International Journal of Dermatology

Review

An approach on the potential use of probiotics in the treatment of skin conditions: acne and atopic dermatitis

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Conflict of interests: The authors declare no conflict of interests.

doi: 10.1111/ijd.13972

Abstract

Acne and Atopic Dermatitis (AD) are chronic inflammatory skin conditions with severe impact on a patient's life. Current treatments are related to adverse effects and do not represent a definitive cure. The present paper reviews the alterations in skin microbiome, specifically in acne and AD, and aims in searching for potential treatments based on benefic microorganisms, called probiotics. The review was made through bibliographic search of the main databases (Science Direct, PubMed, Scielo, Medline) between September 2015 and June 2016. Acne lesions create an environment that facilitates the excess growth of *Propionibacterium acnes* (*P. acnes*). AD is related to an increase in the proportion of *Staphylococcus aureus* (*S. aureus*) during flare-ups. Some microorganisms have been shown to act not only in the prevention but also in the competition for pathogenic microorganisms and beneficially affect the inflammatory process present in these conditions. Despite the high variety of tested bacteria, *Staphylococcus*, *Streptococcus*, *Lactococcus*, *Lactobacillus*, and *Enterococcus* are the ones which showed the highest potential to control acne, and *Vitreoscilla filiformis* (*V. filiformis*), *Staphylococcus epidermidis* (*S. epidermidis*), and species of *Lactobacillus* and *Bifidobacterium* in the treatment of AD. Many of these studies were *in vitro*, and more detailed research should be performed in order to prove the real efficacy and safety of probiotics in these situations. An interesting alternative seems to be the use of Bacteriocin-like inhibitory substances produced by probiotics, responsible for their antimicrobial activity.

Introduction

Skin conditions cause great discomfort because of their visibility and may severely affect patients' quality of life.[1] Complex bacteria, fungi, and virus communities live in our skin. The composition of these communities depends on characteristics such as sebaceous glands' concentration, hydration, temperature, genetics, and environmental factors.[2]

Acne and Atopic Dermatitis (AD) are chronic skin conditions which require long periods of treatment and maintenance. Current approaches are related to adverse effects greatly impacting patients' quality of life and do not represent a definitive cure for these conditions. Reestablishing skin microbiome balance may result in a positive impact for these conditions, especially in the long-term view. It may also show a relevant decrease in adverse effects resultant from these treatments, allowing the use of less aggressive therapies or even eliminating the need for systemic medication.

In the future, we hope for topic therapeutic innovations involving microorganisms' formulations for the control of skin conditions, looking for a balance between the host's ecosystem versus microorganism. In order to make it possible, a greater knowledge about microbiome of different locations in the body, its variations with time and seasonal changes, as well as the effect of factors such as hygiene, lifestyle, geographic locations, etc., will be necessary. The study of skin microbiome shows great potential not only in dermatology but also for research and development of pharmaceuticals for topical treatments, focusing on avoiding the undesirable effects of the current therapeutic arsenal. Both the benefic influence on microorganism's composition and the optimization of its interactions with skin increase the viability of this therapeutic modality.[3,4]

The present study aims to report the alterations present in skin microbiome in acne and AD, searching for potential treatments for these conditions through the use of probiotics.

Methodology

This review was performed through bibliographic search of scientific articles and books related to the topic on the main databases: Science Direct, PubMed, Scielo, and Medline between September 2015 and June 2016.

The keywords consisted of: acne/atopic dermatitis, condition + life quality, condition + treatment, condition + pathophysiology,

skin microbiome, condition + microbiome, condition + probiotics, as well as their counterparts in Portuguese and Spanish.

The criteria taken into consideration when selecting the bibliographic material were titles and abstracts related to the theme for basic research (physiopathology and conditions' treatments) and for specific research (skin microbiome and probiotics use), only material published between 2006 and 2016 was accepted. Manuscripts that were not related to the topic, with no peculiar or interesting information, were excluded.

Results and Discussion

Skin microbiome

Human skin can be an inhospitable environment with acidic pH and constant peeling. Even so, it shows an abundant colonization of bacteria, fungi, and viruses. The composition of these microorganisms is subjected to ecologic and individual variations. Literature remains inconsistent when it comes to skin bacteria density, and a possible explanation for this is the variation in methods used to quantify these microorganisms.[3,5–7]

At least 19 bacterial phyla belong to the skin microbiome. The main ones are Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%). The majority of the genre identified consists of *Corynebacteria*, *Propionibacteria*, and *Staphylococci*.[5] Commonly found fungi include the ones from the genera *Malassezia* and *Candida*.[8,9] Differently from what happens to some members of bacterial microbiome, there is no strong evidence of mutualistic or benefic relationship with the fungal microbiome.[8] However, it is important to consider the still low number of researches performed focusing on the cutaneous fungal microbiome and its possible effects on the host. In general, more diversity seems to show greater advantages, as it is believed that the more diverse the ecosystem, the more resilient.[7]

In a study performed by Grice *et al.*,[5] skin areas representative of distinct niches and affected by dermatologic disorders were selected, and the relative abundance of the main bacterial groups was compared taking into consideration three microenvironments: sebaceous (glabella, alar crease, external auditory canal, occiput, manubrium, and back); moist (nare, axillary vault, antecubital fossa, interdigital web space, inguinal crease, gluteal crease, popliteal fossa, plantar heel, and umbilicus); and dry (volar forearm, hypothenar palm, and buttock). *Propionibacteria* and *Staphylococci* species predominated in sebaceous areas, *Corynebacteria* species predominated in moist areas, and a mixed population of bacteria resided in dry areas, with a greater prevalence of β-*Proteobacteria* and *Flavobacteriales*.

Acne

Acne is a chronic skin disease that affects the pilosebaceous unit as a result of an increase in sebum production induced by hormones, altered keratinization, immunologic processes and inflammation, and bacterial colonization of hair follicles in the face, neck, chest, and back by *Propionibacterium acnes* (*P. acnes*). Its pathologic factors should not be observed individually as they influence each other.[10] Acne may affect 85–90% of population in countries with western diets and has even been considered a normal process of development by some dermatologists.[11]

Acne treatment is generally focused on its severity; recommendations may be based on skin type, clinical classification, and on the presence of preexisting scars.[12] Treatment options include suitable skin care, topical and oral antimicrobial agents, retinoid, benzoyl peroxide, and oral contraceptive. These are frequently combined and can be readjusted as needed.[13,14]

P. acnes are anaerobic gram-positive bacteria that colonize and live in the human skin, especially in pilosebaceous follicles. Even though it is usually defined as commensal, it can present itself as an opportunist pathogen, and it is frequently associated with infections. This bacterium is known by its important role in the development of inflammatory acne *vulgaris*.[15–17]

An acne lesion creates an anaerobic microenvironment that facilitates the excess growth of *P. acnes*, even though other bacteria coexist in this lesion.[18] According to Fitz-Gibbon *et al.*,[19] only a few strains of these bacteria are associated with the condition. The metagenomic study found a strong relationship between specific strains and acne or healthy skin, each with unique genetic elements. The study suggests a relationship between host factors and acne, such as hormonal levels, sebum production, and physical changes in the pilosebaceous unit. In addition, part of the inflammation in acne lesions is a result of immunological response from the host against *P. acnes*.[15,17,19] Thus, *P. acnes* is, at least partially, responsible for two of the main pathogenic factors in acne: bacterial colonization and inflammatory reaction, attracting attention as a potential target in its treatment.

Interestingly, despite the fact that *Malassezia* spp. fungi is commonly found in oily areas,[9] few have been researched about its relationship with acne. Besides, an epidemiological study performed by Song *et al.*[20] did not find evidence that its presence is increased in patients with this condition.

Even with many treatments available for acne, there is no definitive cure for this condition and apart from that, the treatments available show significant side effects. No option uses endogenous molecules from the subject, even though they show potential for less side effects and lower chance of development of antibiotic-resistant bacteria.[18]

In vitro studies have shown the capacity of probiotics, such as *Streptococcus salivarius* and *Enterococcus faecalis,* to directly inhibit *P. acnes* growth through antibacterial proteins' production, as detailed in this article. An example of antibacterial protein is the Bacteriocin-like inhibitory substance (BLIS), which can cause significant inhibition in the growth of *P. acnes*.[21,22] Additionally, its immunomodulatory effects in keratinocytes and epithelial cells suggest a physiological

mechanism to support its use as adjuvant in acne treatment.[21] Probiotics show potential for direct and indirect benefits in the condition's treatment: directly by inhibiting *P. acnes* growth and decreasing the characteristic inflammatory response, and indirectly by softening side effects from current treatments. These may consist in benefic effects that soften collateral effects or event through exchange for a less aggressive treatment, thanks to the improvement in the disease severity because of its use.

An *in vitro* study performed by Wang *et al.*[18] suggested that skin microorganisms, in special *Staphylococcus epidermidis* (*S. epidermidis*), may ferment glycerol and inhibit excess growth of *P. acnes* in culture medium. These skin microorganisms were isolated from the nose surface of an acne-free individual and cultivated in tryptic soy broth. After that, the bacterial suspension was incorporated to molten agar with and without glycerol and placed in Petri dishes. Fingerprints from different individuals were pressed against the surface of this agar. A genetic analysis was performed in bacterial colonies where *P. acnes* inhibition zones were observed. These bacteria were identified as mostly *S. epidermidis*. The posterior isolation of *S. epidermidis* colony confirmed the result. It was also observed that glycerol fermentation consists in indispensable factor for *S. epidermidis'* inhibitory effect over *P. acnes*. Therefore, *S. epidermidis*' presence may be related to a natural skin defense against acne, and its increase through probiotics use could result in a better outcome for patients.

Streptococcus salivarius, oropharyngeal system component, was capable of inhibiting *P. acnes* growth *in vitro* through the production of a BLIS.[22] The study was performed with 106 healthy patients and consisted of a swab of the back of the tongue followed by dilution and inoculation of cultures in agar *mitis-salivarius*. BLIS production was evaluated utilizing modified deferred antagonism test. The authors suggested the possible efficacy of a topic formulation containing BLIS or BLIS-producing bacteria for the treatment of acne *vulgaris*. The same bacteria inhibited proinflammatory cytokine IL-8 in epithelial cells and keratinocytes, suggesting an immunomodulatory action.[23] It was proposed that this behavior comes from the fact that these microorganisms do not promote a proinflammatory action, stimulate an anti-inflammatory action, and modulate genes associated with epithelial layer adhesion and homeostasis. Inhibitory substances produced by bacteria show as an interesting characteristic the capacity to inhibit other bacteria growth without injuring the microbiome present in the skin. In this way, similar benefits to the antibiotics may be obtained avoiding their main side effects. The possibility of having probiotics performing as immunomodulators may bring benefits, especially in the most severe cases of acne (types III and IV), where inflammation is strongly present.

A study performed by Oh *et al.*[24] proved the inhibitory *in vitro* effect of a bacteriocin produced by *Lactococcus sp.* HY 499 in the growth of *S. epidermidis*, *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes*, and *P. acnes* among other bacteria, utilizing spot-on-the-lawn method. In addition, no allergic reaction or irritations were observed as a consequence of the bacteriocin use in a human patch test performed through application of 40 μl of sterilized bacteriocin (12,800 AU/ml) on a Finn Chamber closed with a tape that was removed after 24 hours. Authors suggested the utilization of bacteriocin produced by *Lactococcus sp.* HY 449 as an antimicrobial agent in cosmetic formulations. The absence of allergic reactions and irritations consists in a great potential advantage for the use of probiotics compared to current treatments.

A study performed by Gueniche *et al.*[25] demonstrated inhibition of skin inflammation utilizing *Lactobacillus paracasei* (*L. paracasei*) CNCM I-2116. Alterations, such as a decrease in vasodilation, edema, mast cell degranulation, and TNF-alpha release induced by substance P, were observed. Co-culture cell system Caco-2/PMBC was stimulated on the apical side with probiotics and the resulting medium collected from the basolateral compartment of the cell culture system and tested in *ex vivo* human abdominal plastic skin explant models by substance P-induced skin inflammation and skin barrier reconstruction. This way, through utilization of *ex vivo* skin culture, a faster barrier reconstruction was observed. This benefit is particularly interesting to deal with collateral effects from traditional treatments containing free radicals.

Kang *et al.* (2009)[26] tested the anti-*P. acnes* effect of a lotion produced with *Enterococcus faecalis* SL-5. The bacterium was isolated from feces of a healthy Korean adult and grown in an optimized environment. Concentrated powder was prepared through ultrafiltration utilizing a membrane with cut-off mass of 3 kDa. The retained content was mixed with maltodextrin for a final concentration of 10% p/V. The mixture was tindalized and lyophilized, forming a concentrated powder named CBT SL-5. An aqueous lotion was prepared with a final powder concentration of 6.400 AU/100. The placebo contained the same components as the lotion except for CBT SL-5. An 8-week double-blind randomized phase III study was performed. Seventy patients over 12 years old and with light to moderate acne *vulgaris* diagnosis were included and divided in two groups: (i) CBT SL-5 and (ii) placebo. Patients were instructed to apply the lotion twice a day on affected areas. Exams were performed in the beginning of the study and after 2, 4, and 8 weeks. Results were observed in the first evaluation (2 weeks of treatment). There was a significant reduction in inflammatory lesions on the treated group, indicating that CBT SL-5 lotion inhibits *P. acnes,* decreasing the production of inflammatory mediators synthesized and released by this pathogen.

Muizzuddin *et al.*[27] observed a reduction in light acne lesions with erythema reduction and barrier reconstruction through a clinical study using *Lactobacillus plantarum* (*L. plantarum*). The extract was produced after bacterial growth in *Lactobacillus* yeast previously sterilized for 18–24 hours. Then, the yeast was passed through a heat exchanger to break the majority of the cells. The yeast was filtrated initially through a 0.45 μm filter

followed by a 0.22 μm filter. Oil in water formulations were prepared in concentrations of 1 and 5% of the probiotic. A salicylic acid 1% formulation was prepared as internal control. Ten volunteers between the ages of 18 and 50 were treated with the formulation once a day for 4 days, and the lesions were observed. The formulation containing 5% of bacteria significantly reduced the lesions' size and erythema. The formulation containing 1% of bacteria did not show significant results. This study suggests that the formulation containing 5% of *L. plantarum* may be used in the treatment of light acne lesions, highlighting the dose dependence, considering results were not observed with 1% of the extract formula.

In addition to studies in topical formulations using probiotics to treat acne, oral probiotics may affect skin conditions through different mechanisms, including reduction in systemic inflammation. Considering that inflammation is a part of the pathogenic factors observed in acne, its reduction may be useful to prevent the condition.[21] A research study performed with patients between 18 and 30 years old verified reduction in inflammatory lesions in 38.6% compared to placebo, as well as a selective reduction in skin surface triacylglycerols in individuals with acne after daily ingestion of fermented milk enriched with 200 mg of lactoferrin for 12 weeks.[28] The absence of alterations in skin's hydration levels and pH was also observed. Treatments with oral isotretinoin are known for their relevant collateral effects, such as dry skin and lips, and the use of probiotics as adjunct treatment of acne may help choosing a less severe therapy.

Atopic dermatitis

AD is a multifactorial chronic inflammatory condition with considerable heterogeneity, characterized by pruritic, erythematous, and scaly lesions, frequently localized in flexural surfaces of the body.[29,30] It is a common skin condition that affects children and adults with a prevalence of 1–20% in the world.[31] It is believed that AD is caused by a genetic defect in filaggrin leading to epidermidis disruption.[29] This results in contact between cells from the immune system in dermis and antigen from the external environment leading to inflammation and itchiness. The itching causes an increase in the rupture of the skin's epidermis barrier, therefore characterizing a cycle.[32] Studies indicate that both barrier dysfunction and inappropriate immunologic response contribute to this condition.[30,33]

The main treatment to AD consists of body moisturizers and adoption of behaviors that reduce xerosis. The first-line treatment to control the condition is the use of corticoids and the second line, topical calcineurin inhibitors. When there is evidence of secondary infection, the use of antibiotics is indicated, which must present good results for S*taphylococcus* and *Streptococcus* species.[29,34]

The AD pathogenesis is related to a lower microbial diversity on the predilection areas of the disease, as well as an increase in *S. aureus* proportion during flare-ups.[35] A study performed in mice also found the appearance of *Corynebacterium mastitidis* and *Corynebacterium bovis* in the course of the condition and evidence that specific antibiotics for these bacteria (including *S. aureus*) may reverse dysbiosis.[36] Treatment results in skin microbiome restoration[35] and, as previously observed, it is believed that a higher diversity shows greater advantages.

It is believed that lipophilic yeast *Malassezia* spp. is related to atopic dermatitis contributing to skin inflammation and that antifungal therapy shows benefic effects in some patients as well. Despite the current lack of strong scientific support and comparison to conventional treatment with steroids, topical application of ketoconazole has shown improvement of eczema cases in clinical routine adding to its anti-inflammatory properties.[37] This information is even more interesting when compared to acne. As previously stated, even though this condition is strongly associated with seborrheic areas, no relationship was found between *Malassezia* spp. and its pathogenesis. On the other hand, AD, that commonly affects drier areas in the body, was related to the lipophilic fungi.

S. aureus is a spherical gram-positive cocci bacterium commonly found on skin and nasal cavities. These bacteria can cause problems that go from simple to severe infection. A problem related to *S. aureus* is the development of antibiotic-resistant strains,[38] highlighting the need for new alternatives to deal with its overgrowth in AD.

Even though treating AD with antimicrobial agents may show some benefits,[35] the excessive use of antibiotics is criticized because of its negative effect on the microbiome and potential to harm its benefic functions.[7]

Just like acne, AD comprehends a set of host factors, with intestinal and cutaneous dysbiosis as one of the possible therapeutic targets. With so many factors associated with the disease, it is not clear whether skin biology changes lead to microbiome diversity alterations or if the excess growth of *Staphylococcus* species occurs initially, leading then to the progression of the condition.[39]

A recent study found a relationship between chronic atopic dermatitis and dysbiosis of *Faecalibacterium prausnitzii* (*F. prausnitzii*) in human intestine.[40] After analyzing the intestine of 132 patients, 90 with the condition, it was observed that the enrichment of the intestine with *F. prausnitzii* is strongly related to AD. In addition, the possibility of damage to the intestinal epithelium was verified through observation of anti-inflammatory substances (butyrate and propionate) in patient's feces. Thus, it is possible that the development of methods focusing on *F. prausnitzii* will be useful in the diagnosis and treatment of AD.

A prospective, double-blind, placebo-controlled study tested a lotion containing 5% of nonpathogenic *Vitreoscilla filiformis* lysate. Seventy-five volunteers with AD applied the lotion or placebo twice a day for 30 days. Then, the severity of the disease (*Scoring Atopic Dermatitis* – SCORAD), the transepidermal water loss, the microbiome, and the patient's report on itchiness and sleep loss were evaluated. The lysate has significantly

improved AD in all evaluated items, reducing skin colonization by *S. aureus*. Authors concluded that the results are not only because of *S. aureus* bacterial load reduction but also immunomodulatory effect on the skin.[41] Later, the lysate's immunomodulatory action was proved through analysis of dendritic cells differentiation and effector functions of dendritic and T-helper cells *in vitro* and *in vivo*. The topical treatment with the bacteria significantly reduced inflammation in mice, and the combination of allergen and lysate showed lower induced dermatitis, indicating active immunomodulation. It was observed that the innate sensibility of nonpathogenic bacteria for Toll-Like Receptor 2 (TLR2) induces dendritic tolerogenic cells and Tr1 regulatory cells, suppressing T-effector cells and cutaneous inflammation.[42]

Usually commensal bacteria, *S. epidermidis* showed inhibition of *S. aureus* colonization in the skin, revealing its potential use in antimicrobial defense against cutaneous infections. Undifferentiated human keratinocyte exposure to small sterile and nontoxic molecule of <10 kDa in a medium conditioned with *S. epidermidis* increased mRNA expression of human β-defensins 2 and 3 and the capacity of lysates to inhibit *S. aureus* growth. The effect was also relevant *in vivo* with intradermal injection of medium conditioned with *S. epidermidis* in mice 24 and 2 hours before a local infectious challenge with group A *Streptococcus*. Treated mice showed significantly lower infections when compared to the ones not exposed to *S. epidermidis*. The study revealed the potential of the bacteria to activate TLR2 signalization and to induce the expression of the antimicrobial peptide, increasing skin response against the pathogen.[43] It is believed that serin protease Esp secreted by *S. epidermidis* not only inhibits biofilm formation but also may destroy preexistent *S. aureus* biofilms and increase susceptibility of these biofilms to immunological components.[44] However, it is not known if *S. aureus* and *S. epidermidis* mutually increase each other's colonization or if *S. epidermidis* increases as an antagonic response to an increase in the *S. aureus* population.[2]

In a double-blind study performed by Drago *et al.*,[45] 38 adult patients with moderate to severe atopic dermatitis were randomized in two groups: the first group was given a treatment with probiotic *Lactobacillus salivarius* in a dose of 1×10^9 CFU/g in maltodextrin, and the second group was given placebo, made only of maltodextrin. The treatment consisted of consumption of sachets twice a day for 16 weeks. All patients completed the study, and initially there was no difference in the eczema's severity between groups. After 4 months, a significant SCORAD reduction was observed only in the group treated with the probiotic, and no adverse effects were found during the study. Cytokine's production by peripheral blood mononuclear cells was evaluated in the beginning and in the end of the treatment. Patients treated with probiotics showed no alteration in cytokine production, while patients treated with placebo showed a significant increase in IL-4 production associated with IFN-γ reduction.

Gueniche *et al.*,[25] in an *ex vivo* study, previously discussed, demonstrated inflammation inhibition and barrier reconstruction through utilization of *L. paracasei*. These effects show benefits not only in acne but also in AD, strongly related to cutaneous inflammation and a deficient skin barrier. Another previously discussed study that showed potential benefic effects for both acne and AD was performed by Oh *et al.*,[24] where *Lactococcus sp*. HY 499 inhibitory effects were verified against *S. aureus* and *P. acnes in vitro* growth, among other tested bacteria.[24] These findings are relevant because two clearly different conditions, such as acne and AD, may benefit from the same probiotics. Despite the differences in their pathogenesis, both consist in conditions of inflammatory character and are knowingly affected by skin's dysbiosis. Thus, probiotics with potential to reestablish these factors may contribute for both and even for other conditions, which share these characteristics.

A revision performed by Sikorska and Smoragiewicz (2013)[46] found a series of evidence that various strains of *Lactobacillus* and *Bifidobacterium* isolated from a variety of sources inhibit *in vitro* growth of *S. aureus*. The most active strains were *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG, *Propionibacterium freudenreichii*, *P. acnes*, *L. paracasei*, *L. acidophilus*, *L. casei*, *Lactobacillus plantarum*, *Lactobacillus bulgaricus, Lactobacillus fermentum*, and *Lactococcus lactis*. This revision also included evidence that probiotics may also eliminate or reduce colonization of methicillin-resistant *S. aureus.* According to authors, their effects are mediated by both cellular competitive exclusion and acid or Bacteriocin-Like Inhibitors' secretion. Based on this information, we may conclude that the use of probiotics may not only prevent the development of strains resistant to known antibiotics, making it progressively harder to treat infectious diseases, but also be used as alternative to treat cases of resistant bacteria. We can also highlight the possibility of inhibition of *S. aureus* growth by *P. acnes,* observed in this study.

Interestingly, the use of probiotics during pregnancy and the beginning of life has been related to the prevention of this condition.[47] A meta-analysis of clinical tests involving probiotics and pediatric atopic dermatitis analyzed important data of databases between 1997 and 2007 and concluded that current evidence supports a higher efficacy of probiotics in the prevention than in the actual treatment of AD.[48] This information highlights the importance of microbiome's balance even before the development of the condition.

Despite many studies indicating the efficacy and benefits of probiotics as adjuvants in the treatment of atopic dermatitis, according to Boyle *et al.*,[49] there is also evidence that the treatment with probiotics is not effective and has a small risk of adverse effects involved.

In order to have a safe and effective use of probiotics, extensive studies may be performed to prove the real benefits of their use in dermatologic conditions and guarantee that benefits are overcame by adverse effects that may occur. Additionally, the search for alternatives to deal with the possible side effects is also important. The divergence of information observed by Boyle *et al.*[49]

highlights the importance of highly reliable studies to obtain data that can be applied in the development of AD treatments.

A summary of the main conventional treatments for acne and AD and the relationship between these conditions and skin's microbiome may be observed in Table 1.

Final Considerations

The chronic and inflammatory character, as well as the relationship between acne and atopic dermatitis and dysbiosis, gives these conditions a great potential to be treated with probiotics. In both cases, they would act not only through competition with pathogenic microorganisms but also by helping with characteristic inflammatory processes.

Despite the great variety of tested bacteria, many studies were performed *in vitro*. Here, we highlight the relevance of more detailed studies with bacteria that showed potential in the initial studies, as well as a standardization of utilized strains seeking the highest possible level of homogeneity in the results. Besides the expected benefits, we suggest the performance of studies comparing side effects of both conventional and probiotic treatments. Additionally, we suggest the development of studies that verify if the dysbiosis is reversed in the skin and, if so, how long it lasts, as this seems to be a relevant and still weakly explored topic considering most studies were performed *in vitro*.

Even though the cited studies did not observe adverse effects or allergic reactions as a consequence of the probiotics use, it is important to highlight that the treatment with microorganisms may be dangerous for immunodeficient patients or patients in use of immunosuppressants, considering these are groups of patients at higher risk for infections. The use of probiotics in pregnant women must be handled with caution, but apparently it does not show any risks,[50] when being related to the prevention of AD.

Challenges in the development of formulations containing probiotics seem to be related to the use of specific strains, considering that different strains present different properties, as well as dosage and packaging of these formulations. An interesting alternative is the use of Bacteriocin-like substances, produced by probiotics, responsible for their antimicrobial actions, as well as the possibility of its synthesis.

Despite the growing number of research on the theme, the use of probiotics is still new. In the future, we hope that cosmetic formulations using probiotics or specific antibacterial proteins are available for the treatment of these conditions.

Questions (answers provided after references)

1. Which alternative is correct for normal skin microbiome?
- (a) Species of *Propionibacteria Staphylococci* predominate hydrated areas
- (b) Species of *Corynebacteria* predominate sebaceous areas
- (c) Species of *Corynebacteria* predominate dry areas
- (d) Species of β-*Proteobacteria* e *Flavobacteriales* predominate dry areas

Table 1 Summary of the main conventional treatments and relationship with skin microbiome in acne and AD

Condition	Conventional treatment	Relationship with microbiome	Potentially benefic microorganisms	Main mechanism of action	Experimental model	References
Acne	Topical therapies (retinoid, benzoyl peroxide, antibiotics) Oral antibiotics	Excess growth of *P. acnes*	*Staphylococcus epidermidis*	Fermentation of glycerol	*In vitro*	1, 2, 18, 22, 23, 24, 25, 26, 27
	Hormonal therapy		*Streptococcus salivarius*	BLIS production	*In vitro*	
	Isotretinoin		*Lactococcus sp.*	Bacteriocin	*In vitro*	
			Lactobacillus paracasei	Abrogation of inflammation	*Ex vivo*	
			Enterococcus faecalis	Enterocins	*In vivo*	
			Lactobacillus plantarum	Antimicrobial peptides	*In vivo*	
Atopic Dermatitis	Moisturizers Topical corticoids Topical calcineurin inhibitors	Lower microorganism diversity	*Vitreoscilla filiformis*	Immunomodulatory effect	*In vivo*	2, 24, 25, 29, 34, 35, 41, 42, 43, 44, 45, 46
	Antibiotics	Increase in *S. aureus* proportion	*Staphylococcus epidermidis*	Activation of TLR2 and serine protease secretion	*In vitro*	
			Lactobacillus salivarius	Immunomodulatory effect	*In vitro*	
			Lactobacillus paracasei	Abrogation of inflammation	*In vivo*	
			Lactococcus sp.	Bacteriocin	*In vitro*	
			Strains of *Lactobacillus* and *Bifidobacterium*	Inhibition of *S. aureus* growth	*In vitro*	

Source: elaborated by the author.

2. Acne is related to excess growth of (1) and atopic dermatitis to excess growth of (2)
(a) (1) *Staphylococcus epidermidis*; (2) *Staphylococcus aureus*
(b) (1) *Staphylococcus aureus*; (2) *Propionibacterium acnes*
(c) (1) *Propionibacterium acnes*; (2) *Staphylococcus aureus*
(d) (1) *Propionibacterium acnes*; (2) *Staphylococcus epidermidis*
(e) They are not related to excess growth of any bacteria

3. Which species of microorganisms showed benefits in both acne and atopic dermatitis?
(a) *Lactobacillus*, *Lactococcus*, and *Staphylococcus*
(b) Only *Lactobacillus* and *Staphylococcus*
(c) Only *Lactococcus* and *Lactobacillus*
(d) Only *Staphylococcus*
(e) None of the above

4. Which are the potential benefits of probiotics when compared to conventional treatments?
(a) Inflammation reduction
(b) Skin microbiome restoration
(c) Skin barrier restoration
(d) Less collateral effects
(e) All alternatives above

5. Which factors may influence the results of studies with probiotics and were discussed in this article?
(a) Bacteria cultivation method
(b) Different strains of the studied bacteria
(c) Diet
(d) a, b, and c
(e) Only a and b

6. Which alternative is incorrect?
(a) Probiotics may modulate systemic immunological response
(b) Probiotics are not an alternative for resistant bacteria
(c) The use of antibiotics may lead to the development of resistant strains of *Propionibacterium acnes*
(d) Available treatment for acne and atopic dermatitis does not represent a guarantee of cure and may lead to collateral effects
(e) Skin conditions may severely affect patients' quality of life

7. "Probiotics are an effective, totally safe, and with no side effects alternative for the treatment of inflammatory skin conditions". Regarding this sentence:
(a) Studies still need to be performed to guarantee the efficacy and safety of probiotics in these conditions
(b) The sentence is incorrect, probiotics have known side effects for the skin
(c) Probiotics are not effective
(d) The sentence is correct
(e) It depends on the bacteria

8. All strains of *Propionibacterium acnes* cause acne.
(a) True
(b) False

9. Atopic dermatitis was related to a lower microbiological diversity in the skin. In general, a higher diversity is considered to be better, as it shows greater resilience.
(a) True
(b) False

10. Despite lower evidence regarding a mutualistic relationship between skin and fungal microbiome, one of the main fungi that inhabit the skin is lipophilic *Malassezia*. About this:
(a) It was not related to any of the studied conditions
(b) Because it is lipophilic, it is related to acne
(c) Despite the low number of studies, it was related to atopic dermatitis and not related to acne
(d) It is strongly related to both conditions
(e) It showed benefic effects in atopic dermatitis

References

1 Linda P, Walker C. *Understanding Skin Problems: Acne, Eczema, Psoriasis, And Related Conditions*. Chichester: John Wiley and Sons Ltd, 2003: 1–17.
2 Chen YE, Tsao H. The skin microbiome: current perspectives and future challenges. *J Am Acad Dermatol* 2013; **69**: 143–155.
3 Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. *Nat Rev Immunol* 2012; **12**: 503–516.
4 Tomic-Canic M, Perez-Perez GI, Blumenberg M. Cutaneous microbiome studies in the times of affordable sequencing. *J DermatolSci* 2014; **75**: 82–87.
5 Grice EA, Kong HH, Conlan S, *et al.* Topographical and temporal diversity of the human skin microbiome. *Science* 2009; **324**: 1190–1192.
6 Kong HH. Skin microbiome: genomics-based insights into the diversity and role of skin microbes. *Trends Mol Med* 2011; **17**: 320–328.
7 Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol* 2013; **21**: 660–668.
8 Huffnagle GB, Noverr MC. The emerging world of the fungal microbiome. *Trends Microbiol* 2013; **21**: 334–341.
9 Rodoplu G, Saracli MA, Gümral R, *et al.* Distribution of *Malassezia* species in patients with pityriasis versicolor in Turkey. *J Mycol Med* 2014; **24**: 117–123.
10 Degitz K, Placzek M, Borelli C, *et al.* Pathophysiology of acne. *J Dtsch Dermatol Ges* 2007; **5**: 316–323.
11 Danby FW. The three acnes and their impact. In: Danby FW, ed. *Acne: Causes and Practical Management*. Chichester, UK: John Wiley & Sons Ltd, 2014: 1–30.
12 Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA* 2004; **292**: 726–735.
13 Nguyen R, Su J. Treatment of acne vulgaris. *J Paediatr Child Health* 2011; **21**: 119–125.
14 Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: why not as firstline therapy? facts and controversies. *Clin in Dermatol* 2010; **28**: 24–30.
15 Coenye T, Peeters E, Nelis HJ. Biofilm formation by propionibacterium acnes is associated with increased resistance to antimicrobial agents and increased production of putative virulence factors. *Res Microbiol* 2007; **158**: 386–392.
16 Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? *Br J Dermatol* 2008; **158**: 442–455.

17 Nakatsuji T, Liu YT, Huang CP, *et al.* Antibodies elicited by inactivated Propionibacterium acnes-based vaccines exert protective immunity and attenuate the IL-8 production in human sebocytes: relevance to therapy for acne vulgaris. *J Invest Dermatol* 2008; **128**: 2451–2457.
18 Wang Y, Kuo S, Shu M, *et al.* Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of Propionibacterium acnes: implications of probiotics in acne vulgaris. *Appl Microbiol Biotechnol* 2014; **98**: 411–424.
19 Fitz-Gibbon S, Tomida S, Chiu BH, *et al.* Propionibacterium acnes strain populations in the human skin microbiome associated with acne. *J Invest Dermatol* 2013; **133**: 2152–2160.
20 Song YC, Hahn HJ, Kim JY, *et al.* Epidemiologic study of Malassezia yeasts in acne patients by analysis of 26S rDNA PCR-RFLP. *Ann Dermatol* 2011; **23**: 321–328.
21 Kober MM, Bowe WP. The effect of probiotics on immune regulation, acne, and photoaging. *Int J WomensDermatol* 2015; **1**: 85–89.
22 Bowe WP, Filip JC, DiRienzo , *et al.* Inhibition of Propionibacterium acnes by bacteriocin-like inhibitory substances (BLIS) produced by Streptococcus salivarius. *J Drugs Dermatol* 2006; **5**: 868–870.
23 Cosseau C, Devine DA, Dullaghan E, *et al.* The commensal Streptococcus salivarius K12 downregulates the innate immune responses of human epithelial cells and promotes host-microbe homeostasis. *Infect Immun* 2008; **76**: 4163–4175.
24 Oh S, Kim SH, Ko Y, *et al.* Effect of bacteriocin produced by Lactococcus sp. HY 449 onskin-inflammatorybacteria. *Food ChemToxicol* 2006; **44**: 1184–1190.
25 Gueniche A, Benyacoub J, Phillippe D, *et al.* Lactobacillus paracasei CNCM I-2166 (ST11) inhibits substance P-induced skin inflammation and accelerates skin barrier function recovery *in vitro*. *Eur J Dermatol* 2010; **20**: 731–737.
26 Kang BS, Seo JG, Lee GS, *et al.* Antimicrobial activity of enterocins from Enterococcus faecalis SL-5 against Propionibacterium acnes, the causative agent in acne vulgaris and its therapeutic effect. *J Microbiol* 2009; **47**: 101–109.
27 Muizzuddin N, Maher W, Sullivan M, *et al.* Physiologic effect of a probiotic on the skin. *J CosmetSci* 2012; **63**: 385–395.
28 Kim J, Ko Y, Park YK, *et al.* Dietary effect of lactoferrin-enriched fermented milk on skin surface lipid and clinical improvement of acne vulgaris. *Nutrition* 2010; **26**: 902–909.
29 Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician* 2012; **86**: 35–42.
30 Sugarman JL. The epidermal barrier in atopic dermatitis. *Semin Cutan Med Surg* 2008; **27**: 108–114.
31 DaVeiga SP. Epidemiology of atopic dermatitis: a review. *Allergy Asthma Proc* 2012; **33**: 227–234.
32 Wolff KL, Johnson RI. Atopic dermatitis. In: Wolff K, Johnson RA, Fitzpatrick TB, eds. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6 th edn. New York, NY: McGraw-Hill Medical, 2009: 34–36.
33 Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol* 2003; **112**: S128–S139.
34 Eichenfield LF, Tom WL, Berger TG, *et al.* Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatites with topical therapies. *J Am Acad Dermatol* 2014; **72**: 116–132.
35 Kong HH, Oh J, Deming C, *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; **22**: 850–859.
36 Kobayashi T, Glatz M, Horiuchi K, *et al.* Dysbiosis and Staphyloccusaureus colonization drives inflammation in atopic dermatitis. *Immunity* 2015; **42**: 756–766.
37 Glatz M, Bosshard PP, Hoetzenecker W, *et al.* The Role of Malassezia spp. in Atopic Dermatitis. *J Clin. Med* 2015; **4**: 1217–1228.
38 Santos AL, Santos DO, Freitas CC, *et al.* Staphylococcus aureus: visiting a strain of clinical importance. *J Bras Patol Med Lab* 2007; **43**: 413–423.
39 Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. *Semin Immunol* 2013; **25**: 370–377.
40 Song H, Yoo Y, Hwang J, *et al.* Faecali bacterium prausnitzii subspecies–level dysbiosis in the human gut microbiome underlying atopic dermatitis. *J Allergy Clin Immunol* 2016; **137**: 852–860.
41 Gueniche A, Knaudt B, Schuck E, *et al.* Effects of nonpathogenic gram- negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol* 2008; **159**: 1357–1363.
42 Volz T, Skabytska Y, Guenova E, *et al.* Nonpathogenic bacteria alleviating atopic dermatitis inflammation induce IL-10-producing dendritic cells and regulatory Tr1 cells. *J Invest Dermatol* 2014; **134**: 96–104.
43 Lai Y, Cogen AL, Radek KA, *et al.* Activation of TLR2 by a small molecule produced by Staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections. *J Invest Dermatol* 2010; **130**: 2211–2221.
44 Iwase T, Uehara Y, Shinji H, *et al.* Staphylococcus epidermidis Esp inhibits Staphylococcus aureus biofilm formation and nasal colonization. *Nature* 2010; **465**: 346–349.
45 Drago L, Toscano M, De Vecchi E, *et al.* Changing of fecal flora and clinical effect of L. salivarius LS01 in adults with atopic dermatitis. *J Clin Gastroenterol* 2012; **46**(suppl): S56–S63.
46 Sikorska H, Smoragiewicz W. Role of probiotics in the prevention and treatment of meticillin-resistant *Staphylococcus aureus* infections. *Int J Antimicrob Agents* 2013; **42**: 475–481.
47 Pelucchi C, Chatenoud L, Turati F, *et al.* Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012; **23**: 402–414.
48 Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008; **121**: 116–121.
49 Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, *et al.* Probiotics for treating eczema. *Cochrane Database Syst Rev* 2008; **4**: CD006135.
50 Elias J, Bozzo P, Einarson A. Are probiotics safe for use during pregnancy and lactation? *Can Fam Physician* 2011; **57**: 299–301.

Answers

1. d, 2. c, 3. a, 4. e, 5. e, 6. b, 7. a, 8. b, 9. a, 10. c

