Probiotics in dermatological and cosmetic products – application and efficiency

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Abstract

The term “probiotics” has first been used in 1907 by Elie Metchnikoff. Since then, probiotics have been part of research not only in regards of digestive health, but also inflammatory diseases. Lately, there has been an increased interest of probiotic’s effects in skincare. The management of atopic dermatitis, acne, psoriasis, photo aging, skin cancer, intimate care, oral care, wound healing is getting harder each passing day, due to increased antibiotic resistance and other side effects of conventional therapy. Therefore, new ingredients have been investigated and probiotics have been proved to be effective in treating various skin conditions. This review aims to evaluate the scientific evidence on topical and oral probiotics, and to evaluate the efficacy of cosmetic and dermatological products containing probiotics. Many studies have shown that skin and gut microbiome alterations have an important role in skin health. Although this is a new topic in dermatology and cosmetology, there have been some promising results in lots of research studies that the use of probiotics in cosmetic products may help improve the patient’s outcome. While oral probiotics have been shown to promote gut health, which influences the host immune system and helps treat different skin diseases, the mechanism of action of topical probiotics is not yet fully understood. Although the number of commercial probiotic cosmetic products released in the market is increasing and most of the studies have not shown any serious side effect of probiotics, further studies, in larger and heterogeneous groups are needed.

Keywords: probiotics, acne, atopic dermatitis, photoaging, psoriasis, immune system, wound healing, oral care, intimate care, skin microbiome

Introduction

The integumentary system is formed by the skin and its derivative structures. The skin is composed of three layers: the epidermis, the dermis, and subcutaneous tissue (Kanitakis, 2002). The outermost level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role. The middle layer, the dermis, is fundamentally made up of the fibrillar structural protein known as collagen. The dermis lies on the subcutaneous tissue, or panniculus, which contains small lobes of fat cells known as lipocytes. The thickness of these layers varies considerably, depending on the geographic location on the anatomy of the body. The eyelid, for example, has the thinnest layer of the epidermis, measuring less than 0.1 mm, whereas the palms and soles of the feet have the thickest epidermal layer, measuring approximately 1.5 mm. The dermis is thickest on the back, where it is 30-40 times as thick as the overlying epidermis (James et al., 2006).

Skin is the largest organ of the human body whose primary functions consist of thermoregulation, immune response, a physical barrier that protects from exogenous factors. It is colonized by a diverse and large number of

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Microorganisms. Some of them are commensal and some are transient. Most of them are beneficial to the host in normal conditions, but some of them may be pathogenic. So far, only about 200 microorganisms has been characterized as pathogenic. The rest are either commensal or facultative pathogenic. Due to differences in the environment in different anatomic sites, the abundance of bacteria is also different. Moist areas harbor mostly *Staphylococcus* and *Corynebacteria* species. Sebaceous sites host lipophilic species such as *Propionibacterium*. Dry areas host predominantly *Staphylococcus*, *Propionibacterium*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter* and *Streptococcus* species.

Understanding the skin’s microbiome is crucial to gain insight about the benefits and/or skin diseases caused by its alterations. Culture based methods have been widely used in the identification of skin bacteria. However, some bacteria require fastidious growth conditions and are difficult to isolate. The development of molecular techniques to identify and quantify microbial organisms has enhanced our understanding of the skin bacterial diversity.

Genomic approaches to characterize skin bacteria rely on sequence analysis of the 16S ribosomal RNA genes, which is present in all bacteria and archaea, but not in eukaryotes. The 16S rRNA gene contains variable regions, enabling taxonomic classification and conserved regions, serving as binding sites for PCR primers. Moreover, an organism does not need to be cultured to determine its type by 16S rRNA sequencing (Dethlefsen et al., 2007; Turnbaugh et al., 2007). The disadvantage of this method is that it cannot distinguish between methicillin-resistant and methicillin-sensitive *Staphylococcus* spp. isolates.

Beside metagenomic analysis, metabolomic identification, through mass spectrometry of metabolites, lipids and peptides; bioinformatic software for analysis of phylogenetics, metaproteomics and metabolomics; and artificial intelligence-based data management and prediction of microbial interactions (i.e. artificially created microbial ecosystems [ACMEs]) are now being used in combination for the quantification and profiling of microorganisms, and their genetic material, environmental conditions, and interrelations.

**Skin microbiome**

The microbiota refers to any microorganism present in and on the body, such as gut, nose, oral mucosa, pulmonary mucosa, scalp and the skin. The skin microbiome is the genome of the microorganisms present on the skin to which microorganisms maintain a complex relationship.

The early age development of skin microbiome plays a pivotal role in the establishment of the cutaneous homeostasis and skin immune functions. Because of the environmental changes, from mostly sterile environment in the womb to a gaseous one with constant microbial interaction, the first days after birth mark significant changes in skin barrier composition and function. These changes include reduction in transepidermal water loss, skin pH and sebaceous activity and increase in water content. The early colonization is dominated by *Staphylococci*, but it decreases by the end of the first year of life, contributing to an evenness of population. The predominant species of infant skin are *Firmicutes*, followed in decreasing order by *Actinobacteria*, *Proteobacteria* and *Bacteroidetes*.

The skin region specific bacteria predominance depends on a lot of factors such as: moisture levels, sebum content, temperature, pH and UV exposure. It is also influenced by the place of residence, either urban or rural.

Alterations in skin microbiome caused by intrinsic and extrinsic factors is called dysbiosis. Dysbiosis does not only occur between bacteria, but also between bacteria and other skin commensals, such as bacteria and fungi. A disequilibrium between bacteria and fungi strains on the scalp, has been observed in subjects prone to dandruff.

Host skin cells continuously sample microorganisms that reside in the epidermis and dermis through pattern recognition receptors (PRRs). Part of the activated immune system and how changes are regulated, distinguish a commensal organism from a potential pathogen. Functions of the skin microbiota in health and disease.

**Probiotics in skin homeostasis**

The term probiotic has been defined as “living microorganisms which, when consumed in adequate amounts, confer a health effect on the host” (World Health Organization and Food and Agriculture Organization of the United Nations, 2001). *Lactobacillus* and *Bifidobacterium* have emerged as two of the most commonly used probiotics (Ouwehand et al., 2002), although newer strains such as *Bacillus coagulans* are being investigated with positive results (Benson et al., 2012). Most commonly formulated as fermentation products, probiotics counter pathogenic bacteria, support barrier function, and contribute to the regulation of the innate and adaptive immune responses (Hacini-Rachinel et al., 2009). Probiotics can now be found in household items ranging from yogurt to children’s popsicles to facial cream. In Table 1, the role of probiotics in dermatology as well as in cosmetology is presented.

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Another example of potential use of probiotics for skin health is *Lactobacillus pes-odoris*, which specifically inhibits the odor-producing bacteria of the feet and *Lactobacillus at-a-odoris*, which prevents the formation of odor in armpits. Both *Lactobacilli* cultures can improve the effectiveness of deodorants, foot sprays, or lotions.

Additionally, probiotics can result in significant benefits in protecting and restoring the skin barrier. In patients with acne and rosacea, living microorganisms on the skin are recognized as foreign by the body’s immune system. The immune system springs into action to counter this potential threat resulting in the inflammation, redness, or bumps common in these skin conditions. Probiotics applied topically sit on the skin’s surface and prevent the skin cells from seeing the bad bacteria and parasites that can cause this immune system response. This is known as “bacterial interference,” as probiotics could protect the skin and interfere with the ability of the bacteria and/or parasites to provoke an immune reaction (Bowe, 2013; Sánchez-Pellicer et al., 2022).

When certain types of probiotics are placed in contact with skin cells, they calm the parts of the cells that may want to react to the presence of pathogenic bacteria that they see as a threat. These healthy signals produced by the probiotics stop the skin cells from sending “attack” messages to the immune system that result in flares of acne or rosacea (Yan and Polk, 2011).

**Mechanism of action of probiotics**

The mechanisms whereby probiotics may play a role in skin physiology are not fully elucidated. However, it is proposed that, as shown for other commensal bacteria, probiotics could be directly sampled in the lumen by mucosal dendritic cells, which express tight junction proteins and penetrate the gut epithelial monolayer (Uhlig and Powrie, 2003). It is postulated that upon interaction of the probiotic bacteria (or their components) with the intestinal epithelium and/or direct interaction with dendritic cells, other immune cells, such as Band T lymphocytes may be activated (primed) and immune mediators, including cytokines, may subsequently be released. These cytokines, bacterial fractions, and primed immune cells may be transported via the blood to other organs, including the skin, where they could modulate the immune status.

In addition, the improvement of reactive skin after probiotic supplementation could also result from a direct activity of the ingredient on neurosensitive mechanisms. On the one hand, immune-regulating properties of probiotics at the skin level could modulate the inflammatory reactions generated by the release of neuromediators involved in skin neurosensitivity (Nickoloff and Naidu, 1994; Ohta et al., 2000; Thurin and Baumann, 2003). On the other hand, the capacity of certain probiotics to modulate the production of regulating cytokines and growth factors (as Transforming growth factor beta) may play a role in the proliferation and differentiation of skin keratinocytes, which are important for skin barrier repair (Von der Wied et al., 2001). Such possible effects on the process of generating the stratum corneum allow the quality of the cutaneous barrier function and skin dryness to be improved (Thurin and Baumann, 2003).

**Probiotics in dermatotherapy and cosmetology**

**Acne treatment**

Acne is a chronic inflammatory disease that is caused by hyperproliferation of *Propionibacterium acnes* in hair follicles, hyperkeratinisation and sebum overproduction. Beside androgen levels and pathogenic influence, the alterations in the skin microbiome play an important role in the presence and severity of acne. It is one of the 10 most prevalent disorders in the world and has severe adverse effects on the quality of the life in patients.

The co-morbidity of chronic skin conditions and mental health disorders has long been recognized, and in recent years’ specialty psychodermatology and neurodermatology groups have emerged. Acne vulgaris is a common dermatological disorder frequently associated with depression, anxiety and other psychological sequelae. The mental health impairment scores among acne patients are higher vs. a number of other chronic, non-psychiatric medical conditions, including epilepsy and diabetes. Along with the psychological fallout, there have also been indications that acne patients are at a higher risk for gastrointestinal distress. For example, one study involving over 13,000 adolescents showed that those with acne were more likely to experience gastrointestinal symptoms such as constipation, halitosis, and gastric reflux. In particular, abdominal bloating was 37% more likely to be associated with acne and other seborrheic diseases.

Stokes and Pillsbury made numerous references to the use of *L. acidophilus* and *L. acidophilus-fermented* milk products as a treatment modality in the context of the brain-gut-skin inflammatory process. Indeed, other physicians writing in the 1930s made reference to the popularity of *L. acidophilus* cultures among the general public as an internal means to treat acne. However, despite the apparent appeal of what would later be described as probiotics, there was little research to determine efficacy. The first formal clinical case report series on the potential value of *Lactobacillus probiotics* was published in 1961. A physician from Union Memorial Hospital in Baltimore, Robert H. Siver, followed 300 patients who were administered a commercially available probiotic (Laxtinex tablets providing a mixture of *L. acidophilus* and *L. bulgaricus*). He used a protocol of probiotic supplementation for 8 days followed by two-week washout then re-introduction for an additional eight days. The rationale for such a dosing regimen is unclear. In any case, he reported that 80 percent of those with acne had some degree of clinical improvement, and that the intervention
was most valuable in cases of inflammatory acne. Without a placebo control, Dr Siver concluded merely that ‘interactions of skin manifestations of acne vulgaris and of metabolic processes of the intestinal tract are suggestive’.

Table 2. Beneficial properties and application of some probiotics in dermatology and cosmetology

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Benefit</th>
<th>References</th>
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<tr>
<td><em>Streptococcus thermophilus</em></td>
<td>Increases ceramide production</td>
<td>Di Marzio et al. (1999)</td>
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<tr>
<td><em>Enterococcus faecalis</em></td>
<td>Reduces inflammatory lesions</td>
<td>Kanget al. (2009)</td>
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<td><em>Streptococcus salivarius</em></td>
<td>Immune modulator</td>
<td>Cosseau et al. (2008)</td>
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<tr>
<td><em>Bifidobacterium longum</em></td>
<td>Skin inflammation</td>
<td>Guéniche et al. (2010)</td>
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<tr>
<td><em>Lactobacillus paracasei</em></td>
<td>Skin inflammation</td>
<td>Guéniche et al. (2010)</td>
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<tr>
<td><em>Lactobacillus johnsonii</em></td>
<td>UV protection</td>
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<tr>
<td><em>Lactobacillus plantarum</em> HY7714</td>
<td>Anti photoaging effect</td>
<td>Bouilly-Gauthier et al. (2010)</td>
</tr>
<tr>
<td><em>Lactobacillus acidophilus IDCC 3302</em> tyndallizate</td>
<td>UVB protection</td>
<td>Lee et al. (2015)</td>
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<tr>
<td><em>Lactobacillus buchneri</em></td>
<td>Photoprotection</td>
<td>Kang et al. (2020)</td>
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<tr>
<td><em>Nitrosomonas eutropha</em></td>
<td>Anti-wrinkles</td>
<td>Notay et al. (2019)</td>
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<tr>
<td><em>Lactobacillus fermentum</em></td>
<td>SCORAD reduction</td>
<td>Huang et al. (2017)</td>
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<tr>
<td><em>Lactobacillus plantarum</em> CJLP133</td>
<td>Prevention of AD symptoms</td>
<td>Han et al. (2012)</td>
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<tr>
<td><em>Bifidobacterium lactis</em> UABLA-12</td>
<td>AD improvement</td>
<td>Gerasimov et al. (2010)</td>
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<tr>
<td><em>Vitreoscilla filiformis</em> lysate</td>
<td>Improves AD symptoms</td>
<td>Gueniche et al. (2008)</td>
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<tr>
<td><em>Bifidobacterium dentium</em></td>
<td>Reduces the incidence of AD</td>
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<td><em>Pseudomonas aeruginosa</em></td>
<td>Wound healing</td>
<td>Valdéz et al. (2005)</td>
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<tr>
<td><em>Streptococcus thermophilis</em></td>
<td>Acne treatment</td>
<td>Di Marzio et al. (2008)</td>
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<tr>
<td><em>Enterococcus faecalis SL-5</em></td>
<td>Acne treatment</td>
<td>Kang et al. (2009)</td>
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<tr>
<td><em>Bifidobacterium longum</em></td>
<td>Acne treatment</td>
<td>Guéniche, A et al. (2010)</td>
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<td><em>Lactobacillus johnsonii</em></td>
<td>Photoaging</td>
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<td><em>Lactobacillus fermentum</em></td>
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<td><em>Lactobacillus salivarius</em></td>
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<td><em>Lactobacillus rhamnosus</em></td>
<td>Atopic dermatitis</td>
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<td><em>Bifidobacteria lactis</em></td>
<td>Atopic dermatitis</td>
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<td><em>Lactobacillus sakei</em></td>
<td>Atopic dermatitis</td>
<td>Woo et al. (2010)</td>
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<td><em>Vitreoscilla filiformis</em> lysate</td>
<td>Atopic dermatitis</td>
<td>Gueniche et al., (2008)</td>
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<tr>
<td><em>Propionibacterium freudenreichii</em></td>
<td>Atopic dermatitis</td>
<td>Sikorska and Smoragiewicz (2013)</td>
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<tr>
<td><em>Lactococcus lactis</em></td>
<td>Atopic dermatitis</td>
<td>Sikorska and Smoragiewicz (2013)</td>
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<tr>
<td><em>Lactobacillus bulgaricus</em></td>
<td>Atopic dermatitis</td>
<td>Sikorska and Smoragiewicz (2013)</td>
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<tr>
<td><em>Bifidobacterium dentium</em></td>
<td>Atopic dermatitis</td>
<td>Avershina e. et al., (2017)</td>
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<tr>
<td><em>Bifidobacterium lactis</em> HK019</td>
<td>Atopic dermatitis</td>
<td>Wickens K. et al, 2018</td>
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<tr>
<td><em>Lactobacillus casei CRL 431</em></td>
<td>Immune regulation</td>
<td>Galdeano et al. (2006)</td>
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<tr>
<td><em>Lactobacillus paracasei</em> CNCM I-1518</td>
<td>Immune regulation</td>
<td>Galdeano et al. (2006)</td>
</tr>
<tr>
<td><em>Lactobacillus plantarum</em></td>
<td>Wound healing</td>
<td>Peral et al. (2009)</td>
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The effectiveness of conventional acne treatment including oral and topical antibiotics has been decreasing, due to the increased antibiotic resistance. Another major concern caused by antibiotics is the damage to stable skin microbiome and the resistance of non-target bacteria. In order to overcome these limits and find new ways to improve the treatment outcome, it is recommended to avoid the use of topical and oral antibiotics as monotherapy or polytherapy and supports a combination of a topical retinoid and antimicrobial, eg. Benzoyl peroxide, as the first line therapy.

Recent studies have brought new insights in understanding the pathophysiology of acne. It has been found by metagenomic studies that the abundance of *P. acnes* between healthy individuals and acne patients is similar. Instead, the disbalance between phylotypes of *P. acnes* appears to have a significant role in the triggering of acne. The predominant *P. acnes* strain in acne patients was found to be the phylotype IA1 (also known as the CC18 clonal complex or A1 SLST-type). Moreover, the virulence of phylotypes IA1 and IB in acne is higher than in normal skin. Finally, *P. acnes* types IA and IB were found to induce greater levels of production of the human antimicrobial peptide (AMP), β-defensin 2 (hBD2), from cultured sebocytes, and displayed higher levels of lipase activity than a type II isolate.

As for intestinal permeability in acne vulgaris, there have been hints that the intestinal lining may be compromised. One older study used a blood serum complement fixation test and reported that acne patients were more likely to show enhanced reactivity to bacterial strains isolated from stool. Approximately 66% of the 57 patients with acne showed positive reactivity to stool isolated coliforms, this compared to none of the control patients without active skin disease. Furthermore, a study involving 40 acne patients showed both the presence of, and high reactivity to, lipopolysaccharide (LPS) endotoxins in the blood as measured by the stellate fibrin crystal test. None of the matched healthy controls reacted to the *E. coli* lipopolysaccharide endotoxin (*E. coli* LPS), while 65% of the acne patients did have a positive reaction. The inference of these results is that circulating endotoxins derived from gut microbes is not an uncommon feature of acne vulgaris, and one indicating that intestinal permeability is a potential issue for a sizable group of acne patients.

The first report that ‘topical bacterio-therapy’ (via local *Lactobacillus bulgaricus* application) may be helpful in acne and seborrhea was published in 1912. However, it was not until 1999 that proper scientific technique was used to evaluate some of the potential skin-specific benefits of lactic acid bacterial application. Specifically, researchers showed that the lactic acid bacteria *Streptococcus thermophilus*, a species found in most yogurts, can increase ceramide production when applied to the skin for 7 days as a cream. This work, which has since been replicated, is of relevance to acne, particularly when considering that some of the ceramide sphingolipids, most notably phytosphingosine (PS), provide both antimicrobial activity against *Propionibacterium acnes* (*P. acnes*) and direct anti-inflammatory activity. Sphingolipids have been noted to be low in acne, and the seasonal loss of ceramides may be a driving force behind much higher dermatological office visits for acne during winter months. Indeed, topical application of 0.2% PS reduced papules and pustules by 89% in a recent 2-month pilot study. Additional studies hinting at the value of topical probiotics in acne include recent reports that strains of *Bifidobacterium longum* and *Lactobacillus paracasei* can attenuate skin inflammation mediated by substance P. This is of relevance because substance P may be a primary mediator of stress-induced amplification of inflammation and sebum production in acne. Two separate reports have also indicated that various probiotic lactic acid bacteria can provide in vitro antimicrobial activity against *P. acnes*. The latter study also used a clinical arm, the results showing that topical application of an *Enterococcus faecalis* probiotic lotion for 8 weeks reduced inflammatory lesions by over 50% vs. placebo. Certain substances secreted by bacterial strains, such as antimicrobial peptides, have been shown to inhibit growth of *P. acnes*. *Streptococcus salivarius*, a prominent member of the oral microbiota of healthy humans, has been shown to secrete a bacteriocin-like inhibitory substance (BLIS-like substance) capable of inhibiting *P. acnes*. In addition to the antimicrobial activity, *S. salivarius* bacterial cells themselves inhibit a number of inflammatory pathways, thus acting as immune modulators. Finally, the application of select 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.

In healthy skin, *P. acnes* plays a beneficial role in the cutaneous microbiota of the pilosebaceous unit. It limits the growth of *S. aureus*, such as community-acquired methicillin-resistant *S. aureus*, as well as that of *S. pyogenes* in maintaining an acidic pH of the pilosebaceous follicle by hydrolysing sebum triglycerides and by secreting propionic acid.

However, during puberty, over-colonisation of the pilosebaceous unit by *P. acnes* may lead to a loss of diversification and dysbiosis, potentially causing acne. A recent clinical study using the single-locus sequence typing method investigated *P. acnes* subgroups on the face and back in patients with severe acne and in healthy subjects. In almost 75% of the acne patients, *P. acnes* phylotypes were identical on the face and back, whereas this was only the case in about 45% of the healthy subjects. In the healthy group, phylotypes IA1 (39%) and II (43%) were the main phylotypes, whereas in the acne group IA1 (84%), especially on the back (96%), was the main phylotype. This may confirm the hypothesis that acne severity may be associated with a loss of diversity of *P. acnes* phylotypes.
following a selection of phylotype IA1/clonal complex (CC) 18 present in all acne patients. Therefore, different inflammatory profiles, depending on the phylotype (i.e., phylotype IA1, which has been mainly observed on the face and back of acne patients and cluster of *P. acnes* activating the innate immunity via the expression of protease-activated receptors (PARs), tumor necrosis factor-α, and the production of interferon-γ and interleukins [IL-8], have been observed. Moreover, *P. acnes* activates the release of lipases, matrix metalloproteinases, and hyaluronidases, leading to hyperkeratinisation of the pilosebaceous unit and finally to comedones, papules, and pustules.

The application of live bacteria on skin poses several challenges. Postbiotic is a relatively new term used to describe microbial metabolites. These include short-chain fatty acids, extracellular metabolites, functional proteins, cell lysates and other products derived from a probiotic that can influence the microbiome composition. Postbiotics have a long shelf life, safety and possess multiple health benefits. They have been evaluated for anti-inflammatory, immunomodulatory, anti-obesogenic, antihypertensive, hypcholesterolemic, antiproliferative and antioxidant benefits.

Various research groups have reported the presence of bacteriocins in the *Bacillus* genus. LactoSporin is an extracellular metabolite purified from *Bacillus coagulans* MTCC 5856 fermented broth with an INCI name *Bacillus ferment* filtrate extract. The potential mechanism of LactoSporin as an antimicrobial agent is by pH drop, microbial biofilms inhibition, and draining the ions from the targeted cells.

A study suggests that LactoSporin is a postbiotic that is thermostable and stable at an acidic pH. LactoSporin 2% w/w cream was a safe antiacne formulation with efficacy comparable to the standard treatment of benzoyl peroxide 2.5% gel. The onset of efficacy was very early for LactoSporin as early as three days especially for closed comedones, providing a quicker benefit than benzoyl peroxide. The major finding of this study shows that LactoSporin reduces the sebaceous secretion by its 5-alpha reductase inhibitory and antimicrobial properties, which are better than benzoyl peroxide and can be a potential ingredient for other Seborrheic conditions as well. Considering the clinical efficacy, continuous treatment and patient satisfaction, LactoSporin is highly suitable for treating subjects with mild-to-moderate acne vulgaris. Further studies on a larger sample in multiple ethnic populations may substantiate our findings.

Di Marzio et al. (2008) conducted an *in vitro* study during which he added the bacterium *Streptococcus thermophilus* to human keratinocyte cell cultures and found an increase in the production of ceramides. He believed this was due to *S. thermophilus’* possession of sphingomyelinase, an enzyme that hydrolyzes sphingomyelin into ceramides. Many bacteria have been reported to produce extracellular sphingomyelinase including the genera *Bacillus, Listeria, Staphylococcus, Mycobacterium, Chlamydia, Pseudomonas, Leptospira*, and some species of *Helicobacter*. Although this enzyme primarily functions as a virulence factor for the bacteria, its ability to increase ceramide production may provide a benefit in treating skin diseases. In the next phase of the study, Di Marzio tested this theory in vivo on 17 healthy subjects with normal skin. The subjects were instructed to apply 0.5 g of a topical probiotic formulation consisting of *Streptococcus thermophilus* twice a day to the volar surface of one of their forearms. They applied the vehicle alone to the contralateral forearm for comparison. An additional four subjects were treated with sphingomyelinase purified from *Bacillus cereus* to ensure that the results produced were specific to the sphingomyelinase and not another component within the bacterium. After seven consecutive days of application, the probiotic formulation containing *S. thermophilus* caused an increase in the production of ceramides in the stratum corneum, which was comparable to the results seen using the sphingomyelinase extracted from *B. cereus*. These results demonstrated that the sphingomyelinase produced by *S. thermophilus* may improve skin barrier function.

Ceramides not only have a role in water permeability, but they also play a part in the antimicrobial and anti-inflammatory properties of the skin. The exact antimicrobial mechanism of ceramides has not been confirmed; however, there are many theories: reduction of bacterial adherence to epithelial cells, inhibition of bacterial protein kinases, and/or damage to the cell wall of the bacteria. Aware of their antimicrobial properties, Pavlic et al. performed a study in 2007 to evaluate the role of ceramides in patients with acne. The study consisted of both an *in vitro* and *in vivo* phase. *In vitro*, he found that phytosphingosine (PS), one of the four types of sphingoid bases that make up ceramides, inhibited growth of *Propionibacterium acnes*, an important contributor to acne formation. From these findings, he performed a two-part in vivo pilot study testing a 0.2% PS formulation on subjects with acne. In the first part, 30 subjects with acne applied a topical medication containing PS with benzoyl peroxide (PS-BPO) to half of their face versus benzoyl peroxide (BPO) alone to the contralateral side of their face two times per day. After 2 months, comedones were reduced by 72% and inflammatory papules and pustules by 88% in the PS-BPO group versus 22 and 32%, respectively, in BPO only group. In another arm of the trial, 10 subjects applied PS alone to half of their face and a placebo cream alone to the other side of their face twice a day. After 2 months, the placebo increased comedones by 43% compared to only 6% in the PS group. More significant results were seen in inflammatory acne numbers with an 89% reduction observed in the PS group compared to no change in the placebo group.

A similar study in 2009 by Kang et al. demonstrated the effects of the bacterium, *Enterococcus faecalis* SL-5 (a very common inhabitant of the human gastrointestinal tract) and its effect on *P. acnes*. He conducted *in vitro and*
in vitro studies. In the in vitro aspect of the study, *E. faecalis* proved to be bacteriocidal to *P. acnes* due to a bacteriocidin named ESL5. In the clinical trial, 70 subjects with mild-to-moderate acne were enrolled in an 8-week double-blind, randomized, placebo-controlled phase III study. Subjects were randomized into the probiotic or placebo group. Those in the experimental group applied a lotion containing ESL5 to the areas of the face involved with acne twice per day, and the control group applied a placebo lotion twice daily. After 8 weeks of application, a decrease in the number of comedones was seen in the probiotic group compared to the placebo group; however, these results were not statistically significant. In the inflammatory lesion counts, a statistically significant reduction of greater than 50% was observed in the *E. faecalis* group compared to placebo.

**Photoaging**

Skin aging has intrinsic and extrinsic components. Intrinsic aging is related to genetic factors and is a set of physiologic processes related to the passage of time that includes thinning of epidermal and dermal skin layers and increasing dryness. The extrinsic skin-aging process is characterized by coarse wrinkles, loss of elasticity, epidermal thickening, dryness, laxity, rough appearance, and pigmentation disorder.

Photoaging refers to premature aging of the skin due to repeated light exposure. Its clinical manifestations, histopathology, and biochemical changes are different from the natural aging of skin. Photoaging reduces the amount of mature type I collagen and elastic fibers in the dermis of the skin. The clinical characteristics of photoaging occur mainly on exposed skin, such as the face, neck, and forearm, where rough skin, loss of elasticity, deepening and thickening of wrinkles, a leather-like appearance, pigmentation, and dilated capillaries can occur (Qin et al., 2018). Studies have shown that approximately 65% of patients with melanoma and 90% of patients with non-melanoma skin cancers, including BCC and SCC, are associated with skin photoaging (Damiani and Ulrich, 2016). Many external factors are attributed to photoaging of the skin, such as ultraviolet (UV), infrared, chemical smog, dust, and smog, among which UV radiation is the most significant (Markiewicz and Idowu, 2018).

The occurrence and development of skin photoaging mediated by UV radiation involves multiple pathways, including apoptosis, proliferation, autophagy, DNA repair, checkpoint signal transduction, cell transduction, and inflammation. UV radiation is generally categorized according to wavelength into long-wave UVA (315–400 nm), medium-wave UVB (280–315 nm), and short-wave UVC (200–280 nm). Although UVB radiation (280–315 nm) accounts for only 1–2% of the UV rays of the Sun, it is considered to be the main environmental carcinogen that causes skin cancer and is related to the occurrence and the development of tumors (Panich et al., 2016; Gherardini et al., 2019). Experimental models are the most widely used photoaging models. This type of experimental model often uses UVB because the skin tissue changes caused by UVB are very similar to photoaging of human skin (Kim et al., 2019b).

It has been reported that probiotic bacteria may be highly effective in protecting the skin from photoaging, as oral supplementation prior to UVB exposure was demonstrated to prevent TEWL, increase epidermal thickness, and alleviate damage to tight junction structures and the basement membrane in a mouse model (Bouilly-Gauthier et al., 2010; Satoh et al., 2015). The probiotic gram-positive bacterium *Lactobacillus acidophilus* inhabits the intestines and serves an important role in the maintenance of gut health; however, it is not known whether it can protect against photoaging induced by UV radiation.

Recent clinical trials have shown protective effects of dietary supplements containing *Lactobacillus johnsonii* alone or combined with carotenoids against early UV-induced skin via regulation of immune cells and inflammatory cytokines (Bouilly-Gauthier et al., 2010). Recent experiments in hairless mice have suggested that in addition to regulating immune responses in the skin, orally administered probiotics may exert anti-aging effects by suppressing wrinkle formation and increasing skin elasticity. Furthermore, our recent experiments in hairless mice have shown that oral administration of *L. plantarum HY7714* (HY7714) exerts anti-photoaging effects through reduction of wrinkle formation and suppression of epidermal thickening and that skin hydration increases in association with increasing ceramide level via regulation of serine palmitoyltransferase and ceramide expression in the mice skin (Lee et al., 2015).

A study demonstrated the protective effect of *L. acidophilus IDCC 3302 tyndallizate* on HaCaT keratinocyte damage induced by UVB exposure. Tyndallizate was analyzed for its nutrients including carbohydrate, crude protein, crude fat, moisture, and ash (Smith WP, 1996). For small molecule analysis, lactic acid was detected as a major chemical component and it is highly effective in protecting the skin from photoaging, as photoaging models. This type of experimental model often uses UVB because the skin tissue changes caused by UVB are very similar to photoaging of human skin (Kim et al., 2019b).

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keratinocytes with PELB and that had been exposed to UVB. They found that PELB decreased elastase activity and increased type I collagen expression in the UVB-induced photoaging in vitro model, reduced collagenase activity, and promoted the expression of moisture factor and antioxidan enzymes. The study results show that the PELB could be useful in the cosmetic industry due to its protective effects against UVB-induced photoaging (Kang et al., 2020).

Notay et al. (2019) investigated the use of topical *Nitrosomonas eutropha* for cosmetic improvement of facial wrinkles. They found a significant improvement in wrinkle depth severity, hyperpigmentation of the forehead and glabella in the group receiving high topical concentration of the probiotic formula.

**Atopic dermatitis**

Atopic dermatitis is a chronic inflammatory disease that affects 1 in 10 people in their lifetime. The etiology of atopic dermatitis is very complex. It can be caused by microbiome alterations, genetic factors, environmental factors, immune dysregulation and is characterized by scaly, pruritic, erythematous lesions.

AD is known to initiate with Th2, Th22 and Th17 cell activation (acute phase), before chronicity, defined by the onset of a Th1 cell response alongside the continued activation of Th2 and Th22 cells. This mechanism could be explained by the presence of a positive feedback loop made by TSLP (thymic stromal lymphopoietin), IL-4 and IL-13. TSLP, produced by keratinocytes, drives Th2 polarization and activates dendritic cells, while IL-4 and IL-13 act on keratinocytes to further increase TSLP level. Thymus and activation-regulated chemokine (TARC) levels also increase in the stratum corneum of skin lesions of AD patients, which is correlated with disease severity, especially with erythema, oedema/papules, and oozing/crusts. These two cytokines have been used as indicators of skins inflammation in AD lesions.

The conventional treatment strategy for AD includes hydration with emollients, avoidance of individual trigger factors, anti-inflammatory therapy with topical corticosteroids or calcineurin inhibitors and treatment of secondary infections. For severe AD treatment, a recent antibody has been approved, Dupilumab, which is an injectable human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 cytokine responses, and has provided remarkable results. However, its use is still debated regarding its suitability as a routine treatment. Although anti-inflammatory drugs are considered as the first pharmacological treatment, in recent years, concerns have arisen due to the high incidence of side effects. In addition, corticosteroids are not feasible for delicate parts of the body, such as the eyelids, and are discouraged in childhood.

Increasing evidence shows that patients affected by AD have a modified composition of the gut microbiome and lack microbial diversity compared to healthy controls. This bacterial dysbiosis may be considered a possible target for the treatment and prevention of AD. Therefore, the supplementation of the diet with probiotics, prebiotics and postbiotics may have a role in the management of AD because of their capacity of modulation of the microbiota.

Recent studies have shown that gut microbiomes have been implied in the development and shaping of the host immune system. Gut dysbiosis-alterations of microbial diversity and abundance due to lifestyle and diet correspond to the impaired inflammatory response to a particular antigen. This phenomenon has been demonstrated in patients with AD (Lee JH et al., 2016). In general, it is known for its short-chain fatty acid- (SCFA-) producing capability. *Bifidobacterium*, *Propionibacterium*, *Coprooccus*, *Blautia*, and *Eubacterium* are significantly reduced in patients with AD (Ellis et al., 2019; Zheng et al., 2016). Since SCFA can induce regulatory T (Treg) cell expansion, reduction of SCFA may result in a shift of Treg-17 balance towards 17, T helper cell known for its role in orchestrating proinflammatory immune response. Repopulating gut microbiota has been suggested to be an alternative mechanism to treat various immunologic diseases, including AD (Forbes et al., 2016). However, the approach is still controversial (Williams et al., 2008).

An analysis of the gut microbiota of patients with AD has shown an intraspecies compositional change in *Faecalibacterium prausnitzi* that reduces the number of high butyrate and propionate producers. Butyrate and propionate are microbial-produced short-chain fatty acids with an anti-inflammatory role. Moreover, butyrate has been shown to be a key player in maintaining gut barrier integrity. Therefore, reduced levels in the microbiota of both butyrate and propionate producers may result in a proinflammatory state in the gut and a loss of barrier integrity. All these data indicate the potential role of probiotics as microbiota recovery players, and consequently as potential nutritional supplements in AD treatment.

Huang et al. (2017) included 13 randomized controlled studies (1,070 total subjects) in a recent meta-analysis. The data suggested an overall benefit of probiotics supplementation in children with AD, indicated by a reduction of the SCORAD values of −4.50 (95% confidence interval=−7.45 to −1.54, p value < 0.001) in children aged 1–18 years. The beneficial effect was especially evident for *Lactobacillus fermentum* (mean difference=−11.42, 95% confidence interval=−13.81 to −9.04), *Lactobacillus salivarius* (mean difference=−7.21, 95% confidence interval=−9.63 to −4.78) and a mixture of different strains (mean difference=−3.52, 95% confidence interval=−5.61 to −1.44).

A randomized, double-blind, placebo-controlled study investigated the effects of the use of the *L. plantarum* CJLP133 strain in the prevention of AD symptoms. The study was performed for a time period of 12 weeks among children who were one and 12 years old. It was found that there was an improvement in AD scores (SCORAD), with a concomitant decrease in IFN-γ, eosinophil, and Interleukin-4 counts (Han et al., 2012).
The effect of *Lactobacillus rhamnosus* in the management of AD has been assessed by Kalliomaki et al. (2001) in a double-blind, placebo-controlled, randomized trial. In this trial 159 pregnant women with a family history of allergic disorders such as asthma, allergic rhinitis or eczema received placebo or *Lactobacillus rhamnosus* for 2 to 4 weeks before delivery and for a 6 month period after. The percentage of children aged 2 years old with atopic eczema was 23% in the probiotic group and 46% on placebo (p= 0.008). A subgroup analysis conducted on 57 breastfed infants confirmed the benefit of a defensive effect against eczema from supplementation with *Lactobacillus rhamnosus* (Rautava, 2002). In recent trials by Wickens et al., supplementation with *Lactobacillus rhamnosus* HN001 or *Bifidobacterium lactis* HN019 to mothers and infants showed a significant protective effect only in the groups receiving the supplementation with *Lactobacillus rhamnosus* HN001 by 2 years of age (Wickens et al., 2008) and 4 years of age (Wickens et al., 2012). The reported data suggest that many probiotics may share common properties but their effect may be strain-specific (Allen et al., 2003).

For instance, Gruber et al. (2007) found that *Lactobacillus rhamnosus* strain GG (LGG) exerted no therapeutic effects in infants with mild-to-moderate AD.

Another randomized, double-blind, placebo controlled study investigated the use of *L. paracasei* (LP), *L. fermentum* (LF), and LP+LF together in children, and it was observed that the SCORAD scores were lower in the group that received probiotics than those of the placebo group 4 months after discontinuing the probiotic treatment (Wang and Wang, 2015).

Sistek et al. (2006) conducted a 12-week trial in the UK and found that a combination of LR and *Bifidobacteria lactis* (BL) improved AD symptoms in food-sensitive children.

Woo et al. (2010) compared children who received *L. sakei* supplementation to those who received a placebo in a double-blind, placebo-controlled trial. It was found that the supplementation of *L. sakei* was associated with substantial clinical improvement with concomitant decrease in chemokine levels.

Gerasimov et al. (2010) reported that *Lactobacillus acidophilus* DDS-1 and *Bifidobacterium lactis* UABLA-12 afforded significant clinical improvements in children with moderate-to-severe AD.

A prospective, double-blind, placebo-controlled study tested a lotion containing 5% of nonpathogenic *Vitreoscilla filiformis* lysate. Seventy-five volunteers with AD applied the lotion or placebo twice a day for 30 days. Then, the severity of the disease (Scoring Atopic Dermatitis — SCORAD), the transepidermal water loss, the microbiome, and the patient’s report on itchiness and slittlesecrewp loss were evaluated. The lysate has significantly improved AD in all evaluated items, reducing skin colonization by *S. aureus*. Authors concluded that the results are not only because of *S. aureus* bacterial load reduction but also immunomodulatory effect on the skin. Later, the lysate’s immunomodulatory action was proved through analysis of dendritic cells differentiation and effector functions of dendritic and T-helper cells in *vitro* and *in vivo*. The topical treatment with the bacteria significantly reduced inflammation in mice, and the combination of allergen and lysate showed lower induced dermatitis, indicating active immunomodulation. It was observed that the innate sensibility of nonpathogenic bacteria for Toll-Like Receptor 2 (TLR2) induces dendritic tolerogenic cells and T regulatory cells, suppressing T-effector cells and cutaneous inflammation (Gueniche et al., 2008).

A revision performed by Sikorska and Smoragiewicz (2013) found a series of evidence that various strains of *Lactobacillus* and *Bifidobacterium* isolated from a variety of sources inhibit in vitro growth of *S. aureus*. The most active strains were *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG, *Propionibacterium freudenreichii*, *P. acnes*, *L. paracasei*, *L. acidophilus*, *L. casei*, *Lactobacillus plantarum*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, and *Lactococcus lactis*. This revision also included evidence that probiotics may also eliminate or reduce colonization of methicillin-resistant *S. aureus*. According to authors, their effects are mediated by both cellular competitive exclusion and acid or Bacteriocin-Like Inhibitors’ secretion.

Administration of the strain *Bifidobacterium dentium* in mothers from 36-week gestation to 3 months post-partum reduced the incidence of AD in offspring by 40%. The group responding to the probiotic intervention had a gut microbiota similar to the non-atopic children (Avershina et al., 2017).

In a randomized double blind control trial using *Lactobacillus rhamnosus* HN001 or *Bifidobacterium lactis* HN019 taken (dose 6X109 colony-forming units (CFU) daily) from 35 weeks of gestation to 6 months post-partum reduced the incidence of AD in offspring by 40%. The group responding to the probiotic intervention had a gut microbiota similar to the non-atopic children (Avershina et al., 2017).

In a randomized double blind control trial from 36 weeks of gestation until 3 months’ post-partum, 415 pregnant women were randomized to receive either probiotics (*LGG*, *Lacidophilus La*-5, and *B animalis subsp lactis* Bb-12 dose: 5 x 1010 CFU daily) or placebo. At 6 years, there was a trend toward a lower cumulative incidence of AD in the probiotic group, but the prevalence of asthma and atopic sensitization was not significantly affected by the probiotic regime (Simpson MR et al., 2015). In a RDBCT, a total of 290 participants were randomized to receive a daily mixture of *LGG* and *B animalis subsp lactis* BB-12 each at a dose of 109 CFU, or placebo. During the follow-up (mean age: 16.1 months), a significantly lower incidence of eczema was observed in the probiotic group (Schmidt et al., 2019).

Probiotics’ mechanism of action in atopic dermatitis relies on their immunomodulatory effect, normalizing microbial composition and metabolic effect. The
immunomodulatory effect is achieved by their ability to inhibit the T-helper cell type 2 (Th2) mediated response and improve the Th1/Th2 ratio; inhibiting Th2 cell response, cytokines such as IL-4, IL-5, IL-6 and IL-13 are no longer released, (Nwanodi, 2018) phagocytosis is stimulated, serum IgA is increased. Probiotics can reduce inflammation by reducing proinflammatory cytokines, IL4, IL6, tumor necrosis factor-α (TNF-α), INF-γ and high sensitivity C reactive protein (hsCRP) and by increasing expression of IL-10 and Treg-related cytokines at mesenteric lymph nodes. A new mechanism proposed to demonstrate the effectiveness of probiotics is the inhibition of the mature dendritic cell differentiation and transformation of naïve T cells into Th2. Immunomodulation decreases the susceptibility to inflammatory and allergic factors modulating the intestine skin axis. Probiotics also modulate brain function including stress response on the intestine-brain axis in rats and human subjects (Messoaoudi M. et al., 2010). Normalization of microbial composition provides protection against pathogens at the mucosal surface. It has been shown that the levels of *Bifidobacterium longum* in the feces of healthy children were significantly higher than in children with allergy, suggestingLDEng the role of this strain in preventing the occurrence of bronchial asthma and allergic dermatitis (Akay, 2014).

The metabolic effect via probiotic consumption, can be associated with the reduction of blood glucose, insulinemia and insulin resistance.

**Psoriasis**

Psoriasis is a systemic inflammatory disease characterized by scaly leisioned plaques with defined borders. These lesions are mainly located on the scalp and large areas of the extremities but can occur at any site of the body. The prevalence of psoriasis is around 1–3%, with differences between countries, corresponding the highest prevalence to Western countries.

The etiopathogenesis of psoriasis is not fully known, although most authors postulate that it would be a skin disorder of genetic origin, finally triggered by external factors that would cause changes at the immune level. The disease is associated with inflammation in other systems and organs, as evidenced by the fact of finding a correlation with inflammatory bowel disease, where between 7 and 11% of diagnosed patients also suffer from psoriasis. Other components as triggers of psoriasis are age, the comorbidity, environmental and external factors.

Although data on probiotic supplementation in psoriasis treatment are limited, promising outcomes have been documented with oral probiotics interventions, and more studies are needed to explore the role of topical probiotics in psoriasis therapy.

**Immune regulation**

One of the most important properties required for a potential probiotic strain is the capacity of sticking to the epithelial cells. In this regard, Galdeano et al. (2006) demonstrated using electronic microscopy that 2 probiotic microorganisms, *L. casei CRL 431* and *L. paracasei CNCM I-1518*, adhere to the intestinal epithelial cells (IECs) through the Toll-like receptors (TLRs) and mediate immune stimulation. Following this interaction, an increase in the cytokines production such as IL-6 and macrophage chemoattractant protein 1 from the IECs occurred, without altering the intestinal barrier; only a slight increase in the mononuclear cell infiltration of small intestine was observed. The authors also demonstrated that only fragments of the probiotic bacteria, and not the whole bacteria, were internalized inside the IECs. As a consequence, the IECs initiate a complex network of signals that stimulate the immune cells associated with the lamina propria and activate mainly the innate response and the cytokines released by T cells.

The immunomodulatory effect of probiotics is attributed to the release of cytokines, including interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), transforming growth factor (TGF), and chemokines from immune cells (lymphocytes, granulocytes, macrophages, mast cells, epithelial cells, and dendritic cells (DCs)) (Savan et al., 2006) which further regulate the innate and adaptive immune system (Folligne et al., 2010). In addition, two surface phagocytosis receptors (FcRIII and toll-like receptor (TLR)) are also upregulated by NO (Delcenserie et al., 2008; Schwandner et al., 1999). Probiotics have been reported to interact with enterocytes and dendritic, T1, T2, and Treg cells in the intestine and to modulate the adaptive immunity into pro- and/or anti-inflammatory action. Studies with BALB/c (20–30 g) inbred mice and Fisher-344 inbred rats demonstrated that *Lactobacillus paracasei* subsp. *Paracasei* DC412 strain and *L. acidophilus NCFB 1748* induced early innate immune responses and specific immune markers through phagocytosis, polymorphonuclear (PMN) cell recruitment, and TNFalpha (TNF-α) production (Kourelis A. et al., 2010). In another experimental animal model involving BALB/c mice, oral administration of *L. casei* favored rapid activation of immune cells and produced a higher number of specific markers such as CD-206 and TLR2 cells (Galdeano et al., 2006), while TLRs improve the immunological defense mechanism in terms of pro- and anti-inflammatory cytokine production upon the detection of foreign objects (Anderson, 2000).

One of the ways probiotics promote human health is by inhibiting the growth of pathogenic bacteria through the synthesis of low molecular weight compounds such as organic acid and large molecular weight antimicrobial compounds termed bacteriocins. Organic acids are acetic and lactic acids. These compounds have been proven to exhibit strong inhibitory effects against pathogenic gram-negative bacteria such as *H. pylori*. Some bacteriocins produced by probiotics are lactacin B from *L. acidophilus*, bifidocin B produced by *Bifidobacterium bifidum* NCFB, plantaricin from *L. plantarum*, and nisin from *Lactococcus lactis*.

Probiotics modulate the composition of gut microbial
species by maintaining the balance and suppressing the growth of potential pathogenic bacteria in the gut. It has been reported that *L. acidophilus* or *L. casei* increased LAB with a concomitant decrease of fecal coliforms and anaerobes. In addition, a study by Li et al. (2016) found that probiotics caused shifts in the gut microbiota composition toward specific beneficial bacteria, for example, *Prevotella* and *Oscillibacter*. These bacteria are known to produce anti-inflammatory metabolites, which subsequently decreased the Th17 polarization and favored the differentiation of anti-inflammatory Treg/Type 1 regulatory T (Tr1) cells in the gut.

**Wound healing**

Skin microorganisms contribute to the host immunity via different pathways. *S. epidermidis* has been shown to boost the host immunity by inducing AMPc such as β defensins 2 and 3 to *S. aureus*, by activating mast cell-mediated antiviral immunity, by suppressing uncontrolled inflammatory reactions during wound healing, inducing skin’s AMP production and by stimulating cutaneous T-cell maturation.

The use of *Lactobacillus plantarum* as a potential therapeutic agent for the local treatment of *Pseudomonas aeruginosa* burn infections have shown positive results. The same bacteria has been investigated for the treatment of non-diabetic and diabetic ulcers. Peral et al. (2009) found that it reduced bacterial load, neutrophils, and apoptotic and necrotic cells, modified interleukin-8 production, and induced wound healing.

**Regulatory aspects (labeling, marketing)**

The U.S. Food and Drugs Administration (FDA) categorizes probiotics into different categories, such as dietary supplements, foods, food additives, cosmetics, or drugs, based on each individual product. However, there is no regulation for topical probiotics, and currently there are no topical probiotic products approved by the FDA, which shows a need to improve the regulations for these products.

There are scores of topical cosmetic probiotic skin care products marketed and sold in the U.S., and the number continues to grow. While there is no restriction on including probiotics in cosmetic products, and FDA pre-market approval is not required, companies must still ensure their products are safe before they are marketed to consumers. In addition to testing for safety, products that include live microorganisms should be tested to ensure stability for the anticipated life of the product under normal use indications. FDA continues to evaluate scientific data on the safety of probiotics, but, as of the date of publication, has not issued any guidance documents addressing the use of such ingredients in cosmetics.

As with any other cosmetic product, companies that market topical probiotic skin care products are proscribed from claiming the product affects the structure or function of the body; such claims effectively convert a product from a legally marketed cosmetic into an unapproved drug. For example, claims that a probiotic skin care product can reverse the signs of aging, stimulate the growth of collagen and elastin, or treat acne are structure/function claims that cannot be used to legally market cosmetics in the U.S.

While a number of company’s market probiotic cosmetic products making such claims, they do so at their peril and run the risk FDA will categorize the products as unapproved adulterated drugs that cannot lawfully be marketed in the U.S. without pre-market approval. To avoid regulatory challenges and possible product recall, companies marketing probiotic skin care products should ensure all product claims are truthful and not misleading and refrain from making structure/function or disease claims on the product label or labeling accompanying the product, as well as on company web sites and social media accounts.

In the EU, as with all cosmetics, prebiotics, probiotics and postbiotics must meet key cosmetic principles. However, there is still no specific regulation or guidelines regarding these cosmetically active substances in relation to the microbiome. Namely, although the skin microbiota cannot be separated from the skin, in cosmetic regulation, skin microbiome / microbiota not yet defined, it is not even described. However, the expectation is that scientific results will be implemented in the regulation for cosmetic products and the basic ones will be introduced definitions and security aspects. Most importantly, it should be noted that these cosmetic substances are not prohibited (for example, not listed in Annex II of EC12323 / 2009) and can therefore be used safely. Therefore, they can be considered for "classic" substances, which clearly indicates the need to comply with cosmetics definition and key principles.

Prebiotics and postbiotics can be used and are already used as cosmetics substances. Probiotics, when used in cosmetics, have in order to protect the skin from external influences and to feed healthy bacteria for affect the pH or hydration of the skin, for example. Consequently, in the absence of a cosmetic policy on probiotics, living organisms may for the time being are considered classic cosmetic ingredients that fall under the general definition of cosmetic raw materials.

It is worth mentioning that the Voluntary International Group of Regulatory Authorities for Cosmetics (International Cooperation on Cosmetics Regulation - from Brazil, Canada, China, EU, Japan, Republic of Korea and USA) in 2018 formed a joint working group precisely in order to examine in detail the probiotic-based products in the cosmetics sector. Based on the observations, the group was identified the potential need to develop internationally accepted terminology guidelines, safety and quality of these substances in cosmetic products.

In this regard, it is important to emphasize the cosmetic key principles and their association when it comes to probiotics as active substances. Namely, if we
look at the cosmetic regulatory framework, each country has its own definition of what 31 is a cosmetic product but has similarities in criteria such as location of application and cosmetic function. As such, to be considered a cosmetic product, the product must contain the following:

**Place of application:** The product must be used on the outside of the body, e.g. epidermis, nails, teeth, hair, lips and external genitalia organs.

**Function:** The function of the product should be to clean, beautify, correct body odors or otherwise to keep the body in good condition. While probiotic-based products meet the above criteria above, cosmetic key principles include additional factors such as safety, microbiological quality and permissible claims, as well as shelf life and packaging.

**Safety:** The cosmetic product (and its ingredients) must be safe for its intended use. Safety assessment is a mandatory requirement in EU cosmetics legislation (and widely sought after by companies and regulators in North America, ASEAN countries and China) as proof that the product is safe to use. Security is the responsibility of industry. Probiotics are living organisms that are dynamic and therefore different from other cosmetic substances. Hence, in the cosmetics industry there is a need to adjust and design a safety assessment applicable to cosmetics based on probiotic. For example, it is essential to prove that the microorganism used does not produce toxins, to prove the absence of pathogenicity and to determine antibiotic resistance and metabolic activity (common criteria for a similar safety assessment as in the food sector).

**Microbiological quality:** Cosmetic products are not expected to be sterile, but they still must meet the microbiological quality requirements (total number of aerobic mesophilic microorganisms (bacteria, yeasts and molds) and the absence of specific microorganisms (*Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*). It is described in the instructions of EU Scientific Committee on Consumer Safety (SCCS): even if it is not legally required, this microbiological test is necessary to guarantee the quality of the cosmetic product and the safety of the consumer (Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products).

Hence, it remains unclear how well probiotics meet the requirements for microbiological quality that generally applies to all cosmetic products. Microorganisms are generally considered contaminants, with a focus on pathogens microorganisms, because cosmetics are formulated to minimize their growth. Therefore, it is important to educate both cosmetic companies and consumers/patients about the specifics when it comes to probiotics as active substances in cosmetics products.

**Claims:** Cosmetic claims must be confirmed, not false or unproven. In the context of naming a particular product as a probiotic, that means that the final manufactured cosmetic product must contain probiotics and most importantly, probiotics must be alive throughout shelf life of the product. However, more and more products on the market contain claims to contain probiotic ingredients, but, as already mentioned, research has shown that many of these products on the market contain primarily postbiotics and prebiotics, not live bacteria. As a result, inappropriate use of various undefined terms (probiotic, prebiotic and postbiotic) creates confusion about these products.

It is therefore clear that it is necessary to develop internationally accepted definitions of key terms that need to be used consistently in order to minimize confusion and to avoid misunderstanding, both with regulators and consumers. In the food and food supplements industry, each European country has its own country-specific labeling rules, but in some European countries manufacturers cannot even put the word "probiotic" on the label of the product.

For all the above reasons, the joint working group “Microbiome and ICCR's Cosmetics” works to educate key stakeholders (regulatory bodies, cosmetics industry and consumers) in order to achieve a better understanding and augmentation.

**Conclusion**

Topical probiotics are definitely a promising range of products in treating various skin conditions. It has been demonstrated that different probiotics strains can help improve the outcomes of acne, atopic dermatitis, psoriasis, wound healing, oral and intimate care, but there is yet a lot to be understood.

The lack of knowledge regarding skin’s microbiome, the site-specific diversity of microorganisms makes it difficult for topical probiotics developers to achieve the desired formulation. The optimal dosage and strain for various skin conditions has yet to be determined. However, there is enough topical probiotics evidence to keep searching new ways or strains to achieve their full potential worth it.

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Резиме

Пробиотици во дерматолошки и козметички производи - употреба и ефикасност

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Ключни зборови: пробиотици, акни, атопичен дерматитис, фотостареење, псоријаза, имунолошки систем, засврнување на рани, орална нега, интимна нега, микробиом на кожата

Терминот „пробиотици“ првпат е употребен во 1907. година од страна на Ели Мечникоф. Оттогаш, пробиотиците се дел од истражувањето не само за дигестивното здравје, туку и за воспалителните болести. Во последно време, постои зголемен интерес за ефектите на пробиотиците во негата на кожата. Третирањето на атопичен дерматитис, акни, псоријаза, црните рози, рак на кожата, спроведувањето на интимна нега, орална нега, како и засврнувањето на рани строго еден отворен и возногестиозен интерес кон пробиотиците и другите несакани ефекти од конвенционалната терапија. Согласно претходно наведеното, резултатите од многу истражувањата покажуваат дека пробиотиците се ефикасни во лекувањето на различни кожни забољувања.

Овој преглед има за цел да ги оцени научните докази за локални и орални пробиотици и да ја оцени ефикасноста на козметичките и дерматолошките производи кои содржат пробиотици. Многу студии покажале дека пробиотиците се ефикасни во лекувањето на различни кожни забољувања.