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ORIGINAL ARTICLE

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Natural ingredients in cosmetic products—A suggestion for a screening series for skin allergy

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Abstract

Background: Naturally derived cosmetic product ingredients of both plant and animal origin are being included increasingly in product formulations in order to cater to consumer preferences. They may be an overlooked cause of reactions to cosmetic products in some patients with dermatitis.

Objectives: To identify naturally derived cosmetic product ingredients with allergenic potential (type I and type IV) and propose a cosmetic screening test series.

Methods: The study was conducted in two steps. The first step was a market survey using a nonprofit application helping consumers avoid problematic substances in cosmetic products. The application contained 10 067 cosmetic products that were label checked for naturally derived cosmetic product ingredients. The second step was a literature search to examine how frequently the naturally derived ingredients were described and related to allergic reactions in cosmetics or other topically administered products.

Results: We identified 121 different naturally derived cosmetic product ingredients that were included in at least 30 cosmetic products. In total, 22 ingredients were selected for a screening test series.

Conclusions: We propose a supplemental patch test and a prick test screening series with naturally derived cosmetic product ingredients for patients with skin reactions to cosmetic products, aiming to identify a cause in more patients than is currently possible.

KEYWORDS

cosmetics, food proteins, natural ingredients, patch test, skin prick test

1 | INTRODUCTION

Cosmetic products labeled as natural are increasing in popularity.[1,2] This is due to a general belief among consumers that these products are safe and have health and environmental benefits.[2,3] However, there is no clear official or legislative definition of what natural covers.[2] According to European cosmetic regulations, natural ingredients in cosmetics refer to the origin of the ingredients in the products and production method.[2] In this study, we define natural ingredients as plant- and animal-derived ingredients. Cosmetic products with and without natural ingredients are known to cause skin reactions, but these are underreported, as people tend to just stop using the cosmetic product suspected of causing a skin reaction without seeking medical advice. In addition, due to an often-delayed onset of symptoms most patients do not to suspect the cosmetic product to be the culprit.[3,4]

Type IV allergy from cosmetics is well known and many allergens have been identified.[1] Type I allergy and protein contact dermatitis caused by food proteins are less commonly diagnosed in relation to cosmetics and may be difficult to identify due to the many different natural ingredients used.[5] New allergens are continuously described, but no recommendations exist regarding test methods or how to select natural ingredients for testing. To date, only very few systematic investigations of the allergenicity of the burgeoning number of new cosmetic product ingredients being included in cosmetic product formulations have been performed. We hypothesize that some patients with dermatitis or other skin reactions, where an allergen is not identified, might be reacting to naturally derived cosmetic product ingredients. Our aim is to establish a screening test series with the natural ingredients commonly used in cosmetic products relevant for both type I and type IV allergies. This can potentially identify new causative allergens among patients with type I and type IV allergies suspected to be caused by cosmetic products.

2 | METHODS

The study was conducted in two steps. The first step was a market survey using the application (app) "Kemiluppen" developed in 2015 by The Danish Consumer Council THINK Chemicals, an initiative under the Danish Consumer Council, which is a nongovernmental organization helping consumers avoid problematic chemical substances when shopping for consumer products.[6] The second step was a literature search to examine how frequently these potential allergens were described and related to allergic reactions in cosmetics or other topically administered products.

2.1 | The application "Kemiluppen"

A market survey was conducted between June and September 2017 using "Kemiluppen" (in English translated to "The Chemicals Magnifying Glass"), a free and nonprofit smartphone app providing consumers an easy overview of allergenic, carcinogenic, and other problematic ingredients or suspected endocrine-disrupting chemicals in cosmetic products. The app functions by the consumer scanning the European Article Numbering (EAN) barcode of a cosmetic product with their smartphone camera, and the consumer uploads pictures of the product and ingredients in the app. The product is further investigated by THINK Chemicals, which manually enters the product name, category and International Nomenclature of Cosmetic Ingredients (INCI) labeling in an anonymized database. The database contains no information on the individual consumer who is scanning the product. THINK Chemicals evaluates the ingredients according to different lists of problematic chemicals, and the ingredient list is also sent to the manufacturer to verify that the entered details are correct.[7] If this has already been done, consumers are instantly informed of possible problematic substances in the product.[8]

In June 2017, Kemiluppen included 10 067 products containing a total of 208 341 labeled ingredients covering 4432 different ingredients. On average, each cosmetic product contained 21 ingredients. The ingredients of all cosmetic products included in the app were reviewed for plant- and animal-derived ingredients by the first author of this article.

2.2 | Literature review

A literature search was conducted in the Medline/PubMed database combining the words "contact allergy" OR "urticaria" in association with (by using AND) the individual ingredients listed in Table 1. Inclusion criteria were articles published until June 2019 describing type I or type IV allergic reactions to the respective natural ingredients. Relevant bibliographical references from identified reports were also reviewed. In addition, standard textbooks on cosmetic ingredients, including natural ingredients, were consulted, in particular Monographs in Contact Allergy Volumes 1 and 2 by Anton C. de Groot.[9-11]

2.3 | Development of a screening test series

To establish a screening test series with relevant natural ingredients, we used two selection criteria:

1. Natural ingredients in Kemiluppen that were included in at least 30 cosmetic products

and

2. Ingredients described as the causative allergen:

in cosmetic or topical pharmaceutical products in more than three patient cases.

or

in ≥20 articles from other (or unknown) exposure sources.

A total of 21 ingredients fulfilled the selection criteria and were examined further.

SAS Enterprise Guide software, version 7.1 (SAS Institute, Cary, North Carolina) was used for data management.

3 | RESULTS

In total, we identified 121 different natural ingredients that were included in at least 30 cosmetic products. The 117 plant-derived and 4 animal-derived ingredients that were included in at least 30 cosmetic products are listed in Table 1. Of these, 18 plant-derived ingredients and 3 animal-derived ingredients fulfilled the criteria to be investigated further.

3.1 | Review of 21 selected ingredients from the Kemiluppen database

In total, 21 ingredients were selected for further investigation and categorized into three groups depending on whether they were reported

TABLE 1 The 121 naturally derived cosmetic product ingredients included in at least 30 cosmetic products in Kemiluppen

Ingredients derived from [common name]:	Botanical or animal source	Quantity in cosmetic products
Cinnamon/cinnamal	***Cinnamomum zeylanicum, Cinnamomum cassia***	**1627**
Aloe	*Aloe barbadensis*	1612
Shea nut	*Butyrospermum parkii nut*	1310
Bee products:	**In total:**	**865**
Beeswax/cera alba/cera flava	**Bee**	**798**
Propolis	**Bee**	**25**
Honey	Bee	25
Royal jelly	Bee	17
Sunflower*	***Helianthus annuus***	858
Jojoba	*Simmondsia chinensis*	714
Almond	*Prunus amygdalus*	701
Wheat	***Triticum vulgare***	**602**
Olive	*Olea europaea*	599
Algae, seaweed	Various species	555
Guar bean	*Guar hydroxypropyltrimonium*	500
Lanolin	**Sheep**	**475**
Soybean	***Glycine soja***	**441**
Coconut	*Cocos nucifera*	390
Avocado	*Persea gratissima*	371
Orange	***Citrus aurantium***	**370**
Argan tree	*Argania spinosa*	361
Chamomile*	***Chamomilla recutita, Chamaemelum nobile***	350
Apricot	*Prunus armeniaca*	349
Rosemary	*Rosmarinus officinalis*	338
Rose	**Various rose species**	**329**
Castor oil plant	*Ricinus communis*	307
Brazilian tropical palm tree	*Copernicia cerifera*	277
Corn	*Zea mays*	271
Macadamia	*Macadamia integrifolia*	270
Camellia	*Camellia oleifera*	266
Rape	*Brassica napus*	264
Lavender	***Lavandula augustifolia***	**230**
Mint	***Mentha piperita, Mentha spicata, Mentha aquatica***	**215**
Rice	*Oryza sativa*	212
Candelilla	*Euphorbia cerifera*	210
Pot marigold*	***Calendula officinalis***	205
Cocoa	*Theobroma cacao*	200
Grape wine	*Vitis vinifera*	194
Lemon	***Citrus limon***	**192**
Witch-hazel	*Hamamelis virginiana*	166
Sesame	*Sesamum indicum*	165
Milk	**Cow/horse/donkey**	**150**
Liquorice	***Glycyrrhiza glabra, Glycyrrhiza inflata***	**146**
Oat	***Avena sativa***	**143**

(Continues)

TABLE 1 (Continued)

Ingredients derived from [common name]:	Botanical or animal source	Quantity in cosmetic products
Pomegranate	*Punica granatum*	142
Silk	Insects	141
Pomelo	*Citrus grandis*	137
Cucumber	*Cucumis sativus*	132
Pelargonium	*Pelargonium graveolens*	125
Eucalyptus	***Eucalyptus globulus***	**124**
Safflower	*Carthamus tinctorius*	124
Field mustard	*Brassica campestris*	106
Salvia	*Salvia officinalis*	100
Tapioca	*Manihot esculenta*	95
Açaí palm	*Euterpe oleracea*	94
Apple	*Pyrus malus*	92
Flax	*Linum usitatissimum*	92
Acacia	*Acacia senegal*	90
Evening primrose	*Oenothera biennis*	90
Wild carrot	*Daucus carota*	87
Magnolia	*Magnolia officinalis*	82
Bergamot orange	*Citrus aurantium bergamia*	79
Lemongrass	***Cymbopogon flexuosus, Cymbopogon citratus***	**79**
Irish moss	*Chondrus crispus*	74
Common bamboo	*Bambusa vulgaris*	73
Coneflower*	***Echinacea purpurea, Echinacea angustifolia***	70
Australian tea tree	***Melaleuca alternifolia***	**68**
Mango	*Mangifera indica*	68
Orbignya	*Orbignya oleifera*	67
Moringa	*Moringa oliefera*	65
Ylang-ylang	***Cananga odorata***	**65**
Brazil nut	*Bertholletia excelsa*	64
Sugar	*Saccharum officinarum*	64
Ginger	*Zingiber officinale*	63
Patchouli	*Pogostemon cablin*	63
Levant cotton	*Gossypium herbaceum*	61
Linden	*Tilia vulgaris, Tilia cordata*	60
Blueberry	*Vaccinium angustifolium, Vaccinium corymbosum, Vaccinium myrtillus*	58
Jasmine	*Jasminum officinale*	57
Barley	*Hordeum vulgare*	55
Elder	*Sambucus nigra*	55
Lemon balm	*Melissa officinalis*	53
Raspberry	*Rubus idaeus*	51
Light Red Meranti	*Shorea stenoptera*	50
African oil palm	*Elaeis guineensis*	49
Candlenut	*Aleurites moluccana*	49
Arnica*	***Arnica montana***	48
Ginseng	*Panax ginseng*	47

TABLE 1 (Continued)

Ingredients derived from [common name]:	Botanical or animal source	Quantity in cosmetic products
Potato	***Solanum tuberosum***	**47**
Willow	*Salix nigra*	47
Birch	*Betula alba*	45
Burdock*	***Arctium lappa***	45
Gotu Kola	*Centella asiatica*	44
Maidenhair tree	*Ginkgo biloba*	44
Juniper	*Juniperus communis*	44
Peanut	***Arachis hypogaea***	**44**
Grapefruit	*Citrus paradise*	43
Mandarin	*Citrus nobilis*	43
Horsetail	*Equisetum arvense*	42
Passionflower	*Passiflora*	42
Lime	*Citrus aurantifolia*	40
Vanilla	*Vanilla planifolia, Vanilla tahitensis*	39
Coriander	*Coriandrum sativum*	38
Fennel	*Foeniculum vulgare*	38
Peach	***Prunus persica***	**38**
Blackcurrant	*Ribes nigrum*	37
Thyme	*Thymus vulgaris*	37
Gardenia	*Gardenia florida*	36
Yarrow*	***Achillea millefolium***	36
Cranberry	*Gardenia florida*	35
Hibiscus	*Hibiscus rosa sinensis*	35
Hop	*Humulus lupulus*	35
Larch tree	*Galactoarabinan*	35
Boxthorn	*Lycium barbarum*	34
Buckthorn	*Hippophae rhamnoides*	34
Borage	*Borago officinalis*	33
Iris	*Iris florentina*	33
May Chang	*Litsea cubeba*	32
Meadowfoam	*Limnanthes alba*	32
Melon	*Carica papaya*	32
Myrrh	*Commiphora myrrha*	32
Common nettle	*Urtica dioica*	32
Murumuru	*Astrocaryum murumuru*	31
Strawberry	*Fragaria ananassa*	31
Sandalwood	*Santalum album*	30

Note: The 18 plant-derived and 4 animal-derived ingredients that fulfilled the criteria to be investigated further are written in bold. The seven Compositae plants are also shown with an (*) asterisk.

to cause type I, type I and IV, or type IV allergic reactions. The ingredients causing type IV reactions were further categorized into two subgroups depending on whether they are well-known allergens, already routinely tested in many centers, or rarely reported allergens. The ingredients are listed alphabetically in each category, primarily by their vernacular name followed by their botanical name.

3.2 | Ingredients causing type I allergy

3.2.1 | Milk

Allergy to cow´s milk is the most common food allergy in children, affecting approximately 2% of all children.[12] Allergy onset is often in

TABLE 2 Type I allergic reactions to cow´s milk in cosmetic products reported in the literature

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2019	16	M	Cutaneous application of a cream containing bovine colostrum to a surgical wound 6 mo after operation.	Urticaria, itching, and wheezing occurred within few minutes. Symptoms responded to systemic epinephrine, hydrocortisone, and chlorpheniramine maleate.	Skin prick test strongly positive to cow´s milk protein.	I	15
1996	35	F	Make-up remover containing casein.	Generalized skin pruritus, dizziness, tachycardia, and profuse sweating immediately after the application to the face.	Skin prick tests positive to cow´s milk and casein. α-Lactalbumin and β-lactoglobulin were negative. Specific IgE to cow's milk and casein were 8.90 and 3.70 kU/L, respectively. Specific IgE to the other milk proteins was negative.	I	17
1987	12 months	M	Casein containing ointment to an inflamed diaper area.	Two episodes of anaphylaxis following cutaneous application of ointment.	Significantly elevated specific IgE antibodies to milk and milk proteins.	I	18
1980	11 months	M	Application of ointment to the area of the napkin or diaper dermatitis.	Flushing, generalized urticaria, and angioedema involving face and lip and mild respiratory distress.	Skin prick test positive to whole cow´s milk, cow´s milk albumin, cow´s milk casein, and cow´s milk whey.	I	19

Abbreviations: F, Female; M, Male.

the first year of life.[13,14] The prevalence decreases to <1% in children ≥6 years of age, but can persist into adolescence and adulthood.[13] The mechanism may be immunoglobulin E (IgE) mediated, non-IgE mediated, or mixed IgE- and non-IgE mediated.[14] IgE-mediated type I allergic reactions account for 60% of reactions. Non–IgE-mediated reactions are mostly type IV allergic, delayed skin reactions.[13,14] In IgE-mediated reactions, symptoms may be from the skin, gastrointestinal, and/or respiratory system and can present as life-threatening anaphylaxis.[15] There are more than 25 different proteins in cow´s milk. Four caseins and the whey proteins—α-lactalbumin, β-lactoglobulin, bovine serum albumin, and lactoferrin—have been identified as allergens.[16] Exposure to milk proteins occurs by drinking cow´s milk or formula-based cow's milk, by being passed through breast milk or via the skin in children who are highly sensitive to milk.[15] Treatment is complete avoidance of milk-containing products, and if the child is breastfed, exclusion of dairy products from the mother's diet.[13] The milk-derived ingredients in the milk-containing cosmetic products registered in Kemiluppen are listed in various forms as milk, whey protein, milk lipids, non-fat dry milk extract, casein, and colostrum. Casein and whey are added to cosmetics for claimed antioxidant, moisturizing, and calming effects, although evidence is extremely limited. Four cases of type I anaphylactic reactions to cow´s milk–containing cosmetics, creams, and ointments following cutaneous application have been described in the literature, all in patients with known cow's milk allergy (see Table 2).[15,17-19]

Horse and donkey milk may also induce sensitization. A few cases describing type I sensitization induced by cosmetic products containing mare´s milk have been reported, as well as anaphylaxis to ingested mare´s milk.[20-24] Cross-sensitization between cow´s milk and mare´s milk is rare.[24,25] One case report has described type I and IV allergic reactions to donkey´s milk in a patient previously known with atopic dermatitis, who had been treated with donkey's milk–containing topical products.[26]

3.2.2 | Peach (*Prunus persica*)

Peaches belong to the Rosaceae family.[27] Peaches have two different sensitization routes. Allergy to peach in Northern and Central Europe is associated primarily with the oral allergy syndrome caused by sensitization to birch pollen and labile proteins known as profilins, like Bet v 1 and Bet v 2, due to cross-reactivity between pollen profilin and the peach profilin Pru p 4.[28,29] Profilins cross-react with homologous proteins in fruits from the Rosaceae family, such as peach, apple, and apricot.[30] Peach allergy is the most common food allergy among adults in Southern Europe.[31] In addition to the oral allergy syndrome, it can cause contact urticaria, anaphylaxis, and severe, potentially life-threatening reactions.[32] In Southern Europe, peach allergy is mediated primarily by Pru p 3, a lipid transfer protein (LTP).[28] LTPs are widespread plant food pan-allergens that are stable (due to being heat-resistant and pepsin-resistant) and are highly conserved proteins of around 10 kD.[33,34] Especially the peach surface fuzz has large amounts of LTP, but also the peel and cutin layers of peaches are rich in proteins and have a higher allergenicity than the pulp with its high carbohydrate content.[35,36] Because of the geographic distribution of LTP, sensitization probably occurs through the skin or airways. Rosaceae allergic patients who are hypersensitive to LTP frequently show both skin and in vitro cross-sensitization and cross-reactivity to many botanically unrelated fruits and vegetables.[37] Peach is added to cosmetics for anti-aging, antioxidant properties as well as skin-

recovering properties after UVB skin exposure.[38-40] To our knowledge, no allergic reactions to peach in cosmetics have been reported in the literature yet, but there are a number of reports of patients experiencing type I allergy while preparing LTP-containing fruit and vegetables, including peaches.[29,41]

3.2.3 | Peanut (*Arachis hypogaea*)

Peanut is a grain legume belonging to the Fabaceae family. It is one of the most allergenic foods and the most common cause of food-mediated type I allergy and anaphylaxis. Exposure is through ingestion, skin contact, and inhalation.[42] The mechanism is IgE mediated and symptoms range from mild urticaria to severe anaphylaxis, even with lethal outcome.[42,43] Allergy to peanuts often begins in childhood and affects 1% of children younger than 5-years-old. Only approximately 20% outgrow the allergy, which often makes peanut allergy a lifelong condition.[42] The estimated prevalence of peanut allergy in developed countries is between 0.6% and 1.0%.[42] Thirteen peanut proteins, Ara h 1 to Ara h 13, have been identified as allergens.[44] Sensitivity to the various peanut antigens differs among geographic locations.[44] Peanut allergic patients can have cross-reactivity to tree nut, soy, and other legumes such as beans, peas, lentils, and lupinus.[45] Peanuts can be processed into peanut oil and the derivatives hydrogenated peanut oil, peanut acid, or peanut glycerides. These are commonly used in foods such as salad dressings and margarine; in pharmaceutical products as vehicles for the active ingredient; in topical and other preparations; and in cosmetic products such as soap, skin cleansers, skin care products, and moisturizers.[46] There are, to our knowledge, no reports of allergic reactions to peanut-containing cosmetic products in peanut allergic patients. One case report described type I allergy from peanut butter used on the skin of a 31-year-old woman.[47] It has, however, been proposed that sensitization to peanuts may occur in children using peanut oil–containing products on a damaged or inflamed skin barrier.[48]

3.2.4 | White potato (*Solanum tuberosum*)

White potatoes belong to the Solanaceae family.[49] Potatoes are widely consumed in most of Europe and are frequently used when introducing solid food to infants.[50] Raw and cooked potatoes can cause type I allergic reactions. The symptoms are usually caused by contact or ingestion, or rarely by inhalation.[51-54] Peeling is the primary cause of potato contact allergy and is usually occupational among food handlers and caterers.[55] Localized reactions to raw potato have been reported in patients who do not react to cooked potatoes, due to heat denaturing of the allergenic proteins.[49] Allergic reactions caused by ingestion of raw potatoes are typically associated with oral allergy syndrome caused by allergens having IgE cross-reactivity with predominantly grass and tree pollen.[50] Type I allergic reactions to cooked potatoes have been reported rarely.[50] The common allergen of potatoes is patatin, a large glycoprotein that has been identified as an IgE-binding protein.[56] Patatin is a cross-reactive allergen in latex-associated potato allergy.[57] There are no reports of cases of allergic reactions to potato in cosmetics or other topical remedies.

3.3 | Ingredients described causing type I and IV allergies

3.3.1 | Oat (*Avena sativa*)

Oat is an edible grain belonging to the Poaceae family. Wild oat is the most common of the oat species and has high nutritional value due to its high protein content.[58] Oat is used as an ingredient in food where it may cause type I allergy.[5] Oat is further used in cosmetic products in various forms including oat kernels, oat meals, oat bran, oat protein, oat flour, oat starch, and oat peptide.[59] Moisturizing creams containing oat protein improve skin barrier function because of its anti-inflammatory, anti-oxidant, and anti-pruritic properties.[60] They are known as colloidal oatmeal products consisting of grinded oat boiled into an extract containing protein, lipids, vitamins, polysaccharides, saponins, flavonoids, and polyphenols.[59] Oat-containing moisturizers and bath therapies have been used widely used as topical treatments of various skin conditions, for example, atopic dermatitis, although the risk of being sensitized to oat through the skin increases when the skin barrier is impaired, as in atopic dermatitis.[60,61] This is seen in the cases below, where all patients but one were treated with oat-containing moisturizers or soap for atopic dermatitis and developed type I and/or IV allergy to oats in the cosmetic products (see Table 3).[62-64] One patient developed oral allergy syndrome after sensitization through the skin.[60] Also occupational allergic contact dermatitis is described in the literature.[65-67]

3.3.2 | Soybean (*Glycine max*)

Soybean is a legume belonging to the Fabaceae family.[45] Soy is among the eight most common allergenic foods, with exposure through skin contact, ingestion, and inhalation causing type I allergic reactions.[45] Allergic reactions include skin, gastrointestinal, respiratory, and anaphylactic reactions.[68] Sixteen IgE-reactive soy proteins, including Gly m 1 to Gly m 8 as the most allergenic, have been identified as allergens.[45,69] Food allergy to soy proteins has been described mainly in young children with atopic dermatitis, but may present later; in a study of 30 patients, the first allergic reaction to soy occurred at a mean age of 19 ± 10 years (range, 3-44 years).[70,71] The prevalence of soybean allergy is unknown.[68] Soy bean is a birch pollen–related allergenic food, and recent studies have shown an increased risk of soy allergy among Central European patients who are sensitized to birch pollen due to IgE cross-reactivity between the major birch pollen allergen Bet v 1 and the homologous soy protein, Gly m 4.[68,70,71] Soy allergic patients may also have cross-reactivity to peanuts, tree nuts, and other legumes such as beans, peas, lentils, and lupinus.[45] Soy derivatives are used as active ingredients in make-up and skin- and

TABLE 3 Type I and IV allergic reactions to oat in cosmetic products reported in the literature

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2016	68	F	Cream.	Facial dermatitis.	Positive patch test to cream and *Avena sativa* oat extract 5% aq.	IV	64
2010	33	F	Cosmetic emollient cream moisturizer.	For 6 mo, facial rash immediately after application of creme. Later, itchy, swollen lips, and pruritic, erythematous papules and patchy lesions on the trunk after eating certain biscuits or bread containing oatmeal.	Positive prick tests to the cream and *Avena sativa* alcoholic extract. Elevated total IgE level (1328 kU/L) and slightly elevated specific IgE antibodies to oat (1.23 UA/mL). Patch test negative to emollient cream.	I	60
2007	0-15	8 NK	Emollient creams containing oat.	Five experienced atopic dermatitis flares, two experienced pruritus, one experienced widespread erythema.	Patch test positive to oat.	IV	137
2002	7	F	Oat cream applied to arms and trunk.	After 15 min, swollen lesions and contact urticaria where the cream had been applied.	Open patch test positive to oat. Oat-specific IgE was positive at 0.76 kU/L.	I	138
2000	3	F	Moisturizer.	Flare up after application on the right arm and the hands.	Patch test ++ positive to *Avena* in cream. Prick test positive to oat.	I and IV	62
1988	14 mo, 2, 14	1F, 2 M	Bathed with a product based on oatmeal extract.	Exacerbations of atopic eczema after baths.	Specific IgE antibodies to oat were positive. Patch test to oat was positive.	I and IV	63

Abbreviations: F, female; M, male; NK, not known.

hair-conditioning agents due to a high content of soy phytosterols.[72] Several allergic reactions, both type I and type IV, to soy and maleated soybean oil in cosmetic products, have been described in the literature (see Table 4). Maleated soybean oil is a reaction product of soybean oil and fumaric acid.[73] One atopic dermatitis patient with type I allergic symptoms related to soy-based ingredients in cosmetic products subsequently developed severe type I allergic symptoms including urticaria, dyspnea, and hypotension after eating soy products.[74]

3.3.3 | Wheat (*Triticum vulgare*)

Wheat is an edible grain belonging to the Poaceae family. It is the most common food grain worldwide due to its ability to grow in various climates.[75] Sensitization to wheat proteins can be oral, percutaneous, perimucosal, and/or rhinoconjunctival, and it may cause different disorders with different immunologic mechanisms.[75,76] Impaired skin barrier as in atopic dermatitis may increase the risk of sensitization via skin.[59] The IgE-mediated type I allergic reactions are most common with symptoms such as urticaria, abdominal pain, or systemic anaphylaxis. In addition, food-dependent exercise-induced anaphylaxis, occupational rhinitis, or asthma (known as Baker's asthma) are seen. Wheat gluten is a large group of proteins comprising approximately 85% of the proteins in wheat and consists of water-insoluble wheat proteins, including monomeric gliadins and highly polymeric glutenins.[77,78] These are implicated in IgE-mediated allergy to ingested wheat, and omega-5 gliadin is an important allergen in wheat-dependent exercise-induced anaphylaxis (WDEIA).[79] The remaining 15% of wheat proteins are water-soluble, nongluten proteins, including albumins and globulins, which also are implicated in wheat allergy and cross-react with grass pollen allergens.[75,80] Wheat protein and wheat gluten can be hydrolyzed enzymatically or chemically to its constituent amino acids to overcome insolubility, a process called deamidation.[81] Hydrolyzed wheat protein (HWP) and hydrolyzed wheat gluten (HWG) are added to skin care and hairdressing products for their emulsifying, stabilizing, moisturizing, and volumizing properties.[80,82,83] For almost two decades, severe allergic reactions to HWP and HWG in cosmetics have been described. There are numerous reports of type I allergic reactions and fewer reports of type IV allergic reactions (see Table 5).

3.4 | Ingredients well-known to cause type IV allergy

The cosmetics products registered in Kemiluppen contain various bee products: beeswax (*cera alba*), propolis (bee glue), honey, and royal jelly. This section focuses on propolis and beeswax, since these two bee products have been described primarily as causing contact allergic reactions in cosmetics.

TABLE 4 Type I and IV allergic reactions to soy in cosmetic products reported in the literature

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2015	30	F	Cosmetic lotions containing soy-based ingredients.	Contact urticaria on fingers. Systemic urticaria, dyspnea and hypotension, after eating soy products.	Specific IgE 19.3 UA/mL. Skin prick test positive for soy extract (10 mg/mL), the cosmetic lotion and a commercially available soymilk.	I	74
2005	43	F	Face topicals containing soy.	Erythema of the nasal tip and on the cheeks.	Prior skin prick test positive to soy. Specific IgE antibodies were detected for soy (19.3 UA/mL).	I	139
2001	55	F	Facial cosmetic cream.	Erythema, swelling of the face.	Patch test positive to the cream, soybean extract and ceramide 3 together (2% petrolatum). Immediate slight erythema to soybean extract dilution 20% eth.	IV	140
2000	48	F	Maleated soybean oil in a facial moisturizer.	Face and neck dermatitis.	Patch test positive to cosmetic creams and maleated soybean oil. Repeated open application test with maleated soybean oil strongly positive.	IV	73
1996	44	F	Facial moisturizing cream.	Itching a few hours after application, dermatitis.	Patch test: + to myristyl lactate 0.5%, + to maleated soybean oil 1.5%.	IV	141
1995	45, 47, 62	3F	Skin repair cream.	Redness, itching and edema of the face and neck.	Patch test: ++ positive to skin repair cream and maleated soybean oil.	IV	142

Abbreviation: F, female.

3.4.1 | Propolis

Propolis, also known as bee glue, is produced by honeybees after collecting resinous material from plants, which they mix with saliva and beeswax to produce propolis. The bees use propolis to repair, strengthen, and narrow the entrance to their hives.[11] Due to geographic location and variability of plant species, the composition of propolis is highly variable. It has more than 300 constituents comprising primarily resin and beeswaxes and aromatic oils and pollen. Propolis has antibacterial, antifungal, and antiviral properties and has been used for thousands of years in pharmaceutical products, apitherapy, and folk medicine.[84] Furthermore, it is used as a dietary supplement and as an ingredient in cosmetic products. The most important allergens are esters of caffeic acid: "LB-1," phenethyl caffeate, benzyl caffeate, and geranyl caffeate.[11] Propolis may cross-react with other allergens and there is a well-known association between propolis and *Myroxylon pereirae* (balsam of Peru).[11] Many allergic reactions are caused by use of topical pharmaceutical and cosmetic products as well as occupational exposure in beekeepers.[11,98] Hausen et al have reported 114 original patients and de Groot has summarized the literature of 70 other reported patients in the literature of type IV allergy to propolis in cosmetic and pharmaceutical products.[11,85]

3.4.2 | Beeswax (*cera alba*)

Beeswax is produced and secreted from eight wax glands in the abdomen of the worker bees of the honey bee (*Apis mellifera*).[10] Beeswax is used by the bees to form cells of the honeycomb for honey storage and protection of the brood in the hive. It has more than 300 constituents, mainly esters of fatty acids and free long-chain alcohols, as well as residues of propolis and pollen.[10] Beeswax is used in cosmetic and pharmaceutical products, in food as a food additive (E901), for coating and glazing of candy and fresh fruit, for making beeswax candles, and for making vax and varnish for leather and wood.[10,86] A recent Swedish study published 17 cases of patients with type IV allergy to beeswax.[86] There are a further eight cases of type IV allergy to beeswax in cosmetics and five cases related to non-cosmetic products reported.[10] Some of these cases might be due to a reaction to propolis in propolis-contaminated beeswax. There are no reported cases of type I allergic reactions to beeswax.

3.4.3 | Cinnamon (*Cinnamomum zeylanicum*)

Cinnamon belongs to the Lauraceae family.[87] The essential cinnamon oil is extracted from the bark or leaves of the tree by distillation.[9] The main component of cinnamon bark oil is cinnamal, which gives cinnamon its scent and taste and has a strong sensitizing potential.[88,89] Cinnamal is used as a fragrance ingredient and often as a nature-identical chemical, and is one of the eight components in fragrance mix I (FMI).[88] The main component of cinnamon leaf oil is eugenol. Cinnamon is used as a spice and flavoring agent in food, sweets, gum and drinks, dentifrices, herbal-based products, and cosmetics.[90,91] Exposure can be through ingestion, skin contact, and inhalation. Allergic symptoms such as urticaria and dermatitis are seen.[90,92] More than 15 cases of type IV allergy to cinnamon oil in cosmetic or pharmaceutical products are described.[9] One of these patients developed a

TABLE 5 Type I and IV allergic reactions to wheat in cosmetic products reported in the literature

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2018	34	M	Occupational anaphylaxis.	Type I allergic reactions with 1-y interval, 5 min after cleaning a tank containing an anti-wrinkle cream. First: Rhinitis, conjunctivitis and sneezing. Later: Contact urticaria, conjunctivitis and dyspnea.	Prick test positive for cosmetic product (10% aq.) and wheat extract. Negative for gluten extract.	I	143
2015	21-73	17 F, 1 M	Soap.	Urticaria, WDEIA.	Skin prick test positive to 0.01% Glupearl 19S solution.	I	131
2013	23	F	Sprayable hair conditioner and another hairspray containing HWP.	Rhinitis, conjunctivitis, dyspnea, angioedema of the eyelids, asthma-like symptoms at work (hairdresser). Contact urticaria, burning and tingling of the hands and soles when exercising.	Skin prick test and open application test positive to products containing HWP.	I	144
2013	22	F	Spray products containing HWP.	Urticaria, work-related sneezing, nasal itching, rhinitis. Two episodes of generalized urticaria and eyelid edema when exercising after having eaten wheat-containing food.	Skin prick test and open application test positive to products containing HWP.	I	144
2013	3	M	Moisturizing cream.	Urticaria on both arms and facial angioedema.	Prick test positive to moisturizing cream and HWP. Wheat prick test negative. Wheat flour-specific IgE positive at 0.61 kU/L. HWP-specific IgE positive at 2.96 kU/L.	I	145
2013	35-60	7 F	Soap.	Contact urticaria and WDEIA.	Prick test positive to wheat, bread, 0,1% soap solution supplemented with HWP-A in saline, and 1 mg/mL HWP-A in saline. Specific IgE for wheat and gluten were detected in all seven patients.	I	146
2012	18-46	3 F	Cosmetics, creams, eye-liners, shampoo.	Contact urticaria.	Skin prick test positive to HWP.	I	81
2012	23	M	Face cream.	Pruritic wheals on the face and neck, bilateral palpebral edema.	Patch test positive to the cream and to 1% HWP in water. Prick tests positive for hydrolyzed wheat extract, malt, cereal mix, oats.	I and IV	147
2011	49	F	Hydrolyzed wheat protein-supplemented soap.	Eyelid edema and dyspnoea eight times while working or walking. Facial wheals and nasal discharge after bathing.	Prick test positive to the soap (0.1% in saline). Wheat specific IgE 1.35 kU/L, gluten specific IgE 1.78 kU/L. Oral provocation tests induced eyelid edema, nasal discharge and dyspnea. Face wash with the soap induced facial wheals.	I	148
2010	28, 34	2 F	Cosmetics.	Recurrent contact urticaria, initially on hands, then more diffused immediately after applying cosmetics.	Skin prick test positive to the cosmetics and HWP.	I	83

TABLE 5 (Continued)

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2010	18, 24	NK	Skin tensing cosmetics, facial cream.	Contact urticaria.	Prick test positive to skin tensing cosmetics containing HWP.	I	149
2009-2017	1 -93	2025 F 86 M	Soap or other products containing HWP.	Itching, eyelid edema, nasal discharge and/or wheals within several to 30 min after using soap or other products containing hydrolyzed wheat.	Skin prick test positive to Glupearl 19S solution.	I	150
2008	NK	7 F	Cosmetics, mainly facial cream.	Contact urticaria immediately after applying cosmetics (mainly facial cream), from different brands, containing HWP. Six had anaphylactic reactions or urticaria after eating preserved foods containing modified gluten. Neither had allergic reactions after eating bread.	Skin tests positive to the cosmetics containing HWP, and in case of food allergy, modified gluten. Skin tests negative to natural wheat flour, but specific IgE to wheat flour were positive in two cases. Specific IgE to gluten were positive in three patients.	I	151
2007	42	F	Moisturizing cosmetic cream.	Intense burning on face, neck and scalp several hours after applying a new moisturizing cosmetic cream and development of a florid, itchy rash over face and neck, which lasted several weeks, settling with the use of topical steroids.	Patch test negative to standard, cosmetic, hairdressing and facial series. Testing with the patient's own cosmetic cream showed a positive reaction. Patch test with the diluted constituents of the cosmetic cream identified an isolated allergy to HWP (50% aq.).	IV	152
2007	3	F	Emollient.	Scaly, erythematous lesions on the knees.	Patch test positive to the emollient and the individual components of the emollient for palmitoyl-HWP.	IV	153
2006	21-53	9 F	Moisturizers, shower gels, shampoos and conditioner.	Contact urticaria.	Positive skin prick tests with the suspected cosmetics and the identified HWP. Skin tests negative to wheat flour extract. Low-moderate levels of IgE specific of wheat flour or gluten.	I	78
2006	NK	3 NK	Shower gel, shampoo, mascara.	Generalized erythema, contact eczema, facial angioedema with generalized urticaria.	NK	NK	154
2002	46	F	Eye cream and body moisturizer.	Contact urticaria.	Skin prick test and open application tests positive to HWP.	I	77
2000	64	F	Moisturizing cosmetic cream.	Itchy, erythematous lesions on the eyelids, face and neck.	Patch test positive to cosmetic cream and to the HWP ingredient of the cream (10% aq.).	IV	82
2000	27	F	Cosmetic cream. Moisturizing body cream containing HWP.	Contact urticaria. Pruritic, erythematous, urticarial rash.	Skin prick test positive to HWP.	I	155

Abbreviations: F, female; M, male; NK, not known.

recurrence of dermatitis after eating cinnamon.[93] Other side effects have been described, and irritant contact dermatitis is seen when patients are patch tested with cinnamon oil 2% or higher.[9] Cinnamal is the second most frequently reported individual chemical causing allergy, with around 350 published cases.[89] There are also several cases of patients reacting to cinnamal in spices, foods, and flavorings, as well as occupational type IV allergy in bakers.[9]

3.4.4 | Compositae plants

Daisy flowers belongs to the Compositae family, which is the second largest family of plants in the world, comprising more than 20 000 species.[10,94] The whole plant, roots, leaves, stalks, flower heads, and extract of the leaves and flowers are commonly used in cosmetics, massage oils, essential oils, folk and traditional medicine, and tea and water/alcohol extracts due to supposed anti-inflammatory and other health effects.[10,94] The most commonly used Compositae plants in cosmetics and pharmaceutical products are *Helianthus annuus*, *Calendula officinalis*, *Arctium lappa*, *Arnica montana*, *Achillea millefolium*, *Chamomilla recutita* and *Chamaemelum nobile*, and *Echinacea purpurea* and *Echinacea angustifolia*.[95] Compositae plants are believed to be the most frequent cause of allergic contact dermatitis of all plants in Europe. Symptoms are often localized to hands and face but might spread to the rest of the body.[10,96] If the symptoms are not treated, contact dermatitis often progresses and becomes chronic. The primary sensitization pathway is via direct plant contact, but the plants cross-react with each other and the prevalence of polysensitization is high.[96,97] Severe systemic type IV allergic reactions can also be seen when ingested.[96,98] The most important allergens are sesquiterpene lactones and thiophenes/polyacetylenes, but not all allergens have yet been identified.[10,94] There are reports of hundreds of cases of type IV allergic reactions to Compositae plants in cosmetics, pharmaceuticals, and as occupational sensitization in masseurs, gardeners, greenhouse workers, florists, pharmacists, and drug sellers.[9,10,94,96,98] A few cases of possible type I allergy to chamomile in a cosmetic cream and enemas have been reported.[99,100] In pollen-food allergy syndrome, patients who are sensitized to mugwort pollen may develop type I allergy symptoms and even severe anaphylaxis upon ingesting the Compositae plant chamomile.[99-101]

3.4.5 | Eucalyptus (*Eucalyptus globulus* and *Eucalyptus citriodora*)

Eucalyptus belongs to the Myrtaceae family.[102] There are two main types of eucalyptus oils. *Eucalyptus globulus* oil is derived from the Tasmanian blue gum *E. globulus*, while *Eucalyptus citriodora* oil is derived from the citron-scent gum *E. citriodora*.[9] The composition of these two oils differs. The dominant ingredient in *E. globulus* oil is 1,8-cineole (eucalyptol) constituting more than 50% of the oil, whereas the main component in *E. citriodora* oil is citronellal. Both essential oils are produced by steam distillation of the leaves, buds, fruits, and bark from the tree and widely used as ingredients in perfume and cosmetics.[9,103] More than 17 patient cases of type IV allergy to eucalyptus oil primarily in topical pharmaceutical products but also in cosmetic products have been reported.[9]

3.4.6 | Lanolin

Lanolin is secreted from the sebaceous glands of sheep.[1] Lanolin consists primarily of wax esters, free fatty acids, and water, although the composition varies due to many factors, such as sheep breed, age, and habitat.[10,104,105] The derivative lanolin alcohol is a complex mixture of organic alcohols obtained by hydrolysis of lanolin. Lanolin and lanolin alcohol have great water-binding and emulsifying properties. They are easily absorbed into skin and hair and are commonly used in cosmetic and pharmaceutical products. Lanolin is also used in surgical dressings and adhesive bandages as well as in furniture and shoe polish, papers, print colors, wool clothing, fur, and leather.[10] There are numerous reports of contact allergy to lanolin and lanolin alcohol, with more than 73 cases of type IV allergy to lanolin and 222 cases of type IV allergy to lanolin alcohol in skin care products, herbal cosmetics, and topical pharmaceutical products.[10]

3.4.7 | Lavender (*Lavandula angustifolia*)

Lavender belongs to the Lamiaceae family and is often used as a garden plant, for flavoring in food, sweets, and drinks, and for odor in cosmetic and household products. The essential lavender oil is obtained from the flowers by steam-distillation and used in traditional herbal medicine and aromatherapy.[9] The essential oil contains the terpenes linalool, linalyl acetate, and caryophyllene, which are potentially allergenic. When lavender oil is exposed to air, the terpenes oxidize to strongly allergenic hydroperoxides.[9] Although fresh lavender oil might have limited allergenic potential, air-oxidized lavender oil can thus cause allergic contact dermatitis.[117] There are many reports of type IV allergy to lavender oil, primarily with occupational relevance among masseurs and in aromatherapy as well as in topical pharmaceutical products. There are more than 50 publications of type IV allergy to lavender.[9,106,107]

3.4.8 | Lemon (*Citrus limon*)

The lemon tree belongs to the Rutaceae family.[122] Lemon contains the allergen Cis l 3, an LTP causing type I allergic reactions, including allergic rhinoconjunctivitis, food allergy, and anaphylaxis after ingestion.[108,109] The essential lemon oil is obtained from cold-pressing the peel. The main constituent of the cold-pressed essential oil is the terpene D-limonene, a prehapten, which after air oxidation yields the hydroperoxides limonene-1-hydroperoxide and limonene-2-hydroperoxide. These are both strong contact allergens.[9] Lemon oil and limonene are used as ingredients in perfumery, aromatherapy, and other cosmetic products, and for many other purposes.[9] More than 10 patient cases of type IV allergy to lemon oil in cosmetic products have been reported.[9] Limonene is one of the most commonly used fragrance chemicals in cosmetics, with more than 100 reported cases of type IV allergy.[89]

3.4.9 | Lemongrass (*Cymbopogon* spp.)

Lemongrass belongs to the Poaceae family.[110] Lemongrass resembles the scent of lemon, and the essential oil is obtained by steam

distillation of the lemongrass leaves. There are two types of lemongrass oils: East Indian lemongrass oil derived from *Cymbopogon flexuosus* and West Indian lemongrass oil derived from *Cymbopogon citratus*. Patch testing is performed primarily with material from *Cymbopogon citratus*. Lemongrass leaves and the essential oil are among others used in a variety of cosmetic and pharmaceutical products.[111] The allergens in lemongrass oil are the two ingredients neral and geranial that constitute citral, the active component in lemongrass oil, which is used to measure the quality of the lemongrass oil.[9] Citral is a well-known fragrance allergen.[89] There are more than 25 reports of type IV allergy to lemongrass oil.[9,111]

3.4.10 | Mint (*Mentha piperita* and *Mentha spicata*)

Mint is grown all over the world and belongs to the Labiatae family, including the species spearmint (*Mentha spicata*) and the water mint (*Mentha aquatica*). Peppermint is a hybrid mint produced by crossing *Mentha aquatica* and *Mentha spicata*.[112] Various forms of the plant such as leaf, leaf water, leaf extracts, and oil are commonly used in cosmetics, personal hygiene products, and pharmaceutical products as preservatives due to their antioxidant and antimicrobial effects, in aromatherapy, and in food as spices due to their flavoring properties.[9] The major constituents of mint oils are menthol, menthone, and menthyl acetate. Exposure to mint is through the skin and by ingestion.[112] Most toothpaste contains spearmint, peppermint, or menthol, added to give it a pleasant scent and taste.[112] Both peppermint and spearmint oils are among the most common allergens in toothpaste, causing perioral dermatitis, stomatitis, cheilitis, gingivitis, and glossitis.[113] A large intake of mint-flavored sweets and chewing gum can cause similar symptoms.[112] Smoking of menthol cigarettes coupled with cutaneous exposure has been associated with urticaria.[114] More than 24 cases of type IV allergy to peppermint oil, 14 cases of type IV allergy to spearmint oil, and more than 20 cases of type IV allergy to menthol, all in relation to cosmetic and pharmaceutical products, have been reported in the literature.[9,89]

3.4.11 | Orange—bitter orange (*Citrus aurantium*) and sweet orange (*Citrus sinensis*)

The orange tree belongs to the Rutaceae family. There are two types of oranges, the popular sweet orange primarily cultivated in Brazil and the bitter orange from Paraguay, both native to China. The pulp from the oranges can be eaten fresh or processed into juice. The essential orange oil is obtained by cold-pressing the peel as a byproduct in the juice industry and is used in perfumes, cosmetics, and aromatherapy and for flavoring in food and drinks.[9] Orange oil consists of more than 90% of the prehapten D-limonene, which transforms to limonene hydroperoxides after light and air exposure and becomes strongly allergenic. There are more than 10 patient cases of type IV allergies to orange oil, primarily related to occupation allergy in aromatherapists, masseurs, and people working with perfumes.[9]

3.4.12 | Rose (*Rosa damascena*)

Roses belongs to the Rosaceae family. There are various roses in the cosmetic products in THINK Chemical's Kemiluppen database, but in this section, the focus is on the most commonly used rose in cosmetic products, *Rosa damascena*. The essential oil is obtained from rose flowers by hydro- or steam distillation. Rose oil is expensive, and it takes almost 4000 kg of rose flowers to produce 1 kg of rose oil. It is primarily used as fragrance in finer perfumes, skin products, aromatherapy, and as a fragrance in food and drinks.[115] Furthermore, rose oil might have physiological and psychological relaxation, analgesic, and anti-anxiety effects.[116] The main constituents of rose oil are citronellol and geraniol, which may be the main allergens. There are reports of more than 15 cases of type IV allergy to rose oil in cosmetic products and topical pharmaceutical preparations.[9]

3.4.13 | Australian tea tree (*Melaleuca alternifolia*)

The Australian tea tree belongs to the Myrtaceae family.[117] Tea tree oil is an essential oil hydro-distilled from the leaves of the tea tree.[9] It has a camphoraceous scent with a menthol-like cooling sensation.[117] Tea tree oil is used in cosmetic products, pharmaceuticals, aromatherapy, folk medicine, and household products because of its antimicrobial, antiseptic, and anti-inflammatory properties.[117,118] Tea tree oil is toxic when ingested in higher doses and it can cause skin irritation at higher concentrations. The essential oil contains antioxidants including terpenes that are potentially allergenic. When tea tree oil is exposed to air, light, or warmth, some of the terpenes autoxidize to *p*-cymene, which is representative for the oxidative degradation.[9] Autoxidation leads to the formation of peroxides and other strong sensitizers.[9] Thus, tea tree oil from freshly opened tea tree oil products may elicit no or weak reactions, which is why oxidized tea tree oil should be used for patch testing.[119] There are numerous reports of type IV allergy to tea tree oil with more than 195 patient cases.[9]

3.4.14 | Ylang-ylang (*Cananga odorata*)

The ylang-ylang tree belongs to the Annonaceae family.[120] The essential oil is produced by steam distillation of the flowers from the tree. The quality of the oil depends on the distillation time and is divided into four different grades of oil, with the finest oil being the ylang-ylang oil "extra super" and "extra," with a distillation time of only 30 minutes or less. The four qualities of the oil also differ in the composition of ingredients. The main ingredients in the finest oil are linalool and benzyl acetate. The content of these ingredients decreases in oils with longer distillation time, whereas the content of germacrene D increases with longer distillation time but is low in the finer oils. Ylang-ylang essential oil is primarily used as fragrance in finer perfumes, cosmetics and aromatherapy, and folk medicine and as flavor in food and drinks.[121] Earlier, dihydro-isoeugenol was the primary allergen in ylang-ylang oil and caused several cases of pigmented

contact dermatitis, especially in Japan. After elimination of dihydroisoeugenol, derivatives of geraniol and linalool are probably the main sensitizers.[122] There are more than 17 patient cases of type IV allergy to ylang-ylang oil.[9]

3.5 | Ingredients rarely reported to cause type IV allergy

3.5.1 | Liquorice (*Glycyrrhiza glabra*)

Liquorice is the root of plants belonging to the Fabaceae family, comprising more than 30 species, including *Glycyrrhiza glabra* and *Glycyrrhiza inflata*.[123] Liquorice is commonly used in pharmaceutical products, as a skin-whitening agent in cosmetics, and a skin conditioning agent in sunscreens.[123,124] Liquorice is available in water-soluble and oil-soluble versions. Glabridin is considered the main active agent, which inhibits the production of melatonin within the melanocyte via inhibition of tyrosinase activity and promotes depigmentation. This makes liquorice popular in skin-lightening cosmetics, especially in Asia.[125,126] In the literature, type IV allergic reactions are described in several patients using cosmetic products (see Table 6). The allergenic component is unknown.

4 | DISCUSSION

The aim of this study was to provide an overview of the use of naturally derived cosmetic product ingredients and to identify those most commonly used and those with a documented sensitizing capacity (type I and/or IV) in the literature. We investigated the ingredients of 10 067 cosmetic products based on ingredient labeling. We are not aware of any other similar study. We identified 121 different natural ingredients that were included in at least 30 cosmetic products. Of these, the 10 most commonly used were ingredients derived from cinnamon (cinnamal), aloe, Compositae plants, shea nut, bee products (cera alba and propolis), jojoba, almond, wheat, olive, and algae and seaweed, but only some of these were commonly reported to cause allergic skin reactions from cosmetics. Based on this new knowledge, a cosmetic screening series for potentially allergenic natural ingredients in cosmetic products is proposed.

4.1 | The most common ingredients reported causing type I allergy

Milk, peanuts, peaches, and potatoes are all food proteins known to cause type I allergy when ingested. Especially milk and peanuts are well-known potent allergens causing severe, potentially life-threatening type I allergic reactions. Patients who are highly sensitized to milk may also have severe allergic reactions following cutaneous exposure to milk protein–containing products on inflamed skin, which enhances the absorption of casein and whey leading to anaphylactic episodes. Four cases of type I allergic reactions to milk in cosmetics have been described in the literature, and these are by far the most serious systemic and anaphylactic reactions caused by cutaneous application of food proteins to the skin.[15,17-19]

The use of peanut oil in cosmetic products has frequently been debated due to an increase in the prevalence of peanut allergy and the widespread use in cosmetic products. Two potential problems are identified relating to peanut-containing cosmetic products: (a) the risk that patients can be sensitized to peanut through the skin and develop type I allergy and (b) the risk that patients with known peanut allergy will react to peanut-containing products when applied to the skin. The increase in the prevalence of peanut allergy may be caused by sensitization in the first 6 months of life through the use of cosmetic products containing peanut oil.[48] In a questionnaire study with

TABLE 6 Type IV allergic reactions to liquorice in cosmetic products reported in the literature

Year	Age	Sex	Exposure	Clinical symptoms	Relevant test results	Type of reaction	Reference
2017	60	M	Aftershave containing *Glycyrrhiza inflata*.	Facial dermatitis present for 6 mo.	Patch test positive to aftershave cream (++), *G. inflata* liquorice extract 1% in petrolatum and 1% in eth.	IV	123
2017	70	M	Aftershave containing *Glycyrrhiza inflata*.	Dermatitis of the face, neck, hands and legs.	Patch test positive for G. inflata liquorice extract 1% pet.	IV	123
2016	39	F	Two skin-lightening products.	Itchy, facial erythema.	Patch test positive to two skin-lightening products "as is" and liquorice flavonoid 2% pet.	IV	156
2015	76	F	Cosmetic cream to treat facial pigmented areas.	Facial erythema, mostly around the eyelids and cheek.	Patch test positive to oil-soluble liquorice extract 1% aq.	IV	125
2008	35	F	Facial cream.	Facial erythema and periorbital edema, 1 d after use.	Patch test positive to liquorice root extract 1% pet.	IV	124
1999	43	F	Facial cream, foundation and essence.	Itchy, reddish eruptions on the face of one-month duration.	Patch test positive to oil-soluble liquorice extracts at 0.5%, 1% and 5% pet.	IV	126

Abbreviations: F, female; M, male.

406 patients reporting symptoms on first contact with peanuts, only 19% had been knowingly exposed to peanut before the first documented reaction, implying a potential other route of sensitization.[127] Infants may be exposed to peanut proteins via nipple cream or other topical products for dermatitis, which often contain peanut oil.[128] In a study with 49 children with peanut allergy, more than 80% had been exposed to skin creams containing peanut oil on rashes in the first 6 months of life, which preceded the onset of symptoms of peanut allergy.[48] Topical exposure to peanut allergens may also occur through peanut butter caused by indirect exposure through the skin before peanuts are introduced into an infant's diet.[48] There is still uncertainty whether topical preparations containing peanut oil are safe to use in peanut-allergic patients. The refining process of peanut oil, which includes heat treatment, does not destroy allergenicity completely, which indicates that some allergens are heat stable even if they are present in only trace amounts in refined peanut oil.[129] As there is only insufficient data, there is no safe threshold at which nonallergic or peanut-allergic individuals can safely be exposed to peanut proteins through the skin, but due to latest research, the Scientific Committee on Consumer Safety suggests that refined peanut oil–containing preparations below a protein level of 0.5 ppm are safe for topical use among peanut-allergic patients.[128]

Although no cases have been reported on allergy to peach and potato in cosmetic products, there are several reports describing type I allergic reactions to both, while preparing or ingesting them. A potential sensitization through skin exposure, analogous to peanut, cannot be ruled out.

4.2 | The most common ingredients reported causing type I and type IV allergies

Wheat, oat, and soy have all been reported in the literature to cause both type I and type IV allergies as ingredients in cosmetic products. Wheat is the food protein most commonly causing sensitization through the skin. In Japan, more than 2000 cases of allergic reactions to hydrolyzed wheat gluten (HWG) in facial soaps and other cosmetic products containing 0.3% of HWG called Glupearl 19S have been described. Immediate allergic reactions with eyelid edema and contact urticaria during or after using the soap have been described in many patients, whereas in other patients, symptom onset was more than 2 years after starting to use the soap.[80] Most individuals with hydrolyzed wheat protein (HWP) allergy can eat wheat products, such as bread, pastries, and pasta.[130] However, some patients with contact allergic reactions to HWP and HWG, who are tolerant to food containing unmodified wheat protein, may experience severe allergic reactions when eating food containing deamidated gluten.[7] For example, more than half of the Japanese patients have experienced anaphylaxis after eating wheat-containing food and a number of patients have also experienced wheat-dependent exercise-induced anaphylaxis.[80,131]

New research has shown that HWP and HWG with a molecular weight < 3500 Da and polypeptide lengths ≤30 amino acids are safe for use in cosmetics.[80,130] HWP and HWG with polypeptide lengths ≤30 amino acids cannot trigger a type I allergic reaction as they must have at least two IgE-binding epitopes of at least 15 amino acid residues each to elicit an allergic reaction. By comparison, Glupearl 19S in the above-mentioned Japanese facial soap has an average molecular weight of about 50 000Da.[80] A protein of this size cannot penetrate intact skin. Instead, sensitization may have been achieved by skin exposure to surface-active chemicals (surfactants) present in soaps or detergents, in addition to direct contact to the immune system via rhinoconjunctival and/or oral mucosa. An impaired skin barrier also increases the risk of sensitization through the skin.

Oat has also been reported to cause both type I and IV allergy. Oat is commonly used in the treatment of atopic dermatitis. All reported patients with allergy to oat in cosmetics had atopic dermatitis, except one patient. In the patient cases listed above (Table 3), only one patient was described with subsequent oral allergy syndrome. The potential for sensitization to oat through cosmetics needs to be investigated, including symptoms after ingestion in combination with exercise.

Soy also has the potential to sensitize percutaneously and causes both type I and IV allergies, especially in patients with a reduced skin barrier function such as in atopic dermatitis. In one case described earlier in this article, a patient with atopic dermatitis had a type I allergic reaction to soy-based ingredients in cosmetic products, and subsequently developed anaphylaxis after eating soy products (Table 4).[74] Food allergy to soy proteins has been described mainly in young children with atopic dermatitis, potentially making these patients at higher risk of percutaneous sensitization.[71]

In general, the pathogenesis of percutaneous sensitization from food proteins and food allergy from percutaneous sensitization is yet to be fully elucidated.[74]

4.3 | The most common ingredients reported causing type IV allergy

Regarding well-known type IV allergens, the most common plant-derived sensitizers overall in the cosmetic products in Kemiluppen were cinnamon (cinnamal) and Compositae plants, whereas bee products and lanolin were the most common animal-derived ingredients. Compositae plants, cinnamon (cinnamal), lanolin, and the bee products propolis and cera alba are all well-known sensitizers and, except for cera alba, included in the European baseline series.[9-11]

Especially Compositae plants may be challenging to test. Standardization of patch testing is difficult, as various Compositae plants are of variable composition and the commercialized allergens available might be different from the ingredient included in a cosmetic or topical pharmaceutical product.[3] However, we rely on patch testing with the main sensitizers in Compositae plants complied in the sesquiterpene lactone mix in the baseline series possibly supplemented with a Compositae mix. Patients reacting to Compositae mix and not to sesquiterpene lactones often present with multiple positive reactions to fragrances and other compounds containing terpenes, such as

Myroxylon pereirae resin and colophonium, due to cross-reactivity.[132] Compositae plants may also induce type I allergic reactions when ingested or inhaled due to cross-reactivity to mugwort. A few cases of possible type I allergy to chamomile in cosmetic and pharmaceutical products have been reported.[99-101]

Cinnamal is a chemical substance that is found naturally, but most often produced by chemical synthesis. Cinnamal is an important fragrance allergen and one of the top 10 most frequent sensitizers in fragrances causing type IV allergic reactions.[122] Cinnamal is known to act as a direct histamine releaser, which is why symptoms may be confused with type I allergy.[133] Although there has been reported one case of a potential type I allergic reaction caused by cinnamal in a cosmetic product, the allergenic potential of both cinnamal and Compositae plants as type I allergens needs to be elucidated before they can be defined as type I allergens in cosmetic and pharmaceutical products.[103,134] For this reason Compositae plants and cinnamal are listed as type IV allergens.

Allergy to lanolin and lanolin alcohol is common and has been known for almost a century. A recent Danish study has shown an increase in the prevalence of lanolin contact allergy over more than a decade (2004-2015).[105] Although the specific allergens in lanolin are unknown, it has been suggested that the alcohol fraction of lanolin plays an important role, since reducing this part of the lanolin reduces the frequency of allergic reactions. Hence the derivative lanolin alcohol, and not lanolin "as is," is included in the European baseline series.[10] Propolis has been added recently to the European baseline series. The number of patients with type IV allergic reactions to propolis is expected to increase due to an extensive use of this ingredient and the increasing use of natural products.[135]

Eucalyptus, lavender, lemon, lemongrass, mint, orange, rose, tea tree, and ylang-ylang are known type IV sensitizers. They are all steam-distilled to essential oils, but the chemical composition of the individual essential oil varies depending on the plant, harvest, and distillation parameters.[5] Essential oils are often used as fragrances in perfumes and they are known perfume allergens. Reactions to essential oils include type I and type IV allergies, irritant contact dermatitis, and phototoxic reactions.[136] Most of the essential oils are included in either perfume test series or screening test series with essential oils. Liquorice is a less known sensitizer and only six cases of allergic reactions to liquorice in cosmetic products have been described in the literature.

4.4 | Strengths and limitations

More than 10 000 cosmetic products are included in the free and nonprofit smartphone application (app) that have been scanned anonymously by Danish consumers. Consumers using the app may be more focused on health, allergy, and avoidance of certain ingredients or products compared with the rest of the population, making them biased in their selection of cosmetic products. Due to the app being used on electronic devices, the consumers using the app might belong to a younger and more resourceful group of the Danish population compared to the general consumer. Although it is impossible to verify that the products were randomly selected, due to more than 10 000 cosmetic products included in the app, we believe that the Kemiluppen database is representative of the cosmetic products used by the Danish consumers.

Because there is no clear official or legislative definition of what "natural" covers, our definition of natural ingredients is arbitrary, although inspired by the European cosmetic regulation's definition of natural ingredients in cosmetics that refers to the origin of the ingredients in the products.[2] Other interpretations of "natural ingredients" may have led to other ingredients to be investigated in this study. The use of natural ingredients in cosmetic products is still relatively new, and not all allergic patients are identified and treated, or cases described in the literature. Therefore, by our literature selection criteria, we may have excluded natural ingredients, that, although not well described in the literature, may have the potential to cause allergic symptoms in patients. A selection of a screening test series with the 20 most common ingredients in the cosmetic products could have been another possible way to detect new allergens. However, by selecting the ingredients that were most commonly found in cosmetic products in addition to being described in the literature, we believe that the specific natural ingredients selected in this study were relevant for further investigation.

5 | CONCLUSION

To our knowledge, no other studies have reported the prevalence of allergic reactions to abundant natural ingredients in cosmetic products or developed a screening test series focusing exclusively on natural ingredients in cosmetic products. Based on the information gathered from the database search and literature study, we propose a screening series including patch testing and skin prick testing with the following ingredients:

- Patch test: Cera alba, cinnamal, eucalyptus oil, lanolin, lavender oil, lemon oil, lemongrass oil, liquorice, mint oil, oat, orange oil, propolis, rose oil, sesquiterpene lactone mix, tea tree oil, wheat, and ylang-ylang oil.
- Prick test: Cera alba, milk, oat, peach, peanut, potato, propolis, soy, wheat, and the cross-reacting inhalation allergens birch, grass, and mugwort, which cause potential cross-sensitization to certain foods.

In a future study, we will include these naturally derived cosmetic product ingredients in a supplemental screening test series on consecutive dermatitis patients. We believe that additional testing with these selected natural ingredients in patients with dermatitis may detect the cause of dermatitis in more patients than we are able to today. Standardization of patch-testing products with natural ingredients may be challenging, as the chemical composition of natural ingredients may vary considerably according to their origin, climate conditions, extraction procedures, preservation, and skin metabolism among other factors, thereby eliciting false-negative results. For this reason,

investigation should always include testing with the patients´ own products.

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AUTHOR CONTRIBUTIONS

Jeanne Duus Johansen: Conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing-review and editing. **Claus Zachariae:** Conceptualization; methodology; writing-review and editing. **Christel Kirkeby:** Conceptualization; data curation; methodology; writing-review and editing. **Lene Garvey:** Conceptualization; methodology; project administration; supervision; writing-review and editing. **Maria Anna Bruusgaard-Mouritsen:** Conzeptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing-original draft; Writing-reviews & editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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