



## Major considerations of the nutrients, probiotics and gut microbiota in the treatment of psoriasis and atopic dermatitis: a concise systematic review

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### Abstract

**Introduction:** Skin conditions contributed 1.79% to the global burden of 306 diseases and injuries in recent years. Individual skin diseases varied in size, from 0.38% of the total burden for atopic dermatitis (AD), 0.29% for acne vulgaris, and 0.19% for psoriasis. The microbiome of normal human skin showed high diversity and high interpersonal variation. Imbalance of the intestinal microbiota can promote the onset and progression of human diseases. **Objective:** It was analyzed, through a systematic review, the main considerations of the nutrients, probiotics, and gut microbiota in the treatment of psoriasis and atopic dermatitis. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from January to April 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according

to the Cochrane instrument. **Results and Conclusion:** A total of 120 articles were found, and 29 articles were evaluated in full, and 20 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 23 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with  $X^2=79.5\%>50\%$ . It was concluded that aesthetically healthy skin includes manipulation of intestinal function. Treatments that augment or repair a leaky gut barrier may become important as adjunctive therapy in the management of inflammatory skin conditions and may help increase the effectiveness of standard dermatotherapy. All of this would be aimed at modifying the secretory, metabolic, and hormonal activity of the intestinal epithelium to impact skin inflammation.

**Keywords:** Healthy skin. Nutrients. Probiotics. Psoriasis. Atopic dermatitis. Gut microbiota.

## Introduction

According to epidemiological data, skin conditions contributed 1.79% to the global burden of 306 diseases and injuries in recent years [1,2]. Individual skin diseases varied in size, from 0.38% of the total burden for atopic dermatitis (AD), 0.29% for acne vulgaris, 0.19% for psoriasis [3], 0.19% for urticaria, 0.16% for viral skin diseases [4,5], 0.15% for fungal skin diseases, 0.07% for scabies, 0.06% for malignant cutaneous melanoma, 0.05% for pyoderma, 0.04% for cellulitis, 0.03% for keratinocyte carcinoma, 0.03% for decubitus ulcer and 0.01% for alopecia areata. All other cutaneous and subcutaneous diseases made up 0.12% of the total [6-8].

In this context, it was found that the microbiome of normal human skin presented high diversity and high interpersonal variation. The microbiota compositions of diseased lesional skin (in AD and psoriasis) have shown distinct differences compared to healthy skin [2,3]. The role of microbial colonization in establishing immune system homeostasis has been reported, while host-microbe interactions and genetically determined variation in stratum corneum properties may be linked to skin dysbiosis. Both are relevant to skin disorders with aberrant immune responses and/or disturbed skin barrier function. Modulation of skin microbiota composition to restore host-microbiota homeostasis may be a future strategies to treat or prevent the disease [9].

In the human microbiota, there is a symbiotic relationship between the human organism and microorganisms [4,5]. An adult's organism supports, in a healthy way, a community of microorganisms, including bacteria, viruses, and fungi, and the genetic elements that constitute the human microbiota, where all these microorganisms, beneficial and possible pathogens, coexist. Thus, the human gastrointestinal tract (GIT) contains more than 10 trillion bacteria, covering more than 500 different species. This microbiota can weigh up to 2kg. One-third of our intestinal microbiota is common to most people, the remaining 2/3 is specific to each of us [10].

Microorganisms perform important functions such as conservation and promotion of the development of immunological defenses, they exert considerable influence on a series of biochemical reactions in the host, such as the transformation of dietary fiber into simple sugars, the transformation of short-chain fatty acids, and other nutrients to be absorbed. , production of vitamin K, vitamin B12, and folic acid, participation in the metabolism and recirculation of bile acids, transformation of potentially carcinogenic agents, and activation of bioactive compounds [6,7]. The imbalance

of the intestinal microbiota can promote the onset and progression of human diseases [10].

The presence of bacteria in the intestine is mandatory for the development of various functions of the GIT. Furthermore, the gut microbiota is fundamental for the activation of the immune system, with emphasis on *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA to remove antigens through a non-inflammatory pathway and increasing T and B lymphocytes, in the absence of gut microbiota, the motor function of the intestine is compromised [10]. Lactobacilli and Bifidobacteria inhibit the growth of exogenous and/or harmful bacteria, stimulate immune functions, aid in the digestion and/or absorption of food ingredients and minerals, and contribute to the synthesis of vitamins [11].

In this sense, one of the first skin diseases in which the positive influence of the use of probiotics was noticed was AD. Atopy is a disease that deregulates the immune system, causing respiratory manifestations, such as asthma or bronchitis, and/or skin inflammations, such as eczema. Recent studies have shown that the concomitant use of probiotics with specific treatment in atopic individuals helps to reduce disease attacks [7]. There are two other diseases with some studies regarding the use of probiotics, which are inflammatory acne and psoriasis. In the first case, bacteria are very important and, when the lesions worsen, an imbalance in the microbiota is detected. In psoriasis, the use of probiotics seems to help, reducing skin inflammation [11].

Therefore, the present study analyzed, through a systematic review, the main considerations of the nutrients, probiotics, and gut microbiota in the treatment of psoriasis and atopic dermatitis.

## Methods

### Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: 03/17/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 03/17/2024.

### Data Sources and Research Strategy

The literary search process was carried out from January to April 2024 and developed based on Scopus,

PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The Health Science Descriptors (DeCS/MeSH Terms) were used: "Healthy skin. Nutrients. Probiotics. Psoriasis. Atopic dermatitis. Gut microbiota", and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

### Study Quality and Risk of Bias

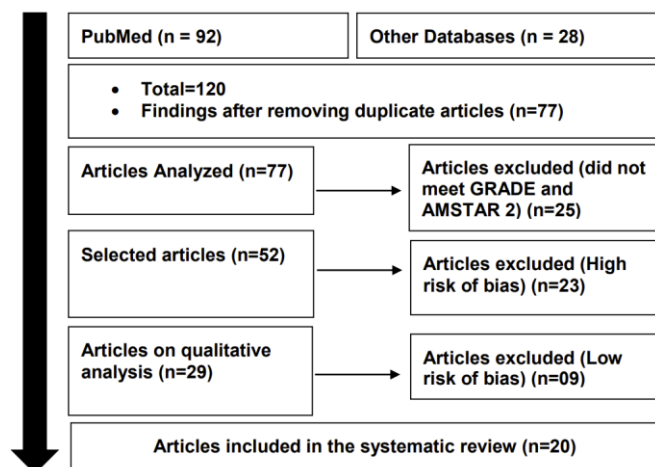
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

## Results and Discussion

### Summary of Findings

A total of 120 articles were found that were subjected to eligibility analysis, with 20 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with  $X^2=79.5% > 50%$ . Considering the Cochrane tool for risk of bias, the overall assessment resulted in 23 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2.

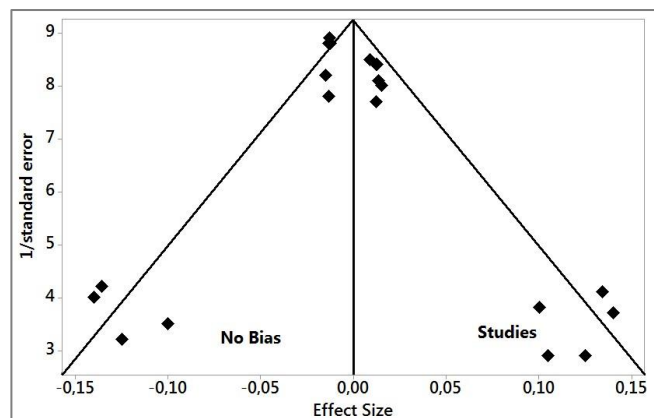
Figure 1. Flowchart - Article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=20 studies).



Source: Own authorship.

### Major Findings

According to the main literature findings regarding the development and understanding of regulatory processes involving the skin-intestinal microbiota axis, chronic inflammation is a crucial factor in the development of autoimmune diseases [1-3]. Specifically, pathological T cells residing in the skin of patients with psoriasis produce excess IL-17 in response to IL-23, triggering the production of pro-inflammatory mediators IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ , and keratinocyte chemoattractants. These signaling molecules sustain chronic skin inflammation and cause epidermal hyperplasia, the main feature of psoriatic plaques. In this context, patients with psoriasis who consumed *B. infantis* 35624 exhibited a decrease in pro-inflammatory markers IL-6, TNF- $\alpha$ , and serum CRP. These effects may be attributed to probiotic-induced Treg proliferation [12].

In this sense, the interaction of hormonal, neuronal, and inflammatory signaling has a major impact on skin health [4-6]. Psychological suffering

alters the physiology of the skin, stimulating pro-inflammatory responses. Indeed, acne, a common skin condition among adolescents and young adults, is correlated with neurogenic inflammation of the skin, which alters the functionality and survival of mast cells and induces the production of vasodilatory and pro-inflammatory factors. Furthermore, psychological stress positively regulates the secretion of prolactin, which in turn determines the proliferation of keratinocytes and the production of sebum by the sebaceous glands. Similarly, the onset of autoimmune skin diseases such as psoriasis and allergic disorders such as AD is correlated with chronic inflammation and mast cell degranulation [12].

In this regard, prolonged underlying inflammatory responses induce keratinocyte apoptosis, contributing to the distinct cutaneous manifestations of these disorders. Current therapeutic approaches are difficult for the patient or have little effect. Probiotic bacteria with anti-inflammatory properties have the potential to bring therapeutic benefits to people suffering from neurogenic skin inflammation or autoimmune skin diseases [7]. However, more clinical evidence is needed to support its routine use in medical practice. Likewise, probiotics that protect keratinocytes from oxidative stress or induce skin reepithelialization may be of invaluable importance for non-healing wounds [11].

In this context, changes in the composition of the skin microbiota and simultaneous bacterial overgrowth in the small intestine are quite common among individuals with acne rosacea. Overpopulation of *Propionibacterium acnes* has been recorded in acne patients. Antibiotics targeting *P. acnes* are conventionally used to resolve acne. It has been reported that the increase in the skin population of *Staphylococcus epidermidis* excludes *P. acnes* from sebaceous hair follicles [7,8]. The antimicrobial effects of *S. epidermidis* are attributed to the production of short-chain fatty acids that exert direct microbicidal actions against *P. acnes*. Interestingly, stimulation of *S. epidermidis* growth can be achieved by strain-specific Lactobacillus supplementation. Indeed, *L. brevis* DSM17250 has been reported to secrete a peptide that stimulates the proliferation of *S. epidermidis*. As a result, supplementation with *L. brevis* DSM17250 may have indirect antimicrobial effects on skin pathogens [12].

Other probiotic strains have been reported to directly inhibit *P. acnes*. Results of in vitro experiments showed that the strains *L. casei* NCFB 161, *L. acidophilus* NCFB 1748, *L. plantarum* DSM 12028, *L. gasseri* NCFB 2233, and *Lactococcus lactis* NCIMB 6681 exerted antimicrobial effects against *P. acnes*, which were improved when combined with prebiotics [7]. Likewise, *Lactococcus sp.* Therefore, probiotic

supplementation can also be used to alleviate inflammation, a key aspect of acne breakout [12].

Added to this, the prevalence of AD in developing countries is approaching that of developed countries, in which AD affects 20% of the pediatric population. This increase is associated with significant variations in hygiene, intestinal microbiota, exposure to bacterial endotoxins, outdoor life with contact with animals, air pollution, climate, and diet [8]. Genetic (change in skin barrier function) and immunological factors coincide with environmental factors [13].

Furthermore, AD is the result of an imbalance of the Th1/Th2 leukocyte population that leads to excessive mast cell degranulation and a Th2-mediated allergic response. Phenotypically, this translates into skin erythema, hemorrhage, and itching that can be triggered by genetic and environmental factors. Most studies on AD relief focus on two parameters; inflammation and composition of the intestinal and skin microbiota [8]. It was demonstrated that supplementation with probiotics changed the differentiation of T cells towards Th1 and Treg populations and, concomitantly, the composition of the microbiota was altered, favoring the reduction of type I hypersensitivity. Likewise, *L. plantarum* IS-10506 attenuated the levels of specific inflammation markers, such as IL-4, IL-17, and interferon- $\gamma$  (IFN- $\gamma$ ), and increased the expression of immunomodulatory factors Forkhead box P3 (Foxp 3+) and IL-10 in pediatric patients with AD who received this probiotic strain orally [12].

In this sense, AD skin lesions are often colonized by high loads of *S. aureus*. Therapeutic interventions that limit this pathogenic population result in clinical improvement of cutaneous manifestations [8]. It was demonstrated that *L. johnsonii* NCC 533 promoted the expression of antimicrobial peptides and inhibited the adhesion of *S. aureus* to an *in vitro* reconstructed human epidermis model. In this text, *S. aureus*-positive AD patients participating in an open-label multicenter study experienced improved skin appearance after topical application of a lotion containing heat-treated *L. johnsonii* NCC 533 cells [12].

In this scenario, it is not surprising that several intestinal pathologies have skin comorbidities. However, the reason for this remains poorly explored, and neither major research in gastroenterology nor dermatology has systematically investigated the skin-intestinal axis [1,2]. Thus, in reviewing the field, several mechanistic levels have been proposed at which the gut and skin may interact in physiological and pathological circumstances. The intestinal microbiota has enormous metabolic capacity along the intestine-skin axis. Dietary or microbiota metabolites are accessible to the skin.

Therefore, after defining key open questions about the nature of these metabolites, how they are detected, and what skin changes they can induce, understanding these pathways will lead to new therapeutic strategies based on targeting one organ to improve the health of the other [14].

A diet with a low glycemic load, rich in plant fiber and low in processed foods, has been associated with an improvement in acne, possibly through intestinal changes or attenuation of insulin levels. While there is much interest in the human microbiome, there is much more unknown, especially along the skin axis [3]. Collectively, the evidence suggests that approaches such as plant-based foods and supplements may be a viable alternative to the current standard of first-line care for moderate acne, which typically includes antibiotics. Although patient compliance with major dietary changes is likely to be much lower than with medications, it is a treatment route that deserves further study and development [15].

Moreover, psoriasis is a common chronic inflammatory systemic disease. The skin and gut microbiota are involved in immunopathogenesis and can substantially modulate psoriasis. Recent innovative methods, such as 16S rRNA sequencing, significantly facilitate the analysis of the intestinal microbiome. Thus, analysis of the microbiome in patients with psoriasis before, during, and after treatment provides a basis for identifying potential biomarkers to predict individual responses to treatment and facilitate the decision on a particular treatment [16]. Besides, dysregulated gut and skin microbiomes were found to be associated with psoriasis vulgaris. There is also a clear association between inflammatory bowel disease and this condition [17].

To the skin microbiome, changes were observed in the relative abundance of Firmicutes, Actinobacteria, and Proteobacteria. Furthermore, *Staphylococcus spp* and *Streptococcus spp* were detected more frequently in lesional skin. Changes in the gut microbiome were characterized by a decrease in the Bacteroidetes phylum and an increase in the *Faecalibacterium genus*. It is therefore suggested that dysbiosis of the skin and intestinal microbiota may contribute to psoriasis [17]. In this context, despite conflicting findings, patients with psoriasis often had a distinct microbial composition in the skin and intestine, especially in the main bacterial phyla, Firmicutes, Bacteroidetes, and genus *Akkermansia* [18]. Furthermore, bacterial DNA has been found in patients with psoriasis, both locally and systemically, suggesting a crucial role of bacteria in psoriatic disease and future studies in this field [19].

In this context, therefore, probiotics and prebiotics are microbiota management tools to improve host

health. They target gastrointestinal effects through the gut. Over the past decade, research on the gut microbiome has accumulated rapidly and has been accompanied by a growing interest in probiotics and prebiotics as a way to modulate the gut microbiota [7]. Given the importance of these approaches to public health, it is timely to reiterate factual and supportive information about their clinical application and use for skin treatments. As examples, strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* have a long history of safe and effective use as probiotics, but *Roseburia spp*, *Akkermansia spp*, *Propionibacterium spp*, and *Faecalibacterium spp* show promise for the future. For prebiotics, glucans and fructans are well proven and there is evidence based on the prebiotic effects of other substances such as mannose oligomers, glucose, xylose, pectin, starches, human milk, and polyphenols [20]. Thus, current scientific evidence reveals the existence of an important Skin-Gut Microbiota axis, highlighting the management of dermatoses through probiotics and prebiotics, as well as lifestyle changes.

## Conclusion

It was concluded that aesthetically healthy skin includes manipulation of intestinal function. Treatments that augment or repair a leaky gut barrier may become important as adjunctive therapy in the management of inflammatory skin conditions and may help increase the effectiveness of standard dermatotherapy. All of this would be aimed at modifying the secretory, metabolic, and hormonal activity of the intestinal epithelium to impact skin inflammation.

## CRedit

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Lorena Lemos de Aquino; **Writing - original draft** - Michelle Silva Rocha, Lorena Lemos de Aquino, Vinícius Bezerra Lopes, Raimundo Nonato de Araújo Soares, Mayta Queiroz Monteiro Braga, Thais Fernandes Borges, Jorge Luiz de Freitas, Sonaldo Marcos Vieira Barbosa, Lucianna Rodrigues Carneiro, Pâmela Crestani Loro; **Writing-review & editing**- Michelle Silva Rocha, Lorena Lemos de Aquino, Vinícius Bezerra Lopes, Raimundo Nonato de Araújo Soares, Mayta Queiroz Monteiro Braga, Thais Fernandes Borges, Jorge Luiz de Freitas, Sonaldo Marcos Vieira Barbosa, Lucianna Rodrigues Carneiro, Pâmela Crestani Loro.

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