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Gut microbiota-skin axis: a systematic review of healthy aging

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Abstract

Introduction: Increasing evidence points to the important relationship between the skin microbiota and its connection with the gut, and vice versa, known as the gut-skin axis, and its anti-aging effects. Integrating the "genome-microbiome-exosome" plays a significant role in aging and skin health. Probiotic-based products are mainly available for the complementary treatment of many dermatological conditions. **Objective:** It was to analyze, through a systematic review, the main anti-aging nutrological aspects of the gut microbiota-skin axis. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from July to September 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 231 articles were found. A total of 57 articles were evaluated in full and 31 articles were included. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=90.7%>50%. The management of healthy skin is related to the manipulation of intestinal function through functional nutrition, probiotics, and prebiotics. Treatments that enhance or repair a leaky gut barrier may become important as adjunctive therapy in the management of inflammatory skin conditions and may help to increase the effectiveness of standard dermal therapy as well as promote tissue regeneration to mitigate skin aging. All of this would be aimed at modifying the secretory, metabolic and hormonal activity of the intestinal epithelium to positively impact the dermal treatment.

Keywords: Healthy skin. Gut microbiota. Health aging. Probiotics.

Introduction

The microbiome plays a significant role in human health, homeostasis, the immune system, and disease pathogenesis. Disrupted communication between the microbiome and the host has been extensively studied in gastrointestinal diseases. To a lesser extent, there is emerging research on the skin microbiome and its connection to the gut, known as the gut-skin axis, and its effects on dermatological conditions. In particular, there is a growing body of research on oral probiotics, prebiotics, and dietary modifications that may help improve symptoms of a variety of dermatological conditions in select demographic groups [1].

In this sense, the skin has a multifactorial aging

process, caused by both intrinsic and extrinsic factors. One of the main theories of aging involves cellular senescence or apoptosis resulting from oxidative damage, as the skin's antioxidant system tends to weaken with age. The human microbiota is a complex ecosystem formed by microorganisms (bacteria, fungi, and viruses). Both the gut and skin microbiota play essential roles in protecting against invading pathogens, mediating inflammatory conditions, and modulating the immune system that is involved in both innate and adaptive immune responses. However, the human microbiome can be altered throughout life and affected by various perturbations.

An alteration of gut bacteria results in "microbial dysbiosis" which is associated with the influence of several diseases, including aging. Furthermore, there is an integration of the "genome-microbiome-exosome" that plays a significant role in aging and skin health. Mitigating the negative impacts of factors that influence the skin interactome should be the future strategy to protect, prevent, and delay skin aging, as well as preserve healthy skin conditions. It is necessary to determine how human microbiomes affect skin aging and to demonstrate potential interventions related to human microbiomes to modulate skin health and aging. Currently, probiotic-based products are mainly available for the adjunctive treatment of many dermatological conditions. However, at this time, there are limited clinical studies on skin anti-aging purposes and more are needed as this evolving concept is on the rise and may provide insight into future therapeutic options [2].

In addition, skin aging inevitably occurs as a natural result of physiological changes over time. In particular, sun exposure of the skin is responsible for up to 90% of skin damage. Numerous studies have examined the ability of dietary constituents to prevent skin aging, and recent research has highlighted the role of functional probiotics in gut function and skin aging. However, the mechanism of the interactions between aging and probiotics has not yet been elucidated. There is a role for exopolysaccharides (EPS) produced by lactic acid bacteria (LAB) identified as Lactobacillus plantarum HY7714 in regulating tight junctions in intestinal epithelial cells and increasing moisture retention in human dermal fibroblast cells [3].

In this regard, microorganisms perform important functions such as preserving and promoting the development of immune defenses, exerting 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 potential carcinogenic agents and activation of bioactive compounds [4,5]. An imbalance in the gut microbiota can promote the onset and progression of human diseases [6].

Thus, the presence of bacteria in the intestine is mandatory for the development of several functions of the gastrointestinal tract (GIT). In addition, the gut microbiota is essential for the activation of the immune system, with emphasis on *Lactobacillus acidophilus, Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA for the removal of antigens by a non-inflammatory pathway and increasing T and B lymphocytes. In other words, in the absence of gut microbiota, the motor function of the intestine is compromised [6]. 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 [7].

Therefore, the present study aimed to analyze, through a systematic review, the main anti-aging nutrological aspects through the gut microbiota-skin axis.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/25/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 07/25/2024.

Search Strategy and Search Sources

The search strategies for this systematic review were based on the keywords (DeCS /MeSH Terms): "Healthy skin. Gut microbiota. Health aging. Probiotics". The search was conducted from July to September 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 15 years were selected. In addition, a combination of keywords with the Boolean terms "OR", "AND" and the operator "NOT" were used to target the scientific articles of interest.

Study Quality and Risk of Bias

The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses.

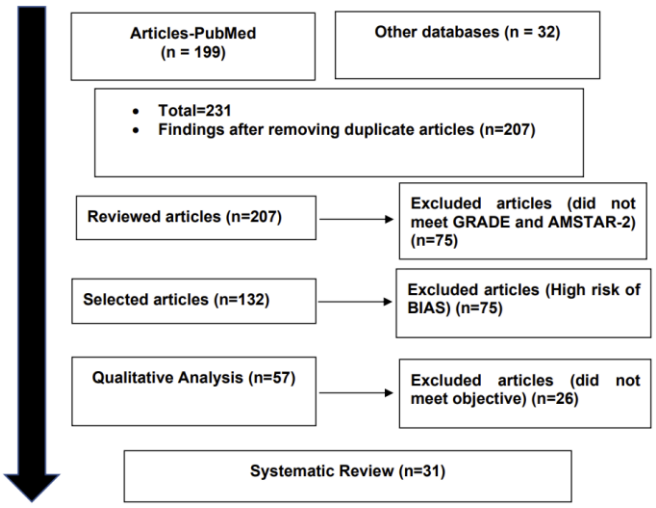
The most evident emphasis was systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 231 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated, and a new exclusion was performed, removing the articles that did not include the topic of this article, resulting in 132 articles. 57 articles were evaluated in full, and 31 articles were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 75 studies with a high risk of bias and 75 studies that did not meet GRADE and AMSTAR-2. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=90.7%>50%.

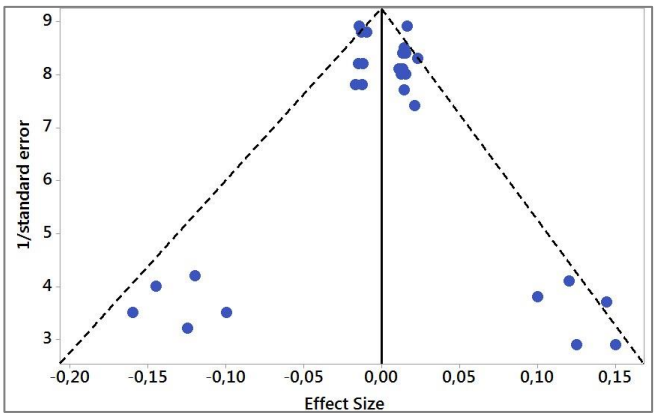
Figure 1. Flowchart showing the article selection process.



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 Cohen's 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 among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=31 studies).



Source: Own authorship.

Major Findings

The gut and skin are densely vascularized organs with important immunological roles and are closely related in purpose and function [8]. Recent work has shown that the gut and skin share a number of crucial features, with diet and gut microbiota affecting the skin [9]. In particular, healthy aging is closely linked to gut-skin communication, as the skin and gut are the main interfaces with the external environment, maintaining physiological homeostasis in both organs is essential [8].

The mechanisms underlying this positive microbial communication have not yet been elucidated, but some are immunologically based. Furthermore, probiotics act as positive modulators in gut health and oxidative immune regulation [10]. In this regard, probiotics that affect skin health have been identified, especially among lactobacilli [11]. For example, a clinical study reported that the H61 strain of L. lactis improved skin elasticity in middle-aged women [12]. Another study has shown that *L. rhamnosus* has the potential to improve skin hydration [13]. Previous work from our group has shown that *L. plantarum* HY7714 increases skin moisture and elasticity and decreases wrinkle depth in humans aged 41–59 years [14]. However, the mechanisms underlying these effects have not been fully elucidated. An attractive hypothesis is that polysaccharides produced by lactic acid bacteria (LAB) are important factors in skin health. Thus, a study developed by authors Lee et al. (2021) [3] investigated whether certain HY7714 polysaccharides could serve as functional substances that act on the gut-skin axis

to alter the properties of dermal cells.

Most exopolysaccharide (EPS) molecules from lactobacilli are heteropolymers consisting of repeated copies of oligosaccharide units [15]. EPS, which are produced intracellularly or extracellularly, contribute to biological activity through specific composition, size, and branching structure, which may differ even among members of the same LAB strain [16]. Given that microbial EPS has various effects to enhance biological and cosmetic functions, it is very important to explore the biodiversity of naturally derived LAB strains that produce high levels of EPS [17]. The yield of EPS synthesized by Lactobacill can be affected by the composition of the medium and growth conditions [18].

In addition, the properties of EPS in the form of sludge may negatively affect the gradual loss of probiotics, therefore efforts should be made to standardize culture methods to maintain the quality and purity of EPS. When HY7714 probiotics are cultured, slippery substances containing EPS are secreted into the environment, making centrifugation difficult. On the other hand, another L. plantarum strain, HY7711, can be centrifuged because it produces a different type of EPS. We observed these differences in microbial properties and then compared and analyzed the specific structure of HY7714 and HY7711 EPS. HPLC analyses performed under two different column conditions revealed that HY7714 and HY7711 EPS have different proportions of the same three monosaccharides, ribose:mannose:glucose, in a ratio of 4.0:1.5:1.0 (HY7714) or 1.5:2.0:1.0 (HY7711), respectively. The molecular species in HY7714 EPS and HY7711 EPS, which account for 30% of the total mass, were about 80 kDa and 57 kDa, respectively. Thus, we can infer that HY7714 EPS possesses a specific phenotype due to the inherent structural features of the complex polysaccharide composition. These findings were corroborated by the fact that HY7714 also produces sugar units with higher molecular weight, as revealed by GPC analysis, indicating that its EPS is larger [3].

The most valuable application of Lactobacillus EPS to date has been in improving the texture and mouthfeel of fermented dairy products [19]. According to a recent hypothesis, EPS can remain for longer periods of time in the gastrointestinal tract, improving colonization by probiotics [20]. Consistent with this, in Caco-2 cells treated with HY7714 EPS, ZO-1 and OCL-1 mRNA levels were higher than in cells treated with TNFα alone, which increases the permeability of intestinal tight junctions. This increased permeability is accompanied by a reduction in ZO-1 and OCL-1 levels, resulting in leakage of pro-inflammatory cytokines into blood vessels and other tissues [21].

According to the results of Lee et al. 2021, HY7714 EPS decreased the secretion of IL-1β and IL-6 in TNFα-treated cells and restored them to their usual levels. According to recent studies, some types of matrix metalloproteinases (MMPs) play vital roles in the development of inflammation in intestinal epithelial cells. Several studies have reported that IL-1β and TNFα increase MMP expression [22,23]. At the same time, MMPs play a role in promoting ECM degradation after UVB damage in the skin dermis and epidermal cells. Notably in this regard, the intestinal environment induces the redistribution of skin homeostasis after UV irradiation [24,25].

Furthermore, UV exposure damages skin structure and function and has therefore been implicated in sunburn, immunity, cancer, and photoaging [26]. UV light is composed of UVC (200–280 nm), UVB (280–315 nm), and UVA (315–400 nm) [27]. In particular, UVB irradiation promotes ROS production and induces the overexpression of MMP1, MMP3, and MMP9 in human fibroblasts, resulting in collagen destruction and ultimately wrinkle formation [28,29]. In this regard, we investigated whether the protective effects of HY7714 EPS against UVB irradiation are governed by its ability to protect against oxidative stress and MMP expression. It was found that UV-induced oxidative damage and the induction of MMPs in HS68 cells were significantly decreased by HY7714 EPS treatment. Therefore, HY7714 EPS has the potential to alleviate UVB damage of dermal connective tissue, a collagenous ECM. MMPs, which degrade skin proteins, are upregulated by UVB irradiation, resulting in loss of elasticity and promoting wrinkle formation. MMPs can be classified into several subgroups: collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), and stromelysins (MMP-3, MMP-10, MMP-11) [3].

Hyaluronic acid (HA) present in skin cells is synthesized by hyaluronic acid synthase (HAS), a membrane-bound enzyme expressed by keratinocytes and dermal fibroblasts. HAS produces HA of various lengths, with HAS1 and HAS2 mainly synthesizing large polymer units of HA [30]. Meanwhile, the decomposition of HA in dermal skin cells after UVB exposure causes wrinkles and loss of elasticity and moisture. UVB exposure also contributes to the inflammatory response by driving the generation of ROS and the secretion of mediators such as inflammatory cytokines. Subsequently, ROS accumulation mediates UVB-induced MMP1 expression. The increase in pro-inflammatory cytokines caused by UVB exposure leads to photoaging in dermal skin cells.

In this context, 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 means of modulating the gut microbiota [5]. Given the importance of these approaches for public health, it is timely to reiterate factual and supportive information on 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 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 [31]. 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

Healthy skin management is related to the manipulation of gut function through functional nutrition, probiotics, and prebiotics. Treatments that enhance or repair a leaky gut barrier may become important as adjunctive therapy in the management of inflammatory skin diseases and may help to increase the efficacy of standard dermatotherapy, in addition to promoting tissue regeneration to mitigate skin aging. All of this would be aimed at modifying the secretory, metabolic, and hormonal activity of the intestinal epithelium to positively impact dermal treatment.

CRediT

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

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