were noted (70).

Minocycline is another second generation tetracycline given at 100 mg twice daily. Of the tetracyclines it has the best gastrointestinal absorption. It can be taken with food but is best absorbed 30 minutes prior to a meal. Compared to tetracycline and doxycycline, minocycline has more rapid clinical improvement. It also demonstrates a more persistent reduction of inflammation. In vitro, minocycline has the greatest reduction of *P. acnes* of all the antibiotics used for acne (65). Minocycline's superior effects are due to its high lipophilicity, and thus better penetration into the pilosebaceous unit. Minocycline can potentially cause a blue-grey hyperpigmentation, vestibular disturbances, or a hypersensitivity drug reaction (70). Three types of hyperpigmentation can occur. Type I hyperpigmentation occurs in areas of scar tissue. Type II hyperpigmentation occurs on previously normal skin, commonly on the anterior shins. Type III hyperpigmentation has a predilection for sun-exposed areas, and often is a diffuse hyperpigmentation. Since minocycline is highly lipophilic it can easily cross the blood-brain barrier. This may result in vestibular disturbances such as dizziness, vertigo, or ataxia. Rarer side effects of minocycline include drug-induced lupus, serum sickness, hepatic failure, and vasculitis. With the exception of serum sickness (which on average occurs 16 days after starting therapy), these side effects often occur after more than a year of therapy (71).

Benign intracranial hypertension, also known as pseudotumor cerebri, can occur with any of the tetracycline antibiotics, and is an increase in cerebrospinal fluid. This increase in intracranial pressure is seen most frequently with minocycline due to its ability to cross the blood-brain barrier. Pseudotumor cerebri can occur between four weeks and 18 months after starting therapy. Patients will complain of a headache that worsens in the evening, diplopia on lateral gaze, and nausea. Papilledema will be demonstrated by ophthalmologic examination. A lumbar puncture can aid in diagnosis, and also be therapeutic by relieving pressure of excess cerebrospinal fluid.

Macrolides

The macrolide antibiotics can also be useful in treating acne. This family of antibiotics works by binding irreversibly to the 50S ribosomal subunit thus inhibiting translocation during protein synthesis. Erythromycin and clindamycin are members of the macrolide family that are commonly used in acne. Both are used alone or in conjunction with benzoyl peroxide as a combination product. When given orally, erythromycin is administered at 500 mg twice daily. Erythromycin can and should be taken with food as it commonly causes gastrointestinal upset. It is safe in pregnancy and in lactating women, although erythromycin estolate should be avoided in these groups as it may cause cholestatic jaundice. Erythromycin inhibits the cytochrome P450 system thus causing reduced clearance of theophylline, warfarin, carbamazepine, and cyclosporine (70,72). Concomitant use of these medications should be avoided.

Clindamycin

The oral use of clindamycin is limited since 20–30% of patients will experience diarrhea. Oral clindamycin can also cause an overgrowth of *Clostridium difficile* in the gut thus causing pseudomembranous colitis (72). Topical clindamycin is generally well tolerated, and is available by prescription in solution, gel, and foam formulations.

Trimethoprim/Sulfamethoxazole

Trimethoprim/sulfamethoxazole is another oral antibiotic option for acne. It is administered 160 mg/800 mg twice daily. It works by inhibiting dihydrofolate reductase thus impeding purine and pyrimidine synthesis. It has a broad spectrum of antimicrobial activity, and therefore should be reserved as a second line agent or for patients with gram-negative folliculitis. Due to its sulfa moiety, trimethoprim/sulfamethoxazole also has the potential to cause a drug hypersensitivity syndrome with multi-organ involvement. Anemia, thrombocytopenia, and agranulocytosis are also potential side effects of trimethoprim/sulfamethoxazole.

Antibiotic Counseling

It is important to discuss and educate patients on the potential side effects of each antibiotic in order to maximize patient compliance. Patients may express several concerns about oral antibiotic use. One of these concerns may be possible reduced efficacy of their oral contraceptives. No pharmacokinetic interaction has been demonstrated between oral contraceptive pill and antibiotics (except rifampin). Oral contraceptive failure rates while on antibiotics, including those used for treating acne, fall within the range of oral contraceptive failure rates of patients not on antibiotics which is 1% to 3% (73). There are some individuals who will have decreased absorption of the oral contraceptive due to changes in the gut flora by antibiotics. It is impossible to predict who these patients will be. Therefore, all patients should be counseled regarding the small risk that their oral contraceptive may be less effective while taking antibiotics. Patients may also express concern regarding the publicized cancer risk with antibiotic use. A study in 2004 showed an increased risk of breast cancer with long-term antibiotic use (74). This risk was the same if antibiotics were being used to treat acne/rosacea or respiratory tract infections. A direct effect was not demonstrated in this study, only an association. It is important to point out to patients that no causal relationship between antibiotic use, and breast cancer was identified in this study.

Frequently antibiotics produce favorable results but sometimes a patient does not respond to antibiotic treatment. Several reasons exist for a poor clinical response. The antibiotic may have been given at an inadequate dose or for an inadequate duration. A maximum response is usually seen in three to four months. The patient may have been given suboptimal instructions on use or had poor compliance. Patients with a high sebum excretion rate (greater than 2.5 micrograms/cm/minute) may not respond due to dilution of the antibiotic in the pilosebaceous unit. Antibiotics may not be helpful if the patient is misdiagnosed with acne when the eruption truly is folliculitis due to gram negative enterobacteria, staphylococci, or yeasts.

Antibiotic Resistance

A patient may also not respond to antibiotics therapy if there is *P. acnes* resistance (75). Antibiotic resistance is a real problem of growing concern. The overall incidence of *P. acnes* antibiotic resistance increased from about 20% in 1978 to approximately 62% in 1996. Resistance of *P. acnes* is most common for erythromycin, clindamycin, tetracycline, doxycycline, and trimethoprim. Minocycline resistance is present in about 1% of patients today (76). There is no resistance to benzoyl peroxide, azeleic acid, or sulfur.

Several things can be done to minimize selection, and spread of antibiotic resistant strains of *P. acnes*. Antibiotics should be used judiciously, and only until control is achieved. The antibiotic should then be discontinued. If repeat treatment with antibiotics is required, the same antibiotic should be reused (unless it has lost efficacy). Patients who

are on oral or topical antibiotics should also use a benzoyl peroxide product to reduce the numbers of antibiotic resistant organisms. Oral, and topical antibiotics with dissimilar properties should not be used concomitantly, as combining these agents may cause cross resistance. Patient education is important to maximize compliance and prevent resistance.

HORMONAL THERAPY

Hormonal therapy is another treatment option for females with acne. Hormonal therapy may be helpful in acne patients with hirsutism, irregular menstrual periods and/or other signs of hyperandrogenism. Patients who have failed isotretinoin or oral antibiotics may still benefit from hormonal therapy. Women with flares of acne around the time of menses and those with excessive seborrhea may also respond well to hormonal therapy. Only oral retinoids and hormonal therapy can decrease sebum production. Anti-androgens, glucocorticoids, and oral contraceptives are all types of hormonal therapies (77).

Spironolactone

The anti-androgens include the androgen receptor blockers spironolactone, cyproterone acetate, and flutamide. Spironolactone is an aldosterone antagonist that also blocks the androgen receptor (72). Oral spironolactone reduces sebum excretion by 45–50%. It is taken 25–100 mg orally twice a day. Patients frequently experience breast tenderness and menstrual irregularities with spironolactone. These side effects increase with the dosage of spironolactone, and can be minimized by using an oral contraceptive. If a woman becomes pregnant with a male fetus, spironolactone as an anti-androgen may lead to feminization of the male genitalia and endocrine dysfunctions (78). Spironolactone can also cause mild elevations of potassium, and should therefore be used with caution in patients with renal or cardiac disease (79,80). For patients taking ethinyl estradiol/drospirinone (Yasmin®) in conjunction with spironolactone, this risk of hyperkalemia is increased.

Cyproterone Acetate

Cyproterone acetate is a hydroxy-progesterone that blocks the binding of androgens to their receptors. It also inhibits the synthesis of androgens in the adrenal glands and in the skin. Cyproterone acetate is not available in the United States but is available in Canada and Europe. It is incorporated in an oral contraceptive pill at 2 mg per day with ethinyl estradiol. Women with abnormal androgen metabolism can take additional 10–50 mg once daily during the first 10 days of their menstrual cycle (81).

Flutamide

Flutamide is a potent anti-androgen that is used to treat prostate cancer, and can also be useful for acne (82). It is administered at 250 mg twice daily in combination with an oral contraceptive. Liver function tests must be monitored in patients on flutamide as it can cause fatal hepatitis (83). Patients with adrenal hyperandrogenism may benefit from a combination of low dose glucocorticoidsteroid with an oral contraceptive. The glucocorticoid works byblocking adrenal androgen production. Prednisone 2.5–5 mg can be given daily at bedtime. Alternatively, dexamethasone 0.25–0.75 mg can be given nightly. Chronic glucocorticoid use may cause adrenal suppression (especially dexamethasone), and should be used with caution (84).

Oral Contraceptive

Oral contraceptives have several mechanisms of action in treating acne. They reduce androgen production by both the ovaries and the adrenal glands. Oral contraceptives also reduce free serum testosterone by increasing sex hormone-binding globulin. Sebum production is decreased with oral contraceptive use, possibly due to androgen reduction or possibly directly due to increased levels of estrogens (77). Most formulations consist of an estrogen in combination with a progestin. Progestin is needed to minimize the increased risk of endometrial cancer with unopposed estrogens. Progestins themselves have intrinsic androgenic activity, which can worsen acne in addition to causing changes in lipid metabolism and glucose intolerance (85). The newer generations of progestins (second and third generations) have been formulated to have lower androgenic properties. The second-generation progestins include ethynodiol diacetate, norethindrone, and levonorgesterol. The third-generation progestins have less cross reactivity with the androgen receptor, and increase sex hormone binding globulin. These oral contraceptives that lessen androgenic activity include: desogestrel, norgestimate, and gestodene. Only two oral contraceptives are currently FDA-approved for the treatment of acne, Ortho Tri-Cyclen® (Ortho, Raritan, NJ) and Estrostep® (Parke Davis Laboratories, Detroit, MI). Ortho Tri-Cyclen® is a triphasic contraceptive containg ethinyl estradiol (35 micrograms) and the third-generation progestin, norgestimate. Estrostep® contains ethinyl estradiol (graduated dose from 20–35 micrograms), and the second-generation progestin, norethindrone acetate (86).

Clinical improvement due to hormonal therapy will be evident as early as three months. Hormonal therapy is especially beneficial for acne in a "beard" distribution, involving the mandible and chin. Co-management with a patient's gynecologist is needed so that patients may be appropriately followed while on an oral contraceptive. Often times, the oral contraceptives approved for acne may not be the best choice for patients experiencing heavy or abnormal menses. Relatively common side effects from oral contraceptives includes: nausea, vomiting, abnormal menses, weight gain, and breast tenderness. More detrimental but rarer side effects include: thrombophlebitis, pulmonary embolism, and hypertension (87). The risk of these serious side effects increases in patients who smoke cigarettes.

ISOTRETINOIN

Isotretinoin (13-cis retinoic acid) is an oral retinoid that has been available for the treatment of acne since 1971 in Europe, and since 1983 in the United States. The Food and Drug Administration (FDA) indication for the use of isotretinoin is severe, nodulocystic acne that has not been helped by other treatments, including antibiotics. However, patients with other forms of acne have also benefited from isotretinoin. These patients include those with: significant acne unresponsive to treatment including oral antibiotics, acne that results in significant physicial or emotional scarring, and patients with gram-negative folliculitis, pyoderma faciale, and acne fulminans (88,89).

The exact mechanism of action of isotretinoin is not known. It is believed that 13-cis-retinoic acid exerts its action by isomerization to all-trans-retinoic acid, which then interacts with the retinoid receptors (90). It is the only acne medicine available that affects all four pathogenic factors of acne. Isotretinoin is comedolytic, reduces sebaceous gland size (up to 90%), and suppresses sebum production which in turn inhibits *P. acnes* and its ability to elicit inflammation (91). During the course of isotretinoin therapy, the pustular lesions generally clear first, and the codemos will be the last to resolve. Lesions on the face and upper arms tend to respond faster to isotretinoin than lesions on the trunk (92).

Dosing

There is variation in the dosing of isotretinoin with daily doses ranging from 0.1 to 2 mg/kg. Typically, 0.5–2 mg/kg/day is recommended for 16–20 weeks to reach a total cumulative dose of 120–150 mg/kg. A lower starting dose may be necessary in patients with significant inflammatory acne to prevent flares in the first month of treatment. Patients at risk for initial flaring may be concomitantly given prednisone to reduce flaring and prevent exuberant granulation tissue. Patients with pyoderma faciale should be controlled on prednisone prior to beginning isotretinoin.

Studies have demonstrated that about 23% of patients using the typical dosing may need to repeat treatment with isotretinoin. 96% of patients who experience a relapse of their acne do so within the first three years. Of patients taking a lower regimen of 0.1 mg/kg/day, 40% need a repeat course (93). Factors contributing to the need for additional courses are lower dose regimens (0.1–0.5 mg/kg/day or cumulatively less than 120 mg/kg), the presence of severe acne, being a female older than 25 years at the start of therapy, and having a prolonged history of acne (94,95). If repeat therapy is needed, at least two to three months should elapse between courses. An even longer interval may be sensible as the effects of isotretinoin can be seen five months after discontinuation.

Side Effects

Since RAR are found in many organs of the body, isotretinoin can cause numerous side effects (Table 9). This profile of adverse effects closely mimics those of hypervitaminosis A (96). Mucocutaneous side effects are the most common and are dose dependent. The most frequently encountered mucocutaneous side effects are: cheilitis, generalized xerosis, and dry mucosa. Cheilitis is so common that its absence would indicate a suboptimal dose or cause suspicion of the patient's compliance. Dry nasal mucosa frequently results in epistaxis (97). Xerophthalmia is common with subsequent contact lens intolerance, and possible conjunctivitis. Photophobia, decreased night vision, keratitis, and optic neuritis are less common, while cataracts, and corneal opacities rarely develop. Hair thinning, and hair loss occurs in less than 10% of patients on isotretinoin (98,99).

Neuromuscular complaints are relatively common in patients taking isotretinoin. About 14% of patients will experience myalgias, and a higher percentage will experience arthralgias and back pain. These neuromuscular complaints may coexist with a transient rise in creatinine phosphokinase, and are more common in physically active patients (100,101).

Nausea, vomiting, diarrhea, and abdominal pain have occurred in patients on isotretinoin but are rare. Transient mild increases in liver transaminases occur in about 15% of patients. Frank hepatitis is very rare, and has been reported in adults but not in children on isotretinoin (102).

Pseudotumor cerebri, or benign intracranial hypertension, is a rare side effect of isotretinoin. Patients who develop this increase in intracranial pressure will complain of headache, blurred vision, double vision, and/or vomiting. If recognized by history, and the finding of papilledema, a lumbar puncture can confirm the diagnosis, and be therapeutic. The likelihood of developing pseudotumor cerebri is increased with concomitant tetracycline use (103).

The impact of isotretinoin on a patient's psychological well-being has incited much attention. From 1982 to May 2000, 37 cases of suicide, 110 cases of hospitalized depression, suicidal ideation, or suicide attempt, and 284 cases of nonhospitalized depression were reported to the FDA's Adverse Event Reporting System (104). In one population-based cohort study comparing isotretinoin users with oral antibiotic users, the relative risk for development of depression or psychosis was approximately 1.0, indicating

Table 9 Isotretinoin Side Effects

Teratogenicity
   Hydrocephalus
   Micorcephaly
   External ear abnormalities
   Microphthalmia
   Craniofacial dysmorphia
   Cardiac septal defects
   Thymus gland abnormalities
Mucocutaneous
   Chelitis[a]
   Xerosis[a]
   Skin fragility[a]
   Palmoplantar peeling[a]
   Dry nose[a]
   Epistaxsis[a]
   Pruritus[a]
   Facial erythema/ rash[a]
   Desquamation
   Atrophy
   Granulation tissue
   Alopecia
   Brittle nails
   Acne fulminans
   Pyogenic granuloma-like lesions
Ophthalmologic
   Xerophthalmia[a]
   Blepharitis
   Papilledema
   Blurred vision
   Night blindness
   Corneal opacities
Gastrointestinal
   Nausea
   Anorexia
   Abdominal pain
   Cirrhosis
Neuromuscular/Psychiatric
   Headache[a]
   Fatigue
   Lethargy
   Myalgias
   Stillness
   Irritiablility
   Depression
   Suicidal ideation
   Psychosis
   Papilledema
   Pseudotumor cerebri
Rheumatologic
   Arthralgias
   DISH-like vertebral hyperostoses

(Continued)

Table 9 Isotretinoin Side Effects (*Continued*)

Altered bone remodeling
Extraspinal tendon and ligament calcification
Premature epiphyseal closure
Demineralization/ osteoporosis
Periosteal thickening
Laboratory
Elevated triglycerides[a]
Elevated cholesterol
Elevated liver function tests
Elevated creatine phosphokinase

[a] Denotes most common side effects.
Source: Adapted from Refs. 100, 129, 130.

no increased risk (105). A recent study demonstrated a decrease in depressive symptoms in patients undergoing treatment with isotretinoin (106). Further studies are needed to resolve this issue of causality.

Isotretinoin is a potent teratogen, and is rated pregnancy category X. The exact mechanism of embryopathy is unknown, but exposed infants have characteristic craniofacial defects as well as cardiac, thymus, and central nervous system abnormalities (107). Approximately 3–4 per 1000 women on isotretinoin become pregnant. In an effort to eliminate pregnancy while on isotretinoin, the manufacturer has implemented several regulations. There are additional consent forms for women regarding the potential teratogenicity. Appropriate contraception must be used one month prior to and one month following a course of isotretinoin. Two negative pregnancy tests must be obtained before starting isotretinoin, and a negative test must be obtained each month while on therapy.

Laboratory Monitoring

In addition to the laboratory tests that need to be performed to ensure that a woman is not pregnant, both men and women must get additional laboratory studies. A complete blood count, liver function test, and a lipid profile is checked at baseline and four weeks after starting isotretinoin. Elevated triglyceride levels occur in about 25–45% of patients (107). Those who have increased cholesterol during therapy often had elevated baseline cholesterol (108). Elevated liver function enzymes are also possible during isotretinoin but rarely does frank hepatitis develop. This elevation is reversible with discontinuation of isotretinoin. Other reversible changes during isotretinoin therapy include: leukopenia, thrombocytopenia, thrombocytosis, and an elevated erythrocyte sedimentation rate.

MANUAL TREATMENTS

In addition to topical and oral medications, physical modalities exist for treating acne. Comedone extraction can provide prompt cosmetic results. The keratinous debris of the open comedo may be extracted by using the Schamberg, Unna, and Saalfield types of comedo extractors. The closed comedo can also be removed by extraction but must first be nicked with an 18-gauge needle or an #11 blade. Extraction should not be attempted on an inflamed comedo or pustule due to the risk of scarring. Electrocautery and electrofulguration have also been reported as effective treatment for comedones. These means are often useful for treating large comedos, also known as macrocomedos. Macrocomedos are often resistant to topical retinoids.

Intralesional triamcinolone can be utilized to decrease both the size and pain of inflammatory cysts or nodules. Triamcinolone acetonide (2–5 mg/ml) is injected into these lesions using a 30-gauge needle. The steroid should be injected until the lesion blanches. The maximum amount of steroid used per lesion should not exceed 0.1 mL. Excess triamcinolone injected into a lesion may result in hypopigmentation, atrophy, telengiectasias, and needle tract scarring.

PHOTOTHERAPY

Various forms of phototherapy are under investigation for their use in treating acne vulgaris. Up to 70% of patients report that sun exposure improves their acne (109). This reported benefit may be due to camouflage by UV radiation-induced erythema and pigmentation, although it is likely that the sunlight has a biologic effect on the pilosebaceous unit and *P. acnes*. Porphyrins are formed endogenously by *P. acnes*, and are also acquired by exogenous sources. Protoporphyrin IX is taken up via cell wall receptors (110), and coproporphyrin III is the major endogenous porphyrin. Coproporphyrin III can absorb light at the near-UV and blue-light spectrum of 415 nm (111). In vitro irradiation of *P. acnes* with blue light leads to photoexcitation of endogenous bacterial porphyrins, singlet oxygen production, and subsequent bacterial destruction (112). Although UVB can also kill *P. acnes* in vitro, it is clinically insignificant since it has low skin penetration, and only high doses causing sunburn have be shown to improve acne (113,114). UV radiation may have anti-inflammatory effects by inhibiting cytokine action (115).

UV Radiation

Studies investigating the effect of UV radiation on acne have demonstrated a modest improvement in only inflammatory acne. There is some effect with UVB radiation alone, and slightly more benefit with combined UVB and UVA radiation. UVA light alone is the least beneficial. Twice-weekly phototherapy sessions are needed for clinical improvement. The therapeutic utility of UV radiation in acne is superseded by its carcinogenic potential (116–120).

Visible light is effective in treating both inflammatory and non-inflammatory acne lesions (121). A high-intensity, enhanced, narrow band (407–420 nm) blue-light source (ClearLight) has been FDA-approved for the treatment of moderate inflammatory acne (122). Red light can also be used to treat acne. It is less effective at photoactivating porphyrins than blue light, but red light can penetrate deeper into the dermis. Red light may also have additional anti-inflammatory properties. Combined blue and red light therapy may be more efficacious than either alone. It can be used twice weekly, taking 15 minutes per session to treat just the face. To treat the face, chest, and back, a 45-minute session is needed. Clinical improvement is maintained for at least one month after the last treatment (121).

Photodynamic Therapy

Photodynamic therapy is another phototherapy option for treating acne. Aminolevulinic acid (ALA) is applied topically one hour prior to exposure to a low-power light source (such as a pulsed excimer laser or a halogen source). The ALA is metabolized in the pilosebaceous units to protoporphyrin IX which is then targeted by the light. This results in the destruction of the sebaceous glands and damage to the hair follicles and epidermis (123,124).

Lasers

Lasers too are beginning to find a role in the treatment of acne. They work by emitting minimally divergent, coherent light that can be focused over a small area of tissue. Pulsed

dye laser (585 nm) can be used at lower fluences to treat acne. Instead of ablating blood vessels and causing purpura, the lower fluence can stimulate procollagen production by heating dermal perivascular tissue (121). The beneficial effects of a single treatment can last 12 weeks (125). The 1450 nm diode laser has also demonstrated significant efficacy in treating acne (126,127). This laser works by causing thermal damage to the sebaceous glands. The concurrent use of a cryogen spray device protects the epidermis (128).

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18
Topical Botanicals

Tracy Cornuelle and Jan Lephart
Research and Development, Nu Skin Enterprises, Provo, Utah, U.S.A.

INTRODUCTION

Botanicals have been part of cosmetics and toiletries since before recorded history. As early as 10,000 BC scented oils and ointments were used to soften skin and mask body odor (1). The ancient Egyptians freshened their breath by chewing pellets made of ground tamarisk leaves (2) and made perfumes from mixtures of essential oils such as myrrh, chamomile, rose, and cedar combined in vegetable oils of olive, sesame, or almond (1). The Picts of the British Isles made blue body paint from woad (*Isatis tinctoria* L). We know this dye was used as war paint from Roman writings of the time. In ancient Persia, and across the ancient world, henna dyes were used to stain hair and faces and the Egyptians used it to paint their fingernails.

Botanicals aren't just for fragrance and color. Many plant extracts have provided important pharmaceutical drugs. For decades, powdered *Digitalis purpurea* (foxglove) leaf (Powdered Digitalis U.S.P.) has been sold as a prescription drug for congestive heart failure. Tubocurarine, the active constituent from curare arrow poison (derived from the South American vine *Chondrodendron tomentosum*) is used as a skeletal muscle relaxant during surgery. Morphine and codeine (from *Papaver somniferum* L.) are still extremely important analgesics. Many important anti-cancer drugs, such as Paclitaxel (from the Pacific yew tree, *Taxus brevifolia*) and vincristine and vinblastine (both from Madagascar periwinkle*, Catharanthus roseus*, a common garden flower), originally were identified from plants.

Plants have the ability to biosynthesize a stunning array of primary and secondary metabolites. Primary metabolites include those constituents that all plants make and are necessary for plants to function. These include carbohydrates, proteins, lipids, etc. Secondary metabolites are compounds that are not generally found in every species of plant. Flavonoids, polyphenols, terpenoids, and alkaloids are usually classified as secondary metabolites. These compounds perform special functions in the plant such as pollinator attractants, anti-feedants, antimicrobials, and antivirals. Plants don't have the ability to get up and move, so they depend on their biosynthetic abilities to protect themselves and to propagate themselves.

The wide variety of chemical constituents found in plants, many of them highly complex chemical structures, have been used as a biochemical resource by mankind.

Plants have been extensively screened for biological activities that are useful to man, including medical and agricultural uses. The unique and complex structures have often shown new types of biological activity and have been a tool for elucidating aspects of how diseases attack our bodies or how pathogens damage crops. When a new mechanism of action is identified, a synthetic method for producing the compound is often pursued. The compound may be used as a template for the development of new drugs. Synthetic variations of the chemical structure can be analyzed for improved activity, fewer side effects, etc.

Biologically active compounds from plants have the ability to provide real health benefits, and perhaps real cosmetic benefits as well. Today botanicals can be found in everything from foot cream to lipstick. Botanical extracts come in many forms. Some are designed to be easily incorporated into cosmetic formulations, but impart little more than a pretty name to the ingredient deck. Other extracts are prepared in such a way as to optimize any potential benefits that the plant may impart. Some of these extracts are standardized to ensure a known concentration of the active compound and that the concentration of the compound will be consistent from batch to batch.

SELECTING PLANT SPECIES

Selection of potential plant species for cosmetic application should be based on ethnobotanical knowledge or scientific research demonstrating beneficial properties. The safety of the plant and the therapeutic constituent in question also needs to be investigated. Once you have determined what type of benefits or claims you are looking for from a botanical extract and which plants could provide the desired effects, you should investigate if any of the plants in question are threatened or endangered species. The Convention on International Trade in Endangered Species of Fauna and Flora Web site is an excellent resource for this type of information (www.cites.org). If the selected plant has no issues in this area, is it being produced in a fashion that will permit sustained harvesting and is it available in the quantities necessary to support your needs?

Wildcrafting, collecting plants from the wild for commercial uses, has been known to devastate species, or at least a local population of plants, and has led to certain species becoming threatened or endangered. Surprisingly, many plant species used in herbal medicines and extracts are still being collected from the wild (3). Many medicinal plants are disappearing at an alarming rate due to rapid agricultural and urban development, uncontrolled deforestation, and indiscriminate collection. Ornamental species, including native orchids, are under these pressures as well. According to the World Conservation Unit Red List of Threatened Plants, 12.5% (or 34,000 plant species) of vascular plants alone are at risk of extinction (4). Even in North America plants such as ginseng (*Panax quinquefolium*) and goldenseal (*Hydrastis canadensis*) have been notably reduced due to over-harvesting (5). *Limonium wrightii* H., a plant used in traditional Chinese medicine, is no longer found growing wild in Taiwan. In order to meet commercial demands, this plant is now farm grown (3).

SOURCING PLANT MATERIAL

Number of sources and reliability of sources available are important considerations when selecting an extract or a supplier. For instance, lauric acid is used widely in soaps and detergents. It used to be obtained mainly from Philippine coconut oil. However, the price

of coconut oil was highly unstable due to drought, aging plantations, typhoons, pests, and diseases in the Philippines. One good typhoon could wipe out an entire years crop. African oil palm (*Elaeis guineensis*) is also an excellent source of lauric oils. It is grown in Indonesia and Malaysia and other parts of the tropics and is now an important commercial source for lauric acid.

Fu Ling or poria (*Poria cocos*) is a fungus widely used in traditional Chinese medicine. When the SARS outbreak occurred, the demand for poria in Asia was so great that it was virtually impossible for western herb companies to obtain (6). Any plant crop that comes from one specific location could potentially be unavailable or the year's crop wiped out due to weather, natural catastrophe, war, or even epidemic. The number and reliability of sources available should be a consideration when selecting a new botanical.

ACCURATE IDENTIFICATION OF PLANT SPECIES

Historically, plants have been identified by an examination by a plant taxonomist of the leaf, fruit, flower, and other plant parts necessary for proper determination (7). Precise notes regarding the specimen's colleting location, including latitude and longitude, village, county, province or state, and country, and a description and photos of the plants height, width, habit, color, fragrance, etc. in its natural habitat, may also be required. Of course, this type of information is usually not available when purchasing an extract or dried plant material from a vendor.

The U.S. Pharmacopeia (8) has thin-layer chromatography (TLC) methods for identifying certain commonly found dietary supplement herbal products, based upon their chemical constituents. Other analytical techniques such as gas chromatography (GC) or high performance liquid chromatography (HPLC) could just as easily be used.

DNA fingerprinting methods can also be developed for identifying plants (9). This is especially useful to ensure that microbial strains, which seem often to be counted as botanicals in the cosmetic world, have maintained their integrity over multiple generations of serial transfers during the culture maintenance process.

HARVESTING PLANT MATERIAL

There are several things to consider when harvesting plants for extraction. Firstly, the plant material harvested should come from healthy, disease-free plants. The plant material is typically air-dried in arid regions or oven-dried in humid regions (to avoid mold) to a moisture content of $\leq 10\%$. The plant material is then ground or milled to a small particle size, typically 1–10 mm. This provides a larger surface area for extraction and a more exhaustive extraction in a shorter period of time.

For some types of extracts, the fresh plant material is extracted without drying. For example, volatile compounds (e.g., monoterpenes, sesquiterpenes) may evaporate off during the drying process. So, the fresh plant material is often steam distilled or extracted as soon as it is harvested. Certain highly sensitive compounds may be degraded during the drying process by heat, light, oxygen, or even enzymes within the plant material. These may also be extracted shortly after harvest in order to maintain biological activity of the final extract.

It is not uncommon for a desired constituent to be found at varying concentrations in different parts of the plant (Table 1). So, for instance, glaberdines, the skin lightening constituents from licorice, are found in higher concentration in the roots of the licorice

Table 1 Concentration of Constituents in Different Parts of the Plant

Plant	Constituent	Leaf	Root	Other	Reference
Astragalus membra neaceus	Isoflavones	0.55 mg g/l dry wt	3.04 mg g/l dry wt.		(10)
Astragalus membra neaceus	Flavonols	3.54 mg g/l dry wt	0.49 mg g/l dry wt.		(10)
Psychotria brachyceras	Brachycerine	0.1–0.2% dry wt (leaves and green stems)	Not detected in roots	0.3% dry wt. in inflorescences 0.045% dry wt. in mature fruits	(11)
Hydrastis canadensis	5-O-(4′-[β-d-glucopyranosyl]-trans-feruloyl) quinic acid	Not detected	1.0% w/w	2.3% w/w in rhizomes <0.1% w/w in stems	(12)
Panax quin-quefolius	Rg3 ginsenoside	7.5 mg/g	10.6 mg/g		(13)
P. quinque folius	Rg2 ginsenoside	11.3 mg/g	Not detected		(13)

plant. For green tea catechins, the leaf is utilized. The beneficial constituents of Saint John's Wort are highest in the flowers, although a combination of flowers and leaves are often used. The entire aerial, or above ground portion of the plant, may be used in other cases. Other aspects to consider are that constituent concentration can vary depending on the weather, time of year, elevation, soil conditions, fertilizer, age of plant, disease state, etc. (14).

COSMETIC EXTRACTS

Extracts that are designed specifically for cosmetic products come in many forms. They are usually liquid extracts in a cosmetically friendly solvent or solvent blend such as water, butylene glycol, glycerin, vegetable oil, or cosmetic ester. Some of them are standardized to a marker compound, but many are not. Many non-standardized extracts are designed simply to add a botanical name to your ingredient deck, but others have in vitro or clinical data from the vendor indicating various benefits to skin. Sometimes these tests have been carried out by an independent lab and sometimes the vendor's own testing facilities have produced the data. It is important to remember that, unlike academic journal articles, this type of data is not peer-reviewed and outside labs do not often repeat the testing to confirm the results. Some larger cosmetic companies will in fact do their own ingredient testing to confirm vendor claims before they choose to use the ingredient in a personal care product.

In most cases, the goal of producing an extract is to increase the potency of the botanical by concentrating the biologically active constituents. Although it is not uncommon for one particular constituent from the plant to be predominantly responsible for the therapeutic benefit derived from the plant, frequently there will be a series of closely related compounds, or in some cases unrelated compounds, each of which

contributes to some degree to the beneficial properties of the plant. For oral supplements, another benefit to producing an extract is that it reduces the total quantity of plant material that must be ingested to achieve an efficacious dose. In the case of topical applications, as in cosmetics, where the benefit of the digestive process is not available, extraction of the biologically active compound increases the bioavailability of the compound to the skin.

Many types of extraction processes are used commercially to produce extracts. For instance, volatile products, such as essential oils, are often extracted by steam distillation. Lipophillic compounds, such as carotenoids, xanthophylls, and, once again, essential oils or their constituents, are more and more often extracted by CO_2 super critical fluid extraction. This process uses pressure and low heat to convert CO_2 into a fluid phase, or physical state, in which it acts as an excellent non-polar solvent. The polarity can be modified, to some extent, by adding more polar solvents, such as ethanol, to the extraction. A major advantage to this process is that it is "green"; no harmful organic solvents are released into the environment. Enzymes such as cellulases can be used to break down the cell walls of the plant tissue causing the cells to expel their contents into the enzyme solution. Despite the many options, solvent extractions are probably still the most common method for extracting small molecules such as the secondary metabolites of plants.

The general approach for solvent extraction is "like dissolves like." In other words, non-polar solvents will extract non-polar constituents and polar solvents will extract polar constituents. So an extraction process needs to be based on the particular compound, or class of compounds, that provide the beneficial properties of the plant in question.

For a high concentration of the target compound(s) in the final extract, the solvent selection and extraction process development must be based upon optimal extraction and purification of the desired compound. Factors such as solvent choice, extraction duration, temperature, etc. of the extraction process must all be evaluated. While applying heat during the extraction process can reduce the required duration of the process and produce a more exhaustive extraction, some compounds are heat labile. Light and oxygen can also cause degradation of certain compounds. If the target compound is highly labile, reducing the extraction temperature may be required. Nitrogen blanketing may decrease degradation, or the addition of antioxidants can also help to protect some highly labile compounds.

A common extraction process would include macerating, or often refluxing, the dried, milled plant material in an alcoholic solvent or water-alcohol mixture. The benefits of alcohol are that it is a powerful solvent capable of extracting many types of molecules, it can preserve the extract and so eliminate the risk of microbial degradation, and alcohol is relatively volatile and is removed fairly easily once the extraction is complete, by vacuum distillation or evaporation.

Alcohol extracts are generally very complex mixtures of constituents. Due to the fact that alcohol is a powerful solvent, it extracts a wide range of constituents from the plant material. A second purification step is often performed in order to obtain a high level of the biologically active compound in the final extract product. The alcohol may be distilled off and a second purification step applied. A simple and common approach is to perform a second extraction on the dried extract using a different solvent. For example, the alcoholic extract of *Centella asiatica* may be dried down to a paste consistency. The paste is then extracted with acetone and the precipitate is recovered by filtration and dried. The precipitate is assayed and adjusted to 40% saponins, milled and packaged as a commercial extract (15). For other types of extracts, the target compound might be recovered from the filtrate instead of the precipitate. Ideally, a solvent will be found in which the desired constituent is only partially soluble. At elevated temperatures the constituent will dissolve in the solvent and any insoluble material can be filtered out. As the extract is cooled

the solubility of the target compound goes down and, under the right conditions, it crystallizes out of solution. The relatively pure compound is then recovered by filtration

Other commonly used purification techniques include ultrafiltration, nanofiltration, and column chromatography. Ultrafiltration and nanofiltration are excellent purification methods for water-based extracts. These methods use membranes to separate compounds based on molecular size. Column chromatography is a procedure by which solutes are separated by differential migration properties in a system consisting of two or more phases. One phase moves continuously in a given direction and the individual compounds within the phase exhibit different mobilities by reason of differences in adsorption, partition, solubility, molecular size, or ionic charge density. The second phase, a stationary phase, may act through adsorption, as in the case of adsorbents such as activated alumina, silica gel, and ion-exchange resins, or it may act by dissolving the solute thus partitioning it between the stationary and mobile phases.

STANDARDIZATION OF EXTRACTS

An extract that has been purified or formulated to contain a consistent, measurable quantity of a target compound (or sometimes class of compounds) in every batch, is referred to as "standardized." The level of the compound is guaranteed to be within a certain range or above a certain minimum in every batch or lot of the extract that you purchase. The exact level of the compound in a particular batch should be reported on the Certificate of Analysis, which most vendors provide with the extract shipment. Common chemical analytical methods such as HPLC, GC, titration, etc. are generally used to measure the content of the target compound within the extract. Although, in some cases, pharmacological bioassays are used to measure the particular type of biological activity within the extract, for example, enzyme activity.

There are two schools of thought regarding how an extract should be standardized. Some people feel that a virtually pure compound is the most efficacious approach to formulating an effective product. Using one pure plant derived compound eliminates any confounding properties that a more complex extract might have. Botanical extracts can contain extremely complex mixtures of compounds. It is possible that some compounds in the mixture may interfere with or counteract the benefits of the target compound. For example, the polyphenol fraction of St. John's Wort (*Hypericum perforatum*) has been found to have immunostimulating activity, whereas the lipophilic fraction had immunosuppressing properties (16). In a complex mixture, you don't know exactly what you have. Complex extracts may cause difficulties formulating, problems with formula stability, or perhaps occasionally problems with safety such as allergic responses to the final product.

The other school of thought seems to stem mainly from ethnobotanical research. Traditional herbal medicines are usually prepared as teas (aqueous infusions of the fresh or dried plant material). In some cases, different compounds within the tea contribute additional or different therapeutic benefits. For instance, ginger (*Zingiber officinale* R.) contains anti-inflammatory compounds and anti-nausea compounds (17). Using a pure form of one of the anti-inflammatory compounds will not give the full range of benefits derived from the traditional medicine.

Valarian (*Valeriana officinalis*), used as a sedative, is another example of an herbal medicine that appears to contain more than one type of compound responsible for the benefits derived from it (18). The volatile oil contains major constituents, including valerenic acid and its derivatives, which have demonstrated sedative properties in animal

models. Valepotriates and their derivatives, which belong to the iridoid class of molecules, have also demonstrated in vivo sedative activity, but they are very unstable and tend to break down over time, making their activity difficult to assess. Valerian extracts also contain gamma-aminobutyric acid (GABA) and aqueous extracts contain glutamine which may be converted into GABA. These compounds may also contribute to valerians sedative effects. In this case, the herbal medicine contains three different classes of molecules, all of which may to contribute to the sedative benefits of the extract.

Another important consideration is whether the extract is standardized to the correct constituent. As can be seen from the previous examples of herbal medicinals, often the compounds responsible for the therapeutic benefits are not well understood, sometimes not known period. For many years the constituents responsible for the anti-depressant benefits of St. John's Wort (*Hypericum perforatum*) were not understood. It was thought that hypericin was the primary active in the herb. Dietary supplements of St. John's Wort were standardized to hypericin, and perhaps still are in some instances. Hypericin is known to be a photosensitizer (19). This property was first recognized in cattle that grazed on this plant. Several instances of photosensitization in people using St. John's Wort herbals have been reported (20–22). Hyperforin is now recognized as the major antidepressant constituent of this plant. Hyperforin has been found to be a strong uptake inhibitor of serotonin, dopamine, noradrenaline, GABA, and L-glutamate (23). Although hyperforin alone is a powerful antidepressant, several other compounds in the plant also appear to contribute to the overall antidepressant benefits from the plant (24). This compound is not a photosensitizer, but it is unstable. Its instability makes it difficult to standardize to and perhaps explains the continued use of hypericin as the marker compound.

QUALITY ISSUES

Quality concerns will differ depending on the particular plant or extract. The typical types of properties that are used to determine the quality or batch to batch consistency of a botanical ingredient would include: appearance, color, odor, botanical characteristics (for plant material), microbial count, pH, residue on evaporation or loss on drying, total ash, acid-insoluble ash, water soluble ash, heavy metal content, alcohol-soluble extractives, water-soluble extractives, foreign organic matter, solvent residue, moisture content, volatile oil content, pesticide residue, and of course the level of marker compound if the extract is standardized. In some cases, a fingerprint method may be developed to ensure that the plant or plant extract is what it claims to be and/or is consistent from batch to batch. This might be a DNA fingerprint, chromatography profile (e.g., TLC, HPLC or GC), or even an IR fingerprint. Generally, five to 10 characteristics are reviewed for a particular product and the assay results will be listed on the Certificate of Analysis which should be available for every batch of product that is purchased.

Microbial contamination is especially common in dried plant material where the microbial counts are generally very high. USP or CTFA plate count methods may be utilized to evaluate this. Irradiation is commonly used to sterilize herbaceous material. Extracts may have microbial issues depending on what solvent was used in the extraction process. Many organic solvents, such as ethanol and methanol, are antiseptics and so will effectively preserve an extract. Other extracts, especially water-based ones, are typically preserved or sterilized.

Pesticide levels can be a concern for some plant based products. The United States Pharmacopeia (8) is a good resource for acceptable levels. A table of 30 or more pesticides

and the maximum limit for each is shown under "General Method for Pesticide Residues Analysis" in the *Chemical Tests* section. Any pesticides not listed are considered unacceptable at any level. These limits were set for dietary supplements, but are a good guideline for cosmetics as well.

Some types of plants have a tendency to accumulate certain heavy metals (14). For instance, mugwort plants (*Artemisia vulgaris* L.) and coneflower roots (*Echinacea* spp.) are known to accumulate iron; black cherry stems (*Prunus serotina* E.) and buckbush stems (*Symphoricarpos orbiculatus* M.) accumulate lead; cassia plants (*Cinnamomum aromaticum* N.) and bladderwrack plants (*Fucus vesiculosus* L.) accumulate mercury (25). Thus, for certain plant materials or extracts heavy metal levels should be assayed and specified on the Certificate of Analysis.

Preservatives, antimicrobials, and/or antioxidants, may be added to extracts and should be identified by the extract manufacturer upon request. Analytical methods such as HPLC may also be applied to identify preservatives within an extract. Ash quantity is often used as a quality specification for extracts. Excessive quantities of ash may indicate the presence of buffers (sometimes used during extraction process to adjust the polarity of the solvent) or drying agents such as silica dioxide.

SAFETY AND TOXICOLOGY

Just because an ingredient is plant-derived doesn't mean it is safe. Just ask Socrates! Poisons such as strychnine come from plants (*Strychnos nux-vomica* L. and other *Strychnos* spp.). And potent allergens, such as the heptadecylcatechols from poison oak (*Toxicodendron diversilobum*) and pentadecylcatedchols from poison ivy (*T. radicans*) are also plant derived (26).

Many plant extracts are considered safe because they are made from ingredients that are Generally Recognized as Safe (GRAS) (27). Toxicology testing is important for other extracts. Highly purified plant constituents, even if they come from plants that are GRAS, may need testing due the increased concentration of the particular constituent. Some ingredients are safe at low levels but cause problems at higher levels. Some of the types of testing that are commonly used to test the safety of cosmetic extracts include repeat insult patch testing (RIPT), cumulative irritation, in vitro mutagenicity (i.e., Ames test), in vitro cell culture methods for assessing potential ocular and/or dermal irritation (e.g., Bovine ocular assay, Irritection™, Eyetex™, Skintex™, etc.), and photosensitization. This may not be adequate in all cases.

A noteworthy example is sanguinarine, an alkaloid extracted from Bloodroot (*Sanguinaria canadendid*). Viadent used sanguinarine as an antiplaque ingredient in their toothpaste and mouthwash. Despite significant toxicology and clinical testing demonstrating the safety of this compound (28–37), a study was conducted by researchers at Ohio State University (38), which showed a strong correlation between the development of oral leukoplakia (potentially cancerous mouth lesions) and the use of oral products containing sanguinarine. Several follow-up studies (39–42) have confirmed this correlation. Surprisingly, other studies appear to indicate that sanguinarine may actually have potential as an anti-cancer agent (43–45). This demonstrates how complicated and confusing these safety and toxicology issues can be. Long-term safety can only be demonstrated by long-term use. When Colgate-Palmolive purchased the brand, they removed the sanguinarine.

CONCLUSIONS

Plant-derived compounds have the ability to deliver real benefits. Considerations in choosing a plant product should include an investigation of the status of the species (is it endangered or threatened), whether sustainable harvesting practices are being used, and whether there is a reliable source with the quantities needed. Many extraction and purification methods are used commercially depending on the desired qualities of the end product. As with all cosmetic ingredients, standard quality assurance techniques should be followed to ensure the quality and consistency of the product or extract. The safety and toxicology of the material should be investigated to eliminate or reduce the risk of harm to consumers.

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19

Herbs in Cosmeceuticals: Are They Safe and Effective?

Carl Thornfeldt

Episciences, Inc., Boise, and CT Derm, Fruitland, Idaho, and Oregon Health Sciences University, Portland, Oregon, U.S.A.

BACKGROUND

Botanicals used for medicinal, flavoring, or fragrances are known as herbs (1,2). The guiding principle of herbal medicine is the naturally occurring mixture of active compounds in plants is more effective and safer than individual molecules and man-made combinations of synthetic molecules. The natural composition is the comminuted, powdered, or galenic extracts of the whole or specific anatomic parts of the plant. Botanical medicinals are focused more on treatment of signs and symptoms of disease while improving total "body condition" than reversing the disease etiology.

The foundation of modern pharmacologic medicine is rooted in ethnobotanical traditions utilizing indigenous flora. Over 200 indigenous medicinals were listed in the first U.S. Pharmacopeia in 1820 including podophyllin resin, white willow bark, wintergreen, and juniper tar, which are still used today (1).

Several botanical treatments for cutaneous diseases have stood the test of time for their effectiveness as documented by modern scientific evidence. Podophyllotoxin is a prescription purified podophyllin resin, a galenic extract of Mayapple (*Podophyllum peltatum*). Capsaicin is a nonprescription therapy for pruritis and pain extracted from Cayenne peppers (*Capsicum species*). Henna (*Lawsonia inermis*) is a hair dye used by people sensitized to other commercial coloring agents (3).

Botanical sales in 2004 exceeded $4 and one-third billion, growing by one-third over only six years. Noni/Morinda was the largest selling botanical in 2004 with sales of nearly $220 million. Now about 70 different herbs are formulated into cosmeceuticals. Botanical product growth has flourished to now consume 25% of all health- and lifestyle-related dollars (4). Thus dermatologists must have a working knowledge of botanicals, especially the most common ones, to provide optimal preventive medical care.

Herbal medicine plays a vital role in current healthcare by: (i) providing alternatives to prescription medications, (ii) enhancing therapeutic effects of other prescriptives, (iii) protecting against adverse reactions to allopathic therapy, and (iv) providing treatment for diseases which there is no current prescription therapy or only poorly effective or high-risk therapy. Herbal and other alternative medical strategies are utilized by over half of the population and especially by those suffering chronic diseases such as psoriasis and those

with less hope for cure such as human immunodeficiency virus (HIV) and terminal diseases (5,6). Extensive public use of complementary and alternative medicine resulted in the National Institute of Health establishing the Office of Alternative Medicine in the United States in 1995 (1).

Unfortunately, two major myths taint herbal medicine. Most patients believe the myth that there are no side effects because herbal medicine uses "natural substances." In fact, experienced Chinese practioners are concerned about the well-known side effects of hepatotoxicity and contact dermatitis with oral and topical Chinese herbal medicinal and preparations, respectively (7).

Many allopathic physicians believe the myth that double-blinded, placebo-controlled studies do not exist for ancient and herbal medicines. Yet, there have been many such studies conducted throughout Asia and India including studies investigating mechanisms of action of the medicinal botanicals (7).

The understanding of the function, metabolism, and interaction of these herbal medicines is often lacking. The specific scientific issues include documenting: (i) complete characterization of the multiple active compounds in each plant source, (ii) activity and synergistic or additive interaction of each of these compounds and their metabolites, (iii) interaction of these active components with food, nutrients, nutritional supplements, and other medicines, and (iv) how the potential toxicity of specific compounds is blunted (2). For example, there are the castor bean in the source of ricin, one of the most poisonous compounds known to man, and azelaic acid, a nontoxic prescription dermatological medicine.

PROCESSING BOTANICALS

Botanicals must undergo a significant amount of processing prior to incorporation into a cosmeceutical which usually significantly affects the biologic activity of the herb. The most important factor for biologic activity is the source of the plant material because each plant part may contain hundreds of different chemicals, ions and molecules. Growing conditions including soil composition, amount of available water, climate variations, plant stress, and harvesting conditions such as time from harvest to transport, care of plant materials during shipping, storage conditions prior to manufacture, and preparation of the herb and final product as well as mixing with other herbs are other factors that may substantially alter solubility, stability, biologic availability, pharmacokinetics, pharmacologic activity, and toxicity.

Galenic extracts are made from leaves, roots, fruits, berries, stems, twigs, barks, and flowers by crushing, grinding, comminuting, boiling, distilling, pressing, drying, or exposing to solvents. Usually, the plant material is heated or processed to obtain essential oils or other distillates that can be easily added to a cosmetic formulation; however, this processing may destroy or adversely modify some of the physiologically active molecules. The results are oil, wax, juice, tincture, decoction, tea, infusion, and/or powders which are then formulated into topical applications including solutions, gels, lotions, creams, ointments, and pastes. Some of these preparations are further applied as fomentation, compress, or poultice (2,8). These terms are defined in Table 1 (9).

The concentration of the herb, its extract, and the active molecules affect therapeutic activity. Usually in cosmeceuticals the medicinal botanicals are added in very small, sub-therapeutic amounts for the marketing story. Most synthetic pharmaceuticals, utilize a very low concentration to provide the desired effect. Few herbs are that potent, thus higher doses (>1%) are needed. Herbal efficacy is challenged by the trans-stratum corneum delivery of mucocutaneous surfaces which is usually difficult due to the

Table 1 Definitions

Antiphlogistic	Preventing and/or relieving inflammation
Astringent	Arrests secretions, contracts tissue, and controls bleeding
Comminuted	Whole plant or portion broken into multiple pieces
Decoction	Liquid extract produced by simmering the plant part in water for over 20 minutes
Elixir	Sweetened alcohol extract
Essential oil	Concentrated oil from the whole plant, usually volatile, and fragrant
Fomentation	Liquid extract soaked cloth
Galenic	Crude plant remedies
Herb	Botanical used for medicine, flavoring, or fragrance
Infusion	Liquid extracts combined in hot water
Mucilage	Botanicals that swell with exposure to water for soothing application
Poultice	Liquid extract combined with powdered herb applied directly to lesions while mass is moist
Rubefacient	Substance that causes cutaneous erythema by counter-irritant effects
Tea	Dried whole or parts of plant simmered in hot water usually 5–10 minutes
Tincture	Alcoholic solution of whole or portion of plant or extract

herb's concentration and multiple active compounds with different solubility, polarity, and therapeutic concentration as well as reactivity of different mucocutaneous receptors.

These complex biologic science and formulation issues indicate the only validation of herbal activity in a cosmeceutical formulation is a human clinical trial conducted by a reputable third-party researcher. Without such studies, health care providers and the public are being asked to trust in products based on voodoo science.

REGULATORY CLIMATE

Medicinal botanicals used in cosmeceuticals are considered food additives or dietary supplements by the United States Food and Drug Administration (FDA) which declared them as safe. The herbs are allowed to be marketed to consumers directly without obtaining drug status or restricted by FDA's over-the-counter monograph requirements. Thus, no standards of herbal potency, concentration in the marketed product, safety, nor efficacy studies exist.

The German Regulatory Authority for herbs is the "Commission E." It is the best expert consensus for weighing the quality of clinical evidence and systemic and topical safety to identify reasonably effective uses of over 300 botanicals (3).

The Physician's Desk Reference for Herbal Medicines, 3rd ed. (2004), by Thomson PDR, Montvale, NJ, published an exhaustive literature review conducted by the respected PhytoPharm U.S. Institute of Phytopharmaceuticals for about 400 more herbs with regard to their use and adverse reactions (3).

ADVERSE REACTIONS

A news magazine in 2001 revealed over 2900 adverse events requiring medical care which were attributed to herbs the previous year. In addition, 104 deaths were attributed primarily to ephedra, St. John's Wort, gingko, and ginseng (10). In 2003 the FDA removed

Ephedra and Ma Huang (*Ephedra sinica*) from the market due to 155 deaths directly attributed to it (11).

The most common adverse cutaneous reactions to herbal products include allergic and/or irritant contact dermatitis. Cross-sensitivity to the most sensitizing botanicals is not uncommon. For example, 12 of 106 dermatitis patients had positive patch test to tea tree oil (TTO) and all these had positive reactions to one or more of 12 other natural compounds including lavender (*Lavandula angustifolia*) (12). Severe cutaneous reactions including angioedema/urticaria, exfoliative erythroderma, linear IgA bullous dermatosis, lupus erythematosus, malignancies, pemphigus, Steven's Johnson syndrome, Sweet's syndrome, ulcerative stomatitis, and vasculitis have all been reported. Ten additional herbs have induced fatal reactions including aristolochia, arnica, cayenne, comfrey, henna, kava kava, mistletoe, rue, senna, and yohimbine. Other severe reactions include anaphylaxis, coma, rhabdomyolysis, and shock (3,13). Herbs known to pose dermatologic surgery dangers include St. John's Wort, gingko, ginseng, garlic, echinacea, kava kava, and valerian (14). See mucocutaneous and severe complications in Table 2.

Even simple plants contain multiple reactive and interactive compounds, but natural medicine advocates and media frequently do not warn the public of the importance of interactions between different herbs and with over-the-counter and prescription drugs. Moreover, 70% of patients fail to disclose their use of herbal products preoperatively. Interactions with medical consequences probably are under-reported (14). There are many herb/food, herb/drug, and herb/herb interactions as in combinations of caution in Table 3 (3).

The medicinal botanicals of proven and potential dermatologic significance are listed by therapeutic uses in Table 4 (3). Multple herbs are effective for several different indications. Herbal medicines may be divided into several groups. Clinically validated ones have published human-controlled clinical trials. These herbs are among the most commonly used by the public and alternative medicine practitioners and would be expected to be the most commonly used in cosmeceuticals. Green and black tea, soy, pomegranate, and date have published human clinical trials for signs of photoaging as the only active. Avocado and black cohosh are included with two other actives in different topical formulations treating photoaging. Other herbs with published human studies treating dermatologic conditions with topical formulations include almond, allantoin and comfrey, aloe, anise, bitter orange, black nightshade, black seed, camptotheca, cayenne, curcumin, date palm, echinacea, german chamomile, horse chestnut, lemon balm, neem, oat, onion, oregon grape, pomegranate, St. John's wort, tea tree, oolong tea, and western medicinal herbal mixtures. Borage, evening primrose, gotu kola, grape seed, ginko biloba, horse chestnut, black tea, and Chinese herbal mixtures have been documented to treat dermatologic conditions when administered orally.

The second group consists of herbs used in current cosmeceuticals with a scientific rationale supported only by animal, in vivo or in vitro studies, and/or proven efficacy in human systemic disease but without clinical data with topical application. These include apple, arnica, cactus pear, eucommia, ginseng, hibiscus, jojoba, licorice, milk thistle, myrtle, olive oil, papaya, prickly pear, rosemary, sandalwood, sarsaparilla, saw palmetto, spearmint, peppermint, wheat germ, and white birch.

The third group consists of herbs approved for therapy of a cutaneous condition by the German Commission E which are currently or potentially will be incorporated into cosmeceuticals. These include agrimony, bittersweet nightshade, butcher's broom, cajuput, chaste tree, English plantain, fenugreek, flax, heartsease, horsetail, jambolan, lavender, marigold, oak, oat, pansy flower, Peruvian balsam, pineapple, poplar, sage, sesame seed, shepherd's purse, sweet clover, walnut, and white nettle.

Table 2 Mucocutaneous and Serious Complications

Category	Herbs
Acne	Chaste Tree (*Vitex agnus-castus*)
Alopecia	St. John's Wort (*Hypericum perforatum*)
Anaphylaxis	Caraway (*Carum carvi*), Cayenne (*Capsicum annuum*), Echinacea (*Echinacea angustifolia*), Flax linseed (*Linum usitatissimum*), German Chamomile (*Matricaria recutita*), Garlic (*Allium sativum*), Horse Chestnut (*Aesculus hippocastanum*), Mistletoe (*Phoradendron species*), Willow Bark (*Salix alba*)
Burning	Cowhage (*Mucuna pruriens*)
Carcinogenic	Alkanet (*Alkanna tinctoria*), Aloe (*Aloe barbadensis; Aloe capensis: Aloe vera*), Alpine Ragwort (*Senecio nemorensis*), Areca Nut (*Areca catechu*), Basil (*Ocimum basilicum*), Bergamot (*Citrus aurantium*), Cascara Sagrada (*Rhamnus purshiana*), Coca (*Erythroxylum coca*), Colt's Foot (*Tussilago farfara*), Comfrey (*Symphytum officinale*), Cypress Spurge (*Euphorbia cyparissias*), Dusty Miller (*Senecio aureus*), Forget-me-not (*Myosotis arvensis*), Golden Ragwort (*Senecio aureus*), Groundsel (*Senecio vulgaris*), Hemp Agrimony (*Eupatorium cannabinum*), Jalap (*Ipomoea purga*), Madder (*Rubia tinctorum*), Morning Glory (*Ipomoea hederacea*), Petasites (*Petasites hybridus*), Ragwort (*Senecio jacobaea*), Red Clover (*Trifolium pratense*), Rue (*Ruta species*), Sassafras (*Sassafras albidum*), Senna (*Cassia species*)
Contact Blistering	American Liverwort (*Hepatica nobilis*), Arnica (*Arnica montana*), Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Black Mustard (*Brassica nigra*), Bulbous Buttercup (*Ranunculus bulbosus*), Buttercup (*Ranunculus acris*), Cashew (*Anacardium occidentale*), Cayenne (*Capsicum annuum*), Clematis (*Clematis recta*), Cypress Spurge (*Euphorbia cyparissias*), Garlic (*Allium sativum*), Gingko (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Henna (*Lawsonia inermis*), Juniper (*Juniperus species*), Marsh Marigold (*Caltha palustris*), Mezereon (*Daphne mezereum*), Pasque Flower (*Pulsatilla pratensis*), Poison Ivy, Oak, Sumac (*Rhus toxicodendron*) Poisonous Buttercup (*Ranunculus sceleratus*), Rue (*Ruta species*), Savin Tops (*Juniperus sabina*), Senna (*Cassia species*), Tea Tree (*Melaleuca alternifolia [IgA linear dermatosis]*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*), Wood Anemone (*Anemone nemorosa*)
Conjunctivitis	Black Mustard (*Brassica nigra*), Cypress Spurge (*Euphorbia cyparissias*), German Chamomile (*Matricaria recutita*), Goa Powder (*Andira araroba*), Psyllium (*Plantago ovata*), Psyllium Seed (*Plantago afra*)
Cutaneous, Nonspecific	American Hellebore (*Veratrum viride*), American Liverwort (*Hepatica nobilis*), Arnica (*Arnica montana*), Artichoke (*Cynara scolymus*), Asarum (*Asarum europaeum*), Birch (*Betula species*), Black Bryony (*Tamus communis*), Blessed Thistle (*Cincus benedictus*), Boneset (*Eupatorium perfoliatum*), Bulbous Buttercup (*Ranunculus bulbosus*), Burdock (*Arctium lappa*), Buttercup (*Ranunculus acris*), Camphor Tree (*Cinnamomum camphora*),

(Continued)

Table 2 Mucocutaneous and Serious Complications (*Continued*)

	Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Chaste Tree (*Vitex agnus-castus*), Chaulmoogra (*Hydnocarpus species*), Chicory (*Cichorium intybus*), Chinese Cinnamon (*Cinnamomum aromaticum*), Chinese Olive (*Canarium species*), Cinnamon (*Cinnamomum verum*), Clematis (*Clematis recta*), Clove (*Syzygium aromaticum*), Cowhage (*Mucuna pruriens*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Elecampane (*Inula helenium*), English Ivy (*Hedera helix*), English Lavender (*Lavandula angustifolia*), Feverfew (*Tanacetum parthenium*), Ginkgo (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Goa Powder (*Andira araroba*), Guaiac (*Guaiacum officinale*), Hemp Agrimony (*Eupatorium cannabinum*), Hops (*Humulus lupulus*), Hydrangea (*Hydrangea arborescens*), Indian Squill (*Urginea indica*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Lesser Celandine (*Ranunculus ficaria*), Marsh Marigold (*Caltha palustris*), Mayapple (*Podophyllum peltatum*), Mugwort (*Artemisia vulgaris*), Nasturtium (*Tropaeolum majus*), Nerve Root (*Cypripedium calceolus*), Night-Blooming Cereus (*Selenicereus grandiflorus*), Orris (*Iris species*), Ox-eye Daisy (*Chrysanthemum leucanthemum*), Pasque Flower (*Pulsatilla pratensis*), Peppermint (*Menthe piperita*), Pipsissewa (*Chimaphila umbellate*), Poisonous Buttercup (*Ranunculus sceleratus*), Poplar (*Populus species*), Poppyseed (*Papaver somniferum*), Savin Tops (*Juniperus sabina*), Saw Palmetto (*Serenoa repens*), Scotch Pine (*Pinus species*), Soapwort (*Saponaria officinalis*), Spikenard (*Aralia racemosa*), Spurge (*Euphorbia resinifera*), Squill (*Urginea maritima*), Stavesacre (*Delphinium staphisagria*), Stillingia (*Stillingia sylvatica*), Tansy (*Tanacetum vulgare*), Tea Tree (*Melaleuca alternifolia*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*), White Mustard (*Sinapis alba*)
Cutaneous Yellowing	Kava Kava (*Piper methysticum*)
Death	Aristolochia (*Aristolochia species*), Arnica (*Arnica montana*), Cayenne (*Capsicum annuum*), Comfrey (*Symphytum officinale*), Henna (*Lawsonia inermis*), Kava Kava (*Piper methysticum*), Mistletoe (*Phoradendron species*), Rue (*Ruta species*), Senna (*Cassia species*), Yohimbine (*Pausinystalia yohimbe*)
Dermatitis	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*) Bloodroot (*Sanguinaria canadensis*), Camphor Tree (*Cinnamomum camphora*) Caraway (*Carum carvi*), Cayenne (*Capsicum annuum*), Garlic (*Allium sativum*), German Chamomile (*Matricaria recutita*), Ginger (*Zingiber officinale*), Gingko (*Ginko biloba*), Hawthorn (*Crataegus species*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*), Juniper (*Juniperus species*), Kava Kava (*Piper methysticum*), Lavender (*Lavandula*), Licorice (*Glycyrrhiza glabra*), Onion (*Allium cepa*) Peppermint (*Mentha piperita*), Quinine (*Cinchona pubescens*) Rue (*Ruta species*), Squill (*Urginea maritima*), Stavesacre (*Delphinium staphisagria*) Tea Tree (*Melaleuca alternifolia*), Turmeric (*Curcuma domestica/longa*), Yarrow (*Achillea millefolium*), Yohimbine (*Pausinystalia yohimbe*)
Dermatitis, Allergic Contact	Black Mustard (*Brassica nigra*), German Chamomile (*Matricaria recutita*), Parsley (*Petroselinum crispum*), Poison Ivy, Oak, Sumac (*Rhus toxicodendron*), Rosemary (*Rosmarinus officinalis*), Tea Tree (*Melaleuca alternifolia*)
Dermatitis, Contact Irritant	Boxwood (*Buxus sempervirens*), Cajuput (*Melaleuca leucadendra*), Copaiba Balsam (*Copaifera langsdorffi*), Feverfew (*Tanacetum parthenium*), Lesser Celandine (*Ranundulus ficaria*), Nutmeg (*Myristica fragrans*)

Dermopathy—Pellagra-like	Kava Kava (*Piper methysticum*)
Dyspigmentation, Hair	Trailing Arbutus (*Epigae repens*)
Dyspigmentation, Skin	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Cayenne (*Capsicum species*), Henna (*Lawsonia inermis*), Trailing Arbutus (*Epigae repens*)
Dyspigmentation, Teeth	Cayenne (*Capsicum annuum*)
Edematous	Aloe (*Aloe barbadensis: Aloe capensis: Aloe vera*), Asa Foetida (*Ferula foetida*)—lips, Bitter Orange (*Citrus aurantium*), Buckthorn (*Rhamnus catharticus*), Butterbur (*Petasites hybridus*), Cascara Sagrada (*Rhamnus purshiana*), Chinese Rhubarb (*Rheum palmatum*), Cypress Spurge (*Euphorbia cyparissias*)—eyelid, Ergot (*Claviceps purpurea*)—local, Flax Linseed (*Linum usitatissimum*)—eyelid, Frangula (*Rhamnus frangula*), Ginseng (*Panax species*), Henna (*Lawsonia inermis*), Juniper (*Juniperus species*), Licorice (*Glycyrrhiza glabra*), Mezereon (*Daphne mezereum*), Mistletoe (*Phoradenfron species*)—lip, Pagoda Tree (*Sophora japonica*)—face, Phellodendron (*Phelldendron species*), Rue (*Ruta species*), Senna (*Cassia species*)
Erythematous	Bergamot (*Citrus aurantium*), Bitter Orange (*Citrus aurantium*), Butterbur (*Petasites hybridus*), Cashew (*Anacardium occidentale*), Flax Linseed (*Linum usitatissimum*), Gingko (*Ginko biloba*), Henbane (*Hyoscyamus niger*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*)—facial, Juniper (*Juniperus species*), Mandrake (*Mandragora officinarum*), Mezereon (*Daphne mezereum*), Mistletoe (*Phoradendron species*), Poison Ivy (*Rhus toxicodendron*), Rue (*Ruta species*), Stavesacre (*Delphinium staphisagria*), Yohimbe Bark (*Pausinystalia yohimbe*)
Erythema Multiforme	Henna (*Lawsonia inermis*), Tea Tree (*Melaleuca alternifolia*)
Erythema Nodosum	Echinacea (*Echinacea angustifolia*), Mistletoe (*Phoradendron species*)
Erythroderma, Exfoliative	St. John's Wort (*Hypericum perforatum*), Yohimbine (*Pausinystalia yohimbe*)
Fasciculation	Horse Chestnut (*Aesculus hippocastanum*), Poppyseed (*Papaver somniferum*), Wormseed (*Artemisia cina*)
Glossodynia	Asarum (*Asarum europaeum*), Black Hellebore (*Helleborus niger*), Celandine (*Chelidonium majus*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Monkshood (*Aconitum napellus*), Mountain Laurel (*Kalmia latifolia*), Night-Blooming Cereus (*Selenicereus grandifloras*), Peppermint (*Mentha piperita*)
Halitosis	Garlic (*Allium sativum*)
High Morbidity	Blue Cohosh (*Caulophyllum thalictroides*)—shock, Gingko (*Ginko biloba*)—coma, Licorice (*Glycyrrhiza glabra*)—rhabdomyolysis
Hypesthesia	Cowage (*Mucuna pruriens*), Croton Seeds (*Croton tiglium*), Cypress Spurge (*Euphorbia cyparissias*), Garlic (*Allium sativum*), Ginseng (*Panax species*), Monkshood (*Aconitum napellus*), Peppermint (*Menta piperita*)—anal, Tea Tree (*Melaleuca alternifolia*), Tree of Heaven (*Ailanthus altissima*)
Hypohidrosis	Henbane (*Hyoscyamus niger*)

(Continued)

Table 2 Mucocutaneous and Serious Complications (*Continued*)

Infection, Predisposition	White Bryony (*Bryonia alba*)
Jaundice	Bishop's Weed (*Ammi visnaga*), Black Cohosh (*Cimicifuga racemosa*), Germander (*Teucrium chamaedrys*)
Keloid	Henna (*Lawsonia inermis*)
Keratosis	Bloodroot (*Sanguinaria canadensis*)
Lichenoid	Henna (*Lawsonia inermis*), Peppermint (*Mentha piperita*)
Leukoplakia	Bloodroot (*Sanguinaria canadensis*)
Lupus Erythematosis	Yohimbine (*Pausinystalia yohimbe*)
Mastitis / Mastodynia / Gynecomastia	Black Cohosh (*Cimicifuga racemosa*), Dong Quai (*Angelica sinensis*), Ginseng (*Panax species*)
Mucositis / Stomatitis	American Liverwort (*Hepatica nobilis*), Arum (*Arum maculatum*), Bitter Apple (*Citrullus colocynthis*), Bulbous Buttercup (*Ranunculus bulbosus*), Buttercup (*Ranunculus acris*), Clematis (*Clematis recta*), Elecampane (*Inula helenium*), Gingko (*Ginko biloba*), Globe Flower (*Trollius europaeus*), Green Hellebore (*Helleborus viridis*), Hedge-Hyssop (*Gratiola officinalis*), Horse Chestnut (*Aesculus hippocastanum*), Horseradish (*Armoracia rusticana*), Marsh Marigold (*Caltha palistris*), Mezereon (*Daphne mezereum*), Orris (*Iris species*), Peppermint (*Mentha piperita*), Poisonous Buttercup (*Ranunculus sceleratus*), Poke (*Phytolacca americana*), Spurge (*Euphorbia resinifera*), Traveller's Joy (*Clematis vitalba*), White Bryony (*Bryonia alba*)
Paresthesia	Echinacea (*Echinacea angustifolia*), St. John's Wort (*Hypericum perforatum*), Mountain Laurel (*Kalmia latifolia*)
Pemphigus	Garlic (*Allium sativum*)
Photoreactions	Angelica (*Angelica archangelica*), Bergamot (*Citrus aurantium*), Bishop's Weed (*Ammi visnaga*), Bitter Orange (*Citrus aurantium*), Burning Bush (*Dictamnus albus*), Celery (*Apium graveolens*), Contrayerva (*Dorstenia contrayerva*), Dill (*Anethum graveolens*), Dong Quai (*Angelica sinensis*), Haronga (*Haronga madagascariensis*), Henna (*Lawsonia inermis*), Hogweed (*Heracleum spondylium*), Kava Kava (*Piper methysticum*), Lovage (*Levisticum officinale*), Masterwort (*Peucedanum ostruthium*), Parsley (*Petroselinum crispum*), Parsnip (*Pastinaca sativa*), Pimpinella (*Pimpinella major*), Rue (*Ruta graveolens*), St. John's Wort (*Hypericum perforatum*), Tolu Balsam (*Myroxylon balsamum*), Wafer Ash (*Ptelea trifoliate*), Yarrow (*Achillea millefolium*)
Pruritis	Arnica (*Arnica montana*), Black Cohosh (*Cimicifuga racemosa*), Chaste Tree (*Vitex agnus-castus*), Cowhage (*Mucuna pruriens*), Cypress Spurge (*Euphorbia cyparissias*), Dan-Shen (*Salvia miltiorrhiza*), Ergot (*Claviceps purpurea*), Feverfew (*Tanacetum parthenium*), Gingko (*Ginko biloba*), Ginseng (*Panax species*), Henna (*Lawsonia inermis*), Horse Chestnut (*Aesculus hippocastanum*), Kava Kava (*Piper metaysticum*), Mistletoe (*Phoradendron species*), Night Blooming Cereus (*Selenicereus grandiflorus*), Poppyseed (*Papaver somniferum*), Quinine (*Cinchona pubescens*), Sandalwood (*Santalum album*), Senna (*Cassia species*), Stavesacre (*Delphinium staphisagria*), St. John's Wort (*Hypericum perforatum*), Tea Tree (*Melaleuca alternifolia*)
Psoriasis	Henna (*Lawsonia inermis*)

Purpura / Hemorrhage / Bleeding	Garlic (*Allium sativum*), Ginger (*Zingiber officinale*), Gingko (*Ginko biloba*), Ginseng (*Panax species*), Horse Chestnut (*Aesculus hippocastanum*), Phellodendron (*Phellodendron species*), Saw Palmetto (*Serenoa repens*), St. John's Wort (*Hypericum perforatum*), Tolu Balsam (*Myroxylon balsamum*)
Pustular	Bitter Orange (*Citrus aurantium*), Black Bryony (*Tamus communis*), Chaste Tree (*Vitex agnus-castus*), Goa Powder (*Andira araroba*)
Sialorrhea	Areca Nut (*Areca catechu*), Black Hellebore (*Helleborus niger*), Daffodil (*Narcissus pseudonarcissus*), Echinacea (*Echinacea angustifolia*), Jaborandi (*Pilocarpus microphyllus*), Kousso (*Hagenia abyssinica*), Mezereon (*Daphne mezereum*), Mountain Laurel (*Kalmia latifolia*), Quebracho (*Aspidosperma quebrachoblanco*), Stavesacre (*Delphinium staphisagria*)
Stomatitis, Ulcerative	Feverfew (*Tanacetum parthenium*), Mezereon (*Daphne mezereum*), Tolu Balsam (*Myroxylon balsamum*)
Sweet's Syndrome	Arnica (*Arnica montana*), Cayenne (*Capsicum species*)
Toxic Epidermal Necrolysis / Necrosis / Ulcers	Arnica (*Arnica montana*), Black Mustard (*Brassica nigra*), Cayenne (*Capsicum annuum*), European Mistletoe (*Viscum album*), Ginseng (*Panax species*), Mezereon (*Daphne mezereum*), Savin Tops (*Juniperus sabina*), White Bryony (*Bryonia alba*)
Urticaria / Angioedema	American Pawpaw (*Asimina triloba*), Black Bryony (*Tamus communis*), Caraway (*Carum carvi*), Chaste Tree (*Vitex agnus-castus*), Echinacea (*Echinacea angustifolia*), European Mistletoe (*Viscum album*), Feverfew (*Tanacetum parthenium*), Garlic (*Allium sativum*), Henna (*Lawsonia inermis*), Milk Thistle (*Silybum marianum*), Psyllium (*Plantago ovata*), Psyllium Seed (*Plantago afra*), Stinging Nettle (*Urtica dioica*), Tolu Balsam (*Myroxylon balsamum*), Yarrow (*Achillea millefolium*)
Vasculitis / Petechiae	Black Cohosh (*Cimicifuga racemosa*), Gingko (*Ginko biloba*)
Xerostomia	Chaste Tree (*Vitex agnus-castus*), Henbane (*Hyoscyamus niger*), Mandrake (*Mandragora officinarum*), St. John's Wort (*Hypericum perforatum*), Yellow Jessamine (*Gelsemium sempervirens*)
Xerosis	Kava Kava (*Piper methysticum*)

Table 3 Combination Cautions of Discussed Herbs

Aloe	Antiarrhythmics (aloe-induced hypokalemia may affect cardiac rhythm), digitalis glycosides (increases effect), corticosteroids, thiazide diuretics, and licorice (increased potassium loss)
Arnica	Anticoagulant, antiplatelet, heparin, salicylates, thrombolytic drugs, and warfarin (increased effect)
Cayenne	Same as above
Chaste Tree	Amantadine, dopamine D1 antagonists, levodopa, pergolide mesylate, pramipexole, and ropinirole (enhance dopaminergic adverse effects). Dopamine D2 antagonists (decreased effectiveness)
Curcumin	Anticoagulant, antiplatelet, heparin, thrombolytic drugs (increase effect)
Echinacea Angustifolia	Corticosteroids, immunosuppressants (interferes with effectiveness)
Evening Primrose	Anticonvulsants including phenothiazines (may lower seizure threshold and decrease effectiveness) anticoagulant, antiplatelet, heparin, and thrombolytic drugs (decrease effectiveness)
Fenugreek	Hypoglycemic drugs (may have an additive hypoglycemic effect)
Flax	Absorption of other drugs may be delayed when taken simultaneously
German Chamomile	Alcohol, benzodiazepines (may increase sedative effect), anticoagulants, and warfarin (increase effect)
Gingko	MAO inhibitors (potentiate effect), anticonvulsants (precipitate seizures), insulin (alters need), anticoagulant, antiplatelet, heparin, thrombolytic, and NSAID drugs (increase effect), nicardipine (reduce hypotensive effect), nifedipine, and papaverine (increase effect), SSRI (precipitate hypomania), thiazide diuretics (increase blood pressure)
Ginseng	Hypoglycemic drugs (increases effect), loop diuretics (increases diuretic resistance), MAO inhibitors (combination increases chance for headache, tremors, mania), insulin (reduces effect), estrogen (increases effect), albendazole (alters effectiveness), anticoagulants (decreases INR), nifedipine (increase effect), opiates (decrease effect)
Green Tea	Alkaline drugs (decrease absorption)
Horse Chestnut	Anticoagulant drugs (additive effect)
Licorice	Aloe, buckthorn, antiarrhythmics, digitalis glycoside, laxatives (increase hypokalemia, increase toxicity), glucocorticoids (potentiates), loop, and thiazide diuretics (additive hypokalemia), anticoagulant, antiplatelet, heparin, thrombolytic drugs, (increase effect), antihypertensives (decrease effect), antidiabetic insulin (reduce effect), MAO inhibitors (increase toxicity), potassium (decrease), testosterone (reduce), oral contraceptive (increase toxicity)

Milk Thistle (Silymarin)	Haloperidol phenothiazines (decrease lipid peroxidation), phentolamine mesylate, yohimbine (antagonize effect)
Oak	Alkaline drugs, alkaloids (absorption reduced)
Papaya	Anticoagulant drugs (additive effect)
Peppermint	CYP450 (increases substrate level)
Pineapple	Anticoagulant, thrombolytic drugs (increase bleeding), tetracycline (increase blood, urine level)
Rue	Hypoglycemic drugs (additive effect)
Saw Palmetto	Alpha-adrenergic blockers (additive effect), androgens (antagonizes), iron (complexes increasing toxicity), warfarin (increase effect)
St. John's Wort	Increased effectiveness: antidiabetic
	Reduced effectiveness: amioradone, anticoagulants, barbiturates, benzodiaze-pines, beta blockers, caffeine, calcium channel blockers, clozapine, chlorzoxazone, cyclophosphamide, cyclosporine, digoxin, etoposide, imatinib mesylate, indinavir, irinotecan, iron, methadone, nonnucleoside reverse transcriptase inhibitors, paclitexal, phenytoin, protease inhibitors, reserpine, sirilimus, statins, tacrolimus, tamoxifen, theophylline
	Increased toxicity: acetretin (birth defects), aminolevulinic acid, tetracycline, sulfonamide, thiazides (photosensi-tivity), buspirone, MAOI, nefazodone, nortryptiline, SSRI, trazadone, tricyclic antidepressants, venlafaxine (increase serotonin syndrome[hypertension, hyperthesmia, myoclonus, mental alterations, coma], loperamide, gingko, opiates (sedation), oral contraceptives (breakthrough bleeding), tyramine, sympathomimetics
	Alters effect: carbamazepine
Soy	Iron (reduced absorption), levothyroxine (decrease effect), tamoxifen (decrease effect), warfarin (reduce effect)
White Willow	Alcohol, barbiturates (enhance toxicity), antiplatelet, NSAID, salicylates (additive effect), carbonic anhydrase inhibitors (potentiate effect)

Table 4 Therapeutic Uses [a]

Acne	Bittersweet Nightshade (*Solanum dulcamara*), Duckweed (*Lemna minor*), Eucalyptus (*Eucalyptus globulus*), German Chamomile (*Matricaria recutita*), Heartsease (*Viola tricolor*), Tea Tree (*Melaleuca alternifolia*)
Alopecia	Arnica (*Arnica montana*), Black Bryony (*Tamus communis*), Boxwood (*Buxus sempervirens*), Cashew (*Anacardium occidentale*), Horsetail (*Equisetum arvense*), Maidenhair (*Adiantum capillus-veneris*), Nasturtium (*Tropaeolum majus*), Oriental Arborvitae (*Thuja orientalis*), Stavesacre (*Delphinium staphisagria*)
Alopecia Areata	Birch (*Betula* species), Burr Marigold (*Bidens tripartita*)
Aphthous Stomatitis	Common Stonecrop (*Sedum acre*), Water Dock (*Rumex aquaticus*)
Bites	Behen (*Moringa oleifera*), Bistort (*Persicaria bistorta*), Black Cohosh (*Cimicifuga racemosa*), Calotropis (*Calotropis procera*), Cane-Reed (*Costus speciosa*), Cotton (*Gossypium hirsutum*), Echinacea (*Echinacea angustifolia*), Great Burnet (*Sanguisorba officinalis*), Matico (*Piper elongatum*), Picrorhiza (*Picrorhiza kurroa*), Plantain (*Musa paradisiaca*), Purple Gromwell (*Lithospermum erytrorhizon*), Quassia (*Picrasma excelsa*), Rauwolfia (*Rauwolfia serpentine*), Red Sandalwood (*Pterocarpus santalinus*), Scarlet Pimpernel (*Anagallis arvensis*), Tea Tree (*Melaleuca alternifolia*), Turmeric (*Curcuma domestica/longa*), Wormseed Oil (*Chenopodium ambrosioides*)
Bitter taste	Chinese thoroughwax (*Bupleurum chinese*)
Bleeding	Agrimony (*Agrimonia eupatoria*), Brooklime (*Veronica beccabunga*), Cane Reed (*Costus speciosa*), Catechu (*Acacia catechu*), Elephant Ears (*Bergenia crassifolia*), Eucalyptus (*Eucalyptus globules*), European Mistletoe (*Viscum album*), Groundsel (*Senecio vulgaris*), Henbane (*Hyoscyamus niger*), Horsetail (*Equisetum arvense*), Lesser Celandine (*Ranunculus ficaria*), Matico (*Piper elongatum*), New Jersey Tea (*Ceanothus americanus*), Periwinkle (*Vinca minor*), Purple Loosestrife (*Lythrum salicaria*), Sage (*Salvia officinalis*), Scotch Broom (*Cytisus scoparius*), Shepherd's Purse (*Capsella bursa-pastoris*)
Bruises / Contusion	Basil (*Ocimum basilium*), Beth Root (*Trillium erectum*), Bittersweet Nightshade (*Solanum nigrum*), Black Bryony (*Tamus communis*), Black Currant (*Ribes nigrum*), Black Nightshade (*Solanum nigrum*), Cajuput (*Melaleuca leucadendra*), Calotropis (*Calotropis procera*), Comfrey (*Symphytum officinale*), Cane-Reed (*Costus speciosa*) German Ipecac (*Cynanchum vincetoxicum*), Horse Chestnut (*Aesculus hippocastanum*), Onion (*Allium cepa*), Rue (*Ruta graveolens*), Smartweed (*Persicaria hydropiper*), Solomon's Seal (*Polygonatum multiflorum*), Spikenard (*Aralia racemosa*), Tansy (*Tanacetum vulgare*), Tolu Balsam (*Myroxylon balsamum*), Turmeric (*Curcuma domestica/longa*), Vervain (*Verbena officinalis*), Wild Daisy (*Bellis perennis*), White Fir (*Abies alba*)
Burns	Hibiscus (*Hibiscus sabdariffa*), Tea Tree (*Melaleuca alternifolia*)
Candidiasis	Cornflower (*Centaurea cyanus*)
Carcinoma, squamous cell prevention of palliaiton	Green and White Tea Catechins (*Camellia sinensis*), Congorosa (*Maytenus ilicifolia*), Spurge (*Euphorbia resinifera*)

Cheilitis, actinic	Areca Nut (*Areca catechu*), Condurango (*Marsdenia condurango*)
Dermatitis	Behen (*Moringa oleifera*), Bilberry (*Vaccinium myrtillus*), Birch (*Betula species*), Bittersweet Nightshade (*Solanum dulcamara*), Borage Oil (*Borage officinalis*), Boxwood (*Buxus sempervirens*), Carline Thistle (*Carlina acaulis*), Celadine (*Chelidonium majus*), Evening Primrose Oil (*Oenthera biennis*), Heartsease (*Viola tricolor*), Henna (*Lawsonia inermis*), Licorice (*Glycyrrhiza glabra*), Marigold (*Calendula officinalis*), Mezereon (*Daphne mezereum*), Mountain Grape (*Mahonia aquifolium*), Oats (*Avena sativa*), Peanut (*Arachis hypogaea*), Quillaja (*Quillaja saponaria*), Stinging Nettle (*Urtica dioica*), Teazle (*Dipsacus silvertris*), Winter's Bark (*Drimys winteri*)
Fissure, Anal	Aloe (*A. barbadensis, A. capensis, A. vera*), Buckthorn (*Rhamnus catharticus*), Cascara Sagrada (*Rhamnus purshiana*), Chinese Rhubarb (*Rheum palmatum*), European Peony (*Paeonia officinalis*), Field Scabious (*Knautia arvensis*), Frangula (*Rhamnus fragula*), Manna (*Fraxinus ornus*)
Furunculosis / Abcess	American White Pond Lily (*Nymphaea odorata*), Ammmoniac Gum (*Dorema ammoniacum*), Arnica (*Arnica montana*), Behen (*Moringa oleifera*), Bistort (*Persicaria bistorta*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Bog Bean (*Menyanthes trifoliata*), Burdock (*Arctium lappa*), Calotropis (*Calotropis procera*), Castor Oil Plant (*Ricinus communis*), Chaulmoogra (*Hydnocarpus species*), Corydalis (*Corydalis cava*), Croton Seeds (*Croton tiglium*), Digitalis (*Digitalis purpurea*), Dogwood (*Cornus florida*), Echinacea (*Echinacea angustifolia*), German Chamomile (*Matricaria recutita*), Great Burnet (*Sanguisorba officinalis*), Ground Ivy (*Glechoma hederacea*), Hibiscus (*Hibiscus sabdariffa*), Larch (*Larix decidua*), Licorice (*Glycyrrhiza glabra*), Marshmallow (*Althaea officinalis*), Myrrh (*Commiphora molmol*), Onion (*Allium cepa*), Plumbago (*Plumbago zeylanica*), Psyllium (*Plantago ovata*), Red-Rooted Sage (*Salvia miltiorrhiza*) Solomon's Seal (*Polygonatum multiflorum*), Vervain (*Verbena officinalis*), White Lily (*Lilium candidum*), White Nettle (*Lamium album*), Wild Indigo (*Baptisia tinctoria*)
Halitosis	Clove (*Syzygium aromaticum*), Coriander (*Coriandrum sativum*), Juniper (*Juniperus communis*)
Hyperhidrosis / Excessive Lacrimation	Arjun Tree (*Terminalia arjuna*), Asiatic Dogwood (*Cornus officinalis*), Belladonna (*Atropa belladonna*), Coral Root (*Corallorhiza odontorhiza*), Japanese Atractylodes (*Atractylodes japonica*), Knotweed (*Polygonum aviculare*), Lycium Bark (*Lycium chinense*), Oak Gall (*Quercus infectoria*), Rehmannia (*Rehmannia glutinosa*), Rice (*Oryza sativa*), Rose (*Rosa centifolia*), Safflower (*Carthamus tinctorius*), Sage (*Salvia officinalis*), Sarsaparilla (*Smilax species*), Schisandra (*Schisandra chinensis*), Soybean (*Glycine soja*), Walnut (*Juglans regia*)
Hyperpigmentation	Wild Carrot (*Daucus carota*), Wormwood (*Artemisia absinthium*)
Hyposalivation	Lemonwood (*Schisandra sphenanthera*)
Ichthyosis / Hyperkeratosis	Burdock (*Arctium lappa*), Cashew (*Amacardium occidentale*), Cypress Spurge (*Euphorbia cyparissias*), English Ivy (*Hedera helix*), Garlic (*Allium sativum*), Peanut (*Arachis hypogaea*)
Infection, Herpes	Goldenseal (*Hydrastis canadensis*), Hibiscus (*Hibiscus sabdariffa*), Mezereon (*Daphne mezereum*), Mountain Laurel (*Kalmia katifolia*), Scarlet Pimpernel (*Anagallis arvensis*), Thuja (*Thuja occidentalis*)

(Continued)

Table 4 Therapeutic Uses (*Continued*)

Infection, Viral	Astragalus (*Astragalus species*), Behen (*Moringa oleifera*), Black Cohosh (*Cimicifuga racemosa*), Cat's Claw (*Unicaria tomentosa*), Coriander (*Coriandrum sativum*), Duckweed (*Lemna minor*), Echinacea (*Echinacea angustifolia*), Eucalyptus (*Eucalyptus globules*), Pasque Flower (*Pulsatilla pratensis*)
Infections, Fungal	Aloe (*Aloe barbadensis; Aloe capensis; Aloe vera*), Beet (*Beta vulgaris*), Henna (*Lawsonia inermis*), Onion (*Allium cepa*), Mountain Laurel (*Kalmia latifolia*), Poke (*Phytolacca americana*), Turmeric (*Curcuma domestica/longa*)
Infections, Bacterial / Cellulitis / Erysipelas / Impetigo / Scarlatina	Anemarrhena (*Anemarrhena asphodeloides*), American Pawpaw (*Asimina triloba*), Black Nightshade (*Solanum nigrum*), Burning Bush (*Dictamnus albus*), Cashew (*Anacardium occidentale*), Coconut Palm (*Cocos nucifera*), Corydalis (*Corydalis cava*), Duckweed (*Lemna minor*), Elecampane (*Inula helenium*), English Ivy (*Hedera helix*), Eucalyptus (*Eucalyptus globules*), Goa Powder (*Andira araroba*), Ground Ivy (*Glechoma hederacea*), Heartsease (*Viola tricolor*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Kamala (*Mallotus philippinensis*), Linden (*Tilia species*), Oak Gall (*Qeurcus infectoria*), Oats (*Avena sativa*), Pasque Flower (*Pulsatilla pratensis*), Pitcher Plant (*Sarracenia purpurea*), Psyllium (*Plantago ovata*), Purple Gromwell (*Lithospermum erytrorhizon*), Tea Tree (*Melaleuca alternifolia*), Teazle (*Dipsacus silvestris*), Thuja (*Thuja occidentalis*), Turmeric (*Curcuma domestica/longa*), Virola (*Virola theiodora*), Wild Indigo (*Baptisia tinctoria*)
Inflammation	Agrimony (*Agrimonia eupatoria*), Arnica (*Arnica montana*), Bear's Garlic (*Allium ursinum*), Behen (*Moringa oleifera*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Bladderwort (*Utricularia vulgaris*), Boxwood (*Buxus sempervirens*), Broad Bean (*Vicia faba*), Burning Bush (*Dictamnus albus*), Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Chaulmoogra (*Hydnocarpus species*), Chickweed (*Stellaria media*), Chicory (*Cichorium intybus*), Club Moss (*Lycopodium clavatum*), Common Stonecrop (*Sedum acre*), Congorosa (*Maytenus ilicifolia*), Cornflower (*Centaurea cyanus*), Dandelion (*Taraxacum officinale*), English Ivy (*Dedera helix*), English Plantain (*Plantago lanceolata*), European Elder (*Sambucus nigra*), European Water Hemlock (*Cicuta virosa*), Evening Primrose (*Oenothera biennis*), Fenugreek (*Trigonella foenum-graecum*), Field Scabious (*Knautia arvensis*), Flax (*Linum usitatissimum*), Fumitory (*Fumaria officinalis*), German Chamomile (*Matricaria recutita*), Haronga (*Haronga madagascariensis*), Heartsease (*Viola tricolor*), Henna (*Lawsonia inermis*), Herb Robert (*Geranium robertianum*), Hibiscus (*Hibiscus sabdariffa*), Horse Chesnut (*Aesculus hippocastanum*), Houseleek (*Sempervivum tectorum*), Indian Nettle (*Acalypha indica*), Jambolan (*Syzygium cumini*), Japanese Mint (*Mentha arvensis piperascens*), Labrador Tea (*Ledum latifolium*), Lady's Mantle (*Alchemilla vulgaris*), Lycium bark (*Lycium chinense*), Marigold (*Calendula officinalis*), Marshmallow (*Althaea officinalis*), Mezereon (*Daphne mezereum*), Moneywart (*Lysimachia nummularia*), Monkshood (*Aconitum napellus*), Mullein (*Verbascum densiflorum*), Oak (*Quercus robar*), Oak Gall (*Quercus infectoria*), Oats (*Avena sativa*), Olive (*Olea europaea*), Pasque Flower (*Pulsatilla pratensis*), Peanut

(Arachis hypogaea), Periwinkle (Vinca minor), Purple Gromwell (Lithospermum erytrorhizon), Purple Loosestrife (Lythrum salicaria), Quinine (Circhona pubescens), Red Clover (Trifolium pratense), Rosemary (Rosmarinus officinalis), Rue (Ruta graveolens), Saw Palmetto (Serenoa repens), Scotch Pine (Oinus species), Soapwart (Saponaria officinalis), Spurge (Euphorbia resinifera), St. John's Wort (Hypericum perforatum), Tolu Balsam (Myroxylon balsamum), Turmeric (Curcuma domestica/longa), Walnut (Juglans regia), White Lily (Lilium candidum), White Nettle (Lamium album), Witch Hazel (Hamamelis virginiana), Wormseed Oil (Chenopodium ambrosioides)

Keloid / Hypertrophic	
Leprosy	Henbane (Hyoscyamus niger), Onion (Allium cepa) Betel Nut (Piper betle), Black Nightshade (Solanum nigrum), Calotropis (Calotropis procera), Cashew (Anacardium occidentale), Chaulmoogra (Hydnocarpus species), Coriander (Coriandrum sativum), Cumin (Cuminum cyminum), Giant Milkweed (Calotropis gigantea), Gotu Kolu (Centella asiatica), Henna (Lawsonia inermis), Hwema Bark (Corynanthe pachyceras), Jasmine (Jasminum officinale), Kamala (Mallotus philippinensis), Lemongrass (Cymbopogon citrates), Lily-of-the-Valley (Convallaria majalis), Luffa (Luffa aegyptica), Neem (Antelaea azadirachta), Northern Prickly Ash (Zanthoxylum americanum), Storax (Liquidambar orientalis), Turmeric (Curcuma domestica/longa)
Mastitis / Mastodynia	Adrue (Cyperus articulatus), Bugleweed (Lycopus virginicus), Chaste Tree (Vitex agnus-castus), Dandelion (Taraxacum officinale), Pipsissewa (Chimaphalia umbellata)
Miliaria	Speedwell (Veronica officinalis)
Mucocutaneous pain	Black Currant (Ribes nigrum), Bladderwrack (Fucus vesiculosus), Comfrey (Symphytum officinale), Echinacea (Echinacea angustifolia), Houseleek (Sempervivum tectorum), Indian Nettle (Acalypha indica), Marshmallow (Althaea officinalis), Onion (Allium cepa), Poplar (Populus species), Quince (Cydonia oblongata), Reed Herb (Phragmites communis), Rue (Ruta graveolens), Tobacco (Nicotiana tabacum), White Fir (Abies alba), Wild Indigo (Baptisia tinctoria), Wild Thyme (Thymus serpyllum), Wormwood (Artemisia absinthium)
Mucocutaneous Pruritus	Butcher's Broom (Ruscus aculeatus), Buckwheat (Fagopyrum esculentum), Cabbage (Brassica oleracea), Cashew (Anacardium occidentale), Chaulmoogra (Hydnocarpus species), Club Moss (Lycopodium clavatum), Evening Primrose (Oenothera biennis), Fumitory (Fumaria officinalis), Golden Shower Tree (Cassia fistula), Gotu Kola (Centella asiatica), Heartsease (Viola tricolor), Houseleek (Sempervivum tectorum), Jasmine (Jasminum officinale), Knotweed (Polygonum aviculare), Plantain (Musa paradisiaca), Poison Ivy (Rhus toxicodendron), Sarsaparilla (Smilax species), Scarlet Pimpernel (Anagallis arvensis), Scotch Pines (Pinus species), Speedwell (Veronica officinalis), Storax (Liquidambar orientalis), Sweet Gale (Myrica gale), Thyme (Thymus vulgaris), Turmeric (Curcuma domestica longa) Vervain (Verbena officinalis), Wheat (Triticum aestivum), Wild Thyme (Thymus serpyllum)
Photodermatosis	Wild Carrot (Daucus carota)
Pruritis, Anii	Field Scabious (Knautia arvensis), Mullein (Verbascum densiflorum)

Table 4 Therapeutic Uses (*Continued*)

Psoriasis	Agrimony (*Agrimonia eupatoria*), Black Nightshade (*Solanum nigrum*), Burdock (*Arctium lappa*), Cashew (*Anacardium occidentale*), Chaulmoogra (*Hydnocarpus species*), Goa Powder (*Andira araroba*), Hogweed (*Heracleum sphondylium*), Mountain Grape (*Mahonia aquifolium*), Mountain Laurel (*Kalmia latifolia*), Olive (*Olea europea*), Pasque Flower (*Pulsatilla pratensis*), Red Clover (*Trifolium pratense*), Sarsaparilla (*Smilax species*), Sunflower (*Helianthus annuus*)
Radiation Dermatitis	Sea Buckthorn (*Hippophaë rhamnoides*)
Scabies / Pediculosis	Angelica (*Andelica archangelica*), Black Catnip (*Phyllanthus amarus*), Black Pepper (*Piper nigrum*), Bog Bean (*Menyanthes trifoliata*), Burning Bush (*Dictamnus albus*), Carambola (*Averrhoa carambola*), Celandine (*Chelidonium majus*), Chaulmoogra (*Hydnocarpus species*), Field Scabious (*Knautia arvensis*), Fish Berry (*Anamirta cocculus*), Gotu Kola (*Centella asiatica*), Grape (*Vitis vinifera*), Ground Ivy (*Glechoma hederacea*), Henna (*Lawsonia inermis*), Lycium Berries (*Lycium barbarum*), Morning Glory (*Ipomoea hederacea*), Oleander (*Nerium oleander*), Picrorhiza (*Picrorhiza kurroa*), Plantain (*Musa paradisiaca*), Plumbago (*Plumbago zeylanica*), Poisonous Buttercup (*Ranunculus sceleratus*), Pyrethrum (*Chrysanthemum cinerariifolium*), Quassia (*Picrasma exselsa*), Safflower (*Carthamus tinctorius*), Smartweed (*Persisicaria hydropiper*), Stavesacre (*Delphinium staphisagria*)
Scrofulosis	Bistort (*Persicaria bistorta*), Coriander (*Coriandrum sativum*), English Ivy (*Hedera helix*), Ground Ivy (*Glechoma hederacea*), Oregano (*Origanum vulgare*), Stavesacre (*Delphinium staphisagria*)
Seborrhea	Stavesacre (*Delphinium staphisagria*)
Sjogren's Syndrome	Borage Oil (*Borago officinalis*), Evening Primrose Oil (*Oenthera biennis*)
Skin Care	Almond (*Prunus dulcis*), Avocado (*Persea americana*), Jojoba (*Simmondsia chinesis*), Peanut (*Arachis hypogaea*), Sorb Apple (*Sorbus domestica*)
Snakebite	Calotropis (*Calotropis procera*), Cane Reed (*Costus speciosa*), Cashew (*Anacardium occidentale*), Contrayerva (*Dorstenia contrayerva*), Cotton (*Gossypium hirsutum*), Echinacea (*Echinacea angustifolia*), German Ipecac (*Cynanchum vincetoxicum*), Muskmallow (*Abelmoschus moschatus*), Rauwolfia (*Rauwolfia serpentine*), Red Sandalwood (*Pterocarpus santalinus*), Scotch Broom (*Cytisus scoparius*)
Stomatitis / Gingivitis	Acacia (*Acacia arabica*), Agrimony (*Agrimonia eupatoria*), Amaranth (*Amaranthus hypochondriacus*), American Pawpaw (*Asimina triloba*), Anise (*Pimpinella anisum*), Arnica (*Arnica montana*), Basil (*Ocimum basilicum*), Bilberry (*Vaccinium myrtillus*), Black Currant (*Ribes nigrum*), Black Pepper (*Piper nigrum*), Blackberry (*Rubas fruticosus*), Bladderwort (*Utricularia vulgaris*), Bugle (*Ajuga reptans*), Catechu (*Acacia catechu*), Cayenne (*Capsicum annuum*), Cinquefoil (*Potentilla erecta*), Cleavers (*Galium aparine*), Clove (*Syzygium aromaticum*), Coffee (*Coffea arabica*), Colt's Foot (*Tussilago farfara*), Comfrey (*Symphytum officinale*), Echinacea Purpurea (*Echinacea purpurea*), English Chamomile (*Chamaemelum nobile*), English Plantain (*Plantago lanceolata*), Eucalyptus (*Eucalyptus globulus*),

	European Five-Finger Grass (*Potentilla reptans*), European Golden Rod (*Solidago virgaurea*), Gambir (*Uncaria species*), German Chamomile (*Matricaria recutita*), Herb Robert (*Geranium robertianum*), Hollyhock (*Alcea rosea*), High Mallow (*Malva sylvestris*), Houseleek (*Sempervivum tectorum*), Iceland Moss (*Cetraria islandica*), Jack-in-the-Pulpit (*Arisaema atrorubens*), Jambolan (*Syzygium cumini*), Japanese Mint (*Mentha arvensis piperascens*), Knotweed (*Polygonum aviculare*), Lady's Mantle (*Alchemilla vulgaris*), Larch (*Larix decidua*), Lesser Galangal (*Alpina officinarum*), Marigold (*Calendula officinalis*), Marshmallow (*Althaea officinalis*), Myrrh (*Commiphora molmol*), Oak (*Quercus robar*), Oak Gall (*Quercus infectoria*), Onion (*Allium cepa*), Peppermint (*Mentha piperita*), Pimpinella (*Pimpinella major*), Potentilla (*Potentilla anserina*), Rhatany (*Krameria triandra*), Rose (*Rosa centifolia*), Rue (*Ruta graveolens*), Sage (*Salvia officinalis*), Scotch Pine (*Pinus species*), Self-Heal (*Prunella vulgaris*), Sloe (*Prunus spinosa*), Speedwell (*Veronica officinalis*), Spruce (*Picea species*), Strawberry (*Fragaria vesca*), Sweet Violet (*Viola odorata*), Tamarind (*Tamarindus indica*), Tea Tree (*Melaleuca alternifolia*), Thyme (*Thymus vulgaris*), Tomato (*Lycopersicon esculeutum*), Tropical Almond (*Terminalis chebula*), Turmeric (*Curcuma domestica/longa*), Usnea (*Usnea species*), White Nettle (*Lamium album*), Wild Indigo (*Baptisia tinctoria*), Willow Herb (*Epilobium angustifolium*)
Styes	Eyebright (*Euphrasia officinalis*)
Syphilis / T. Pallidum Infections	Brazilian Pepper Tree (*Schinus terebinthifolius*), Calotropis (*Calotropis procera*), Dill (*Anethum graveolens*), Giant Milkweed (*Calotropis gigantea*), Gotu Kola (*Centella asiatica*), Guaiac (*Guaiacum officinale*), Indian-Hemp (*Apocynum cannabinum*), Kava Kava (*Piper methysticum*), New Jersey Tea (*Ceanothus americanus*), Poke (*Phytolacca americana*), Sassafras (*Sassafras albidum*), Stillingia (*Stillingia sylvatica*)
Ulcers, Skin / Decubitus, Leg, Vascular	American Adder's Tongue (*Erythronium americanum*), Ash (*Fraxinus excelsior*), Bilberry (*Vaccinium myrtillus*), Bittersweet Nightshade (*Solanum dulcamara*), Black Nightshade (*Solanum nigrum*), Burdock (*Arctium lappa*), Calotropis (*Calotropis procera*), Cashew (*Anacardium occidentale*), Castor Oil Plant (*Ricinus communis*), Catechu (*Acacia catechu*), Cleavers (*Galium aparine*), Clematis (*Clematis recta*), Congorosa (*Maytenus ilicifolia*), Digitalis (*Digitalis purpurea*), Echinacea (*Echinacea angustifolia*), English Adder's Tongue (*Ophioglossum vulgatum*), English Ivy (*Hedera helix*), Field Scabious (*Knautia arvensis*), Frostwort (*Helianthemum canadense*), Ground Ivy (*Glechoma hederacea*), Henna (*Lawsonia inermis*), Indian Nettle (*Acaltpha indica*), Lady's Mantle (*Alchemilla vulgaris*), Linden (*Tilia species*), Marigold (*Calendula officinalis*), Martagon (*Lilium martagon*), Myrrh (*Commiphora molmol*), Ox-Eye Daisy (*Chrysanthemum leucanthemum*), Periwinkle (*Vinca minor*), Petasites (*Petasites hybridus*), Quinine (*Cinchona pubescens*), Southern Bayberry (*Myrica cerifera*), Scurvy Grass (*Cochlearia officinalis*), Storax (*Liquidambar orientalis*), Tea Tree (*Melaleuca alternifolia*), Tolu Balsam (*Myroxylon balsamum*), Turmeric (*Curcuma domestica/longa*), Wild Indigo (*Baptisia tinctoria*), Yellow Lupin (*Lupinus leteus*)

(Continued)

Table 4 Therapeutic Uses (*Continued*)

Venous Insufficiency / Varicosities / Venous Stasis / Lymphedema	Ammoniac Gum (*Dorema ammoniacum*), Beth Root (*Trillium erectum*), Buckwheat (*Fagopyrum esculentum*), Butcher's Broom (*Ruscus aculeatus*), Clematis (*Clematis recta*), Club Moss (*Lycopodium clavatum*), Echinacea (*Echinacea angustifolia*), Figwort (*Scrophularia nodosa*), Garlic (*Allium sativum*), Gotu Kola (*Centella asiatica*), Grape (*Vitis vinifera*), Great Burnet (*Sanguisorba officinalis*), Horse Chestnut (*Aesculus hippocastanum*), Lemon Verbena (*Aloysia triphylla*), Marigold (*Calendula officinalis*), Pimpinella (*Pimpinella major*), Purple Loosestrife (*Lythrum salicaria*), Rue (*Ruta graveolens*), Smartweed (*Persicaria hydropiper*), Sweet Clover (*Melilotus officinalis*), Sweet Woodruff (*Galium odoratum*), Witch Hazel (*Hamamelis virginiana*), Yarrow (*Achillea millefolium*)
Warts / Condyloma acuminata	Behen (*Moringa oleifera*), Bittersweet Nightshade (*Solanum dulcamara*), Broad Bean (*Vicia faba*), Calotropis (*Calotropis procera*), Cashew (*Anacardium occidentale*), Celandine (*Chelidonium majus*), Common Stonecrop (*Sedum acre*), Cypress Spurge (*Euphoria cyparissias*), Garlic (*Allium sativum*), Giant Milkweed (*Calotropis gigantean*), Houseleek (*Sempervivum tectorum*), Indian-Hemp (*Apocynum cannabinum*), Mayapple (*Podophyllum peltatum*), Oats (*Avena sativa*), Onion (*Allium cepa*), Savin Tops (*Juniperus sabina*), Scarlet Pimpernel (*Anagallis arvensis*), Spurge (*Euphorbia resinifera*), Sundew (*Drosera ramentacea*)
Wound Care	Agrimony (*Agrimonia eupatoria*), Alkanet (*Alkanna tinctoria*), American White Pond Lily (*Nymphaea odorata*), Ammoniac Gum (*Dorema ammoniacum*), Ash (*Fraxinus excelsior*), Basil (*Ocimum basilicum*), Behen (*Moringa oleifera*), Beth Root (*Trillium erectum*), Birthwort (*Aristolochia clematitis*), Bistort (*Persicaria bistorta*), Black Catnip (*Phyllanthus amarus*), Black Currant (*Ribes nigrum*), Black Nightshade (*Solanum nigrum*), Bladderwort (*Utricularia vulgaris*), Blessed Thistle (*Cnicus benedictus*), Brazillian Pepper Tree (*Schinus terebinthifolius*), Broad Bean (*Vicia faba*), Bugle (*Ajuga reptans*), Burning Bush (*Dictamnus albus*), Cajuput (*Melaleuca leucadendra*), Carline Thistle (*Carlina acaulis*), Cascara Sagrada (*Rhamnus purshiana*), Cat's Claw (*Unicaria tomentosa*), Catechu (*Acacia catechu*), Chickweed (*Stellaria media*), Cinnamon (*Cinnamomum verum*), Cinquefoil (*Potenilla erecta*), Clematis (*Clematis recta*), Club Moss (*Lycopodium clavatum*), Coconut Palm (*Cocos nucifera*), Coffee (*Coffea arabica*), Cola (*Cola acuminata*), Common Kidney Vetch (*Anthyllis vulneraria*), Common Stonecrop (*Sedum acre*), Congorosa (*Maytenus ilicifolia*), Corydalis (*Corydalis cava*), Costus (*Saussurea costus*), Date Palm (*Phoenix dactylifera*), Digitalis (*Digitalis purpurea*), Dogwood (*Cornus florida*), Echinacea (*Echinacea angustifolia and purpurea*), Elm Bark (*Ulmus minor*), English Ivy (*Hedera helix*), English Plantain (*Plantago lanceolata*), English Lavendar (*Lavandula angustifolia*), Eucalyptus (*Eucalyptus globulus*), European Goldenrod (*Solidago virgaurea*), Fenugreek (*Trigonella foenum-graecum*), Feverfew (*Tanacetum parthenium*), Galbanum (*Ferula gummosa*), German Chamomile (*Matricaria recutita*), Goldenseal (*Hydrastis canadensis*), Gotu Kola (*Centella asiatica*), Goutweed (*Aegopodium podagraria*), Great Burnet (*Sanguisorba officinalis*), Ground Ivy (*Glechoma hederacea*), Heather (*Calluna vulgaris*), Henna (*Lawsonia inermis*), High Mallow (*Malva sylvestris*), Horehound (*Marrubium vulgare*), Horsetail (*Equisetum arvense*), Hound's Tongue (*Cynoglossum officinale*), Houseleek (*Sempervivum tectorum*),

Iceland Moss (*Cetraria islandica*), Indian Nettle (*Acalypha indica*), Jambolan (*Syzygium cumini*), Jujube (*Zyzyphus jujube*), Lady's Bedstraw (*Galium verum*), Lesser Celandine (*Ranunculus ficaria*), Licorice (*Glycyrrhiza glabra*), Loosestrife (*Lysimachia vulgaris*), Lungwort (*Pulmonaria officinalis*), Male Fern (*Dryopteris fili-max*), Marigold (*Calendula officinalis*), Marsh Marigold (*Caltha palustris*), Marshmallow (*Althaea officinalis*), Moneywort (*Lysimachia nummularia*), Monkshood (*Aconitum napellus*), Mouse Ear (*Pilosella officinarum*), Mullein (*Verbascum densiflorum*), Myrrh (*Commiphora molmol*), Nasturtium (*Tropaelum majus*), Oak Gall (*Quercus infectoria*), Onion (*Allium cepa*), Ox-Eye Daisy (*Chrysanthemum leucanthemum*), Petasites (*Pentasites hybridus*), Peruvian Balsam (*Myroxylon balsamum*), Pimpinella (*Pinpinella major*), Pineapple (*Ananas comosus*), Poplar (*Populus species*), Poley (*Teucrium polium*), Quinine (*Cinchona pubescens*), Rauwolfia (*Rawolfia serpentina*), Rose (*Rosa centifolia*), Rosemary (*Rosemary officinalis*), Safflower (*Carthamus tinctorius*), Scarlet Pimpernel (*Anagallis arvensis*), Sea Buckthorn (*Hippophaë rhamnoides*), Shepherd's Purse (*Capsella bursa-pastoris*), Slippery Elm (*Ulmus rubra*), Smartweed (*Persicaria hydropiper*), Speedwell (*Veronica officinalis*), Spikenard (*Aralia racemosa*), Squill (*Urginea maritima*), St. John's Wort (*Hypericum perforatum*), Storax (*Liquidambar orientalis*), Sunflower (*Helianthus annuus*), Tansy (*Tanacetum vulgare*), Teazle (*Dipsacus silvestris*), Thyme (*Thymus vulgaris*), Tolu Balsam (*Myroxylon balsamum*), Traveller's Joy (*Clematis vitalba*), Tropical Almond (*Terminalia chebula*), Turmeric (*Curcuma domestica/longa*), Vervain (*Verbena officinalis*), Virola (*Virola theiodora*), Water Dock (*Rumex aquaticus*), Water Germander (*Teucrium scordium*), White Fir (*Abies alba*), White Lily (*Lilium candidum*), White Nettle (*Lamium album*), White Willow (*Salix nigra*), Wild Daisy (*Bellis perennis*), Wild Indigo (*Baptisia tinctoria*), Willow Herb (*Epilobium angustifolium*), Witch Hazel (*Hamamelis virginiana*), Wood Sage (*Teucrium scorodonia*), Woodsorrel (*Oxalis acetosella*), Wormwood (*Artemisia absinthium*), Woundwort (*Stachys palustris*), Yarrow (*Achillea millefolium*), Yellow Toadflax (*Linaria vulgaris*), Zedoary (*Curcuma zedoaria*)

Xerosis   Marigold (*Calendula officinalis*), Mountain Grape (*Mahonia aquifolium*)

[a] These herbs are approved by the German Commission E. for this indication.

SPECIFIC HERBS

Allantoin and Comfrey (*Symphytum officinale*)

Comfrey is approved by the Commission E to treat blunt injuries due to the activity of triterpene saponins, tannins, and silicic acid as well as allantoin (3).

Allantoin has been extracted from the comfrey root and leaves but is now commercially manufactured. Allantoin is an antipholgistic, antioxidant, and soothing keratolytic that has antitrichomonal effect and induces cell proliferation. It is listed in the FDA over-the-counter monograph as a safe and effective skin protectant at 0.1% to 2.0% (15). Allantoin- and/or comfrey-based products are used to treat wounds, ulcers, burns, dermatitis, psoriasis, impetigo, and acne. When formulated with surfactant and benzalkonium chloride it is an effective hand sanitizer and onychomycosis therapy (3).

Comfrey contains hepatotoxic pyrriolizidine alkaloids which have resulted in deaths with oral consumption. It is carcinogenic and contraindicated in pregnancy and lactation (3).

Allantoin formulated with onion (*Allium cepa*) extract in a proprietary topical formulation improved the signs and symptoms of scars and keloids (16,17). No photo-aging clinical trials using topical allantoin and/or comfrey have been published.

Aloe (*Aloe barbadensis*, *A. capensis*, *A. vera*)

Aloe is used in asian medicine for therapy of fungal and other infections, infestations, tumors, and other skin diseases. The aloe substance released from comminuted leaves contains mucopolysaccharides, glucommamman including beta-mannan, allantoin, anthracenes such as aloin and emodin, alkylchromone including aletinic acid, and choline salicylate, flavonoids, amino acids, hydroxyquinine glycosides, carboxy-peptidases, and minerals (3). The hydroxyanthraquinone emodin inhibits neuroecto-dermal tumors such as Merkel cell carcinoma (18). Acetylated mannans and lectins appear to have immunomodulatory effects. Aloe is antibacterial to *Staphylococcus aureus*, *Helicobacter pylori*, and dermatophyte fungus. It is viricidal to herpes simplex and varicella zoster and is clinically effective in treating genital herpes. This herb inhibits thromboxane vasconstriction. Aloe inhibits photoimmunosuppression of UVB and inhibits cyclooxygenase for anti-inflammatory effects. It also increases collagen biosynthesis and degradation in granulation tissue (3). The antineoplasia effect is improved with melatonin and ascorbic acid. Aloe vera applied topically is accepted therapy for radiation and stasis dermatitis and ulcers, frostbite, burns, fungal and bacterial infections, cold sores, pruritis, pain, psoriasis, and contact irritant dermatitis. The latter two were documented in blinded studies (19,20).

No photoaging clinical studies using topical aloe vera have been published despite its use as one of the two most common extracts in skin care formulations. The health risks of aloe are cutaneous eruptions and mutagenicity. It is contraindicted in pregnancy and lactation (3,18).

Anise (*Pimpinella anisum*)

Commission E has approved this herb for mucocutaneous inflammation. The galenic formulations consist of 30% fatty oil, 20% proteins, 4% volatile oils of which 94% is anethole, caffeic acids such as chlorogenic acid, and flavonoids. This herb has antibacterial, antiviral, antiphlogistic, insect repellant, and estrogenic functionalities. Anise is administered as oil or infusion. It has very rarely produced sensitization (3).

A recent blinded clinical trial in 119 children with scabies documented efficacy of 92% cure, identical to the mix of prescriptives used as the control. The anise formulation also included coconut oil and ylang ylang, an essential aromatic oil (21).

Avocado (*Persea americana*)

The oil from this food heals wounds, treats sclerosis and has long been used in products for skin aging. The oil primarily consists of monosaturated lipids (22).

Bitter Orange (*Citrus aurantium*)

Although this herb has no dermatologic indications in Asian, homeopathic or Commission E, it has been evaluated in clinical trials for cutaneous disease and has been added to multiple cosmeceuticals. The active compounds include flavonoids, triterpenoid bitter principles (limonoids), furocoumarins, methyl anthranilate, and volatile oils including limonene, nerol, and linalool. Bitter orange may cause sensitization, phototoxicity, and hyperpigmentation. It is administered as a tonic, tea, tincture, or galenic drops (3).

A blinded, three-arm trial of 65 patients suffering from tinea corporis was conducted. One arm used a poultice of 100% of this herb applied once daily for three weeks while another arm used 25% emulsion three times daily for four weeks and both were compared to imidizole twice daily for four weeks. At two weeks, 93% of the 100% bitter orange poultice were clinically cured and 80% were cured with the emulsion of this herb while none were cured with the imidizole (23).

Black Cohosh (*Cimicifuga racemosa*)

This North American herb is primarily prescribed to reduce menopause symptoms. It is also known as an insect repellant, to treat acne and warts and improve skin appearance. This herb contains salicylic acid, tannins, long-chain fatty acids, glycosides and phytoestrogens (22).

Black Nightshade (*Solanum nigrum*)

This herb is used in Asian medicine for abcess, furuncle, erysipelas, leprosy, psoriasis, wound, ulcer, and hemorrhoid but is not approved by Commission E for any indication. The active compounds include steroid alkaloid glycosides, alkaloids such as solasonine, and steroid saponins including tigogenin. The major clinical effect is anesthetic/analgesic, but recent studies focus on the anti-infective effects. The nightshades have no reported health hazards. They are administered as liquid extract or tinctures (22).

Two blinded comparative studies tested this herb and *Solanum chrysotrichum* to document clinical antifungal efficacy. The first compared *Solanum nigrum* to nystatin in 100 patients suffering from vaginal candidiasis. This herbal product cured the same number of patients in 25 days with treatment twice daily as nyststin did in 15 days (24). The other study consisted of the 28 patients suffering from tinea pedis who were treated twice daily for four weeks. The test products were 2% micronazole and 5% *Solanum chrysotrichum* each applied to one foot. The herb cure rate was 45% vs. no cure for micronazole (25).

Black Seed (*Nigella sativa*)

This herb has traditionally been a hemorrhoid, skin condition, and cancer treatment and has an immune stimulant effect. Its active compounds include nigellone and thymoquinone. Black seed has antioxidant, antiphlogistic, antibacterial, and antihelminthic effects (22).

Four clinical studies documented efficacy of this herb for treatment of atopic dermatitis and asthma when administered orally. The score of subjective symptomotology in each study decreased with a $p < 0.05$ significantly (26).

Cayenne (*Capsicum species*)

This spicy pepper extract uniquely depletes substance P of the peripheral C nerves. It is approved by the FDA for treatment of pruritis and pain. The active compounds are primarily amides of vanillylamine with fatty acids known as capsaicinoids. Other active compounds include anti-inflammatory carotenoids such as capsantain, flavonoids including apiin, steroid saponins, and volatile oils. Capsaicin rarely has induced anaphylaxis, death, and ulceration. Burning during the first few applications is common (2). It is now available as nonprescription products (3).

Two other human trials documented significant resolution of visible psoriatic lesions with six weeks of use four times daily (27,28). Other clinical studies document efficacy for chilblains, post herpetic neuralgia, and pruritis (3).

Camptotheca acuminata Decne

This herb is one of the few Chinese herbal products with a single botanical applied topically reported in the English medical literature. Many combinations of Chinese herbs administered as teas have documented effectiveness for dermatitis and psoriasis. Topically applied *Camptotheca acuminata* Decne was equally effective as 1% hydrocortisone in treating psoriasis but suffered a 12% incidence of allergic contact dermatitis (29).

Chinese medicine herbs must be used cautiously because in Taiwan 40% were adulterated with corticosteroids, nonsteroidal anti-inflammatories, and/or central nervous system medicines. Over 50% of the Chinese herbal medicines have two or more of these synthetics (30).

Curcumin Derived from Turmeric (*Curcuma domestica/longa*)

This herb is not approved for dermatologic conditions but is used in Asian medicine for cutaneous inflammation, bruising, bites, pruritis, wounds, fungal infections, and ulcers. Its active compounds include volatile oils, such as tumerone, which provides the unique aroma, 4% curcuminoids, heptanoids, and 30–40% starch. This extract provides the yellow color and much of the flavor for curry in foods (3). These molecules provide antioxidant, antitumor, antimicrobial, antifertility, anti-inflammatory, and insect repellent effects. Curcumin may color cosmeceuticals claiming to be free of artificial ingredients. Tetrahydrocurcumin is an off-white color that protects cosmeceutical formulations with antioxidant effect that appears superior to tocopherol. Curcumin is contraindicated in pregnancy due to abortifacient effect.

Clinical studies demonstrating any impact upon parameters of photoaging are lacking. A paste containing curcumin and neem (*Antelaea azadirachta*) clinically cured 97% of 814 children afflicted with scabies within 15 days (31).

Date Palm (*Phoenix dactylifera*)

This food stuff is an Asian medicine therapy for inflamed wounds. The active compounds include 50% sugars such as saccharose, 10% fatty oils, leukoanthocyanidins, phytohormones, and piperidine derivatives including pipecolic acid. It has no reported health hazards (3).

A placebo-controlled trial with 5% date versus placebo in 10 patients was applied to the eye lid twice daily for five weeks. Statistically significant reduction in wrinkle surface (27.6%) and wrinkle depth was achieved. Six of the participants said visual improvement occurred (32).

Echinacea (*Echinacea angustifolia*, *E. purpurea*, *E. pallida*)

This medicinal botanical has the largest domestic sales volume. It is among the most useful herbs for dermatologic treatment and prevention of skin diseases. *E. angustifolia* was originally used by the Sioux Native Americans for the treatment of snake bites and war wounds because if its antiseptic and analgesic properties (2). Echinacea is known to the public because of its clinically documented immunostimulating effects in treating and aborting respiratory viral infections (3). All three Echinacea species stimulate immunity, protect collagen, and have antioxidant activity. They are also cytotoxic to multiple bacteria and viruses, *E. purpurea* is approved by Commission E for treatment of mucosal inflammation, wounds, burns, and to prevent infection. It is formulated in several cosmeceuticals. *E. angustifolia* is approved for viral therapy and prophylaxis. Unproven therapies include abcesses, ulcers, and measles. An *E. purpurea* formulation did not effectively treat recurrent genital herpes simplex (33).

Of all three species the two most active compounds in the above ground plant include the immunostimulating polysaccharides, echinacin, and inulin. Echinicin has an anti-inflammatory effect similar to corticosteroids but maintains collagen and ground substance integrity. It also stimulates wound healing. Inulin is a potent stimulator of the alternative complement pathyway, viral neutralization, bacterial destruction, and leukocyte chemotaxis. Other active compounds in Echinacea include caffeic and ferulic acid derivatives such as chlorogenic acid, echinoside, flavonoids including rutin, pyrrolizidane alkaloids, alkamides, polyenes, and volatile oils. The roots additionally contain immunostimulating glycoproteins that function like interferon (IFN). *E. purpurea* also contains pyrrolizidane alkaloids and glycoproteins which are lacking in *E. pallida* and *E. angustifolia*. In vitro studies suggest this herb protects against cutaneous ultraviolet light damage (2).

Echinacea species adversely effect fertility and pregnancy. They must not be combined with immunosuppressants. Echinacea is administered as comminuted herb for juice, decoction, tea, and tincture (3).

Garlic (*Allium sativa*)

Homeopathy employs garlic for mucosal inflammation. The biologic activity is primarily due to alkylcysteine sulfoxides, particularly alliins which are converted to allicin then dried resulting in oligosulfides and ajoene. These thiosulfinates are the major active components. Others include fructosans and saponins. Garlic is a proven oral and topical broad spectrum antimicrobial against gram-positive and gram-negatives with potency comparable to many antibiotics (3). The anti-yeast activity is comparable to nystatin and antifungal activity compares to seven other medicines including gentian violet. Garlic has antiviral activity against influenza B and herpes hominis I (11). This herb inhibits carcinogeneisis and cancer cell growth. Garlic tablets stimulate natural killer T cells to fight cancer, viral, and certain bacteria as well as enhance glutathione in cells. Ajoene inhibits clotting and bleeding times and platelet aggregation yet enhances fibirinolysis by inhibiting thromboxane, adenosine diphosphate, and collagen release. Garlic is also a major source of vitamins A, B-1, and C. Virtually odorless garlic based products are being marketed (3).

The adverse reactions due to topical garlic are contact irritant and allergic dermatitis and the distinctive halitosis (13). Avoid garlic while breastfeeding. Orally administered garlic increases bleeding during surgery especially if administered with other anticoagulants. It is administered in capsules, tablets, powder, and oil. A 0.4% ajoene cream successfully cleared all 34 patients of tinea pedis with 14 days of therapy (34).

German Chamomile (*Matricaria recutita*)

Matricaria recutita functions as an anti-allergic, antimicrobial, anti-inflammatory, antioxidant analgesic approved by Commission E for inflammatory mucocutaneous diseases, wound, and burn therapy. The major components of German chamomile include the primary anti-inflammatory agents: alpha-bisabolol, chamazulene, levomenol, and matricine. Other active compounds include bisaboloxides, farnesenes, choline, glycosides, flavonoids such as apigenin, rutin, tannins, hydroxycoumarins such umbelliferone, mucilages, saccharides, fatty acids, and salicylates (3,35).

Chamazulene inhibits leukotriene B4 synthesis via inhibition of lipoxygenase and cyclo-oxygenase, lipid peroxidation, leukocyte infiltration, and histamine release. Levomenol is an anti-inflammatory hydrating agent that diminishes the signs of photodamage and reduces pruritis. Apigenin inhibits adhesion molecules. Bisabolol promotes granulation tissue (35).

Clinical studies showed topical chamomile cream was superior to 0.5% hydrocortisone in treating dermatitis and sunburn and statistically significantly decreased wound area and healing time (29). In another trial, it was not as effective as 0.25% hydrocortisone in treating dermatitis. This herb is administered as oil for infusion, tea, ointment, gel, wash, gargle, or capsule.

Chamomile is a compositae that has a significant risk of contact sensitization, conjunctivitis, angioedema, and anaphylaxis. It also has an additive anticoagulant effect to warfarin (3).

Gingko (*Ginko biloba*)

The efficacy of this herb for human dementia and peripheral occlusive arterial disease therapy are well documented. The mechanisms of action include antioxidant, stimulating fibroblasts, prevent lipid peroxidation, stabilize membranes, reduce neutrophil infiltration, and protect against ischemia. The major active compounds include proanthocyanidins which comprise 8–12%, biflavonoids such as gingkgetin, flavonoids including kaempferol, and trilactonic diterpenes such as ginkolide and sesquiterpene bilabolids (36,37).

The major health hazard encompasses spontaneous hemorrhage including intracranial. Others include adverse effects on oocytes and cutaneous allergic reactions. Gingko is administered as liquid extract for infusion and powder for tablets and capsules (3).

One double-blind, placebo-controlled study documented reduction in the frequency of attacks of Raynaud's disease with ingestion (38). Another double-blind, placebo controlled trial with 40 mg thrice daily halted vitiligo progression in 20 of 47 patients and produced marked improvement in 10 (39).

Grape Seed (*Vitis vinifera*) / Pycnogenol / OPCs

The pharmacologic activity of grape seed extract (GS) along with French maritime pinebark (Pinus pinaster) extract primarily resides in the potent antioxidant proanthocyanidins. These are the two richest natural sources and most commercially viable. Other rich natural sources include green and black tea, red wine, red apple, red cabbage, black currant, sangre de drago, bilberry, blackberry, blueberry, strawberry, black cherry, cranberry, peanut skins, almonds,

cocoa, parsley, onions, legumes, hawthorn, and witch hazel bark (3,22). The standardized pinebark extract is patent protected Pycnogenal (PYC), which has been the generic term for proanthocyanidins. These polyphenolic bioflavonoids are also known as procyanidins, procyandiol oligomers, leukoanthocyanidins, condensed tannins, and oligomeric proantho- cyanidins (OPCs). OPCs consist of dimers of catechins and oligomers of epicatechin and catechin and their gallic acid esters. These compounds are scavengers of both reactive oxygen and nitrogen species. GS also includes other therapeutic compounds including flavonoids such as kaempferol and quercetin glucosides, stilbenes such as resveratrol and viniferins, fruit acids, tocopherols, essential fatty acids, and phenylacrylic acids such as caffeoyl and feruloylsuccinic acid. Resveratol is a potent antioxidant which inhibits angiogenesis and carcinogenesis, is antiviral against herpes, and has phytoestrogen activity. PYC also contains monomeric epicatechin and catechin (3,22,40).

GS applied topically improved cutaneous photoprotection to UVB, inhibits histamine synthesis, promotes wound healing, reduces apoptosis induced by chemother- apy, reduces vascular engorgement, is cytotoxic to adenocarcinoma, and inhibits streptococcus. GS protects DNA against oxidation more effectively than vitamins C and E and stabilizes collagen and elastin by inhibiting MMPs. It treats chronic venous insufficiency (CVI) and postoperative edema in clinical studies. All these functions of GS strongly suggest is should improve photoaged skin and protect against further damage. GS has been used for centuries in Asia to treat a variety of cutaneous conditions (3,22,40).

PYC increases nitric oxide levels, stimulates T and B cell function, inhibits nuclear receptor transcription factors nuclear factor-kappa B (NF-kappa B) and AP-1 and the adhesion molecule ICAM-1 as well as IFN-gamma. It recycles both vitamins C and E. Topically applied PYC reduces sunburn, immunosupression, and tumor formation by UV light while raising the minimal erythema dose in mice (22,29). PYC administered orally reduced the area of severity of melasma within 30 days and the signs and symptoms of CVI by 60 days (29).

A topical formulation consisting of grape seed, jojoba, lavender, rosemary, and thyme was to treat alopecia areata. After seven months of daily use, statistically significant improvement in hair re-growth occurred (44% vs. 15% for placebo) (41). It has been used in anti-aging creams for several years (22). No controlled clinical studies evaluating these herbs for treatment of photoaging have been published.

Horse Chestnut (*Aesculus hippocastanum*)

This herb is approved by German Commission E for CVI, lupus and ulcer therapy. In homeopathy horse chestnut treats hemorrhoids. The mechanisms of action include inhibition of elastase and hyaluronase primarily by aesin, a triterpene saponin which has anti-exudative effects by decreasing capillary permeability, inhibits leukocyte activation, and induces vasoncontriction. The active compounds in seeds of this herb contain 50% polysaccharides and oligosaccharides, other triterpene saponins, fatty oils, sterols and flavonoids including quercetin and OPCs (3,22).

Leg circumference, heaviness, and pain were statistically significantly reduced in multiple CVI trials with oral therapy. Topically applied horse chestnut reduced the symptoms of CVI in one trial and hemorrhoids in another (42). Photoaging clinical studies are lacking.

The health risks of horse chestnut include hepatotoxicity, renal toxicity, urticaria, anaphylaxis, and mucocutaneous irritant and allergic dermatitis. It may also interact with salicylates and warfarin. This herb is administered as tea, tincture for infusion, gel, or ointments (3,22).

Lemon Balm (*Melissa officinalis*)

This herb has antibacterial, antiviral, antioxidant, and anti-hormonal effects. The active compounds include volatile oils such as citronellal, glycosides, caffeic acids such as rosmaric acid, triperpene acids including ursolic acid, and flavonoids such as cynaroside. Lemon balm has one reported case of contact irritation. It is administered as powder, tea, and infusion (22).

A 1% cream applied five times a day in 116 patients in a double-blinded trial for Herpes Simplex documented complete clearing by day 8 in 96%. Lesion size and healing time were statistically significantly superior to placebo (43).

Milk Thistle (*Silybum marianum*)

The extract of this herb is silymarin which consists of three flavonoids: silybin (about 75%), silydianin, and silychristine. Silymarin has potent antioxidant, antiphlogistic, antiangiogenic, and antitumor activities. A 92% reduction in UVB-induced murine skin tumors was produced with topical silymarin (44). Topical silybin decreased the formation of pyrimidine dimers and UVB-induced apotosis was enhanced in mice (45). It also inhibits cyclooxygenase-2 (46). Other active molecules in milk thistle include fatty oil which accounts for 20–30% flavonoids including apigenin and quercetin, steroids such as beta-sitosterol, fumaric acid, and polyynes. This herb is administered as a comminuted drug for liquid extracts and tinctures for infusion. No allergic reactions have been reported (3).

Neem (*Antelaea azadirachta*)

This medicinal botanical is used in Asian medicine to treat inflammatory diseases, infestations, wounds and leprosy. It has documented anti-inflammatory, antihelminthic, antipyretic, antiphlogistic, and insecticide activity due to its triterpenes, tannins, and volatile oils. Neem is administered as a decoction, tincture or ointment. It was formulated in a paste with curcumin to treat 814 children with scabies. A 97% cure rate was achieved within 15 days (22,29,31).

Onion (*Allium cepa*)

This herb is approved for mucosal inflammation therapy and to reduce the tendency toward infection. In Asian medicine it treats wounds fungal, bacterial, and helminthic infections. The active compounds include alliins (alkylcysteine sulphoxides), polysaccharides, saccharose, flavonoids, and steroid saponins. In addition to anti-inflammatory effects, this herb inhibits gram-negative bacteria and thrombocytes and has anti-allergic effects. Onion rarely produces contact irritant reactions.

This herb effectively modulates scars and keloid formation in two human trials when formulated with allantoin (16,17). In a study for treatment of patchy alopecia areata of 23 patients, re-growth of terminal coarse hairs started after two weeks of treatment with crude onion juice. At six weeks, the hair re-growth was observed in 20 patients. The tap-water-treated control group experienced hair re-growth in only two patients at eight weeks of treatment (p < 0.0001) versus the onion juice group (47).

Oregon Grape (*Mahonia aquifolium*)

This herb is traditionally used for psoriasis therapy and disinfectant. The active molecules are isoquinoline alkaloids such as berberine and oxyacanthine which are antibacterial,

antihelmintic, and immunostimulating. It can induce pruritis, contact irritant and allergic dermatitis. This herb is administered in powder, cream, and ointment (22).

Two psoriasis clinical studies have been reported. The open study documented improvement in psoriasis symptoms and quality of life (48). The blinded study found oregon grape ointment to be superior to placebo in less than half of the patients (49).

Pomegranate (*Punica granatum*)

This herb was used in ancient Egypt for inflammation of the skin, mucosa, and joints. Punica granatum may contain a more potent antioxidant mixture than grapeseed, Pycnogenol, blueberry, cranberry red wine, or green tea. The major constituents are tannins (25–28%), including punicalagin, polyphenols such as ellagic acid, ascorbic acid, niacin, potassium, piperidine alkaloids and phytoestrogens. Pomegranate functions as an astringent that also inhibits NF-kappa B. It has documented antimicrobial activity for gram-negative bacteria, saccharomyces fungus, parasites, and viruses (22). Topical and oral administration of this herb induced photoprotection to UVB in a human clinical trial (50).

Topically applied, pomegranate can induce contact urticaria/angiodema and conjuctivitis. It is administered as a decoction (3,22).

Soy (*Glycine soja*)

This antioxidant, antiproliferative, antiangiogenic phytoestrogenic extract is used to treat hyperhidrosis in Asian medicine (22). Epidemiologic studies indicating much lower malignancy and cardiac disease rates in people eating a diet high in soy resulted in thorough investigations revealing multiple medicinal uses. The major components of soy are phospholipids (45–60%) such as phosphatidyl choline and essential fatty oils (30–35%). The minor components include the most active compounds such as isoflavones, saponins, essential amino acids, phytosterols, calcium, potassium, iron, and the proteases soybean trypsin inhibitor and Bowman-Burke inhibitor. The most potent isoflavones are the phytoestrogens genistein and daidzein. Topical estrogens have been shown to increase skin thickness and promote collagen synthesis; thus, soy phytoestrogen stimulatation of human fibroblast collagen synthesis is expected. Genistein, the most potent antioxidant, inhibits lipid peroxidation and chemical- and UVB-induced carcinogenesis. The two protease inhibitors lighten pigmented lesions and reduce unwanted facial and body hair in human clinical trials (3,51,52).

Soy products have rarely caused dermatitis and pruritis as well as asthma and gastrointestinal symptoms (3,22).

St. John's Wort (*Hypericum perforatum*)

This widely used herb is popular due to its sedative, anxiolytic, and antidepressant action. St. John's Wort is approved for wound healing, burns, and cutaneous inflammation. Asian medicine employs it for dermatitis topical therapy. This herb has antistaphylococcal, anti-inflammatory, antineoplastic, antioxidant activity yet stimulates wound healing and T lymphocytes. The active compounds include flavonoids such as quercetin, catechins, oligomeric procyanidines, xanthones, anthracenes including hypericin, and caffeic acids such as chlorogenic acid. This herb is administered by powders, liquid, tincture, and tea (3). St. John's Wort induces multiple health hazards including dangerous ones such as mutagenicity to oocytes. It interacts with many major systemic drugs including beta-blockers, anticoagulants, calcium channel blockers,

immunosuppressives, anti-hypertensives, antibiotics, contraceptives, statins, SSRI, analgesics, and photosensitizers (13,22).

Human clinical trials from Russia support its wound healing effectiveness (2). In a 21-patient, blinded, clinical trial of mild to moderate atopic dermatitis the improvement of the intensity of the eczematous lesions by 1.5% hypericum-cream was significantly superior to the vehicle at all clinical visits (p <0.05) (53).

Tea Tree (*Melaleuca alternifolia*)

This essential oil has become one of the most commonly used nonprescription remedies for mucocutaneous disorders. TTO active compounds include terpinenes such as cineole. The monoterpene terpinen is the major sensitizing compound in TTO which has become one of the most common contact allergens. The terpene alcohols such as terpin in -4-ol are the major constituents comprising 40% of TTO. They reduce histamine induced edema and wheal volume in type I hypersensitivity reactions. TTO does not have antioxidant activity nor does it suppress neutrophil superoxide. Its wide antimicrobial spectrum includes *Propionobacterium acnes*, *Escherichia coli*, *Staphylococcus aureus*, Herpes simplex, *Candida albicans*, *Trichophyton dermatophytes* and *Sarcoptes scabeii* (3,54,55).

Multiple double-blinded clinical trials document that TTO effectively treats acne and fungal/yeast infections. TTO failed to effectively treat atopic dermatitis and CVI (3,22,55).

TTO is cytolytic to epithelial cells and fibroblasts so it should not be used for burns. Photodamaged TTO is a stronger sensitizer and has induced erythema multiforme with topical application. Thus, the use of TTO in cosmeceuticals for sun exposed tissue is not scientifically sound (55).

Teas—Black, Green, Oolong, and White (*Camellia sinensis*)

All true teas are derived from *Camellia sinensis*. Black tea is the most processed (fermented) with white tea recently supplanting green tea as the least processed; oolong is partially fermented. Green tea contains 8–12% polyphenols and 2–4% caffeine (10-80 mg/cup). White tea is a more potent antioxidant and more effective than green tea in inhibiting bacterial dysplastic mutations (3,22,56). Green tea decreases melanoma cells in tissue culture and squamous cell carcinoma cell formation with topical and oral administration in mice. It also increases keratinocyte cell differentiation improving wound healing. This tea inhibits Streptococcus species and *Escherichia coli*. It also inhibits bradykinin and prostaglandins in animals (57). Black tea has a much lower content of catechins than green tea, but a higher content of other flavonoids such as kaempferol and theaflavin. The largest catechin and most active antioxidant in any tea is epigallocatechin gallate (EGCG). Green tea has the highest concentration of EGCG (3).

Topical green tea provided photoprotection beginning at 24 hours and lasting 48–72 hours. It reduced the number of sunburn cells by 66% when applied 30 minutes prior to UVB. When applied at 1–10% concentrations, a dose response inhibition of UV-induced erythema occurred (58). This extract prevented psoralen UVA photodamage with pre- and post-treatment by reducing erythema, hyperplasia, and hyperkeratosis (59,60). Green tea is used to soothe sunburn, reduce baggy eyelids, reduce gingivitis and produce hemostasis and prevent UV induced carcinogenesis including oral leukoplekis (2,22). Black tea extracts applied pre- and post-ultraviolet light challenge decreased signs of cutaneous photodamage, carcinogenesis, and inflammation in human and mouse skin (22). Oral administration of black and oolong

teas, like green tea, suppressed both type I and IV allergic reactions in the skin (61). Oral oolong tea effectively treated atopic dermatitis (62).

A recent double-blinded trial of 51 patients treated for 12 weeks with topical green tea extract containing 5.5–8.5% EGCG did not reduce the number of actinic keratoses on forearms compared to placebo (63).

The major adverse reactions are gastrointestinal upset, constipation, irritability, and very rare hepatotoxicity, delirium, and seizures. Caution should be used during pregnancy and lactation with excessive consumption ($>$3 cups or 300 mg per day) (22).

Western Herbal Mix

This consists of grape seed, jojoba, lavender, rosemary, and thyme. It was massaged into the scalp of 86 patients suffering from alopecia areata. After seven months of daily use statistically significant improvement in hair re-growth occurred (44% western herbal mix vs. 15%) for placebo (64).

Witch Hazel (*Hamamelis virginiana*)

The bark and leaf of this herb yield galenic formulations with 5–12% tannins, catechins including EGCG, OPCs, flavonoids such as quercitrin, and volatile oils. Astringent, antiphlogistic, and hemostatic effects result from these potent active compounds. Witch hazel is approved by Commission E and in homeopathy for mucocutaneous inflammation, wound, burn, venous insufficiency, and hemorrhoid therapy. Contact irritant dermatitis is rarely reported. Hepatotoxicity possibly occurs with chronic ingestion. It is administered in various topical formulations via extract of comminuted drugs, steam distillate, decoction or tea, gels, and ointments (3).

Witch hazel is formulated into acne and vein cosmeceuticals. Clinical studies document this herb is less effective than 1% hydrocortisone in reducing UV-induced erythema (65). In 36 atopic dermatitis patients, witch hazel significantly reduced inflammation and pruritis (66).

Scientifically Rational Herbs

There are a number of well-known, commonly used medicinal botanicals incorporated into many cosmeceuticals that have not been studied in any dermatologic human trials but have demonstrated biologic effects in nondermatologic diseases, in vitro, in vivo, or animal models. The lack of FDA regulation allows companies to formulate these herbs into skin care products and market them. Cosmeceuticals that lack human clinical data, contain herbs with only in vitro scientific data, contain subtherapeutic concentrations, lack documented delivery systems for the herbal molecules, and lack proof of chemical stability of the formulation should be viewed with great skepticism by clinicians.

Apple (*Malus domestica*)

Extracts of this foodstuff has been used for years in cosmeceuticals for fruit acids particularly malic, ascorbic acid, and pectin. Other active compounds include tannins such as quercetin and caffeic acids such as quinic acid. Procyanidin B-2 is a protein kinase C inhibiting tannin recently demonstrated to promote hair cell growth and anagen induction in vitro (67).

Arnica (*Arnica montana*)

Arnica, of the compositae family, is approved for treating inflammation of cutaneous and muscosal surfaces and blunt injury and reducing the risk of developing infection. This herb functions as an analgesic, antidandruff, antiseptic, anti-inflammatory, and antiphlogistic but is an immunostimulant. The major active compounds include sesquiterpene lactone esters including helenalin, flavonoids, including flavonol glycosides, polyynes, volatile oils such as thymol, free fatty acids, caffeic acids such as chlorogenic acid, and hydroxycumarines.

Extract, tincture, and powder of arnica are administered topically as infusion, poultice, gel, plaster, oil, and ointment. The health hazards are primarily contact allergic and irritant dermatitis, but erosions and necrosis occur rarely (3). One death and one case of Sweet's syndrome have been reported. The literary giant Johann Wolfgang von Goethe ingested arnica tea to relieve angina in the 19th century (29). It is controversial regarding its safety with oral administration although it is used in cosmetic surgery (unpublished). One author suggests it should not be administered orally and another states the FDA considers arnica to be unsafe (13,22).

Cactus Pear (*Opuntia ficus-indica*)

This herb decreases oxidative damage to lipids and improves antioxidant status in healthy humans after oral supplementation. Vitamin C at a comparable dosage orally also enhances overall antioxidant defense but does not significantly decrease body oxidative stress (68).

Eucommia Ulmoides Oliver (EUOL)

This Chinese herb contains geniposidic acid which statistically significantly increased stratum corneum turnover in aging mice (69).

Ginseng (*Eleutherococcous senticosus, Panax ginseng, P. quinquefolius*)

The most potent species is Siberian ginseng which is *Eleutherococcus senticosus*. *Panax ginseng* is also from the Orient while *Panax quinquefolius* grows in America. This is a widely used oral herb that has recently entered cosmeceutical products without dermatologic studies or historical use in mucocutaneous disorders.

The major active ingredients of *Panax ginseng* are triterpene and steroid saponins known as ginsenosides, polysaccharides, aglycones, and polyynes. Eleutherococcus also contains steroid glycosides, hydroxycoumarins, phenylacrylic acids, and lignans (3). These actives all contribute to antioxidant, anti-inflammatory, anti-platelet, antitumor, and antiviral effects. Protein synthesis is also enhanced. The efficacy of oral ginsengs against systemic viruses is documented. Red ginseng applied topically appeared to inhibit chemically induced skin tumors in mice (29).

Ginseng is contraindicated in pregnancy, lactation, cardiac disease, and diabetes. Unfortunately 25% of 133 patients using ginseng for two years developed skin reactions. These also indicate ginseng abuse syndrome. Topical application to the face has induced postmenopausal vaginal bleeding. This herb increases effects of antidiabetic and anti-coagulant drugs, estrogen, and MAO inhibitors. It is administered as a powder for infusion (3).

Hibiscus (*Hibiscus sabdariffa*)

This is an Asian medicine for cutaneous inflammation and edema, carbuncle, scalding, and herpes zoster therapy. The active compounds include fruit acids (15–30%),

anthocyanidins, flavonoids, and mucilages. It is administered as tea. Hibiscus has no reported health hazards (3).

Jojoba (*Simmondsia chinensis*)

The galenic formulations of this herb are used in many products as an antioxidant thickener and to exfoliate skin for treatment of acne, psoriasis, sunburn, chapped skin, hair restorer and wounds although it is not approved for any cutaneous indication. The wax esters consist of 20–22 carbon atom length fatty acids arranged in waxy globules, alcohols, and 14% erucic acid. Health hazards include rare contact dermatitis and systemic toxicity (3,22).

Licorice (*Glycyrrhiza glabra and G. uralensis*)

The extracts of this herb are incorporated into cosmeceuticals to improve skin brightness but are used in Asian medicine for wounds and carbuncle therapy. The active components consist of triterpene saponins such as glycyrrhizin (3–15%), flavonoids including licoricidin, isoflavones such as glabridin, hydroxycoumarins including glycycoumarin, cumestans such as glycynol, sterols such as beta-sitosterol, and volatile oils including eugenol. Glycyrrhizin inhibit replication of varicella zoster, hepatitis B, cytomegalovirus, and HIV and stimulates IFN production. It is also anti-estrogenic, antistaphylococcal, antiprotozoal, anti-fungal, anti-yeast, antioxidant, anti-inflammatory, antiplatelet, anti-thrombin, anti-cancer and sebostatic effects. Glabridin is anti-inflammatory, antioxidant, and inhibits tyrosinase reducing UVB-induced erythema and pigmentation (3).

Licorice is administered by comminuted drug, powder, juice, decoction, and tea for infusions. This herb is contraindicated in pregnancy, lactation, hepato-, and renal toxicity and cardiac disease. It may induce rhabdomyolysis, pseudoaldosteronism, and hypokalemic alkylosis. Licorice interacts adversely with anti-arrythmic, antihypertensive, anticoagulant, and antidiabetic drugs, contraceptives, diuretics, laxatives, MAO inhibitors, and corticosteroid drugs (13,22).

Myrtle (*Myrtus communis*)

Cosmeceuticals incorporate this herb to calm the skin. The active compounds include monoterpenes and sesquiterpenes such as cineol and pinene. Tannins, acylphloruglucinols, and volatile oils are present. Antibacterial, fungicidal, and antiseptic effects result from the active molecules. It is administered as infusion. This herb is contraindicated in children and infants due to potential of including glottal spasm when used on the face. It should also be avoided in pregnancy and lactation (3).

Noni (*Morinda citrifolia*)

In 2003 and 2004 Noni was the largest selling single herb in the U.S. It has no reliable published clinical research. Noni's unproven uses are for many systemic diseases including diabetes, infections, fever, arthritis and wounds.

The active ingredients are iridoids including asperulosid. Topically, it is an emoltient used to reduce signs of skin aging. The active ingredients are iridoids including asperulosid, retinol, ascorbic acid, ursolic and linoleic acids (3,22).

Olive (*Olea europaea*)

The ancient Greeks had many uses for this plant and its by products. Olive oil has traditionally been used to treat burns, dermatitis, psoriasis, rosacea, and xerosis. The major components include 56–83% oleic acid, 8–20% palmitic acid, and 4–20% linoleic acid. Steroids including B-sitosterol and tocopherols are present. Extra virgin oil also has a significant amount of polar polyphenols which provide antioxidant effect and contribute to the anti-inflammatory function of olive oil. When applied to murine skin following UVB exposure, significantly fewer tumors developed. This herb is a weak irritant. An increasing number of cosmeceuticals incorporate olive oil into the formulation (70,71).

Papaya (*Carica papaya*)

This foodstuff enhances resolution of bruises and wounds. It is also used for cosmeceuticals to modify the appearance of scars. The juice from the unripened fruit is primarily papain, a mixture of proteinases, lipases, and phosphatases that additionally have anti-ulcerative, antimicrobial, and antihelminthic effects. This herb also contains polyketide alkaloids such as carpane, glucosinolates, saponins, and ficin. Papaya galenic extracts interact with warfarin, induce bleeding, and contact reactions. It is contraindicated in pregnancy. It has no reported health hazards (3).

Prickly Pear (*Opuntia streptacantha*)

The juice of this medicinal botanical soothes cutaneous wounds, burns, and dermatitis due to its mucilages consisting of mucopolysaccharides, sucrose, lignans, and fruit acids. It also is an antiviral against herpes simplex and HIV. This herb is administered as a powder or galenic for a variety of topical formulations. Prickly pear has no reported health hazards (22).

Pumpkin (*Cucurbita pepo*)

The German Commission E approved this herb for prostate therapy. Folk medicine uses pumpkin for helminthic infections. Pumpkin seeds comprise fatty oils (about 50% of total weight) including linoleic acid (55% of fatty oils) and oleic acid (25%). This extract is also rich in gamma-tocopherol, carotenoids including lutein, sterols, and the amino acid curcurbitin which is antihelminthic active (22). Pumpkin seed is antiphlogistic, antioxidant, and antihelminthic. This herb has no reliable published studies for any topical preparations or dermatologic disease (3,22).

There are no photoaging studies despite its use in cosmeceutical chemical peels and other products for nearly a decade.

The reported adverse reactions include gastrointestinal distress.

Rosemary (*Rosmarinus officinalis*)

This medicinal botanical soothes mucocutaneous tissue leading to its formulation into cosmeceuticals. It also has antimicrobial, antiviral, and antioxidant effects. Rosemary applied topically inhibited chemically induced murine epithelial tumors. The active components include flavonoids, triterpenes such as ursolic acid, diterpenes including carnosolic acid, and volatile oils in addition to caffeic and rosmarinic acids.

This herb is contraindicated in pregnancy and has a mild risk of sensitization (3).

Sandalwood (*Santalum album*)

This herb is an Asian therapy for heatstroke and sunstroke and for urethral inflammation in homeopathy. Preliminary data suggests it may be chemopreventive for cutaneous malignancy (57). The antiseptic and therapeutic effects result from tannins, resins, and volatile oils. Sandalwood is administered as oil. It has minimal potential for sensitization. It is contraindicated in pregnancy (3).

Sarsaparilla (*Smilax medica*)

This herb is a homeopathic remedy for pruritic and inflammatory cutaneous diseases including psoriasis, leprosy and syphilis. The active molecules include steroid saponins such as sarsasapogenin, phytosterols including beta-sitosterol, and quercetin. This preferred flavoring agent of the Old West is also an antiseptic and antipruritic. Sarsaparilla can induce asthma and renal failure. It is administered as a powder, decoction, and liquid extract (3,22).

Saw Palmetto (*Serenoa repens*)

This medicinal botanical has documented anti-androgenic, anti-estrogenic, anti-inflammatory, and anti-exudative effects. An unproven use is eczema therapy. Its major components are sitosterols and their glucosides, flavonoids, free fatty acids, and polysaccharides. Multiple blinded human trails document effectiveness in treating prostate disease. This compound has been introduced in at least two cosmeceuticals for photoaging and three for hair growth because of its documented inhibition of 5-alpha reductase. It is contraindicated in pregnancy and lactation and interacts with warfarin. This herb is administered in galenic formulations from comminuted herb (3).

Sesame (*Sesamum orientale*)

This herb is used in folk medicine to treat crusts and as a massage oil. The active ingredients are nearly completely fatty oils including linoleic and loeic acid (35-50% each), palmitic acid (10%), lignans, and sterols (3).

The lignan sesamine is immunosuppressive in vitro. No clinical studies have been published. It has limited risk of sensitization.

Spearmint (*Mentha spicata*)

The distinctive aroma is due to carvone which comprises 40–80% of the extracts of this herb. Other active compounds include caffeic acids such as rosmaric acid, flavonoids including thymonin, and volatile oils. These molecules provide spearmint with antimicrobial and insecticide activity (72).

This herb applied topically produced a statistically significant decrease in oxidative damage and tumor promotion as it decreased thymidine uptake. It is used for mucocutaneous inflammation, arthritis, neurogenic pain, urticaria and pruritis (22).

Wheat Germ (*Triticum aestivum*)

The oil of this medicinal botanical is used in cosmeceuticals to dissolve dirt and makeup and as a skin protectant. The active components include 60–75% triacylglycerols, 50–65%

linoleic acid, 15–22% oleic acid, 7–18% palmitic acid, and 9–14% phospholipids. Wheat germ oil also contains other active compounds including glycolipids, sterol esters, tocopherol, tocotrienols, and carotenoids. It has minimal risk of sensitization. This oil is administered orally or topically (3).

White Birch (*Betulae folium*)

This herb is included in cosmeceuticals to decrease fine lines because of its relatively high concentration of ascorbic acid, OPCs, and flavonoids including hyperoside and quercetin. Other actives include caffeic acids, such as chlorogenic acid, D-glucosides, monoterpene glucosides, and sesquiterpene oxides. This herb is used to treat hair loss and dandruff. White birch is administered as comminuted herb for tea and topicals. There are no reports of sensitization but use with caution in people with renal failure (3).

German Commission E Approved Herbs

Herbs approved by the German Commission E for treatment of mucocutaneous indications not previously discussed are listed alphabetically below. Familiarity with these medicinal botanicals is important because these herbs should be among the most likely candidates for incorporation into future cosmeceuticals. Several have very recently been formulated into novel cosmeceuticals due to the confidence in their known biologic activity, mechanisms of action, and relative safety. Human clinical trials are needed to document any cutaneous efficacy with these formulations just as in the previous group of botanicals.

Agrimony (*Agrimonia eupatoria*)

This herb is approved for treatment of inflammation of cutaneous and mucosal tissues. Asian medicine uses it for hemostyptic effects. Agrimony acts as an astringent due to the active compounds being catechin tannins. This herb is administered by decoction for poultice. There are no reported health risks with agrimony (3).

Bittersweet Nightshade (*Solanum dulcamara*)

This herb is approved to treat warts, acne, dermatitis, and furuncles. It is homeopathy for skin infection. The active compounds include steroid alkaloid glycosides and steroid saponins. The glycosides account for the stimulation of phagocytosis, hemolytic, cytotoxic, antiviral, anticholinergic, anesthetic, and desensitizing effect. The saponins promote resorption of the glycosides. Bittersweet nightshade is administered as decoction and tea for compress and rinse. This medicinal botanical is contraindicated in pregnancy and lactation (3).

Butcher's Broom (*Ruscus aculeatus*)

This medicinal botanical is approved to treat venous conditions including venous insufficiency and hemorroids. The therapeutic activity is due to increasing venous tone while reversing inflammation. The major active compounds include steroid saponins ruscine and ruscoside which comprise 5% of the extract by weight. The other group of active compounds include benzofuranes including euparone. These extracts are orally administered as capsules with only rare gastrointestional adverse reactions reported (3).

Cajuput (*Melaleuca leucadendra*)

This herb is approved to treat wounds and burns and reverse a tendency toward infection. The antimicrobial and rubefacient effects are produced by cineol, terpineol, and other sesquiterpenes and phenones. Cajuput is administered as oil but must not be applied to the face of infants or children due to potential glottalspasm or bronchospasm. Contact allergic reactions rarely occur. This herb must not be ingested (3).

Chaste Tree (*Vitex agnus-castus*)

Known as Vitex, this medicinal botanical is approved for treating premenstrual acne with oral administration. The active compounds include flavonoids such as casticin, glycosides, fatty, and volatile oils. It suppresses follicle-stimulating and luteinizing hormone levels to increase progesterone and reduce estrogen levels. The main adverse effects are gastrointestinal tract distress and allergic eruptions (29).

English Plantain (*Plantago lanceolata*)

The extracts of this herb are approved to treat cutaneous and mucosal inflammation. The active compounds include mucilages such as glucomannans, monoterpenes including aucubin, flavonoids such as apigenine glucoside, caffeic acids including chlorogenic acid, hydroxycoumarins such as aesculetin, silicic acid, tannins, and saponins. Therapeutic effects include acceleration of hemostasis and enhanced epithelialization and are bactericidal. Monoterpenes and saponins account for most of these effects. There are no health hazards reported with English plantain. It is administered as a liquid extract, juice, or tea for lozenge or infusion (3).

Fenugreek (*Trigonella foenum-graecum*)

This herb is approved to treat inflammatory cutaneous diseases. It acts as soothing emollient via its major active compounds mucilages including mannogalactans which account for 25–45% of the extract. Proteins comprise another 25–30% of the extract, while steroid saponins including trigofoenosides and foenugracein account for about 15%. Trigonelline, sterols, volatile oils, and flavonoids such as orientin and vitexin are the other active compounds. Topical sensitization is rare. Fenugreek must not be administered during pregnancy (3).

Flax (*Linum usitatissimum*)

This medicinal botanical is approved to treat inflammatory cutaneous disorders. Asian medicine employs flax to treat superficial infections. This herb functions as a soothing anti-inflammatory emollient due to the linolenic, linoleic, and oleic acids which combined comprise 30–45% of the extract weight. Proteins account for another 20–27% of the extract while mucilages comprise about 10%. Antioxidant, antimycotic, and estrogenic effects result from lignans, whose most abundant source is flax. Cyanogenic glycosides and phenylpropanes are the other active compounds in this extract.

The adverse cutaneous reactions have only been reported to linseed, the oil extracted from flax. They include irritation, erythema, eyelid edema, and one case of an anaphylaxis (3,13,22). Flax is administered as a cracked or ground seed, powder, linseed oil, or a poultice.

Heartsease (*Viola tricolor*)

Heartsease is approved for treatment of cutaneous inflammation and sehorrheic dermatitis in infants. Homeopathy employs it for eczema therapy. The active compounds function as soothing anti-inflammatory emollients. Mucilages account for 10% of the extract by weight. Other actives include tannins, salicylic acid (0.3%) and other phenolics, flavonoids including rutin, saponins, and vitexin, and hydroxycoumarins such as umbelliferone. This herb has no reported health hazards.

Heartsease is administered by powder, decoction or tea for infusion, bath additive, ointment, and shampoo (3).

Horsetail (*Equisetum arvense*)

This herb is approved for treatment of wounds and burns. The major active compound is the astringent silicic acid which comprises 5.0–7.7% of the extract by weight. Flavonoids such as apigenin glucoside contribute to the astringent effect. Other actives are caffeic acids including chlorogenic acid and pyridine alkaloids such as nicotine. Horsetail should not be used in patients with cardiac or renal compromise even topically (13). The liquid extract is administered as a decoction or tea for infusion or compress (3).

Jambolan (*Syzygium cumini*)

The extract of the bark of Jambolan is approved for treatment of cutaneous and mucosal inflammatory diseases but the seed extract is not. It has similar use in Asian medicine. The therapeutic effect is as an astringent primarily due to the tannins such as ellagic acid. Other active compounds include sterols such as beta-sitosterol, triterpenes including eugenin, and flavonoids such as myricetin and kaempferol. There are no reported health hazards with Jambolan. It is administered as a powder or decoction for a gargle, infusion, or compress (22).

Lavender (*Lavandula angustifolia, L. officinalis*)

Lavandula officinalis was used by the ancient Greeks for its fragrant essential oil. English lavender (*Lavandula angustifolia*) is approved for balneotherapy for circulatory disorders. Tannins comprise 13% of this extract by weight. Other active compounds include volatile oils of which linalool and linoyl acetate comprise 90%, and hydroxycoumarins such as umbelliferone, caffeic acids including rosmaric acid, flavonoids, and triterpenoids are the active molecules. Lavender oil inhibits mast cell degranulation and has antimicrobial and antiphlogistic effects (73).

Lavender has weak sensitization potential but cross reacts rarely with TTO (13). It is administered as a liquid extract for tea, infusion, poultice, bath additive, or other topical formulations (3).

Marigold (*Calendula officinalis*)

The flower of this medicinal botanical is approved to treat wounds, burns, and mucosal inflammation. The above ground parts of the Marigold plant are not approved for therapy. This herb is homeopathy for frostbite, burns, and poorly healing wounds. The therapeutic mechanisms include antimicrobial activity to *Staphylococcus aureus*, *Klebsiella pneumoniae*, Candida species, and HIV. Acceleration of granulation tissue, angiogenesis, and epithelialization of wounds are additional therapeutic effects. Faradiol is a terpene alcohol extracted from Marigold with anti-inflammatory effect equivalent to indomethacin

in two animal studies. The major active compounds include polysaccharides such as arabinogalactans which comprise 15% of the extract by weight and triterpene saponin glycosides which comprise 2-10%. Other active compounds include flavonoids such as quercetin glycoside, hydroxycoumarins including scopoletin, volatile oils such as cadinol, and carotinoids including lutein and zeaxanthine.

A very low risk of sensitization (0.2%) is the only health hazard. Marigold flower is administered as a liquid extract, powder, tincture, tea, or decoction for infusion, oil, gel, ointment, solution, and shampoo (3).

Oak (*Quercus robar*)

This herb is approved for treatment of cutaneous and mucosal inflammatory disorders due to its astringent, antiviral, antihelminthic, and antiphlogistic effects. All of the therapeutic activity resides in the multiple tannins which account for 12–16% of the extract by weight. The catechin tannins include monomeric and dimeric catechins, oligomeric proanthocyanidin, and leucocyanidins (3).

The only health hazard occurs with whole body baths for "widespread open" wounds or dermatitis if the patient has cardiac insufficiency stages III and IV and hypertomia stage IV. Oak is administered as powder or tea as a bath additive (22).

Oat (*Avena sativa*)

Oat straw is approved for treatment of cutaneous inflammation, pruritis, varicella and warts. The oat herb and fruit are not approved for therapy. The active compounds include oligosaccharides and polysaccharides including beta-glucan, silicic acid, steroid saponins such as avencoside, amino acids such as avenic acid, and flavonoids including vitexin, apigenin and tocotrienols. The anti-inflammatory effect results from several of these actives. Beta-glucan inhibits prostaglandin biosythesis yet stimulates cell-mediated immunity which provides antiviral and antitumor functionality.

There are no reported health hazards with oat straw. It is administered as decoction, tea, or tincture for bath additive and other topicals (3,22).

Peruvian Balsam (*Myroxylon balsamum*)

This resinous herb is from scorched tree trunks while Tolu balsam is a resin from incised tree trunks of the same plant. Peruvian balsam is approved for treatment of wounds, burns, and hemorrhoids while Tolu balsam treats mucosal inflammation by homeopathy.

Balsams treat wounds as an antiseptic and promoting granulation. Peruvian balsam is also antiparasitic especially for scabies due to benzyl benzoate and benzyl cinnomoate which combined comprise 50–75% by weight. Resins consisting of cinnamic ester polymers comprise another 20–30%. Volatile oils such as nerolidol are other active compound extracted from this herb. There are significant mucocutaneous reactions to both balsams including allergic contact dermatitis, contact urticaria, oral ulcers, purpura, angioedema, photosensitivity, and phototoxicity. Renal failure with widespread topical use has been reported (3,22).

Pineapple (*Ananas comosus*)

This foodstuff is also approved for therapy of wounds and burns. The activity is due to a mixture of five cysteine proteinases known as bromelain. These enzymes stimulate wound

healing by providing fibrinolytic and proteolytic activity while inhibiting thrombocyte aggregation. Bromolain also has anti-inflammatory and antineoplastic effects. The health hazards of pineapple consist of contact allergic and irritant reactions. Pineapple extract is administered as tablets or granules or in compounded topical formulations (3).

Poplar (*Populus species*)

Poplar leaf buds, but not the bark, and leaves, are approved to treat wounds, burns, and hemorrhoids due to the antiphlogistic, antibacterial, analgesic, and wound healing effects. The active compounds are primarily salicylic acid glycosides and esters such as salicin and populin. Flavonoids including propolis and chrysin, zinc lignans, and the volatile oil caryophyllene are the other active compounds.

This herb is contraindicated in hypersensitivity to salicylates, peruvian balsam, and propolis. The cutaneous health hazards consist of allergic and irritant contact dermatitis. Poplar leaf buds are administered as topical semisolid extracts (3).

Sage (*Salvia officinalis*)

This flavoring and medicinal botanical is approved to treat excessive perspiration, burns, and wounds. Its most frequent use in homeopathy is also for excessive perspiration. The active compounds are caffeic acids such as chlorogenic acid, triterpenes including ursolic acid, diterpenes such as carnosolic acid, volatile oils including thujone and camphor and flavonoids such as apigenin- and luteolin-7-glucosides. These active compounds provide astringent, secretolytic, antiperspirant, fungistatic, virostatic, and bactericidal effects.

This herb is contraindicated in pregnancy but has no other health hazards. It is administered via juice, tincture, and distillate for infusion, gargle, rinse, compress, and poultice (3).

Shepherd's Purse (*Capsella bursa-pastoris*)

This herb is approved for treatment of burns and wounds. It is homeopathy for mucosal bleeding. The active compounds consist of caffeic acids such as chlorogenic acid, flavonoids including rutin, glucosinolates, sinigrin, and cardioactive steroids. Shepherd's purse is contraindicated in pregnancy and used with caution in widespread cutaneous lesions. It is administered by tea for infusion (3).

Sweet Clover (*Melilotus officinalis*)

Hemorrhoids, venous conditions including insufficiency, and blunt injuries are approved indications for this herb. It has antiphlogistic, anti-exudative, and anti-edematous effects while it improves venous reflux, lymphatic kinetics, and wound healing. The active compounds include free coumarins including melilotol, hydroxycoumarins such as umbelliferone, flavonoids including kaempferol glycosides, triterpene saponins such as melilotigenin, and volatile oils (3).

Oral administration may lead to hepatoxicity. No cutaneous sensitization or irritation has been reported, but red clover (*Trifolium pratense*) is a mutagen (13). Sweet clover is administered as a comminuted herb for galenic formulation for infusion, poultice, ointment, suppository, and herbal sachet (3).

Walnut (*Juglans regia*)

This foodstuff is approved for treatment of excessive perspiration and cutaneous inflammation, including abcesses, acne, dermatitis and ulcers. Asian medicine employs it as an antihelminthic and aphrodisiac. The active compounds include tannins such as galloylglucose, flavonoids such as hyperoside, and the naphthalene juglone which accounts for the staining effect. The therapeutic effects with include astringent, antibacterial, antiviral and fungistatic (3).

Juglone is mutagenic inducing leukoplakia and tongue carcinoma (3,22). No other health hazards are reported. Walnut is administered by decoction for infusion.

White Nettle (*Lamium album*)

Treatment for cutaneous and mucosal inflammation is among the approved indications for this herb. It is used in Asian medicine to treat carbuncles and inflamed wounds. White nettle functions as an astringent and emollient due to the active mucilages, flavonoids including kaempferol glycosides, caffeic acids such as chlorogenic acid, triterpene saponins, and monoterpenes including lamalbide.

There are no reported health hazards. This herb is administered by tea for infusion, bath additive, poultice, compress, and rinse (3).

SUMMARY

There are multiple herbs currently incorporated into cosmeceuticals with valid scientific rationale and supported with human clinical studies or have documented biologic activity by in vitro, in vivo, or animal studies. Cosmeceuticals containing these herbs may currently be or potentially will be valuable contributions to dermatology and skin care if clinical efficacy can be confirmed by controlled human clinical trials conducted by third-party researchers with the finished marketed product. The cosmeceutical only has scientific integrity if the herbal components are stable, of therapeutic concentrations, and can be adequately delivered across human stratum correum.

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20
Topical Anti-inflammatories

Bryan B. Fuller and Dustin R. Smith
*Department of Biochemistry and Molecular Biology, University of Oklahoma
Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.*

INTRODUCTION

Inflammatory skin diseases are extremely common dermatological problems that present in a variety of forms, from occasional rashes accompanied by skin itching and redness to more chronic conditions such as atopic dermatitis, rosacea, seborrheic dermatitis, and psoriasis. Combined, these conditions affect over 35 million Americans who annually spend over $2 billion to treat their symptoms. This chapter will provide an overview of the inflammation process, review current drug, over-the-counter (OTC), and cosmetic topical treatments for several inflammatory diseases, discuss research approaches that can be used to identify new anti-inflammatory compounds to treat various aspects of inflammation, and finally, provide an overview of how topical formulations containing novel anti-inflammatory compounds can be developed and characterized.

BIOLOGY OF SKIN INFLAMMATION

Skin inflammation, which is characterized by redness, swelling, heat, itching, and pain, can exist in either an acute or chronic form with acute disease frequently progressing to a more chronic condition. Acute inflammation can result from exposure to UV radiation (UVR), ionizing radiation, allergens, or to contact with chemical irritants (soaps, hair dyes, etc.). Assuming that the triggering stimulus is eliminated, this type of inflammation is typically resolved within one to two weeks with little accompanying tissue destruction. A chronic inflammatory condition, however, can last a lifetime, and cause considerable damage to the skin. Some of the cellular and biochemical events which occur in the skin in response to a triggering stimuli (e.g., UVR, chemical, or antigen) and which lead to an inflammatory response are shown in Figure 1. Within minutes of exposure of skin to an insult there is a rapid release of inflammatory mediators from keratinocytes and fibroblasts and from afferent neurons. In response to a triggering stimulus, keratinocytes produce a number of inflammatory mediators including PGE-2 and TNF-alpha as well as the cytokines, IL-1, IL-6, and IL-8. Dermal fibroblasts also respond to the insult and to IL-1 produced by keratinocytes by increasing production and secretion of cytokines including IL-1, IL-6, IL-8 as well as PGE-2. One of the principal actions of PGE-2 produced and secreted by both keratinocytes and fibroblasts is to increase vasodilation and vascular
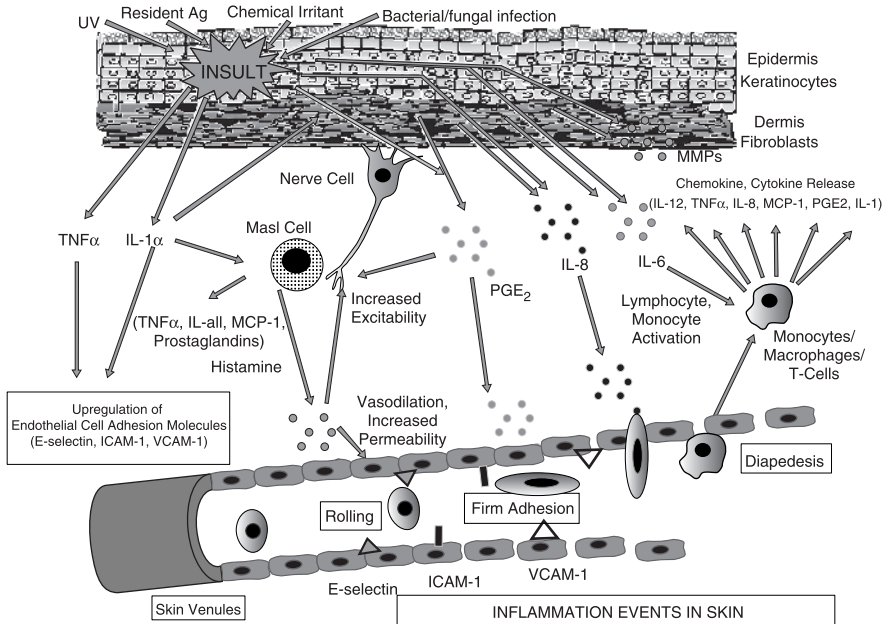
Figure 1 Diagram of cellular events which occur during a cutaneous inflammatory response.

permeability. In addition, PGE-2 aids in the degranulation of mast cells and increases the sensitivity of afferent neuronal endings. The increased sensitivity of nerve endings by prostaglandins and cytokines results in the release of neuropeptides, including substance P and calcitonin gene related peptide (CGRP) (1). Neuron depolarization also increases resulting in the sensation of pain. Substance P and CGRP released by neurons, along with PGE-2, cause degranulation and release of histamine from mast cells, and they also stimulate the cell to produce a variety of inflammatory cytokines. If IgE is bound to its receptor on mast cells, exposure of skin to an IgE specific antigen can also trigger the degranulation and activation of the mast cell (2,3). Increased vasodilation and vascular permeability by PGE-2 and histamine leads to increased blood flow and extravasation of fluid from blood vessels. This causes visible redness and swelling in the inflamed area. The increased production of inflammatory mediators by keratinocytes and fibroblasts, particularly TNF-alpha and IL-1, leads to the expression of intracellular adhesion molecules, such as VCAM and ICAM, on endothelial cells of the blood vessels (4). These proteins, as well as P and E selectin, serve as anchoring elements for monocytes and neutrophils passing through the blood. The attachment of these leukocytes to the adhesion molecules slows their movement through the bloodstream and finally causes their firm adhesion to the endothelial wall (5). In the presence of chemokines, particularly IL-8 produced and released by both keratinocytes and fibroblasts, the adherent leukocytes undergo chemotaxis and migrate from the blood vessel out into the skin where they act to scavenge the area of debris and also produce additional inflammatory mediators. The initial acute response occurs within minutes of the insult to the skin and involves the production of inflammatory mediators, the degranulation of mast cells, and the vasodilation of blood vessels (6). The subsequent movement of neutrophils and monocytes into the "wounded" area typically takes up to 48 hours to occur. If the triggering stimulus is eliminated, inflammatory mediator production by keratinocytes,

fibroblasts, and mast cells ceases, the influx of leukocytes to the "wounded" area decreases and inflammation subsides.

In contrast to acute inflammation which typically resolves in one to two weeks, chronic inflammation results from a sustained immune cell mediated inflammatory response within the skin itself and is long-lasting. Antigen presenting cells (APCs) in the skin, called Langerhans cells in the epidermis and dendritic cells (DCs) in the dermis, can be activated by innate mechanisms and by exposure to the inflammatory cytokines, IL-1 and TNF-alpha, produced by fibroblasts and keratinocytes in response to a triggering stimulus. The activated APCs bind to and transport skin antigens (allergens) through the lymphatics during which time they undergo a maturation process. This maturation step allows the APCs to efficiently present the antigen to T-lymphocytes. This presentation, in turn, triggers the maturation of a specific subset of naïve T-lymphocytes into memory cells and the activation of resident antigen specific T-lymphocytes. The skin-homing T-lymphocytes, which express a cell surface epitope, termed cutaneous lymphocyte antigen (CLA), migrate to the involved area of skin, and adhere to endothelial cell walls initially through an interaction between the CLA expressed on the surface of the T-lymphocyte and E-selectin expressed on endothelial cells (7). Other specific receptors on T-lymphocytes, which aid in the binding and chemotaxis of these cells into the skin, include CCR4 and LFA1 (8). Once T-lymphocyes have migrated into the skin from the circulation, they not only undergo proliferation, but also produce and secrete a wide range of inflammatory mediators as well as matrix-eroding enzymes, such as matrix metalloproteinase-1 (MMP-1; collagenase). Cytokines produced by T-lymphocytes can stimulate fibroblasts and keratinocytes to produce additional cytokines and chemokines, and can also induce the expression of a variety of tissue-destructive enzymes by fibroblasts, including MMP-1 (collagen), MMP-3 (stomelysin-1) and MMP-9 (gelatinase B). As long as the antigen or insult stimulus persists in the skin, the inflammatory response will continue, resulting in significant and serious tissue destruction (9).

Inflammatory processes in the skin, particularly those triggered by long-term exposure to solar radiation, not only cause the more obvious symptoms of redness, swelling, and itching, but also trigger molecular pathways that escalate the aging process. Actinic aging, or photoaging, that occurs following prolonged exposure of the skin to ultraviolet (UV) light from the sun results in increased cytokine production with attendant activation of genes in both keratinocytes and fibroblasts that cause erosion of the normal skin structure. Matrix metalloproteinases (MMPs), which break down the skin extracellular matrix causing sagging and wrinkling, are stimulated in sun-exposed skin. Furthermore, dermal fibroblast synthesis and assembly of collagen, which is required to maintain and restore the extracellular matrix, is inhibited while elastin production is over-stimulated, leading to elastosis. It is now widely accepted that sun-exposed skin in most individuals remains in a constant state of low level UV-induced inflammation, and that this "smoldering" inflammation is responsible for the signs of skin aging that appear in middle age (10–12).

PRESCRIPTION AND OVER-THE-COUNTER TREATMENTS FOR INFLAMMATION AND MECHANISM OF ACTION

Steroids

Given the complexity of the inflammatory process in skin, developing topical products that can effectively resolve the myriad of inflammatory disease states that exist is challenging. By far the most effective and commonly used prescription drugs for treating inflammation are the corticosteroids, particularly the glucocorticoid related steroids. They are very

effective for many forms of eczema, including atopic dermatitis, allergic contact dermatitis, seborrheic dermatitis (in concert with an anti-fungal agent), and have some utility in ameliorating the symptoms of psoriasis. They are not particularly effective, however, in treating acute inflammation, like UVR-induced sunburn, which is not primarily an immune cell driven inflammatory response. Corticosteroids can be used topically or orally. Topical corticosteroids have been classified into groups based on potency. For example, the corticosteroid clobetasol proprionate is ranked as a very potent steroid, while betametasone diproprionate and fluocinolone acetonide can range from potent to moderately potent. OTC topicals containing hydrocortisone are, of course, the least potent (13). Although newer methods are being studied, topical steroid potency is still determined using the MacKenzie vasoconstrictor assay established over 40 years ago. In this assay, a topical steroid is applied to the forearm and the extent and duration of skin blanching due to vasoconstriction assessed by visual examination and rated on a scale of 0 (normal skin, no blanching) to 4 (intense blanching). Although subject to variability, the assay has proved to be a reliable estimate of corticosteroid potency (14).

Given the efficacy of corticosteroids in treating many different types of skin inflammation as well as efficacy in treating autoimmune-based inflammatory diseases such as rheumatoid arthritis, asthma, lupus erythematosus, and allergic rhinitis, considerable research has been directed toward understanding their mechanism of action.

Corticosteroids act on target cells by binding to the glucocorticoid receptor present primarily in the cytosol. This binding "activates" the receptor, resulting in its translocation to the nucleus. The steroid hormone receptor complex then binds, as a homodimer, to DNA regulatory elements along the promoter regions of specific genes. This binding usually results in the up-regulation of gene activity but can also cause transcriptional repression of the target gene (15). The effectiveness of corticosteroids as inhibitors of inflammation stems from the ability of the steroid activated glucocorticoid receptor complex to interfere with the activation of genes regulated, principally, by two transcription factors, NF-kappa B and AP-1 (16,17). These two transcription factors are primarily responsible for the transcriptional activation of a wide variety of pro-inflammatory genes including those for cytokines IL-1, IL-2, IL-3, IL-4, IL-6, IL-11, IL-12, and IL-13, TNF-alpha, and GM-CSF, the chemokine genes IL-8, RANTES, MCP-1, the adhesion molecules ICAM-1, VCAM-1, and E-selectin, the rate-limiting enzyme for PGE-2 production, COX-2, and the matrix-metalloproteinase genes, including MMP-1 (18).

A diagram showing the signaling pathway in cells that leads to the activation of either NF-kappa B or AP-1 and, thus, to the activation of inflammatory genes is shown in Figure 2. Briefly, when a surface receptor on a target cell binds a specific ligand, such as a hormone or cytokine, the receptor is "activated" and this in turn leads to the activation of a signal cascade within the cell. The signaling pathway involves a variety of kinases which are sequentially activated. In the case of the NF-kappa B activation pathway, one of these kinases, IKK, when activated, phosphorylates the protein IkB. This protein, in its unphosphorylated state, binds to NF-kappa B in the cytosol and prevents NF-kappa B from translocating to the nucleus and activating target genes. When IkB is phosphorylated by IKK, it dissociates from NF-kappa B and is degraded. Once freed from the IKB, NF-kappa B can translocate to the nucleus where it binds to the promoter region of specific genes and activates them (19).

As mentioned above, while many inflammatory genes are activated by NF-kappa B, others are regulated by the transcription factor AP-1. This transcription factor is a dimer consisting of either a Jun-Fos heterodimer or a Jun-Jun homodimer. For most cytokine genes, only the Jun-Fos heterodimer functions as a transcriptional activator. As is shown in Figure 2, binding of a ligand such as IL-1 or TNF-alpha to its receptor activates a signaling
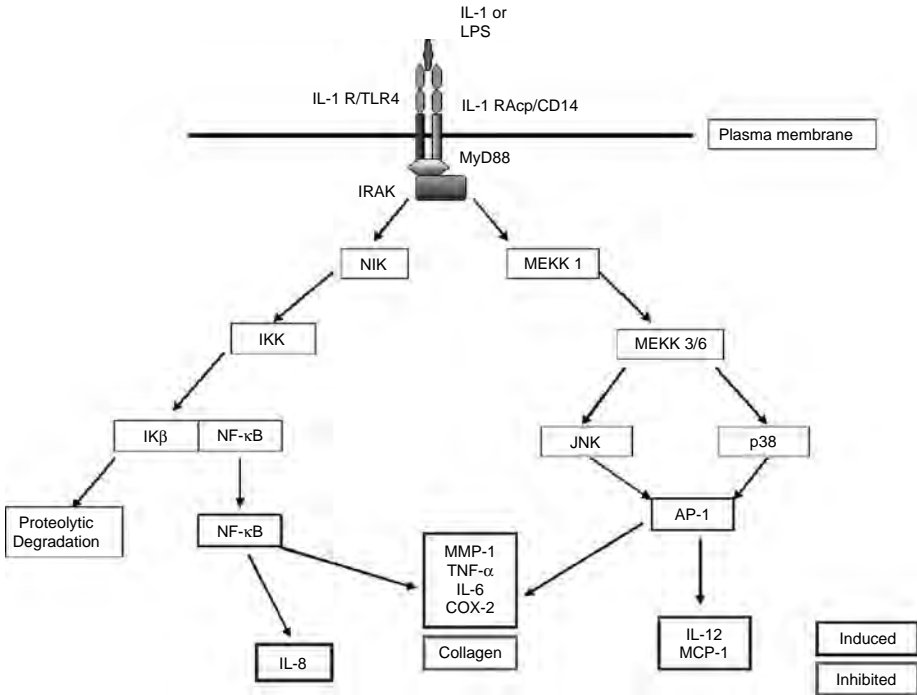
Figure 2 Intracellular signaling cascade leading to the activation of inflammatory genes.

cascade that involves sequential activation of a variety of kinases, some of which are members of the MAP kinase family. Either one of two members of this family, JNK (c-Jun N-terminal kinase) or p38 map kinase, when activated by this signaling cascade, phosphorylates, and activates c-Jun and this forms a dimer with the Fos protein to form the functional transcription factor. The Jun-Fos heterodimer will only form if Jun is first phosphoryated by JNK. The Jun-Fos heterodimer forms the AP-1 complex that activates inflammatory target genes (16).

While some genes are regulated only by either NF-kappa B or AP-1 other inflammatory genes have both an NF-kappa B and AP-1 binding site in their promoter regions and, thus can be regulated by either or both transcription factors. Recent data suggests that the control of gene activity by either AP-1 or NF-kappa B depends on both the placement of the transcription factor binding site along the promoter region of the gene and on the level of expression of the transcription factor. To some extent the transcription factor binding site that is closest to the start of transcription plays a predominant role in regulating the activity of the gene. Thus, for example, the MCP-1 gene is strongly regulated by the AP-1 site that lies close to the transcription start site even though there are three NF-kappa B binding sites in the promoter of this gene. Examples of the placement of NF-kappa B and AP-1 transcription factor binding sites in the promoter regions of some inflammatory genes are shown in Figure 3.

As mentioned above, the anti-inflammatory activity of corticosteroids comes from their ability to repress either the activation or activity of the NF-kappa B and AP-1 transcription factors thereby suppressing transcription of genes coding for inflammatory mediators. In the case of NF-kappa B, the actual mechanism of action of the glucocorticoid receptor complex in repressing inflammatory genes activated by this transcription factor is not well understood, but evidence suggests a couple of likely possibilities. One mechanism
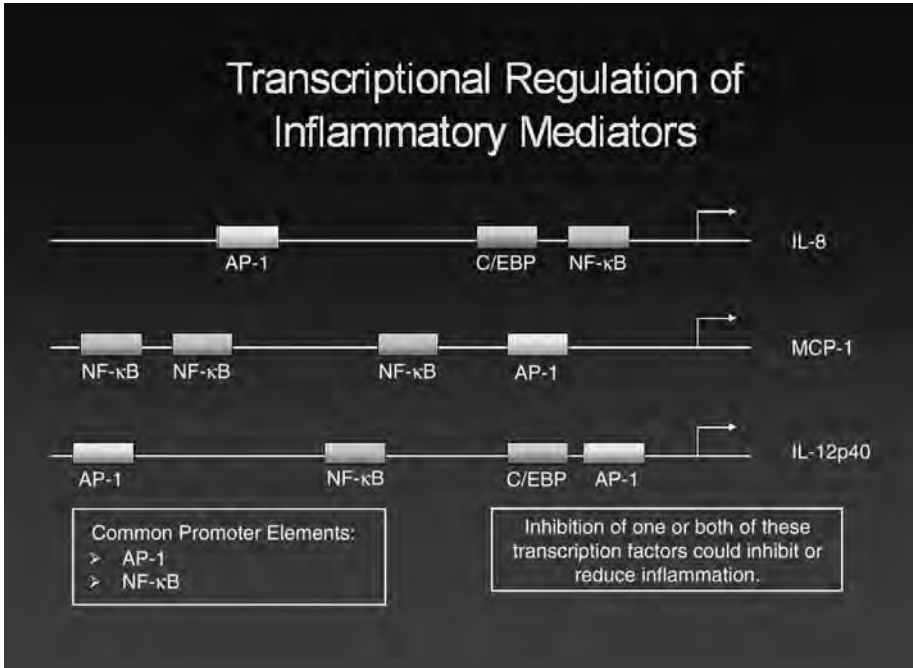
Figure 3 Diagram of transcriptional elements that regulate the activation of inflammatory genes.

involves the steroid activated glucocorticoid receptor up-regulation of the gene coding for IKB. This produces a cellular excess of this protein which then complexes to and inactivates NF-kappa B, preventing its translocation to the nucleus.

Other data suggests that the glucocorticoid receptor does not block the translocation of NF-kappa B but rather inhibits either binding of the transcription factor to its regulatory site in the promoter region of target genes or alternatively interferes with NF-kappa B's ability to activate the target gene after binding the promoter region (19–22). Regardless of which specific mechanism is correct, the end result of corticosteroid activation of the glucocorticoid receptor is the repression of NF-kappa B activity and a down-regulation of inflammatory gene activity. In regard to the suppression of the AP-1 stimulation of genes, recent evidence suggests that glucocorticoids block AP-1 phosphorylation and activation by two mechanisms. First, glucocorticoids can suppress AP-1 activity by physically interacting with the Jun component of the dimer, thereby blocking its binding to fos and preventing the formation of an active complex. Secondly, recent studies show that glucocorticoids stimulate the transcription of the MAPK phosphatase-1 gene thereby increasing its abundance in the cell and blocking the phosphorylation of Jun (16).

While the glucocorticoids have been shown to be extremely effective in suppressing the activation of pro-inflammatory genes because of their ability to block NF-kappa B and AP-1 functioning, steroids produce a variety of undesirable side effects. First, due to their potent inhibition of genes involved in an immune cell driven inflammatory response, they have an overall immune suppressive effect. Prolonged use of glucocorticoids leads to a reduction in B- and T-lymphocyte populations, and a reduced ability to fight skin infections. Further, steroids adversely affect the ability of dermal fibroblasts to synthesize collagen and at high doses they reduce the proliferation rate of these cells. Consequently, long-term use of topical steroids can lead to skin thinning and a decrease in the dermal matrix. Other potential negative side effects caused by prolonged use of steroids include

altered carbohydrate metabolism, suppression of the hypothalamic-pituitary-adrenal axis, increased osteoporosis, and increased risk of developing cataracts.

Due to the undesirable side effects which limits the length of time steroids can be used to treat inflammatory diseases, non-steroidal topical therapeutics have been developed to treat inflammation. One group of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years as oral drugs to control inflammatory responses.

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

The most well-known of all the NSAIDS, aspirin, has been used for over 100 years to control various forms of inflammation and today Americans consume over 80 billion tablets of aspirin a year. NSAIDS are available in OTC and prescription forms. Common OTC forms are ibuprofen, naproxen, aspirin, and acetaminophen. Those available with a prescription include celecoxib (Celbrex®), diclofenac (Votaren®), etodolac (Lodine®), indomethacin (Indocid®), ketoprofen (Orudis®) and Rofecoxib (Vioxx®) to name a few. While many topical forms of NSAIDs including Voltaren Emulgel®, Indocid® (indomethacin), Nidol® (nimesulide), Feldene gel® (piroxicam), Oruvail® (ketoprofen), and Pennsaid® (diclofenac) are available in Europe and elsewhere without prescription, in the U.S. none are available as either OTC or prescription drugs (23). One topical prescription NSAID that has received FDA approval in the U.S. is Solareze® (diclofenac) which is indicated for the treatment of actinic keratoses (24). Perhaps due the availability of topical NSAIDS in Europe but not in the U.S., a number of non-FDA approved topical NSAID products have now emerged for sale without a prescription on various Web sites. These include such products as ProzRelief® (12% ibuprofen) and IbuCream (10% ibuprofen).

When one examines the published data on the efficacy of topical NSAIDS in treating various inflammatory symptoms, the results show considerable disparity. A statistical analysis of clinical data from a wide number of trials with various topical NSAID preparations for treating inflammation associated with arthritis concluded that while relief from symptoms was higher in the NSAID group versus the placebo group for the first two weeks, after that time, there was no measurable difference between the two treatment groups (25). Many other reports, however, do suggest that topical NSAID treatment for joint pain provides relief beyond that observed with the placebo group (26,27). A very recent clinical study with over 200 patients suffering from knee osteoarthritis found that the topical application of diclofenac provided significantly more effective relief from pain and stiffness than the vehicle control group (28). In another recent study, the product, Nidol®, which contains 2% of the COX-2 inhibitor, nimesulide, was found to be significantly more effective than topical diclofenac in reducing the pain of shoulder periarthritis (29). Considering that few studies have yet to evaluate topical formulations containing newer NSAIDs, including the specific COX-2 inhibitors, and considering that few topical formulations for NSAIDs have been developed and optimized, there is a considerable amount of research to be carried out to fully assess the efficacy of topical NSAIDs in treating inflammation (30,31). Certainly, it seems likely that a topical preparation of a potent NSAID that delivers adequate levels of an effective COX inhibitor through the skin would likely be effective in treating a variety of inflammatory conditions in which PGE-2 is indicated as a causative factor. Such products would be preferred over the use of oral dosing because of minimal risk topically applied NSAIDs present for stomach irritation.

The mechanism of action of NSAIDs involves the inhibition of prostaglandin production, particularly PGE-2. The common target for NSAIDS is the enzyme

cyclooxygenase (COX), which exists in two forms, COX-1, and COX-2. While most older versions of NSAIDS including aspirin, ibuprofen, and acetaminophen are not selective inhibitors of any particular form of COX, newer drugs have been designed to target primarily COX-2. The effort to design COX-2 specific inhibitors stems from findings that COX-1 plays a protective role in preserving the stomach lining, and thus, NSAIDs that target both COX-1 and COX-2 can erode the stomach lining and cause ulcer formation when taken orally (32,33). This deleterious side effect would however, likely be significantly reduced with topically applied NSAIDS. If so, COX inhibitors, whether specific for COX-2 or not, could be used with equal effectiveness in treating symptoms of inflammation.

Perhaps one of the most obvious and effective uses of a topical NSAID would be to treat the symptoms associated with sunburn. This type of inflammation is primarily driven by the UVR-induced production of PGE-2, which, as mentioned above, causes vasodilation, enhances sensitivity of nerve endings, causes histamine release from mast cells, and stimulates the production of additional inflammatory mediators in fibroblasts. By blocking or reducing the UVR-induced production of PGE-2 from keratinocytes and fibroblasts it should be possible to minimize the onset and progression of a sunburn. Thus, it seems likely that the topical use of a COX inhibitor might be able to not only slow the progression of a sunburn but decrease the magnitude of the UVR induced erythema. At present in the U.S. there are no topical prescription or OTC drugs that either effectively prevent the onset of sunburn (other than sunscreens that simply block UVR at the skin's surface) or eliminate existing erythema resulting from a sunburn. Topical steroids have been shown to reduce the onset of erythema resulting from a minimal erythema dose (MED) of 2 but are ineffective at higher MED values (34). Further, they cannot reverse existing UVR-induced erythema.

Studies with topical NSAIDs have shown that these are effective in both retarding the onset of UVR-induced erythema and decreasing the magnitude of the sunburn response. Topical indomethacin (1%) if administered immediately after sun exposure is more effective than steroids, being able to block the onset of sunburn produced by a 6 MED dose of UVB radiation (34). Further, topical application of the COX-2 inhibitor, celecoxib, after UVB irradiation of skin reduced erythema, edema, PGE-2 levels, the number of sunburn cells, and dermal infiltration of neutrophils (35). The topical NSAID, diflofenac (branded Solareze®), which is approved for use in the U.S. to treat actinic keratoses, has been shown to reduce sunburn symptoms when applied within four hours of the initial onset of sunburn (36). It is quite likely that other NSAIDS would be similarly effective in reducing the intensity of a sunburn if applied topically, and may also show the same efficacy as topical diclofenac in treating actinic keratoses. Interestingly, several studies implicate PGE-2 as a causative factor in skin cancer, and results from mouse experiments show that topical application of a PGE-2 inhibitor lowers the UVB-induced number of papillomas detectable 12 weeks after UVB dosing (37–40).

Immunomodulators

A newer type of NSAIDS is represented by the immunomodulators. Two anti-inflammatory drugs that have received FDA approval for topical use are the immunomodulators, Tacrolimus and the related drug Pimecrolimus. These drugs, along with cyclosporine, which exerts its effects through the same mechanism of action, had their origin as immunosuppressive agents used to prevent organ rejection after transplant surgery (41). Although cyclosporine has been used fairly successfully for years as an oral therapeutic for psoriasis, attempts to show that a topical formulation of it is efficacious for this disease have been unsuccessful. Both Pimecrolimus and Tacrolimus have been

approved for topical use in treating atopic dermatitis, but not for psoriasis. However, clinical studies show that systemically delivered Tacrolimus, like cyclosporine, is an effective therapeutic for psoriasis. As is the case with the glucocorticoids, the immunomodulators inhibit the production of inflammatory mediators but unlike the corticosteroids, both Tacrolimus and Pimecrolimus are more cell specific in that they target primarily mast cells and T-lymphocytes. The drugs have fewer inhibitory effects on Langerhans cells/DC, fibroblasts, and keratinocytes (42). Thus, the skin thinning complications seen with topical corticosteroids are eliminated (43,44).

Tacrolimus, Pimecrolimus, and cyclosporine all repress inflammatory genes in target cells through a common mechanism that involves the repression of activity of a ubiquitous calcium-activated phosphatase, calcineurin, that is involved in the activation of specific inflammatory genes (45). When specific receptors on T-cells bind to an antigen, this binding activates the receptor causing an increase in intracellular calcium. The increased calcium causes the activation of calmodulin which then binds to the calcium-dependent enzyme calcineurin and activates it. The activated calcineurin enzyme is a phosphatase, which can dephosphorylate the cytosolic subunit of a transcription factor, nuclear factor of activated T-cells, cytosol (NFATc). The dephosphorylation of the cytosolic NFAT subunit allows it to translocate to the nucleus where it forms a complex with the nuclear subunit of NFAT (NFATn) whose synthesis was induced by the signaling cascade initiated by the antigen binding to the T-cell surface receptor. Once the NFAT dimer has formed in the nucleus, it can bind to the promoter region of several inflammatory genes including those for IL-2, IL-3, IL-4, and TNF-alpha (46,47). A diagrammatic representation of calcineurin activation is shown in Figure 4.

When the drugs Tacrolimus, pimecrolimus, or cyclosporine enter the cell they bind to a cytosol protein, either FKBP for Tacrolimus or Pimecrolimus or Cyclophilin for cyclosporine. Once formed, this complex is able to bind to and inactivate calcineurin.
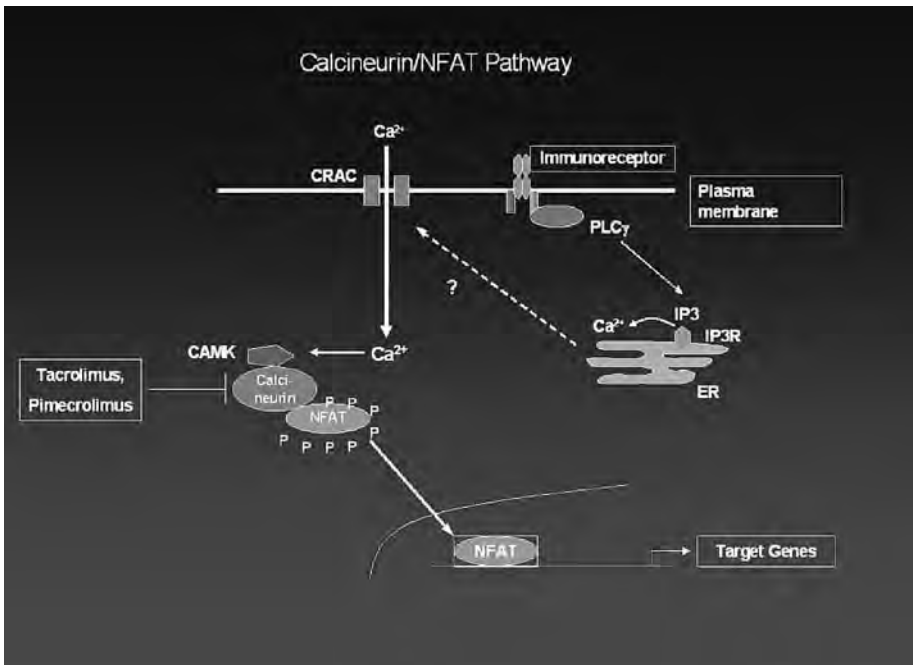
Figure 4 Diagram of calcineurin and NFAT activation.

The now inactive calcineurin can no longer dephosphorylate NFATc, which results in the transcription factor remaining unactivated and in the cytosol. Thus, the NFATn protein in the nucleus has no binding partner and cannot bind to and activate inflammatory genes (46). One of the genes in T-cells that is inhibited by Tacrolimus is the IL-2 gene, which is necessary for full T-cell activation. Thus, in the presence of these immunomodulators, T-lymphocytes do not differentiate in response to antigen stmulation. In addition to their inhibitory effect on inflammatory gene regulation, these immunomodulators inhibit the degranulation of mast cells, a property which may help explain their efficacy in treating some of the symptoms of atopic dermatitis.

While Tacrolimus and other calcineurin inhibitors are much more specific than corticosteroids in terms of the types of cells they act on, they still inhibit a wide variety of inflammatory genes by inactivating calcineurin and blocking NFAT activation. Another class of immunomodulators, called biologic response modifiers (BRM) or simply "biologics" because they are made from living organisms, have been developed over the past five years (48–50). These are essentially "designer" drugs because they target a specific event or mediator involved in inflammation. Anti-inflammatory drugs in this category include the TNF-alpha inhibitors, Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) (51–53). Of these Enbrel has received FDA approval for psorasiatic arthritis and more recently for severe psoriasis. Remicade and Humira have been approved for arthritis and approval for psoriasis is pending. Enbrel is a fusion protein containing the extracellular TNF-alpha binding region of the TNF-alpha receptor.It is injected twice a week by the patient at home. Remicade is a humanized monoclonal antibody to TNF-alpha and is injected intravenously. A second and third dose at two weeks and six weeks after initial dosing is recommended for arthritis (54). Humira is another anti-TNF monoclonal antibody designed to bind TNF-alpha, thereby preventing its attachment to and activation of target cells. Humira is injected every other week by the patient at home.

In addition to the TNF-alpha blockers other BRM drugs that suppress immune responses through different mechanisms have been approved for use in treating various forms of inflammation (55). Two of these, Raptiva (Efalizumab) and Amevive (Alefacept) have been approved as injectables for treating arthritis. Amevive, the first FDA approved drug for psoriasis, is a dimeric fusion protein containing the CD-2 binding site of the leukocyte antigen, LFA-3. When injected (once a week) Amevive binds to the CD2 binding site on T-lymphocytes thereby preventing binding between the LFA-3 antigen present on APC and the CD2 binding site on T-lymphocytes. Thus, the lymphocytes are not activated by antigen presentation. Another "humanized," "biologic" therapeutic which is injected weekly is the monoclonal antibody, called Raptiva, which binds to CD11a, which is part of the LFA-1 protein expressed on leukocytes. By occupying this binding site Raptiva prevents the leukocytes from binding an adhesion molecule, ICAM, which is present on endothelial cells. By preventing the adhesion of T-lymphocytes to the blood vessel wall, Raptiva prevents the activation of T-lymphocytes as well as their movement into the skin, thereby reducing the level of T-cell mediated inflammation. CD11a is also expressed on the surface of B-lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Thus, Raptiva has the potential to down-regulate responses by other immune cells further reducing inflammatory responses (52).

These new protein-based "biologic" immunomodulators, although effective and useful for treating various dermatological conditions, are, however, not without side effects. Because of their potent immunosuppressive effects, particularly on T-lymphocytes, the risk of infection among patients taking these medications is elevated (56–58). Enbrel, for example, has been found, in post-marketing use, to cause serious infections, sepsis, and even fatalities in patients predisposed to infections, and this warning is now included with

the drug information. Further, as is the case with all of protein-based biological response modifier drugs, none are capable of being delivered topically because of their size.

Given the myriad of immune driven events which occur in skin in response to exposure to antigens or other external stimuli, it is easy to see why immunomodulators and biologics are effective in treating inflammatory diseases such as atopic dermatitis and psoriasis. In the case of Tacrolimus and Pimecrolimus, by blocking the calcineurin pathway, these drugs can suppress the activity of the TNF-alpha and IL-2 genes in T-lymphocytes, thus preventing the activation of these lymphocytes as well as preventing their binding to adhesion proteins along the endothelium. Further, recent studies have shown that the calcineruin/NFAT pathway is active in epidermal keratinocytes and inhibited by either cyclosporine or Tacrolimus (47). Since keratinocytes produce a variety of inflammatory mediators such as IL-1 and TNF-alpha which, in turn, exert effects on a number of cells including fibroblasts (up-regulate PGE-2, cytokines), mast cells (degranulation) and endothelial cells (increased expression of adhesion moledule, ICAM, and VCAM, an inhibitory effect on IL-1 and TNF-alpha production would slow the production of inflammatory mediators and suppress the movement of immune cells into the skin. Similarly, the BRMs can be expected to be effective treatments for atopic dermatitis, and psoriasis based on their designed function of either blocking TNF-alpha action or T-lymphocyte activation. However, as mentioned these drugs can only be used by injection and not applied topically.

Other Anti-inflammatory OTC and Prescription Drugs

There are a large number of FDA approved topical drugs that are useful for treating various types of inflammatory dermatological conditions but which are not steroids, NSAIDs, or immunomodulators. One well-known example of this class is the antibacterial/anti-protozoal drug, metronidazole, which is used to treat rosacea, a skin disease that affects 14 million Americans (59,60). Rosacea is sometimes characterized mistakenly as adult-acne because patients present with a reddened face and acne-like symptoms. Individuals with this disease experience redness, pain, and itching on the face, chest, back, and as the disease progresses small blood vessels and small papules appear. Severe rosacea involves the ocular area and causes disfigurement to the nose, termed, rhinophyma. The causes of rosacea are not known, although there appears to be some genetic predisposition for the disease. Metronidazole (sold under the trade name Metrogel®) has been shown to be effective in alleviating some of these symptoms and, although the mechanism of action is unknown, efficacy is not thought to be related solely to its antimicrobial activity. Rosacea is also treated with the oral antibiotic tetracycline, but again, the mechanism of action is not known. Other topical non-steroidal, non-NSAID treatments for rosacea include azaleic acid, sodium sulfacetamide, and Accutane (61). While somewhat effective none of these products resolve all of the redness and other symptoms of rosacea.

Other non-steroidal, non-NSAID topical products used to treat inflammatory conditions such as eczema, psoriasis, and seborrheic dermatitis include coal tar, tazarotene (a retinoid derivative), anthralin, and even the simple OTC keratolyic compound, salicylic acid. However, for most inflammatory conditions the most effective treatments are still the corticosteroids, the immune modulators and recently the "biologics."

ANTI-INFLAMMATORY COSMECEUTICAL "ACTIVES"

The demand for effective non-prescription topical products to treat inflammatory diseases such as eczema, atopic dermatitis, seborrheic dermatitis, and even psoriasis has led to the

introduction of products based on either novel synthetic chemicals or on botanical "actives" which claim to be effective anti-inflammatory compounds. Some of the many purported botanical anti-inflammatory "active" ingredients in cosmeceutical products include bee pollen, curry extract, calendula extract, chamomile, jewelweed, green tea extract, geranium essential oil, aloe, bilberry, tea tree oil, lavender essential oil, boswellia, and willow bark, to mention only a few. Given the abundance of botanicals which claim anti-inflammatory activity, is there any scientific evidence to suggest that any actually have inhibitory effects on the production or action of inflammatory mediators in the skin? The answer is yes for a few botanically derived ingredients. Clearly the botanically derived substance most widely studied for its anti-inflammatory activity is curcumin, the active ingredient in turmeric, the root used in curry dishes. A large number of scientific studies published in peer-reviewed scientific journals over the past 5–10 years have shown remarkable and potent anti-inflammatory activities of curcumin (62). In fact, given curcumin's broad inhibitory effects on the production of inflammatory mediators by a wide number of cell types including immune cells, the compound could be classified as an immune suppressor or at the very least an immune modulator. Curcumin is effective in blocking both AP-1 and NF-kappa B driven inflammatory genes including COX-2, IL-8, IL-1, IL-12, and TNF-alpha (63). An example of the potency of curcumin in blocking IL-1 induced inflammatory gene expression in human fibroblasts is shown in Figure 5. Note that curcumin at concentrations below 10 μM can suppress the IL-1 induced increase in PGE-2 and IL-8. The compound is also very effective in blocking TNF-alpha production in normal human fibroblasts.

Although the mechanism of action of curcumin in suppressing the expression of inflammatory genes is not completely understood, it appears that at least one mechanism involves a block of the intracellular signaling pathway that leads to AP-1 and NF-kappa B activation (64). Recent evidence suggests that this blockade occurs near the start of the signaling pathway, that is, at the activated receptor, e.g., the IL-1 activated receptor (65).

Another plant derived "active" that has been shown through rigorous scientific studies to have anti-inflammatory activity is quercetin, a flavonoid derived from several plants and fruits, including apples. Its efficacy as an antioxidant and anti-inflammatory seems to provide some substantiation for the old expression, "an apple a day keeps the doctor away." Recent studies have shown that quercetin, like curcumin, can block NF-kappa B driven genes and thus prevent the production of a variety of inflammatory mediators (66,67). Other plant derived compounds that have been scientifically shown to
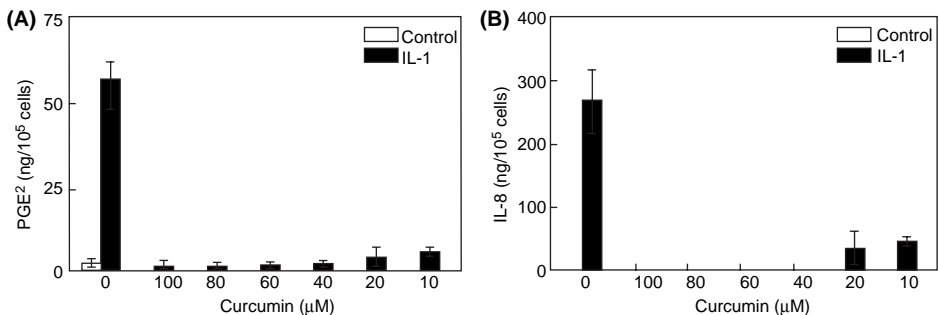
Figure 5 Effect of curcumin on inflammatory mediator production. Cultured dermal fibroblasts were treated with IL-1 and curcumin for 24 hours. Cell culture media was removed and assayed for the production of (**A**) PGE_2 and (**B**) IL-8.

have anti-inflammatory activities, at least in cell culture model systems, include resveratrol, derived from grapes, boswellic acid, derived from Boswellia, the polyphenol Epigallocatechin gallate, derived from green tea, and bisabolol, derived from Chamomile. All of these compounds have been shown to exert some anti-inflammatory effect on cells in culture, either inhibiting the production of PGE-2, cytokines, chemokines, adhesion molecules, or other molecules involved in the inflammatory process.

BIOLOGICAL SCREENING ASSAYS TO IDENTIFY NOVEL ANTI-INFLAMMATORY COMPOUNDS

The search for novel anti-inflammatory compounds that can be successfully formulated into either prescription or cosmetic topical products that show efficacy in treating dermatological conditions requires the availability of appropriate skin cell culture-based assays. Clearly, the cell types needed for such studies must include, at a minimum, normal human keratinocyte and fibroblast cell strains. In addition, because chronic skin inflammatory disease involves the activity of immune cells, cultures of human monocytes and T-lymphocytes should also be incorporated into the screening strategy. Finally, when one considers the important role that adhesion molecules, expressed on the surface of endothelial cells, play in directing leukocytes into the skin, being able to assess the effect of putative anti-inflammatory compounds on adhesion molecule expression in cultured endothelial cells would add an additional important screening capability.

Once the cell culture models have been established, the appropriate screening assays must be selected. These screens should focus on the effect that a potential anti-inflammatory molecule has on the expression of one or more key inflammatory mediators. Due to the fact that one of the most common activators of skin inflammation is sunlight, specifically UVB radiation, the determination of a compound's ability to block the induction of pro-inflammatory PGE-2 by UVR in both keratinocytes and fibroblasts represents a logical first step in the screening process. In addition, because skin inflammation is often triggered by contact with chemical irritants or allergens, the use of tetradecanoylphorbol acetate (TPA), which is a potent "irritant" stimulator of inflammatory mediators in skin, provides an additional model for the analysis of anti-inflammatory activities of test compounds. Finally, because IL-1 is one of the most important mediators and propagators of inflammation and is rapidly induced by an inflammatory stimulus, such as UVR, determining the ability of a potential anti-inflammatory compound to block either the production or action of IL-1 is a critically important initial screening study (68–70).

ELISA-Based Screening

To carry out initial screening experiments, cultured cells are first treated with the potential anti-inflammatory molecule followed by treatment with the inducing agent (ex. IL-1, UVR, TPA), which up-regulates the expression of inflammatory mediators. After a period of time (six to 24 hours), the media is removed and tested for the production of a particular inflammatory mediator using an enzyme-linked immunosorbent assay (ELISA). The ELISA method is based on the recognition of a particular antigen, such as some inflammatory mediator of interest, by a specific antibody, called the capture antibody. While there are many different forms of this assay, one of the simplest variations, the "sandwich assay," is shown in Figure 6. In this assay, the capture antibody is typically bound to a well in a plastic plate. When the media containing the inflammatory mediator of interest is added to the well, the bound capture antibody binds to the antigen. After binding, the well

is then washed and an additional antibody, called the detection antibody, is added to the well. The detection antibody also binds to the antigen, but in addition this antibody contains a "tag" (for example, an enzyme that reacts with a colorless substrate to produce a colored product) which allows for the amount of bound antigen to be quantified. Thus, if the culture media being tested contains a high amount of the antigen being measured, e.g., IL-1, then a high amount of detection antibody will bind, and a pronounced color reaction will occur when substrate is added. If, however, the anti-inflammatory compound blocks the production of the inflammatory mediator, for example, IL-1, then when the culture medium is added to the assay well, there will be little antigen to bind the capture antibody, and consequently very little detection antibody will bind. The result is very little color formation when the substrate is added.

The advantage of ELISA methods is that they are rapid, can accommodate a large number of samples simultaneously, require very little material for assay (a few microliters of culture medium), are very sensitive (pmole range), and are cost-effective. Commercial ELISA-based assays are available for most cytokines and chemokines, and thus, media from cell cultures can be assayed simultaneously for a variety of inflammatory mediators.

Figure 7 shows a flow chart of a screening strategy designed to identify anti-infammatory compounds. As is shown, all putative anti-inflammatory compounds are first screened for the ability to block the IL-1, TPA, or UVR induction of PGE-2, one of the most important inflammatory mediators produced in skin. Although there are exceptions, typically if a candidate anti-inflammatory compound cannot inhibit signaling pathways leading to increased PGE-2 production, it is unlikely to block the production of other inflammatory mediators. Compounds that effectively block PGE-2 production at a concentration of 100 μm or less are then subjected to more demanding dose-response studies and are tested for their ability to block additional inflammatory cytokines and chemokines. For these screening assays, it is important that, where possible, only primary cell strains of human fibroblasts and keratinocytes be used since the use of normal cells increases the probability that results from in vitro studies will be predictive of effects of a given compound when applied topically. Unfortunately, when screening protocols are used for leukocytes, it is difficult to obtain enough normal cells for such studies, and thus, permanent T-lymphocytes and monocyte cell lines are used.
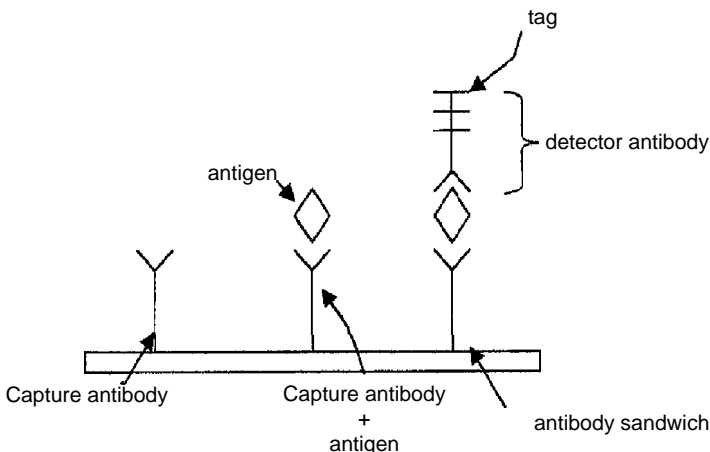
Figure 6   Sequence of steps for enzyme-linked immunosorbent assay.
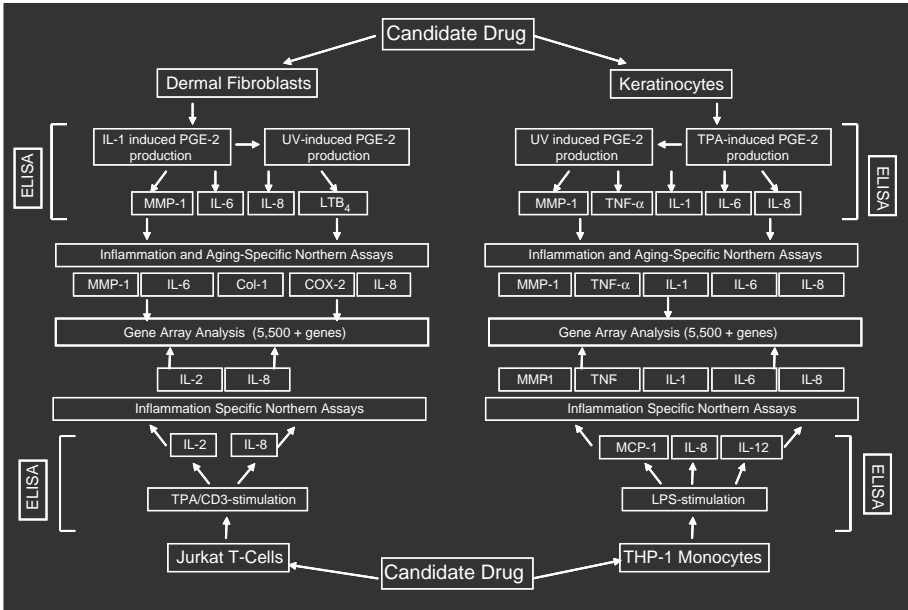
Figure 7 Screening strategy for assessment of anti-inflammatory activity of a candidate drug.

The results of studies with one putative anti-inflammatory compound are shown in Table 1. The compound was found to effectively inhibit the expression of several inflammatory mediators produced in skin cells in response to various stimuli including UVR, TPA, and IL-1. The table lists the concentration of this particular compound that is effective at inhibiting the induction of an inflammatory mediator by 50% (IC_{50}).

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

While ELISAs are an excellent method for obtaining information on the ability of a given compound to inhibit a wide variety of inflammatory mediators, it cannot determine HOW the anti-inflammatory compound is working. For example, if a compound is identified that inhibits PGE-2 production in keratinocytes, is the compound acting as a direct COX-2 inhibitor, as do most NSAIDS, or is it acting at the gene level to inhibit the activation of the COX-2 gene or other genes necessary for PGE-2 production? The method of reverse transcriptase-polymerase chain reaction (RT-PCR) is commonly used to quickly assess the expression levels of a particular gene, and thus can determine if an anti-inflammatory compound has any suppressive (or stimulatory) effect on a particular gene (71). The method uses the enzyme reverse transcriptase to reverse transcribe mRNA isolated from experimental tissue or cultured cells into complementary DNA (cDNA). This cDNA is then denatured and incubated with DNA primers that hybridize (anneal) specifically to the cDNA of interest. Once the primers are attached to the cDNA, a new DNA strand is produced by enzymatic extension of the hybridized primers followed by denaturing the newly formed double-stranded DNA. This process of primer annealing, extension, and strand separation is repeated as much as 40 times and this results in the logarithmic amplification of a specific region of the gene of interest (Fig. 8). The amplified products are then separated by gel electrophoresis, stained with the fluorescent DNA binding dye ethidium bromide, and visualized under UV light. By quantitating the intensity of the

Table 1 Screening Strategy for Assessment of Anti-inflammatory Activity of a Candidate Drug

Human dermal fibroblasts IC$_{50}$ (μM)		
Inflammatory mediator	Stimulus—UVR 50 mJ	Stimulus—IL-1α 100 pg/ml
PGE-2	5	0.01
IL-6	Not tested	50
IL-8	10	50
TNF-α	Not tested	Not Tested
MMP-1	50	10

Human epidermal keratinocytes (% Inhibition-100 μM)		
Inflammatory mediator	Stimulus—UVR 75 mJ	Stimulus—TPA 32 nM
PGE-2	100	100
IL-6	100	100
IL-8	100	100
TNF-α	100	100
MMP-1	100	100

fluorescence of the amplified PCR products, which, in turn, is proportional to the amount of DNA product made, it is possible to determine the relative abundance of a particular mRNA, and thus to determine what effect any compound had on the activity of the inflammatory mediator gene.

Gene Arrays

The use of ELISA, RT-PCR, and Northern and Western blot analyses are very useful in identifying specific inflammatory mediators which are inhibited by anti-inflammatory compounds. However, when one is designing topical formulations for treating an inflammatory skin condition, it is not only necessary to identify the inflammatory mediators that can be inhibited by topical application of a lotion or gel containing a given
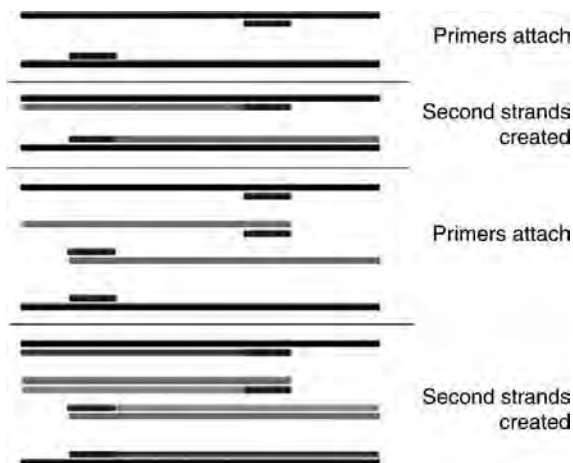
Figure 8 Diagram of the polymerase chain reaction (PCR) showing how gene sequences are amplified.

anti-inflammatory compound, but it is also important to have some knowledge of what beneficial genes and proteins may be *inhibited* by the topical product. For example, although corticosteroids are potent anti-inflammatory agents when used topically, they have negative side effects including the inhibition of collagen production in the skin, the reduction of the immune response to a point where a risk of skin infections increases, and at high doses, inhibition of fibroblast proliferation. Thus, to develop an effective and safe topical anti-inflammatory product that does not damage skin structure and function, it is important to determine what potentially beneficial genes in keratinocytes, fibroblasts, and immune cells, for example, IL-10, collagen III, or tissue inhibitor of metalloproteinase (TIMP), may be suppressed by the anti-inflammatory compound. One of the most effective methods for screening anti-inflammatory compounds for both their positive and negative effects on gene expression is the use of gene array technology (72). With this technique it is possible to assess the expression level of hundreds to thousands of genes simultaneously. Gene arrays are membrane filters or glass slides to which are bound small pieces of known and/or unknown (EST-expressed sequence tags) human genes. A typical nylon gene array filter may contain as few as fifty or as many as 5000 different gene sequences on a single filter, and some arrays have even been designed with specific tissues or diseases in mind, such as inflammation. The sequence of steps involved in a gene array analysis is shown in Figure 9. The first step involves isolating mRNA from untreated cells (control group) and from cells exposed to some experimental condition (experimental group). After hybridization, any unbound cDNA is washed away and the hybridized cDNA is detected and quantified. Since the location and identity of each gene on the filter is known, by comparing the quantified spots on the array produced from the control group to those spots produced from the experimental group, one can determine if a particular gene in the experimental group is up-regulated or down-regulated compared to the control
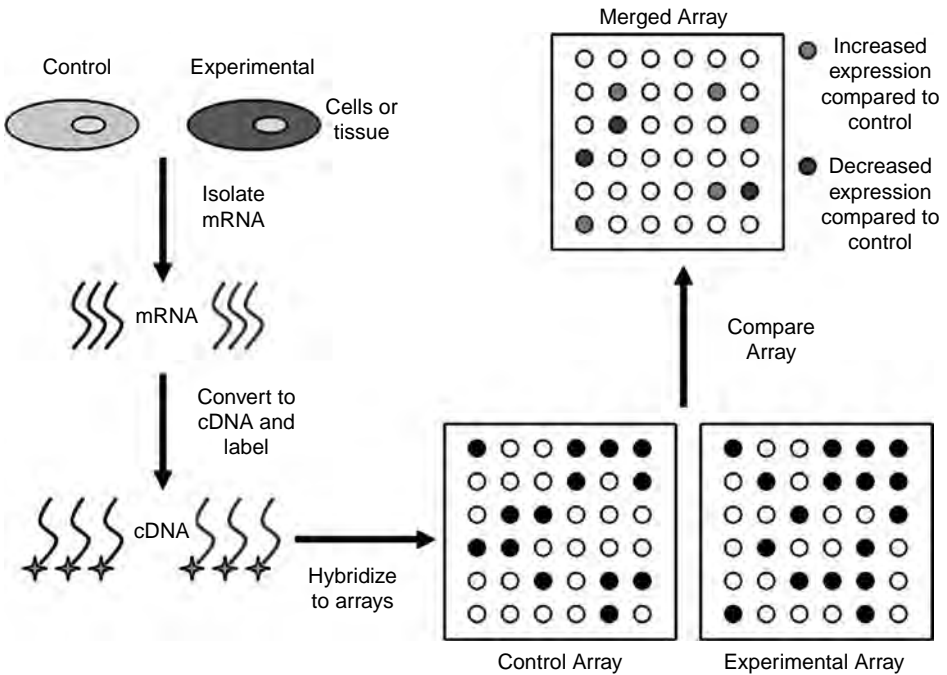
Figure 9 Steps involved in gene array analysis.

group. Given the complexity of gene arrays, a computer software program is used to aid in the quantification and analysis of the large amount of data that is obtained. The software produces an "overlay" image of the filters from both the control and experimental groups, calculates the difference in expression level for each gene between the two groups, and then converts this relative expression data into a color image. For example, a gene that is up-regulated in the experimental group compared to the control group is shown as a green spot on the computer generated image, while a gene that is down-regulated in the experimental group is shown as a red spot. By using this method the effect of any compound on the expression of genes that code for pro- and anti-inflammatory mediators as well as other genes expressed in epidermal and dermal cells can be rapidly determined. An example of the use of this technology is shown in Figure 10. In this experiment human fibroblasts were treated with quercetin and the effect of this compound on the expression of inflammatory and dermal matrix altering genes determined. The cDNA array images from untreated (A) or quercetin (B) treated fibroblasts captured by the phosphoimager were merged and colorized by the computer software to yield the image in panel C. Genes that were down-regulated in quercetin treated fibroblasts relative to those in untreated cells are displayed by the software as either red or yellow while those genes up-regulated by quercetin are displayed as green. In this study, quercetin was found to lower the expression of MCP-1 and collagenase (MMP-1) while up-regulating a gene that blocks MMP activity (TIMP-1). Table 2 shows the results of an array analysis of genes that are up- and down-regulated by quercetin in TPA-treated keratinocytes. Note that quercetin up-regulates genes that are play a role in protecting the dermal matrix and down-regulates matrix destroying genes.

DEVELOPMENT OF EFFECTIVE TOPICAL FORMULATIONS

Although screening assays are critical for identifying new anti-inflammatory compounds, unless these compounds can be formulated into a topical product that delivers the compound across the stratum corneum and down to the target cells in the epidemis and/or dermis, the product will be ineffective. The steps to developing an effective topical product involve: (i) assessing likelihood of skin penetration from molecular weight and log P values, (ii) determining solubility and stability of the anti-inflammatory compound in acceptable formulation solvents, (iii) preparing prototype formulations that are physically stable and which maintain biological activity of the compound, (iv) testing the prototype formulation by Franz cell percutaneous absorption analysis to determine the rate and quantity of compound that can penetrate into human skin, and (v) subjecting the formulation to placebo-controlled clinical studies to determine topical efficacy in a patient population.

The stratum corneum is an effective barrier against entry of foreign objects into the skin, and this includes most proteins, peptides, and even small molecules. Thus, the development of topical products which allow penetration of compounds into the skin is not a trivial undertaking. Typically, unenhanced formulations may "deliver" 0.1% to 1% of a "biologically active" compound across the stratum corneum. Even formulations that are engineered to optimize delivery of a given compound may result in, at best, 10% of the applied dose moving across the stratum corneum and down into the skin. In addition, if the molecule to be delivered into the skin is highly hydrophobic, it will likely pass easily into the stratum corneum but not move into the more aqueous environment of the epidermis (73). Thus, a significant percentage of the active compound in the product will never diffuse through the skin to reach the target cells. To aid in formulation development of a given "active" compound, the use of log P values has become popular to predict efficacy in skin
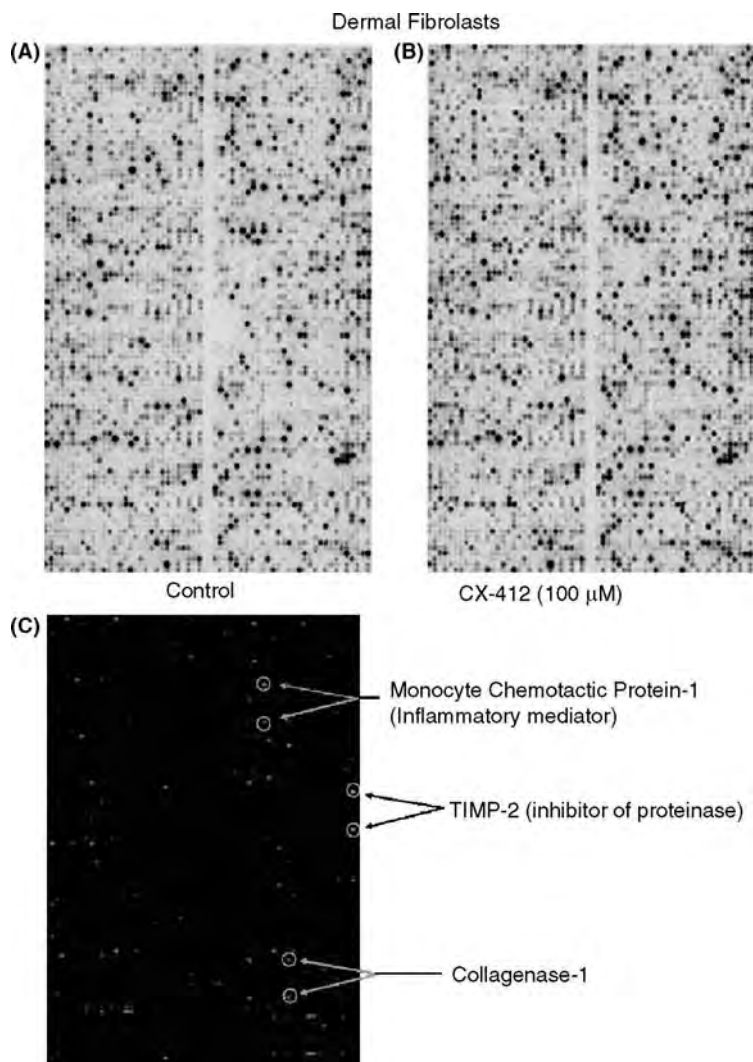
Figure 10 Gene array filters showing hybridization signals (black dots) from (**A**) untreated and (**B**) quercetin treated fibroblasts were "merged" and colorized by software analysis to show genes that are upregulated or downregulated (shown here in gray scale) by this compound. (**C**) In the merged image, arrows point to 2 genes, MCP-1 and MMP-1, that are downregulated in fibroblasts treated with quercetin and one gene, TIMP-1, that is upregulated by this compound.

penetration of a given molecule. Log P measurements show the degree to which a given compound will partition between water and octanol (or other non-miscible solvent). For example, a compound that has a Log P of 1 will prefer an organic solvent to an aqueous one by a factor of 10. A compound with a log P of 0 has an equal affinity for water or an organic solvent. From a topical formulation perspective, compounds that have a logP of around 2.5 will likely have a fairly high probability of skin penetration from a suitable formulation (74). In addition to log P values, the ability of any compound to penetrate the stratum corneum depends on its size. Compounds with molecular weights above 1000 are not going to easily move through the stratum corneum regardless of their log P value. Two other factors that influence skin penetration of any compound from a formulation are the solubility and

Table 2 Effects of Quercetin on Gene Expression in TPA-Treated Human Epidermal Keratinocytes Determined by Integriderm Dermarray™

Upregulated	*Downregulated*
Tissue inhibitor of metalloproteinases-2 (TIMP-2)	Collagenase-1 (MMP-1)
Tissue inhibitor of metalloproteinases-3 (TIMP-3)	Stromelysin-2 (MMP-10)
Serine proteinase inhibitor	MTI-MMP (MMP-14)
Proliferating cell nuclear antigen	ADAM 9
Metallothionein	Urokinase-type plasminogen activator (uPA)
Keratin 6	Plasminogen activator inhibitor I (PAI-1)
Keratin 14	Plasminogen activator inhibitor II (PAI-2)
Keratin 16	Monocyte chemotactic protein-1
	RANTES
	Envoplakin
	Interleukin-8
	Cystatin
	Involucrin
	Small proline rich protein-1

concentration of the compound in the formulation. Those formulations that contain a near-saturated (or even super-saturated) concentration of a compound will deliver more of the compound into the skin. Conversely, the more soluble a compound is in the formulation the less potential it will have for leaving the formulation and entering the skin. To increase the movement of compounds into the skin, a number of penetration enhancers may be used. These are solvents that temporarily disrupt the integrity of the stratum corneum allowing molecules to penetrate this layer of skin. Although over 300 penetration enhancers are known, ony a few are used routinely for topical formulation development. Common enhancers used in cosmetic formulations include simple alcohols, propylene glycol, oleic acid, ethoxydiglycol, polyolprepolymer-2 (and PP-14 and PP-15), some terpenoids, cyclodextrins, urea, and sodium lauryl sulfate to name a few (75,76).

Percutaneous Absorption Analysis

Once a compound's size, log P value, and solubility properties in various acceptable formulation solvents have been determined, the next step in formulation development involves either measuring the penetration through skin of the compound dissolved in a single solvent or its skin penetration from simple formulations. Regardless of which approach is taken, measuring a compound's "flux" through skin requires the use of some type of diffusion cell. The most common apparatus for measuring the penetration of topical formulations through skin is the Franz diffusion cell, shown in Figure 11. The unit consists of an upper chamber into which the test formulation is applied and the lower reservoir chamber which is filled with buffer. A piece of human skin (animal skin or a synthetic membrane is sometimes used) is mounted in between the two chambers and held in place with a clamp. The formulation to be tested is applied to the stratum corneum surface of the mounted skin and at various times, samples of the lower reservoir buffer are removed and assayed for the presence of the anti-inflammatory compound in the

formulation. For compounds that are not made radioactive, the presence of the compound in the lower chamber of the Franz cell is typically determined by high-performance liquid dramatography (HPLC) analysis. In order to obtain results which more accurately reflect the rate of skin penetration that will be obtained in vivo, human skin, either dermatomed or full thickness, should be used. The use of Franz diffusion cell analysis to measure percutaneous absorption of anti-inflammatory compounds from topical formulations provides information needed to optimize the formulation prior to initiating clinical studies. Based on dose-response studies in cell culture systems, it is possible to predict what level of skin penetration a given anti-inflammatory compound likely needs to attain to show efficacy in vivo. Formulations can be modified and re-tested by Franz cell analysis until the predicted "flux rate" of compound into the skin is achieved.

It is useful to keep in mind that, as a general rule, compounds which show efficacy in blocking inflammatory mediators in cell culture systems with IC_{50} values of less than 100 uM (preferably 10 uM) have a reasonable chance of being efficacious when applied topically, assuming the flux rate of the compound from the formulation is optimized. However, topical formulations containing anti-inflammatory compounds that are only effective in cell culture at concentrations higher than 100 uM have a low probability of being good anti-inflammatory products because of the difficulty of delivering enough of the compound into the skin and to the target cells over a long enough period of time to be effective. In our laboratory, compounds with anti-inflammatory IC_{50} values higher than 100 uM are not considered for product development.

Another consideration when developing topical formulations concerns "residence time" of the active ingredient. To effectively treat inflammatory conditions, a topical formulation must not only deliver enough of the active ingredient into the skin to be effective, but should also deliver the active continuously over many hours. Typically a topical product is applied to the affected area twice a day, once in the morning and once in the evening. Thus, the time between applications can be as much as 12 hours. If the topical formulation delivers a high level of the anti-inflammatory compound into the skin for a short period of time, for example one hour, the compound is going to reach the target cells at a high enough concentration to begin to inhibit inflammation, but after an hour the concentration falls as the active continues to traverse the skin and dissipate into the capillary beds. When one considers that only about 1–2 ml of any topical product is
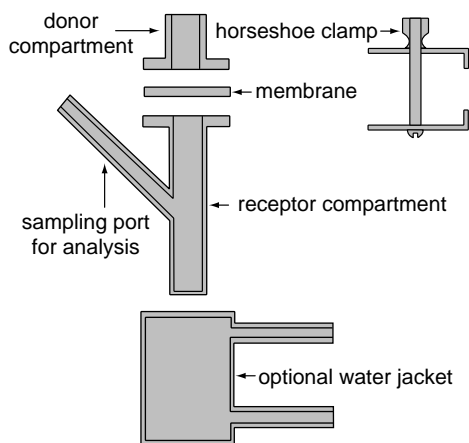
Figure 11   Diagram of Franz diffusion chamber.

applied to 100 cm^2 of skin, developing formulations that deliver enough of the active into the skin continuously over a 12-hour period is not a trivial undertaking. Obviously, if the bioactive compound is effective at nanomolar levels, the product can be designed as an "unenhanced" formulation, which will result in a slower rate of skin penetration and theorectically provide a longer residence time or "depot" of drug needed to affect cell functioning for a 12-hour period. Further, if the water solubility of the active compound is low, it is likely to be retained in the stratum corneum, and only move into the edidermis slowly at a low concentration. If the compound's bioactivity is in the nanomolar range this low rate of movement into the epidermis will be ideal for maintaining a high residence time in the skin.

Assessment of Anti-inflammatory Activity by UVR Clinical Study

Although careful and thorough analysis of the biological activities of a given anti-inflammatory compound using a variety of cell culture models can provide information on which inflammatory conditions a given compound is likely to be effective in treating, and although skin penetration studies will aid in the development of a formulation that theoretically delivers adequate levels of the compound into the skin, of course the only way to know if the topical formulation is truly effective in treating inflammatory conditions is to conduct clinical studies. In this regard, there are several different approaches to designing and implementing a clinical study. The least scientifically credible study design is one in which no placebo is run, where there is no blinding of either the clinical investigator or patients, and where the efficacy of a product formulation is simply determined comparing some parameter (redness, tone, skin roughness, etc.) at the end of the treatment period to baseline readings determined at the beginning of the study. In order to determine the efficacy of a novel anti-inflammatory compound in a formulation, it is necessary to conduct clinical studies under blinded, placebo-controlled conditions, where the efficacy of the formulation containing the anti-inflammatory "active" is statistically compared to the placebo group.

One of the easiest and quickest clinical studies to conduct to assess the potential anti-inflammatory activity of a topical formulation is a UVR erythema study. In this protocol, the patient is exposed to a 3 MED dose of UVB radiation from a light source that irradiates a small area (20 mm diameter) of skin. Multiple areas on the inner arm are irradiated. Immediately after irradiation, one spot is left untreated while a second spot is treated with the topical formulation containing the anti-inflammatory compound. The third irradiated area is treated with a "vehicle" lotion that is identical to the treatment lotion but does not contain the putative anti-inflammatory compound. For these studies it is important that the skin is not pre-treated with the test lotions. The reason for this is that if the putative anti-inflammatory compound in the formulation absorbs UV light, then applying the product before irradiation may result in protection from erythema simply because of the UV absorbing properties of the compound. At hourly intervals after irradiation, surface spectrophotometric measurements and photographs of the treated areas are taken to quantify the level of erythema. Clinical photographs of one patient from a study conducted on a novel anti-inflammatory compound developed in our laboratory are shown in Figure 12. The photograph shows that even 24 hours after irradiation and after a single application of an anti-inflammatory formulation, the area treated with this formulation has markedly less erythema than the area treated with the vehicle formulation (the exact formulation but without the anti-inflammatory compound).
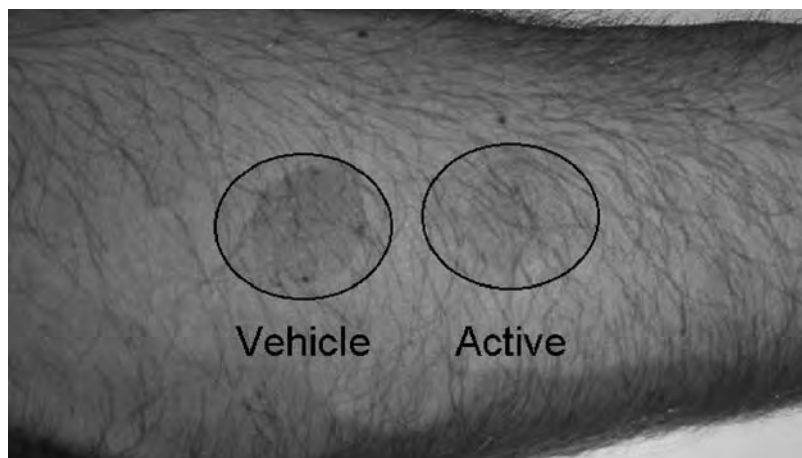
Figure 12 Effect of anti-inflammatory topical formulation on UVB radiation-induced sunburn 24 hours post-irradiation.

CONCLUSIONS

By using multiple cell culture-based inflammatory mediator assays to identify the anti-inflammatory capabilities of a given compound, followed by the development of topical formulations that are analyzed by Franz cell percutaneous absorption analysis to ensure that adequate amounts of the compound are being delivered into the skin, it is possible to develop novel topical anti-inflammatory products that have a very high probability of being effective treatments for a variety of inflammatory skin conditions. There are a number of botanically derived compounds which have been shown to have excellent anti-inflammatory activity, and results of screening assays in our laboratory suggest that perhaps as many as 50 fairly common botanically derived compounds could be developed into topical anti-inflammatory products that would effectively lower the level of many inflammatory cytokines and chemokines in the skin including PGE-2, IL-1, TNF-alpha, MCP-1, IL-12, and IL-8. Further, these compounds can not only block the *production* of cytokines but can also suppress the ability of a target cell to *respond* to a given cytokine or chemokine. When one considers the known deleterious side effects that have been reported for the anti-inflammatory steroids and recently for the newer class of oral or injectable anti-inflammatory immunomodulator drugs, it seems that the development of topical anti-inflammatory products that are less immunosuppressive and which are delivered directly to the affected areas of the skin instead of systemically might represent a safer approach. Such products could be designed to reduce or "reset" cytokine and chemokine levels in affected areas of the skin to a more non-inflamed "ground state." Such a product would reduce the inflammatory response but yet leave the immune system intact to fight infection and to conduct surveillance. From our research it appears very likely that a number of botanically based compounds could be formulated into topical products to meet this goal.

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21
Topical Nutritional Antioxidants

Karen E. Burke

Department of Dermatology, Mount Sinai Medical Center and
Department of Medicine, Cabrini Medical Center, New York, New York, U.S.A.

INTRODUCTION

In recent years, more and more cosmetic products have been formulated with antioxidants. These new products claim to "moisturize," "protect," and "rejuvenate" the skin.

The skin naturally uses nutritional antioxidants to protect itself from free-radical damage. Indeed, many antioxidants—most prominently vitamins C and E, the trace mineral selenium (Se), the soy extract genistein and ubiquinone—have been proven effective in protecting against ultraviolet (UV) damage to the skin and in actually reversing the appearance of aging by decreasing solar hyperpigmentation and small wrinkles when applied to the skin. Also, α-lipoic acid and ubiquinone may retard and reverse intrinsic as well as photoaging. Topical application of these antioxidants can give far higher concentrations in the skin than even maximal oral intake. However, the correct formulation is of utmost importance to attain eficacy. The challenge is to use the *correct form* of the antioxidant molecule, to keep the antioxidant *active* to attain a reasonable shelf-life for the product, and to achieve effective *transcutaneous* absorption that delivers effectively high concentrations of the active antioxidant to the dermis as well as the epidermis.

VITAMIN C

Background

Vitamin C (L-ascorbic acid) is the body's major aqueous phase antioxidant and is absolutely vital for life. All animals make their own vitamin C, except for humans and other primates, one species of Indian fruit-eating bat, and the guinea pig. In fact, a 130-pound goat synthesizes 13 grams of vitamin C per day, almost 200 times the American Food and Drug Administration (FDA) requirement (1). Not only do other animals make hundreds of times the vitamin C we ingest, but also, when under stress, they can make more than ten times their normal amount of vitamin C, a capability that we humans do not have (1).

377

Our skin is the organ that suffers most from environmental free-radical stress from exposure to sunlight, cigarette smoke, and other pollution. Furthermore, this contact actually depletes the level of vitamin C in skin. Even minimal UV exposure of 1.6 minimal erythema dose (MED) decreases the level of epidermal vitamin C to 70% of the normal level, and exposure to 10 MED decreases the vitamin C to only 54% (2). Exposure to 10 parts per million of ozone in city pollution decreases the level of epidermal vitamin C by 55% (3).

Mechanisms of Action

Vitamin C is itself not a sunscreen. Topical vitamin C protects against solar damage primarily as an antioxidant which deactivates the UV-induced free radicals, most significantly the superoxide anion, singlet oxygen, and the hydroxyl radical. Vitamin C is equally effective in protecting against both UVB (290–320 nm) and UVA (620–400 nm) (4). On both porcine and human skin, applying vitamin C decreases the acute erythema and sunburn suffered even when applied after sun exposure (4). Protection is confirmed by histologic examination. Treatment of porcine skin in vivo with topical 10% vitamin C decreases the number of abnormal apoptotic "sunburn cells" by 40% to 60% (4) and reduces the UV damage to DNA by 62% (4).

Topical vitamin C further prevents UV-induced immonosuppression (5). In approximately one-third of humans, the activity of the immune system is inhibited after exposure to sunlight. This immunosuppression is measured by the class of contact hypersensitivity to sensitizers such as poison ivy. Sunscreens only partially aid in the prevention of UV immunosuppression. Animal studies demonstrate that topical vitamin C prevents this UV-induced loss of contact hypersensitivity as well as UVB-induced tolerance.

Topical vitamin C is also directly anti-inflammatory (further accounting for decreased erythema after sun exposure). Laser resurfacing causes redness for at least three to four months. With vitamin C applied before and after laser resurfacing surgery, redness is decreased after only two months (6). Dermatologic surgeons recommend using topical vitamin C as long as possible prior to laser resurfacing and beginning again as early as fourteen days following surgery. Topical vitamin C can also be used effectively to treat the inflammation of rosacea (7).

The main action of vitamin C on the skin is direct stimulation of collagen synthesis. Vitamin C is an essential cofactor for the two enzymes required for collagen synthesis, prolyl hydroxylase (which makes the collagen molecule stable) and lysyl hydroxylase (which cross-links the collagen to give structural strength) (8). Recent research has further demonstrated that vitamin C acts directly on DNA to increase the transcription rate and to stabilize the pro-collagen messenger RNA, thus regulating and maintaining the intercellular amount of collagen (9).

Exciting experiments have demonstrated that vitamin C also has anti-aging effects. Studies in vitro compared newborn with elderly (80–95 year-old) fibroblasts (10). Elderly cells proliferate in vitro at only one-fifth of the rate of newborn cells. However, when vitamin C is added to the culture medium, the elderly cells actually proliferate better than normal newborn fibroblasts. Even the newborn fibroblasts proliferate almost four times better when exposed to vitamin C (10).

Not only do fibroblasts increase proliferation in the presence of vitamin C, but they also synthesize more collagen. Newborn fbroblasts synthesize a larger percentage of collagen than elderly cells, but again, when elderly cells are exposed to vitamin C in vitro,

they produce more collagen than the normal, newborn fibroblasts (10). Surprisingly, also the newborn cells double the amount of collagen synthesized (10).

Vitamin C further reverses the adverse appearance of photoaging by inhibiting tyrosinase (11), thereby fading unattractive solar lentigos. Because L-ascorbic acid may inhibit elastin biosynthesis (12), it may reduce the solar elastosis of photoaged skin.

Another important action of vitamin C on the skin is that topical vitamin C actually increases the synthesis of several very specific lipids of the skin surface (13). Not only does this mean that vitamin C helps the natural moisturization of the skin, but it also enhances the protective barrier function of the skin (14).

Challenges in Formulation

To optimize percutaneous absorption and full activity of vitamin C, the precise formulation is of utmost importance (15). Fortunately, the skin level of vitamin C can be increased significantly by topical application. Topical absorption was proven by radioactive-labeling studies in pigs. After treatment with 10% vitamin C cream, 8.2% was found in the dermis, and 0.7% was in the blood (4). Formulations containing 5%, 10%, 15%, 20%, or 25% vitamin C were tested: after 24 hours, 20% resulted in the highest skin levels, with maximized concentration in the skin after three days (16). Indeed, the level of vitamin C in the skin attained by topical application was over 27 times the level attained by high oral intake (16).

Since L-ascorbic acid is an inherently unstable molecule—making it an excellent antioxidant—creation of an effective topical delivery system is crucial. Many products contain stable derivatives which are not metabolized by the skin (such as ascorbyl-6-palmitate or magnesium ascorbyl phosphate) and therefore have no activity (16). Other formulations do not result in measurable absorption of vitamin C because they are not at the correct pH. Delivery of L-ascorbic acid depends upon removing the ionic charge achieved optimally at a pH of 3.5 (16). Having the pH below the pKa of ascorbic acid (pHa=4.2) gives optimal activity as an antioxidant.

Substantiation of Efficacy

As cited above in the presentation of "Mechanisms of Action," the effcacy of topical vitamin C in neutralizing reactive oxygen species (ROS), protecting against both UVA and UVB damage, stimulating collagen synthesis, preventing UV immunosuppression, alleviating infammation, decreasing UV-induced pigmentation, and enhancing surface moisturization and skin barrier function has been repeatedly documented in controlled experiments.

Clinically, daily application of topical vitamin C 15% can partially reverse the appearance of photoaged skin. Improvement can be noted in as little as two to four months with optimal correction after at least four to six months. As shown in Figures 1 and 2, small wrinkles decrease and solar lentigines fade. Thus vitamin C not only prevents but also reverses much of the damage induced by UV.

VITAMIN E

Background

Like vitamin C, vitamin E is an essential nutrient, not synthesized by humans and supplied only by oral intake. The main natural sources are fresh vegetables, vegetable oils, cereals,

Figure 1   Decrease in small periorbital rhytides after daily application of vitamin C serum 15% (SkinCeuticals) for one year. *Source*: Photo courtesy of SkinCeuticals, Dallas, Texas, U.S.A.

and nuts. Natural vitamin E is the most important lipid-soluble, membrane-bound antioxidant in the body. Vitamin E is especially abundant in stratum corneum, delivered there by sebum (17,18). Its concentration is highest at the lower levels of the stratum corneum with a decreasing gradient outward. As the outermost defense of the body, the stratum corneum is first to absorb the oxidative stress of sunlight and pollution. Vitamin E is depleted in the process, so topical application can be particularly advantageous, especially since the lipophilic structure makes it cosmetically attractive for application and absorption.

Mechanisms of Action

The redox and free radical chemistry of vitamin E are well-documented (19). The major antioxidant role is the arrest of chain propagation by scavenging lipid peroxyl radicals. One molecule of tocopherol has the ability to scavenge two peroxyl radical molecules (20).
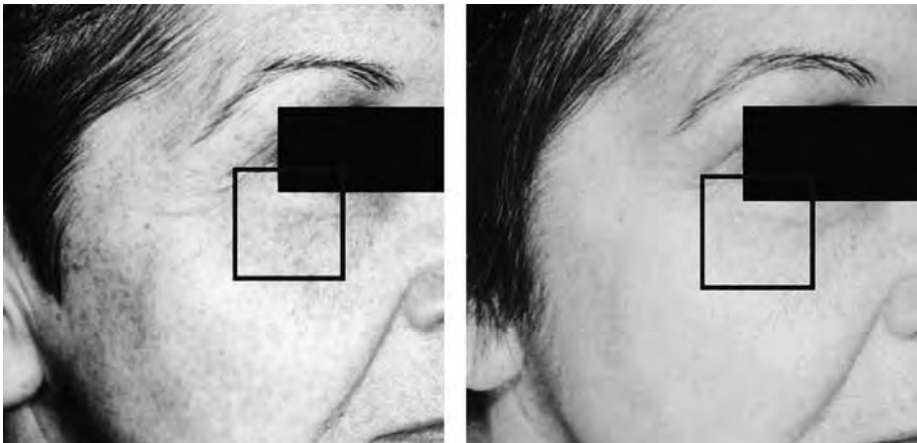
Figure 2   Lightening of UV-induced lentigines and hyperpigmentation after daily application of vitamin C serum 15% (SkinCeuticals) for one year. *Source*: Photo courtesy of SkinCeuticals, Dallas, Texas, U.S.A.
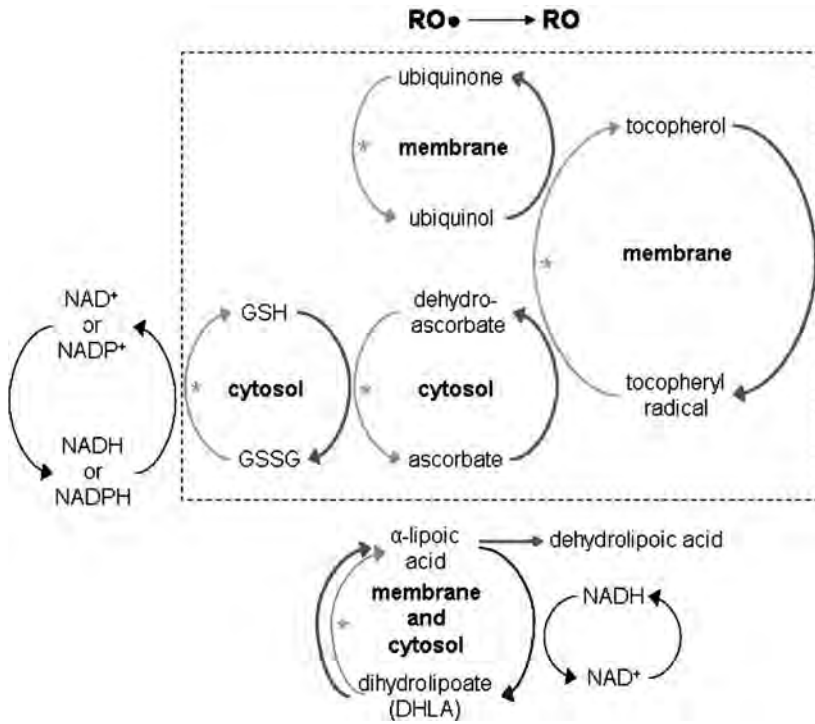
Figure 3 Interactions of low molecular weight antioxidants. The reactions which directly quench oxygen free radicals (RO•) are indicated by the dark gray arrows (RO• →RO); the reactions regenerating these antioxidants are also indicated by the light gray arrows. Reactions with arrows touching are directly linked. RO• generated in a cell membrane is reduced by tocopherol, forming a tocopheryl free radical which can in turn be quenched within the membrane by ubiquinol or at the membrane-cytosol junction by ascorbate (vitamin C). RO• generated in cytosol is directly reduced by ascorbate. The oxidized dehydroascorbate is reconverted to ascorbate by glutathione (GSH). Both α-lipoic acid and dihydrolipoic acid (DHLA) directly reduce oxygen free radicals. Also DHLA is itself a potent reducing agent which regenerates the oxidized forms of vitamin C, vitamin E, and oxidized glutathione (GSSH); this linkage is indicated by an asterix. *Source*: Adapted from Refs. 21, 22.

As shown in Figure 3, several hydrophilic coantioxidants, such as ascorbate and glutathione, regenerate vitamin E from the tocopheryl radical and thereby enhance the antioxidant capacity of vitamin E (21–23). Also, ubiquinol (coenzyme Q10) protects α-tocopherol from photo-oxidation by recycling (24).

There is extensive scientific evidence from animal studies that vitamin E is photoprotective. Topical vitamin E [even the metabolically less potent racemic or ester forms (see "Challenges in Formulation" below)] significantly reduces acute erythema, edema, and sunburn (25–30) if applied prior to UV exposure or (in some studies) immediately after. This has been confirmed histologically by decreased "sunburn cells" (27) and by electron microscopy showing epidermal cell repair and anti-inflammatory effects (28). Less DNA photodamage after UV with concomitant decreased p53 expression has been observed (29). Topical all-*rac*-α-tocopheryl acetate applied before UV exposure protected the hairless mouse epidermis against decreased DNA-thymidine incorporation and lipid peroxidation; given orally, this protected only against lipid peroxidation (30). This protection results from antioxidant (31) and/or anti-inflammatory activity (32,33).

UV radiation directly alters DNA and induces free redicals (34,35) and epidermal lipid peroxidation (36), thereby initiating and promoting skin cancer (37). Vitamin E protects the skin from this chronic damage by: (i) quenching free radicals [as confirmed in vitro by protection by reducing radiation-induced lipid peroxidation (38)], and (ii) protecting specific membrane proteins containing Se or sulfur (39). Indeed, all-*rac*-α-tocopherol has been shown to prevent epidermal chemical carcinogenesis (40–42) as well as UV-induced photocarcinogenesis (43–46).

In hairless mice both oral (43) and topical all-*rac*-α-tocopherol combined with ascorbic acid (44) increased the latency period and decreased the number of UV-induced tumors. In Skh:2 hairless mice, both topical d-α-tocopherol (5%) and d-α-tocopheryl succinate (5%) as well as oral d-α-tocopheryl acetate signifcantly retarded the onset and decreased the incidence of UV-induced skin tumors; the topical succinate was less effective than the other two forms (25).

Challenges in Formulation

Several forms of vitamin E exist in natural dietary sources. The form which is found in mammalian tissues and has by far the greatest biologic activity is pure, nonesterified d-α-RRR-tocopherol (47,48) which has three methyl groups on the 6-chromal ring (Fig. 4). Humans use predominantly α-tocopherol because a specific α-tocopherol transfer protein selectively transfers α-tocopherol into lipoproteins (49). The other natural forms are beta, gamma, and delta which contain only one or two methyl groups on the 6-chromal ring. Relative to the alpha form, the beta, gamma, and delta RRR-tocopherols give only 42%, 72%, and 40%, respectively, of the protection against post-UV edema (50). The synthetic form is "dl" or "all-*rac*," a mixture of eight stereoisomers. Not only is the decreased activity of the all-*rac* mixture of vitamin E important (51), but also the mixed all-*rac* form of vitamin E has been reported to cause allergic contact dermatitis (52) and erythema multiforme (53) when applied topically. No such adverse reactions have been reported with pure d-α-tocopherol.

Instead of the pure d-α-tocopherol, the synthetic isomers are esterified (to acetates and succinates) for use in commercial vitamins and some topical formulations because the esters are far more stable. The ester vitamin E acetate has been shown to be absorbed into the skin (54–56). This ester must be hydrolyzed to the active free tocopherol form before there is any biologic activity, a reaction which readily occurs in the stomach after oral ingestion or in cell and organ culture, but there is conflicting evidence as to what extent

	R$_1$	R$_2$
α	CH$_3$	CH$_3$
β	CH$_3$	H
γ	H	CH$_3$
δ	H	H
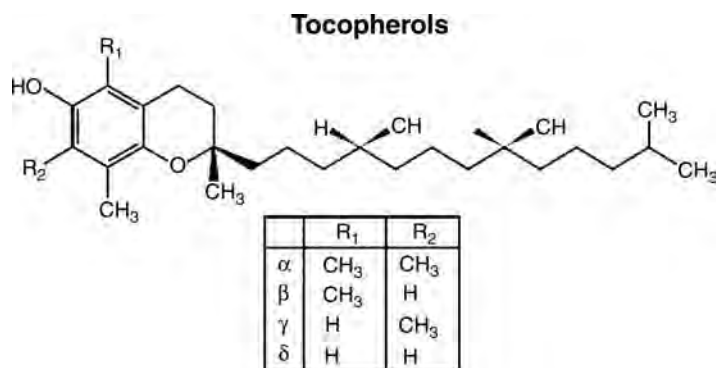
Figure 4 Molecular structures of tocopherols.

this conversion occurs, especially in the stratum corneum (57–59). Thus the antioxidant potential of esterified vitamin E is far less than the natural tocopherol form (60). There is greater bioconversion in the lower nucleated epidermal cells (58,59) depending on the formulation (61). UVB exposure may enhance this conversion (62).

Stabilization of the non-esterified d-α-tocopherol to give a product an effective long shelf-life is a challenge in formulation. The stability can be enhanced by packaging in dark, sealed ampules for one application-only delivery, by formulating within liposomes, or by stabilizing chemically, often using other antioxidants. (Patents are pending for the latter two methods).

Substantiation of Efficacy

The scientific evidence of the benefcial role of vitamin E in protection from UV damage was discussed in detail above. Vitamin E has several other possible therapeutic roles in dermatology. Many anecdotal reports support the use of topical vitamin E to enhance wound-healing and to prevent hypertrophic scars; however, the benefits are controversial. Two controlled studies failed to show scar prevention by topical vitamin E (63,64). The stability and formulation of the topical vitamin E used may have effected these inconclusive studies. New research on diabetic mouse models suggests involvement of oxidative stress in diabetic wound healing showed significantly improved wound healing with topical vitamin E (65,66). Vitamin E may have a role in treating atopic dermatitis. Forty-three patients treated with oral vitamin E for eight months showed improvement and near-remission concomitant with a 62% decrease in serum IgE levels (67).

Furthermore, very exciting recent evidence suggests that oxidative stress is involved in the pathophysiology of melanoma and nonmelanoma cancer (68) and that vitamin E slows melanoma growth by promoting tumor cell apoptosis and inhibiting vascular endothelial growth factor-mediated angiogenesis (69,70).

Of great interest to the cosmeceutical formulations, there is the clinical evidence that topical vitamin E is indeed effective in reversing the appearance of photoaging. Figure 5 demonstrates the dramatic correction of periorbital wrinkles after four months of once-daily application of 5% d-α-tocopherol cream. Histologic confirmation of correction of the UV-induced epidermal hypertrophy with thickened stratum corneum, increased apoptotic "sunburn cells" in the basal layer, and disruption of dermal collagen and elastin was demonstrated in mice after eight weeks of topical treatment (KE Burke, L Ricotti, EG Gross, unpublished observation). Resolution of post-UV inflammation was also observed. Further electron microscopic analysis confirmed correction of collagen and elastin fiber
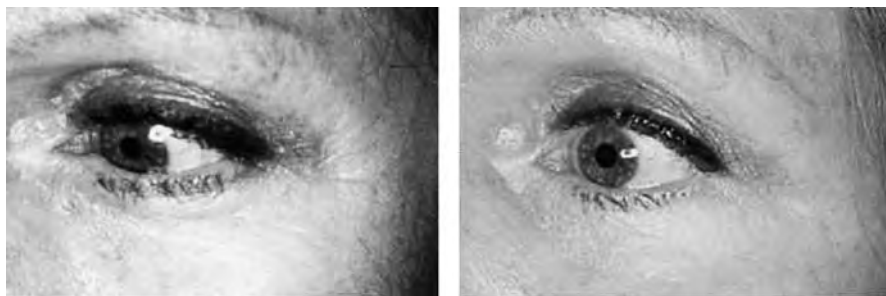
Figure 5 Correction of periorbital wrinkles after four months of once-daily treatment with 5% d-α-tocopherol cream.

damage and demonstrated repair of UV-induced disruption of collagen fibers and basement membrane anchoring fibrils. This correction of UV damage by topical d-α-tocopherol (5%) is as effective as that of topical tretinoin (retinoic acid), the "gold standard" of topical anti-aging.

SELENIUM

Background

Selenium (Se) was recognized to be an essential trace element in humans and animals in the late 1950s. A decade later, anticarcinogenesis was suggested by statistical correlation of decreased cancer mortality with increased Se in the diet in the United States (71). Scientific evidence indicates that indeed Se plays a role in cancer prevention (72–76). Se was shown to inhibit growth and to stimulate programmed cell death in a variety of cell culture studies, including human tumor cell lines in vitro (77). Hundreds of animal studies demonstrate that Se can reduce tumor yields: moderate Se supplementation at levels above the dietary requirements has been shown to decrease the number of tumors induced by several chemical carcinogens and viruses and to reduce the incidence of spontaneous mammary tumors (78) as well as the growth of other transplanted tumors (78).

Some, but not all, epidemiological studies have found a reduced risk for several kinds of cancer associated with a higher blood concentration of Se (79,80). A decreased Se concentration and glutathionine peroxidase (GPX) activity in blood and, interestingly, an increase of these parameters in malignant tissue was found in lung cancer patients (80). An initial study of 240 non-melanoma skin cancer patients in good general health demonstrated a significantly lower mean plasma Se concentration than control subjects without skin cancer (81). In fact, those patients whose blood concentrations were in the lowest decile had 4.4 times the incidence of skin cancer as those in the highest decile (81).

In a 10-year prospective study of 1312 patients with a history of basal cell or squamous cell carcinomas of the skin, Se treatment did not protect against further development of such skin cancers; however, it did reduce total cancer incidence, total cancer deaths, and the incidence of lung, colorectal, prostate, and total non-skin cancer (82,83).

Mechanisms of Action

There is extensive evidence that Se prevents the accumulation of free radicals, thereby protecting from UV damage and fortifying the immune system. Se is an essential cofactor for the intracellular antioxidant enzymes GPX and thioredoxin reductase (TDR) (84). Se is incorporated covalently into proteins of this GPX-TDR family of selenoenzymes (85) as well as into other selenoproteins (86) that may mediate some of the protective effects of Se on UVB-induced cell damage. Through the activities of these enzymes, Se quenches free radicals which would otherwise damage DNA proteins and cellular membranes.

Precise molecular mechanisms are being extensively researched. Protection of keratinocyte DNA was demonstrated by decreased 8-hydroxy-2-deoxyguanosine formation after UV irradiation (87,88), though there was no protection from pyrimidine dimer formation (87). There is evidence that L-selenomethionine (SeMet) induces a DNA repair response in human fibroblasts in vitro (89), perhaps by redox regulation of the DNA repair branch of the p53 pathway (90). In fact, different chemical forms of Se differently modify p53 (each by phosphorylation of specifc cysteine and threonine residues) to induce DNA repair or apoptosis after DNA damage (91). Further cellular protection has been

demonstrated by a decrease in UVB-induced lipid peroxides in keratinocytes (87) and fibroblasts (92) by pre-treatment with SeMet.

Finally, in vitro both SeMet and Se sulfide protect keratinocytes (87,93,94), melanocytes (87,93), and apoptosis (87,95). Interestingly, keratinocytes have twice the GPX activity of fibroblasts which correlates with greatly increased resistance to UVA-induced cell death for keratincytes (96). The fact that Se may prevent UV-induced cell death by p53-independent pathways is evidenced by the demonstration that pre-incubation of cultured human keratinocytes with sodium selenite or SeMet protects from UVB-induced apoptosis without decreasing levels of UVB-induced p53 (97).

Se may also be of particular importance in pigmentation through TDR. Located on keratinocyte membranes, TDR prevents UV oxidation of thioredoxin (which would otherwise enhance tyrosinase synthesis of dihydroxyphenylalanine, the precursor of melanin) (98,99).

Se has other advantageous action on the skin. Clinically, a direct anti-inflammatory effect by oral sodium selenite in Selye granuloma induction in rats was demonstrated (100). This anti-inflammatory action might be a direct result of decreased oxidative damage to cell membranes.

Finally, Se also increases cellular immune responses by several mechanisms, including increasing interleukin IL-2 receptor function (101–103) (thus making cells more resistant to oxidative stress) and through enhanced production of eicosanoids (101).

Effective Topical Formulation

Topical preparations containing Se sulphide are frequently used for the treatment of tinea versicolor, seborrheic dermatitis, and dandruff. However, the Se from these preparations is not absorbed by the skin (104). Se can be effectively absorbed transdermally when applied as SeMet, giving increased skin and liver levels of Se after topical application of 0.02% SeMet to mice (105).

Substantiation of Efficacy

Topical SeMet was shown to be effective in protecting against acute and chronic UV damage to the skin. Concentrations as low as 0.02% increased the MED in humans (106) and decreased acute erythema and blistering as well as later UV-induced tanning and skin cancer in Skh:2 mice (105).
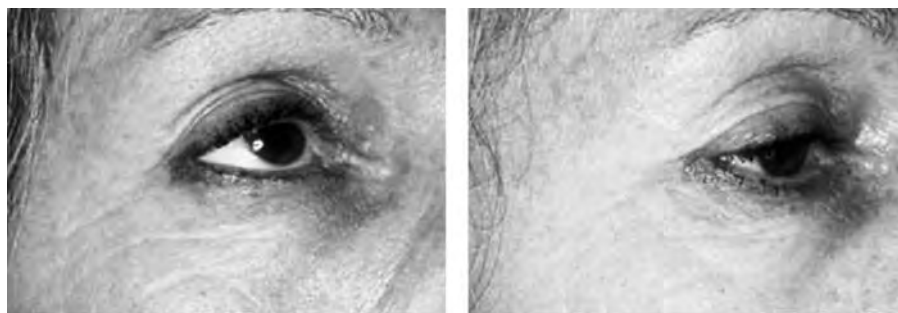
Figure 6 Correction of periorbital wrinkles after four months of once-daily treatment with 0.05% L-selenomethioinine lotion.

Furthermore, topical SeMet is highly effective not only in preventing but also in reversing the appearance of photoaging. As shown clinically in Figure 6, periorbital rhytides are decreased significantly in a 56-year-old woman after four months of once-daily application of SeMet (0.05%) cream.

This enhancement of repair of chronic photoaging at the cellular and molecular level was confirmed by histologic and electron microsopic analysis in mice (107). UV-induced hyperkeratosis and epithelial hyperplasia markedly decreased; irregular, damaged collagen was replaced with newly synthesized, fine fibrillar homogeneous collagen; solar elastosis was repaired; and UV-induced infammation resolved—all as (or more) effectively as comparable treatment with topical tretinoin (107). Electron microscopy confirmed repair of dermal collagen and basement membrane anchoring fibrils.

NEW COMBINATIONS OF ANTIOXIDANTS

Vitamin C with Vitamin E

As shown in Figure 3, the skin uses predominantly vitamin C to protect the aqueous environment and vitamin E to protect membranes from lipid peroxidation. Since vitamin C is naturally present intracellularly in relatively high concentrations, L-ascorbic acid not only acts directly as an antioxidant and as an essential cofactor in the synthesis of collagen, but also regenerates oxidized membrane vitamin E, so that the vitamin E need not be replaced (108). Oral vitamin C with E in high doses protects against UV-induced erythema in humans (109,110) whereas either vitamin alone is less effective (110). Alone each topical L-ascorbic acid (15%) and α-tocopherol (1%) give two-fold protection, whereas combined they provide four-fold protection against UV-induced erythema and thiamine dimer formation in porcine skin (111). This protection from UV-induced erythema (112) and tanning (113) by vitamins C and E combined with melatonin was further demonstrated in humans. Fortunately, mixing these hydrophilic and lipophilic antioxidants in a topical formulation stabilizes each (111) for a cosmetically attractive application.

Vitamins C and E with Ferulic Acid

Ferulic acid is a potent phenolic antioxidant found ubiquitously and in high concentrations in the cell walls of grains, fruits, and vegetables where it is conjugated with mono-, di-, and poly-saccharides and other compounds (114,115). As a potent antioxidant, ferulic acid protects membranes from lipid peroxidation and is synergistic with ascorbic acid (116). Anticarcinogenesis has been demonstrated for pulmonary (117) and colon cancers (118). Topical ferulic was shown to inhibit UVB-induced erythema (119). In a topical preparation, ferulic acid stabilized vitamins C and E and added substantial synergistic photoprotection doubling efficacy as measured by both erythema and sunburn cell formation from four-fold to eight-fold (120). Inhibition of apoptosis correlated with decreased thymine dimer formation and reduced induction of both caspase-3 and downstream caspase-7 (120).

Vitamin E with L-Selenomethionine

In many biologic systems, vitamin E and Se often act synergistically. Borek et al. (121) demonstrated that Se and RRR-α-tocopheryl succinate act alone by different mechanisms to prevent radiogenic and chemically induced transformation in vitro. They further showed that there was additive protection when both were used together (121).

Comparing and combining topical SeMet with oral d-α-tocopheryl acetate and topical d-α-tocopherol (122), the topical combination was less effective than topical vitamin E alone in prolonging the onset and in decreasing the incidence of UV-induced skin cancers in mice (122). Topical SeMet with oral vitamin E was more effective than either alone. In reducing UV-induced pigmentation, topical SeMet with topical or with oral vitamin E was more effective than any one antioxidant alone, particularly during the first eight weeks of UV exposure (122). Topical SeMet (alone or with vitamin E) prevented all blistering after initial UV exposure.

SOY EXTRACT: GENISTEIN

Background

Genistein is an isoflavone isolated from soy, the structure of which is shown in Figure 7. Recent interest in genistein has been stimulated by epidemiological studies which correlate diets high in soy with reduced incidence of cardiovascular disease (123), osteoporosis (123), and certain cancers in humans (124–126).

The direct anticarcinogenic action of genistein is documented. Animal studies demonstrate protection against bladder, breast, colon, liver, lung, prostate, and skin cancer with oral genistein (124,127), and dietary soy inhibits chemically induced skin cancer in mice (128). Growth of many in vitro cancer cell lines is inhibited by genistein (127). Genistein also arrests the growth and induces the differentiation of malignant melanoma cells in vitro (129) and inhibits pulmonary metastases of malignant melanoma cells in vivo (130,131).

Mechanism of Action and Substantiation of Efficacy

The mechanism by which genistein inhibits carcinogenesis may be through inhibition of tyrosine protein kinases, the enzymes which phosphorylate proteins necessary for the regulation of cell division and transformation (132). Of particular importance is phosphorylation of TPK-dependent epidermal growth factor receptors which are related to tumor promotion, including initiation of transcription factors, release of inflammatory mediators (as prostaglandins), and stimulation of cell proliferation (133). Genistein was found to downregulate both UVA- and UVB-induced EGF-R phosphorylation in human epidermoid carcinoma cells in vitro (134,135). In mouse skin, genistein also blocks the UVB-induced expression of the photo-oncogenes c-fos and c-jun which promote cell

GENISTEIN: BENEFITING SKIN

Chemical Structure of Genistein
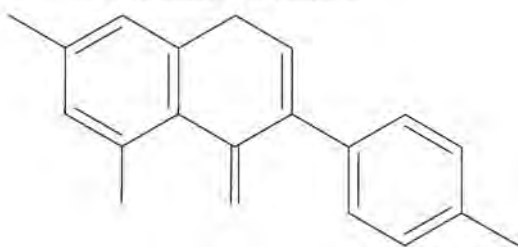
Figure 7 The molecular structure of genistein.

proliferation in oncogenesis (136). Similarly, genistein retards UV-induced apoptotic changes—including caspace-3 and p21-activated kinase 2 activation of human epidermal carcinoma cells (137) and phosphokinase C-delta in human keratinocytes (138).

Genistein is also a potent antioxidant. Genistein scavenges peroxyl free radicals, thereby protecting against lipid peroxidation in vitro (139) and in vivo (140). The decreased incidence of cardiovascular disease with high soy diets may be due to genistein's inhibiting the oxidation of low density lipoprotein (LDL) cholesterol in both aqueous and lipophilic environments. Of direct importance in protection from UV-induced skin damage, genistein has been shown to inhibit in vitro chemical and UV-induced DNA oxidation (141) as well as psoralen plus UVA (PUVA) DNA damage (142,143). The fact that genistein also reduces erythema and histologic inflammation caused by PUVA may have implications for PUVA therapy by reducing possible short- and long-term adverse reactions.

Topical genistein (10 µmol/cm^2) protects against acute and chronic UV damage to the skin (134,135). After exposure of Skh:1 hairless mice to UVB, topical genistein blocked acute skin burns and inhibited UVB-induced cutaneous wrinkling, as demonstrated clinically in Figures 8 and 9 (134,135). Histologic analysis confirmed that topical genistein blocks the signs of chronic photodamage—epidermal hyperplasia and reactive acanthosis with nuclear atypia (Fig. 10) (134,135). At a molecular level, UV-induced damage to DNA (as measured by the biomarker 8-hydroxy-2′-deoxyguanosine) was reduced (144). Inhibition of acute UV-induced erythema with topical genistein (5 µmol/cm^2) was also demonstrated in humans (134,135): Topical genistein (applied 30 minutes before UVB) inhibited by 1 MED the UVB-induced erythema, as shown in Figure 11. Thus, topical genistein may protect human skin against photodamage.

Equally impressive is the fact that topical genistein also inhibits skin cancer, a consequence of chronic UVB damage. Both the incidence and the multiplicity of UVB-induced skin tumors in Skh:2 hairless mice were reduced by about 90% after 25 weeks of UVB exposure (134,135). Figure 12 shows protection from carcinogenesis of representative mice treated with genistein before UVB exposure. Also, after chemical induction and promotion of skin tumors, topical genistein inhibited tumor cell number by 60–75% (144).

Another possible dermatologic benefit of genistein is as a phytoestrogen. The skin has both alpha and beta nuclear estrogen receptors (145) through which estrogen binding can regulate linked genes of proliferation and differentiation. Genistein has a 30-fold

Figure 8 Effect of genistein on UVB-induced acute skin burns in mice were treated topically with 5 µmol genistein 60 minutes before UVB at a dose of 1.8 kJ/cm^2 for 10 days. Photographs were taken 24 hours after last UVB irradiation. (**A**) Negative control (sham irradiation), (**B**) vehicle before UVB, (**C**) 5 µmol genistein before UVB. *Source*: From Ref. 135.
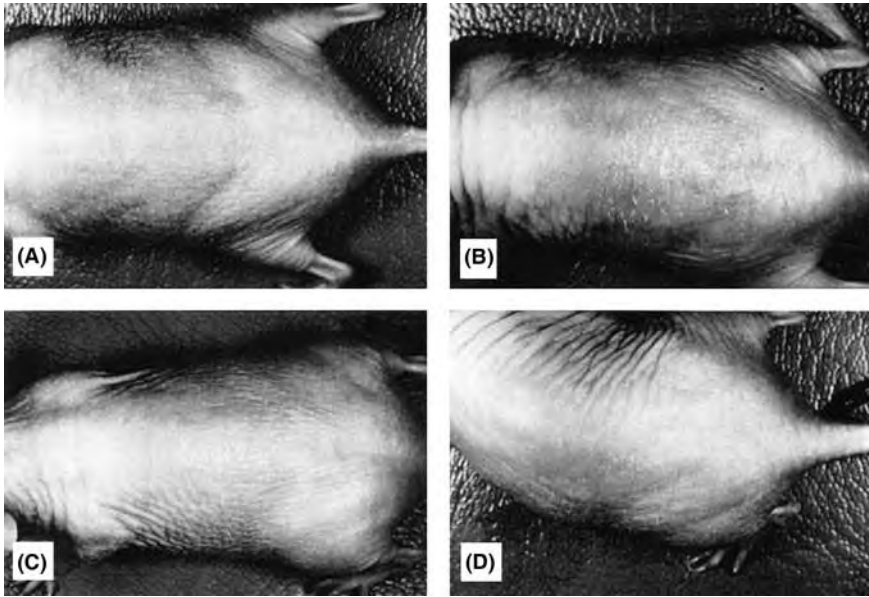
Figure 9 Effect of genistein on UVB-induced chronic photodamage in mice. Skh:1 hairless mice were treated topically with 5 μmol genistein 60 minutes before or five minutes after twice-weekly UVB at a dose of 0.3 kJ/cm^2 for four weeks. Photographs were taken 24 hours after last UVB irradiation. (**A**) Negative control (sham irradiation), (**B**) vehicle plus UVB, (**C**) 5 μmol genistein before UVB, (**D**) 5 μmol genistein after UVB. *Source*: From Ref. 135.

higher affinity for ER-beta than ER-alpha (146), but a greater ER-alpha agonist activity than ER-beta (147). Though estradiol has 700-fold more ER-alpha and 45-fold more ER-beta activity than genistein, the possible biologic effect of genistein through dietary soy isoflavones may be important. Oral (148,149) and topical estrogen (150,151) increase the collagen content of skin which diminishes with aging. This effect is especially dramatic in women during and after menopause (152). Genistein may reduce the atrophic appearance
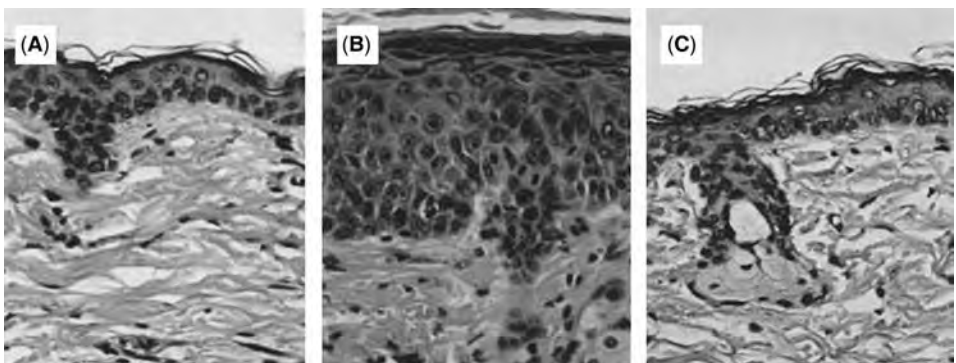
Figure 10 Effect of genistein on histological alterations in mice exposed to UVB. Skh:1 hairless mice were treated topically with 5 μmol genistein 60 minutes before UVB at a dose of 0.3 kJ/cm^2 twice weekly for four weeks. Mice were killed 24 hours after the last UVB irradiation and skin specimens were taken for histology. (**A**) Negative control (sham irradiation), (**B**) vehicle plus UVB, (**C**) 5 μmol genistein before UVB. *Source*: From Ref. 135.
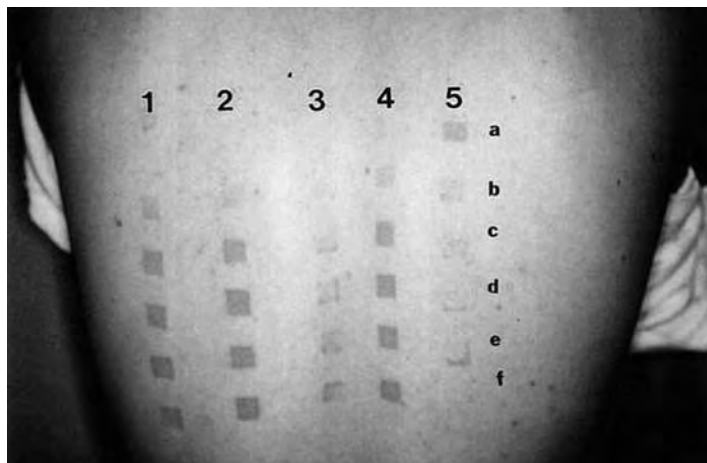
Figure 11 Effect of genistein on UVB-induced erythema in human skin. The study was performed in the phototherapy unit in the Department of Dermatology, Mount Sinai Hospital. UVB fluences used a range from 0 to 100 mJ/cm^2. Genistein was applied to dorsal skin either 60 minutes before or five minutes after UVB exposure. Photographs were taken 24 hours after UVB irradiation. A minimal erythema dose (MED) for this individual was 40 mJ/cm^2. Lane 1: Vehicle before UVB; lane 2: no treatment before or after UVB; lane 3: 1μmol genistein/cm^2 of skin before UVB; lane 4: 1μmol genistein/cm^2 of skin after UVB; and lane 5: dose response of topical genistein applied before UVB (1 MED) at a dose ranging from 0.05 to 5 μmol/cm^2. *Source*: From Ref. 135.

of aging skin both by preventing photodamage through inhibition of metalloproteinases in human skin (independent of sunscreen effect) and by stimulating collagen synthesis. Indeed, genistein does increase collagen gene expression in fibroblasts in vitro (153).

Thus, topical genistein shows promise not only in protecting the skin against acute and chronic photodamage but also in enhancing the diminished collagen synthesis of normal intrinsic aging.

Challenges in Formulation

As described above, topical 5 μmol genistein has been studied extensively and has been proven to protect from UV damage. Unlike vitamin C, genistein is a stable molecule. Unlike vitamin E and Se, genistein is absorbed transcutaneously to give protective activity. The only challenge in formulation is to have a pure source of genistein without other soy contaminants.

ALPHA-LIPOIC ACID

Background

R-Alpha lipoic acid (α-LA) is synthesized in the mitochondria of plants and animals, including humans. Natural α-LA is covalently bound to proteins via lysine; thus only minimal free α-LA enters the circulation after biosynthesis or eating α-LA-rich food (22). The lipoamide is a required co-factor for two enzymes in the citric acid cycle. It is also essential for the formation of a cofactor required in nucleic acid synthesis and for the metabolism of branched-chain amino acids.
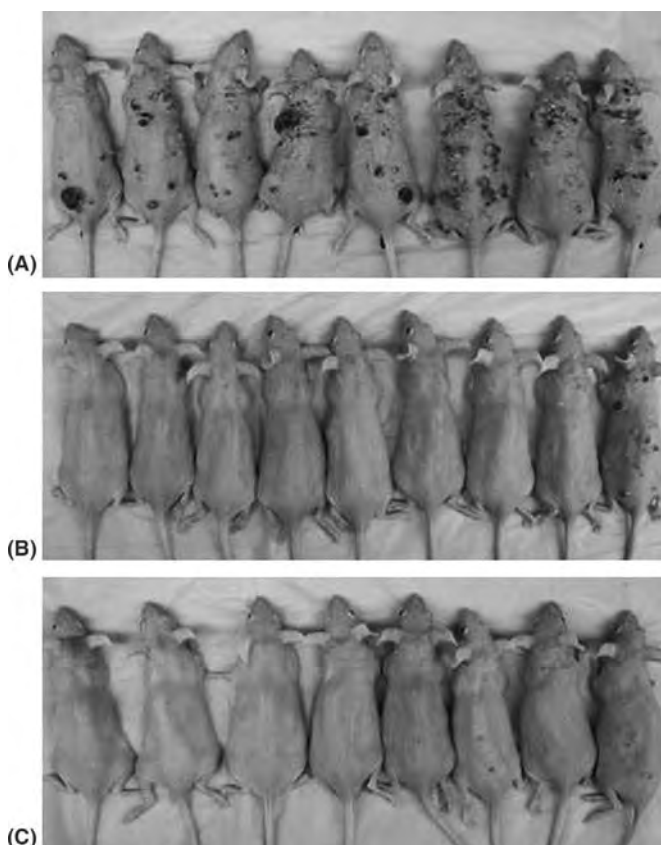
Figure 12 Representative photograph of inhibition of photocarcinogenesis in mice treated with genistein. (**A**) Hairless mice irradiated with 0.3 kJ/m^2 thrice weekly for 25 weeks. (**B**) Mice treated with 1 μmol genistein before UVB exposure. (**C**) Mice treated with 5 μmol genistein before UVB irradiation. *Source*: From Ref. 135.

With oral supplements of free α-LA, unbound α-LA is transported to tissues (22). Free α-LA is rapidly metabolized by the liver, so that the half-life in blood after absorption is only about 30 minutes, limiting the amount delivered (22). High tissue levels are short-lived since most free α-LA is rapidly reduced to dihydrolipoic acid (DHLA), as shown in Figure 13 (21,22).

Notwithstanding this transient availability, free α-LA has been shown to be therapeutic for autoimmune liver disease by binding autoantibodies, heavy metal intoxication by trapping circulating metals, diabetic polyneuropathy by preventing oxidative damage, and mushroom poisoning (22). Although not normally found in significant amounts in the skin, α-LA is a good candidate for topical application (21,154):

- As a small, stable molecule, it could successfully be percutaneously absorbed.
- As a potent antioxidant it might protect from UV and other free radical environmental changes;
- Because it is soluble in both aqueous and lipid environments, it can interact with oxidants and antioxidants in many cellular compartments.
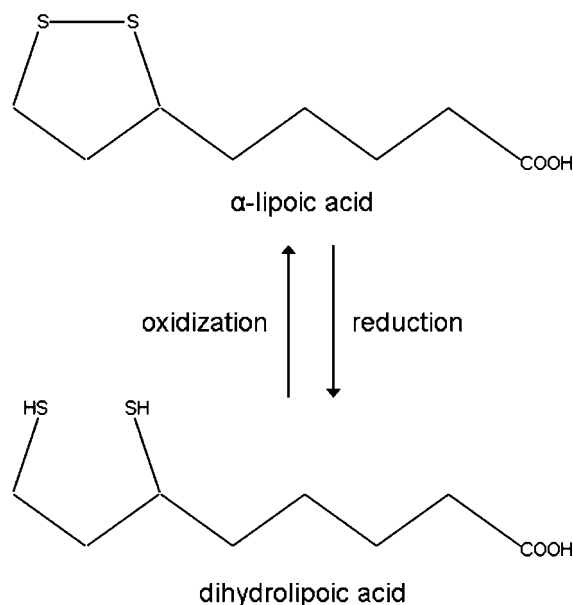
Figure 13 The molecular structures of α-lipoic acid and dihydrolipoic acid.

Mechanisms of Action

Topical α-LA with its metabolite DHLA could protect the skin from oxidative stress in several ways. Both α-LA and DHLA are highly effective antioxidants, as summarized in Table 1 (22). DHLA is actually the more potent form. Both successfully scavenge ROS in vitro and in vivo. However, pro-oxidant activity has been observed. This occurs when an antioxidant reacts with a ROS scavenger, forming a product that is more harmful than the scavenged ROS. Fortunately α-LA can act as an antioxidant against the pro-oxidant activity of DHLA (22). Both α-LA and DHLA further provide antioxidant activity by chelating Fe2+ and Cu2+ (α-LA) and Cd2+ (DHLA) (22).

      DHLA, unlike α-LA, has the capacity to regenerate the endogenous antioxidants vitamin E, vitamin C, gluthatione, and ubiquinol, as illustrated in Figure 3. This is clearly

Table 1 Antioxidant Activity of α-Lipoic Acid and Dihydrolipoic Acid (DHLA)

	α-Lipoic acid	DHLA
Antioxidant	+	+ +
Scavengers reactive oxygen species (ROS)	+	+
Chelates metals: Fe^{2+}, Cu^{2+}	+	−
Cd^{2+}	−	+
Regenerates endogenous antioxidants (vitamin E, vitamin C, glutathione, ubiquinol)	−	+
Repairs oxidatively damaged proteins	−	+
Pro-oxidant	+	+

Abbreviations: +, indicates activity; + +, indicates greater activity; −, indicates no activity.
Source: Adapted from Ref. 22.

of great importance for skin, since UV exposure directly depletes especially ubiquinone and vitamin E as well as vitamin C, thereby stressing the other linked antioxidants (154). Regeneration of these major membrane and cytosol antioxidants gives cascading protection. Increases in the other important antioxidants (intracellular glutathione and extracellular cysteine) are noted when α-LA is added to cell cultures (22). Vitamin E deficient animals do not show symptoms (weight loss, neuromuscular abnormalities) when supplemented with α-LA (155).

Although α-LA is a potent antioxidant, it provides no effective protection against UV-induced erythema or cell damage measured as sunburn cells (156). However, α-LA (but not DHLA) acts as an anti-inflammatory agent by reducing the production and inhibiting the binding of transcription factors such as nuclear factor-kappa B (NF-kappa B), thereby indirectly affecting the gene expression of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins (157). DHLA (but not α-LA) can repair oxidatively damaged proteins, which in turn regulate the activity of proteinase inhibitors such as α1-AP, an inflammatory modulator (158). As antioxidants, both α-LA and DHLA are directly anti-inflammatory by virtue of their quenching oxidants secreted by leukocytes and macrophages at sites of inflammation (158).

α-LA may prove to retard and correct both intrinsic and extrinsic aging of the skin as well as other organs (159). By damaging DNA, the ROS continuously formed in normal metabolism may be largely responsible for the functional deterioration of organs with aging. A decrease in cellular protein and DNA as well as in α-LA levels has been measured in aged rat liver, kidney, and spleen (160). Supplementation with α-LA increases nucleic acid and protein levels in the elderly organs (160). Similarly, the age-related decrease of mitochondiral function in cardiac and brain cells can be improved with α-LA supplementation (161). Clearly, aging skin might similarly benefit.

Formulation

α-LA has been found to penetrate rapidly into murine and human skin to dermal and subcutaneous layers. Two hours after application of 5% α-LA in propylene glycol, maximum levels of α-LA were attained in the epidermis, dermis, and subcutaneous tissue (154). The stratum corneum concentration of α-LA predicted the penetration and levels in the underlying skin. 5% of the α-LA was converted to DHLA in both the epidermis and dermis, leading the researchers to conclude that both keratinocytes and fibroblasts reduce α-LA (154).

Efficacy

To evaluate possible improvement to photodamage, a split-face study was done on 33 women (162). Topical application twice daily of 5% lipoic acid cream for 12 weeks decreased skin roughness by 50.8% (as measured by laser profilometry) when compared with the placebo. Clinical and photographic evaluation showed reduction in lentigenes and fine wrinkles in this and one other study (163). Clearly, topical α-LA should be further investigated by quantitative techniques to confirm these results and to elucidate mechanisms of action.

UBIQUINONE

Background

Ubiquinone (coenzyme Q10, Figure 14) is so named because it is ubiquitous in virtually all living cells, excluding some bacteria and fungi, although the level is quite variable. Since most human tissues synthesize ubiquinone, it is not considered to be a vitamin.

Ubiquinone is primarily located in the inner mitochondrial membrane where it is essential for the production of the ATP required for all vital cellular functions (164). Until recently, ubiquinone was thought to function only in energy transduction; however, with the discovery that ubiquinone is also an antioxidant within subcellular membranes, new roles are now being recognized. Ubiquinone can regenerate reduced tocopherol, as depicted in Figure 3. In fact, within membranes the amount of ubiquinone is from three to thirty times that of tocopherol (165). Without ubiquinone, the regeneration of tocopherol would be very slow (166,167).

Mechanisms of Action

The fact that ubiquinone can serve not only as an energy generator but also as an antioxidant in the skin has been investigated (168,169). In cultured human keratinocytes exposed to hydrogen peroxide, the detrimental increase in the activity of phosphotyrosine kinase was suppressed and the loss of glulathione was prevented (169). Ubiquinone (0.3%) also suppressed the UVA-induced reduction of mitochondrial membrane potential in fibroblasts from both young and old human donors (169). Finally, the UV-induced oxidative damage to DNA in keratinocytes in vitro was reduced significantly with ubiquinone (169).

Ubiquinone can retard loss of hyaluronic acid and slowdown of cell division—both manifestations of intrinsic aging. Aged human fibroblasts in vitro produce less glycosaminoglycan and proliferate more slowly than young cells. The addition of ubiquinone increased levels of glycosaminoglycan as well as rates of cell division (169).

Ubiquinone further protects from the UVA-induced degradation of collagen. Both ubiquinone and vitamin E were shown in vitro to suppress fibroblast production of UVA-induced collagenase, thereby markedly retarding collagen breakdown (169). Ubiquinone suppressed collagenase expression over a longer period of time than did vitamin E.
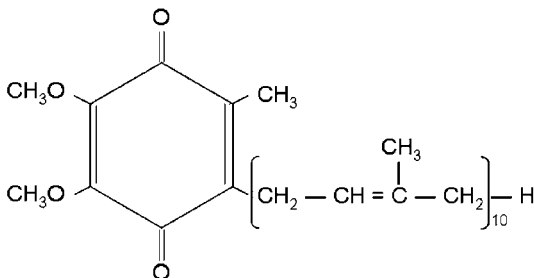
Figure 14   The molecular structure of ubiquinone. The "head" of the ubiquinone molecule is a fully substituted quinone ring which does not allow addition reactions with thiol groups in the cell (such as GSH). Ubiquinones vary by the length of the "tail": Q10 has 10 isoprene units. Humans can synthesize Q10 out of the other coenzymes Q1 to Q9, though this ability decreases with age.

before treatment   week 5   week 10
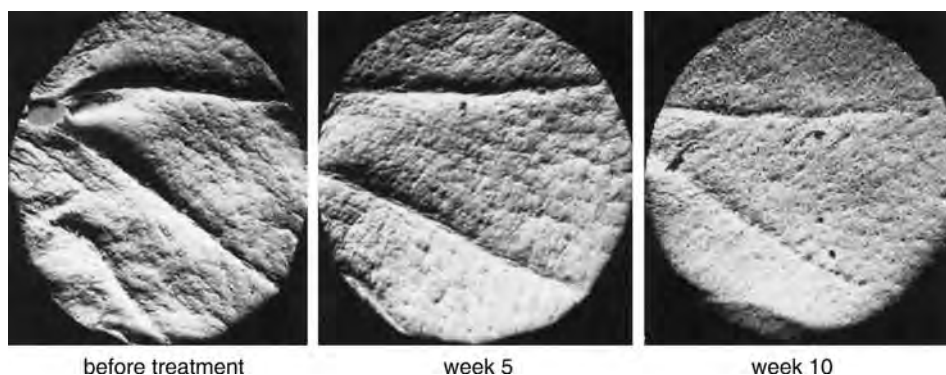
Figure 15 Reduction of wrinkles with ubiquinone. Silicone replicas of the skin, analyzed by laser profilometry, show a significant reduction in the depth of periorbital fine lines and wrinkles in a 46-year-old female after 10 weeks of twice-daily application of ubiquinone cream (Eucerin Q10 Anti-Wrinkle Sensitive Skin Creme). *Source*: From Ref. 168.

Formulation

The concentration of ubiquinone is highest in organs with high rates of metabolism such as heart, kidney, and liver, where it functions as an energy transfer molecule (164). In skin, the level of ubiquinone is relatively low, with 10-fold higher levels in the epidermis than in the dermis (169). Thus, the epidermis might potentially benefit from topical ubiquinone. Indeed it has been demonstrated that ubiquinone can be topically absorbed. Application of ubiquinone in ethanol to porcine skin achieved 20% penetration into the epidermis and 27% into the dermis (169).

Substantiation of Efficacy

Ubiquinone's antioxidant action in skin was confirmed in vitro by sophisticated ultra-weak photon emission (UPE) (169). Increased antioxidants result in decreased UPE. Elderly volar skin demonstrated 33% reduction in antioxidant activity when compared with young skin. This was corrected after one week of twice-daily topical application of 0.3% ubiquinone. After UVA irradiation, a decrease in antioxidant activity was noted; this loss was significantly corrected with topical 0.3% ubiquinone.

    The efficacy of ubiquinol in reversing photoaging was further studied clinically (168). Ubiquinol cream (0.3%) was applied to one-half of the face and placebo to the other once daily for six months. Casts were made of the periorbital rhytides. The improvement can be appreciated in the photographs shown in Figure 15. Quantitative microtopography demonstrated a 27% reduction in the mean wrinkle depth.

    Another clinical measure of photoaging is stratum corneum cell size. With deceased cell turnover time in aged skin, comeocytes become larger. Treatment once daily for six months with ubiquinone cream decreased corneocyte size equivalent to rejuvenation of 20 years (168). Thus, ubiquinone is be an effective antioxidant protecting the dermal matrix from both intrinsic and extrinsic aging, making it a potentially important cosmeceutical.

SUMMARY

Nutritional antioxidants represent a novel category of cosmeceuticals. There is no doubt that higher levels are achieved in the skin through topical application than with oral

supplementation, thus providing a protective antioxidant reservoir in the skin. Current research indicates that topical vitamin E and C and L-SeMet provide UV photoprotection and reverse photoaging. Ubiquinone and genistein may provide photoprotection. In addition, they as well as topical α-lipoic acid may retard both intrinsic aging and photoaging. There is further evidence that α-lipoic acid and ubiquinone may also reverse photoaging. Thus, topical antioxidants continue to be an important area of cosmeceutical research.

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22

What Is Next in Skin Care Cosmetic Products?

Lauren A. Thaman

P&G Beauty, Sharon Woods Technical Center, Cincinnati, Ohio, U.S.A.

The cosmetic industry has changed dramatically over the past 20 years with the introduction of daily UV lotion in the late 1980s to fight future aging. No longer are women searching for hope in a jar but focusing on the latest over-the-counter breakthrough products with clinically demonstrated biological activity. This quest for skin health and youthful beauty has driven many consumers to explore a variety of approaches. It has also triggered a renaissance in the world of skin care where health, beauty, and technology are converging to create new and exciting opportunities.

This frantic search for beauty and youth has stimulated a remarkable growth in the skin care industry. Skin care advances are moving quickly as they mirror advancing technology in pharmaceuticals and biotechnology. Global retail sales of anti-aging skin care products have increased 71% since 2000 (1). In 2004 skin care sales topped $12 billion, with $7 billion of that being spent on facial treatments alone (2). As biotechnological and pharmaceutical research continues to result in technologic advances, skin care companies will continue to spend millions of dollars on incorporating these advances into skin care products. The average woman will find more choices to aid her in the battle against aging, including customized products and new novel ingredients with increased effectiveness and more precise delivery.

COSMECEUTICALS

Clearly cosmeceuticals are the fastest growing segment of the skin care market (3) and are currently the driving force in the field of skin care research (4). Cosmeceuticals are cosmetics that contain biologically active ingredients, and while these ingredients are not classified as drugs, they do have documented functional treatment benefits. When cosmeceuticals are labeled and marketed as cosmetics, they are not regulated by the FDA.

Cosmeceuticals are used primarily to combat the effects of aging on the skin. More women are yearning for healthy, youthful skin, fueling the demand for these anti-aging products. Younger women are also looking to these products as a preventive strategy against aging. Cosmetic companies are investing millions of dollars to develop new and

better actives for anti-aging products, and women of all ages are constantly trying the newest product and consulting their dermatologists for therapeutic approaches to fight the signs of aging.

Retinoids are the most recognized anti-aging ingredient, comprising a family of compounds with structures and mechanisms of action that resemble those of vitamin A. Retinoids are essential nutrients which play a role in cell growth and differentiation (5). Tretinin, the most popular retinoid, increases dermal collagen, cellular differentiation, and proliferation. It has been shown to improve skin's global appearance, particularly affecting fine and coarse wrinkling, roughness, pigmentation, and sallowness (6,7). However, tretinoin is a drug regulated by the FDA. Retinol, first generation retinoid, is often added to over-the-counter cosmetics (8). Retinol must be converted to retinaldehyde and then to all-trans-retinoic acid within the keratinocyte to become active (9). Because retinol is a cosmetic ingredient, it is not labeled as an active ingredient. While not labeled as such, many published studies demonstrate the significant biological action and efficacy of this cosmetic vitamin A derivative. Retinoids and other alternate metabolisms of vitamin A will continue to be key mainstay cosmeceutical ingredients.

Another popular cosmeceutical affecting cellular proliferation is alpha-hydroxy acid (AHA). AHAs increase the type I collagen, mRNA, and hyaluronic acid content of the epidermis and dermis (3). They also renew the stratum corneum by promoting desquamation. Glycolic acid, lactic acid, and malic acid are all examples of AHAs. Newer generation polyhydroxy acids are also being studied; these PHAs provide additional moisturization compared to AHAs, and do not cause the irritating response associated with AHAs (10). They also possess antioxidant properties (10).

A major class of cosmeceutical ingredients is antioxidants that mediate free-radical damage from UV radiation. Since the skin's own supply of free-radical scavengers is limited, topical antioxidants, which scavenge free radicals and protect cells from damage, can attenuate skin damage from UV radiation. Topical antioxidants include vitamins C and E, alpha-lipoic acid (ALA), and coenzyme Q10. In addition to their antioxidant effects, these agents all have other documented anti-aging properties. Vitamin C has collagen stimulating properties and has been shown to be photoprotective (4). Vitamin E decreases free-radical production as well as inhibits collagenase production (11). ALA is a strong intracellular free-radical scavenger (12). It also has anti-inflammatory action, inhibiting the production of pro-inflammatory mediators (3). Coenzyme Q10 (ubiquinone) is present in every cell in the body and acts as a coenzyme in energy production. It has also been shown to improve skin texture (13). One of the bigger challenges to the future use of antioxidants is assuring biological activity from a cosmetic preparation and measuring the antioxidant benefit in a clinical environment. As these challenges become resolved, a significant increase in use and benefit of these ingredients is expected.

The renewed focus on health in today's society has also created a niche for natural and organic products. Women are interested in natural ingredients that make therapeutic claims. This has led to increased popularity of skin care products containing plant or mineral ingredients, especially in the spa market. Organic advocates are willing to pay extra for skin care products that are clearly organically produced (14). Therefore, one of the hottest areas for cosmeceutical ingredients is the utilization and understanding of botanicals. Topical botanicals have been shown to combat reactive oxygen species, as well as often having various secondary effects. Some strong botanicals include tetrahydro-curcumin, pycnogenol, silymarin, and soy extracts (15). The usage of botanicals for their anti-inflammatory function continues to grow. Botanicals have been shown to block inflammatory changes that may result in cutaneous aging. Some common anti-inflammatory botanicals include aloe vera, green tea, and allantoin (15). However, some

newer research suggests the molecular structure, as well as the formulation delivery system, strongly affects the biological activity of botanicals. Understanding the effect and potential of botanicals as cosmeceutical ingredients will likely continue to be a key industry focus.

There are several different types of growth factors of both plant and animal origin that have been incorporated into cosmeceuticals. Furfuryladenine (kinetin), a synthetic plant growth factor that delays senescence of plant cells, has shown in vitro benefits in retarding cellular aging (16). Transforming growth factor-beta 1 is an important human growth factor with therapeutic potential because of its role in neocollagenesis (3). Human growth factors are relatively under explored by the cosmetic industry today and given the negative public view associated with this class of ingredients it is unlikely that they will be a top focus area in the coming years.

Stimulating the skin's natural repair and rejuvenation system by topically adding skin functional ingredients like peptides, hyaluronic acid, niacinamide (vitamin B3), estrogen, and dimethylaminethanol will continue to show promise in improving the appearance and texture of skin. Delivering these relatively large molecules to the biological key targeted area to maximize the effect remains the key barrier to skin aging damage reversal or stimulation. Research in this area will continue with the next wave of cosmeceutical ingredient breakthroughs.

NUTRACEUTICALS

Nutraceuticals provide beauty benefits from the inside out; their goal is to enhance beauty by improving health. There are several dietary supplements that have been developed to promote skin health in particular. These supplements provide vitamins and nutrients especially involved in skin physiology. The challenge for the nutraceutical industry is to definitively measure the benefit of these oral supplements in clinical testing. In the future it is expected that more published clinical data will be available, as well as industry-regulated labeling systems to describe the claimed benefits.

MEDICAL MIMICS

The growing demand for anti-aging products has led to the development of "medical mimics." These are new cosmetic alternatives to costly dermatologic procedures and surgeries. "Facial relaxers" are gaining popularity as an alternative to Botox injection. Argireline, a synthetic peptide that has been touted to relax facial muscles by inhibiting the neurotransmitter catecholamine, has been advertised as having impressive wrinkle reduction effect (17). Several companies have developed home products that mimic microdermabrasion. These products use lower dose crystals and sometimes a warming agent to smooth, polish, and resurface the skin, producing results similar to office dermabrasion. Utilizing lower levels and less aggressive chemical peel acid ingredients, at-home chemical peels have also become popular. While home laser treatments are not yet available, it is expected that low dose home lasers are in the not so distant future for skin texture improvement and hair removal. It is expected that the "medical mimic" trend will continue as women try to balance their busy lives.

CUSTOMIZED PRODUCTS

The genomics revolution has already begun to transform the pharmaceutical industry, and it is now making its mark on the cosmetic industry as well. At the heart of this revolution is the ability to generate and assemble massive amounts of DNA sequence information. We are now able to identify key genes in biological processes such as skin aging through a method called gene expression profiling. Single nucleotide polymorphisms (SNPs) represent the genetic basis for inter-individual differences in disease susceptibility, including aging. The identification and mapping of these SNPs is an area of active biotechnologic research.

As a result of these advances, two promising applications of the genomics revolution are beginning to develop: (i) the use of an individual's DNA sequence information as the basis for the development of improved clinical study design and preventative and diagnostic strategies and (ii) the use of DNA sequence information to develop personalized medicines and products. There are several factors that will influence when and how the DNA sequencing will be applied to the development of cosmetic products (18). These include the progression of the science, consumers' willingness to use their DNA sequence for product choices, and market considerations. Ideally, this genetic technology will allow cosmetic companies to identify specific skin qualities—such as texture, pigmentation, hydration, and wrinkles—and alter products to meet individual skin needs.

SKIN TONE ALTERATION

Skin tone is an area of dissatisfaction for many women around the world. Clear, fair skin tones are the goal in Asia, and skin lighteners have been popular there for many years. However, they are now gaining popularity in the west as well. They can also be used to treat disorders of hyperpigmentation, such as age spots. Tyrosinase is a key enzyme in the production of melanin. Phenolic skin lightening agents such as hydroquinone interfere with melanogenesis by acting as competitive inhibitors of tyrosinase, so that the skin is less pigmented. Non-phenolic skin lightening agents, including glucosamine, kojic acid, azelaic acid, and licorice extract, also inhibit tyrosinase activity. Skin lightening agents are now being incorporated into bar soaps and color cosmetics as well.

In western countries, where darker skin is often idealized, self-tanners continue to increase in popularity. These usually contain dihydroxyacetone, which reacts with keratin protein in the stratum corneum to form melanoidins to give the temporary brown color to the skin. Because the stratum corneum is continually sloughed, the results are temporary. Manufacturers continue to work toward developing self-tanners that are odorless, quick to dry, and unlikely to streak (19). They also are working to improve delivery systems, including wipes, sprays, and foams.

Optical technology is now being incorporated into products to improve the appearance of skin. These new products do not change the skin at all, but when they are applied to the skin, they improve its appearance. The basis for this technology is that tiny particles can reflect and emit visible light from the skin. When used in cosmetics, the resultant reflected light can help hide wrinkles, large pores, and even cellulite and make the skin appear healthier (20).

Cosmetic companies continue to actively research and promote products to decrease cellulite. Ingredients such as caffeine, kiwi and green apple extracts, shiitake mushroom extract, gingko biloba, and seaweed extracts are all being incorporated into products

intended to firm the skin, increase elasticity, and decrease cellulite (21). Although none of these products have delivered the cure, women everywhere continue to have hope.

DELIVERY SYSTEMS

Active research continues in the area of delivery systems for cosmetic products. Particulate delivery systems such as liposomes, which are tiny, hollow lipid spheres, are used to carry active ingredients into the skin. However, smaller, more specialized transportation systems are being developed; these include nanoparticles, microcapsules, and millicapsules.

Nanotechnology is making its way to the forefront of the cosmetic industry. Nanoparticles are solid hydrophobic spheres with an average particle size of less than one micron; they have high cationic charge density to improve their deposition onto the target site and prevent them from being washed off during rinsing (22). This bioadhesive quality also reduces the need for reapplication. The hydrophobic quality of the nanospheres sustains the diffusion rate of the active ingredients, which allows their release over an extended period of time. The nanospheres have improved stability when compared with emulsion-based delivery systems, such as liposomes. This enhanced stability prolongs product shelf life. In addition, the substance to be delivered does not have to be soluble in the vehicle, since it can be dispersed in the solid matrix. Incorporating an ingredient such as a sunscreen into nanoparticles in a skin care product allows the product to block UV light, but does not interfere with the look and feel of the lotion. As nanotechnology advances, it may enable the development of more customized and effective personal care products.

NEW USERS

Male grooming is one of the fastest growing sectors in the cosmetic industry (23). There are significant differences between men's and women's skin; men's skin tends to be less acidic, thicker, oilier, and hairier (24,25). By using products developed specifically for their skin type, men will achieve better results. Products being developed particularly for men include not only moisturizers, but also products to combat aging, self-tanners, blemish-control products, concealer products, and bath and shower products. These cosmetic products will be developed and promoted to seem masculine, so that the average male will feel comfortable using them. Consistent with this trend it is expected there will be an increase in male visitors to the dermatologist's office for cosmetic procedures.

THE SKIN CARE MARKET

More effective anti-aging ingredients and formulations are being developed every day. Cosmetic alternatives to dermatological procedures will be increasingly available for the average woman, and technical innovations to cosmeceuticals will allow skin care products to deliver active ingredients more effectively and with greater precision. Emerging genetic-based technology will enable the development of targeted products that are customized to meet the needs of today's individual man or woman. In addition, the growing concern for personal health will further expand the nutraceutical market. With the increase in consumer expectations and the continuation of changing trends, the collaboration between the dermatology professional community and skin care product innovators must continue to be fostered.

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Index

409