

Review

# Role of Nutribiotics in Skin Care

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**Featured Application:** This review deals with the use of nutribiotics in skin care, which is of great interest as a nutritional supplement therapy in skin dysbiosis and related diseases.

**Abstract:** The study of the human microbiome has been a hot topic during the recent decades. More recently, the skin microbiome has attracted great interest as well. So, the scientific community has become interested in the role of the skin microbiome in skin health and its relationship with different disorders, such as atopic dermatitis, psoriasis, acne, and rosacea, among others. Numerous studies and investigations have been performed to study the role of pre- and probiotics as nutraceuticals in the treatment of skin diseases, with growing evidence over the recent ten years. This review gathers information on the use of “nutribiotics” in skin care health, focusing on the main dermatological diseases and other skin conditions. Clinical studies show that nutribiotics could be a new tool to improve skin health, and pre-, pro-, syn-, post-, and para-probiotics seem to be beneficial for several skin disorders as well as for repairing the skin barrier and promoting wound healing. In conclusion, the skin microbiome has become a new field with great potential to develop innovative products to manage skin health and diseases. Future advances in this field may facilitate the treatment of skin dysbiosis, with nutribiotics being a suitable method for skin care.

**Keywords:** nutraceuticals; prebiotics; probiotics; postbiotics; skin microbiome; skin disorders



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## 1. Introduction

The study of the human microbiome, which began in the recent century, has sparked growing interest due to its complexity and its importance in human health.

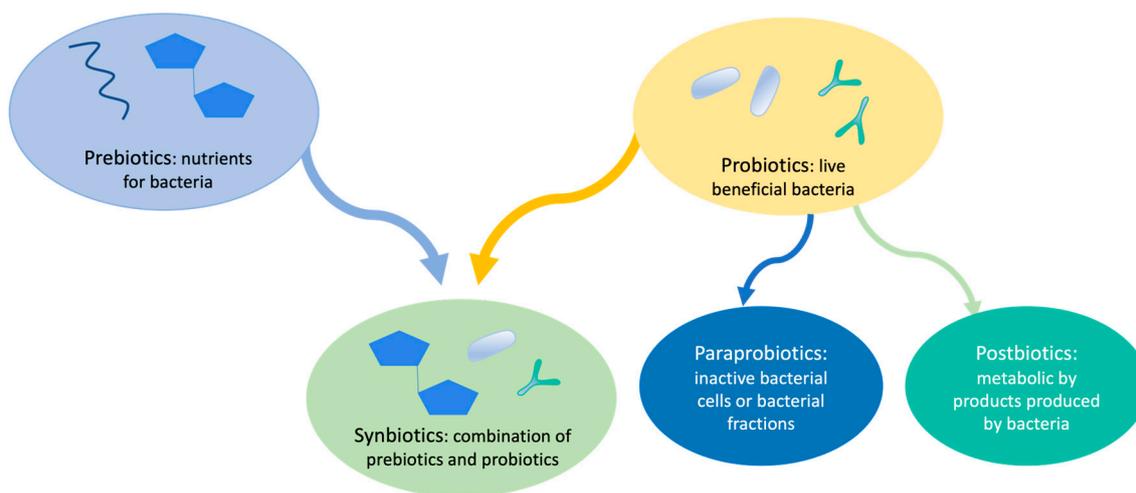
The main milestone has been the Human Microbiome Project of the National Institute of Health in the United States (Human Microbiome Project, NIH), with the aim of identifying and characterizing the microorganisms that settle in the different structures of the human body and that can play a role and therefore influence both health and disease. From that moment on, numerous scientific publications and studies have linked the imbalance of the microbiome with different diseases.

A recent review related to the role of the human microbiome in health and disease in the United Kingdom concluded that the human microbiome plays a fundamental role in health and disease with multiple facets [1]. Various studies have shown that the intricate and complex communities of microorganisms that live inside and on the surface of our body have important and marked effects on several aspects of human physiology, from metabolism or digestive processes to immune function. Furthermore, researchers demonstrated that a balanced and diverse microbiome can contribute to global wellbeing by protecting against pathogens, assisting in nutrient absorption, and modulating immune responses. In contrast, dysbiosis, that is, alterations or imbalances in the microbiome, has been linked to a wide variety of health conditions, including inflammatory bowel disease,

obesity, allergies, and neurological disorders, among others [2]. One of the objectives of current research is to deepen our knowledge of the intricate relationships between the microbiome and human health in order to develop ways to use the microbiome for therapeutic purposes [1].

The term “human microbiota” has been described as the group of symbiotic microorganisms that co-occur with the human organism in balance and without causing damage. The term “microbiome” refers to the entire microbiota habitat, including microorganisms, their genomes, and the surrounding environment. Likewise, the aim of the use of prebiotics and probiotics in nutritional therapy is to alleviate these imbalances in the microbiota, and, in parallel, an important industry linked to these nutritional supplements, also called “nutraceuticals”, has emerged. At the same time, the concept of nutraceuticals emerged, understood as a general term to refer to the set of microbotics for human use, also called microbial biotherapy.

The role of probiotics in regulating intestinal health has been widely studied in recent decades [3]. Besides that, the concept of prebiotics has been developed, and, later on, the concept of synbiotics, postbiotics, and para-probiotics [4–9]—in the form of nutraceuticals as oral supplements and for topical applications—was also developed, with the aim of repairing or balancing the microbiota. All these concepts are summarized in Figure 1.



**Figure 1.** Concept of prebiotics, probiotics, synbiotics, para-probiotics, and postbiotics (adapted from Mourelle et al., 2023) [10].

Since the Russian scientist Elie Metchnikoff (1845–1916) coined the concept of probiotic in 1907 [11], numerous studies followed; finally, a consensus definition was proposed by the International Scientific Association of Probiotics and Prebiotics (ISAPP) in 2014, 2017, and 2021, which includes prebiotics, probiotics, and postbiotics definitions. Probiotics were defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [4]. Prebiotics were defined as “a substrate that is selectively utilized by host microorganisms conferring a health benefit” [5]. Postbiotics were defined as follows: “preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” [8]. Later on, the concept of synbiotics emerged, being defined as the combination of both prebiotics and probiotics [8].

The current definition of probiotics does not include inactivated or dead cells; therefore, the concept of postbiotic has emerged more recently, referring to the use of dead or inactivated cells (non-viable microorganisms), cell extracts, or metabolites of these microorganisms that can provide favorable effects on human health, observing that the action of probiotics depends fundamentally on their metabolites, rather than on living organisms [12,13]. Later on, the concept of para-probiotics emerged, consisting of inactivated, dead, or non-viable microbial cells of intact or broken probiotics containing cellular components of probiotic cells after lysis [14]. Thus, in the recent ten years, several studies

have been conducted using inactivated or heat-killed probiotics [15]; however, the terms ‘postbiotics’, ‘para-probiotics’, and ‘inactivated probiotics’ have been used indistinctively in multiple research studies [16–20]. Postbiotics include the metabolites generated by the microbiota, such as exopolysaccharides, short-chain fatty acids (SCFAs), cell wall fragments, enzymes/proteins, and other metabolites [21], but also structural ones, such as teichoic acids, peptides, and plasmalogens, or ones based on their basic composition (proteins, carbohydrates, lipids, vitamins, etc.) [22]. In this context, several postbiotics have been shown to improve gut health by reinforcing the gut barrier, reducing inflammation, and promoting antimicrobial activity against gut pathogens [23].

According to the most recurrent definition, para-probiotics, also known as non-viable probiotics, inactivated probiotics, tyndallized probiotics, or ghost probiotics, are “non-viable microbial cells (either intact or broken), or crude cell extracts, which, when administered (orally or topically) in adequate amounts, confer a benefit on the human or animal consumer” [7,24]. A recent review by Mehta et al. [25] focused on the ability of different types of para-probiotics and postbiotics to modulate the immune system. The most used strains to develop as para-probiotics are *Lactobacillus* and *Bifidobacterium* strains. The postbiotic components that modulate the biological reactions include lipoteichoic acids, bacteriocins, SCFAs, peptidoglycan, and exopolysaccharides [25]. Some studies showed that prescribing live probiotic cells to people with weakened immune systems increases inflammatory responses. In such cases, a combination of dead cells can be a good alternative. Thus, the use of killed or inactive probiotics created a new field and various scientists tried to come up with new terms to describe the mentioned cases [26]. Additionally, Lee et al. [9] described the techniques to obtain para-probiotics, which include thermal treatments, sonication, ionizing radiation, high pressure, ultraviolet rays, and pH modification.

In terms of efficacy, Cuevas-González et al. [6] revised the bioactivities, health-promoting effects, and applications, among other issues, related to post and para-probiotics, referring that *in vitro* and *in vivo* studies have shown that some postbiotics and para-probiotics exhibit bioactivities that are immunomodulatory, anti-proliferative, anti-inflammatory, antimicrobial, and antioxidant. The authors postulated that these bioactivities could be involved in the observed health-improving effects, both in clinical trials and in humans; however, more investigations are needed, as the mechanisms of action and the signaling pathways involved have not been fully elucidated. They concluded that para-probiotics and postbiotics are of great interest for the development of nutraceutical products due to their potential for improving health [6].

In the recent decade, several studies evaluated the potential uses of pre-, pro-, syn-, post-, and para-probiotics mainly focusing on inflammatory bowel diseases [27], other inflammatory diseases, and even in brain dysfunction, oral cavity dysbiosis, and a few of them related to skin diseases [9,14,23,28]. There are also studies in pregnancy, showing that reduced microbiome diversity (dysbiosis) during pregnancy, cesarean delivery, prematurity, and formula feeding can bring on dysbiosis in the newborn; so, microbiota therapy may be a path to restore eubiosis in pregnant women and their babies [29]. Moreover, the use of probiotics in the course of antibiotic therapy does not have enough evidence. Éliás et al. [30] conducted a systematic review and meta-analysis of randomized controlled trials that evidenced differences in gut microbiome diversity between patients receiving antibiotic therapy with and without concomitant probiotic supplementation, showing that the results of available randomized controlled trials cannot endorse supplementation with probiotics along antibiotic therapy to avoid decreasing microbiome diversity [30]. On the other hand, other studies showed that probiotics can be used to change the microbiome, but an individual approach is needed. Patil and Singh [31] suggested that by studying and harnessing individualized microbiota, personalized probiotic therapies could help improve the microbial environment and aid in improving overall health. However, more studies and partnerships between different fields are needed [31].

On the other hand, there is a great field of interest regarding the use of probiotics and nutraceuticals in foods, both for animal nutrition and for humans in terms of functional foods [32], and also in the pharmaceutical industry [22,33].

Finally, it is worth mentioning that multiomics (defined as a biological analysis approach in which the data sets are multiple “omes”, such as the genome, proteome, transcriptome, epigenome, metabolome, and microbiome) is a useful tool to select probiotics and understand their functions in the host microbiome, ensuring that probiotics and the microbiome can be better understood [34].

This review describes the growing aspects of the use of nutraceuticals within the field of nutraceuticals in skin care health, focusing on the main dermatological diseases and other skin conditions.

## 2. The Skin Microbiome: A Unique Environment

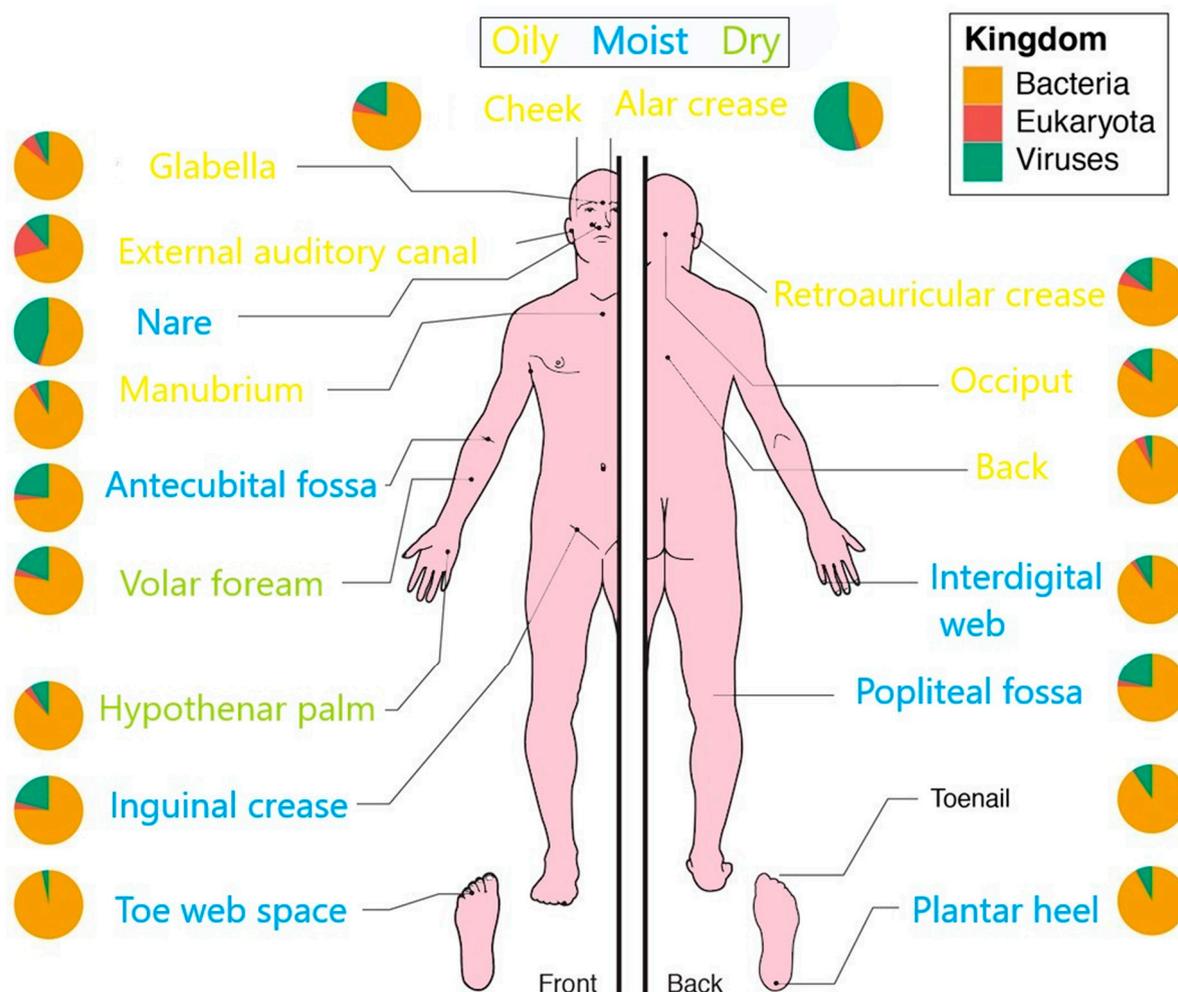
The skin is a protective organ that performs important barrier functions against external agents in addition to preventing the loss of body fluids. The cells of the epidermis, but also the microorganisms present on its surface, intervene with barrier function.

The microbiome and the skin are part of a whole that coexists and interrelates with each other. This invisible ecosystem of microorganisms performs important functions in the health of the skin, protecting it against external aggressions and acting as a second genome, interacting with other parts of the body to ensure healthy functioning. Its main role is the defense of the skin and interrelation with the environment that surrounds it. Furthermore, the skin microbiome has been found to play an important role in pathogen protection, inflammatory regulation, and overall health [35].

The skin microbiome also helps maintain skin homeostasis and the epidermal barrier, aiding in the process of epidermal renewal by the production of protease enzymes. The secretion of lipases by the microorganisms present on the skin surface also plays a regulatory role, since they break down the lipids secreted by the sebaceous gland. In addition, the skin microbiome produces bacteriocins [36]. Also, quorum sensing seems to exert a critical role on skin barrier function, with a recent study showing that interspecies quorum sensing among bacteria in human skin is considered a necessary defense mechanism to suppress the ability of *Staphylococcus aureus* to damage the epidermis [37].

Over the recent few years, several studies have focused on the composition of the skin microbiome and how it changes with development or how external factors may affect its diversity. On the other hand, it is well known that the composition of the skin microbiome varies according to the areas of the body that constitute various ecological and physicochemical niches, mainly related to moisture and sebum content on the surface of the skin [38]. These differences influence resident bacteria and fungi; oily surfaces such as the forehead harbor lipid-loving bacteria that differ from dry areas, such as the forearm, in which there is lower microbial density [39]. In this regard, *Cutibacterium* spp., *Staphylococcus* spp., and *Streptococcus* spp. are the most abundant bacteria on dry sites; *Staphylococcus* and *Corynebacterium* spp. prefer moist areas; on sebaceous sites, lipophilic *Cutibacterium* species (spp.) are the most abundant [40,41]. *Malassezia* spp. is the most abundant fungus throughout the body, except in the areas of the foot that present greater diversity [42–44]. On the other hand, it has been observed that two phyla, *Bacteroidetes* and *Firmicutes*, tend to predominate in the microbiome of adults, while *Actinobacteria* and *Proteobacteria* constitute a smaller portion. Even so, variations can be found in the proportions of these phyla and the species from person to person [45].

Mites are also found in the skin microbiome. *Demodex* spp. are characteristic of sebaceous glands and hair follicles, with the most numerous representatives being *D. folliculorum* (hair follicles) and *D. brevis* (sebaceous and meibomian glands) [45]. The skin virome has also been explored; it is very heterogeneous and complex with various polyomaviruses (Polyomaviridae), circoviruses (Circoviridae), and papillomaviruses (Papillomaviridae) [46,47]. Figure 2 summarizes the relative abundance of bacterial, fungal, and viral components of the microbial community in different skin microenvironments.



**Figure 2.** Relative abundance of bacterial, fungal, and viral components of the microbial community in the different skin microenvironments: sebaceous (yellow), moist (blue), and dry (green). Toenail (black) does not match these major microenvironments (Adapted from Belkaid and Segre, 2014) [39].

Studies of the skin microbiome (microbial and genomic components) in different age groups have shown that skin microbial communities exhibit dynamics that vary throughout life, developing in the early stages of life after exposure to the maternal microbiome, and are followed by changes in terms of diversity and community structure until old age [48].

Thus, it has been observed that the microbiomes in neonates looks like maternal vaginal communities when delivered vaginally (*Lactobacillus* and *Prevotella* spp.), or maternal skin communities if delivered by cesarean section (*Staphylococcus*, *Streptococcus*, *Corynebacterium*, and *Propionibacterium* spp.). *Staphylococcus*, *Corynebacterium*, and *Prevotella* abound in premature infants, while *Brevundimonas*, *Flavobacterium*, and *Sphingobacterium* predominate in full-term infants [41].

At birth, the pH of the skin is neutral, but, in the first hours of life, the development of the cutaneous acid mantle begins, favoring colonization by commensal organisms and inhibiting the growth of pathogens. Breast milk contains microbes, antimicrobial metabolites, IgA antibodies, and cytokines that facilitate the development of the microbiome and the neonatal immune response. The microbiome is influenced by close contacts, and it evolves throughout childhood; thus, *Firmicutes* (*Staphylococcus* and *Streptococcus*) predominate in the skin of babies, followed by *Actinobacteria*, *Proteobacteria*, and *Bacteroidetes* [49,50]. Microbiota diversity increases at least during the first eight years of life, which appears to be related to a reduced dominance of *Lactobacillales* (especially of the genus *Streptococcus*) in the skin. In 14 year olds, there is greater interindividual variation in diversity than in

younger age groups; the number of *Staphylococcus* or *Streptococcus* species decreases, and the amount of *Actinobacteria* and *Proteobacteria* species increases [51].

Puberty is another stage of changes in the skin microbiota; thus, *Firmicutes* (*Streptococcus* spp.), *Bacteroidetes*, and *Proteobacteria* are abundant, while the fungal community becomes more diverse [41]. The hormonal stimulus that occurs in the post-pubertal stage entails the stimulation of the sebaceous glands, with an increase in sebum production, favoring the overgrowth and spread of lipophilic microorganisms, such as *Propionibacterium* spp., *Corynebacterium* spp., and *Malassezia* spp. [41]. At the adult stage, *Corynebacterium*, *Propionibacterium*, *Streptococcus*, and *Staphylococcus* predominate [49]; finally, in the elderly population, the number of *Firmicutes*, including *S. aureus* and *Cutibacterium* species, decreases [52,53], with the production of antimicrobial peptides also decreasing, thus increasing susceptibility to bacterial infections [49].

Jo et al. [54] investigated the skin mycobiome, showing that *Malassezia* predominated on the scalp, trunk, and arm skin of adults (age 20–30), and children (age < 14) had more diverse fungal communities, for example, Eurotiomycetes, which includes common dermatophytes, with *M. globosa* being the most predominant in children.

### 3. Skin Microbiome: Influence of Intrinsic and Extrinsic Factors

The skin microbiome depends on internal (or intrinsic) and external (or extrinsic) factors. Among the intrinsic factors, genetics, age, gender, hormones, immunity, sleep and stress factors, and metabolism must be mentioned. The exposure of the skin to external factors (UV, pollution, humidity, environmental bacteria, cosmetics, etc.) also has a great influence on the skin microbiome. Skowron et al. [55] reviewed the impact of extrinsic factors (external exposome) on the skin microbiome, and, in short, the most important are climate, sunlight (UV radiation), hygiene and cosmetics routine, and environment (air and water pollution, exposure to chemicals), with physical activity and diet also being factors that can be added.

Several studies focused on internal factors, finding that among the genetic factors that determine the skin microbiome, ethnicity seems to be secondary, although not insignificant, since some differences have been found; for example, the number of *Cutibacterium* on the armpits and scalp of males in Africa and Latin America is lower than in other ethnicities (Caucasian, African American, East Asian, and South Asian), and differences have also been found in the microbiomes of the arms of different ethnicities [56].

Differences linked to gender were also found; the female skin microbiome is characterized by a higher species diversity than that of males, probably due to several factors, such as sweat production and the influence of hormones [57].

The relationship between the skin and gut (the so-called gut–skin axis) could explain the influence of the stress factors and metabolism in the skin microbiome [58] as well as nutrition [59]. Furthermore, diet and obesity were found to influence the skin microbiome, with high-fat diets favoring the growth of *Corynebacterium*, probably because they promote skin inflammation through the expression of mycolic acid. Furthermore, the balance between *Firmicutes* and *Bacteroidetes* in obese people is altered, and, during weight loss, changes occur in the composition of the microbiota, decreasing *Firmicutes* and increasing *Bacteroidetes* [60].

The environment of a given individual also has great influence on the skin microbiome, with the profession or the type of daily activity also having an effect. Some studies suggested that the time children spend outdoors could be relevant along with other factors (e.g., cultural differences), and the constant and close contact with animals could influence the composition and diversity of the skin microbial communities in healthy people [61,62]. Some authors postulate that differences in the skin microbiome of urban and rural residents may be related to the exposure to microorganisms from the soil, water, and other factors, such as the biomass used in agriculture or livestock [63].

The external environmental conditions also have an important influence on the skin microbiome, including temperature, humidity, and sunlight. When skin is exposed to

UV radiation, several impacts may occur. The exposure of the skin to UV rays inhibits the growth of *S. aureus* and *C. acnes*; the latter is associated with a decreased production of porphyrins [64]. Furthermore, UV exposure results in a reduction in Lactobacillaceae and Pseudomonadaceae and an overall increase in Cyanobacteria [65]. Additionally, it has been shown that repetitive and intense exposure to UV radiation may increase the skin's vulnerability to infections and worsen associated symptoms, e.g., herpes simplex virus (HSV) [66]; on the contrary, *Staphylococcus aureus* was reduced by UVB radiation. However, there are benefits derived from exposure to light; thus, the antimicrobial effects of photodynamic therapy (APDT) were demonstrated [67]; some studies suggest that blue light treatment and conventional UV phototherapy may act beneficially in acne vulgaris by reducing *Corynebacterium acnes* density [68–70]. On the other hand, several studies concluded that the skin microbiome has a useful role in the protection against UV irradiation, which is linked with immune responses since TNF and IL-6 activity was observed [71].

Furthermore, using 16S ribosomal DNA and internal transcribed spacer ribosomal DNA sequencing to profile the microbiomes, Li et al. [72] studied the microbial communities of different ages and several pathways related to aging (e.g., base excision repair, biosynthesis of amino acids, pantothenate and CoA biosynthesis, and D-arginine and D-ornithine metabolism and oxidative phosphorylation, among others), concluding that the skin microbiomes may play key roles in skin aging by regulating immune responses, UV light resistance, and the biosynthesis of different substances involved in aging.

Other authors postulated that climate change, pollution, and the loss of biodiversity, together with other external factors, such as the role of environmental substances (pollen, detergents, tobacco, as well as microplastics and nanoparticles) or the increase in the consumption of fatty acids in the diet, derange the epithelial barrier, causing a leaky epithelium and resulting in microbial dysbiosis—including commensals and opportunistic pathogens—and translocation of this content into the interepithelial and sub-epithelial compartments, inducing microinflammation [73].

Finally, the impact of antibiotics on the skin microbiota should be cited. The use of antibiotics in the treatment of skin diseases is effective but may have a great impact on skin microbiota diversity. For example, orally administered doxycycline significantly reduces the number of *C. acnes* [74]; minocycline decreases the abundance of *Cutibacterium*, *Corynebacterium*, *Prevotella*, *Lactobacillus*, and *Porphyromonas* [75]; lymecycline reduces the presence of *Cutibacterium* and increases the number of *Streptococcus*, *Staphylococcus*, *Micrococcus*, and *Corynebacterium* [76], and fluoroquinolones (pefloxacin) and macrolides (erythromycin) significantly decrease the number of *C. acnes* [77].

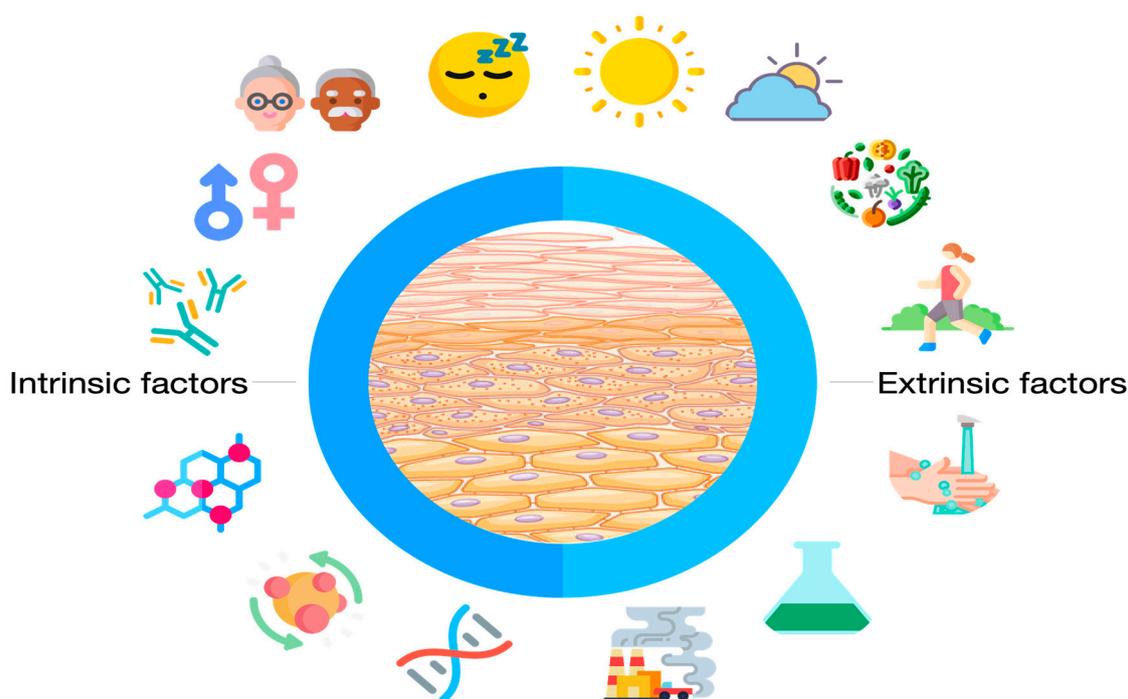
Despite the lack of studies, some research showed that cosmetics may affect the skin microbiome's diversity. For example, Bouslimani et al. [78] reported that antiperspirants and foot powders increased the diversity of the skin microbiome, but the effect disappeared after stopping antiperspirant application, and, in contrast, arm and face lotions had little effect on bacterial communities and archaea.

Other cosmetics, such as soap, effectively reduce the number of microorganisms. However, too frequent use of soap or other antiseptics for hand disinfection can alter the microbiome and reduce its diversity due to damage to the skin barrier, weakening its function [55]. So, more studies are needed to elucidate the effects of cosmetics on the skin microbiota.

Clothing is also of interest when studying the skin microbiome. Skin–clothing contact can cause microorganism transference and the formation of a so-called textile and volatile microbiome. Microorganisms that adhere to the fibers can use the lipid components of sebum and dirt as a substrate and produce volatile substances as byproducts that contribute to unpleasant odors [55]. Furthermore, Ferro de Oliveira et al. [79] investigated the role of clothing on the skin microbiome, finding that different textile compositions can lead to the growth or inhibitions of certain microorganisms. For example, *Staphylococcus hominis* had a high affinity for cotton but did not grow in fleece and viscose; *Staphylococcus* spp. showed

significant adhesion to textile fibers; and cotton and wool enhanced the growth of different bacteria species, including *Staphylococcus epidermidis*, *Enhydrobacter* spp., *Cutibacterium* spp., and *Micrococcus* spp. Additionally, cellulose-based fibers exhibited low microbial growth rates for most axillary bacteria, except for *Staphylococcus* spp., and polyester facilitated a greater growth of *Cutibacterium* spp., *Enhydrobacter* spp., and *Micrococcus* spp. Therefore, the authors revised the existing bioactive textiles based on their specificity against microorganisms, i.e., antifungal, antibacterial, and antiviral textiles, and concluded that this knowledge may be an opportunity for the development of microbiota-friendly textiles or antimicrobial textile products capable of targeting specific populations of the skin microbiota with the aim of alleviating skin disorders, allergies, or bad odors, preventing growth and the spread of pathogenic microorganisms [79].

Figure 3 summarizes the intrinsic (genetics, age, gender, hormones, immunity, sleep and stress factors, and metabolism) and external factors (climate, sunlight, hygiene, and cosmetics routine, air and water pollution, exposure to chemicals, physical activity, and diet) that influence the skin microbiome.



**Figure 3.** Intrinsic and extrinsic factors that influence the skin microbiome.

#### 4. Skin Microbiome and Dermatological Disorders

It is very well known that the skin microbiome plays an important role in developing and maintaining homeostasis and in the regulation of the host immune system. Belkaid and Segre [39] summarized the “dialogue between skin and immune system” as follows: Microorganisms present on the surface and skin appendages (bacteria, fungi, viruses) can produce antimicrobial peptides and regulate the production of antimicrobial peptides by keratinocytes as well as the production of immune mediators, such as complement and IL-1. These molecules can directly or indirectly improve skin immunity by improving cellular microbicidal function and by promoting cytokine production and the recruitment of effector cells. Furthermore, IL-17 production by the microbiota may promote the effector function of keratinocytes against invading microbes. Additionally, skin-residing microbes can release defined metabolites that can be captured directly by skin-residing dendritic cells [39].

Skin disorders such as acne, atopic dermatitis, and psoriasis have all been associated with dysbiosis of the skin microbiota. Dysbiosis is the alteration in the composition,

activity, or distribution of the cutaneous microbiota. According to Mustari et al. [80], three mechanisms can be involved: (1) overgrowth of a microbiota member (e.g., *Cutibacterium acnes* in acne); (2) elimination of a microbiota member; and (3) invasion by non-member microorganisms (e.g., *Staphylococcus aureus* in atopic dermatitis) [80]. Dysbiosis is associated with various dermatological conditions, such as psoriasis, atopic dermatitis (AD), seborrheic dermatitis, acne, rosacea, vitiligo, hidradenitis suppurative, lepra, and others linked to viruses, but it is not entirely clear if the changes in the microbiota cause diseases or whether certain conditions cause an imbalance in microbial communities [81].

The gut microbiome also plays a role in some skin disorders; there appears to be a bidirectional link between the gut and the skin, which in turn is linked to the body's homeostasis, the so-called gut–skin axis. The gut microbiota modulates the functionality and composition of the innate and adaptive immune system, and vice versa. This fact could explain why some skin diseases are linked to intestinal dysbiosis and an imbalance of skin homeostasis, suggesting a role of the intestinal microbiota in the pathogenesis of several inflammatory skin diseases [82]. Multiple studies support a connection between them, and several skin diseases associated with gastrointestinal disorders, but more studies are needed to attribute a cause-and-effect relationship between the gut microbiome and dermatological conditions. For example, between 10% and 25% of patients with gastrointestinal diseases, such as Crohn's and celiac disease and ulcerative colitis, also have associated skin disorders, specifically skin ulcers and psoriasis [83].

Inchingolo et al. [81] postulated that the intestinal microbiota contributes to the allostasis and homeostasis of the integumentary system after any inflammatory process due to the relationship with innate and adaptive immunity. Proinflammatory cytokines could damage the intestinal barrier, and severe intestinal dysbiosis provokes inflammation beyond the intestinal, and therefore low-grade systemic inflammation with skin involvement.

Many studies have shown that the overgrowth (or decline) of pathogens on the skin is a common occurrence in various skin diseases and conditions. The main changes are summarized in Table 1.

**Table 1.** Changes in the skin microbiota profile is the most frequent skin disorders.

Skin Disease or Condition	Microbiome Disbalance	Reference
Acne	Proliferation or presence of certain strains of <i>Cutibacterium acnes</i>	Sánchez-Pellicer et al., 2022 [82]; Dreno et al., 2017 [84]; 2020 [85]; Condrò et al., 2022 [86]
	The relative abundance of <i>S. epidermidis</i> increases at the expense of <i>C. acnes</i>	Xu et al., 2019 [75]
	<i>C. acnes</i> inhibits the development of <i>S. epidermidis</i>	Dagnielle et al., 2022 [87]; Claudel et al., 2019 [88]
	<i>Firmicutes</i> spp., <i>Proteobacteria</i> spp., <i>Actinobacteria</i> spp., <i>Staphylococcus</i> spp., and <i>Streptococcus</i> spp. are increased; <i>S. epidermidis</i> is decreased	Weng & Cheng, 2022 [89]
Atopic Dermatitis	<i>Staphylococcus aureus</i> skin colonization	Wollina, 2017 [90]
	Increase in the abundance of <i>S. aureus</i> and loss in anaerobic species	Fyhrquist et al., 2019 [91]
Psoriasis	Increase in <i>Streptococcus</i> and <i>Staphylococcus</i> and decrease in <i>Malassezia</i> and <i>Cutibacterium</i>	Lewis et al., 2019 [92]
	Taxonomic diversity reduction; increase in <i>Firmicutes</i> and <i>Actinobacteria</i>	Alekseyenko et al., 2013 [93]
	Decrease in <i>Staphylococcus epidermidis</i> and <i>Cutibacterium acnes</i> that leads to a higher colonization with <i>Staphylococcus aureus</i>	Chang et al., 2018 [94]

Table 1. Cont.

Skin Disease or Condition	Microbiome Disbalance	Reference
	<i>Demodex folliculorum</i> mites that are suspected carriers of <i>Bacillus oleronius</i>	Sánchez-Pellicer et al., 2022 [82]
Rosacea	Involvement of <i>Staphylococcus epidermidis</i> , <i>Demodex folliculorum</i> , <i>Helicobacter pylori</i> , <i>Bacillus oleronius</i> , and <i>Chlamydia pneumonia</i> in pathogenesis	Zhu et al., 2023; Lacey et al., 2007; Murillo et al., 2014; Kim HS et al., 2020; Yuan et al., 2020 [95–99]
	Higher proportions of <i>Firmicutes</i> and <i>Proteobacteria</i> Lower proportions of <i>Actinobacteria</i>	Weng & Chen, 2022 [89]
	Role of <i>Malassezia</i>	Paulino et al., 2016 [100]
Seborrheic Dermatitis	<i>Acinetobacter</i> , <i>Staphylococcus</i> , and <i>Streptococcus</i> dominated the skin microbiome of lesions	Tanaka et al., 2016 [101]
	Over-colonization of <i>Staphylococcus epidermidis</i>	An et al., 2017 [102]
	Dandruff (middle SD) increased the colonization with <i>Malassezia restricta</i> and <i>Staphylococcus</i> species	Wang et al., 2015 [103]
Hidradenitis suppurativa	<i>Propionibacterium</i> may be part of the pathogenesis via a dysbiotic condition of the microbiota	Ring et al., 2017 [104]
Tinea pedis	Increase in fungal diversity and decrease in bacterial diversity compared to healthy controls Increase in <i>Trichophyton rubrum</i> Most prevalent bacteria phyla: <i>Firmicutes</i> , <i>Actinobacteria</i> , and <i>Proteobacteria</i> ; <i>Staphylococcus</i> (more than 30% of the bacterial genera)	McLoughlin et al., 2022 [105]

Acne is a chronic inflammatory skin disease characterized by the presence of comedones, papules, pustules, and sometimes nodules and scars that appear in oily areas of the face and upper trunk. The pathogenesis of acne vulgaris is multifactorial and involves an increased production of cutaneous sebum, hyperplasia of sebaceous glands due to the androgenic influence, and infra-infundibulum hyper-keratinization, which leads to ductal obstruction; proliferation, or presence of certain strains of *Cutibacterium acnes* and the infiltration of inflammatory cells. In terms of skin microbiota changes, *C. acnes* is considered the most likely acne pathogen, but there are several recognized sub-groups of *C. acnes* (I, II, and III) and different ribotypes [82]. Thus, more investigations are needed to clarify its role in the pathogenesis of acne. In addition to its role in inflammation, *C. acnes* also intervenes in the homeostasis of the skin microbiome by interacting with other skin microorganisms, such as *Staphylococcus epidermidis*, *Streptococcus pyogenes*, and *Pseudomonas* species. In the microbiome of healthy skin, *S. epidermidis* may limit the over-colonization with *C. acnes* strains and reduce *C. acnes*-induced IL-6 and TNF- $\alpha$  production by keratinocytes. In turn, *C. acnes* may limit the proliferation of *S. aureus* and *S. pyogenes* by promoting triglyceride hydrolysis and propionic acid secretion, which collaborates in the maintenance of the acidic pH in the pilosebaceous follicle. Furthermore, in the pilosebaceous follicles, *C. acnes* inhibits the development of *S. epidermidis* by the same mechanisms, hydrolyzing sebum triglycerides, secreting propionic acid, and maintaining the acidic pH of the pilosebaceous follicle [87,88]. In acne, a modified profile of *C. acnes* is observed, with different phylotypes differing between patients with and without acne [84–86].

Weng and Cheng [89] carried out a comprehensive review in which studies on the relationships between the skin microbiome and acne vulgaris, rosacea, and skin aging were included. Authors summarized that in acne *Firmicutes* spp., *Proteobacteria* spp., *Actinobacteria* spp., *Staphylococcus* spp., and *Streptococcus* spp. were increased, while *S. epidermidis* were decreased [89].

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting approximately 20% of children. In 95% of cases, AD's first manifestation appears within the first 5 years of

life, and, in 25% of the cases, AD continues into adulthood [106]. Genetic and epigenetic factors modulate AD: exposure to indoor and outdoor allergens and pollutants, nutrition, and microbiome are considered to influence and contribute to the development and severity of AD [90]. AD is characterized by an abnormal immune response; high levels of pro-inflammatory cytokines (e.g., IL-4, IL-13, IL-22) promote skin inflammation and contribute to barrier derangement and dysfunction. Due to inflammation, the skin may produce antimicrobial peptides (AMPs), such as defensins and cathelicidins, which can disbalance the skin microbiome [107].

AD has long been linked with *Staphylococcus aureus* skin colonization; disease outbreaks are associated with a spread of *S. aureus* in injured areas of the skin and a substantial loss of biodiversity in the skin microbiome. Staphylococcal exoproteins and superantigens cause inflammatory reactions in the host [90]. Fyhrquist et al. [91] also reported a significant increase in colonization by *S. aureus* and a loss of anaerobic species in AD. Koh et al. [108] appointed that *S. aureus* isolated from patients with AD also expresses higher levels of virulence factors and a propensity to develop biofilms to promote its colonization. So, therapies aim to reduce *S. aureus* (with antimicrobials) but also aim to balance the diversity of the skin microbiome.

Psoriasis is an immune-mediated inflammatory skin disease, the development of which is linked to both genetic factors and external triggers [109,110]. However, its pathogenesis is still not fully understood, and the influence of the gut and skin microbiota is still being investigated. Psoriasis is characterized by multiple erythematous lesions with scaly plaques that arise mainly on the elbows, knees, scalp, navel, and lower back, but, in some cases, the disease spreads throughout the body in the form of erythroderma. Increased vascularization can also be found, which allows the accumulation of inflammatory subpopulations of neutrophils, dendritic cells, and T lymphocytes.

Psoriasis is frequently associated with inflammation in other organ systems. Thus, 7–11% of patients with inflammatory bowel disease (IBD) are also diagnosed with psoriasis, reflecting a strong association with gastrointestinal inflammation. Changes in the gut microbiome in psoriasis are similar to those observed in patients with IBD; in both diseases, *Faecalibacterium prausnitzii*, *Bifidobacterium* spp., *Lactobacillus* spp., *Parabacteroides*, and *Coprobacillus* were underrepresented, while the abundance of *Salmonella* sp., *Campylobacter* sp., *Helicobacter* sp., *Escherichia coli*, *Alcaligenes* sp., and *Mycobacterium* sp. was increased [111]. Other studies showed that psoriatic exacerbation was considered to be associated with increased colonization of *Staphylococcus aureus*, *Candida albicans*, and *Malassezia* in the skin and gut [112]. Another similarity between psoriasis and IBD is the reduced abundance of two beneficial bacteria species (*Parabacteroides* and *Coprobacillus*) observed in patients with psoriasis and psoriatic arthritis and in those with IBD [113]. Thus, it is generally accepted that the inflammatory and immune mechanisms of psoriasis are based on the dysregulation of the gut–brain–skin axis [114].

Additionally, a decrease in *Bacteroidetes* and an increase in *Firmicutes* in the intestines of patients with psoriasis compared to control patients were also found [115]. Similar findings were reported by other authors who found an increased abundance of *Firmicutes*, *Proteobacteria*, and *Actinobacteria*, together with a decrease in *Bacteroidetes* in the gut microbiome of patients with psoriasis [116,117].

Other recent studies confirmed this relationship between the gut microbiota and psoriasis. Zang et al. [118] identified nominal protective roles of *Bacteroidetes* and *Prevotella* in the risks of acquiring psoriasis. Moreover, some bacterial taxa were recognized as risk factors, including *Lactococcus*, *Ruminiclostridium* 5, and *Eubacterium fissicatena*; but *Odoribacter* demonstrated a protective effect against psoriasis [119].

When revising the role of the skin microbiome in psoriasis, studies have shown relative increases in *Streptococcus* and *Staphylococcus* and decreases in *Malassezia* and *Cutibacterium* [92].

On the other hand, Alekseyenko et al. [93], comparing swap samples of patients with psoriasis and healthy controls, demonstrated that the microbiome of psoriatic lesions

is characterized by an increase in *Firmicutes* and *Actinobacteria* and a general taxonomic diversity reduction. Additionally, Chang et al. [94] found that the microbiome of psoriatic skin has reduced stability compared to the microbiome of healthy skin. Further, the loss of community stability and decrease in immunoregulatory bacteria such as *Staphylococcus epidermidis* and *Propionibacterium acnes* may result in increased colonization with pathogens, such as *Staphylococcus aureus*, which can exacerbate skin inflammation along the Th17 axis [94].

Rosacea is an inflammatory chronic skin disease that appears exclusively on the central area of the face, such as the cheeks, nose, and chin, symmetrically, and on the central forehead. It is characterized by flushing, papules and pustules, telangiectasia, and sometimes phymatous alterations, which are accompanied by stinging or itching [120]. Generally, rosacea is classified into four morphologic subtypes: phymatous rosacea, papulopustular rosacea, erythematotelangiectatic rosacea, and ocular rosacea [121].

The clinical manifestations of rosacea are multifactorial and are linked to abnormal neurovascular activation, dysregulated production and release of inflammatory molecules, and overgrowth of microorganisms that naturally inhabit the skin [122].

*Demodex folliculorum* is found to be implicated in rosacea; still, Demodex is unlikely to be the only cutaneous microorganism that contributes to the disease since Demodex mites are suspected of carrying *Bacillus oleronius*, a pro-inflammatory Gram-negative bacterium that is receptive to many antibiotics recurrently used to treat rosacea [82], resulting in an amelioration of the disease when treating it with antibiotics.

The origin of rosacea development is unclear, but several factors are involved, including genetic factors, local skin immune imbalance, disorders of neuroimmune function, skin barrier dysfunction, and skin microbiota dysbiosis, as well as alterations in neurovascular circuitry [123]. The role of the microbiota in rosacea pathogenesis is supported by several sources. Studies conducted by different authors have pointed to the implication of *Staphylococcus epidermidis*, *Demodex folliculorum*, *Helicobacter pylori*, *Bacillus oleronius*, and *Chlamydia pneumonia* in the pathogenesis of rosacea [95–99]. However, there are discrepancies between the results of these investigations and the specific mechanisms by which the microorganisms are involved in the pathogenesis of rosacea are not clear as they are commensal microorganisms. More specifically, the distribution, relative abundance, mechanisms involved, and thus the role of *Cutibacterium acnes* and *S. epidermidis* in rosacea need to be further investigated to provide evidence for future probiotic therapy [124].

Finally, the aforementioned review by Weng and Chen [89] described that, in papulopustular rosacea, the proportions of *Firmicutes* and *Proteobacteria* are higher and *Actinobacteria* proportions are lower.

Seborrheic dermatitis (SD) is an inflammatory rash that appears on sebaceous areas of skin, such as the scalp, face, and trunk [102]. The incidence of SD reaches the highest point at three ages of life—infancy, puberty, and in adults over 50 years old—suggesting the role of hormones in sebum production in its pathogenesis [45]. SD is generally associated with *Malassezia*; however, its role in the development of SD is still poorly understood [100]. Some studies suggest that there are other microorganisms involved. For example, Tanaka et al. [101] found that *Acinetobacter*, *Staphylococcus*, and *Streptococcus* are the dominant genera on the skin microbiome of lesional areas affected with SD compared to healthy skin; An et al. [102] found that patients with SD have a significant over-colonization of *Staphylococcus epidermidis*, concluding that this high colonization along with alteration of the skin barrier function, which is more permeable, contributes to the appearance of SD.

Dandruff, considered a form of middle seborrheic dermatitis, has also been found to be linked to *Malassezia*. A study performed by Wang et al. [103], using molecular techniques, showed increased colonization of *Malassezia restricta* and of *Staphylococcus* species when compared to healthy scalps.

Other skin disorders have also been associated with skin microbiome dysbiosis. Hidradenitis suppurativa was found to be linked to the dermal microbiota as the microbial composition differs significantly from that of healthy individuals. Overall, the following

five types of microbes were identified: *Corynebacterium* spp. (type I), *Acinetobacter* and *Moraxella* spp. (type II), *Staphylococcus epidermidis* (type III), *Peptoniphilus* spp. and *Porphyromonas* (type IV), and *Propionibacterium acnes* (type V), suggesting that *Propionibacterium* may be involved on its pathogenesis [104].

Tinea pedis is a dermatophyte infection that especially affects the interdigital network and/or the sides of the feet. Different factors have been found that may be related to its appearance, such as sweating, occlusive footwear, trauma, and an immunocompromised state, among others. When studying the skin microbiota, epidermal samples from patients with tinea pedis have been shown to exhibit decreased bacterial diversity and increased fungal diversity compared to healthy controls; an increase in *Trichophyton rubrum* was observed in patients with tinea pedis compared to healthy controls, with the most prevalent bacterial phyla being *Firmicutes*, *Actinobacteria*, and *Proteobacteria*, while *Staphylococcus* constituted more than 30% of the bacterial genera [105].

Finally, it is worth mentioning the relationship between the microbiome and melanoma. Fortman et al. [125] revised the studies related to the microbiome and cancer, showing that there is evidence that the gut microbiome can alter the responses to chemotherapy and immune checkpoint inhibitors (ICIs). Authors concluded that preclinical and clinical studies have demonstrated the effects of the gut microbiome's modulation upon ICI response and immune-related adverse event development in advanced melanoma, with significant evidence supporting the ability of the gut microbiome to improve ICIs' responses in advanced melanoma through an increased intake of dietary fiber and a fecal microbiome transplant.

## 5. Nutribiotics: An Opportunity to Improve Skin Health

The history of probiotics can be tracked back to ancient times, nearly 10,000 years ago, since probiotic microorganisms and fermented products, such as kefir, kumis, bread beer, and wine, were very frequently used for nutritional and therapeutic purposes [126]. Knowing that the composition of the human microbiota is directly linked with the development and function of the immune system, oral supplementation with prebiotics and probiotics could be a tool for improving overall human health, but more research is needed to better understand the interactions between the diet, the microbiome, and the immune system to design specific diets with the aim of treating various diseases [127]. Gao et al. [128] explain the immunological pathway of oral probiotics as follows: when probiotics enter, the intestinal tract can interact with the host, improving intestinal homeostasis; moreover, they take part in immunomodulation, gut microbiota homeostasis, digestion, and the absorption of nutrients, improving the intestinal mucosal barrier.

The use of probiotics in skin care is more recent since the gut-skin axis was investigated. Polak et al. [129] revised the use of prebiotics and probiotics in chronic skin diseases, finding studies mainly on atopic dermatitis (children and adults) but also on acne, chronic ulcers, seborrheic dermatitis, and burns. Later on, in a similar revision, Kianmehr et al. [130] showed that the administration of prebiotics, probiotics, and synbiotics has auspicious effects on preventing and treating various inflammatory skin disorders, such as atopic dermatitis and acne [131,132]. The oral administration of probiotics affects the intestinal microbiome and can improve skin conditions, such as atopic dermatitis, acne, or rosacea [133,134]. Moreover, other studies showed that using probiotics during gestation and early life can reduce the incidence and severity of atopic dermatitis via immune modulation and by promoting the maturation of the gut barrier's function [130,135,136]. Additionally, probiotics were investigated to treat different allergy illnesses, including atopic dermatitis, asthma, allergic rhinitis, and food allergy [137]. Despite of this, Małolepsza and Dembowski [138], after reviewing several studies, concluded that alterations in the intestinal microbiome play an important role not only in the development and aggravation of many skin diseases but also influence skin aging, although more research is necessary to evaluate the impact of probiotics.

On the other hand, Pimentel et al. [139] revised the health effects of postbiotics, including skin conditions both in vitro and in vivo, and Mehta et al. [25] discussed the

potential of para-probiotics and postbiotics to modulate the immune system. There are also studies about the topical use of pre-, pro-, and postbiotics for skin care, but this issue exceeds the aim of this work.

The following sections describe the use of pre-, pro-, syn-, post-, and para-probiotics in skin care. Table 2 summarizes the clinical studies.

**Table 2.** Oral pre-, pro-, syn-, post-, and para-probiotics used in skin care (clinical studies).

Skin Disease or Condition	Pre/Pro/Synbiotics	Key Results *	Reference
Acne	<i>Lactobacillus acidophilus</i> and <i>Lactobacillus bulgaricus</i>	80% clinical improvement	Siver 1961 [140]
	<i>L. acidophilus</i> and <i>Bifidobacterium bifidum</i>	Adjuvant in antibiotic therapy	Marchetti et al., 1987 [141]
	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus delbrueckii bulgaricus</i> , and <i>B. bifidum</i>	67% reduction in lesion counts after twelve weeks	Jung et al., 2013 [133]
	<i>Lactobacillus rhamnosus</i> SP1	Adult acne improvement 32% reduction in IGF-1 and a 65% increase in FOXO1	Fabbrocini et al., 2016 [142]
	<i>B. lactis</i> W51, <i>B. lactis</i> W52, <i>L. acidophilus</i> W55, <i>L. casei</i> W56, <i>L. salivarius</i> W57, <i>L. lactis</i> W58	Increase in IL-10 levels	Rahmayani et al., 2019 [143]
	<i>Lactobacillus paracasei</i> NCC2461	Inhibition of CD-4+ T cell activation and induction of the anti-inflammatory cytokines IL-10 and TGF- $\beta$ .	Benyacoub et al., 2014 [144]
	Konjac glucomannan hydrolysates + ( <i>L. casei</i> , <i>L. plantarum</i> , <i>L. gasseri</i> , <i>L. lactis</i> )	Inhibition of bacteria growth	Al-Ghazzewi et al., 2010 [145]
	<i>Escherichia coli</i> Nissle 1917	80% clinical improvement	Manzhali et al., 2016 [146]
	<i>Bifidobacterium breve</i> BR03 DSM 16604, <i>Lactocaseibacillus casei</i> LC03 DSM 27537, and <i>Ligilactobacillus salivarius</i> LS03 DSM 22776 + <i>Solanum melongena</i> and <i>Echinacea</i> botanical extract	Decrease in the number of acne lesions, rate of desquamation, rate of sebum secretion, and presence of <i>C. acnes</i>	Rinaldi et al., 2022 [147]
	<i>Nitrosomonas eutropha</i>	Significant reduction in overall severity Reduction in the number of inflammatory lesions	AOBiome [148]
Atopic dermatitis	Oligosaccharide prebiotic-supplemented formula	Lower 5-year cumulative incidence of AD	Arslanoglu et al., 2012 [149]
	Mixture of neutral oligosaccharides and pectin-derived acidic oligosaccharides	Primary prevention of AD in low-atopy-risk infants	Grüber et al., 2010 [150]
	<i>Lactobacillus rhamnosus</i> GG	Improvement in SCORAD Decrease in TNF- $\alpha$ and fecal $\alpha$ 1-antitrypsin	Isolauri et al., 2000 [151]
	<i>Lactobacillus rhamnosus</i> GG	Anti-inflammatory activity Increased levels of IL-10 and (TGF- $\beta$ 2)	Pessi et al., 2000; Rautava et al., 2002 [152,153]
	<i>Lactobacillus rhamnosus</i> 19070-2 and <i>Lactobacillus reuteri</i> DSM 12246	Moderate improvement in clinical severity	Rosenfeldt et al., 2003 [154]
	<i>Lactobacillus rhamnosus</i> GG	Decreased proportions of IgA- and IgM-secreting cells	Nermes et al., 2011 [155]
	<i>Bifidobacterium lactis</i> HN019 and <i>Lactobacillus rhamnosus</i> HN001	Improvement in natural killer cell and phagocytic activity	Ouwehand et al., 2009 [156]

Table 2. Cont.

Skin Disease or Condition	Pre/Pro/Synbiotics	Key Results *	Reference
Atopic dermatitis	<i>Lactobacillus rhamnosus</i> GG, <i>Lactobacillus acidophilus</i> GKA7, <i>Bifidobacterium longum</i> GKL7, <i>Lactobacillus plantarum</i> GKM3, <i>Bifidobacterium bifidum</i> GKB2, and <i>Lactobacillus paracasei</i> GKS6 + inulin, isomalto-oligosaccharides, and fructo-oligosaccharides	Improvement in EASI with no adverse effects Increase in <i>Bacteroides fragilis</i> and <i>Lactobacillus acidophilus</i>	Choy et al., 2023 [157]
Psoriasis	<i>Bacillus indicus</i> (HU36), <i>Bacillus subtilis</i> (HU58), <i>Bacillus coagulans</i> (SC208), <i>Bacillus licheniformis</i> (SL307), and <i>Bacillus clausii</i> (SC109) + fructooligosaccharides, xylooligosaccharides, and galactooligosaccharides	Improvement in PASI, DLQI, inflammatory markers, and skin thickness	Buhas et al., 2023 [158]
	<i>Lactobacillus sporogenes</i>	Lesion involution in pustular psoriasis	Vijayashankar and Raghunath, 2012 [159]
Rosacea	<i>Escherichia coli</i> Nissle 1917	Improvement in quality of life and clinical signs of dermatosis Increase in IgA levels to normal values Suppression of the proinflammatory cytokine IL-8	Manzhali et al., 2016 [146]
	Doxycycline (40 mg/day) + <i>Bifidobacterium breve</i> BR03 and <i>Lactobacillus salivarius</i> LS01	No relapse or flare-up of disease	Fortuna et al., 2016 [160]
Seborrheic dermatitis	<i>Lactobacillus paracasei</i> NCC 2461	Improvement in adherent dandruff, erythema, and the global clinical score	Reygagne et al., 2017 [161]
Wound healing	<i>Lactobacillus plantarum</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i> , and <i>Lactobacillus rhamnosus</i>	Lower incidence of surgical site infections, foot ulcer infection, and burn infections	Fijan et al., 2019 [162]
	<i>Lactobacillus plantarum</i> HY7714	Improvement in skin hydration, gloss, elasticity Decreased wrinkle depth	Lee et al., 2015 [163]
Ageing and photoaging	<i>Lactobacillus johnsonii</i> La-1	Restoration of CD1a Langerhans cell markers after UV radiation	Peguet-Navarro et al., 2008 [164]
	<i>Lactobacillus johnsonii</i> La-1, lycopene, and $\beta$ -carotene	Increase in intercellular adhesion molecule-1 (ICAM-1) **	Marini et al., 2014 [165]
	Butyrate supplementation	Counterbalance age-related microbiota dysbiosis	Boyajian et al., 2021 [166]
	<i>L. casei</i> Shirota <i>B. animalis</i> ssp. <i>lactis</i> HN019	Improvement in innate immunity	Dong et al., 2013; Miller et al., 2017 [167,168]
	<i>Bifidobacterium longum</i> subsp. <i>longum</i> BB536, <i>B. longum</i> subsp. <i>infantis</i> M-63, <i>Bifidobacterium breve</i> M-16V and <i>B. breve</i>	Improvement in mental condition and bowel movement Decrease in body mass index	Inoue et al., 2018 [169]
	<i>Lactobacillus johnsonii</i> + carotenoids	Prevention of UV-DL-induced decrease in Langerhans cell density Increase in factor XIIIa+ type I dermal dendrocytes Reduction in dermal inflammatory cells	Bouilly-Gauthier et al., 2010 [170]

Table 2. Cont.

Skin Disease or Condition	Pre/Pro/Synbiotics	Key Results *	Reference
Other skin care: skin barrier and hydration	<i>B. breve</i> strain Yakult + galactooligosaccharides (in fermented milk)	Optimum level of skin hydration, and decreased cathepsin L-like endopeptidase activity and phenol content in serum and urine	Kano et al., 2013 [171]
	<i>L. casei</i>	Reduction in transepidermal water loss (TEWL) and skin flakiness	Saito et al., 2017 [172]
Other skin care: melasma	<i>Lactococcus lactis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium infantis</i> , and <i>Bifidobacterium bifidum</i> , +fructo-oligosaccharide, skim milk powder, lactose, maltodextrin, and citric acid	Reduction in melasma score	Piyavatin et al., 2020 [173]
Systemic lupus erythematosus	<i>L. helveticus</i> , <i>B. infantis</i> , <i>B. bifidum</i> + fructo-oligosaccharides	Decrease in systemic inflammation Mitigation of SLE disease activity	Widhani et al., 2022 [174]
	<i>L. rhamnosus</i> GG		Österlund et al., 2007 [175]
Oral mucositis	Kefir containing <i>Lactobacillus</i> spp., and <i>Bifidobacterium</i> spp.		Topuz et al., 2008 [176]
	<i>L. brevis</i> CD2		Sharma et al., 2012 [177]
	<i>B. longum</i> , <i>L. lactis</i> , and <i>Enterococcus faecium</i>	Protective effect against oral mucositis in patients with cancer	Jiang et al., 2019 [178]
	<i>L. brevis</i> CD2		De Sanctis et al., 2019 [179]
	<i>L. plantarum</i> MH-301, <i>B. animalis</i> subsp. <i>Lactis</i> LPL-RH, <i>L. rhamnosus</i> LGG-18, and <i>L. acidophilus</i>		Xia et al., 2021 [180]
	<i>Bacillus clausii</i>		Mirza et al., 2022 [181]
Atopic dermatitis	Heat-killed <i>Lactobacillus plantarum</i> + mixture of <i>Lactobacillus rhamnosus</i> GG, <i>Lactobacillus acidophilus</i> GKA7, <i>Lactococcus lactis</i> GKL2, <i>Lactobacillus casei</i> GKC1, <i>Lactobacillus paracasei</i> GKS6, <i>Bifidobacterium bifidum</i> GKB2, and <i>Bifidobacterium lactis</i> GKK2 + inulin, galacto-oligosaccharides, and fructo-oligosaccharides	Improvement in AD severity Improvement in the diversity of gut microbiome	Wang et al., 2022 [182]
	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BS01 (LMG P-21384), <i>Lactocaseibacillus rhamnosus</i> LR05 (DSM 19739), and <i>Lactiplantibacillus plantarum</i> LP14 (DSM 33401) (Atopicina <sup>®</sup> , Milan, Italy)	Reduction in severity scores: erythema, edema/papules, excoriation, TIS, and PRURIScore	Colombo et al., 2023 [183]
Aging and Photoaging	Heat-killed <i>Lactococcus lactis</i> H61 cells	Antioxidant activity	Kimoto-Nira 2018 [184]
Other skin care: skin barrier and hydration	Heat-killed <i>L. lactis</i>	Decrease in melanin content and cheek elasticity Increase in sebum content	Kimoto-Nira et al., 2012 [185]

\* Clinical studies. \*\* In prevention of polymorphic light eruption.

### 5.1. Acne

As mentioned above, the gut and skin microbiomes influence each other and contribute to skin health through immune modulation. The preservation of skin homeostasis and the reinforcement of the skin's barrier function is one of the major objectives in skin care, and the axis gut-skin may take part in it [186].

Probiotics aim to modify the skin's environment to prevent over-colonization of *C. acnes* and other bacteria linked to acne. It has been shown that probiotics directly inhibit *C. acnes* via the synthesis of antibacterial proteins and organic acids by certain bacterial strains. Additionally, a large-scale review on acne vulgaris concluded that oral probiotic administration was associated with a decrease in acne breakouts [187].

One of the first studies was performed by Robert H. Sawyer in 1961, who reported on the potential benefits of probiotic *Lactobacillus*. He followed up 300 patients who consumed commercial probiotics, that is, Lactinex<sup>®</sup> (Benton, UK) tablets comprising a mixture of *L. acidophilus* and *L. bulgaricus*. The protocol consisted of 8 days of an oral probiotic, a 2-week washout, and another 8 days of treatment. An improvement of 80% was found, with it being more notable in cases of inflammatory acne [140]. Later on, similar results were found in studies performed in patients under antibiotic therapy with supplementation of oral probiotics *L. acidophilus* and *Bifidobacterium bifidum* as adjuvant therapy [141]. In 2018, Mottin et al. [188] carried out a review of the main strains used in the treatment of acne and atopic dermatitis, finding that those that showed the highest potential to control acne were *Staphylococcus*, *Streptococcus*, *Lactococcus*, *Lactobacillus*, and *Enterococcus*, and *Vitreoscilla filiformis*, *Staphylococcus epidermidis*, and species of *Lactobacillus* and *Bifidobacterium* in the treatment of atopic dermatitis.

In addition, other studies demonstrated that antibiotics and oral probiotics can provide a synergistic effect, especially in inflammatory acne. A randomized, prospective open-label trial demonstrated that the consumption of *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *B. bifidum* was as effective as minocycline in the treatment of acne, with a 67% reduction in lesions after twelve weeks of oral treatment, finding fewer side effects [133].

Another randomized controlled study with twenty subjects showed that the oral administration of *Lactobacillus rhamnosus* SP1 concluded with an improvement or marked improvement in adult acne compared to the placebo [142]. Researchers also measured gene expression on the skin of IGF-1, a hormone involved in acne development, and FOXO1, a transcription factor whose deficiency is associated with acne pathogenesis. The intervention also showed a 32% reduction in IGF-1 and a 65% increase in FOXO1 [142].

Other studies focused on interleukin-10 serum levels in acne vulgaris before and after 30 days of oral probiotics, which was a sachet containing *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W55, *L. casei* W56, *L. salivarius* W57, and *L. lactis* W58 with total bacterial cells > 10<sup>8</sup> CFU. Results showed a significant increase in IL-10 levels after this therapy [143].

Additionally, in an in vitro cell culture skin model, the probiotic strain *Lactobacillus paracasei* NCC2461 demonstrated dose-dependent inhibition of CD-4+ T cell activation and induction of the anti-inflammatory cytokines IL-10 and TGF- $\beta$  [144].

Moreover, in a review performed by Goodarzi et al. [189], the authors concluded that probiotics can be effective as an adjunct therapy both in topical or oral administrations by preventing the growth of opportunistic bacteria or by controlling inflammation. They suggested that, despite numerous in vitro and in vivo studies, interventional studies using more samples and long-term follow-ups to demonstrate the effectiveness of these type of probiotics and determine potential advantages and disadvantages are needed.

Other studies combine probiotics and plants in oral formulations. For example, Tolino et al. [190] conducted a double-blind clinical trial in men with mild to moderate acne treated with an oral supplement containing probiotics, biotin, vitamin E, zinc, nicotinamide, beta-sitosterol, and *Boswellia serrata* extract. After 12 weeks of treatment, these patients presented clinical improvement, which was shown by the reduction in the Global Acne Grading System (GAGS) score [190].

Oral synbiotics were also investigated. In 2010, Al-Ghazzewi et al. [145] studied the capacity of konjac glucomannan hydrolysates and probiotics (*L. casei*, *L. plantarum*, *L. gasseri*, *L. lactis*) to inhibit *C. acnes*, finding that significantly inhibited the growth of bacteria, suggesting further research to confirm the use of this type of synbiotics as a therapeutic or prophylactic [145].

The *Escherichia coli* Nissle 1917 strain has also been used in clinical trials in patients with acne. Manzhaliy et al. [146] performed a study in which this strain was orally administered to 82 patients with intestinal-borne dermatoses (some of them were diagnosed with acne, and others with papular-pustular rosacea and seborrheic dermatitis). They compared two groups of patients: one group of patients were treated with conventional topical therapy, and other with the probiotic *E. coli* Nissle 1917 strain administered orally for one month. A total of 89% of the patients treated with *E. coli* Nissle 1917 improved significantly, while 56% improved in the group treated with the conventional therapy. After studying the composition of gut microbiota and other parameters, the authors concluded that the *E. coli* Nissle 1917 strain was able to restore the intestinal microbiota, protect the intestinal barrier, and ameliorate the mentioned diseases [146].

Rinaldi et al. [147] evaluated the efficacy of a mixture of the probiotic strains *Bifidobacterium breve* BR03 DSM 16604, *Lactocaseibacillus casei* LC03 DSM 27537, and *Ligilactobacillus salivarius* LS03 DSM 22776 combined with a botanical extract of *Solanum melongena* and *Echinacea* in subjects with mild to moderate acne over an 8-week study period through a randomized, placebo-controlled clinical trial. Results showed a decreased presence of *C. acnes*, number of acne lesions, rate of sebum secretion, and rate of desquamation in patients who were treated with the probiotic mixture and the botanical extract as well as the mixture of both, concerning placebo treatment. The most notable effects were observed with the probiotic mix plus the botanical extract [147].

The ammonia-oxidizing bacteria *Nitrosomonas eutropha* was also used to treat adult patients with mild or moderate acne, finding that, after 12 weeks of treatment, a significant reduction in overall severity was seen, along with as a tendency of a reduction in the number of inflammatory lesions compared to the control group [148].

Topic probiotics could also be useful in treating acne. The production of short-chain fatty acids (such as succinic acid) on the skin can inhibit *C. acnes* growth [191]. Lactic acid [192] and ceramide [193] produced after topical probiotic administration showed direct antimicrobial activity against *C. acnes*.

Additionally, Kang et al. [194] used a cell-free culture supernatant from *E. faecalis* SL-5 in patients with mild to moderate acne with a topical application. The study concluded that this bacteriocin was able to reduce inflammation; thus, researchers suggested that *E. faecalis* could be an alternative option in future acne therapy [194].

Additionally, a bacteriocin produced by *Lactococcus* sp. HY499 exerted an inhibitory effect on inflammatory and pathogenic bacteria in the skin, such as *S. epidermidis*, *Staphylococcus aureus*, *S. pyogenes*, and *P. acnes*, without affecting the growth and proliferation of fibroblasts. The authors recommended this bacteriocin as an antimicrobial in cosmetic formulations [195].

## 5.2. Atopic Dermatitis

There are few studies about the use of oral prebiotics to prevent atopic dermatitis. A meta-analysis by Osborn and Sinn [196] analyzed 4 studies (1218 infants) exploring the effect of specific prebiotics in the prevention of allergy. They found a significant reduction in eczema when using a fructooligosaccharide and galactooligosaccharide combination [196]. Additionally, another research study showed that infants at risk of atopy who were fed with an oligosaccharide prebiotic-supplemented formula during the first 6 months of life had a significantly lower cumulative incidence of AD in 5 years [149]. Furthermore, a formula containing a specific mixture of neutral oligosaccharides and pectin-derived acidic oligosaccharides was effective as the primary prevention of AD in low-atopy-risk infants [150]. Additionally, Kim et al. [197] demonstrated that AD-like skin lesions induced in NC/Nga mice were reduced via an oral administration of a prebiotic diet (long-chain fructooligosaccharides, inulin, or  $\beta$ -glucan), and intestinal microbiota richness and diversity were also increased with this prebiotic treatment.

Several studies confirm the positive effects of oral probiotic supplementation in AD. Fanfaret et al. [198] reviewed the most relevant articles related to the use of probiotics or

prebiotics alone and in combination, finding that the most studied probiotics strains were *Lactobacilli* and *Bifidobacteria*. However, the authors concluded that the results are difficult to interpret as, in many studies, the authors suggest that the disease may tend to improve over time in some groups of patients [198].

Oral supplementation with *Lactobacillus rhamnosus* GG (LRGG) for 1 month caused a significant improvement in the AD severity score of the atopic dermatitis (SCORAD) index with decreased levels of inflammatory markers, such as tumor necrosis factor (TNF- $\alpha$ ) and fecal  $\alpha$ 1-antitrypsin [151]. LRGG also demonstrated anti-inflammatory activity with significantly increased levels of IL-10 and transforming growth factor- $\beta$ 2 (TGF- $\beta$ 2) in patients with AD [152,153]. In addition, the administration of probiotic *Lactobacillus* strains (a mixture of *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 12246) to children with AD has been shown to result in a moderate improvement in clinical severity [154].

Other studies in vitro and in vivo confirmed the potential use of probiotics in AD. *Lactobacillus casei* (LC) is one of the most studied species. Several studies in vivo and in vitro showed that LC may exert an immunomodulatory effect, and the active component has been identified as a protein P14 that has been shown to selectively downregulate serum IgE and interleukin-4 cytokine levels as well as the AD index and scratching score in AD-like NC/Nga mice [199].

Kim et al. [200,201] investigated the immunomodulatory capacity of Duolac ATP, a mixed formulation of probiotics, composed of four different strains of probiotics: *L. casei* CBT LC5 (KCTC12398BP), *L. plantarum* CBT LP3 (KCTC10782BP), *L. rhamnosus* CBT LR5 (KCTC12202BP), and *B. lactis* CBT BL3 (KCTC11904BP), both in vitro and in vivo [200,201]. Results showed that Duolac ATP regulated IL-10 and TGF-beta expression and allowed DCs to become functionally tolerant and potentially induce Treg differentiation. Additionally, this formulation regulated transcription factors and cytokines to drive naïve T cell differentiation toward Th1 lineages. The authors concluded that this formula could be a good ally in the management of AD symptoms and serve as an immunomodulatory agent for AD [201].

In another study, the probiotic strain *Lactobacillus rhamnosus* GG decreased the proportions of IgA- and IgM-secreting cells in babies with AD. There were no significant differences in the species composition of intestinal bifidobacteria between the studied group and the control group. On the skin, bacterial counts of the genus *Bifidobacterium* versus *Clostridium coccooides* in treated and untreated infants were similar [155]. Additionally, the oral administration of probiotic bacteria *Bifidobacterium lactis* HN019 and *Lactobacillus rhamnosus* HN001 has been observed to improve natural killer cells and phagocytic activity [156].

Later studies showed that AD symptoms can be improved using *Lactobacillus paracasei* KBL382 isolated from the feces of healthy Koreans. In this study, mice with *Dermatophagoides farinae* extract (DFE)-induced AD were fed with *L. paracasei* KBL382 for 4 weeks, demonstrating that oral administration of *L. paracasei* KBL382 significantly reduced AD-associated skin lesions, epidermal thickening and serum levels of immunoglobulin E, and immune cell infiltration. Furthermore, the administration of *L. paracasei* KBL382 was able to change the gut microbiota composition in mice with AD [202].

Several studies focus on oral probiotic supplementation during pregnancy and breastfeeding. D'Elios et al. [203] revised the efficacy of the most commonly studied probiotic strains for the prevention and treatment of AD, concluding that probiotic supplementation during the prenatal and postnatal periods seems to reduce the incidence of AD in infants and children who are at high risk, especially beginning in gestation and through the first 6 months of life. The revised studies included monostrain probiotics such as *Bifidobacterium dentium* [204], *Lactobacillus rhamnosus* MP108 [205], and heat-treated *Lactobacillus paracasei* [206]; multi-strain probiotics such as *Lactobacillus acidophilus* La-5, and *Bifidobacterium animalis* subsp. *lactis* Bb-12 [207], *Lactobacillus paracasei* and *Lactobacillus fermentum* [208]; *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. *lactis* [209]; and

multi-strain *Bifidobacterium lactis* CECT 8145, *B. longum* CECT 7347, and *Lactobacillus casei* CECT 9104 [210].

A systematic review and meta-analysis of randomized controlled trials performed by Cuello-Garcia et al. [211] concluded that probiotic supplementation during the last trimester of pregnancy or breastfeeding could reduce the risk of eczema in infants, although the certainty of the evidence was low. Li et al. [212] achieved similar findings, concluding that the use of probiotics during both the prenatal and the postnatal period significantly reduced the incidence of AD; however, the analysis of studies of probiotics administered prenatally only or postnatally only did not reach statistical significance. Similarly, Tan-Lim et al. [213] revised randomized clinical trials related to the use of oral probiotics to prevent AD, finding that the top 3 probiotic preparations in terms of efficacy in reducing the risk of AD are multi-strain *Lactobacillus paracasei* ST11, *Bifidobacterium longum* BL999, and *Lactobacillus paracasei* ssp. *paracasei* F19, *Lactobacillus rhamnosus* GG, and *Bifidobacterium animalis* ssp. *lactis* Bb-12.

Recently, a meta-analysis and systematic review performed by Chen et al. [214] evaluated the efficacy of probiotic supplementation for the prevention of AD in infants, showing that oral probiotic supplementation in both mothers and infants was effective in preventing AD in infants.

Synbiotics also seem to be useful in AD. Children with mild to moderate AD, aged 1 to 10 years, were treated with one sachet of a novel synbiotics formula daily, which contained a mixture of six types of gastro-resistant probiotics (not less than  $1.5 \times 10^{10}$  CFU/sachet at the time of production), and triple prebiotics containing inulin, isomalto-oligosaccharides, and fructo-oligosaccharides for 8 weeks. The probiotic mixture was composed of *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus* GKA7, *Bifidobacterium longum* GKL7, *Lactobacillus plantarum* GKM3, *Bifidobacterium bifidum* GKB2, and *Lactobacillus paracasei* GKS6. Results showed an important improvement in Eczema Area and Severity Index (EASI) without any adverse effects. The presence of key microbial drivers, including *Bacteroides fragilis* and *Lactobacillus acidophilus*, was significantly increased at week 8. The authors also found that high responsiveness to an 8-week probiotic treatment was associated with improvements in the gut microbiome profile with greater relative abundance of probiotic species [157].

Post- and parabiotics were also studied. In 2016, Choi et al. [215] assessed the effect of heat-killed *Enterococcus faecalis* EF-2001 (EF-2001) on AD in an in vivo AD model by repeated local exposure of *Dermatophagoides farinae* extract, finding that the symptoms and pathological signs were attenuated and so was the production of Ig and the expression of various pathogenic cytokines in the ears, lymph nodes, and splenocytes. Considering previous studies in allergic diseases, which reported that heat-killed *Lactobacillus casei* Shirota suppressed pro-inflammatory, Th1, and Th2 cytokines in splenocytes [216], authors suggested that EF-2001 is able to significantly inhibit the inflammatory response by blocking both Th1 and Th2 in AD lesions of the tissues in the ears as well as in the cervical lymph nodes and splenocytes [215].

Formulas including a mixture of prebiotics, probiotics, and postbiotics have also been tested. Patients with a diagnosis of AD were treated for 8 weeks with an oral formula containing seven types of gastro-resistant probiotics (mixture of *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus* GKA7, *Lactococcus lactis* GKL2, *Lactobacillus casei* GKC1, *Lactobacillus paracasei* GKS6, *Bifidobacterium bifidum* GKB2, and *Bifidobacterium lactis* GKK2, no less than  $2 \times 10^{10}$  CFU/capsule), a postbiotic heat-killed *Lactobacillus plantarum* (10 mg/capsule), and triple prebiotics containing inulin (22 mg/capsule), galactooligosaccharides (8.1 mg/capsule), and fructooligosaccharides (0.9 mg/capsule). Results showed an improvement in the diversity of the gut microbiome and a significant improvement in AD severity [182].

Colombo et al. [183] performed a real-life, multi-center, retrospective observational investigation designed to evaluate the efficacy and tolerability of a commercial pre- and post-biotic supplement. Patients consumed a daily sachet containing a concentration exceeding  $2.5 \times 10^9$  AFU (active fluorescent units) of three patented probiotic species: *Bifidobacterium*

*animalis* subsp. *lactis* BS01 (LMG P-21384), *Lactocaseibacillus rhamnosus* LR05 (DSM 19739), and *Lactiplantibacillus plantarum* LP14 (DSM 33401). Results showed a significant overall and even intra-individual reduction in all severity scores: erythema, edema/papules, excoriation, TIS (Three Item Severity score), and PRURIScore [183].

While the use of orally administered probiotics for the prevention and treatment of AD have been largely studied, only a small number of studies have focused on the topical application of probiotics, which may be due to the difficulty of delivering viable bacteria to the skin, given that creams and lotions typically have to be preserved [217].

The most used probiotics and postbiotics for a topical application in AD are heat-inactivated *Lactobacillus johnsonii* NCC533 [218], *Aquaphilus dolomiae*, and *Vitreoscilla filiformis*, which are able to reduce *S. aureus* colonization [219], and *Lactobacillus reuteri* DSM 17938, which showed a statistically and clinically significant improvement in the SCORAD index and local SCORAD in adults suffering from AD after 4 and 8 weeks of continuous use [220]. Previous studies showed that the production of the anti-inflammatory molecule IL-10 by dendritic cells was increased after a local application of *Vitreoscilla filiformis* extracts on skin with AD [221,222].

In a study performed by Nakatsuji et al. [223], a strain of *Staphylococcus hominis* A9 (ShA9) was selected and applied to the skin of patients with AD, showing that ShA9 can inhibit skin inflammation by inhibiting quorum sensing. Phase II of clinical trials is ongoing, and results are still not available.

As was mentioned before, *Nitrosomonas eutropha* (B244) is a bacterium that produces nitric oxide, a potential anti-inflammatory molecule. In phase II of a randomized controlled trial (RCT) in adults, B244, which was administered as a spray, induced a significant improvement in pruritus. Additionally, an open-label phase Ib pediatric trial showed a similar effect on itching [224].

Finally, it is also worth citing the studies of Myles et al. [225,226] on topical microbiome transplantation with *Roseomonas mucosa*, which was able to reduce *S. aureus* colonization.

### 5.3. Psoriasis

Chen et al. [227] conducted an in vivo study where the oral administration of *Lactobacillus pentosus* GMNL-77 was found to significantly decrease erythematous scaling lesions. Real-time polymerase chain reaction showed that treatment with *L. pentosus* GMNL-77 significantly decreased the mRNA levels of proinflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor-alpha, and the IL-23/IL-17A axis-associated cytokines (IL-23, IL-17A/F, and IL-22) in the skin of imiquimod-treated mice.

Buhas et al. [158] performed a 12-week open-label, single-center clinical trial with the aim to evaluate the efficacy of probiotics: *Bacillus clausii* (SC109), *Bacillus coagulans* (SC208), *Bacillus indicus* (HU36), *Bacillus subtilis* (HU58), and *Bacillus licheniformis* (SL307), and prebiotics such as xylooligosaccharides, fructooligosaccharides, and galactooligosaccharides in patients with psoriasis under topical therapy. Results showed that patients with psoriasis receiving anti-psoriatic local therapy and probiotic and prebiotic supplementation performed better results in Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores, inflammatory biomarkers, and skin thickness compared with those not receiving supplementation [158].

Finally, it is worth mentioning a case report related to the treatment of a case of pustular psoriasis resistant to steroids, dapsone, and methotrexate that responded well to *Lactobacillus sporogenes*. The patient was administered one sachet thrice daily with biotin 10 mg, and all other drugs were stopped immediately. Within fifteen days, the fever decreased, the lesions began to regress, and no new lesions appeared after two weeks. Therefore, the authors concluded that future research should be conducted in this field [159].

### 5.4. Rosacea

According to the ROSacea International Expert Group (ROSIE), comprising European and US rosacea experts, treatment for rosacea aims to reduce symptoms such as facial

flushing and telangiectasias, and the eruption of papules and pustules, to prevent or delay the exacerbation of disease manifestations as well as to maintain remission [228]. Treatments are based on topical and systemic therapies (antibiotics, retinoids, etc.), light therapies (e.g., laser), and dermocosmetics [228]. In the literature, there is a lack of studies focused on nutraceuticals, although some are promising.

The aforementioned study by Manzhaliy et al. [146] in patients with papulopustular exanthema (including 36% with rosacea) who received the bacteria *Escherichia coli* Nissle 1917 as an oral probiotic as well as a standard topical therapy, demonstrated that oral probiotics therapy had better results than patients who only received standard treatment, improving quality of life and the clinical signs of dermatosis.

Clinical improvement was associated with the suppression of the proinflammatory cytokine IL-8 and a significant increase in IgA levels to normal values in serum. Fortuna et al. [160] also reported a case of rosacea with scalp involvement that was treated with a combination of low-dose doxycycline (40 mg/day) and oral probiotics (*Bifidobacterium breve* BR03 and *Lactobacillus salivarius* LS01) for 8 weeks, followed by probiotics alone. No relapse or worsening of the disease was observed during the 6 months of follow-up.

### 5.5. Seborrheic Dermatitis

Dandruff, seborrheic dermatitis, and scalp-associated disorders showed significant improvements after the oral supplementation of *Lactobacillus paracasei* NCC 2461 ST11, observing that free and adherent dandruff, erythema, and the global clinical score improved significantly after 56 days of oral intake of a sachet containing ST11 ( $1 \times 10^9$  CFU) compared to placebo [161].

Additionally, Di Domenico et al. [229] assessed the impact of a topical oily suspension containing *Lactobacillus crispatus* P17631 and *Lacticaseibacillus paracasei* I1688 in patients affected by severe to moderate seborrheic dermatitis, finding that this mixture was able to reduce symptoms and modulate the microbiome composition, showing that the topical administration of probiotics could also be useful in seborrheic dermatitis.

### 5.6. Wound Healing

It has been shown that the absence of microbiota can decrease healing time; furthermore, wound infections appear when exogenous bacteria become dominant over systemic and local host resistance factors, and only when a balance is achieved between bacteria and the host can healing processes develop [230].

The most effective wound management strategy is to prevent infections, promote healing, and prevent excess scarring, and probiotics may aid in skin repair by exerting antagonistic effects against pathogens and stimulating the production of immune cells [231]. In a comprehensive review performed by Fijan et al. [162], the authors found that the most commonly used probiotics against pathogens of wound infections were well-known strains of the species *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus*. All in vitro studies showed effective inhibitions of wound pathogens by selected probiotics. In all in vivo studies, probiotics showed strong activities in counteracting wound infections. Most clinical studies showed a mild or statistically significant lower incidence of surgical site infection, foot ulcers, or burn infections in patients using probiotics [162].

Tagliari et al. [232] investigated the effect of the perioperative oral administration of probiotics on the healing of skin wounds in rats. The probiotic group was supplemented with *Lactobacillus paracasei* LPC-37, *Bifidobacterium lactis* HN0019, *Lactobacillus rhamnosus* HN001, and *Lactobacillus acidophilus* NCFM<sup>®</sup> (Raleigh, NC, USA) at a dose of 250 mg/day, and the control group was supplemented with oral maltodextrin 250 mg/day, both daily for 15 days. In the intervention group, a faster reduction in the wound area was observed, and the authors postulated that this may probably be attributed to a reduction in the inflammatory phase, an acceleration of the fibrosis process, and collagen deposition.

On the other hand, Togo et al. [233] conducted a systematic review focused on the currently available evidence on the effect of enteral or oral probiotic therapy on wound healing both of the skin and oral mucosa, which included seven studies involving 348 people. The results showed that four studies reported positive results for better healing after probiotic therapy, and none of the studies reported adverse effects or increases in wound healing time. The authors concluded that the results do not generate strong evidence regarding the effectiveness of probiotics for wound healing.

Later on, Tembhe et al. [234] revised the role of probiotics in chronic wounds, finding 14 articles and concluding that probiotics help eliminate pathogenic bacteria and restore normal wound flora when applied topically. The main probiotic strains were from the *Lactobacillus* species: *L. plantarum*, *L. acidophilus*, *L. rhamnosus*, and *Saccharomyces cerevisiae* [234]. *S. cerevisiae* was shown to achieve an overall improvement in the healing process; specifically provoking an increase in the expression levels of collagen type 1 and transcription growth factor beta 1 (TGF- $\beta$ 1), as well as an improvement in the morphological and biomechanical characteristics of the healing wounds [235]. In vitro study *L. acidophilus* and *L. casei* demonstrated antibacterial activity against Methicillin-resistant *Staphylococcus aureus* [236]; and *L. reuteri* and *L. rhamnosus* reduced the ability of the pathogen to induce keratinocyte cell death [237]. Additionally, *L. fermentum* showed an increased wound closure concurrent with the production of nitric oxide (gNO) [238].

Recently, Canchy et al. [239] revised the relationship between the skin microbiome and the wound healing process. Most of the studies (as in the previous revision by Tembhe et al. [234]) are related to probiotics topical administration, and the main probiotics strains were again from the *Lactobacillus* species; the authors suggested that probiotics mainly affect the inflammation phase, which plays an important role in wound healing impairment, and the suspected mechanism of action is through the regulation of AMPs and, thus, control microbial proliferation [239]. In the same revision, the use of prebiotics and postbiotics in wound healing was revised, finding very little research on this topic. *Vitreoscilla filiformis* has been shown to increase keratinocyte proliferation, epidermal regeneration in vitro, and stratum corneum renewal rate in vivo, as well as stimulate the expression of collagen I and IV. These results may indicate that this strain could be useful for increasing re-epithelization in wound healing applications [222,239,240].

Another field of interest is phage therapy. Bacteriophages are viruses that infect and replicate within bacteria which have long been used to treat human bacterial infections. Phages are specific to the species and often the strain level in targeting and infecting bacteria. Topical phage therapies have been reported for the treatment of several types of refractory chronic skin infections, such as diabetic ulcer, venous stasis, or burn-mediated [241], and other investigations focused on the benefits of using phages to reduce *S. aureus* biofilm mass and to treat *S. aureus* infections [242,243].

### 5.7. Aging and Photoaging

Since Elia Metchnikoff proposed that all microorganisms are not harmful and that several intestinal bacteria “produce useful substances against a premature aging”, favoring instead a “healthy aging” [11], several studies were carried out to investigate the effects of oral probiotic supplementation on skin aging and photoaging [244]. Thus, protection and recovery from sunburn have been one of the first research objectives of probiotics for the skin. These first studies were carried out with fractions of bifidobacteria applied to the skin, with contradictory results [245].

The oral administration of *Lactobacillus johnsonii* (La1) at  $10^8$  CFU/day for 10 days protected against the UVR-induced suppression of contact hypersensitivity, increasing IL-10 serum levels and decreasing epidermal Langerhans cell density [246]. Additionally, another study demonstrated that *Lactobacillus sakei* lipoteichoic acid inhibited MMP-1 induced by UVA in normal human dermal fibroblasts [247].

Kim et al. [248] evaluated the effect of *Lactobacillus plantarum* HY7714 against UVB-induced photoaging in human dermal fibroblasts and hairless mice. The results showed

that treatment with *L. plantarum* HY7714 effectively recovered UVB-reduced procollagen expression by inhibiting UVB-induced matrix metalloproteinase (MMP)-1 expression in human dermal fibroblasts. Furthermore, the oral supplementation of *L. plantarum* HY7714 showed an inhibition of the number and depth of wrinkles in hairless mouse skin and also was able to inhibit UVB-induced epidermal thickness in mice. In addition, zymography western blot data also demonstrated that *L. plantarum* HY7714 effectively inhibited MMP-13 expression as well as MMP-2 and -9 activities in dermal tissue [248].

Additionally, a randomized double-blind clinical trial demonstrated the antiaging effect of the oral administration of *L. plantarum* HY7714 ( $10^{10}$  CFU/day for 12 weeks), with a significant improvement in the hydration, shine, and elasticity of the skin and also in the reduction in the depth of wrinkles [163].

Gueniche et al. [246] showed that oral supplementation with *Lactobacillus johnsonii* at  $10^8$  CFU/day for 10 days was able to protect against the UVR-induced suppression of contact hypersensitivity, decreased epidermal Langerhans cell density, and increased IL-10 serum levels. Furthermore, in a randomized, double-blind controlled trial, the oral administration of *Lactobacillus johnsonii* La-1 demonstrated a restoration of CD1a Langerhans cell markers compared to placebo on day 4 after UV irradiation [164].

Weill et al. [249] investigated the effect of lipoteichoic acid (LTA) from *Lactobacillus rhamnosus* GG against UV-induced carcinogenesis in hairless mice. The results showed that T-cells in the inguinal lymph node of LTA-treated mice produced higher levels of interferon-gamma in lymph nodes and numbers of total, helper, and cytotoxic T-cells compared to controls. A delay in tumors induced by ultraviolet radiation was also found.

Other studies confirmed the use of *Lactobacillus* to prevent aging. Tyndallized *Lactobacillus acidophilus* was shown to suppress matrix metalloproteinases (MMPs) for wrinkle prevention in photoaged skin through the inhibition of elastase activity [250,251] and also exerted anti-melanogenesis activity by inhibiting the cAMP pathway and suppressing melanin secretion [251].

*Bifidobacterium breve* strain Yakult (BBY) was also investigated in hairless mice and was shown to be able to suppress UV-induced elastase and IL-1 $\beta$  production and prevent the loss in elasticity associated with exposure to UV [252]. Similar studies demonstrated that the administration of *Bifidobacterium breve* B-3 to hairless mice suppressed changes in transepidermal water loss, skin hydration, and epidermal thickening and reduced damage to the basement membrane and tight junction structure induced by chronic UVB irradiation, showing a protective effect on skin photoaging [253].

Several studies performed by Kimoto-Nira (2018) focused on *Lactococcus lactis* H61, finding that the oral intake of heat-killed or live cells improved skin status in Japanese women; in addition, heat-killed cells of strain H61 demonstrated an antioxidant effect [184].

The prevention of polymorphic light eruption has also been studied. Marini et al. [165], in a study with light-sensitive patients, investigated the administrations of a combination of *Lactobacillus johnsonii* La-1,  $\beta$ -carotene, and lycopene; the results showed that this mixture was able to improve the alteration, and an increase in intercellular adhesion molecule-1 (ICAM-1) was also observed, suggesting an immunological response.

Prebiotics seem also to be useful for preventing aging. A diet rich in SCFA-producing dietary fibers may also help age-related microbial dysbiosis and, in turn, suppress the senescent phenotype. That is the case of butyrate supplementation which was demonstrated to be able to counteract age-related microbiota dysbiosis [166].

Recently, the term “gerobiotics” has been proposed by Tsai et al. [254] to define those probiotic strains and their derived postbiotics and para-probiotics that have been shown to reduce physiological aging processes by attenuating the mechanisms of aging, thus improving the health span of the host. In an extensive review, the authors highlight the importance of the new field of gerobiotics, research and updating, biomarkers for potential targets, and provide recommendations for the development of gerobiotic products, highlighting its potential to improve health and longevity in the future. In this review, several strains were highlighted. *B. longum* BB68, *L. gasseri* SBT2055, *L. fermentum* MBC2,

*B. infantis* ATCC15697, and *B. subtilis* PXN21 (in *C. elegans* model) were able to increase lifespan. *L. brevis* OW38, *L. paracasei* PS23, and *L. paracasei* K71 (in mice model) were able to increase memory and/or cognition; *L. plantarum* AR501 (in mice model) reduced liver damage; *L. helveticus* KLDS1.8701 improved the gut microbiota and memory. In rat models, *L. plantarum* NDC 75017 increased learning and memory, and *L. fermentum* DR9 improved exercise capacity [254]. *Bifidobacterium animalis* ssp. *lactis* HN019 and *L. casei* Shirota improved innate immunity in humans [167,168]. Additionally, supplementation with a mixture of *Bifidobacterium longum* subsp. *longum* BB536, *B. longum* subsp. *infantis* M-63, *Bifidobacterium breve* M-16V, and *B. breve* was able to improve mental condition and decrease body mass index in humans [169].

Teng et al. [255] revised the mechanisms of action of probiotics in photoaging, concluding that oral and topical probiotics, by modulating the skin microbiome and gut–skin microbial interactions, could be useful in preventing and treating skin photoaging through multiple pathways, including reducing oxidative stress, the inhibition of ECM remodeling, the inhibition of inflammatory cascade reactions, and the maintenance of immune homeostasis [255]. Most of the studies are *in vitro* and *in vivo*, and a few of them are clinical studies. An example is the investigation performed by Bouilly-Gauthier (2010) to assess an oral supplement containing *Lactobacillus johnsonii* and nutritional carotenoids on early UVR-induced skin damage, finding that intake of this mixture for 10 weeks prevented UV-DL-induced decrease in Langerhans cell density and increase in factor XIIIa+ type I dermal dendrocytes and reduced dermal inflammatory cells [170].

#### 5.8. Other Uses of Nutriotics

One of the main issues in skin care is the maintenance of skin barrier and hydration. A double-blind trial involving combinations of probiotics and prebiotics (*B. breve* strain Yakult + galactooligosaccharides) supplemented with fermented milk (100 mL/day for 4 weeks) resulted in the maintenance of an optimal level of skin hydration, a decrease in the activity of cathepsin L-type endopeptidase and the phenol content in serum and urine, exerting beneficial effects on both the intestine and the skin [171]. Additionally, a trial with *L. casei* ( $1 \times 10^{11}$  bacteria/day for 8 weeks) conducted by Saito et al. [185] demonstrated a significant reduction in TEWL (trans-epidermal water loss) and skin flakiness [172]. Furthermore, the oral administration of heat-killed *L. lactis* (60 mg/day for 8 weeks) significantly modulated various skin properties, such as skin elasticity, melanin content, and sebum content, with a notable effect in the younger age groups. And a para-probiotic prepared from Kimchi-derived *Lactobacillus plantarum* K8 improved the skin hydration in human keratinocyte [256].

Taking into account that skin immune conditions, such as acne, rosacea, and atopy, are associated with skin barrier disruption and that the restoration of this barrier is associated with an amelioration of the conditions [257], the topical application of probiotics is also considered. For example, Gueniche et al. [258] found *Lactobacillus paracasei* CNCM I-2116 (ST11) to inhibit P-substance-induced skin inflammation and accelerate the regeneration, contributing to epidermal barrier repairment; finding that significantly eliminates all the effects of P-substance, including vasodilatation, edema, mast cell degranulation, and TNF- $\alpha$  release compared to the controls. Moreover, the ST11-associated skin barrier recovery was found to be accelerated in an *ex vivo* skin culture [258]. In a review performed by Benyacoub et al. [144] related to the immune modulation properties of *Lactobacillus paracasei* NCC2461 (ST11) strain, the authors concluded that this strain contributes to the reinforcement of the skin barrier function and modulates the skin's immune system, reducing skin sensitivity, which leads to an improvement in defenses and the preservation of skin homeostasis.

Melasma could be also a target for nutriotics. Piyavatin et al. [173] performed an experimental study employing a prospective, double-blind, randomized controlled trial in patients suffering from facial melasma. Participants were randomly treated with oral synbiotics or placebo, one sachet daily for 12 weeks; melasma severity and skin health were evaluated at baseline at weeks 4, 8, and 12. Synbiotics consisted of a combination

of 50 billion CFUs of six probiotics strains: *Lactobacillus acidophilus*, *Lactococcus lactis*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Bifidobacterium infantis*, with prebiotic fructo-oligosaccharide, skim milk powder, lactose, maltodextrin, and citric acid. The results showed that the melasma score in the synbiotics supplement group was significantly lower than that in the placebo group [173].

Regarding the use of probiotics in systemic lupus erythematosus (SLE), a systematic review performed by Mirfeizi et al. [259] identified 22 articles examining the effects of probiotics on SLE. These studies, which include in vivo tests, in vitro research, and clinical trials, indicated that probiotics may be effective against inflammation, improving immunological responses as well as the metabolic profiles in SLE patients. The main strains were *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* [260–263]; a mixture of *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus johnsonii*, *Lactobacillus oris*, and *Lactobacillus gasseri* [264]; and *Lactobacillus plantarum* [265]. In a double-blind randomized clinical trial, Widhani et al. [174] investigated the effect of a synbiotic formula comprising *L. helicus*, *B. infantis*, *B. bifidum*, and fructo-oligosaccharides, finding that this formulation may be effective in decreasing systemic inflammation, reducing SLE disease activity, and inducing changes in both the composition and functions of the intestinal microbiota.

Another field of interest is the treatment of oral mucositis. According to Feng et al. [266], probiotics exerts a significant protective effect against oral mucositis in cancer patients. In recent review, Liu et al. [267] found eight trials on patients who were treated with chemotherapy or/and radiotherapy. The oral probiotics used were as follows: *L. rhamnosus* GG, one capsule, two times a day during the whole chemotherapy course [175]; oral lavage with kefir containing *Lactobacillus* spp., and *Bifidobacterium* spp., swallowed, 250 mL, two times a day after meal, and first 5 days of each chemotherapy cycle [176]; *L. brevis* CD2 lozenges, one lozenge, six times a day to be dissolved in the mouth and then swallowed for 8 weeks [177]; oral rinse containing *L. lactis*, 15 mL, three or six times a day [268]; combination of *B. longum*, *L. lactis*, and *Enterococcus faecium* on capsules two times a day for 7 weeks [178]; *L. brevis* CD2 lozenges, one lozenge six times/day to be dissolved in the mouth and then swallowed up to one week after the end of cancer treatment [179]; probiotic combination of *L. rhamnosus* LGG-18, *L. plantarum* MH-301, *B. animalis* subsp. *Lactis* LPL-RH, and *L. acidophilus*, one capsule, two times a day for 7 weeks [180]; *Bacillus clausii* oral suspension, 5 mL, two times a day, until the completion of radiotherapy course [181]. Therefore, nutraceuticals may be useful in this type of sequelae of cancer therapies.

In scientific literature, oral probiotics in post-surgery can be also found. Trone et al. [269] scrutinized how prebiotics, probiotics, and synbiotics may play a role in modulating the immune response in the perioperative period and the degree to which they may affect surgical outcomes. The authors suggested that even short-term gut microbiome prehabilitation could significantly alter surgical outcomes, and future studies should consider evidence-based formulations comprising specific strains and also study the optimal treatment duration. In addition, dietary interventions, such as high-fiber diets and fermented foods, should be considered in perioperative regimens [269].

And in terms of topical application, a research study tried to develop a plaster/bandage for the application of inhibitory substances produced by probiotics when applied to diseased skin; Lactobacillales were the most active against *Cutibacterium acnes*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The authors suggested that probiotic-containing pads can be applied topically for the treatment of skin disorders, either replacing antibiotic treatment or as adjunctive therapy [270].

## 6. Conclusions and Future Perspectives

Intense research into the gut microbiome has provided tools to explore the role of the microbiota in other physiological systems, including the skin. Despite the scarce knowledge about the physiological role of skin microbiota in cutaneous biology, several strategies have been implemented to modulate the microbiome and improve skin health. The most recent strategy is the use of pre, pro, syn, and post and para-probiotics, which seems to

be beneficial on different skin disorders as atopic dermatitis, psoriasis, acne, seborrheic dermatitis, etc., as well as repairing the skin barrier, preventing aging, or promoting wound healing.

Nevertheless, a deeper understanding of the skin microbiome, the distribution of cutaneous microbial communities, as well as the differences between microbiomes in healthy and altered skin is needed. Thus, metagenomic technologies could facilitate the functional characterization of the microbiome and perhaps even provide a personalized approach to diagnosing and treating conditions underpinned by microbial dysbiosis [44].

It should also consider the potential adverse effects of probiotics, such as risk of systemic infections, excessive immune stimulation in susceptible individuals, minor gastrointestinal side effects [271], or disturbances in the abundance in the gut *Bifidobacteria*, as shown in subjects who take unregulated probiotics having a significantly lower relative abundance of *Bifidobacteria*, which could potentially have a detrimental impact on health [272].

New investigations about the use of nanotechnology in the probiotic's formulation are also of great interest as its delivery without any effect on gastrointestinal digestion is one of the most important points for their application [273]. Additionally, the genetic engineering of microbiomes has recently become an area of interest for researchers since it provides solutions to a significant health problem. In this context, strategies such as conjugative plasmids, bacteriophage, mating-assisted genetically integrated cloning (MAGIC), and environmental transformation sequencing (ETSeq) could be effective in the genetic modification of the microbiome [2].

In conclusion, skin microbiome has emerged as a new field with high potential to develop innovative solutions to manage skin health and disease. Future advances in this field may facilitate the treatment of skin dysbiosis through means that are more sensitive to the physiology of the skin, with nutraceuticals being a suitable method for skin care.

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