

Review Articles

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Use of probiotics in Dermatology - Review

Uso dos probióticos em Dermatologia - Revisão

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RESUMO

Tem crescido o número de evidências dando suporte à existência de uma correlação “eixo intestino-pele”. Há indícios também de que a modulação da microbiota intestinal pode ter um papel importante nas doenças dermatológicas. Estudos têm mostrado que o uso de probióticos pode ter efeitos benéficos no tratamento de doenças de pele com origens inflamatórias, como dermatite atópica, acne, entre outras. Todavia, não há uma padronização sobre em que doses ou quais espécies devem ser utilizadas para os tratamentos. Este artigo tem o objetivo de elaborar um panorama a respeito do uso de probióticos como tratamento de doenças dermatológicas, com foco em mecanismos de ação e resultados clínicos relatados na literatura.

Palavras-chave: Dermatopatias; Pele; Probióticos

ABSTRACT

The number of evidence supporting the existence of a “gut-skin axis” correlation has grown. There is also a suggestion that the intestinal microbiota modulation may play an essential role in dermatological diseases. Studies have shown that probiotics' oral use can have beneficial effects in treating skin diseases with inflammatory origins such as atopic dermatitis, acne, and others. However, there is no standardization as to what doses or species should be used for the treatments. We provide an overview of the use of probiotics as a treatment for dermatological diseases, focusing on mechanisms of action and clinical results reported in the literature.

Keywords: Probiotics; Skin; Skin diseases

INTRODUCTION

The importance of the human microbiome for health has been extensively researched in the last decade. Studies have shown that the microbiota and the host share a positive dependency, and the disruption in the balance between them can have significant consequences.¹ In 2001, the World Health Organization (WHO) defined probiotics as living microorganisms that benefit humans and animals when consumed in adequate quantities.²

The intestinal microbiome strongly influences the host's immune system by protecting against external pathogens and initiating immunoprotective responses.³ Thus, changes in the intestinal microbiome can lead to the development of inflammatory or autoimmune diseases in organs distant from the intestine, such as the skin.³ A considerable change in the relationship between the microorganisms that inhabit the intestine characterizes the intestinal dysbiosis, as well as the expansion of new

bacterial groups, generating an imbalance in the microbiome and possible clinical effects in the human body.⁴ The number of evidence pointing to a correlation between the disease and intestinal dysbiosis has increased in common inflammatory dermatological diseases, such as atopic dermatitis (AD), acne vulgaris, psoriasis, rosacea, and even melasma (Table 1). Also, there is evidence that some peptide-secreting cells with regulatory function present in the skin, brain, and intestine would have the same embryonic origin in the ectoderm.⁵ This type of information corroborates and supports the existence of the "skin-gut axis"⁶ and "gut-brain-skin axis", considering that the emotional state can influence the individual's inflammatory state.⁷ Furthermore, recent research and hypotheses have suggested that the main mechanism by which the skin and the intestine microbiota can affect each other is through modulation of the endocrine and immune system.³

TABLE 1: CLINICAL STUDIES USING PROBIOTICS

Title	Dermatological disease	Treatment	Result
A randomized trial of <i>Lactobacillus plantarum</i> CJLP133 for the treatment of atopic dermatitis ¹⁹	Atopic dermatitis	Two daily doses of <i>L. plantarum</i> 5x10 ⁹ UFC for 12 weeks	Reduction of the SCORAD index significantly higher than the placebo group with a reduction in eosinophil counts and levels of IFN-gamma and IL-4 at the end of treatment.
<i>Lactobacillus</i> ¹⁶ <i>plantarum</i> IS-10506 supplementation reduced SCORAD in children with atopic dermatitis ¹⁶	Atopic dermatitis	Two daily doses of <i>L. plantarum</i> 10x10 ⁹ UFC for 12 weeks	SCORAD and IL-4, INF-gamma, and IL-17 levels were significantly lower at the end of the study in the treated group compared to placebo. IgE levels have not changed significantly.
Effects of probiotics on atopic dermatitis: a randomized controlled trial ¹⁷	Atopic dermatitis	Two daily doses of <i>L. fermentum</i> VRI-033 PCC 1x10 ⁹ UFC for eight weeks	Significant reduction in the SCORAD index in the treated group compared to placebo.
Children with atopic dermatitis show clinical improvement after <i>Lactobacillus</i> exposure ¹⁸	Atopic dermatitis	A daily dose of <i>L. paracasei</i> 2x10 ⁹ UFC, <i>L. fermentum</i> 2x10 ⁹ UFC or a mixture of <i>L. paracasei</i> and <i>L. fermentum</i> 4x10 ⁹ UFC for three months	The treated groups showed a significant reduction in the SCORAD index and an improvement in the quality of life indices compared to placebo. There was no significant difference between groups in the reduction of IgE levels.
Supplementation with <i>Lactobacillus rhamnosus</i> SP1 normalizes skin expression of genes implicated in insulin signaling and improves adult acne ²⁶	Acne	Daily dose of <i>L. rhamnosus</i> SP1 3.0x10 ⁹ UFC for 12 weeks	Significant improvement in the appearance of acne on the skin. Normalization of the expression of genes related to insulin signaling, without this effect in the placebo group.
<i>Bifidobacterium infantis</i> 35624 modulates host inflammatory processes beyond the gut ³⁹	Psoriasis	Daily dose of <i>B. infantis</i> 35624 10 × 10 ⁹ CFU for eight weeks	Significant decrease in plasma levels of TNF-α and C-reactive protein, when compared to placebo.
Clinical Evidence of Effects of <i>Lactobacillus plantarum</i> HY7714 on Skin Aging: A Randomized, Double Blind, Placebo-Controlled Study ⁵³	Rejuvenation	Daily dose 10 × 10 ⁹ CFU/day of <i>L. plantarum</i> HY7714 for three months	Reduction in transepidermal water loss, in the depth of wrinkles, and increase in skin brightness after treatment. Significant 21.73% increase in skin elasticity in the treated group compared to placebo.

The use of probiotics to manipulate the intestinal flora and thus obtain positive results in organs distant from the intestine, such as the skin, is an old practice. However, there is no standardization regarding which doses or species should be used for treatments. This study aims to overview the use of probiotics as a treatment for dermatological diseases, focusing on mechanisms of action and clinical results reported in the literature.

METHODS

In April 2020, we researched the PubMed database for publications covering the use of probiotics in the treatment of atopic dermatitis, acne, psoriasis, rosacea, aging, and melasma. Studies explaining the mechanism of action and clinical trials were prioritized, including original articles and reviews or meta-analyses regarding the topics covered.

Atopic dermatitis

Excessive colonization of pathogenic bacteria on the skin due to epidermal barrier dysfunction and immune deregulation that affects patients characterizes the AD.⁸ There is a reduction in the microbiome's diversity,^{8,9} mainly during episodes of worsening of the disease,⁹ in addition to the high colonization by bacteria such as *Staphylococcus aureus*, which is directly related to the severity of the disease.¹⁰ In the same direction, effective treatments were associated with the microbiota's re-colonization and greater diversity of bacteria.⁸ Evidence suggests a connection between the disease and microbiota dysbiosis, without a specific invading pathogen, in addition to the already known disorders characteristic of atopic dermatitis, such as filaggrin genes mutations and Th-2 response deregulation.⁹

Modulation of the intestinal microbiota has emerged as an alternative in treating atopic dermatitis since it is related to the clinical disease's outcome. A study showed that children with eczema associated with IgE have a lower proportion of bifidobacterium species and less microflora's diversity during childhood.¹¹ Another study revealed that the early colonization of the intestine by *Escherichia coli*, during the second month of life, could bring long-term health benefits, since a lower incidence of atopic dermatitis was noticed in colonized patients when they reached six years.¹²

AD treatment in children using probiotics has been widely studied in recent years. Although the results found may be divergent, a recent meta-analysis showed that intestinal modulation in children could reduce the values of Scoring Atopic Dermatitis (SCORAD).¹³ Still, information about the effective dose, the best time for administration, and which strains are most effective for the treatment remains unclear.¹⁴

A literature review assessed different complementary and integrative therapies (CIT) to treat atopic dermatitis in children.¹⁵ The study observed that supplementation of probiotics remains the best CIT validated by studies for the childhood AD treatment.

The most robust evidence is related to treatment with *Lactobacillus plantarum* and *Lactobacillus fermentum* in children aged 12 months or older. Two different randomized clinical trials evaluated each probiotic, with a duration of 12 months. The stu-

dies showed a reduction in SCORAD when administered alone, without other probiotics strains.¹⁶⁻¹⁹ The improvement was clinically significant because, on average, an improvement of 8.7 points on the SCORAD scale resulted in an improvement of 1.0 point on the global severity scale. However, although another study on the treatment with *L. plantarum* has not shown effectiveness,²⁰ Nevertheless, the latter lasted only six weeks while the others lasted 12 weeks, potentially indicating the beneficial effect of longer treatments.

Acne

Acne is a dermatological disease related to the pilosebaceous unit. It can manifest itself in an inflammatory form, with papules and pustules, or non-inflammatory, with open or closed comedones. Overproduction of sebum, follicular hyperkeratinization, and increased secretion of pro-inflammatory cytokines characterize the condition.²¹

Several factors may be related to the onset of the disease. Western carbohydrate diets have a well-established relationship with acne.²² High glucose loads induce insulin and insulin-like growth factor (IGF -1) production, promoting sebocyte and keratinocyte proliferation, and causing the lipids production in the sebaceous glands.²³ The *Cutibacterium acnes* bacteria role in acne's pathogenesis has been widely studied, although it has not been completely elucidated. Just as the intestinal flora can induce IGF-1,²⁴ it has been shown that *C. acnes* can stimulate the IGF-1 system/ IGF-1 receptors on the skin.²⁵ Thus, it can be suggested that an imbalance of the intestinal flora may lead to a higher production of sebum and higher colonization of the skin by *C. acnes*, disturbing the close balance between the skin flora's members and creating a disease's synergistic cycle.

Oral supplementation of probiotics can be an adjuvant therapy in acne treatment. A study with humans observed that the consumption of *Lactobacillus rhamnosus* SP1 3x10⁹ UFC/day improved the acne appearance on the adults' skin. The therapy could normalize the expression of genes related to insulin signaling, and this change was not seen in the control group.²⁶ Also, a clinical study assessed the synergistic effect of probiotics and minocycline consumption in the treatment of acne compared with the probiotic and antibiotic alone. All groups showed clinical improvement, but the group treated with the association had the lowest number of total lesion, with a significant difference from the other two groups. Also, two patients in the minocycline-treated group had to leave the study because they had vaginal candidiasis, and the probiotic supplementation was an option for possible prevention of adverse events secondary to chronic antibiotic use.²⁷

The use of lactobacilli topically can also be beneficial in reducing acne symptoms. *In vitro* studies have shown that some probiotics strains can inhibit *C. acnes* and other non-beneficial species through bacteriocins' secretion.²⁸ *In vitro* and *in vivo* studies with *Streptococcus thermophilus* demonstrated that the probiotic could increase the production of beneficial lipids in the stratum corneum, such as ceramides, which can retain moisture in the skin,²⁹ and phytosphingosine, which acts against *C. acnes*.³⁰ Topical probiotics can also act by an immunomodulatory me-

chanism on keratinocytes and epithelial cells. The *Streptococcus salivarius* K12 strain was able to inhibit the production of pro-inflammatory cytokines, such as IL-8, in epithelial cells and keratinocytes, most likely by inhibiting the NK-kappa B pathway.³¹

Psoriasis

Psoriasis is an immune-mediated genetic disease that manifests itself in the skin, joints, or nails. It has different clinical manifestation forms, which can be more or less intense, but with typical symptoms such as scaling and plaques on the skin, inflammation, and stiffness of the tissue.³² Although its pathogenesis is not fully understood, Th17 cells and the cytokines produced by them, such as IL-17, IL-22, and IL-23, play critical roles in psoriasis' pathogenesis. The intestinal microbiome is believed to be involved in the development of psoriasis, as well as in the activation of pro-inflammatory Th17 cells.³³ It has been shown that patients with psoriasis and inflammatory bowel disease (IBD), two inflammatory conditions, have a similar pattern of dysbiosis, suggesting the presence of a "gut-microbiome-skin axis" in psoriasis and IBD. The lower presence of symbiotic bacteria, including *Lactobacillus* spp., *Bifidobacterium* spp., *Faecalibacterium prausnitzii*,³⁴ characterize this dysbiosis, as well as the colonization by certain pathobionts, such as *Escherichia coli*, *Salmonella* sp., *Helicobacter* sp., *Campylobacter* sp., *Mycobacterium* sp. and *Alcaligenes* sp.³⁵ Also, *S. aureus* colonizes more abundantly the skin of psoriasis patients than that of individuals without the disease.^{36,37} These reduced levels of beneficial bacteria can lead to deleterious consequences, including changes in specific inflammatory proteins and poor regulation of intestinal immune responses that can affect distant organs.

Probiotic supplementation can play a significant role in the treatment of psoriasis. One study showed that oral administration of *Lactobacillus pentosus* GMNL-77 significantly decreased erythematous lesions and epidermal thickening in mice with imiquimod-induced psoriasis when compared to placebo. The treatment significantly reduced mRNA levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin (IL)-6 and IL-23/IL-17A. Also, the study found that treatment with *Lactobacillus pentosus* GMNL-77 also decreased the spleen weight of the group treated with imiquimod and reduced the number of CD4⁺ T cells producing IL-17 and IL-22 in the spleen.³⁸

Furthermore, a placebo-controlled study showed that supplementation with *Bifidobacterium infantis* 35624 in patients with psoriasis led to a significant decrease in plasma levels of pro-inflammatory markers, such as TNF- α and C-reactive protein, when compared to placebo.³⁹ A case study observed that supplementation with *Lactobacillus sporogens* three times daily combined with 10 mg biotin once daily was able to improve a severe case of pustular psoriasis not responsive to steroids, dapson, and methotrexate.⁴⁰

Rosacea

The possibility that intestinal bacteria and their products may contribute to the development of skin lesions, such as rosacea, has also been studied. In a clinical study, it was found that patients

with inflammatory skin diseases had an imbalanced intestinal microbiome. Rosacea patients had a significantly higher prevalence of small intestinal bacterial overgrowth (SIBO) than patients without the disease. Also, and more importantly, the SIBO eradication induces an almost complete regression of skin lesions in patients with rosacea.⁴¹ In a case study, it was seen that the treatment of a patient affected by rosacea on the scalp with low dose doxycycline and *Bifidobacterium breve* BR03 together with *Lactobacillus salivarius* LS01 was able to promote improvement in skin and eye symptoms.⁴² Although more research in this area are necessary, patients can be counseled on measures to maintain a healthy intestinal microbiome, including consumption of a diet rich in fiber (prebiotics) or modulation of intestinal microflora via oral probiotics.

Photoaging and melasma

Ultraviolet radiation (UVR) is considered the most potent inducer of extrinsic aging. Studies have shown that exposure to UVR can induce significant changes in the human immune system, such as reducing the number of Langerhans cells, change in their morphology, and their ability to present antigens.⁴³ Also, an increase in immunosuppressive cytokines like IL-10 has already been reported.⁴⁴ The use of lactobacilli may represent an alternative skin protection to UVR.

A study with mice demonstrated that supplementation with *Lactobacillus johnsonii* (La1) was able to protect the skin from the harmful effects of UVR, such as a reduction in the number of Langerhans cells and a higher level of IL-10, post-exposure to radiation.⁴⁵ A study with humans tested, for ten weeks, the oral administration of *Lactobacillus johnsonii* and 7.2 mg of carotenoids to healthy women, pre-exposed to simulated or natural sunlight. Compared to placebo, dietary supplementation prevented the UVR-induced decrease in Langerhans cell density and accelerated the recovery of immune system homeostasis after exposure to UVR. The comparison of the minimum erythema dose (MED) showed that, in those who received supplementation, MED increased by 20%.⁴⁶

The study evidenced the association's benefit, despite requiring the comparison between treatment with carotenoids and isolated probiotics. Another study also assessed the association of carotenoids and probiotics. A study with humans tested the effectiveness in treating melasma with a supplement containing beta-carotene, lycopene, and *Lactobacillus johnsonii*. The results showed that the treated group had a significant melasma improvement when it evaluated the Taylor scale and the Melasma Area and Severity Index (MASI) scale.⁴⁷

A study with hairless mice indicated that oral administration of *Bifidobacterium breve* prevented UVR-induced transepidermal water loss compared to mice that received placebo. Also, the administration of *B. breve* suppressed the UVR-induced increase in hydrogen peroxide levels, protein oxidation, and xanthine oxidase activity in the animals' skin.⁴⁸ Another study with mice showed that oral administration of *Lactobacillus acidophilus* reduced the formation of fine lines induced by exposure to UVB radiation. The study attributed this protection to the reduction in the expression of metalloproteinases, such as MMP-1 and MMP-9.⁴⁹

Rejuvenation

The use of probiotics can also benefit other aspects related to skin aging. The use of probiotics can influence intrinsic factors, such as genetics, hormonal status, and oxidative metabolic reactions, and extrinsic factors, such as exposure to solar radiation, tobacco, and psychological stress.

Healthy, normal skin exhibits a slightly acidic pH in the range of 4.2 to 5.6, which helps prevent pathogenic bacterial colonization, regulates enzyme activity, and maintains a moisture-rich environment.⁵⁰ However, after the age of 70, the skin's pH increases significantly, stimulating the proteases' activity.⁵¹ As probiotic metabolism frequently produces acidic molecules, decreasing the pH of the environment,⁵² using probiotics could restore the normal pH of the skin and, consequently, return the levels of proteases' activity to closer to those observed in young and healthy skin.

A clinical study, controlled by placebo, assessed patients between 41 and 59 years, who had dry skin and wrinkles. The study showed that the administration of 1×10^{10} CFU/day of *Lactobacillus plantarum* HY7714 significantly suppressed the loss of transepidermal water, reduced the depth of wrinkles, and increased the skin brightness after three months of treatment compared to day zero. Furthermore, at the end of the study, the group's skin elasticity treated with probiotics increased by 21.73%, with a significant difference in relation to the placebo group.⁵³ These data suggest that the use of probiotics may work as a nutricosmetic (Table 1).

CONCLUSION

The balance or imbalance of the human's microbiome can produce effects in different body organs, such as the skin and the intestine. Various dermatological diseases, usually with inflammatory factors involved, end up responding to the imbalance or modulation of the intestinal microbiota significantly. It occurs mainly due to the suppression or activation of the immune system caused by the modulation of cytokine production and activation of the body's defense cells, which interferes with the disease's pathophysiology.

Probiotic supplementation to treat dermatological diseases has been studied for many years. Although it is seen mainly as a complementary therapy in clinical practice, the use of probiotics alone can present a positive result. When combined with conventional therapy, it manages to improve the clinical outcome of the treatment further. Also, its use reduces the adverse events of more aggressive therapies, such as systemic antibiotics. With clear benefits, concrete results have emerged more and more with the growing number of studies on this subject. However, there are still gaps in knowledge and information that need to be better understood, such as the best strains to be used, the effective doses, or best dosing schedule. ●

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