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REVIEW ARTICLE

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Major approaches on the nutrition and gut microbiota to health skin: a systematic review

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Abstract

Introduction: In the scenario of dermatological diseases. All other cutaneous and subcutaneous diseases accounted for 0.124% of the total. In this sense, several predictors can influence the composition of the microbiome. The composition of the diet modulates the GM balance, influencing the inflammatory response. One of the first dermatoses in which the positive influence of the use of probiotics was perceived was atopic dermatitis 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 by reducing skin inflammation. **Objective:** To carry out a concise systematic review of the main relationships of the nutrition-gut microbiota-skin axis, highlighting the importance of nutrology and gut microbiota for dermatological health. **Methods:** The research was carried out from June 2021 to July 2021 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, following the Systematic Review-PRISMA rules. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** It was found that in the context of the interaction of nutritional health, metabolism encompasses the interactions between diet, microbiota, and cellular enzymatic processes that generate the chemical pathways necessary to maintain life. For the understanding of the regulatory processes that involve the nutrition-gut microbiota-skin axis, chronic inflammation is a crucial factor for the development of autoimmune diseases. For example, 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-1β, IL-6, IL-8, TNF- α, and keratinocyte chemoattractants. The interaction of hormonal, neuronal, and inflammatory signaling has a major impact on skin health. **Conclusion:** Several studies have scientifically demonstrated the important relationship between GM and adequate nutrition for the establishment of the nutrition-gut microbiota-skin axis, highlighting the management of dermatoses with probiotics and prebiotics, as well as changes in lifestyle.

Keywords: Nutrition. Nutrology. Gut microbiota. Skin. Dermatosis.

Introduction

In the scenario of dermatological diseases, it is estimated that skin diseases contribute about 1.80% of 306 diseases and lesions in total, with approximately 0.40% for atopic dermatitis (AD), 0.31% for acne vulgaris 0.21% for psoriasis, 0.20% for urticaria, 0.17% for viral skin diseases, 0.16% for fungal skin diseases, 0.075% for scabies, 0.065% for malignant cutaneous melanoma, 0.054% for pyoderma, 0.042% for cellulitis, 0.033% for keratinocyte carcinoma, 0.035% for decubitus ulcer and 0.014% for alopecia areata. All other cutaneous and subcutaneous diseases accounted for 0.124% of the total [1-5].

Given this epidemiological context, the human gastrointestinal tract contains more than 10 trillion bacteria, with more than 500 different species. About 1/3 of our GM is common to most people, and the remaining 2/3 is specific to each of us [6]. Due to the importance of the gut microbiota (GM) in the pathogenesis of dermatological diseases, it is necessary to better understand the close relationship of the nutrition-gut microbiota-skin axis [7].

In this sense, one of the first dermatoses in which the positive influence of the use of probiotics was perceived was atopic dermatitis. 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 a specific treatment, in atopic individuals, helps to reduce disease crises. There are two other diseases with some studies on the use of probiotics, which are inflammatory acne and psoriasis. In the first, 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 by reducing skin inflammation [4].

Therefore, the present study aimed to carry out a concise systematic review of the main relationships of the nutrition-gut microbiota-skin axis, highlighting the importance of nutrology and gut microbiota for dermatological health.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-HTTP://www.prisma-statement.org/) were followed [10].

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*nutrition, nutrology, gut microbiota, skin, and dermatosis*". The research was carried out from June 2021 to July 2021 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. Also, a combination of the keywords with the booleans "OR", "AND", and the operator "NOT" were used to target the scientific articles of interest.

Study Quality and Bias Risk

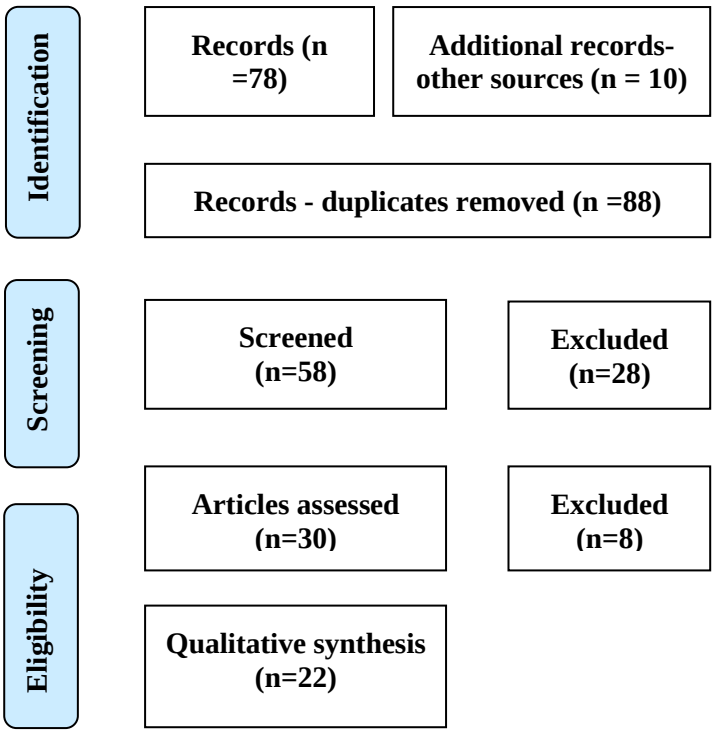
The quality of the studies was based on the GRADE instrument [11] and the risk of bias was analyzed according to the Cochrane instrument [12]. Two independent reviewers carried out research and study selection. Data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided on some conflicting points and made the final decision to choose the articles.

Results and Development

After the selectivity of articles and literary findings through the following descriptors nutrition, nutrology, gut microbiota, skin, and dermatosis, a total of 88 studies were analyzed, with only 22 medium and high-quality studies selected, according to the rules of the GRADE, and with bias risks that do not compromise scientific development, based on the Cochrane instrument (**Figure 1**).

As a corollary to the exploration of the 22 studies, it was found that in the context of the interaction of nutritional health, metabolism encompasses the interactions between diet, microbiota, and cellular enzymatic processes that generate the chemical pathways necessary to maintain life. Endogenous metabolites and nutrients in the diet can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate, controlling chromatin accessibility and downstream gene expression patterns [13].

Figure 1. Scheme for selecting the studies.



Included

Systematic Review (n=22)

Most substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways such as the tricarboxylic acid cycle, methionine cycle, folate cycle, glycolysis, β-oxidation, and the hexosamine pathway. These complex and interconnected networks generate intermediates that coactivate epigenetic enzymes and/or serve as direct substrates for modifications, including acetyl-CoA, alpha-ketoglutarate (α-KG), succinate, fumarate, S-adenosyl methionine (SAM), UDP-GlcNAc, ketone bodies, lactate, NADH, $FADH_2$ [13].

Furthermore, nutrients can modulate the activity of the signaling pathway, such as the mechanistic target signaling pathway of rapamycin (mTOR) and, in particular, the mTOR 1 complex (mTORC1), which regulates cell growth only when nutrients and factors of growth are present. Depletion of specific nutrients including arginine, leucine, and S-adenosyl methionine prevents growth factor-induced activation of mTORC1 by blocking Rag GTPase-mediated mTORC1 recruitment to the lysosome where it can be activated by Rheb GTPase [13].

Another way is through the AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulates cell growth and autophagy. Furthermore, transcription factors can be directly regulated by metabolites. Kynurenine tryptophan is an endogenous agonist for the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) that binds and activates IKKβ and initiates NF-κβ signaling [13].

In this nutritional setting, the Western diet is characterized by excessive consumption of refined sugars, salt, and saturated fat, and low dietary fiber intake, as well as low overall dietary variability. Micronutrient deficiencies and the overabundance of calories and macronutrients trigger inflammatory processes, susceptibility to infections [14]. Several micronutrients are especially important for immunonutrition, including vitamins such as vitamins A, C, D, and E, folic acid, beta-carotene, and trace elements such as zinc, selenium, manganese, and iron. Zinc and vitamin A, C, and D deficiencies can reduce the functions of natural killer cells [15,16].

In this aspect, for the understanding of the regulatory processes that involve the nutrition-gut microbiota-skin axis, chronic inflammation is a crucial factor for the development of autoimmune diseases. For example, 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-1β, IL-6, IL-8, TNF- α, and keratinocyte chemoattractants. These signaling molecules support chronic skin inflammation and cause epidermal hyperplasia, the hallmark of psoriatic plaques. Patients with psoriasis who consumed B. infant 35624 exerted a decrease in the pro-inflammatory markers IL-6, TNF-α. These effects can be attributed to the proliferation of Tregs induced by probiotics [17].

The interaction of hormonal, neuronal, and inflammatory signaling has a major impact on skin health. Psychological suffering alters the physiology of the skin, stimulating pro-inflammatory responses. 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 vasodilators and pro-inflammatory factors. Also, psychological stress positively regulates prolactin secretion, which in turn determines the proliferation of keratinocytes and sebum production by the sebaceous glands. Likewise, the appearance of autoimmune skin diseases, such as psoriasis, and allergic disorders, such as atopic dermatitis, is correlated with chronic inflammation and mast cell degranulation [17].

Prolonged underlying inflammatory responses induce keratinocyte apoptosis, contributing to distinct cutaneous manifestations of these diseases. Current therapeutic approaches are hard on 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. 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 can be invaluable for non-healing wounds [8].

In this context, changes in the composition of the skin microbiota and simultaneous bacterial overgrowth in the small intestine are quite common in individuals with acne rosacea. Overpopulation of *Propionibacterium acnes* has been reported in patients with acne. Antibiotics targeted at *P. acnes* are conventionally used to resolve acne. Furthermore, it has been reported that the increase in the cutaneous population of *Staphylococcus epidermidis* excludes *P. acnes* from the sebaceous hair follicles. 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 suppleman-

tation with strain-specific *Lactobacillus*. *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 [17].

Also, 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 exerted antimicrobial effects against *P. acnes*, which were improved when combined with prebiotics. Likewise, *Lactococcus sp*. Therefore, supplementation with probiotics can also be used to relieve inflammation, a fundamental aspect of the appearance of acne [17].

Also, the incidence of AD in developing countries reaches about 20% of the pediatric population. This increase, associated with hygiene, gut microbiota, exposure to bacterial endotoxins, outdoor living with contact with animals, air pollution, climate, and diet. Genetic factors (altered skin barrier function) and immunological factors coincide with environmental factors. Only the systematic study of all these elements can better elucidate the epidemiology of AD [18].

Thus, AD is the result of an imbalance in 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 of AD relief focus on two parameters; inflammation and composition of the GM and skin. It was shown that supplementation with probiotics altered the differentiation of T cells to 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 (Fox^{3+}), and IL-10 in pediatric AD patients who received this probiotic strain orally [19].

In this sense, cutaneous lesions with AD are frequently colonized by high loads of *S. aureus*. Therapeutic interventions that limit this pathogenic population result in clinical improvement of cutaneous manifestations. It was shown 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 who participated in an open multicenter study experienced an improvement in skin appearance after topical application of a lotion containing heat-treated *L. johnsonii* NCC 533 cells [19].

Aged skin is characterized by increased pH, oxidative stress, and matrix metalloproteinase activity, which result in wrinkle formation, dehydration, and discoloration. The accumulation of preclinical and clinical evidence suggests that probiotics can neutralize phenotypic changes in the skin, restore flexibility in the stratum corneum, and improve hair quality after local or oral administration. Environmental factors, such as ultraviolet (UV) radiation, accelerate skin aging through skin dehydration and the formation of wrinkles. Probiotics appear to have regenerative effects on UV-induced photo-damaged skin. Oral administration of L. acidophilus reduced the formation of wrinkles caused by UV irradiation, while supplementation with *Bifidobacteria breve* B-3 restored skin hydration and inverted basement membrane and basement membrane photos [17].

In this scenario, as crucial interface organs, the gut and the skin have a lot in common. Therefore, it is not surprising that several intestinal pathologies present with cutaneous comorbidities. However, the reason for this remains poorly explored, and neither major research studies in gastroenterology nor in dermatology have systematically investigated the intestinal axis of the skin. Thus, in reviewing the field, several mechanistic levels have been proposed at which the gut and skin can interact under physiological and pathological circumstances. The GM has enormous metabolic capacity along the gut-skin axis. Dietary metabolites or microbiota are accessible to the skin. Therefore, after defining the main open questions about the nature of these metabolites, how they are detected, and what changes in the skin they can induce, the understanding of these pathways leads to new therapeutic strategies based on targeting one organ to improve the health of the other [19]. Furthermore, psoriasis is a frequent chronic systemic inflammatory disease. It is associated with changes in the microbiome, which can trigger psoriasis and influence the course of the disease [20].

Skin and GM is involved in immunopathogenesis and can substantially modulate psoriasis. Antimicrobial peptides can serve as a link between the microbiome and the immunological mechanisms of psoriasis, regulating the microbiome at interfaces and can trigger psoriasis as antigens. 16S rRNA sequencing significantly facilitates microbiome analysis. Thus, microbiome analysis 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 [21].

Psoriasis vulgaris is a chronic inflammatory skin disease. However, the systemic inflammatory nature of this disease was confirmed by the presence of a wide range of dysregulated cytokines and inflammatory markers in the serum of these patients.

Dysregulated gut and skin microbiomes associated with psoriasis have been found. There is also an evident association between inflammatory bowel disease and this condition [22].

Regarding the skin microbiome, changes in the relative abundance of Firmicutes, Actinobacteria and Proteobacteria were observed. Furthermore, *Staphylococcus* and *Streptococcus spp*. were most frequently detected in damaged skin. Changes in the intestinal microbiome were characterized by a decrease in the phylum of Bacteroidetes and an increase in the genus Faecalibacterium. It is suggested, therefore, that dysbiosis of the skin and GM may contribute to psoriasis, promoting the translocation of microbes from these sites to the bloodstream [22]. Consistent with the hypothesis of iron dysregulation and dormant microbes, these microorganisms are in a physiologically dormant state, but can be awakened periodically and release their cell wall components such as lipopolysaccharide and lipoteichoic acid [23].

Besides, systemic sclerosis (SS) is an immune-mediated fibrotic disease that affects the skin, lung, and intestine, all of which have an established microbiome. Altered GM can occur and contribute to the onset, progression or severity of the disease. However, dysbiosis can also be secondary to disease or immunosuppressive therapy. Dysbiosis is strongly involved in the mechanism and treatment of the disease. This may be highly relevant to the molecular pathology of the skin in SS and may increase the inflammatory gene signature seen in some skin biopsies [24].

Furthermore, there is a clear shift in the microbial molecular signature with a decrease in the lipophilic rate and a marked increase in a wide range of gram-negative rates in SS. Notably, there is no clear association observed with more severe diffuse forms of SS that might have aided the progression of severity. The possible link with inflammatory gene expression signatures in the skin increases the possibility that the microbial environment may be stimulators of the innate or adaptive immune system relevant to pathogenesis. However, the skin, intestine and lung are also structurally and architecturally highly altered in SS and therefore these findings may reflect that perhaps the skin in SS is especially susceptible to colonization by these microorganisms and reflects an altered host rather than a role in etiopathogenesis [24].

In this context, therefore, probiotics and prebiotics are microbiota management tools to improve host health. They target gastrointestinal effects through the intestine. In the last decade, research on the GM has accumulated rapidly and has been accompanied by a growing interest in probiotics and prebiotics as a way to modulate the GM. Given the importance of these approaches to public health, it is timely to reiterate factual and supporting information about their clinical application and use. 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* hold promise for the future. For prebiotics, glucans and fructans are well proven and based on evidence on the prebiotic effects of other substances such as mannose oligomers, glucose, xylose, pectin, starches, human milk and polyphenols [25].

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