Probiotics: Benefits on Skin Health and Therapeutical Potential

Stavrakidis, Konstantin Karl Stergios

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GRADUATION THESIS

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Thesis mentor: Associate Professor Lara Batičić, PhD

The graduation thesis was graded on 17/06/2024 in Rijeka, before the Committee composed of the following members:

1. Assistant Professor Jelena Marinic, PhD (President of the Committee)
2. Associate Professor Dijana Detel, MD, PhD
3. Professor Vlatka Sotošek, MD, PhD

The graduation thesis contains 41 pages, 4 figures, 3 tables, 101 references.

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List of abbreviations and acronyms

AD	Atopic Dermatitis
AGA	Androgenetic Alopecia
AMPs	Antimicrobial Peptides
AP-1	Activator Protein 1
C. acnes	*Cutibacterium acnes* (formerly *Propionibacterium acnes*)
GI	Gastrointestinal
IgG	Immunoglobulin G
IL	Interleukin
JNK/AP-1	c-Jun N-terminal kinase/Activator Protein 1
LHMW	*Lactobacillus helveticus*-fermented milk whey
LsR	*Lindera strychnifolia* root extract
LR	*Lactobacillus rhamnosus*
MAPK	Mitogen-Activated Protein Kinase
MMP-1	Matrix Metalloproteinase-1
MMPs	Matrix Metalloproteinases
M. restricta	*Malassezia restricta*
NO	nitric oxide
NOS	nitric oxide synthase
p-ERK	phosphorylated form of extracellular signal-regulated kinase
PFS	post-finasteride syndrome
qPCR	Quantitative Polymerase Chain Reaction
ROS	reactive oxygen species
SA-β-galactosidase	Senescence-Associated Beta-Galactosidase
SCFAs	Short-chain fatty acids
SD	seborrheic dermatitis
SH	*Sphingomonas hydrophobicum*
sLTA	sakei Lipoteichoic Acid
SLS	sodium dodecyl sulfate
S. geniculata	*Streptomyces geniculatus*

TEWL	Trans Epidermal Water Loss
TLR2	Toll-like receptor 2
TNF	Tumor Necrosis Factor
Tregs	regulatory T cells
UV	Ultraviolet

1 Introduction

Skin accounts for a substantial proportion of adult body weight and surface area. Its role is to serve as a mechanical barrier against microorganisms that can cause diseases and harmful substances. Its functions extend to prevent the loss of water, the regulation of heat, structural support, and the synthesis of vitamins, all vital for maintaining health (1,2).

The pursuit of beauty and effective skin treatment is ongoing, with challenges arising from both external and internal factors. While many cosmetic products contain potentially harmful chemicals, herbal medicine extracts, though used, sometimes fail to meet quality and efficacy expectations. This underscores the need for reliable and efficient skin treatment ingredients. Probiotics have proven to be a potential solution for this, offering potential benefits with minimal toxicity (3).

This thesis examines probiotics and their use in skin care, including whitening, anti-aging, moisturizing, anti-wrinkle treatments, and the elimination of body odor, providing a basis for their future application. The application of probiotics in topical treatments started in the early 20th century, with recent years witnessing a surge in such products. However, challenges remain in their formulation and regulatory approval (4).

This paper also considers the role of probiotics that are taken orally, in the treatment of skin disorders, given their interaction with intestinal homeostasis and subsequent impact on skin conditions. This approach aims to offer possible solutions and clinical insights for effective skin treatments (5).

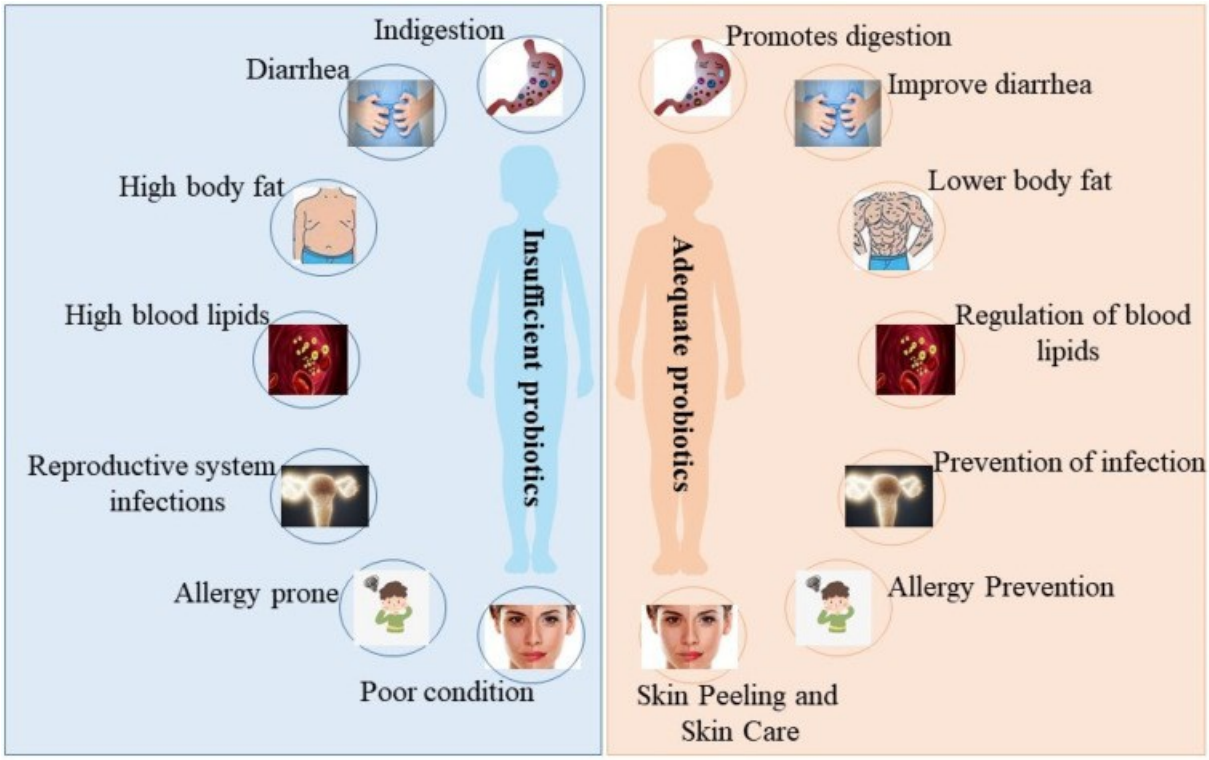

Figure 1. The impact of probiotics on the body (6).

Probiotics have a substantial favorable impact on the body. A lack of sufficient probiotics can lead to several health problems, including digestive issues, diarrhea, increased body fat, elevated blood lipids, infections in the reproductive system, a higher susceptibility to allergies, and poor skin health (illustrated in Figure 1 on the left side). Conversely, when the body has an adequate supply of probiotics, it experiences numerous benefits: enhanced digestion, alleviated diarrhea, reduced body fat, balanced blood lipids, protection against infections in the reproductive system, a lower risk of allergies, and improved skin health, including better skin hydration and care (illustrated in Figure 1 on the right side).

If we take a closer look at the skin care use of probiotics, we can see in Table 1 that there are already numerous probiotic products on the market.

Table 1. Cosmetic products marketed as probiotics as percentage of type of product (4).

PRODUCT TYPE	PROPORTION OF PRODUCTS
Cream	24%
Serum	16%
Mask	12%
Exfoliant	10%
Gel	10%
Cleanser	10%
Foundation	6%
Balm	4%
Soap bar	4%
Primer	2%
Deodorant	2%

These cosmetic products are promoted as probiotics. The percentage describes how many products of the type of product are promoted as probiotics. This information is based on data from 50 products that are being promoted by leading cosmetic retailers.

2 Aims and objectives

This review paper focuses on understanding the mechanisms by which probiotics affect skin health and their therapeutic potential for skin diseases. It delves into the interaction between probiotics and the skin microbiome, assessing how these interactions improve skin health and function. The paper also evaluates the effectiveness of probiotics in treating various skin conditions, emphasizing their role in inflammation modulation and antimicrobial defense. Furthermore, it explores the biological pathways and molecular mechanisms behind probiotics' influence on the skin. The goal is to offer a condensed yet comprehensive overview of probiotics in dermatology, highlighting their importance in current treatments and potential future applications.

3 Literature review

3.1 Probiotics

3.1.1. Historical overview

German scientist Werner Kollath first coined the word “probiotic,” blending Latin and Greek roots to mean “for life” in 1953, to describe substances crucial for healthy life development. Later, in 1965, Lilly and Stillwell used it differently, signifying that one organism secreted substances to promote the growth of another. In 1992, Fuller refined this definition, describing probiotics as live microbial supplements that improve the microbial balance of the intestine and by that beneficially affecting the host (7,8).

The modern history of probiotics started in the early 1900s with Nobel Prize winner Elie Metchnikoff's pioneering work at the Pasteur Institute in Paris. Metchnikoff found a connection between the longevity of the rural population in Bulgaria to their often intake of fermented dairy products, like yogurt, which he connected to the Bulgarian bacillus, identified by Bulgarian physician Stamen Grigorov. Metchnikoff advised that lactobacilli could combat decay in the digestive tract, contributing to illness and aging. His work laid the groundwork for France's dairy industry, using fermented milk from *Bacillus bulgaricus*. By 2013, a consensus among experts stated that probiotics are live microorganisms that, when given in sufficient quantities, provide health benefits to the host.

The concept of probiotics, however, is as ancient as human civilization, intimately tied to the history of fermented foods. As early as 10,000 years ago, with the advent of farming, humans began producing fermented foods and beverages. This practice was evident among various ancient civilizations, including the Sumerians, who developed animal husbandry, and the ancient Indians, whose Ayurvedic texts associated dairy consumption with health and longevity. The earliest visual evidence of milking dates back to 3100 BC in Ur, Mesopotamia. The ancient Egyptians and Phoenicians also practiced milk fermentation, utilizing bacteria similar to today’s *acidophilus* and *bulgaricus*.

Fermentation, a method of food preservation and flavor enhancement, has been a universal practice, with evidence of fermented beverage production as early as 7000 BC in China and 5000 BC in Mesopotamia. From Asia’s rice-based drinks to the fruit wines of Egypt and Mesopotamia, each civilization developed unique fermented products. The use of

fermented milk products, mentioned in sacred Hindu texts and the Bible, was widespread across cultures, with Hippocrates and Pliny acknowledging their gastrointestinal benefits.

The introduction of dairying marked a significant innovation in early agriculture, integrating milk and its fermented derivatives like cheese and yogurt into our ancestors' diets. Nearly every culture developed some form of food fermentation, signifying its importance in human history.

In modern times, the concept of probiotics and functional foods has evolved, focusing on foods that extend beyond nutritional value to enhance health and well-being. This development reflects the ancient understanding of the connection between nutrition and health, now substantiated by contemporary scientific research exploring the microbiota of the gut and its function in human diseases. The historical journey of probiotics, from ancient fermentation practices to their current status in biomedical research, underscores their enduring significance in human health and nutrition (7).

3.1.2. Types of Probiotics

In Figure 2, the frequency of different probiotic bacteria used in 50 cosmetic products marketed as probiotics is illustrated, showing the prevalence of specific strains like *Lactobacillus* spp., *Lactococcus* spp, and *Bifidobacterium* spp. Together with *Nitrobacter* spp., lactobacilli and bifidobacteria are most commonly implicated in the regulation of skin physiology.

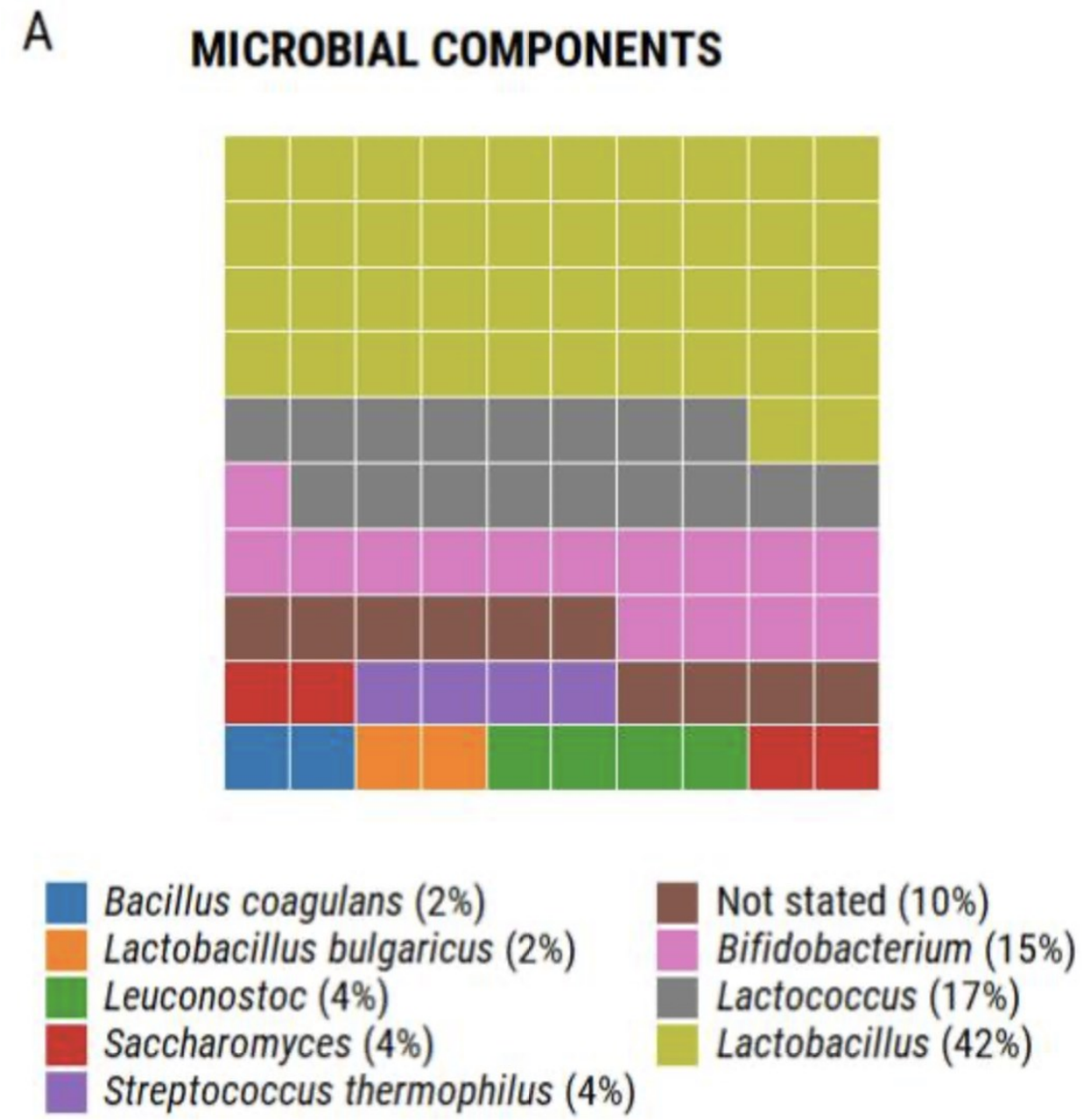

Figure 2. Frequency in which each probiotic bacteria was used in 50 cosmetic products marketed as probiotics (4).

3.1.2.1. *Nitrobacter*

Nitrobacter, a nitrifying bacterium, produces nitrate, which can have benefits for the host's skin. Studies indicate that consuming nitrate-rich foods, like green leafy vegetables, yields several positive outcomes. These include improved blood flow to muscles used during exercise, reduced need for oxygen during exercises, enhanced exercise capacity in individuals with peripheral arterial diseases, and lowered blood pressure. These effects are primarily attributed to an increase in nitric oxide (NO) synthesis that does not depend on nitric oxide synthase (NOS). In healthy individuals, this mechanism is believed to enhance cutaneous reflex vasodilation through NOS-independent pathways (9). Additionally, *Nitrobacter spp*. have demonstrated antifungal properties, providing protection against skin infections caused by dermatophytes and *Staphylococcus aureus* (10). The nitrate production capability of *Nitrobacter* might also supply the skin with nitrates, a role demonstrated to shield progenitor cells of the skin against UV-induced harm (11).

3.1.2.2. *Lactobacillus*

Lactobacillus, a widely recognized genus of lactic acid bacteria, exhibits notable anti-inflammatory effects on keratinocytes of the host and has been demonstrated to specifically impede the growth of *Staphylococcus epidermidis*, *in vitro* (12,13). Additionally, it helps suppress inflammatory responses in the skin triggered by substance P and contributes to enhancing skin barrier functions. Clinical research has demonstrated that a regimen for six weeks with *Lactobacillus johnsonii* orally can significantly improve the recovery of skin immune functions following immunosuppression caused by UV light. In another detailed study, a double-blind, randomized trial involving adult subjects that was controlled with a placebo was conducted. Fabroccini et al. (14,15) found that including *Lactobacillus rhamnosus* in the treatment regimen helped normalize the activity of insulin-associated genes in the skin, which contributed to significant improvements in adult acne.

Moreover, a study found out that tyndalized *Lactobacillus acidophilus* used orally reduced the formation of wrinkles in mice caused by UV irradiation. These effects are because of a decrease in MMPs (Matrix Metalloproteinases). Additionally, an *in vitro* study by Park and Bae (16) demonstrated that the combined fermentations of *Lactobacillus* and *Bifidobacterium* with *A. koreanum* extract could inhibit the aging phenotype in skin fibroblasts. This aging, often

caused by the exposure to UV or hydrogen peroxide, was partially mitigated through the modulation of MMP-1 (16).

3.1.2.3. *Bifidobacterium*

Evidence shows that *Bifidobacterium breve* B-3 orally significantly reduced Trans Epidermal Water Loss (TEWL), dry skin, altered epidermal depth, and improved the stability of the tight junction structure and basement membrane in mice exposed to excessive UV radiation. This supplementation also reduced the skin`s UV-induced IL-1β production (17).

Both *Lactobacillus* and *Bifidobacterium*, when used as lyophilized powders in capsules, reduce sensitivity to food allergens in atopic individuals and lower the occurrence of atopic eczema during early childhood (18). For adults suffering from atopic dermatitis (AD), oral supplementation with *Bifidobacterium bifidum* has demonstrated antipruritic effects, which are linked to elevated concentrations of the antipruritic and analgesic compound acetonide (19). Additionally, in a double-blind, placebo-controlled, randomized trial, consuming fermented milk enriched with galactooligosaccharides and *Bifidobacterium breve* was shown to maintain hydration in the stratum corneum, reduce activity of histone-like proteases, and lower phenol concentrations in both serum and urine among healthy adult female participants (20).

3.1.3. Mechanism of action

3.1.3.1. Immunologic Pathway

Regarding immunity against *Staphylococcus aureus*, a prevalent bacterial strain impacting AD, there's a link between the intestine and the skin. *Staphylococcus aureus* is frequently present on the skin of AD individuals. Interestingly, a recent study suggests that early contact with *S. aureus*, much like other skin strains, might actually help prevent AD in infants by aiding the development of their immune system. It appears that *Staphylococcus aureus* strains present on mucosal surfaces could offer protective benefits through immune stimulation (21).

Distinct gut microbiota and their common byproducts, like retinoic acid or polysaccharides from certain bacterial species, are known to encourage the growth of regulatory

T cells (Tregs) and lymphocytes that drive anti-inflammatory responses. Short-chain fatty acids (SCFAs), particularly butyrate, have a function in regulating immune cell activities (22).

The gut microbiome is gaining recognition for its role in the immune pathways of skin disorders, with a particular focus on probiotics. Oral probiotics interact with the GI lining and lymphatic tissues which is associated with the gut, a major site of immune cells. These probiotics can engage with various cells in the gut in different ways, depending on their strain. Some stimulate immune responses, producing cytokines like IL-12 and TNF-α, while others encourage tolerance by triggering anti-inflammatory cytokines like IL-10 and TGF-β (23–25). This can result in the production of induced Tregs, crucial for maintaining immune balance. Moreover, variations in the gut microbiome, especially in infants with AD, might influence the development of immune cell functions, potentially linked to variations in the genetic makeup of the gut microbiome (26).

3.1.3.2. Metabolite Pathway

Byproducts produced by the intestinal microbiota, like SCFAs, are essential in connecting the gut and the skin via microbial interactions. SCFAs, particularly those secreted by gut bacteria like *Akkermansia muciniphila*, are significant in understanding the development and progression of AD, linking it to the skin's immune system. Research indicates that certain fatty acids can alleviate AD symptoms and influence the intestinal microbiota in mice (27).

Additionally, studies on neonatal intestinal microbiota have identified different subgroups that contribute to early allergic sensitization (28). One of these subgroups, associated with multiple allergies, tends to have lower levels of certain beneficial bacteria. An interesting find is a specific metabolite known for its inflammatory properties, which was notably present in this subgroup and also found in the protective layer coating newborns' skin. These findings hint at a complex metabolite pathway connecting the gut and skin, suggesting a deeper interplay between our internal and external environments (21).

3.1.3.3. Neuroendocrine Pathway

Similar to the skin, the gastrointestinal (GI) tract lining comes into direct contact with external factors such as food and microbes. Both the skin and the intestines are vital in stopping pathogenic bacteria from entering the body. Microorganisms residing in these organs are essential for this protective function, as they help eliminate pathogens through immune responses. Maintaining a balanced microbiota in both areas is key to good health. Moreover, the skin and gut microbiomes can communicate with each other through neuroendocrine signals, which can be either direct or indirect (21).

For instance, in a patient with AD, tryptophan produced by gut microbes can lead to itching skin, representing a direct interaction. On the other hand, substances like γ-aminobutyric acid, secreted by *Bifidobacterium* and *Lactobacillus* in the gut, can help reduce itchy skin (29).

Gut microbes indirectly influence systemic functions by modulating levels of cytokines in the bloodstream, such as interleukin-10 and interferon-gamma, potentially affecting cognitive processes and leading to symptoms of anxiety and stress (21). Cortisol, the hormone released in response to stress, has the ability to alter the intestinal lining's integrity and its permeability by modifying the gut microbiota's composition (30). Furthermore, it can impact the concentration of certain neuroendocrine molecules circulating in the blood, including tryptamine and serotonin, which can subsequently improve both skin barrier function and immunological responses (31).

3.1.4. Gut-skin axis connection

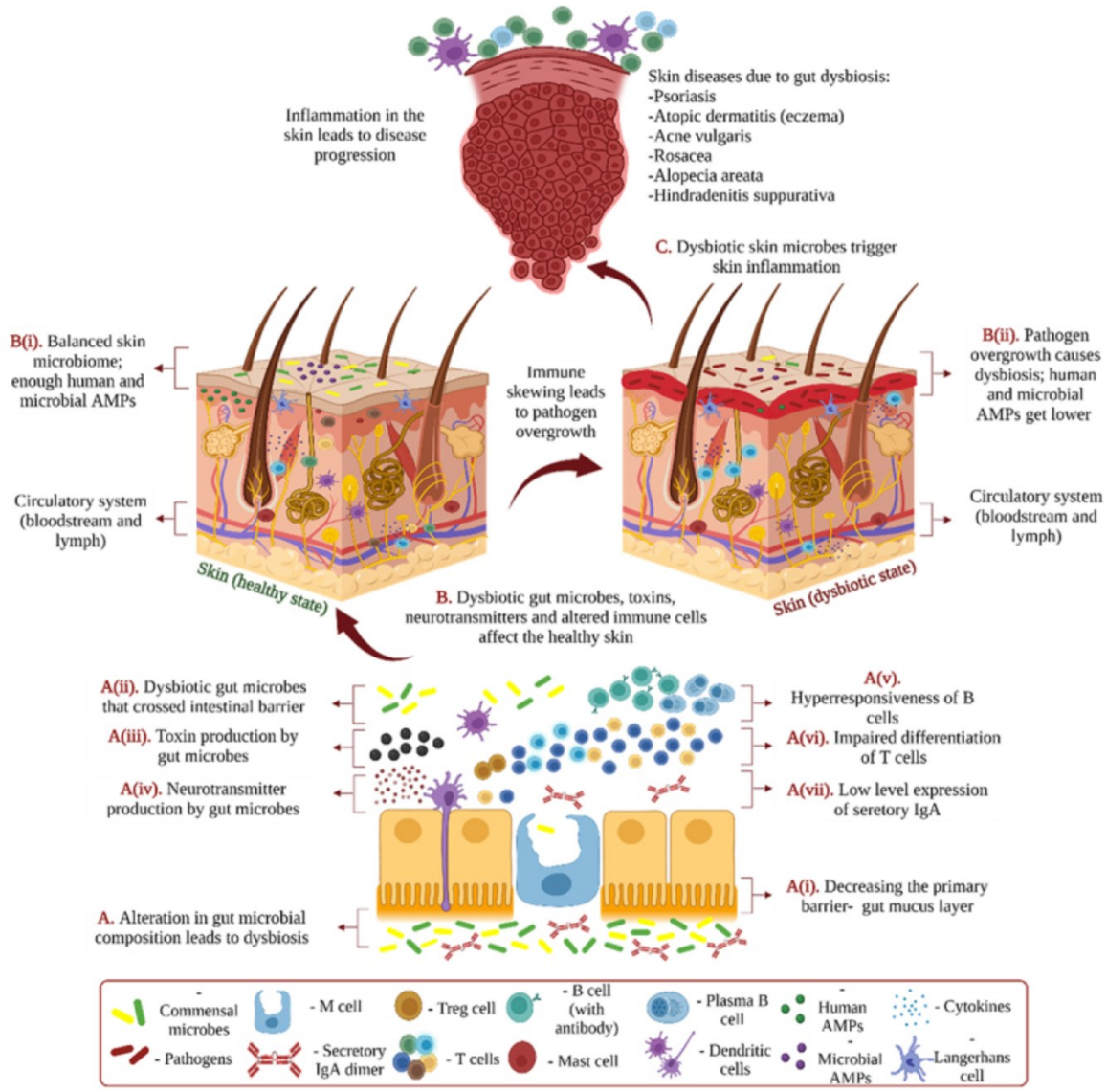

Figure 3. Processes of communication within the gut-skin axis (32).

Figure 3 illustrates the processes of communication within the gut-skin axis, highlighting how changes in the gut microbiota affect skin health. It shows that a balanced microbiome supports a healthy skin state by maintaining adequate antimicrobial peptides (AMPs) and immune balance. Conversely, gut dysbiosis can result in skin inflammation and diseases like psoriasis, rosacea, and eczema by disrupting immune responses and skin barrier functions. This interaction emphasizes the role of gut microbes in producing toxins and neurotransmitters that negatively influence skin condition. Overall, Figure 3 suggests that maintaining gut health is crucial for preventing and managing skin disorders.

3.1.4.1. Oxidative Stress Level Decreases

Skin photoaging is closely linked to oxidative stress, primarily driven by reactive oxygen species (ROS). This process involves the activation of specific cellular pathways and a reduction in matrix metalloproteinases (MMPs) and collagen, all contributing to the aging of the skin. Research has explored how probiotics can counteract these effects. For instance, using a *Lactobacillus*-fermented extract of *Agastache rugosa* topically has shown potential in reducing UV-induced ROS and MMP levels in skin cells, while increasing antioxidant activities like total glutathione and superoxide dismutase (33).

Additionally, certain strains of *Lactobacillus*, such as *Lactobacillus acidophilus* topically, have demonstrated strong antioxidant properties, effectively reducing ROS levels in skin cells exposed to UV light and mitigating oxidative damage. These strains also help by enhancing the skin's antioxidant capacity, increasing hydrating cytokines, and suppressing MMP synthesis through the modulation of cellular pathways like Mitogen-Activated Protein Kinase (MAPK) (34).

Furthermore, oral supplementation with *Bifidobacterium breve* Yakult has been found to lower ROS levels and mitigate skin barrier damage resulting from UV exposure and oxidative stress. Using plant extracts fermented with *Lactobacillus buchneri* topically also shows promise in improving skin conditions affected by UV-induced photoaging by increasing collagen production, reducing elastase synthesis, and modulating MMP levels in skin cells (35–37).

Limosilactobacillus fermentum topically has been identified as beneficial in enhancing the function of mitochondria, as well as reducing ROS in UV-damaged skin cells, thus maintaining skin health (38). Recent studies also highlight the antioxidant role of strains like *Lacticaseibacillus rhamnosus* GG and *Lacticaseibacillus casei* Shirota in improving skin photoaging. These findings underscore the capacity of probiotics in managing and mitigating the impacts of skin aging due to oxidative stress (39,40).

3.1.4.2. Inflammatory Response Suppression

Heightened skin inflammation can result in a compromised barrier function, enhanced trans-epidermal water loss (TEWL), greater epidermal penetrability, and rapid skin aging because of exposure to light. Research indicates that *Bifidobacterium breve* B-3 orally can significantly decrease UV-induced levels of IL-1β in dermal layers of mice, which aids in lowering TEWL, alleviating skin dryness, and reducing thickening of the outer skin layer (41,42). Additionally, *Lactobacillus acidophilus* IDCC3302 orally, renowned for its antioxidant capabilities, further mitigates skin inflammation triggered by UV light by suppressing the MAPK signaling pathway and inhibiting the release of inflammatory agents (34).

Additionally, *Lactobacillus reuteri* DSM 17938 orally has demonstrated anti-inflammatory effects, countering UV-induced increases in IL-6 and IL-8, thus aiding in improving skin photoaging (43). Research by Keshari et al. (44) indicates that butyrate, produced by a novel probiotic strain of *Staphylococcus epidermidis*, can diminish UV-induced pro-inflammatory IL-6 through SCFA receptors. Furthermore, oral oligosaccharides have been found effective in regulating inflammatory immune responses triggered by UV exposure, reducing TEWL and sunburn erythema, thus helping to prevent skin photoaging. These findings underscore the potential of probiotics and their metabolites in managing skin health, particularly in mitigating the effects of UV exposure (45).

3.1.4.3. Immune Homeostasis Maintaining

Several probiotics, like *Lactobacillus paracasei*, serve a vital function in controlling immune reactions and controlling pathogens. They also help maintain immune balance by preventing undesirable immune reactions, particularly in chronic inflammatory diseases. This could be due to their ability to modulate the number of Tregs, which are essential in decreasing the immune responses associated with skin photoaging (46).

For example, *Lactobacillus johnsonii* orally has been observed to counteract the UV-induced reduction of Langerhans cell density in the epidermis, aiding in the reestablishment of the skin's immunological balance. Probiotics demonstrate varying effects depending on the immune status. In a normal physiological state, they can reduce cytotoxic T cell activity on the skin, impair the function of CD8+ T cells, activate inactive dendritic cells, and enhance the function of Tregs subsets (47).

Clinical studies examining dietary supplements containing *Lactobacillus johnsonii* and carotenoids have shown promising results in mitigating early skin damage caused by UV exposure. These findings suggest that such supplements could be beneficial against the prolonged and recurrent exposure to UV radiation, particularly in terms of photoaging. Additionally, oral supplements with *Bifidobacterium longum* and galacto-oligosaccharides have been found to shield the skin from photoaging caused by UV light, due to their anti-inflammatory and antioxidant effects. Also, serum levels of SCFAs and acetates are increased, these are known to enhance and activate skin-resident regulatory T cells through histone acetylation-dependent mechanisms (48).

3.1.4.4. ECM Remodeling Suppression

Contact to UV light elevates ROS, resulting in an increase in Matrix Metalloproteinases (MMPs), consequently causing the degradation of skin elastin and collagen, leaving the skin rough, dry, and less firm. Probiotics have shown promise not just in reducing ROS levels directly but also in managing MMP levels in the skin, thereby contributing to the protection against the breakdown of collagen and elastin after UV exposure (49).

Peroral consumption of *Lactobacillus acidophilus* KCCM12625, for instance, has been observed to lower MMP mRNA levels in photoaged skin by interfering with the AP-1 signaling pathway and enhancing procollagen levels and decreasing the loss of collagen proteins in the dermis. Studies also indicate that peroral *Lactobacillus plantarum* HY7714 can decrease the excessive production of certain MMPs in cell damage caused by UV-radiation by reducing the JNK/AP-1 pathway. Similarly, oral *Lactobacillus sakei* has been found to inhibit the MAPK pathway, thereby up-regulating dermal collagen and improving photoaging of the skin (35,50,51).

Studies have shown that extracellular polysaccharides from *Lactobacilli* can decrease levels of MMPs and elevate MMP inhibitors. For instance, the polysaccharides from *Lactobacillus casei* B9-1 boost the skin's defenses against collagenase and enhance anti-elastase activity, effectively preventing collagen degradation from UV light. Kimchi contains plant extracts fermented with *Lactobacillus brucei*, which have been noted to substantially diminish UV-stimulated elastase activity and MMP production, while concurrently promoting the synthesis of type I collagen. Moreover, research by Negari and colleagues (52) has revealed that compounds from the probiotic *S. epidermidis*, using Cetearyl isononanoate as a nutrient

substrate, are capable of repairing collagen damage and supporting collagen production via the activation of the phosphorylated form of extracellular signal-regulated kinase (p-ERK), aiding in the prevention of skin photoaging.

3.1.5 Types of Microbial Ingredients in Topical and Orally Administered Formulations

Microbial ingredients in skincare formulations can be broadly categorized into live microorganisms (probiotics), by-products of microbial growth (postbiotics), and inactive dead strains.

Probiotics are live microorganisms that, when taken in sufficient quantities, offer health advantages to the human body (53). In skincare, these probiotics can help sustain a healthy skin microbiome by balancing the microbial communities on the skin. For example, particular strains of *Bifidobacterium* and *Lactobacillus* are used in cosmetic formulations to enhance skin barrier function and lessen inflammation (53).

Postbiotics are inert bacterial products or metabolic derivatives from probiotics that exert biological activities within the human body (53). These include compounds like SCFA, bacteriocins, and other metabolites. Postbiotics are beneficial in skincare because they can enhance skin barrier function, reduce oxidative stress, and provide anti-inflammatory effects (4). For instance, lysates from *Bifidobacterium longum* are known to improve skin hydration and reduce sensitivity (4).

Inactive dead strains, also called paraprobiotics or ghost probiotics, are non-viable microbial cells that can still confer health benefits similar to their live counterparts (4). These are used in skincare products for their immunomodulatory and anti-inflammatory properties. For example, lysates of *Lactobacillus rhamnosus* have been demonstrated to enhance tight-junction barrier strength in the skin (53).

3.1.6 Regulatory Aspects of Probiotics in Skincare

The regulatory landscape for probiotics in skincare is complex and varies by region. As stated by the US Food and Drug Administration (FDA), cosmetics are defined as products meant for cleansing, beautifying, enhancing attractiveness, or modifying appearance, but they do not include any health claims (4). Probiotic cosmetics, therefore, must adhere to these definitions and cannot make disease treatment claims without proper evidence and approval.

One major challenge in regulating probiotics in cosmetics is ensuring that the products contain viable microorganisms at the time of use. For a product to be considered truly probiotic, it must contain sufficient live microorganisms at the time of use, and these strains must be well-characterized and supported by scientific evidence demonstrating their benefits. However, many products labeled as probiotics do not meet these criteria, leading to misleading claims (4).

Cosmetic products containing probiotics must meet stringent safety criteria to guarantee they do not harbor pathogenic bacteria. In the EU, for instance, cosmetics are required to have a low content of microorganisms, making it challenging to include live probiotics without compromising safety (4).

Products containing postbiotics or inactive dead strains must be clearly labeled and should not be promoted as probiotics if they do not include live bacteria. Regulatory bodies emphasize the need for scientific validation of the health benefits claimed by these products (4).

Innovative approaches, such as using nanoparticles to deliver probiotics and postbiotics, are being explored to enhance their stability and effectiveness in skincare products. These nanosystems can protect probiotics during formulation and ensure their delivery to the target site on the skin (53).

In conclusion, while the potential of probiotics, postbiotics, and paraprobiotics in skincare is significant, there is a need for rigorous scientific validation and transparent regulatory practices to ensure consumer safety and product efficacy.

3.2. Benefits on skin health

3.2.1. Cosmetics

3.2.1.1. Skin Whiting

The growing interest in skin lightening has led to a focus on products that reduce melanin content and reduce excessive pigmentation (54). Melanin, while shielding the skin from UV radiation, can cause uneven skin tone and disorders like freckles and melasma when overproduced (55,56). Melanin production involves several enzymes, with tyrosinase being a key player. Many skin-whitening cosmetics aim to inhibit tyrosinase activity, thereby reducing melanin and enhancing skin brightness. Recently, the use of probiotics in such products has increased, owing to their strong inhibitory effects on tyrosinase (54).

Research has shown that topical *Bifidobacterium adolescentis* culture filtrate can counteract mushroom tyrosinase activity, reducing melanin levels in skin cells. This filtrate seems to regulate tyrosinase activity through its antioxidant properties, leading to decreased melanin and a brightening effect. Additionally, lactic acid found in *Lactobacillus* can inhibit melanin production by decreasing the function of tyrosinase and indirectly by influencing its expression, thus aiding in the brightening of the skin (57,58).

Probiotics have the capacity to diminish melanin not solely by affecting tyrosinase but also via alternate pathways. For instance, fermented milk supernatant from *Lactobacillus helveticus* NS8 (NS8-FS) orally has been observed to reduce melanin production in skin cells by suppressing tyrosinase and related protein activities (35). When tested on guinea pigs, NS8-FS was effective in enhancing skin pigmentation, possibly through influencing the activity of Nrf2, a regulator involved in melanogenesis. Similarly, *Rhodobacter spheroides* has been observed to suppress melanin production in a dose-dependent manner, particularly following α-MSH supplementation in skin cells. These results highlight the emerging function of probiotics in skin lightening and melanin regulation (59,60).

3.2.1.2. Skin Moisturization

Numerous factors, including shifts in the environment and harm to the skin barrier, can result in dry skin, affecting both health and appearance since skin hydration is vital for bodily functions and aesthetic appeal (61). The search to find agents that maintain skin moisture is ongoing. Probiotics have been recognized for their efficacy in decreasing TEWL and alleviating dryness of the skin, proving to be beneficial in managing such conditions and supporting skin hydration through the enhancement of the skin's barrier capabilities (62).

Scientific evidence has shown that the oral intake of *Lactobacillus plantarum* HY7714 can boost ceramide concentrations, which are critical for preserving the skin's structural integrity and hydration. This uptick in ceramides contributes to lowered TEWL and better skin moisture. Furthermore, research on *Lactobacillus acidophilus* IDCC 3302 has illustrated its beneficial effects on skin moisture levels, significantly improving skin dryness and reducing TEWL (63–65).

Furthermore, Baba and colleagues (66) have discovered that administration of *Lactobacillus helveticus*-fermented milk whey (LHMW) significantly reduces TEWL in intact skin and increases skin hydration. This suggests that LHMW has potent moisturizing properties, making it a encouraging ingredient for cosmetic use. These results shows the possibility of probiotics as beneficial agents in skincare, particularly for enhancing skin hydration and treating dry skin conditions.

3.2.1.3. Skin Barrier Integrity

Impairment of the barrier function of the skin can disrupt its moisture balance, leading to various skin issues. Research by Ye-On Jung and colleagues (67) has shown that *Lactobacillus rhamnosus* (LR) is able to significantly enhance barrier of the skin, making it a potential ingredient for moisturizing skincare products. Their study used immunofluorescence staining to reveal increased concentrations of occludin and claudin-1, two key molecules for tight skin binding. They observed that the stratum corneum, the outermost layer of the skin treated with LR lysate, appeared more organized and tighter.

Additionally, the result of the qPCR indicated higher levels of filaggrin and loricrin expression, both crucial for restoring skin barrier function. The study also found that enhanced skin barrier function could be inferred from reduced cytotoxic effects caused by sodium dodecyl

sulfate (SLS) and decreased skin permeability. These findings underscore the potential of *Lactobacillus rhamnosus* in improving skin health by strengthening its barrier function and enhancing its moisture-retaining capabilities (68).

3.2.2. Anti-ageing

Skin aging primarily occurs in two ways: chronological aging and photoaging. Internal factors cause chronological aging. Photoaging is largely a result of external influences like sun exposure. Although these two aging processes are distinct, they share some underlying regulatory mechanisms. Interestingly, probiotics have been found to positively impact both types of skin aging, offering benefits that help counteract the effects of time and environmental exposure on skin health. This highlights the versatile role of probiotics in skincare, addressing both intrinsic and extrinsic aging factors (69).

3.2.2.1. Anti-Chronological Aging

Chronological aging, closely linked to genetic factors, is a natural part of the human aging process. As we grow older, our bodies, including our skin, undergo changes such as thinning and dryness. Probiotics are known to combat aging primarily by inhibiting cellular decay and extending the cell cycle. Research by Sandie Gervason and team (70) highlighted that removing *Sphingomonas hydrophobicum* (SH) could reduce the production of aging-related proteins like P16 and P21, as observed in their immunohistological experiments. These proteins are known to hinder the cell cycle and contribute to cellular aging (71).

In their study, the levels of P16 and P21 were markedly reduced in the treated cohort with SH extract in comparison to the control group. Additionally, SH extract was shown to decrease the level of SA-β-galactosidase, an enzyme related to aging, thereby aiding in cell rejuvenation. Furthermore, the study observed an increase in fibrillin-1 and versican following SH extract supplementation. Fibrillin-1 is involved in forming elastic skin fibers, and a higher level of versican helps prevent fibroblast apoptosis. Both outcomes contribute to slowing down cellular aging. These results demonstrate that SH extract could be a possible ingredient for anti-aging skincare products (72).

3.2.2.2. Anti-Photoaging

Photoaging, often resulting from external factors like UV radiation and environmental toxins, leads to various skin issues like loss of elasticity, moisture, and increased roughness and thickness. Probiotics play a crucial role in treating photoaging, mainly by inhibiting collagen breakdown.

Studies have shown that individuals who take *Lactobacillus plantarum* HY7714 experienced reduced loss of skin moisture, lessened depth of the wrinkles, and improved elasticity and gloss of the skin (34). Additional studies have shown that heat-treated *Lactobacillus acidophilus* IDCC 3302 can oppose the decrease in collagen production induced by UV radiation. This probiotic has also been observed to notably reduce the concentrations of MMP-1, MMP-2, and MMP-9 in skin cells, levels of which usually rise following UV exposure, largely through the suppression of the MAPK signaling cascade. Additionally, it helped reduce inflammation by lowering concentrations of pro-inflammatory cytokines like IL-1β, IL-8, and TNF-α, demonstrating its effectiveness in mitigating photoaging and UV-induced inflammatory responses. Another study by You et al. (51) suggested that *Lactobacillus sakei* lipoteichoic Acid (sLTA) could inhibit the phosphorylation of MAPK, subsequently blocking MMP-1 synthesis in response to UV exposure. These findings underscore the capacity of probiotics in managing and improving skin conditions associated with photoaging.

3.2.3. Anti-Wrinkle

Wrinkles mainly result from skin thinning and the continuous contraction of subdermal facial muscles. The incorporation of probiotics into skincare is increasingly acknowledged for their effectiveness in managing facial wrinkles, primarily attributed to their antioxidant and anti-wrinkle qualities. One of the key mechanisms behind wrinkle formation is the MMP-1 induced breakdown of collagen, which is synthesized by fibroblasts. Probiotics have been found effective in inhibiting MMP-1 synthesis, thus reducing collagen degradation and consequently, wrinkles.

Studies have demonstrated that tyndallized *Lactobacillus* KCCM12625P (AL) orally can inhibit the synthesis of MMP-1, thereby suppressing the development of wrinkles. This strain significantly aids in reducing wrinkles primarily via these processes.

Additionally, Hyun Mee Kim and colleagues (50) discovered that *Lactobacillus plantarum* HY7714 could block UV-induced MMP-1. This strain not only inhibits MMP-1 expression but also the function of MMP-2 and MMP-9, leading to improvements in wrinkle area and depth. Another study revealed that heat-treated *Lactobacillus acidophilus* IDCC 3302 orally substantially lowered the levels of MMP-1, MMP-2, and MMP-9 in skin cells exposed to UV radiation, indicating its potential in diminishing wrinkles by targeting MMPs. These findings highlight the promising function of probiotics in anti-wrinkle skincare solutions (50).

3.3. Therapeutic potential

3.3.1. Wound healing and scarring

Research has shown that probiotics, including *L. plantarum*, *L. fermentum, S. cerevisiae* and kefir, can significantly enhance wound healing across various models such as thermal injuries, infected and non-infected wounds, and diabetic ulcers. While the exact mechanisms remain largely unexplored, evidence suggests that applying probiotics topically can lead to better outcomes by increasing granulation tissue, boosting collagen levels, and promoting angiogenesis. This improvement is not universal across all models, indicating a need for further investigation to understand the conditions under which probiotics are most effective (73).

For successful wound healing, it is critical to maintain bacterial levels below a certain threshold and ensure the absence of harmful bacteria like beta-hemolytic *Streptococcus*. Bacteria and their toxins can disrupt the healing process by causing inflammation and hindering key healing stages such as epithelialization and collagen deposition. Preventing wound infection is thus a vital component of care (74).

Traditional methods for preventing wound infection, like silver dressings, iodine, and antibacterial skin products, have their limitations, including potential for cellular toxicity, resistance, and dermatitis. Probiotics, on the other hand, offer a promising alternative with few side effects and maintained antimicrobial efficacy. Specifically, kefir has demonstrated antimicrobial action against several pathogens (74).

The antimicrobial effects of probiotics are believed to be multifaceted, involving the production of immunostimulatory exopolysaccharides, species-specific antagonism to reduce pathogenic bacteria, and the regulation of antimicrobial peptides (AMPs). These peptides are

crucial for maintaining skin integrity, reducing inflammation, and preventing biofilm formation, thus supporting a conducive environment for wound healing (74).

Explorations into topical probiotic therapy have shown its potential in reducing infections and augmenting healing in both animal and human studies, including those with thermal injuries and chronic venous ulcers. Probiotics have been as effective as traditional treatments in decreasing bacterial loads and supporting a more favorable inflammatory response.

Biofilms, which are implicated in up to 80% of human infections and significantly impair healing, pose a challenge due to their resistance to treatments. However, probiotics have shown promise in inhibiting biofilm formation by pathogens, offering a potential strategy for managing chronic wounds (74–76).

In non-pathological contexts, topical probiotics have also been effective, showing benefits such as reduced erythema and edema post-laser therapy, decreased skin sensitivity, and improved skin hydration and ceramide levels. Despite these promising results, not all studies have found probiotics to outperform traditional treatments, indicating the requirement for additional study to completely comprehend their benefits and constraints in wound care (74).

In reviewing the antimicrobial impact of probiotics against wound pathogens, Table 2 shows that various probiotic strains have demonstrated significant potential for treating different wound infections.

Table 2. Antimicrobial effect of probiotics against wound pathogens (73).

First author, year	Pathogen species	Probiotic(s)	Type of Method	Result	Possible application for humans
Varma, 2011	P. aeruginosa, S. aureus	*L. fermentum* *	Well diffusion and coculturing assay	Both were inhibited	Common wound pathogens were inhibited
Thomas, 2011	P. aeruginosa, S. aureus, Candida albicans	*Lactobacillus casei**, *Lactobacillus reuteri* ATCC 55730, *L. plantarum**	Triphasic and wound model	Different efficiency of probiotics against different pathogens	Possible advantages of colonizing wounds with single or mixed probiotics
Jones, 2010	Staphylococcus aureus, Escherichia coli, MRSA, P. aeruginosa, Trichophyton rubrum, Trichophyton mentagrophytes	*Lactobacillus fermentum* NCIMB 7230	Well diffusion method	Nitric oxide patch with probiotics eradicated common bacterial and fungal wound pathogens	Uses of antimicrobial agents for treating infected wounds
Valdez, 2005	Pseudomonas aerouginosa	*Lactobacillus plantarum* ATCC 10241	Coculturing	Greatest inhibitory activity with whole culture, lower inhibition with acid filtrate	Topical treatment for burn infections

*Strain not specified

3.3.2. Treatment of diseases affecting the skin

3.3.2.1. Introduction

Establishing the connection between the impact of probiotic formulations and the management of different skin problems requires an understanding of the skin, skin microbiota/microbiome, and skin dysbiosis.

The skin microbiota is crucial for maintaining skin homeostasis by shielding it from pathogens and modulating the immune system. When the balance of the skin microbiota is disrupted by factors like pH changes, environmental toxins, or certain skincare products, result in conditions like psoriasis, eczema, and acne. Additionally, probiotics and postbiotics have been found to enhance skin barrier function, reduce inflammation, and enhance the appearance of skin prone to acne or eczema (77).

The skin serves as a physical barrier that shields the body against possible invasions by harmful substances or pathogens. This barrier function is supported by microorganisms that live in symbiosis with the skin, helping to protect against harmful situations. These microorganisms directly protect the human body from pathogens, control inflammation, and modulate adaptive immune pathways. The skin's uneven surface and different areas provide ideal living conditions for various microorganisms, making it a perfect ecosystem for both resident and temporary microbes (77).

The microbiota is diverse, comprising bacteria, viruses, fungi, and mites, which engage with the human body's cells, including epithelial and immune cells, and coexist with other microorganisms in the same environment. The skin microbiota composition is unique to each individual and varies across different parts of the body. For instance, sebaceous areas like the face and back are dominated by lipophilic bacteria such as *Cutibacterium acnes*, while moist areas like the elbow and knees are primarily colonized by *Staphylococcus* and *Corynebacterium* (77).

If the skin microbiota is in an imbalance, known as dysbiosis, it can result in several skin disorders like AD, rosacea, alopecia areata, seborrheic dermatitis (SD), and acne. For example, AD patients often exhibit reduced microbial diversity, characterized by increased levels of *Staphylococcus aureus* and depletion of *Staphylococcus epidermidis* and *Corynebacterium* spp.. Similarly, SD is characterized by a reduction in *Corynebacterium* spp. and domination by *Staphylococcus* spp., *Pseudomonas* spp., and *Micrococcus* spp. (77).

The application of probiotics and postbiotics in skincare is still in the early stages, but their potential to regulate the skin microbiota and treat dermatological conditions is promising. Studies have shown that certain probiotic strains have the ability to endure and effectively colonize the skin, prompting keratinocytes and sebocytes to synthesize antimicrobial peptides and other biological compounds that suppress or kill pathogens. For instance, *Lactobacillus plantarum* has demonstrated effectiveness against acne-causing bacteria and skin pathogens, while also exerting rejuvenating effects through enhanced dermal thickness and improving barrier function (77).

In summary, probiotics and postbiotics can significantly impact skin health by maintaining a balance in the skin microbiota, reducing inflammation, and enhancing skin barrier function. Understanding the dynamic interaction between favorable microorganisms and the diverse microbial communities on the skin can aid in optimizing probiotic formulations and treatment plans for various skin problems (53). This approach holds the potential for more natural, microbiome-friendly therapies in dermatological practice.

The effectiveness of probiotics in treating various skin diseases is illustrated in Figure 4, which highlights specific probiotic strains used for conditions like acne, psoriasis, AD, wound healing, dandruff, and rosacea.

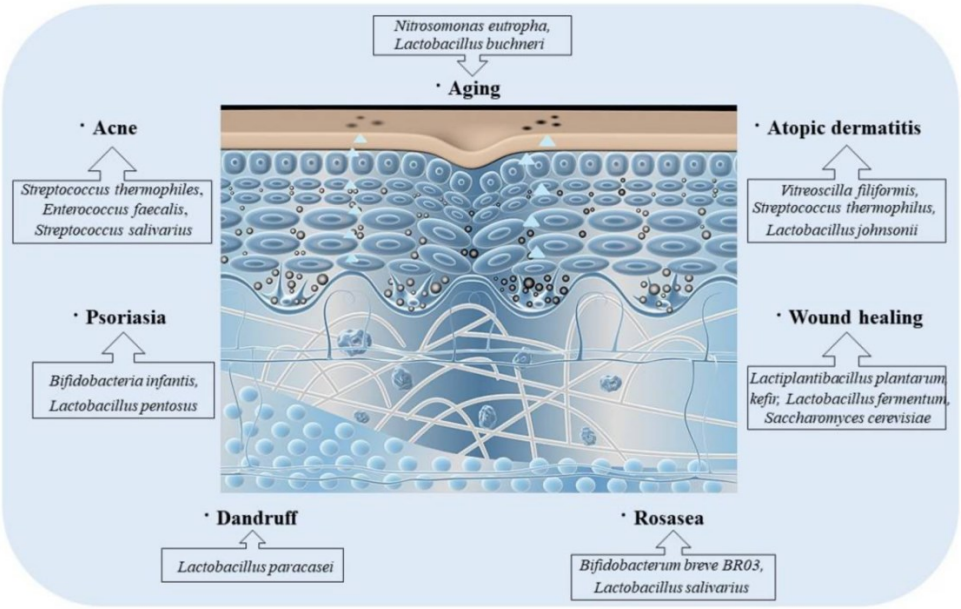

Figure 4. Treatment of skin diseases with probiotics (6)

Probiotics are effective in treating various skin conditions. Specific strains target different issues. For instance, *Lactobacillus buchneri* and *Nitrosomonas eutropha* can help with skin aging; *Enterococcus faecalis*, *Streptococcus thermophilus*, and *Streptococcus salivarius* are good for acne management; *Streptococcus thermophilus*, *Vitreoscilla filiformis*, and *Lactobacillus johnsonii* aid in alleviating symptoms of AD, while *Lactobacillus pentosus* and *Bifidobacteria infantis* are beneficial for psoriasis treatment. Additionally, *Lactobacillus fermentum*, *Lactiplantibacillus plantarum* kefir, and *Saccharomyces cerevisiae* are known to enhance wound healing; *Lactobacillus paracasei* helps reduce dandruff; and *Bifidobacterium breve* BR03 along with *Lactobacillus salivarius* can improve symptoms of rosacea.

3.3.2.1. Acne

Acne patients often possess a distinct skin microbiome distinguished by an elevated abundance of *Cutibacterium acnes* and an imbalance in microbial communities. This leads to more inflamed skin in general, with increased sebum production and an exaggerated inflammatory response, which contributes to the development and severity of acne. Traditional acne treatments present various challenges, as they can damage the skin's mechanical barrier, leading to dryness and irritation. However, research exploring the skin-gut axis has revealed that probiotics can enhance immune responses beyond the intestines, positively affecting skin health. Increasing research supports the idea that topical probiotics can also regulate the skin's mechanical barrier and enhance the production of antimicrobial peptides (78).

An example of this is the lactic acid bacterium *Streptococcus thermophilus*. When formulated into a cream and applied for one week, either in laboratory settings or directly on the skin, this bacterium has been shown to promote ceramide synthesis. Ceramides are essential for maintaining skin moisture, and specific ceramide sphingolipids, like sphingomyelin, possess antibacterial qualities that combat *Cutibacterium acnes*, the bacteria responsible for acne. By enhancing ceramide production, probiotics not only strengthen the skin's mechanical barrier but also soothe irritated, acne-prone skin (79,80).

Consequently, many probiotics offer a multifaceted approach to acne treatment. They can strengthen the skin's protective barriers, inhibit acne-causing bacteria, reduce the appearance of pustules, and alleviate skin irritation in individuals with acne. This positions probiotics as a promising and holistic solution in the management and treatment of acne, contributing to overall skin health and comfort.

In Table 3, we can observe the effectiveness of various probiotic strains in treating acne vulgaris, highlighting their ability to suppress the growth of *C. acnes* and other acne-related pathogens through different mechanisms.

Table 3. Treatment of Acne vulgaris with probiotics *in vitro* (79).

Reference	Probiotic(s)	Outcome
Bowe et al. (81)	*Streptococcus salivarius*	*C. acnes* growth was inhibited by bacteriocin
Oh et al. (82)	*Lactococcus sp.* HY 449	*C. acnes* growth was inhibited by bacteriocin
Deidda et al. (83)	*Lactobacillus salivarius* LS03	*C. acnes* growth was inhibited by bacteriocin
Lee et al. (84)	*Bifidobacterium adolescentis*	Antimicrobial effects on *C. acnes* and *S. aureus*
Wang et al. (85)	*Staphylococcus epidermidis*	Succinic acid production via glycerol fermentation
Cosseau et al. (86)	*Streptococcus salivarius* K12	Anti-inflammatory response; regulation of genes linked to epithelial adhesion
Gueniche et al. (87)	*Lactobaillus paracasei* CNCM I-2126	barrier function of the skin improved
Al-Ghazzewi et al. (88)	*L. plantarum* DSM 12028, *L. casei* NCFB 161, *L. gasseri* NCFB 2233, *L. acidophilus* NCFB 1748, and *Lactococcus lactis* NCIMB 66 plus glucomannan hydrolysates of Amorphophallus konjac	*C. acnes* growth was inhibited
Lopes et al. (89)	Several *Bifidobacterium* and *Lactobacillus* strains	Binding to keratin; prevention of biofilm formation by pathogenic bacteria; reduced adherence to *C. acnes*

3.3.2.2. Atopic dermatitis (AD)

AD is primarily linked to a reduction in microbial diversity, with *Staphylococcus aureus* being a predominant microorganism in AD patients. Research increasingly suggests that oral probiotics might be a superior treatment option for AD. One study highlighted that *Streptococcus thermophilus* significantly alleviated eczema associated with AD and reduced symptom severity. Another investigation underscored the benefits of *Streptococcus thermophilus*, particularly its ability to enhance ceramide concentrations in the skin's stratum corneum, offering potential relief for AD symptoms (80,90,91).

In a randomized, double-blind study involving patients with AD, the impact of *Lactobacillus*-based emollients was compared to those of standard emollients. The results revealed that emollients infused with *Lactobacillus* not only inhibited the spread of *Staphylococcus aureus* but also provided a mechanical barrier and symptom relief for AD sufferers. An additional study focusing on lotions containing heat-treated *Lactobacillus johnsonii* NCC demonstrated significant improvements in clinical symptoms and reduced *Staphylococcus aureus* colonization in AD patients (16,92).

Moreover, other research examining the use of *Roseomonas mucosa* supplements reported notable reductions in disease severity, the need for topical steroids, and the burden of *Staphylococcus aureus*, all without any adverse reactions or complications. Together, these studies demonstrate that probiotics can positively affect individuals suffering from AD, offering a promising, well-tolerated alternative to traditional treatments. These findings open up new avenues for the management of AD, emphasizing the potential of probiotics in enhancing skin health and combating dermatological conditions (93).

3.3.2.3. Psoriasis

Psoriasis, a chronic autoimmune skin condition, is typically managed with topical emollients and peroral immunosuppressants. Recently, the function of topical probiotics as a potential psoriasis therapy has gained attention, despite limited research so far. Changes in the skin microbiota have been suggested to influence psoriasis symptoms, hinting at a connection between microbial balance and skin health in this context.

While there's growing evidence that peroral probiotics can have therapeutic benefits on the clinical symptoms of psoriasis in certain patients, the extent of their efficacy remains under-researched. Studies specifically examining the effectiveness of oral probiotics in psoriasis patients are crucial to establish their clinical benefits convincingly. Such research would not only validate the application of oral probiotics as a complementary therapy for psoriasis but also help in understanding the complexities of how gut health impacts skin conditions. This exploration into the potential of probiotics for psoriasis treatment reflects a broader interest in the interplay between internal health and skin conditions, and it holds promise for more personalized and effective management strategies for this challenging autoimmune disorder (39,94).

3.3.2.4. Seborrheic Dermatitis (SD)

Dandruff and SD, common scalp conditions, are often attributed to an overgrowth of yeast and a reduced diversity of scalp microbiota. In recent years, the possibility of probiotics as a therapy option for these conditions has been a subject of considerable research interest. One study involving 60 participants showed promising results, with a notable reduction in erythema, scaling, and itching following the topical use of filamentous *Staphylococci*. This suggests that manipulating the scalp microbiota with specific microbial strains can alleviate symptoms associated with these scalp conditions (80).

Another intriguing study highlighted the role of *Vitreoscilla filiformis* lysate in boosting regulatory T cell (Treg) activity. This was achieved through the stimulation of interleukin-10 (IL-10) production by dendritic cells, indicating a potential pathway through which probiotics can exert their therapeutic effects. Furthermore, oral supplementation with *Lactobacillus paracasei* has been observed to yield positive outcomes in managing dandruff, SD, and related scalp disorders (95).

However, despite these encouraging findings, more in-depth investigation is required to fully comprehend and validate the local efficacy of probiotics in treating these scalp conditions. Such studies would contribute significantly to developing targeted probiotic-based therapies, potentially offering a novel, effective treatment avenue for individuals suffering from dandruff, SD, and similar scalp issues. This line of inquiry is especially relevant given the growing interest in exploring the microbiome's function in various skin and scalp disorders and the increasing preference for non-traditional, microbiome-friendly treatment options (96,97).

3.3.2.5. Rosacea

Rosacea, a skin condition characterized by inflammation and altered skin microbiota, is often linked to the overexpression of TLR2 (Toll-like receptor 2) receptors. This overexpression triggers an inflammatory response, adding to the development and exacerbation of rosacea symptoms. In the field of treatments, antibiotics like doxycycline are commonly prescribed to manage this condition by targeting the bacterial aspect of the disease (74,98).

However, the role of oral probiotics in treating rosacea, particularly scalp rosacea, has started to gain attention. Probiotics, known for their ability to influence the body's microbiome and immune response, offer a potential alternative or complementary treatment to traditional antibiotic therapies. They work by restoring the balance of skin microbiota and reducing inflammation, thereby addressing two critical aspects of rosacea pathology.

Despite the promising application of oral probiotics for rosacea, the exploration of topical probiotics as a direct treatment option for this skin condition remains largely uncharted. This gap in research presents an opportunity for further investigation into how topical probiotics could potentially benefit rosacea patients, especially considering the direct interaction these probiotics would have with the skin's surface. Developing and studying topical probiotic formulations could lead to new, innovative ways to manage rosacea, offering patients more options and possibly more effective treatments (99).

The exploration of probiotics, both oral and topical, in the treatment of rosacea aligns with a growing interest in leveraging the microbiome for skin health. It represents an exciting new area in dermatological therapy, one that holds the promise of more natural, microbiome-friendly approaches to managing complex skin conditions like rosacea.

3.3.2.6. Alopecia

In recent research, Park et al. (100) explored the effects of an oral probiotic product made from cheonggukjang and kimchi on male and female patients with androgenic alopecia, they received 80mL Mogut® two times a day. The probiotic product comprised the following ingredients: a culture medium containing fermented bacilli from cheonggukjang and kimchi (including *Leuconostoc holzapfelii*, *Leuconostoc mesenteroides*, and *Lactobacillus sakei*; 99.7%), Hasuo extract (*Pleuropterus multiflorus*; 0.1%), persimmon vinegar (0.1%), and an extract of Korean black soybean (Rhynchosia volubilis Lour; 0.1%). This probiotic drink,

consumed twice daily for four months, led to significant increases in hair count and thickness after one and four months of therapy. Notably, 93% of the subjects showed improvements, suggesting that the probiotic might enhance blood flow to the scalp (100).

However, more studies are necessary to fully comprehend how oral probiotic supplementation influences hair growth, especially with larger sample sizes and control groups.

Additionally, a study on post-finasteride syndrome (PFS) in patients treated with finasteride for androgenic alopecia revealed significant changes in the gut microbiome. This syndrome includes persistent adverse effects such as sexual, neurological, physical, and mental health issues. The research compared stool samples from 21 male PFS patients with those from ten healthy male controls. The analysis showed a marked suppression in the richness, diversity, and composition of the gut microbiome in the PFS group, as indicated by α- and ß-diversity metrics. Particularly, there was a notable decrease in *Ruminococcaceae* UCG-005 and *Faecalibacterium spp.* and an increase in *Odoribacter spp.* and *Alloprevotella* in PFS patients compared to healthy individuals. It should be emphasized that this study focused on the gut microbiome and did not evaluate the microbiome of the scalp or hair follicles (101).

These studies collectively suggest a complex interplay between the microbiome, both gut and scalp, and hair health. They open up potential new avenues for treating hair loss conditions like AGA, emphasizing the need for further exploration into the function of the microbiome in hair growth and the potential of probiotic therapies.

4 Conclusion

In conclusion, the exploration of probiotics in skin health and therapeutic potential represents a promising new area in dermatology and skincare. The comprehensive review of literature underscores the multifaceted roles of probiotics, from enhancing wound healing and mitigating scarring to addressing various skin disorders like acne, AD, psoriasis, SD, rosacea, and alopecia. The evidence points to probiotics not only improving the microbial balance of the skin but also offering anti-inflammatory, antimicrobial, and skin barrier-enhancing effects. These benefits are crucial for managing chronic skin conditions and improving overall skin health.

The therapeutic potential of probiotics extends beyond traditional treatments, offering a natural, minimally invasive approach to managing skin disorders and promoting skin health. Whether applied topically or taken orally, probiotics have shown promising results in enhancing skin moisture, reducing signs of aging, and providing protective barriers against environmental damage. However, despite these promising findings, more research is necessary to completely comprehend the mechanisms of action, optimal strains, and formulations for specific skin conditions.

The shift towards integrating probiotics into skincare and therapeutic protocols reflects an evolving understanding of the skin microbiome's role in health and disease. As the field advances, probiotics hold the promise of revolutionizing skincare and dermatological treatments, offering a holistic approach to skin health that harmonizes with the body's natural processes. The future of skincare and dermatology may well lie in harnessing the power of probiotics, emphasizing the importance of continued research and innovation in this area.

5 Summary

This thesis comprehensively explores the substantial impact of probiotics on skin health and their therapeutic potential across various dermatological conditions. It delves into the historical context of probiotics, tracing their use from ancient fermentation practices to contemporary biomedical research, highlighting their enduring relevance in promoting health and nutrition. The study systematically reviews the effects of different probiotic strains, such as *Nitrobacter*, *Lactobacillus*, and *Bifidobacterium*, on skin health, including their roles in enhancing immune responses, modulating microbial populations, and improving skin barrier functions.

A critical analysis of the literature reveals probiotics' multifaceted benefits in treating skin conditions like acne, AD, psoriasis, SD, rosacea, and alopecia. These benefits range from antimicrobial and anti-inflammatory actions to the maintenance of skin barrier integrity and modulation of the skin's immune system. The thesis emphasizes the potential of probiotics to revolutionize skincare and dermatology by offering natural, effective treatment alternatives that leverage the skin-gut axis and the microbiome's health-promoting capabilities.

Furthermore, the thesis underscores the need for further research to unravel the complex mechanisms through which probiotics influence skin health, identify optimal strains and formulations, and establish standardized therapeutic protocols. By highlighting the promising yet underexplored potential of probiotics in dermatology, critical appraisal of published research papers in this thesis lays the groundwork for future studies that could lead to innovative, microbiome-friendly skincare solutions and treatments for chronic skin disorders.

Key-words: probiotics, skin health, skin-aging, skin diseases, gut microbiome

6 Literature

1. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLOS Biol. 2016; 14(8): e1002533.

2. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol. 201; 9(4): 244–53.

3. Dréno B, Alexis A, Chuberre B, Marinovich M. Safety of titanium dioxide nanoparticles in cosmetics. J Eur Acad Dermatol Venereol. 2019; 33(S7): 34–46.

4. Puebla-Barragan S, Reid G. Probiotics in Cosmetic and Personal Care Products: Trends and Challenges. Mol Basel Switz. 2021; 26(5): 1249.

5. Szántó M, Dózsa A, Antal D, Szabó K, Kemény L, Bai P. Targeting the gut-skin axis—Probiotics as new tools for skin disorder management? Exp Dermatol. 2019; 28(11): 1210–8.

6. Gao T, Wang X, Li Y, Ren F. The Role of Probiotics in Skin Health and Related Gut-Skin Axis: A Review. Nutrients. 2023; 15(14): 3123.

7. Gasbarrini G, Bonvicini F, Gramenzi A. Probiotics History. J Clin Gastroenterol. 2016; 50(Supplement 2): S116–9.

8. Ozen M, Dinleyici EC. The history of probiotics: the untold story. Benef Microbes. 2015; 6(2): 159–65.

9. Levitt EL, Keen JT, Wong BJ. Augmented reflex cutaneous vasodilatation following short-term dietary nitrate supplementation in humans. Exp Physiol. 2015; 100(6): 708–18.

10. Maguire M, Maguire G. The role of microbiota, and probiotics and prebiotics in skin health. Arch Dermatol Res. 2017; 309(6): 411–21.

11. Opländer C, Suschek CV. New Aspects of Nitrite Homeostasis in Human Skin. J Invest Dermatol. 2009; 129(4): 820–2.

12. Sun Z, Harris HMB, McCann A, Guo C, Argimón S, Zhang W, et al. Expanding the biotechnology potential of lactobacilli through comparative genomics of 213 strains and associated genera. Nat Commun. 2015; 6(1): 8322.

13. Holz C, Benning J, Schaudt M, Heilmann A, Schultchen J, Goelling D, et al. Novel bioactive from Lactobacillus brevis DSM17250 to stimulate the growth of Staphylococcus epidermidis: a pilot study. Benef Microbes. 2017; 8(1): 121–32.

14. Fabbrocini G, Bertona M, Picazo Ó, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with Lactobacillus rhamnosus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. Benef Microbes. 2016; 7(5): 625–30.

15. Im AR, Kim HS, Hyun JW, Chae S. Potential for tyndalized Lactobacillus acidophilus as an effective component in moisturizing skin and anti-wrinkle products. Exp Ther Med. 2016; 12(2): 759–64.

16. Park MJ, Bae YS. Fermented Acanthopanax koreanum Root Extract Reduces UVB- and H2O2-Induced Senescence in Human Skin Fibroblast Cells. J Microbiol Biotechnol. 2016; 26(7): 1224–33.

17. Satoh T, Murata M, Iwabuchi N, Odamaki T, Wakabayashi H, Yamauchi K, et al. Effect of Bifidobacterium breve B-3 on skin photoaging induced by chronic UV irradiation in mice. Benef Microbes. 2015; 6(4): 497–504.

18. Allen SJ, Jordan S, Storey M, Thornton CA, Gravenor MB, Garaiova I, et al. Probiotics in the prevention of eczema: a randomised controlled trial. Arch Dis Child. 2014; 99(11): 1014–9.

19. Makarova KS, Grishin NV, Shabalina SA, Wolf YI, Koonin EV. A putative RNA-interference-based immune system in prokaryotes: computational analysis of the predicted enzymatic machinery, functional analogies with eukaryotic RNAi, and hypothetical mechanisms of action. Biol Direct. 2006; 1(1): 7.

20. Kano M, Masuoka N, Kaga C, Sugimoto S, Iizuka R, Manabe K, et al. Consecutive Intake of Fermented Milk Containing *Bifidobacterium breve* Strain Yakult and Galacto-oligosaccharides Benefits Skin Condition in Healthy Adult Women. Biosci Microbiota Food Health. 2013; 32(1): 33–9.

21. Yokoyama S, Hiramoto K, Koyama M, Ooi K. Impairment of skin barrier function via cholinergic signal transduction in a dextran sulphate sodium-induced colitis mouse model. Exp Dermatol. 2015; 24(10): 779–84.

22. Salem I, Ramser A, Isham N, Ghannoum MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Front Microbiol. 2018; 9: 1459.

23. Lebeer S, Vanderleyden J, De Keersmaecker SCJ. Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. Nat Rev Microbiol. 2010; 8(3): 171–84.

24. Ueno N, Fujiya M, Segawa S, Nata T, Moriichi K, Tanabe H, et al. Heat-killed body of lactobacillus brevis SBC8803 ameliorates intestinal injury in a murine model of colitis by enhancing the intestinal barrier function: Inflamm Bowel Dis. 201; 17(11): 2235–50.

25. Smits HH, Engering A, Van Der Kleij D, De Jong EC, Schipper K, Van Capel TMM, et al. Selective probiotic bacteria induce IL-10–producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin. J Allergy Clin Immunol. 2005; 115(6): 1260–7.

26. Lee MJ, Kang MJ, Lee SY, Lee E, Kim K, Won S, et al. Perturbations of gut microbiome genes in infants with atopic dermatitis according to feeding type. J Allergy Clin Immunol. 2018; 141(4): 1310–9.

27. Kaikiri H, Miyamoto J, Kawakami T, Park SB, Kitamura N, Kishino S, et al. Supplemental feeding of a gut microbial metabolite of linoleic acid, 10-hydroxy- *cis* -12-octadecenoic acid, alleviates spontaneous atopic dermatitis and modulates intestinal microbiota in NC/nga mice. Int J Food Sci Nutr. 2017; 68(8): 941–51.

28. Johnson AMF, DePaolo RW. Window-of-opportunity: neonatal gut microbiota and atopy. HepatoBiliary Surg Nutr. 2017; 6 (3): 190–2.

29. Jin UH, Lee SO, Sridharan G, Lee K, Davidson LA, Jayaraman A, et al. Microbiome-Derived Tryptophan Metabolites and Their Aryl Hydrocarbon Receptor-Dependent Agonist and Antagonist Activities. Mol Pharmacol. 2014; 85(5): 777–88.

30. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012; 13(10): 701–12.

31. Zipperer A, Konnerth MC, Laux C, Berscheid A, Janek D, Weidenmaier C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. Nature. 2016; 535(7613): 511–6.

32. Mahmud MdR, Akter S, Tamanna SK, Mazumder L, Esti IZ, Banerjee S, et al. Impact of gut microbiome on skin health: gut-skin axis observed through the lenses of therapeutics and skin diseases. Gut Microbes. 2022; 14(1): 2096995.

33. Shin D, Lee Y, Huang YH, Lim HW, Jang K, Kim DD, et al. Probiotic fermentation augments the skin anti-photoaging properties of Agastache rugosa through up-regulating antioxidant components in UV-B-irradiated HaCaT keratinocytes. BMC Complement Altern Med. 2018; 18(1): 196.

34. Im A, Lee B, Kang D, Chae S. Protective effects of tyndallized Lactobacillus□acidophilus IDCC 3302 against UVB-induced photodamage to epidermal keratinocytes cells. Int J Mol Med [Internet]. 2019 [cited 2024 Apr 21]; Available from: http://www.spandidos-publications.com/10.3892/ijmm.2019.4161

35. Lim HY, Jeong D, Park SH, Shin KK, Hong YH, Kim E, et al. Antiwrinkle and Antimelanogenesis Effects of Tyndallized Lactobacillus acidophilus KCCM12625P. Int J Mol Sci. 2020; 21(5): 1620.

36. Ishii Y, Sugimoto S, Izawa N, Sone T, Chiba K, Miyazaki K. Oral administration of

Bifidobacterium breve attenuates UV-induced barrier perturbation and oxidative stress in hairless mice skin. Arch Dermatol Res. 2014; 306(5): 467–73.

37. Kang YM, Hong CH, Kang SH, Seo DS, Kim SO, Lee HY, et al. Anti-Photoaging Effect of Plant Extract Fermented with Lactobacillus buchneri on CCD-986sk Fibroblasts and HaCaT Keratinocytes. J Funct Biomater. 2020; 11(1): 3.

38. Chen H, Li Y, Xie X, Chen M, Xue L, Wang J, et al. Exploration of the Molecular Mechanisms Underlying the Anti-Photoaging Effect of Limosilactobacillus fermentum XJC60. Front Cell Infect Microbiol. 2022; 12: 838060.

39. Yau YF, El-Nezami H, Galano J, Kundi ZM, Durand T, Lee JC. *Lactobacillus rhamnosus* GG and Oat Beta-Glucan Regulated Fatty Acid Profiles along the Gut-Liver-Brain Axis of Mice Fed with High Fat Diet and Demonstrated Antioxidant and Anti-Inflammatory Potentials. Mol Nutr Food Res. 2020; 64(18): 2000566.

40. Mai C, Qiu L, Zeng Y, Tan X. Lactobacillus casei Strain Shirota Enhances the Ability of Geniposide to Activate SIRT1 and Decrease Inflammation and Oxidative Stress in Septic Mice. Front Physiol. 2021; 12: 678838.

41. Ansel JC, Luger TA, Green I. The Effect of In Vitro and In Vivo UV Irradiation on the Production of ETAF Activity by Human and Murine Keratinocytes. J Invest Dermatol. 1983; 81(6): 519–23.

42. Kupper TS, Groves RW. The Interleukin-1 Axis and Cutaneous Inflammation. J Invest Dermatol. 1995; 105(1): S62–6.

43. Khmaladze I, Butler É, Fabre S, Gillbro JM. *Lactobacillus reuteri* DSM 17938—A comparative study on the effect of probiotics and lysates on human skin. Exp Dermatol. 2019; 28(7): 822–8.

44. Keshari S, Balasubramaniam A, Myagmardoloonjin B, Herr DR, Negari IP, Huang CM. Butyric Acid from Probiotic Staphylococcus epidermidis in the Skin Microbiome Down-Regulates the Ultraviolet-Induced Pro-Inflammatory IL-6 Cytokine via Short-Chain Fatty

Acid Receptor. Int J Mol Sci. 2019; 20(18): 4477.

45. Hong KB, Jeong M, Han KS, Hwan Kim J, Park Y, Suh HJ. Photoprotective effects of galacto-oligosaccharide and/or *Bifidobacterium longum* supplementation against skin damage induced by ultraviolet irradiation in hairless mice. Int J Food Sci Nutr. 2015; 66(8): 923–30.

46. Goodarzi A, Mozafarpoor S, Bodaghabadi M, Mohamadi M. The potential of probiotics for treating acne vulgaris: A review of literature on acne and microbiota. Dermatol Ther [Internet]. 2020 [cited 2024 Apr 21];33(3). Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.13279

47. Kober MM, Bowe WP. The effect of probiotics on immune regulation, acne, and photoaging. Int J Womens Dermatol. 2015; 1(2): 85–9.

48. Kim D, Lee KR, Kim NR, Park SJ, Lee M, Kim OK. Combination of *Bifidobacterium longum* and Galacto-Oligosaccharide Protects the Skin from Photoaging. J Med Food. 2021; 24(6): 606–16.

49. Lavker RM, Zheng P, Dong G. Morphology of Aged Skin. Clin Geriatr Med. 1989; 5(1): 53–67.

50. Kim HM, Lee DE, Park SD, Kim YT, Kim YJ, Jeong JW, et al. Oral Administration of Lactobacillus plantarum HY7714 Protects Hairless Mouse Against Ultraviolet B-Induced Photoaging. J Microbiol Biotechnol. 2014; 24(11): 1583–91.

51. You GE. Lactobacillus sakei Lipoteichoic Acid Inhibits MMP-1 Induced by UVA in Normal Dermal Fibroblasts of Human. J Microbiol Biotechnol. 2013; 23(10): 1357–64.

52. Negari IP, Keshari S, Huang CM. Probiotic Activity of Staphylococcus epidermidis Induces Collagen Type I Production through FFaR2/p-ERK Signaling. Int J Mol Sci. 2021; 22(3): 1414.

53. AL-Smadi K, Leite-Silva VR, Filho NA, Lopes PS, Mohammed Y. Innovative Approaches for Maintaining and Enhancing Skin Health and Managing Skin Diseases through

Microbiome-Targeted Strategies. Antibiotics. 2023; 12(12): 1698.

54. Pillaiyar T, Manickam M, Jung SH. Recent development of signaling pathways inhibitors of melanogenesis. Cell Signal. 2017; 40: 99–115.

55. Brenner M, Hearing VJ. The Protective Role of Melanin Against UV Damage in Human Skin †. Photochem Photobiol. 2008; 84(3): 539–49.

56. Iozumi K, Hoganson GE, Pennella R, Everett MA, Fuller BB. Role of Tyrosinase as the Determinant of Pigmentation in Cultured Human Melanocytes. J Invest Dermatol. 1993; 100(6): 806–11.

57. Huang HC, Chang TM. Antioxidative properties and inhibitory effect of Bifidobacterium adolescentis on melanogenesis. World J Microbiol Biotechnol. 2012; 28(9): 2903–12.

58. Huang HC, Lee IJ, Huang C, Chang TM. Lactic Acid Bacteria and Lactic Acid for Skin Health and Melanogenesis Inhibition. Curr Pharm Biotechnol. 2020; 21(7): 566–77.

59. Chaiprasongsuk A, Onkoksoong T, Pluemsamran T, Limsaengurai S, Panich U. Photoprotection by dietary phenolics against melanogenesis induced by UVA through Nrf2-dependent antioxidant responses. Redox Biol. 2016; 8: 79–90.

60. Liu WS, Kuan YD, Chiu KH, Wang WK, Chang FH, Liu CH, et al. The Extract of Rhodobacter sphaeroides Inhibits Melanogenesis through the MEK/ERK Signaling Pathway. Mar Drugs. 2013; 11(6): 1899–908.

61. Kim H, Kim JT, Barua S, Yoo SY, Hong SC, Lee KB, et al. Seeking better topical delivery technologies of moisturizing agents for enhanced skin moisturization. Expert Opin Drug Deliv. 2018; 15(1): 17–31.

62. Harding, Watkinson, Rawlings, Scott. Dry skin, moisturization and corneodesmolysis. Int J Cosmet Sci. 2000; 22(1): 21–52.

63. Holleran WM, Uchida Y, Halkier-Sorensen L, Haratake A, Hara M, Epstein JH, et al. Structural and biochemical basis for the UVB-induced alterations in epidermal barrier function. Photodermatol Photoimmunol Photomed. 1997; 13(4): 117–28.

64. Ra J, Lee DE, Kim SH, Jeong JW, Ku HK, Kim TY, et al. Effect of Oral Administration of Lactobacillus plantarum HY7714 on Epidermal Hydration in Ultraviolet B-Irradiated Hairless Mice. J Microbiol Biotechnol. 2014; 24(12): 1736–43.

65. Im AR, Lee B, Kang DJ, Chae S. Skin Moisturizing and Antiphotodamage Effects of Tyndallized *Lactobacillus acidophilus* IDCC 3302. J Med Food. 2018; 21(10): 1016–23.

66. Baba H, Masuyama A, Yoshimura C, Aoyama Y, Takano T, Ohki K. Oral Intake of *Lactobacillus helveticus* -Fermented Milk Whey Decreased Transepidermal Water Loss and Prevented the Onset of Sodium Dodecylsulfate-Induced Dermatitis in Mice. Biosci Biotechnol Biochem. 2010; 74(1): 18–23.

67. Jung YO, Jeong H, Cho Y, Lee EO, Jang HW, Kim J, et al. Lysates of a Probiotic, Lactobacillus rhamnosus, Can Improve Skin Barrier Function in a Reconstructed Human Epidermis Model. Int J Mol Sci. 2019; 20(17): 4289.

68. Draelos ZD. New treatments for restoring impaired epidermal barrier permeability: Skin barrier repair creams. Clin Dermatol. 2012; 30(3): 345–8.

69. Trojahn C, Dobos G, Lichterfeld A, Blume-Peytavi U, Kottner J. Characterizing Facial Skin Ageing in Humans: Disentangling Extrinsic from Intrinsic Biological Phenomena. BioMed Res Int. 2015; 2015: 1–9.

70. Gervason S, Napoli M, Dreux-Zhiga A, Lazzarelli C, Garcier S, Briand A, et al. Attenuation of negative effects of senescence in human skin using an extract from *Sphingomonas hydrophobicum* : development of new skin care solution. Int J Cosmet Sci. 2019; 41(4): 391–7.

71. Dolan DWP, Zupanic A, Nelson G, Hall P, Miwa S, Kirkwood TBL, et al. Integrated Stochastic Model of DNA Damage Repair by Non-homologous End Joining and p53/p21-

Mediated Early Senescence Signalling. Xia Y, editor. PLOS Comput Biol. 2015; 11(5): e1004246.

72. Sheng W, Wang G, Wang Y, Liang J, Wen J, Zheng PS, et al. The Roles of Versican V1 and V2 Isoforms in Cell Proliferation and Apoptosis. Mol Biol Cell. 2005; 16(3): 1330–40.

73. Fijan S, Frauwallner A, Langerholc T, Krebs B, Ter Haar (Née Younes) JA, Heschl A, et al. Efficacy of Using Probiotics with Antagonistic Activity against Pathogens of Wound Infections: An Integrative Review of Literature. BioMed Res Int. 2019; 2019: 1–21.

74. Knackstedt R, Knackstedt T, Gatherwright J. The role of topical probiotics on wound healing: A review of animal and human studies. Int Wound J. 2020; 17(6): 1687–94.

75. Togo C, Zidorio AP, Gonçalves V, Botelho P, de Carvalho K, Dutra E. Does Probiotic Consumption Enhance Wound Healing? A Systematic Review. Nutrients. 2021; 14(1): 111.

76. Menni A, Moysidis M, Tzikos G, Stavrou G, Tsetis JK, Shrewsbury AD, et al. Looking for the Ideal Probiotic Healing Regime. Nutrients. 2023; 15(13): 3055.

77. De Almeida CV, Antiga E, Lulli M. Oral and Topical Probiotics and Postbiotics in Skincare and Dermatological Therapy: A Concise Review. Microorganisms. 2023; 11(6): 1420.

78. França K. Topical Probiotics in Dermatological Therapy and Skincare: A Concise Review. Dermatol Ther. 2021; 11(1): 71–7.

79. Sánchez-Pellicer P, Navarro-Moratalla L, Núñez-Delegido E, Ruzafa-Costas B, Agüera-Santos J, Navarro-López V. Acne, Microbiome, and Probiotics: The Gut–Skin Axis. Microorganisms. 2022; 10(7): 1303.

80. Di Marzio L, Cinque B, De Simone C, Cifone MG. Effect of the Lactic Acid BacteriumStreptococcus thermophilus on Ceramide Levels in Human KeratinocytesIn Vitro and Stratum Corneum In Vivo. J Invest Dermatol. 1999; 113(1): 98–106.

81. Bowe WP, Filip JC, DiRienzo JM, Volgina A, Margolis DJ. Inhibition of propionibacterium acnes by bacteriocin-like inhibitory substances (BLIS) produced by Streptococcus salivarius. J Drugs Dermatol JDD. 2006; 5(9): 868–70.

82. Oh S, Kim SH, Ko Y, Sim JH, Kim KS, Lee SH, et al. Effect of bacteriocin produced by Lactococcus sp. HY 449 on skin-inflammatory bacteria. Food Chem Toxicol. 2006; 44(8): 1184–90.

83. Deidda F, Amoruso A, Nicola S, Graziano T, Pane M, Mogna L. New Approach in Acne Therapy: A Specific Bacteriocin Activity and a Targeted Anti IL-8 Property in Just 1 Probiotic Strain, the L. salivarius LS03. J Clin Gastroenterol. 2018; 52(Supplement 1): S78–81.

84. Lee DK, Kim MJ, Ham JW, An HM, Cha MK, Lee SW, et al. In Vitro evaluation of antibacterial activities and anti-inflammatory effects of Bifidobacterium spp. addressing acne vulgaris. Arch Pharm Res. 2012; 35(6): 1065–71.

85. Wang Y, Kuo S, Shu M, Yu J, Huang S, Dai A, et al. Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of Propionibacterium acnes: implications of probiotics in acne vulgaris. Appl Microbiol Biotechnol. 2014; 98(1): 411–24.

86. Cosseau C, Devine DA, Dullaghan E, Gardy JL, Chikatamarla A, Gellatly S, et al. The Commensal *Streptococcus salivarius* K12 Downregulates the Innate Immune Responses of Human Epithelial Cells and Promotes Host-Microbe Homeostasis. Infect Immun. 2008; 76(9): 4163–75.

87. Gueniche A, Benyacoub J, Philippe D, Bastien P, Kusy N, Breton L, et al. Lactobacillus paracasei CNCM I-2116 (ST11) inhibits substance P-induced skin inflammation and accelerates skin barrier function recovery in vitro. Eur J Dermatol EJD. 2010; 20(6): 731–7.

88. Al-Ghazzewi FH, Tester RF. Effect of konjac glucomannan hydrolysates and

probiotics on the growth of the skin bacterium *Propionibacterium acnes in vitro*. Int J Cosmet Sci. 2010; 32(2): 139–42.

89. Lopes EG, Moreira DA, Gullón P, Gullón B, Cardelle-Cobas A, Tavaria FK. Topical application of probiotics in skin: adhesion, antimicrobial and antibiofilm *in vitro* assays. J Appl Microbiol. 2017; 122(2): 450–61.

90. Ambrożej D, Kunkiel K, Dumycz K, Feleszko W. The use of probiotics and bacteria-derived preparations in topical treatment of atopic dermatitis—A systematic review. J Allergy Clin Immunol Pract. 2021; 9(1): 570-575.e2.

91. Dimarzio L, Cinque B, Cupelli F, De Simone C, Cifone MG, Giuliani M. Increase of Skin-Ceramide Levels in Aged Subjects following a Short-Term Topical Application of Bacterial Sphingomyelinase from *Streptococcus Thermophilus*. Int J Immunopathol Pharmacol. 2008; 21(1): 137–43.

92. Fang Z, Li L, Zhang H, Zhao J, Lu W, Chen W. Gut Microbiota, Probiotics, and Their Interactions in Prevention and Treatment of Atopic Dermatitis: A Review. Front Immunol. 2021; 12: 720393.

93. Myles IA, Castillo CR, Barbian KD, Kanakabandi K, Virtaneva K, Fitzmeyer E, et al. Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair. Sci Transl Med. 2020; 12(560): eaaz8631.

94. Lu W, Deng Y, Fang Z, Zhai Q, Cui S, Zhao J, et al. Potential Role of Probiotics in Ameliorating Psoriasis by Modulating Gut Microbiota in Imiquimod-Induced Psoriasis-Like Mice. Nutrients. 2021; 13(6): 2010.

95. Volz T, Skabytska Y, Guenova E, Chen KM, Frick JS, Kirschning CJ, et al. Nonpathogenic Bacteria Alleviating Atopic Dermatitis Inflammation Induce IL-10-Producing Dendritic Cells and Regulatory Tr1 Cells. J Invest Dermatol. 2014; 134(1): 96–104.

96. Reygagne P, Bastien P, Couavoux MP, Philippe D, Renouf M, Castiel-Higounenc I, et al. The positive benefit of Lactobacillus paracasei NCC2461 ST11 in healthy volunteers with

moderate to severe dandruff. Benef Microbes. 2017; 8(5): 671–80.

97. Truglio M, Sivori F, Cavallo I, Abril E, Licursi V, Fabrizio G, et al. Modulating the skin mycobiome-bacteriome and treating seborrheic dermatitis with a probiotic-enriched oily suspension. Sci Rep. 2024; 14(1): 2722.

98. Knackstedt R, Knackstedt T, Gatherwright J. The role of topical probiotics on wound healing: A review of animal and human studies. Int Wound J. 2020; 17(6): 1687–94.

99. Fortuna MC, Garelli V, Pranteda G, Romaniello F, Cardone M, Carlesimo M, et al. A case of Scalp Rosacea treated with low dose doxycycline and probiotic therapy and literature review on therapeutic options: Doxycycline and probiotic in scalp rosacea. Dermatol Ther. 2016; 29(4): 249–51.

100. Park DW, Lee HS, Shim MS, Yum KJ, Seo JT. Do Kimchi and *Cheonggukjang* Probiotics as a Functional Food Improve Androgenetic Alopecia? A Clinical Pilot Study. World J Mens Health. 2020; 38(1): 95.

101. Borgo F, Macandog AD, Diviccaro S, Falvo E, Giatti S, Cavaletti G, et al. Alterations of gut microbiota composition in post-finasteride patients: a pilot study. J Endocrinol Invest. 2021; 44(6): 1263–73.

7 Curriculum Vitae

Konstantin Karl Stergios Stavrakidis, born on April 14, 2000, in Heilbronn, Germany, began his educational journey in 2006 at elementary school. Following a 12-year academic path, he successfully earned his Abitur in 2018 from the Herzog-Christoph-Gymnasium in Beilstein. In the same year, he started his higher education, enrolling in the English Study Program of Medicine at the University of Rijeka in Croatia. He is on track to complete his medical studies by the summer of 2024. Additionally, during his semester breaks, Konstantin has actively engaged in medical practice, gaining hands-on experience in various inpatient and outpatient medical settings.