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REVIEW ARTICLE

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Major approaches to the skin-gut microbiota axis under the light of the nutrology of probiotics and prebiotics: a systematic review

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Abstract

Introduction: Skin conditions contributed with about 2.0% to the global burden of 306 diseases and injuries in recent years. The microbiota compositions of lesional skin in atopic dermatitis and psoriasis showed distinct differences compared to healthy skin, as well as healthy skin presented a healthy gut microbiota in the light of nutrology. **Objective:** It was to analyze, through a systematic review, the main considerations on the Skin-Gut microbiota axis, presenting the importance of intestinal health through nutrology, probiotics and prebiotics. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from August to October 2022 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:** A total of 255 articles were found. A total of 76 articles were evaluated in full and 20 articles were included. Current scientific evidence reveals the existence of an important Skin-Gut microbiota axis in the presence of nutrients responsible for this, highlighting the management of dermatoses through probiotics and prebiotics, as well as changes in lifestyle. **Conclusion:** Management of aesthetically healthy skin includes manipulation of bowel 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 to enhance the effectiveness of standard dermal therapy.

Keywords: Healthy skin. Gut microbiota. Nutrology. Probiotics. Prebiotics.

Introduction

As epidemiological data, skin conditions contributed about 2.0% 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 to atopic dermatitis (AD), 0.29% to acne vulgaris, 0.19% to psoriasis **[3]**, 0.19% to 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 showed high diversity and high interpersonal variation. Microbiota compositions of diseased lesional skin (in AD and psoriasis) showed 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 for 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 strategy to treat or prevent the disease **[9]**.

In the human microbiota, there is a symbiotic relationship between the human body and microorganisms **[4,5]**. The body of an adult sustains, 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 eventual pathogens, live together. Thus, the human gastrointestinal (GI) tract contains more than 10 trillion bacteria, comprising more than 500 different species. This microbiota can weigh up to 2 kg. One-third of our gut microbiota is common to most people, the remaining 2/3 are specific to each of us **[10]**.

Also, microorganisms perform important functions such as conservation and promotion of the development of immunological defenses and exert considerable influence on a series of biochemical reactions of the host such as the transformation of dietary fiber into simple sugars, a 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, a transformation of potentially carcinogenic agents and activation of bioactive compounds **[6,7]**. The imbalance of the gut microbiota can promote the appearance and progression of human diseases **[10]**.

Thus, the presence of bacteria in the intestine is mandatory for the development of several functions of the GI tract. In addition, 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 noninflammatory path 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 disrupts the immune system, causing respiratory manifestations, such as asthma or bronchitis, and/or skin inflammation, such as eczema. Recent studies have shown that the concomitant use of probiotics with specific treatment, in atopic individuals, helps to reduce disease crises **[7]**. There are two other diseases with some studies regarding the use of probiotics, which are inflammatory acne and psoriasis. First, bacteria are very important and, when the lesions worsen, an imbalance of the microbiota was detected. In psoriasis, the use of probiotics seems to help by decreasing skin inflammation **[11]**.

Therefore, the present study aimed to analyze, through a systematic review, the main considerations on the skin-gut microbiota axis, presenting the importance of intestinal health through nutrology, probiotics, and prebiotics.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and metaanalysis: //www.prisma-statement.org/).

Search Strategy and Search Sources

The search strategies for this systematic review were based on the keywords (MeSH Terms): *"Healthy skin. Gut microbiota. Nutrology. Probiotics. Prebiotics"*. The research was carried out from August to October 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 5 years were selected. In addition, a combination of keywords with the Booleans "OR", "AND" and the operator "NOT" were used to target scientific articles of interest

Study quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, 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 through the analysis of the Funnel Plot graph, using Cohen's test (d).

Results and discussion

Summary of Findings

A total of 255 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 76 articles. A total of 76 articles were evaluated in full and 20 articles were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 68 studies with a high risk of bias and 87 studies that did not meet GRADE. According to the GRADE instrument, most studies showed homogeneity in their results, with I^2=37.6%<50%.

Figure 1. Flowchart showing the article selection process.

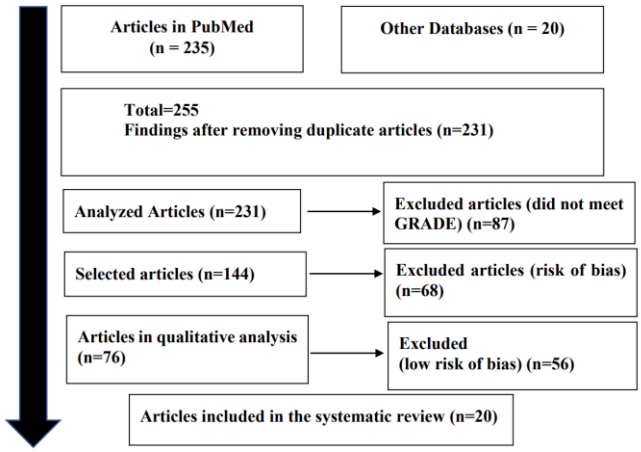
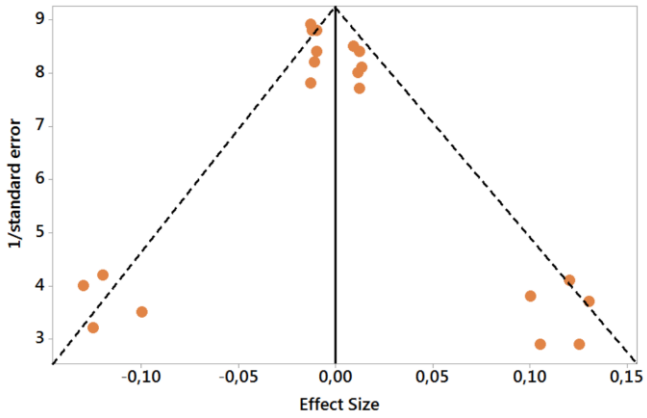


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This chart had a symmetrical behavior,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

Figure 2. The symmetrical funnel plot does not suggest a 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 literary findings regarding the development and understanding of the regulatory processes involving the skin-gut 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 psoriasis patients produce excess IL-17 in response to IL-23, triggering the production of pro-inflammatory mediators IL-1β, IL-6, IL-8, TNF-α, and keratinocyte chemoattractants. These signaling molecules underpin chronic skin inflammation and cause epidermal hyperplasia, the hallmark of psoriatic plaques. In this context, patients with psoriasis who consumed *B. infantiles* 35624 exerted a decrease in the pro-inflammatory markers IL-6, TNF-α, and serum CRP. These effects can be attributed to the proliferation of Tregs induced by probiotics **[12]**.

In this sense, the interaction of hormonal, neuronal, and inflammatory signaling has a great 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 skin inflammation, which alters mast cell functionality and survival and induces the production of vasodilators and proinflammatory factors. Furthermore, psychological stress positively regulates prolactin secretion, which in turn determines keratinocyte proliferation and sebum production by the sebaceous glands. Likewise, 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 arduous 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 re-epithelialization may be of inestimable importance for non-healing wounds **[11]**.

In this context, alterations in the composition of the skin microbiota and simultaneous bacterial overgrowth in the small intestine are quite common among individuals with acne rosacea. Indeed, the overpopulation of *Propiobacterium acnes* has been recorded in acne patients. Antibiotics targeting *P. acnes* are conventionally used to resolve acne. Furthermore, it has been reported that the increased 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, growth

stimulation of *S. epidermidis* can be achieved by strain-specific Lactobacillus supplementation. Indeed, it has been reported that *L. brevis* DSM17250 secretes 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]**.

Furthermore, other probiotic strains have been reported to directly inhibit *P. acnes*. Results of in vitro experiments showed that *L. casei* NCFB 161, *L. acidophilus* NCFB 1748, *L. plantarum* DSM 12028, *L. gasseri* NCFB 2233, and *Lactococcus lactis* NCIMB 6681 strains exerted antimicrobial effects against *P. acnes*, which were enhanced when combined with prebiotics **[7]**. Likewise, *Lactococcus sp*. Therefore, supplementation with probiotics can also be used to alleviate inflammation, a key aspect of acne breakouts **[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 increment is associated with significant variations in hygiene, gut microbiota, exposure to bacterial endotoxins, outdoor living with contact with animals, atmospheric pollution, climate, and diet **[8]**. Genetic (alteration of the skin barrier function) and immunological factors coincide with environmental ones **[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 both genetic and environmental factors. Most studies on AD relief focus on two parameters; inflammation and gut and skin microbiota composition **[8]**. It was shown that supplementation with probiotics changed the differentiation of T cells for 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-γ (IFN-γ), and increased the expression of immunomodulatory factors Forkhead box P3 (Foxp 3+) and IL10 in pediatric patients with AD who received this probiotic strain orally **[12]**.

In this sense, skin lesions with AD are often colonized by high loads of *S. aureus*. Therapeutic interventions that limit this pathogenic population result in clinical improvement of cutaneous manifestations **[8]**. *L. johnsonii* NCC 533 was shown to promote the expression of antimicrobial peptides and inhibit the adhesion of *S. aureus* to an in vitro reconstructed human epidermis model. In this text, *S. aureus*-positive AD patients who participated 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 underexplored, and neither major research in gastroenterology nor dermatology has systematically investigated the intestinal axis of the skin **[1,2]**. Thus, in reviewing the field, several mechanistic levels at which the gut and skin may interact under physiological and pathological circumstances have been proposed. The gut microbiota has enormous metabolic capacity along the gut-skin axis. Dietary or microbiota metabolites are accessible to the skin. Therefore, after defining open key 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]**.

Thus, a low-glycemic-load diet high in plant fiber and low in processed foods has been linked to an improvement in acne, possibly through bowel 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 food and herbal supplements may be a viable alternative to the current standard of first-line care for moderate acne, which typically includes antibiotics. While 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]**.

Also, 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 gut 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]**. Furthermore, dysregulated gut and skin microbiomes are associated with psoriasis vulgaris. There is also a clear association between inflammatory bowel disease and this condition **[17]**.

Regarding the skin microbiome, changes were observed in the relative abundance of Firmicutes,

Actinobacteria, and Proteobacteria. In addition, *Staphylococcus spp* and *Streptococcus spp.* were detected more frequently in lesional skin. Changes in the gut microbiome were characterized by a decrease in the phylum Bacteroidetes and an increase in the genus Faecalibacterium. It is thus suggested that dysbiosis of the skin and gut microbiota may contribute to psoriasis **[17]**. In this context, despite conflicting findings, patients with psoriasis often have 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 for 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 via the gut. Over the past decade, research on the gut microbiome has rapidly accumulated and has been accompanied by a growing interest in probiotics and prebiotics as a way to modulate the gut microbiota **[7]**. Given the public health importance of these approaches, it is timely to reiterate factual and supportive information about their clinical application and use for skin treatments. For example, Lactobacillus, Bifidobacterium, and *Saccharomyces strains* 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 established 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 changes in lifestyle.

Conclusion

Healthy skin management includes manipulation of bowel function through functional nutrology, probiotics, and prebiotics. 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 to enhance the effectiveness of standard dermal therapy. All of this would be aimed at modifying the secretory, metabolic, and hormonal activity of the intestinal epithelium to impact cutaneous inflammation.

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Ethical Approval

Not applicable.

Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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