

Use of oral probiotics in inflammatory skin diseases. Literature review

Probióticos orais em doenças inflamatórias da pele. Revisão de literatura

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Abstract

The gut microbiome is an important in the health and pathogenesis of some diseases. Beyond digestion, it interferes with the immune system and even with the skin health. Evidence shows that intestinal changes can be involved in dermatological manifestations, such as rosacea, acne, and atopic dermatitis. The use of probiotics has been studied, because it is possible to create a strategy to modulate the immune system and reduce the manifestations of these diseases. In this study, we performed a bibliographic review of the clinical evidence on the use of oral probiotics in the treatment of rosacea, acne, and atopic dermatitis. The search was made in electronic databases, such as PubMed, Scientific Electronic Library Online (SCIELO), Latin American Literature in Health Sciences (LILACS), and Google Scholar, in the past 5 years. A limited number of studies have been found, but all have shown the benefit and improvement of lesions in patients, as well as the reduction of pro-inflammatory cytokines by the mechanism of immunomodulation. Search results found out that the use of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Bifidobacterium bifidum* are promising in the three pathologies. Moreover, probiotics used in association with oral antibiotics obtained better responses than when used alone. Despite the positive response, more efforts are required to fully understand the exact mechanisms and therapeutic effects of probiotics in the management of inflammatory dermatological diseases.

Keywords: Acne vulgaris. Dermatitis. Atopic. Microbiota. Probiotics. Rosacea.

Resumo

A microbiota intestinal tem importância na saúde e na patogênese de algumas doenças, pois além da digestão, interfere no sistema imunológico e até mesmo na saúde da pele. Evidências mostram que alterações intestinais podem gerar manifestações dermatológicas, como rosácea, acne e dermatite atópica. O uso de probióticos vem sendo estudado pois é possível criar estratégias para modular o sistema imunológico, os quais diminuem a manifestação dessas doenças. Nesse estudo, foi realizado uma revisão bibliográfica das evidências clínicas sobre o uso dos probióticos orais no tratamento da rosácea, acne e dermatite atópica através de uma pesquisa nos bancos de dados eletrônicos, como PubMed, Scientific Electronic Library

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Online (SCIELO), Literatura Latino-Americana em Ciências da Saúde (LILACS) e Google Scholar, nos últimos 5 anos. Foram encontrados um número limitado de estudos, mas todos evidenciaram o benefício e melhora das lesões da rosácea, acne e dermatite atópica, assim como a diminuição de citocinas pró-inflamatórias. Os resultados encontrados sugerem que o uso de *Lactobacillus acidophilus*, *Bifidobacterium lactis* e *Bifidobacterium bifidum* são promissores nas três patologias. Concomitante, os estudos mostraram que os probióticos usados em conjunto aos antibióticos orais obtiveram melhores respostas do que usados isoladamente. Apesar da resposta positiva, são imprescindíveis mais esforços para a compreensão total dos mecanismos exatos e efeitos terapêuticos dos probióticos orais no manejo de doenças dermatológicas inflamatórias.

Palavras-chave: Acne Vulgar. Dermatite atópica. Microbiota. Probióticos. Rosácea.

Introduction

The intestinal microbiota is important for the health and may be involved in the pathogenesis of some diseases. In addition to digestion, it interferes with the immune system, intestinal permeability, hormonal actions, inflammatory reactions, and even the skin health¹⁻⁴. The intestinal microbiome is unique in each individual, influenced by genetic and environmental factors; however, there are common aspects in the composition and function among healthy subjects as well as among subjects with certain diseases. This denotes that it is essential to have a balanced microbiota for the maintenance of the individual's health¹. In adult individuals, most bacteria that make up the intestinal flora are from the phyla *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Proteobacteria*. Infants have greater microbiota variability, but there is stabilization after infancy. The gut microbiome is subject to changes during life due to environmental factors and different pathologies¹.

Intestinal bacteria are essential for the health and regulation of the immune system. The imbalance of this flora allows the colonization of the host by opportunistic and/or pathogenic microorganisms, which may cause chronic inflammatory diseases. There is evidence that the intestinal microbiota influences skin health; therefore, intestinal alterations can contribute to dermatological manifestations, such as rosacea, acne, and atopic dermatitis¹. One of the skin functions is to protect the organism by acting as a barrier to extrinsic factors, including to microorganisms, and the skin microbiome has a significant part to play in this role as a barrier, as it has a strong symbiotic relationship. Moreover, the mechanisms of homeostasis and dysregulation of the intestinal microbiota have many applications for the skin^{2,3}. The intestinal microbiota and probiotics can interfere in inflammatory processes, oxidative stress, blood glucose control, tissue lipid composition, and emotional behavior, and the use of oral probiotics can help in the regulation of intestinal microflora, which can be beneficial for the

individual's health, even indirectly interfere when used in the treatment of inflammatory dermatological diseases, such as rosacea, acne, and atopic dermatitis¹⁻³.

The balance of intestinal microbiota is essential for the homeostasis of the host organism, and it is important to understand the role of these bacteria and how their dysregulation can lead to the emergence of diseases; thus, it is possible to create strategies to modulate the immune system through probiotics and generate beneficial effects for the individual's health^{1,3}.

The aim of this study was to carry out an exploratory systematic review, to address the effectiveness of oral probiotics in the treatment of inflammatory skin diseases such as acne vulgaris, rosacea, and atopic dermatitis, analyze the frequency of improvement in these dermatological diseases, check if probiotics showed a concomitant action with other drugs, and compare the results of the use of probiotics in acne vulgaris, rosacea, and atopic dermatitis, highlighting which of these conditions had the best results.

Methods

This study includes a search developed to perform a review on the effectiveness of oral probiotics used in three inflammatory dermatological diseases, namely, atopic dermatitis, acne vulgaris, and rosacea.

For this study, 60 articles were reviewed and 24 were selected. The data search was performed, collecting complete articles in Portuguese and English, and published between the years 2015 and 2020. The electronic databases used were PubMed, Scientific Electronic Library Online (SCIELO), Latin American Literature in Sciences of the Health (LILACS), and Google Scholar, always using the keywords: "probiotics"; "acne"; "rosacea"; "atopic dermatitis"; and "dermatology." All studies that did not mention or performed experimental intervention in humans were excluded from the study.

Results and discussion

Acne vulgaris

Acne is a chronic inflammatory skin condition that occurs as a result of an inflammatory process of the pilosebaceous complex⁵. There are several types of acne, the most common is acne vulgaris, which clinically presents with comedones, papules, pustules, nodules, and cysts^{6,7}. Despite being a multifactorial and polymorphic disease, acne mainly affects teenagers, since at puberty androgens begin to be produced and secreted by the adrenal and sex glands. These hormones stimulate keratinocytes to cause follicular occlusion, and increase and modify the secretion of the sebaceous glands, leading to an imbalance in the environment^{5,8}. Consequently, there is overproliferation of the bacteria that reside in sebaceous follicles (*Cutibacterium acnes*, *Corynebacterium*, and *Staphylococcus*) which dysregulates the innate immune system, through cytokines (TNF-alpha, IL-1, and IL8), and activation of toll-like receptors (TLR) and CD14 receptors⁹. The mechanism mentioned previously leads to the secretion of inflammatory mediators resulting in skin lesions^{5,6}.

In research studies, supplementation with oral probiotics has shown to be promising. It is believed that they can function as immunomodulators, reducing oxidative stress, and the release of inflammatory mediators from the skin^{1,5,6}. Thus, studies have shown that supplementation with *Lactobacillus acidophilus*, *Lactobacillus delbueckii bulgaricus*, and *Bifidobacterium bifidum* was as effective as minocycline in treating acne vulgaris, with a 67% reduction in lesions after 12 weeks. Furthermore, combination with the antibiotic resulted in an even more evident effect³. The strains of *L. acidophilus* and *L. bulgaricus*, administered for two periods of 8 days with a 2-week interval, were also efficient in 300 patients, who improved by 80%¹⁰.

The combination of probiotic therapy (250 mg of *L. acidophilus* and *B. bifidum*) with oral antibiotics demonstrates good results in another study with 40 patients, with an improvement of skin lesions and better tolerance to antibiotics^{10,11}. A clinical trial showed that a 6-week regimen of oral *Lactobacillus johnsonii* accelerated the recovery of the skin's immune system. Since this system is strengthened, there is an improvement in the acne condition, as it reduces the proliferation of pathogenic bacteria, which are responsible for the formation of such lesions¹². Trials showed that probiotics can also decrease the glycemic index and reduce cutaneous insulin-like

growth factor 1 signaling, decreasing predisposition and induction of acne¹³. Another study also showed that the consumption of a liquid supplement containing *Lactobacillus rhamnosus* for 12 weeks resulted in improvement in adult acne through normalization of insulin signaling¹⁴.

Rosacea

Rosacea is a chronic inflammatory dermatological disease that affects the face, especially the cheeks, forehead, nose, and chin¹⁵. Clinically, its symptoms are frequent flushing, erythema, papules, pustules, and telangiectasia and may have secondary manifestations such as a burning sensation, plaques, edema, and ocular manifestations, among others^{8,9}. Rosacea is classified into four types, the most common being the erythemato-telangiectatic. It is a multifactorial dermatosis⁸ with an important genetic background and may be associated with dysregulation of the innate and adaptive immune system, neurovascular changes and microbiome imbalance^{8,9}. Exposure to UV rays or extreme temperatures, changes in microbiota, consumption of certain foods, and stress can be triggering factors for the disease¹⁶.

Several mechanisms trigger the inflammatory response in rosacea, namely, the overexpression of the TLR-2 in epidermal skin cells^{9,16}, causing an exacerbation of keratinocyte activation and modification in the behavior of bacteria in the skin microbiota, such as *Staphylococcus epidermidis*, so that it secretes more proteins and antigens, which are recognized by TLR-2. Rosacea seems to be associated with some bacteria such as *Helicobacter pylori*, *S. epidermidis*, *Chlamydia pneumonia*, *Bacillus oleronorum* and mites like *Demodex*. Furthermore, there seems to be a relationship between alteration in the intestinal microbiota and rosacea skin lesions. Consequently, there is an increase in kallikrein and the other inflammatory mediators, and cathelicidin that may be associated with this pro-inflammatory status or linked to this overexpression of TLR observed in rosacea. Thus, it is possible to affirm that the pathogenicity has some similarities with acne, with some the exceptions, like the bacteria *Cutibacterium acnes*, which does not seem to play such an important role in rosacea¹⁷. Different from acne, rosacea has no follicular obstruction or comedones, one of the most important differences from acne¹⁷.

There are few studies evaluating the use of oral probiotics in the treatment of rosacea, but it has been reported that most patients with rosacea tend to have

systemic comorbidities, including gastrointestinal tract diseases such as gastroesophageal reflux, Crohn's disease, celiac disease, irritable bowel, and colitis, suggesting a relationship between rosacea and the digestive tract, namely, the bowel^{17,18}. One study reported that rosacea improved in patients who were treated with a low dose of doxycycline (40 mg/day) concomitantly with the use of oral probiotics (containing *Bifidobacterium breve* BR03 and *Lactobacillus salivarius* LS01) for 8 weeks¹⁹.

Atopic dermatitis

As a chronic inflammatory skin disease, atopic dermatitis affects all age groups, but its acute form is predominant in children and infants, manifesting with erythema, vesicles, lichenification, and intense itching, which usually appear on the face and upper and lower limbs⁶. Although its etiology and pathophysiology are still not fully understood, there is an interaction between genetic susceptibility and pre and postnatal environmental conditions²⁰, with a significant impairment of the epidermal skin barrier and consequent disturbances of the skin microbiome. The genetic impairment of the skin barrier can cause and in turn be aggravated by a cytokine imbalance (IL-4; IL-13), with predominant activation of Th2 lymphocytes, resulting in increased total IgE immunoglobulin serum levels, and increased circulating eosinophils⁶. As already mentioned, intestinal microbiota influences the development of the newborn's immune system, and is associated with the induction of cell maturation responsible for regulating immune responses⁶. This immunoregulatory action was tested in patients with atopic dermatitis by supplementation with oral probiotics. A meta-analysis with duration of 12 weeks. This study showed an improvement in the SCORAD index in 1070 children (no specified age) with moderate atopic dermatitis supplemented daily with *Lactobacillus fermentum* and *L. salivarius*, and another showed that the mixture of strains of *Bifidobacterium* and *Lactobacillus casei* had an equally promising effect³.

Bindurani showed in their study, with a duration of 8 weeks, that atopic dermatitis lesions in infants aged 12-36 months were considerably reduced with supplementation for twice a day with *L. acidophilus* and *Bifidobacterium lactis*¹³. In another study, the mixture of *Lactobacillus paracasei* GMNL-133, *L. fermentum* GM090 also reduced the SCORAD index and total IgE levels, in addition to a statistically significant reduction of IL-4 levels in the epidermis, showing that intestinal immunomodulation through microbiome modification,

especially in early childhood, contribute to the prevention of atopic dermatitis and to reduce the exacerbation of allergic sensitization caused by overactivation of Th2 cells and production of cytokines, such as IL-4, IL-5, and IL-13²¹. A similar treatment response was evident in a randomized double-blind study that administered *B. lactis* CECT 8145, *B. longum* CECT 7347 and *Lactobacillus casei* CECT 9104 capsules, using maltodextrin as a vehicle for 12 weeks, in patients aged 4-17 years²².

Conclusion

It is evident that the studies demonstrate a significant improvement and benefit from the use of oral probiotics in the treatment of acne, rosacea, and atopic dermatitis. Although more tests are needed to determine dosage, most appropriate age and which strains are definitely effective, the results of the studies suggest that the use of *L. acidophilus*, *B. lactis*, and *B. bifidum* is promising in the three diseases. At the same time, probiotics used in conjunction with oral antibiotics had better responses than those used alone. On a large scale, the results are still insufficient, but the effects are more favorable in relation to acne and atopic dermatitis, compared to rosacea, where studies are scarce, and some are controversial. However, more efforts are needed to fully understand the exact mechanisms and therapeutic effects of oral probiotics in the management of inflammatory skin diseases.

What does this study add?

By reading this article, you will be able to review the most recent data on this subject and analyse which strains were mostly used with the best results, so you can draw your conclusions about the probiotics and skin health.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of people and animals. The authors declare that for this investigation no experiments were carried out on humans and/or animals.

Data confidentiality. The authors declare that no patient data appears in this article.

Right to privacy and written consent. The authors declare that no patient data appears in this article.

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