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Review article:

Health effects of probiotics on the skin

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Abstract

Skin is the largest organ of the body and is constantly exposed to physical, chemical, bacterial and fungal challenges. It is well known that probiotics are helpful for specific disorders and different clinical studies have indicated that probiotics have special effects in cutaneous apparatus directly or indirectly which can be considerable from versatile aspects. Probiotic bacteriotherapy can have great potentials in preventing and treating the skin diseases including eczema, atopic dermatitis, acne, allergic inflammation or in skin hypersensitivity, UV-induced skin damage, wound protection and cosmetic products. The current article comprehensively reviews the different health effects of probiotics on the skin.

Key words: Allergy, Atopic dermatitis, Eczema, Probiotic, Skin

1. Introduction

Skin is the body's interface with the environment. The skin forms a critical structural boundary and a perceptual interface for the Human and it is an immunogenic organ that works as the first defense and biologic sensor against external allergens. Recent research efforts to understand the control of skin barrier functions point to a close association among physical, immunological and cell biological characteristics of the skin and its microflora (Elias and Choi, 2005). Enhancing skin barrier may be of importance particularly in certain inflammatory diseases where barrier function is impaired such as atopic dermatitis, dry skin or in aging. Barrier function experiences a variety of tests on a daily basis including environmental, chemical or physical factors (UV radiation, pollution, hot and cold temperatures, air-conditioning, low humidity level, etc.), psychological stress and/or dietary deficiencies (Guéniche et al., 2010b).

Probiotics are "live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host" (Anon., 2006). It has been speculated that the skin status could benefit from reinforced gut homeostasis (Salminen et al., 2005). Diet variations determine individual characteristics of intestinal microflora, according to age, feeding, lifestyle, interactions among numerous constituents of the same flora, and pathologic conditions. Probiotic formulations are becoming increasingly available for healthy skin care, prevention and treatment of skin diseases, and antiaging benefits, thus representing an emerging area for skin health (Cinque et al., 2011). The advantages of probiotic-treatment (probiotic-prevention and/or probiotic-therapy) are that this method is efficient to the patients and also it has no side effect on them. Therefore, probiotic-therapy for the skin is potentally comparable to the ordinary methods of treatments.

Modern lifestyle negatively influences the intestinal ecosystem, and there may be cumulative degradation of the intestinal microflora. Linear changes in environmental conditions and lifestyle may lead to nonlinear changes in the gut flora possibly to an increasing susceptibility to skin diseases (Schmidt, 2004). A number of clinical studies suggest that probiotic strategies induce systemic effects which extend beyond the gut and may even affect selected functions of the skin (Ouwehand et al., 2002, Guenche et al., 2006).

Many experimental studies have shown that probiotics exert specific influences in the intestinal on epithelial cells and immune cells with antiallergic potential (Caramia et al., 2008). Also, an emerging approach in dermatology to help preventing and treating skin conditions, including the external signs of aging, acne, rosacea, yeast and bacterial infections, psoriasis, and dermatitis, is represented by topical probiotics, as shown by the growing marketplace for topical probiotic formulations available for skin care and antiaging benefits (Cinque et al., 2011). Totally, probiotics exert their health effects to the skin directly through cutaneous formulations or indirectly through dietary supplementary formulations and intestinal microflora improvement.

There are some review articles in which some parts are related to the relationships between probiotics and the skin in pediatrics (Caramia et al., 2008) and some parts are related to specifics disorders such as atopic dermatitis (Flohr et al., 2005, Halvarsson and Lodén, 2007) or briefly summarized critical overview about the use of pre- and/or probiotica in clinical dermatology (Krutmann, 2009). Also, there are some reviews about the effects of probiotics on allergic diseases (Michail, 2009, Kirjavainen et al., 1999, Boyle and Tang, 2006, Rautava et al., 2005, Ogden and Bielory, 2005), probiotics in aging skin (Cinque et al., 2010), dermal applications of probiotics (Cinque et al., 2011) and gut-brain-skin axis (Bowe and Logan, 2011). However, in

none of them, the effects of different probiotics on skin health along with the related mechanisms are comprehensively and extensively discussed. This article fulfills mentioned apects.

2. Microorganisms of the skin and the position of probiotics

The skin microflora plays a significant role in competitive exclusion of pathogens that are aggressive and provoke infection in the skin and in the processing of skin proteins, free fatty acids, and sebum (Cinque et al., 2011). Scientific research in the composition and function of the skin's microflora is recently experiencing a revival, and has become one of the most interesting and developing areas in cutaneous biology (Cogen et al., 2008).

The skin has a normal microbiota (Tannock, 1995). This normal microbiota of the skin is likely to be involved in competitive exclusion of pathogens, a function that could possibly be enhanced with the use of probiotics (Ouwehand et al., 2003). Certain probiotics can contribute to modulate cutaneous microflora, lipid barrier, and skin immune system, leading to the preservation of the skin homeostasis (Cinque et al., 2011). Cutaneous immune surveillance is required to protect the organism from infections but also to detect and remove transformed cells, which eventually may give rise to skin carcinomas (Euvrard et al., 2003, Woods et al., 2005).

A limited number of Gram-positive species have evolved to take advantage of the harsh environmental conditions that are being offered by the skin (Leyden et al., 1987). Resident microbial species including Proprionibacteria (*P. acnes*, *P. avidum* and *P. granulosum*), coagulase-negative Staphylococci (*S. epidermidis*), Micrococci, Corynebacteria and *Acinetobacter*, and transient species including *S. aureus*, *E. coli*, *Pseudomonas aeroguinosa* and *Bacillus* species are present on the skin (Krutmann, 2009). Recent studies using 16SrRNA gene

survey strategies showed that the human skin microbiota is far more complex (Grice et al., 2008). It has been noted that *S. epidermidis* is the dominant aerobic bacteria resident in skin (Grice et al., 2008) and the presence of this species could affect the skin barrier function and/or the development of innate immune responses in human skin. The resident microflora may be regarded as ‘‘beneficial’’ to the ‘‘normal, healthy’’ host, but may become dangerous to the host with disturbed skin integrity (Krutmann, 2009). There is some evidence that the skin microflora activates the adaptive (not non-adaptive) immune system. In this regard, microorganisms on the skin have been shown to be coated with immunoglobulins which are most likely derived from eccrine gland secretions (Metze et al., 1991).

The number of microbial species existing on human skin is determined by a variety of physical (including the number and size of follicles and glands, gland function, the flow of secretions, the integrity of barrier function, skin pH and osmotic potential) and biochemical factors (including soluble micronutrients derived from sebum- such as lipids and aminoacids- and sweat- such as vitamins and lactate and amino acids- as well as those produced as a consequence of the metabolic activity of microorganisms on the skin; e.g., lantibiotics produced by *Staphylococcus* spp., methantiol, bacteriocins, organic acids and lytic enzymes) (Krutmann, 2009).

Cutaneous pH can control bacterial populations on skin surface affecting resident microflora and can regulate epidermal permeability barrier homeostasis and stratum corneum integrity (Feingold, 2007). Elevation in stratum corneum pH is associated with several cutaneous disorders, such as acute eczema, atopic dermatitis, and seborrheic dermatitis. In these diseases the increased pH could adversely affect cutaneous functions exacerbating these conditions

further with more severe clinical manifestations (Cinque et al., 2010). Use of probiotics with fermentative metabolism that are able to produce lactic acid and obtain energy from the fermentation of lactose, glucose, and other sugars to lactate via homofermentative metabolism (Chiba, 2007, Farmer, 2005) could be an interesting approach.

In atopic skin reduced level of sphingosine is suggested to be responsible for the changed pattern of microorganisms on the skin surface. Reduction of sphingosine has been found linked to the increased numbers of bacteria including *S. aureus* present in the upper stratum corneum (Arikawa et al., 2002). The presence of the lipophilic yeasts *Malassezi* spp. (formerly known as *Pityrosporum ovale* and *orbiculare*) has been suggested to be responsible for an exacerbation of the eczema of the head, neck, and shoulders named 'head-and-neck dermatitis' in young adults (Halvarsson and Lodén, 2007).

2. Health benefits of probiotics to the Skin

Probiotic microorganisms can improve health of skin by oral consumption (*in vivo* usage) or by local application on it (*in vitro* usage). Oral consumption has been the subject of many studies in recent years. Probiotics might exhibit preventive or therapeutic effects on the skin.

The health consequences of probiotics to the skin are shown in Figure 1. Figure 2 indicates the main mechanisms involved in health benefits of probiotics to the skin.

It has been revealed that not only diseased, but also healthy skin may profit from the oral ingestion of probiotic bacteria (Holma et al., 2011). Research about the skin health benefits of probiotics indicated that oral consumption might reduce skin sensitivity and support the skin's immune function. In one clinical trial, oral consumption of a *Lactobacillus johnsonii* supplement

for six weeks appeared to accelerate the recovery of the skin's immune system compared to the placebo (Gueniche et al., 2009), while another study indicated a combination of *Lactobacillus paracasei* and *Bifidobacterium lactis* decreased the skin's neurosensitivity in women with reactive skin (Gueniche et al., 2007). Puch et al. (2008) in a double-blind, randomized clinical study have indicated that a 24-week skin nutrition intervention with a fermented dairy product containing *L. casei*, *L. bulgaris* and *Streptococcus thermophilus* in female volunteers with dry and sensitive, but healthy skin reduced transepidermal water loss and thus improved stratum corneum barrier function (Puch et al., 2008).

It has been found that oral consumption of probiotic bacteria may represent a novel approach to protect the skin immune system against ultraviolet radiation. Some effects have been reported in hairless mice and it has been indicated that nutritional supplementation with *L. johnsonii* provided protection of the skin immune system against ultraviolet B radiation-induced immunosuppressive effects (Gueniche et al., 2006). It has been hypothesized a unifying model, gut–brain–skin axis, which suggesting that modulation of the microbiome by deployment of probiotics can exert beneficial influences on skin inflammation, skin homeostasis, hair growth, and peripheral tissue responses to stress (Arck et al., 2010).

Bifidobacteria can produce a further riboflavin (vitamin B2). Deficiencies in riboflavin, a co-enzyme involved in numerous redox reactions, can lead to skin disorders (Lakshini, 1998). Two bifidobacteria strains (*B. infantis* CCRC 14633 and *B. longum* B6) have been reported to increase the levels of riboflavin during a 48-h fermentation in soymilk (Hou et al., 2000). Physiological and measurable changes *in vivo* show at an ingested quantity of at least 10^8-10^9 cfu per day, so that immune modulating effects are inducible with a daily ingestion of 100 g probiotic yogurt

with 10^6 cfu per gram (Karimi et al., 2011, Karimi et al., 2012, Korbekandi et al., 2011). It has been reported that *L. rhamnosus* GG, in high concentrations (lyophilic capsule form), exhibited positive effects on skin especially to its some diseases such as atopic eczema, and this cannot be efficiently achieved by intake of available supplemented foods (Bunselmeyer and Buddendick, 2010). The main positive effects of probiotics on skin health are discussed below:

2.1. Effects of probiotics on eczema and atopic dermatitis

Atopic dermatitis is the most common chronic skin condition in infants and children, with a prevalence of 10% to 20% (Laughter et al., 2000, Schultz-Larsen, 2002, Kliegman et al., 2007). It has been defined as "a skin condition characterized by intense dryness of the skin, pruritus, and chronic erythematous lesions with a relapsing course" (del Giudice jr et al., 2002). Atopic dermatitis is a chronic relapsing inflammatory skin disease which usually starts during the first years of life. In patients with the disease, the quality of skin is severely affected, and this is closely linked to a reduced quality of life. The course of atopic dermatitis is characterized by sub-acute and chronic stages, as well as the acute flare stage. The sub-acute stage includes mild scaling and mild lichenification (thickened skin caused by scratching) of the skin and the chronic stage includes prominent scaling with distinct lichenification (Carroll et al., 2005). An increasing prevalence of this disease has been observed during recent years (Halvarsson and Lodén, 2007). Atopic dermatitis has been linked to food hypersensitivity, especially milk and egg proteins (Sicherer and Sampson, 1999).

Epidemiological studies have shown lower incidence of atopic skin and hypersensitivity complaints among children with stable gastrointestinal populations of lactobacilli and

bifidobacteria compared with those who had a paucity of gut probiotic microorganisms (Cross, 2002). On the other hand, impairment of the intestinal mucosal barrier appears to be involved in the pathogenesis of atopic dermatitis (Rosenfeldt et al., 2004). The ‘‘hygiene hypothesis’’ is a current popular theory to describe why we are experiencing a surge in atopic disease prevalence (Noverr and Huffnagle, 2005). According to this theory, our environments are now too clean and we are not exposed to as many antigens (bacterial, fungal, viral) as previous generations. With a reduction in infectious exposure, certain individuals over time may produce altered gastrointestinal, immunologically active microorganisms, leading to a T_H2 immune shift (Duramad et al., 2006). Numerous researches also have supported a correlation among early life antibiotic exposure and atopy in children (Johnson et al., 2005, Kummeling et al., 2007).

Clinical investigation of probiotics' therapeutic potential in atopic dermatitis reflects a growing interest in therapeutic targeting of intestinal colonization and T_H1/T_H2 immunologic maturation (Lee et al., 2008a). Atopic diseases involve T_H2 responses to allergens (Romagnani, 1996). Probiotics can potentially modulate the toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to activation of dendritic cells and a T_H1 response. The resulting stimulation of T_H1 cytokines can suppress T_H2 responses (Winkler and al., 2007). Although it has long been appreciated that some are at higher risk for atopic disorders based on family history, it should be recognized how complicated the nature–nurture equation might be (Rosen and Breuner, 2007). Even single nucleotide polymorphisms (SNPs, or very small DNA shifts) may not only account for the presence or absence of atopy in a given person but may also affect the severity of disorder, the likelihood of other atopic conditions developing, and the success of various therapies (Negoro et al., 2006). A baby who has a given genomic

predisposition, under certain environmental conditions, manifests immune dysregulation, resulting in an imbalance between T_H1-dominant and T_H2-dominant responses (Kidd, 2003). T_H2 dominance leads to immune dysregulation marked by a proliferation of inflammatory cellular mediators (eg, cytokines, interleukins, leukotrienes). Inflammation involves excess mucous production and other clinically observable phenomena which are called allergies.

Pediatric studies suggest that probiotic use in children with atopic conditions such as atopic dermatitis results in enhancement of IFN-production and decrease d IgE and antigen-induced TN F-, IL-5, and IL-10 secretion (Flinterman and al., 2007, Prescott et al., 2005, Taylor and al., 2006). The use of probiotic microorganisms in the primary prevention of atopic disease is based on the ability to reverse increased intestinal permeability, a characteristic of children with atopic eczema and food allergy (Caramia et al., 2008). Specific species and strains of indigenous gastrointestinal microflora have been indicated to have important influences on the physiology and immunology of the host. *L. rhamnosus* GG and *B. lactis* Bb-12 are an effective adjunct to extensively hydrolyzed formula in treating infants with mild atopic dermatitis, and the combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460 is effective in patients with moderate to severe atopic dermatitis (Caramia et al., 2008). It has been suggested that topical application of *Vitreoscilla filiformis* exerts beneficial effects in patients with seborrheic dermatitis and atopic eczema (Gueniche et al., 2007, Gueniche et al., 2006).

Majamaa and Isolauri (1997) studied the first double-blind placebo-controlled intervention regarding cutaneous pathologies to improve the atopic manifestations, dermatitis/eczema with probiotics (Majamaa and Isolauri, 1997). They studied the immunologic and clinical effects of cow's milk elimination in children with or without *L. rhamnosus* GG in hydrolyzed formula

which administered to mothers of 10 breast-feed children with atopic eczema and cow's milk allergy. In their study, a significant improvement in atopic dermatitis was observed after 1 month of intervention only in those receiving *L. rhamnosus* GG. The concentrations of fecal α1-antitrypsin and tumor necrosis factor α (determined as markers of intestinal inflammation before and after dietary intervention) significantly decreased in the group receiving *L. rhamnosus* GG. They concluded that probiotic bacteria may be effective probably by improving endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and minimizing intestinal inflammation may act as a useful tool in the treatment of food allergy (Majamaa and Isolauri, 1997).

In the research performed by Isolauri et al. (2000), the effects of probiotics in atopic eczema in a randomized double-blind study were monitored. A total of 27 infants with atopic dermatitis during exclusive breast-feeding were divided into 3 groups: probiotic- supplemented, *B. lactis* Bb-12 or *L. rhamnosus* GG, and extensively hydrolyzed whey formulas or the same formula without probiotics. A significant reduction in SCORAD score (severity scoring of atopic dermatitis) (Anon., 1993, Kunz et al., 1997, Charman and Williams, 2000, Pucci et al., 2005) was seen after 2 months in the probiotic-supplemented groups. Also, a decrease in the serum concentration of inflammatory markers (such as the marker of T-cell activation) and urinary eosinophil protein X (a marker of eosinophilic inflammatory activity) was also seen, suggesting that probiotics may counteract inflammatory responses beyond the intestinal tract (Isolauri et al., 2000).

In the study accomplished by Rautava et al. (2002), *L. rhamnosus* GG was administered (2×10^{10} cfu) to 62 mother-infant pairs during the 4 weeks before birth and during breastfeeding

for 3 months. In their double-blinded, placebo-controlled study, the immunoprotective potential of breast milk was increased with *L. rhamnosus* GG, as assessed by the amount of anti-inflammatory transforming growth factor-β2 in milk of mothers receiving probiotics versus placebo. Their study revealed that the risk of developing atopic eczema throughout the first 2 years of life in babes whose mothers received probiotics was significantly decreased. Also, it was argued that infants most likely to benefit from probiotics are those with elevated cord blood IgE concentration (Rautava et al., 2002). However, this has limited applications because this particular study involved exclusively breast-feeding mothers who ingested the probiotics and presumably passed it to their infants through breast milk. Also, in this regard, Kalliomäki et al. (2003) administered *L. rhamnosus* GG (10^{10} cfu) in a double-blind, randomized, placebo-controlled trial during 4 weeks before birth and throughout breast-feeding for 3 months to mothers who had at least 1 first-degree relative with atopic eczema and to their infants after birth for 6 months. In their study, chronic recurring atopic eczema, which is the major sign of atopic disease in the first years of life, was the primary end point. The frequency of atopic eczema in the probiotic group was half that of the placebo group. They concluded that *L. rhamnosus* GG was effective in prevention of early atopic disease in children at high risk, and the preventive effect was still effective after 4 years (Kalliomäki et al., 2001, Kalliomäki et al., 2003).

Hattori et al. (2003) studied 15 children with atopic dermatitis with *Bifidobacterium*-deficient microflora. 8 children were given oral administration of lyophilized *B. breves* M-16V strain. Significant improvement of allergic and cutaneous symptoms was seen in the bifidobacteria-administered group (Hattori et al., 2003). Kirjavainen et al. (2003) investigated 35 infants (mean age of 5.5 months) with atopic eczema in a randomized, double-blind research. The infants were

assigned to receive either extensively hydrolyzed whey formula as placebo group or the same formula supplemented with viable *L. rhamnosus* GG or heat-inactivated LGG. Scores in SCORAD in the viable *L. rhamnosus* GG group tended to be more than within the placebo group, suggesting the possible benefits of probiotics as a primary intervention in eczema. While live probiotic administration resulted in statistically significant improvement of scores, the use of heat- inactivated *L. rhamnosus GG* was associated with adverse gastrointestinal symptoms (Kirjavainen et al., 2003). Another study by Kirjavainen et al. (2002) suggested that *B. lactis* Bb-12 modifies gut microflora to alleviate early onset atopic eczema (Kirjavainen and al., 2002).

In the study of Rosenfeldt et al. (2003), the use of probiotics as an adjuvant to topical steroids (hydrocortisone or hydrocortisone butyrate) in the treatment of established atopic dermatitis in a double-blind, placebo-controlled crossover study was investigated. The subjects aged 1 to 13 years with severe chronic eczema took either a combination of 2 *Lactobacillus* strains (*L. rhamnosus* GG 19070-2 and *L. reuteri* DSM 122460) or placebo for 6 weeks. In their study 56% of probiotic-treated patients experienced subjective symptom improvement compared with 15% of placebo-group patients and eczema extent decreased. Also, serum eosinophilic cationic protein values used to monitor disease activity in atopic dermatitis decreased with probiotic therapy. Probiotic therapy was accompanied by only moderate changes in production of the cytokines IL-4, IFN-γ IL-10. The modest influence of the probiotics on the improvement of atopic dermatitis could be attributed to the older age of the subjects and the severity of the eczema (Rosenfeldt et al., 2003). Also, Rosenfeldt et al. (2004) in a double-blinded, placebo-controlled, cross-over study administered *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246 to 41 children with moderate and severe atopic dermatitis for 6 weeks. In their study, gastrointestinal

symptoms were registered before and during treatment. Small intestinal permeability was also measured by the lactulose-mannitol test because patients with atopic dermatitis appear to have an increased intestinal permeability (Caffarelli et al., 1993, Pike et al., 1986). It was found that there is a positive association between the lactulose to mannitol ratio and the severity of the eczema. They concluded that probiotic supplementation may stabilize the intestinal barrier function and decrease gastrointestinal symptoms in children with atopic dermatitis (Rosenfeldt et al., 2004).

In the study of Pohjavuori et al. (2004), *L. rhamnosus* GG and a mixture of 4 bacterial species or placebo were administered for 4 weeks to infants with suspected IgE-associated dermatitis in a randomized, double-blind study with elimination diet and skin treatment. Between the infants who received *L. rhamnosus* GG, the level of secreted interferon γ increased in those with IgE-associated dermatitis in comparison to the placebo group. Deficiency in interferon γ appears to be related to production rises with the addition of *L. rhamnosus* GG. Interferon γ rises in infants with IgE-associated dermatitis. This may reflect the beneficial immunomodulatory signals that probiotics can provide (Pohjavuori et al., 2004). Weston et al. (2005) studied 56 children with moderate or severe atopic dermatitis in a randomized, double-blind, placebo-controlled trial. The children received *L. fermentum* VRI-033 PCC or an equivalent volume of placebo for 8 weeks. Reduction in severity and extent of atopic dermatitis was significant in the probiotic group at the end of the study. Children with moderate or severe disease receiving probiotics had a SCORAD index that was more than baseline at the end of the study (Weston et al., 2005). In the study of Prescott et al. (2005), it was indicated that the administration of *L. fermentum* was correlated with an increase, from peripheral blood mononuclear cells, in T-helper type 1 cytokine interferon γ responses and *S. aureus* enterotoxin B at the end of the 8-week

supplementation period. The increase in interferon γ responses to *S. aureus* enterotoxin B was directly proportional to the decrease in the severity of atopic dermatitis (Prescott et al., 2005).

Viljanen et al. (2005) treated a total of 230 infants aged 1.4-11.9 months with atopic eczema/dermatitis syndrome in a randomized, double-blinded study a mixture of 4 probiotic strains (*L. rhamnosus* GG ATCC 53103, *L. rhamnosus* LC705, *B. breve* Bbi99 and *P. freudenreichii* ssp. *shermanii* JS) or placebo for 4 weeks. After four-week treatment, IgA levels tended to be higher in probiotic groups than in the placebo group, and α_1- antitrypsin decreased in the probiotic group but not in other treated groups. They did not report any date on cutaneous findings after treatment. They reported that the combining LGG with other probiotic strains suppressed the effect seen with LGG alone (Viljanen et al., 2005a). Smits et al. (2005) studied monocyte-derived dendritic cells cultured *in vitro* with *L. reuteri* and *L. casei*. They explain the beneficial effect of noted probiotics in the treatment of several inflammatory diseases including atopic dermatitis through the production of cytokines without increasing the production of immunomediator IL-10 (Smits et al., 2005). Penders et al., (2006) revealed that *C. dificile* colonization at one month of age was associated with an increased likelihood of eczema, recurrent wheezing, and atopic dermatitis. In their study *E. coli* colonization was associated with eczema rather than recurrent wheezing or atopic dermatitis. Also, no association with *bifidobacteria* colonization, *B. fragilis* or *lactobacilli* colonization was observed (Penders and al., 2006). Sistek et al. (2006) showed efficacy of the probiotic *L. rhamnosus* and *B. lactis* on atopic dermatitis in food-sensitized children (Sistek and al., 2006).

Gruber et al. (2007) investigated the therapeutic benefit of *L. rhamnosus* GG (LGG) in infants with atopic dermatitis. In their study infants 3-12 months of age with mild-to-moderate

atopic dermatitis were randomized to receive LGG or placebo as a food supplement for 12 weeks. Fifty-four infants received LGG and 48 infants received placebo. Symptoms improved overtime after 4, 8, and 12 weeks, without any group being statistically different (Gruber and al., 2007). Michail et al. (2008) in a meta-analysis including ten randomized, controlled trials, found a significant overall benefit after the use of probiotics, resulting in a reduction of the dermatitis scores (SCORAD) compared to placebo. In their study, *L. rhamnosus* GG appeared to be more effective than other probiotic preparations and children with more severe disease were more likely to benefit from the use of probiotics (Michail et al., 2008). Other studies have shown less atopic eczema with supplementation with *Lactobacillus rhamnosus* GG (LGG) (Kalliomäki et al., 2007). *L. rhamnosus* GG *in vitro* has been shown to inhibit antigen-induced IgE production in murine lymphocytes (Shida et al., 1998).

Wickens et al. (2008) studied the role of probiotics in prevention of development of eczema and atopy in early life at 2 years in a double-blind, randomized placebo-controlled trial. In their study, pregnant women were randomized to take *L. rhamnosus* HN001, *B. animalis* subsp. *lactis* strain HN019 or placebo daily from 35 weeks gestation until 6 months if breastfeeding, and their infants were randomized to receive the same treatment from birth to 2 years. They found that supplementation with *L. rhamnosus*, but not *B. animalis* ssp. *lactis*, substantially reduced the cumulative prevalence of eczema, but not atopy, by 2 years (Wickens et al., 2008). Similar results were found in other studies (Osborn and Sinn, 2007, Lee et al., 2008a). In the study of Bard et al. (2008), 19 subjects with atopic dermatitis aged 6 months to 8 years were randomized to receive 10-20×10^9 cfu of LGG or placebo daily during a 9- to 12-week intervention phase. It was concluded from their research that LGG may lead to a significant decrease in IgE sensitized

patients and although the final average SCORADs for both the LGG and placebo groups were comparable, patients receiving LGG had a significant greater decrease in severity of symptoms over the first three weeks of treatment as compared to the control group (Bard et al., 2008).

Kim et al. (2009) indicated that supplementation of probiotics at 4-8 weeks before delivery and continuing until 6 months after delivery can prevent the development of eczema in infants at high risk. They also showed that the prevalence of eczema at 1 year in the probiotic group was significantly lower than in the placebo group (Kim et al., 2009). A recent prospective, double-blind, randomized, placebo-controlled clinical trial performed on 50 subjects aged 3–47 months with moderate/severe AD showed that 12 months of *L. reuteri* supplementation may be beneficial in the longterm control of eczema (Gromert and Axelsson, 2009). In the study of Niers et al. (2009) a mixture of probiotic bacteria including *B. bifidum*, *B. lactis*, and *Lactococcus lactis* was prenatally administered to mothers of high-risk children and to their offspring for the first 12 months of life. In their study parental-reported eczema during the first 3 months of life was significantly lower in the intervention group and there was significant decrease in IL-5 production compared with placebo group. Also they showed that the preventive effect of the combination of particular probiotic bacteria on the incidence of eczema sustained during the first 2 years of life (Niers et al., 2009).

Kuitunen et al. (2009) in a double-blinded, placebo-controlled study randomized 1223 mothers with infants at high risk for allergy to receive a probiotic mixture (*L. rhamnosus* LC705 DSM 7061, LGG 53103, *B. breve* Bb99 DSM 13692 and *P. freudenreichii* ssp. *shermanii* JS DSM 7076) or placebo during the last month of pregnancy and their infants to receive it from birth until age 6 months. Infants also received a prebiotic galactooligosaccharide or placebo. At 5

years the cumulative incidence of eczema was evaluated. No significant difference appeared between the probiotic and placebo groups in frequencies of eczema or atopic eczema. However, significantly fewer IgE-associated eczema occurred in cesarean-delivered children receiving probiotics. In vaginally delivered children no significant differences appeared between treatment groups (Kuitunen et al., 2009). Farid et al. (2011) studied the clinical and immunologic effects of mixture of seven strains of probiotic bacteria (*L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis, L. bulgaricus*) and Fructooligosaccharide in 40 infants and children aged 3 months to 6 years with atopic dermatitis. They concluded that the mixture of seven strains of probiotics and Fructooligosaccharide can clinically improve the severity of atopic dermatitis in young children (Farid et al., 2011).

Despite some disparities between studies, the weight of evidences suggests a protective role for at least some *Lactobacillus* species in the pathogenesis of eczema, but there is little evidence overall that this is mediated through effects on allergic sensitization (Wickens et al., 2008). In the study of Abrahamsson et al. (2007) the mothers received the probiotic daily from gestational week 36 until delivery and their babies then continued with the same product from birth until 1 year of age and were followed up for second year. In their research using *L. reuteri* ATCC 55730 no overall effect on the cumulative incidence of eczema was found despite a reduction in IgE-associated eczema (Abrahamsson et al., 2007). Also, some studies have found no effect of *L. acidophilus* LAVRI-A1 (Taylor et al., 2007) or *L. rhamnosus* GG (Kopp et al., 2008) on atopic dermatitis and even it has been reported that *L. acidophilus* supplementation actually increase the risk of atopic sensitization (Taylor et al., 2007). It is interesting that the results of Kopp et al. (2008) were in sharp contrast with the study of Kalliomaki et al. (2001) although an identical

probiotic strain was used (LGG) in an also otherwise comparable study design. There were two main differences between Taylor's study (2007) and the other researchers. The type of probiotic product was different as well as the timing of the introduction of the probiotic. Taylor et al. (2007) administered the probiotic supplement postnatally, while other studies administered probiotics before and after birth. Prenatal supplementation may prove to be crucial for the preventive benefit of probiotics in this disorder.

Brouwer et al. (2006) and Folster-Holst et al. (2006) showed no effect of *L. rhamnosus GG* in infants with atopic dermatitis regardless of their IgE sensitization status (Brouwer et al., 2006, Folster-Holst and al., 2006). In the research of Osborn and Sinn (2007), a meta-analysis described five studies enrolling 1477 infants. They concluded that there was no current evidence to support the administration of probiotics to prevent eczema and recommended further studies to determine reproducibility (Osborn and Sinn, 2007). In the study of Lee et al. (2008), in a meta-analysis no therapeutic difference was shown among children receiving probiotics (Lee et al., 2008a). Their evidence is more convincing for probiotics' efficacy in prevention than treatment of pediatric atopic dermatitis. There have been some reports of adverse reactions when pediatric patients with cow's milk protein allergy ingested probiotics (Lee et al., 2007). It is necessary to mention that prescribing such probiotics especially in the sensitized children need more caution.

Although there is still a potential role for probiotics in preventing childhood atopic dermatitis and other allergic diseases, there are many unanswered questions, including species/strain selection, dosing and timing of probiotic administration and the population or populations most likely to benefit (Ji, 2009, Kopp and Salfeld, 2009, von Hertzen et al., 2009, Ly et al., 2011).

Understanding how probiotics act to prevent eczema requires further investigation and more research is needed to determine the ideal composition of different types of pre- and probiotics for atopy prevention and treatment. The main studies of probiotic effects on atopic dermatitis are summarized in Table 1.

2.2. Effects of probiotics on acne

In some investigations, the impacts of internal application of probiotic supplements on acne has been discussed (Bowe and Logan, 2011). There are some studies that made no positive correlation among fermented dairy products and acne (Adebamowo et al., 2008, Adebamowo et al., 2006, Adebamowo et al., 2005). On the other hand, some studies have stated that there is an association between acne and growth hormones of milk (Melnik and Schmitz, 2009). Acne is driven with insulin-like growth factor I (IGF-I) and IGF-I can be absorbed across colonic tissue (Quadros et al., 1994). It should be noted that probiotic bacteria utilize IGF-I throughout the fermentation when added to milk, with a resultant 4-fold lower level of IGF-I in fermented versus skim milk (Kang et al., 2006).

In a study, 40 patients added: an oral supplement of 250 mg freeze-dried *L. acidophilus* and *B. bifidum* as an adjuvant to standard care in half of the group. In addition to better clinical outcomes among the patients supplemented with probiotics, the researchers reported better tolerance and compliance with antibiotics (Marchetti et al., 1987). Another research supported the benefit of probiotics added to standard care, with a reported acceleration in time to significant clinical improvement in those who had been administered probiotics (Volkova et al., 2001). The study of Kim et al. (2010) showed that the consumption of a *Lactobacillus*-fermented dairy

beverage improved clinical aspects of acne over 12 weeks. They found that the probiotic drink consumption led to significant reductions in total lesion count in association with a marked reduction in sebum production. Although in their study the added lactoferrin (an anti-inflammatory milk protein) to the probiotic drink provide higher efficacy in the decrease of inflammatory lesions, the benefits of the probiotic drink lonely lend more support to the notion that probiotics have an adjuvant role to play in acne therapy (Kim et al., 2010).

Various probiotic lactic acid bacteria can provide *in vitro* antimicrobial activity against *P. acnes* (Al-Ghazzewi and Tester, 2010, Kang et al., 2009). Kang (2009) found that topical application of an *Enterococcus faecalis* probiotic lotion for 8 weeks reduced inflammatory lesions by over 50% versus placebo (Kang et al., 2009). *S. salivarius* (a prominent member of the oral microbiota of healthy humans) has been indicated to secrete a bacteriocin-like inhibitory substance capable of inhibiting *P. acnes* (Bowe et al., 2006). In addition to the antimicrobial activity, *S. salivarius* inhibit a number of inflammatory pathways, thus acting as immune modulators (Cosseau et al., 2008).

Acne vulgaris is multifactorial condition and is characterized by hypercolonization with *P. acnes*, inflammation, and immune responses. Propionibacteria have been shown to have adjuvant and antitumor activities (Eady and Ingham, 1994) and also same species are of pathogenic relevance in acne and folliculitis (Leyden et al., 1998). The synbiotic ability of probiotic bacteria and Konjac glucomannan hydrolysates to inhibit the growth of *P. acnes* in an *in vivo* study has been recently reported suggesting that the development of a new alternative involving probiotic therapy for reducing acne episodes *in vivo* could be encouraging (Al-Ghazzewi and Tester, 2009).

The local burden of lipid peroxidation in acne is high, such that it appears to place a great demand upon blood-derived antioxidants (Bowe and Logan, 2010). Some recent studies have shown that orally consumed pre- and probiotics can reduce systemic markers of inflammation and oxidative stress (Schiffrin et al., 2007, Mikelsaar and Zilmer, 2009). Then the ability of oral probiotics to limit systemic oxidative stress may be an important therapeutic pathway (Fu et al., 2010). Oral administration of probiotics regulates the release of inflammatory cytokines within the skin (Hacini-Rachinel et al., 2009), and a specific reduction in interleukin-1α (Cazzola et al., 2010), would be of potential benefit in acne (Bowe and Logan, 2011).

Researchers have shown that *S. thermophilus* can increase ceramide production when applied to the skin for 7 days as a cream (Di Marzio et al., 1999, Di Marzio et al., 2003, Di Marzio et al., 2008) and some of the ceramide sphingolipids, most notably phytosphingosine, provide both antimicrobial activity against *P. acnes* and direct anti-inflammatory activity (Pavicic et al., 2007). Sphingolipids have been reported to be low in acne (Yamamoto et al., 1995), and the seasonal loss of ceramides can be a driving force behind much more dermatological office visits for acne throughout winter months (Hancox et al., 2004).

Substance P may be a primary mediator of stress-induced amplification of inflammation and sebum production in acne (Lee et al., 2008b). It has been reported that strains of *B. longum* and *L. paracasei* can attenuate skin inflammation mediated by substance P (Guéniche et al., 2010b, Gueniche et al., 2010a). In this regard, Gueniche et al. (2010a) showed that *L. paracasei* CNCM-I 2116 was able to abrogate vasodilation, edema, mast cell degranulation, and TNF-alpha release which induced by substance P, compared to control. They showed that medium conditioned with *L. paracasei* (in ex vivo skin organ culture) induced a significantly faster barrier function

recovery after sodium lauryl sulphate disruption, compared to control (Gueniche et al., 2010a). Also, Gueniche et al. (2010b) performed an in vitro and a clinical trial using *B. longum* extract proved that these nonreplicating bacteria forms applied to the skin were able to improve sensitive skin in various parameters associated with inflammation such as decrease in vasodilation, edema, mast cell degranulation, and TNF-alpha release. Their findings suggested that *B. longum* bacterial extract may prevent negative environmental effects (cold in winter, air dryness) and its application contributes to reinforce skin homeostasis and to improve skin resistance to external abuse (Guéniche et al., 2010b).

2.3. Anti-allergic and anti-inflammatory effects of probiotics on the skin

The role of probiotics in prevention of allergic disease is still not clearly established. It has been shown that probiotics exert specific antiallergic effects on epithelial cells and immune cells. The allergen penetration through the skin can lead to a systemic sensitization involving the intestinal mucosa. Also, it has been reported that inflammation plays an important role in photoageing of human skin in vivo (Pillai et al., 2005).

Intervention strategies have been elaborated to balance the intestinal microecology with oral administration of probiotics (Miraglia and De Luca, 2004, Ogden and Bielory, 2005). The composition of the intestinal microflora is the main element in allergic diseases, and species of probiotics could play a role in the development of healthy immunity response, participating in enteric microecology, preventing and potentially treating allergic diseases (Noverr and Huffnagle, 2004, Macpherson and Harris, 2004, Zutavern et al., 2006). It should be mentioned that not all probiotics have the identical immunological characteristics. The anti-inflammatory

properties of probiotics have been shown of cell homogenates of *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. animalis* Bb-12, *L. acidophilus* NCFB-L61748, *L. bulgaricus* ATCC 11842, *S. thermophilus* T101, and *P. freudenreichii Shermanii* strain JS (Kankaanpaa et al., 1998). Similar findings have been reported in other studies (Kankaanpaa et al., 2002). It has been reported that *L. reuteri* has displayed a slightly different profile than other probiotic bacteria and seems to possess more pronounced anti-inflammatory properties, as demonstrated in animal and human *in vitro* studies (Ma et al., 2004, Peňa et al., 2005, Smits et al., 2005, Zeuthen et al., 2005). Probiotic bacteria may mediate antiallergenic effects by stimulating production of T_H1-cytokines (Hessle et al., 1999, Miettinen et al., 1998), transforming growth factor-β (Isolauri et al., 2000, Paganelli et al., 2002) and and gut IgA (Fukushima et al., 1999, Kirjavainen et al., 1999). Allergic responses are thought to arise if there is absence of microbial exposure while the immune system is still developing. Exposure to microbial flora early in life allows for a change in the T_H1/T_H2 balance, favoring a T_H1 cell response (Ouwehand, 2007, Ogden and Bielory, 2005).

Dietary supplementation using particular probiotic strains has been found to increase interferon activity in the blood of human, and children born to families who consume traditional *Lactobacillus*-rich fermented foods experience fewer allergies than those from families who consume more sterile foods (Caramia et al., 2008).

It has been confirmed that children who develop allergies present low levels of bifidobacteria, gram-positive aerobic organisms, and enterococci, but more elevated levels of clostridia and *S. aureus* in their enteric microflora. Increased fecal levels of i-caproic acid which are indicators of high level of *Clostridium difficile*, suggest that the enteric microflora could be

changed in allergic children. Many factors exert the alteration of gastrointestinal flora equilibrium such as genetic factors, diet, and infection frequency, antibiotic therapies, passive smoke, pollution, vaccinations, psychologic stresses, reduction of immunologic activity, and development of allergic diseases and some inflammatory diseases (Alm, 2002, Halken, 2004). For example, antibiotic therapy leads to changes in intestinal, bacterial, and fungal components and also to overgrowth of *Candida albicans*, which can secrete potent prostaglandin-like immune response modulators and subsequently promote the development of allergic events in distal mucosal sites such as the skin (Noverr et al., 2005). It should be noted that not all probiotic microorganisms have the same immunologic properties and specific probiotic microorganisms of the developing intestinal microflora that most influence skin health need to be defined because specific deviations in intestinal microflora may exert predisposition to allergic disease (Caramia et al., 2008). Totally, allergic responses may also be affected by dose and viability of the probiotic and these factors in turn potentially modified by the host environment (Wickens et al., 2008).

Atopic infants have been shown to have overactive phagocytes (Isolauri et al., 1997), which may contribute to the allergic inflammation. Probiotics appear to modulate phagocytosis differently in healthy and allergic subjects (Pelto et al., 1998). For example, *L. rhamnosus* GG has been demonstrated to be capable of alleviating the overactive phagocytic process induced by cow's milk challenge in milk-hypersensitive subjects (Kirjavainen et al., 1999). Also in other studies its has been demonstrated that LGG administration, along with milk, was associated with immunostimulatory effects in healthy hosts, whereas in milk hypersensitive infants, it was associated with anti-inflammatory effects (Pelto et al., 1998).

Halper et al. (2003) investigated the anti-inflammatory potential of probiotics, the in vitro and in vivo effects of supernatants from *L. acidophilus* 4356 and 43121 on tissue repair and angiogenesis. They found that *Lactobacillus* supernatant promoted proinflammatory processes including chemoattraction of polymorphonuclear cells, macrophages, angiogenesis and stimulation of production of TNFα and other cytokines including interleukins and interferons (Halper et al., 2003). It has been indicated that allergic sensitization/IgE-associated status and greater pediatric atopic dermatitis severity correlated with stronger therapeutic response to probiotics supplementation (Lee et al., 2008a). However, in a meta-analytic study, it has been noted that there was no significant change to confirm that IgE sensitization was indeed a factor in determining the efficacy of probiotics (Michail et al., 2008).

2.4. Effects of probiotics on ultraviolet-induced skin damage

Ultraviolet radiation (UVR) is responsible for both acute and long-term effects (Moyal and Fourtanier, 2004). UVR also induces cutaneous inflammation with development of erythema, edema and hyper-proliferation of the epidermis giving rise to flaking or scaling (Soter, 1990). Approximately 50% of UVR-induced damage has been estimated to result from production of reactive oxygen species (Bernstein et al., 2004).

Some researchers pertained to the use of probiotics for the preparation of a carrier for balancing the skin's immune function under stress conditions, such as a exposure to ultraviolet radiation, specifically for enhancing the skin's immune activity and reducing the tendency to develop allergic reactions under such conditions (Baur et al., 2003). Bouilly-Gauthier et al. (2010) used *L. johnsonii* La1 and nutritional doses of carotenoids in 139 healthy women over 18

years of age for 10 weeks to protect skin immune system homeostasis following ultraviolet (UV) exposure. They concluded that nutritional supplementation *containing L. johnsonii* and doses of carotenoids reduced early UV-induced skin damage caused by simulated or natural sun exposure (Bouilly-Gauthier et al., 2010). In their study, sun protection factor measurement was based on the determination of the minimal erythemal dose. Their findings indicated that probiotic dietary supplement intake resulted in a 19% increase in the UV dose required to produce erythema. This increase could be perceived as small regarding the sun protection factor provided by sunscreens, but the tested nutritional supplement exhibited this increase of minimal erythemal dose without the absorbing or reflecting properties of sunscreens (Bouilly-Gauthier et al., 2010). It should be noted that lower skin erythema could result in less infiltration by neutrophils which release proteolytic enzymes such as elastase and metalloproteases that could play a role in skin photoageing (Rijken et al., 2005). Bouilly-Gauthier et al. (2010) also observed that cumulative exposures to suberythemal doses of UV daylight resulted in a significant decrease in Langerhans cell density. It was shown that probiotic dietary supplement intake significantly prevented this decrease, suggesting a positive effect of dietary supplement in sustaining the cutaneous immune system following Ultraviolet radiation exposure. Also they found that probiotic dietary supplementation significantly reduced the induced increase in CD45+ dermal inflammatory cells, suggesting a beneficial effect of probiotic dietary supplement intake on UV-induced inflammation and probably on photoageing (Bouilly-Gauthier et al., 2010).

Gueniche et al. (2006) studied the oral supplementation of probiotic *L. johnsonii* La1 in hairless Skh:hr1 mice for 10 days to protect against UV-induced suppression of contact hypersensitivity, decrease of Langerhans cell density and increase of interleukin-10 serum levels.

They found that in the absence of UV exposure, *L. johnsonii* La1 had no detectable effect on the immune system of the skin, thus acting only to re-establish skin homeostasis. They also demonstrated that ingested probiotic bacteria can maintain cutaneous immune capacity after UV exposure. Their results suggested that La1 contributes mainly to reinforce skin homeostasis rather than boosting the cutaneous immune defense *per se* (Gueniche et al., 2006). It has been revealed that *L. johnsonii* La-1 accelerate the recovery of Langerhans cell functionality after Ultraviolet radiation exposure in humans (Peguet-Navarro et al., 2008). In another study it has been shown that the probiotic strain *L. casei* DN-114001 is able to decrease skin inflammation in a dinitrofluorobenzene contact hypersensitivity model (Chapat et al., 2004) showing an effect in the absence of any UV challenge.

2.5. Effects of probiotics on wound protection

Many authors have demonstrated that certain bacterial probiotic extracts have anti-adhesion and anti-microbial properties when applied to cutaneous and mucous surfaces (Rodriguez et al., 2005). Probiotic microorganisms use different mechanisms, such as by lowering pH, to preserve skin health and to inhibit the growth of pathogens (Arck et al., 2010). The acidic skin environment is indeed very important as it discourages bacterial colonization and provides a moisture barrier through absorption or moisture by aminoacids, salts, and other substances in the acid mantle (Lambers et al., 2006, Mauro, 2006).

The potential use of probiotic microorganisms capable of producing antimicrobial toxins (bacteriocins, bacteriocin-like substances, organic acids, and H_2O_2) (Bernet-Camard et al., 1997, Coconnier et al., 1998) has received increasing attention to successfully prevent pathogen

adhesion and outcompete undesired species (Gillor et al., 2008). Teodorescu (1999) used a mixture of three *L. acidophilus* strains, LD-11, LR-13, and LV-17 in a eubiotic product for the maintenance and treatment of tegument. The three noted strains could ferment raffinose, trehalose, and dextrin, respectively. Also these strains were capable to maintain the skin pH at physiological values, to destroy the pathogenic microflora and to be resistant in cosmetic composition (Teodorescu, 1999).

Oh et al. (2006) reported the efficacy of the bacteriocin from *Lactococcus* sp. HY 449 in controlling skin-inflammation and acnes by clinical skin irritation test. They demonstrated that this bacteriocin was able to inhibit the growth of skin inflammatory bacteria such as *S. epidermidis*, *S. aureus*, *S. pyogenes*, and *P. acnes* due to bacteriolytic action on the cell wall and cell membranes especially in *P. acnes* (Oh et al., 2006). It has been claimed that extracts of *Lactobacillus* could stimulate the production of beta-defensins in skin cells, which can be beneficial in the reduction or prevention of growth of microbial populations on the skin, in a dose-dependent manner (Sullivan et al., 2009). Effective amounts of *Lactobacillus* extracts can be applied to an open cut or wound on the skin that may have been in contact with dirt or undesirable microbes; or on a chronic basis, applied to clean skin to maintain a healthy level of skin flora. Also, *L. plantarum* extract are shown to reduce the incidence of both inflamed and noninflamed acne lesions. The extracts had further been proposed as a preservative in cosmetic of pharmaceutical products, in particular the *L. plantarum*, which possesses a broad spectrum of activity against both Gram-positive and Gram-negative bacteria (Cinque et al., 2011).

It has been suggested that *L. plantarum* and/or its products are potential therapeutic agents in the local treatment of *P. aeruginosa* burn infections. Regarding this matter, it has been also

shown that the in vitro treatment with *L. plantarum* is able to inhibit the production of the *P. aeruginosa* quorum-sensing signal molecules, acyl-homoserine-lactones, and two virulence factors controlled by these signal molecules elastase and biofilm (Valdéz et al., 2005). Peral et al. (2009a) studied the effect of topical *L. plantarum* treatment on infected and non-infected second-degree burn patients and on infected third-degree burn patients. They found that the ability of *L. plantarum* to prevent infection, to decrease in the bacterial load, to promote granulation tissue, and to heal wounds was comparable to the silver sulphadiazine cream one (Peral et al., 2009a). Also the study of Peral et al. (2009b) showed the efficacy of *L. plantarum* bacteriotherapy on the chronic infected leg ulcers of diabetic and nondiabetic patients (Peral et al., 2009b).

Hansen and Jespersen (2010) invented a tissue dressing comprising bacteria (including *L. sporogenes*, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. brevis*, *L. delbruckii*, and *L. lactis*) having the property of producing lactic acid by fermentation of the sugars, to use in healing wounds or in accelerating the wound healing (Hansen and Jespersen, 2010). These species of lactic acid bacteria were capable of lowering the pH in an open wound environment, securing an intraspecies competitive exclusion thus preventing growth of undesirable bacterial species, exerting an immunomodulatory effect by inducing "wound healing-promoting substances" and producing certain bacteriocins such as toxins that can sustain a wound-healing process. Jones et al. (2010) showed that the NO-producing probiotic patch device containing lyophilized alginate-immobilized *L. fermentum*, glucose, and nitrite salts can produce sufficient levels of gaseous NO over a therapeutically relevant duration, to kill common bacterial and fungal pathogens existed in the wounds of humans (Jones et al., 2010).

Ouwehand et al. (2003) studied the *in vitro* potential use of probiotic Propionibacteria (*P. acidipropionici* 4900, *P. freudenreichii* ssp. *Shermanii* 4902, *P. freudenreichii* ssp. *Freudenreichii* 20271, *P. thoenii* 20277 and *P. jensenii* 20278) and *L. rhamnosus* for the skin and their production of anti-microbial substances against selected skin pathogens (*Malassezia furfur* 6170, *M. furfur* L1510, *M. furfur* L1796, *C. albicans* 1665, *C. albicans* 3454, *S. aureus* 346 and *S. aureus* 20231) as well as their adhesion to human keratin (the main protein of the skin). In their study, *P. freudenreichii* ssp. *freudenreichii* 20271 and *L. rhamnosus* 5.5a exhibited significantly higher adhesion to keratin than the other tested strains. Also they found that *C. albicans* strains were found to be sensitive and *S. aureus* 346 exhibited higher adhesion to keratin, significantly better than all other tested strains, both the potential probiotics and the target strains. According to their results, although *P. freudenreichii* ssp. *Freudenreichii* 20271 and *L. rhamnosus* 5.5a adhered in relatively high levels to the immobilized keratin, they were not able to prevent the adhesion of the tested target organisms (Ouwehand et al., 2003). In some studies, to avoid the risk of infection, it has been advised not to apply probiotics to damaged skin (Ouwehand et al., 2003). Some selection criteria for probiotics in the skin have been advised to apply. For example, adhesion, inhibition of pathogen adhesion and production of antimicrobial substances is important for an application on the skin (Ouwehand et al., 2003).

3. Mechanisms of intestinal effects of probiotics on the skin

Studies suggest that probiotics potentially act favorably in the host through several different mechanisms. The knowledge of these mechanisms provided a useful molecular model to focus on innovative therapeutic applications. The mechanism of probiotic bacteria in atopic dermatitis

patients is not exactly understood, but it has been reported that inflammatory responses have been detected after treatment with probiotic bacteria, indicating that an innate immune response pattern may underlie the therapeutic effect (Viljanen et al., 2005a).

A number of immunologic pathways have been indicated to be influenced by probiotic microorganisms, involving different mechanisms. Probiotic effects may be local, and potentially include reduction of permeability and systemic penetration of antigens, alteration of local inflammation or tolerance induction, anti-inflammatory effects mediated by Toll-like receptors, activation of tolerogenic dendritic cells, T_H1 skewing of responses; alteration of T-regulatory function, and increased local IgA production (Wickens et al., 2008). Systemic effects with increased monocytes and effects on T cells, B cells, and stem cells have also been suggested (Prescott and Bjorksten, 2007). Some strains of lactobacilli and bifidobacteria have been shown to modulate IL- 10 production, possible enhancing regulatory or tolerance-inducing mechanisms (Niers et al., 2005). It has been reported that certain probiotic bacteria are able to stimulate the production of T_H1 cytokines (Hessle et al., 1999, Miettinen et al., 1998), transforming growth factor beta (Paganelli et al., 2002), and gut IgA (Fukushima et al., 1999, Kirjavainen et al., 2003). Also, in other studies it has been reported that the transient protection offered by probiotics against IgE-associated allergic diseases is based on stimulation of Toll-like receptors, which produce mediators such as IL-6 and these further induce IgA differentiation from naive B cells (Sato et al., 2003).

It has been indicated that *L. rhamnosus* weakly stimulates dendritic cell maturation (Veckman et al., 2004). Its peptidoglycan cell wall binds to Toll-like receptor 2 (Yoshimura et al., 1999) and induces the expression of proinflammatory and anti-inflammatory cytokines

(Netea et al., 2004). Probiotic strains that stimulate the expression of regulatory cytokines have effectively prevented or alleviated eczema (Kalliomäki et al., 2001, Majamaa and Isolauri, 1997, Ling et al., 2004). In a research, combining LGG with three other probiotics suppressed the beneficial effects seen with LGG alone, perhaps due to an interference of immunostimulating effects between the strains (Viljanen et al., 2005a).

Allergic diseases are associated with an imbalance in the T_H1/T_H2 cytokine, activation of T_H2 cells and with stimulation of IgE and IgA synthesis, leading to allergic reactions (Kruisselbrink et al., 2001, Winkler and al., 2007). Probiotics inhibit the T_H2 response while stimulating the production of T_H1 and T_H1 cytokines, such as interferon γ (Isolauri et al., 2001, Ghadimi et al., 2008). Also, some studies on the effect of lactobacilli on immune cells in animal or in vitro models have shown promotion of T_H1-like responses with IFN-g, IL-12, and IL-18 activation, which inhibites development of a T_H2-like deviation in infants (Vaarala, 2003). Probiotics have a strain-dependent capability to endow T cells with regulatory properties (Tregs). Such induction of Tregs by probiotics may involve APCs (monocytes, dendritic cells), or a direct action on T cells, and may take place in the intestine, where these cells encounter commensal bacteria (Feleszko et al., 2007, Adkinson et al., 2009, Fink, 2010). It has been found that the use of probiotics is associated with an inhibition of allergen-induced tumor necrosis factor α, IgE, and several allergy-induced cytokine (Flinterman and al., 2007, Prescott et al., 2005).

It has been demonstrated that in atopic dermatitis and allergic contact dermatitis, skin-activated T cells stimulated Fas-induced keratinocyte apoptosis. In particular, diseased skin-infiltrating T cells produce IFN-γ that increasing Fas receptor number on keratinocyte membrane renders them susceptible to apoptosis by Fas ligand expressed on or released by T cell surface

(Trautmann et al., 2001). The discovery of T_H17, a new lineage of T_H cells that produce IL-17 and effects of microbiota on the balance between these cells and T cells with regulatory properties development is a new era for research (Mucid and Salek-Ardekani, 2009).

It can be concluded that the mechanism of the effects of probiotic gut flora on skin is represented by changes in systemic immune responses. In particular, modulation of specific T-cell subsets such as stimulation of T_H1 cells in the gut mucosa which may subsequently influence immune responses in other tissues can be the main influential factor (Pohjavuori et al., 2004, Lammers et al., 2003, Prescott et al., 2005). Although evidence supporting probiotic efficacy against atopic diseases is quite convincing, further studies investigating the mechanisms of disease pathogenesis are required.

4. Cosmetic approach of the probiotics regarding the skin

To date, only a few specialized suppliers propose primarily ultrasound-inactivated bacterial extracts from lactic bacteria or yeasts for potential use in cosmetic products (Guéniche et al., 2010b). Nowadays, recent studies have demonstrated the successful development of a prebiotic cosmetic approach to balance the composition of the cutaneous microbiota (Simmering and Breves, 2009). In these studies skin microbiota has been analyzed by fluorescence in situ hybridization method (Bockmühl et al., 2006). In this method, drawbacks of cultural methods are avoided and the direct observation of bacteria is allowed (Harmesen et al., 2000).

It has been observed that twice daily using of a cosmetic product containing selected plant extracts from either Ginseng or Black currant or pine to human skin for a total of three weeks was effective in preventing the growth of *P. acnes*, whereas coagulase negative staphylococci were not impressed (Bockmühl et al., 2006). It can be concluded that it is totally feasible to ameliorate the composition of the skin microbiota and to restrict or reduce the growth of pathogenic species and at the same time to preserve and stimulate the growth of beneficial bacteria. Accordingly, such a probiotic cosmetic approach is obviously preferable to antibacterial cosmetic products which unselectively decrease bacterial growth using antibiotics or antimicrobial agents (Holland and Bojar, 2002). Gueniche (2010) disclosed methods directed to the cosmetic use of an effective amount of at least one probiotic microorganism especially from the genus *Lactobacillus* and/or *Bifidobacterium*, or a fraction thereof and/or a metabolite thereof, as an active agent for limiting, preventing or treating skin irritation, and/or irritative skin disorders (Gueniche, 2010).

Environmental stress such as UV irradiation may cause oxidative stress in exposed skin. Both UVB and UVA light can induce the generation of reactive oxygen or nitrogen species (ROS/RNS) in the skin (Xu and Fisher, 2005). Increased ROS/RNS production induced by UV light alters gene and protein structure and function, leading to skin damage (Rittié and Fisher, 2002). Many evidences indicate that probiotics may be helpful as antioxidant agents, both *in vitro* and *in vivo* (Lin and Chang, 2000) and in some studies probiotics have been reported to exert systemic protection from oxidative stress and decrease human low-density lipoprotein oxidation (Peguet-Navarro et al., 2008, Bouilly-Gauthier et al., 2010). It has been concluded that

probiotics represent a useful therapeutic tool for the prevention of epidermal oxidative stress either via the topical route or via ingestion (Cinque et al., 2011).

Probiotics' ability to act as antioxidant can be attributed to the presence of antioxidant enzymes such as superoxide dismutase (Shen et al., 2010) to the release of antioxidant compounds such as glutathione (Peran et al., 2006) and to the production of extracellular polysaccharide biomolecules (Kodali and Sen, 2008). Considering the role of nitric oxide (NO) in inflammatory conditions, *L. brevis* (having arginine deiminase) metabolize arginine to citrulline and ammonia and subsequently it can inhibit NO generation by competing with nitric oxide synthase (NOS) for the same substrate, arginine (Di Marzio et al., 2001). De Simone (2003) revealed the use of bacteria such as *L. brevis* endowed with arginine deiminase to induce apoptosis and/or reduce an inflammatory reaction, and pharmaceutical compositions containing such bacteria, including creams and ointments (De Simone, 2003). Also, it has been indicated that the presence of *L. brevis* extracts in cell culture strongly inhibited inducible nitric oxide synthase (NOS) activity, IFN-g/PGE2 production, and MMP activity in LPS-activated macrophages (Della Riccia et al., 2007).

Guéniche (2010) reported three potential mechanisms may account for the effect of *Bifidobacterium* lysate on skin sensitivity including a direct action by inhibiting the release of neuro-mediators involved in sensitivity phenomena, a direct action by decreasing neurogenic inflammation frequently associated with sensitive skin symptoms and an indirect action by improving skin barrier function and protecting neurones from external stimuli (Guéniche et al., 2010b). Baba et al. (2006) reported that *L. helveticus*-fermented milk was able to promote differentiation of cultured normal human epidermal keratinocytes by enhancing production of the

differentiation-related element profilaggrin, a precursor of a natural moisturizing factor that controls normal epidermal hydration and flexibility (Baba et al., 2006).

Some preliminary researches have suggested that there could be a link between probiotics and the youthfulness of the skin. Bifidobacterial species may enhance the production of hylauronic acid in the skin. Hylauronic acid is involved in the elasticity of the skin (Tannis, 2008). Two studies have tested the ability of a bifidobacteria-fermented soy milk extract to stimulate hylauronic acid and improve properties of the skin. The results showed that there was an improvement in the appearance of the skin (Miyazaki, 2003, Miyazaki, 2004).

5. Effects of prebiotics on the skin

Prebiotics have been defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limiting number of, bacteria in the colon (Mohammadi and Mortazavian, 2010, Heydari et al., 2011). Manipulation of the composition and function of the skin microbiota by prebiotic strategies (in contrast to antibiotics), may allow selective inhibition of detrimental and at the same time preservation and stimulation of beneficial bacteria, is therefore of obvious interest in dermatology (Cogen et al., 2008). Studies have suggested that prebiotics can modulate the immune system and prevent allergic disorders (Arslanoglu et al., 2008). In the other words, prebiotics are potentially important regulators of immune response and have been used in the prevention and treatment of the immune-mediated disorders such as allergies (Holma et al., 2011). Prebiotics may modulate the immune system directly through ligation of carbohydrate or pattern recognition receptors on immune and epithelial cells (Seifert and Watzl, 2007, Roberfroid et al., 2010).

Prebiotic oligosaccharides have been shown to reduce the incidence of atopic dermatitis when given to infants at risk for atopy during the first six months of age (Moro et al., 2006). Several randomized controlled trials have pointed toward a positive effect of synbiotics and prebiotics on the course of atopic dermatitis in older children (Passeron et al., 2006) and it has been found that both groups had a significant reduction in the SCORAD (severity scoring of atopic dermatitis) score after 3 months. In the study of Passeron and Lacour (2005) children with atopic dermatitis receiving placebo treatment improved significantly within a much shorter than expected time. They used cellulose and maltose dextran as placebo, which could have a prebiotic effect thus explaining the improvement seen in the placebo group (Passeron and Lacour, 2005). Kukkonen et al. (2007) used a combination of 4 probiotics, including 2 *Lactobacillus* species in pregnant women carrying high risk children for 2 to 4 weeks before delivery. In their study the infants received the same probiotics plus galacto-oligosaccharides for 6 months. Their results suggest an inverse association between atopic diseases and colonization of the gut by probiotics. This study demonstrated a reduction in eczema that was stronger for the subgroup with atopic eczema (Kukkonen et al., 2007). Also they concluded that probiotics especially affect IgE-associated dermatitis is also supported by the findings that boys benefited from the treatment more than did girls and the boys' total IgE level was also higher. Similar results have been reported in other studies (Kukkonen et al., 2008).

It has been reported that consumption of galactooligosaccharides together with probiotics (mixture of *L. rhamnosus* GG, *L. rhamnosus* 29 LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS, and *B. breve* Bb-99) stimulates the *in vitro* peripheral blood mononuclear cell proliferation and interferon γ production (Holma et al., 2011). As it was previously discussed, the

increase in interferon γ was directly proportional to the decrease in the severity of atopic dermatitis (Prescott et al., 2005). A number of studies have found conflicting results concerning the effect of synbiotics on atopic dermatitis. Some studies have failed to show efficacy of probiotics or synbiotics in treating atopic dermatitis (Boyle et al., 2009, Kopp and Salfeld, 2009, van der Aa et al., 2010). Optimal dosage, frequency and duration of treatment, single strain or a mixture of probiotics and effects of prebiotics should be determined because different probiotic strains vary in their ability to modulate the immune system (Gill and Prasad, 2008).

Researches have revealed that prebiotics help to balance the composition of the skin's microflora by inhibiting the growth of *P. acnes* and in the mean time preserving the growth of beneficial bacteria such as *Staphylococcus epidermidis*, which is regarded as a commensal bacterium that serves to protect human skin from infections (Krutmann, 2009). Main mechanisms for healthful effects of prebiotics on the skin are presented in Figure 3.

Conclusion

Recent researches about health effects of probiotics are hopefully favorable. They have a potential role in the prevention and treatment of skin diseases such as atopic dermatitis. However, the articles regarding this matter are unanimous that more evidences are needed to prove the impact of probiotics in the treatment of skin diseases especially allergic disorders. Application of the probiotic bacteria to the skin may provide a protective shield, similar to a physical barrier. This so-called bacterial interference, through competitive inhibition of binding sites, is thought to prevent colonization by other, potentially pathogenic, bacterial strains. It is necessary to identify other probiotic strains or combinations of strains that could potentially

show efficacy. The effects of probiotics are strain-specific, and also depend on the immunological condition of the host. Furthermore, probiotic combinations should be planned using careful in vitro preclinical studies on their properties and strain interactions, prior to proceeding to clinical trials in humans. Further investigations are required, *in vitro* and in clinical trials, with different species and strains of probiotic microorganisms in relevance to their effects on the skin, investigating their modes of action and considerably more supporting evidence beyond what is currently provided in this review. Also, customers should be more aware of healthful role of probiotics in skin-therapy. This important could be implemented via planning by national health organizations in the countries of use and proper advertisements by media.

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Table 1. Studies of probiotic effects on atopic dermatitis

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. rhamnosus GG ATCC53103 *B. lactis* Bb-12	27 children (mean age 4.6 mo)	3×10^{8} cfu/g 1×10^{9} cfu/g	2 mo	Improvement in skin condition, modification of allergic inflammation, reduction in SCORAD score	(Isolauri et al., 2000)
L. rhamnosus GG	159 infants	1×10^{10} cfu/capsule two capsules daily for 2–4 weeks before expected delivery	6 mo	Prevention of early atopic disease in children at high risk	(Kalliomäki et al., 2001)
L. rhamnosus 19070–2 *L. reuteri* DSM 122 460	Infants aged 1–13 years (mean age 4.6 mo)	2×10^{10} cfu/day 2×10^{10} cfu/day	6 wk	More pronounced effect in patients with positive skin prick test response and increased IgE levels	(Rosenfeldt et al., 2003)
L. fermentum VRI-033 PCC	56 children aged 6-18 mo	3×10^{9} twice daily	8 wk	Improved extent and severity of atopic dermatitis in the probiotic group	(Weston et al., 2005)
L. rhamnosus GG	57 infants	2×10^{10} cfu daily	3 mo	Reduction in AD prevalence compared with placebo	(Rautava et al., 2002)

L. rhamnosus GG	107 infants	10^{10} cfu	4 y follow up of study by Kalliomaki et al. (2001)	Protective effect against AD	(Kalliomäki et al., 2003)
B. bifidum W23 *B. lactis* W52 *Lc. lactis* W58	156 infants	1×10^9 daily 1×10^9 daily 1×10^9 daily	1 y	significant decrease in IL-5 production, significant lower eczema during the first 3 mo in probiotic group	(Niers et al., 2009)

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. rhamnosus GG ATCC 53103 *L. rhamnosus* LC705 DSM7061 *B. breve* Bb99 DSM 13692 *P. freudenreichii* ssp. *shermanii* JS DSM 7076	925 infants	5×10^9 cfu 5×10^9 cfu 2×10^8 cfu 2×10^9 cfu daily	6 mo	No effect of probiotics vs placebo on cumulative incidence of allergic diseases, but tended to reduce IgE-associated (atopic) diseases, probiotics reduced eczema	(Kukkonen et al., 2007)
L. acidophilus LAVRI-A1	178 infants	3×10^9 cfu daily	6 mo	No reduction in AD at 6 mo vs placebo groups, Paradoxical increase in sensitization to allergens in	(Taylor et al., 2007)

				probiotics supplemented infants	
L. reuteri ATCC 55730	188 infants	10^8 cfu daily	mothers from gestational age 36 wk to delivery, then infants supplemented for 1 y, then followed for 1 y	Cumulative incidence of eczema similar in probiotics and placebo groups, Probiotics group had less IgE-associated eczema during second year	(Abrahamsson et al., 2007)
L. rhamnosus GG ATCC53013	31 Infants aged 2.5-15.7 mo	5×10^8 cfu	4 wk	After 4 wk of intervention, significant SCORAD score reduction in probiotic group, decrease of α1-antitrypsin and tumor necrosis factor α	(Majamaa and Isolauri, 1997)
L. rhamnosus GG ATCC 53103 *L. rhamnosus* GG *L. rhamnosus* LC705 *B. breve* Bbi99 *P. freudenreichii* ssp. Shermanii JS	119 infants aged 1.4–11.5 m (mean age 6.5 m)	-	4 wk	Increase of IFN- γ in those with IgE-associated dermatitis	(Pohjavuori et al., 2004)

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. rhamnosus 19070-2 *L. reuteri* DSM 12246	43 patients aged 1-13 y	10^{10} cfu twice daily	18 wk	No overall significant change in total SCORAD after treatment, 56% of patients who took probiotics experienced improvement of eczema, compared with 15% of patients who took placebo, probiotic effect seen only in IgE-sensitized group	(Rosenfeldt et al., 2003)
L. rhamnosus GG	35 Infants, Mean age 5.5 mo	3×10^{8} cfu	0.4 to 45.3 wk	SCORAD scores decreased 19 to 5 in viable LGG group, Treatment with heat inactivated LGG associated with adverse gastrointestinal symptoms and diarrhea	(Kirjavainen et al., 2003)
LGG ATCC53103 *L. rhamnosus* LC705 *B. breve* Bbi99 *P. freudenreichi* ssp *shermani* JS	230 Infants aged 1.4–11.9 mo (mean age 6.4 mo)	5×10^{9} cfu 5×10^{9} cfu 2×10^{8} cfu 2×10^{9} cfu	4 wk	IgA levels tended to be higher in probiotic groups, α_1- antitrypsin decreased in the probiotic group, IL-6 and IL-10 increased in LGG and MIX groups more so than in placebo	(Viljanen et al., 2005a)

				for IgE independent AD, Probiotic effect seen only in IgE-sensitized group	
L. fermentum VRI-033 PCC	53 children aged 6-18 mo	1×10^9 cfu	8 wk	Older children (mean age, 11.5 mo) with more severe dermatitis are more likely to show improvement of lesions statistically with probiotics, More children in probiotics group significantly had score improvement than those given placebo	(Weston et al., 2005)

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. rhamnosus GG	19 children aged 6 mo to 8 y	$10\text{-}20 \times 10^9$ cfu	9-12 wk	Significant greater decrease in severity of symptoms in probiotic group	(Bard et al., 2008)
L. rhamnosus GG ATCC 53013	53 children aged 1–55 mo	5×10^9	-	No improvement over placebo	(Folster-Holst and al., 2006)
L. rhamnosus Lcr35	39 children aged 2–12 y	1.2×10^9 cfu 3 times daily	3 mo	Improvement in prebiotic and synbiotic groups	(Passeron et al., 2006)

L. rhamnosus GG ATCC 53013	102 children aged 3–12 mo	5×10^9	12 wk	No significant improvement in AD among probioticand placebo groups	(Gruber and al., 2007)
L. rhamnosus GG ATCC 53103 *L. rhamnosus* LC705 DSM7061 *B. breve* Bb99 DSM 13692 *P. freudenreichii* spp. *Shermanii* JS DSM 7076	925 infants	5×10^9 cfu/capsule 5×10^9 cfu/capsule 2×10^8 cfu/capsule 2×10^9 cfu/capsule	2 years	Decrease of prevalence of AE at age of 2 years (eczema without IgE sensitization)	(Kukkonen et al., 2007)
L. rhamnosus GG	94	-	2 years	No difference in prevalence of AE at age of 2 years	(Kopp et al., 2008)
L. rhamnosus HN001 *B. animalis* subsp. *lactis* HN019	446 infants	6×10^9 cfu 9×10^9 cfu daily	2 years	Decrease of prevalence of eczema in *L. rhamnosus* group	(Wickens et al., 2008)
L. rhamnosus LC705 DSM 7061 LGG 53103 *B. breve* Bb99 DSM 13692 *P. freudenreichii* ssp. *shermanii* JS DSM 7076	891 infants	5×10^9 cfu 5×10^9 cfu 2×10^8 cfu 2×10^9 cfu twice daily	6 mo	No change in AE prevalence at the age of 5 years, decrease of prevalence of AE at 5 years of life in cesarean-delivered children	(Kuitunen et al., 2009)

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. casei *L. rhamnosus* *S. thermophilus* *B. breve* *L. acidophilus* *B. infantis* *L. bulgaricus* (mixture)	40 infants and children aged 3 mo to 6 y	1×10^9 cfu twice daily	8 wk	Improvement of atopic dermatitis with the mixture of the seven strains of probiotics and Fructooligosaccharide	(Farid et al., 2011)
L. fermentum PCC	56 infants aged 6–18 mo	-	8 wk	Increase of IFN-γ and TNF-α, decrease of IL-13 and decrease in the severity of AD in probiotic group	(Prescott et al., 2005)
B. breve M-16V	15 children	$5–15 \times 10^9$ cfu	1 mo	Improvement of allergic and cutaneous symptoms	(Hattori et al., 2003)
L. rhamnosus GG *B. lactis* Bb-12	15 infants	3×10^8 cfu/g 1×10^9 cfu/g	-	Significant changes in plasma lipid PUFA composition were detected, both groups influenced the proportions of n-3 PUFA in neutral lipids; both reduced the proportion of α-linolenic acid	(Kankaanpaa et al., 2002)
B. lactis Bb-12	13 infants	8×10^{10} cfu/kg body weight	-	SCORAD drop in 50% of placebo group and 100% of probiotics group	(Kirjavainen and al., 2002)
L. rhamnosus and *B. lactis* (Combined)	59 Children aged 1–10 y	2×10^{10} cfu daily	12 wk	Significant AD improvement only observed in food sensitized children	(Sistek and al., 2006)

Probiotic microorganisms	Patients (N, age)	Administered dose	Period of study	Conclusions and remarks	References
L. rhamnosus LGG	50 Infants aged 1.1–5.2 mo	5×10^9 cfu/100 mL formula 3×10^8 cfu/100 mL formula	12 wk	No significant clinical effect of probiotics on AD severity was detected, Differences in SCORAD at randomization and subsequent decrease in SCORAD during treatment were not significant	(Brouwer et al., 2006)
L. rhamnosus 19070-2 *L. reuteri* DSM12246	41 Children aged 1-13 y (mean age 4 y)	10^{10} cfu	18 wk	Small intestinal permeability (Lactulose-Mannitol test)	(Rosenfeldt et al., 2004)

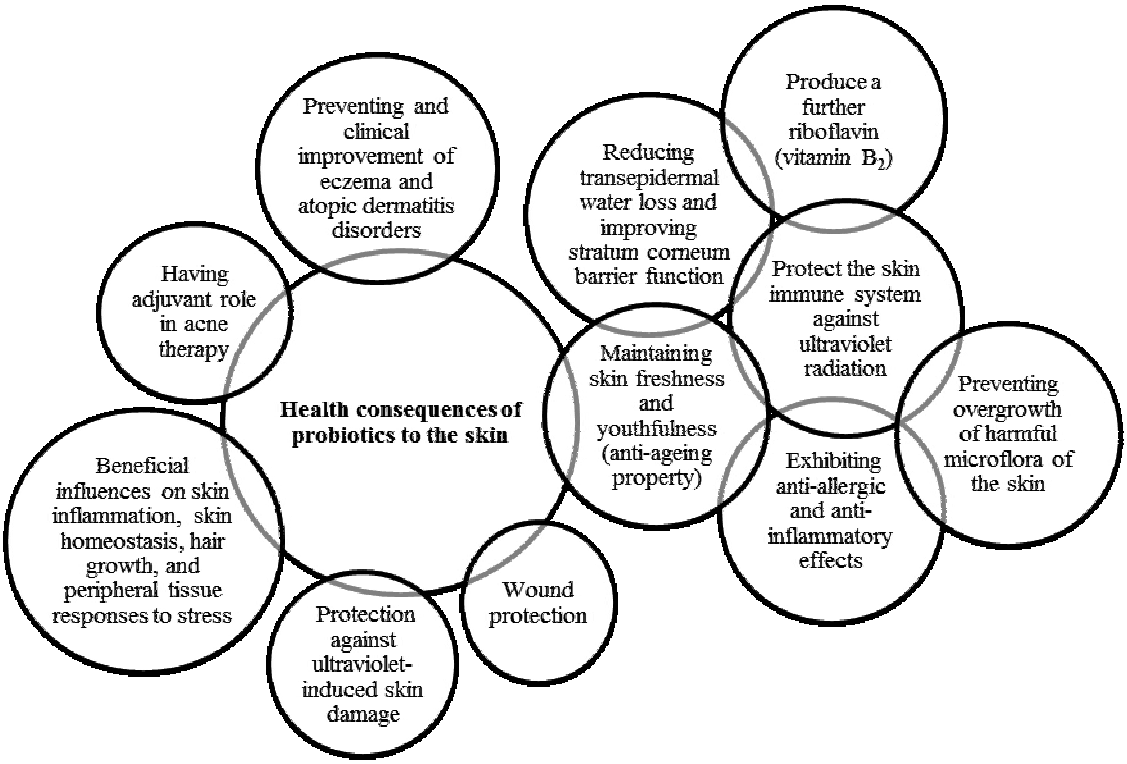

Figure 1. Health consequences of probiotics to the skin.

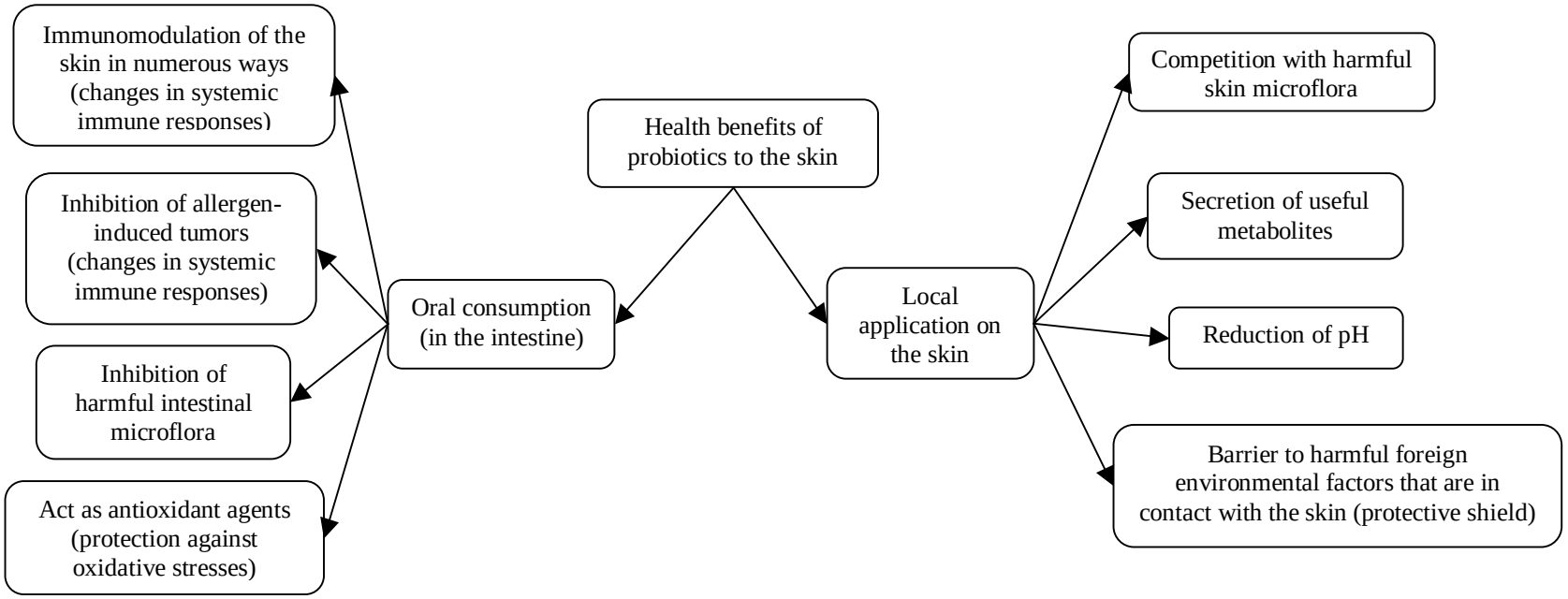

Figure 2. The main mechanisms involved in health benefits of probiotics to the skin.

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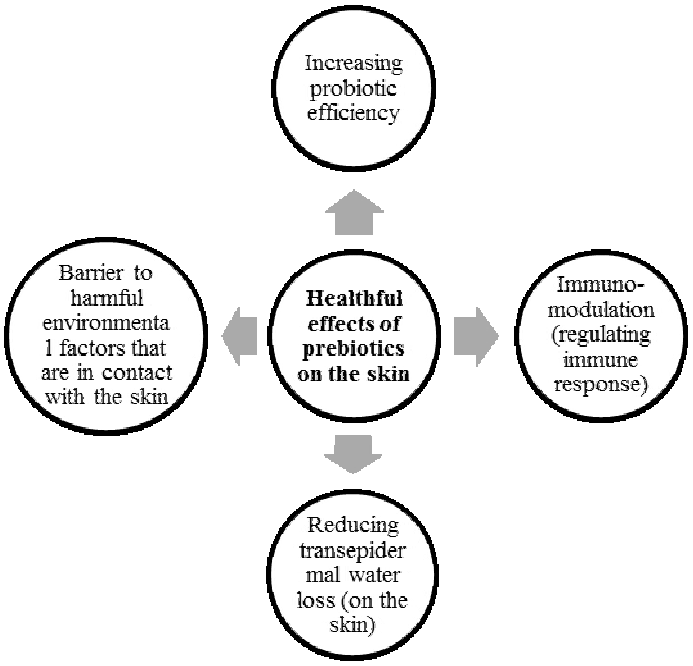

Figure 3. Main mechanisms for healthful effects of prebiotics on the skin.

