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REVIEW ARTICLE

Major clinical outcomes of the gut microbiota-skin axis through exosomes and probiotics: a systematic review

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Abstract

Introduction: Skin diseases have contributed significantly to the increasing burden of disease and injury in recent years, and the gut microbiota, probiotics, and exosomes contribute to reducing this burden. These vesicles have emerged as a focus of fundamental research in regenerative medicine. Exosomes participate in intercellular communication, tissue repair, and disease pathogenesis. **Objective:** The study analyzed the main scientific evidence on the relationship between gut microbiota and skin, emphasizing the importance of intestinal health through probiotics and exosomes for aesthetically healthy skin. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from May to July 2025 in the Scopus, Embase, 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 122 articles were found, 52 of which were fully evaluated, and 23 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in seven studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2 criteria. Most studies showed homogeneity in their results, with X^2=88.9%>50%. It was concluded that exosomes and the gut microbiota directly impact skin regenerative processes. Despite the challenges, their complexity and versatility reinforce their potential in the development of personalized strategies for skin health. To establish aesthetically healthy skin, it is imperative to manipulate the gut microbiota to achieve balance. Therefore, treatments that elevate or repair the gut are essential as adjunctive therapy in the management of inflammatory skin diseases and may contribute to the effectiveness of standard dermatotherapy.

Keywords: Skin. Gut microbiota. Healthy skin. Exosomes. Probiotics.

Introduction

Skin diseases have contributed significantly to the increasing burden of disease and injury in recent years, and the gut microbiota, probiotics, and exosomes contribute to reducing this burden. There is overexpression of the senescence-associated secretory phenotype, composed of pro-inflammatory cytokines, chemokines, growth factors, proteases, lipids, and extracellular matrix components **[1-3]**. Cellular senescence is an intrinsic aging process that has recently been linked to microbial imbalance. With age, cells become senescent in response to stress, undergoing irreversible growth arrest while maintaining high metabolic activity **[4,5]**.

Due to the distinct advantages of mesenchymal stem cell-derived exosomes, these vesicles have emerged as a focus of fundamental research in regenerative medicine. Exosomes participate in intercellular communication, tissue repair, and disease pathogenesis. In dermatology, exosomes influence skin health and the progression of various dermatological conditions **[6]**.

In this sense, an accumulation of senescent cells has been associated with several chronic and aging pathologies due to an overexpression of the senescence-associated secretory phenotype composed of pro-inflammatory cytokines, chemokines, growth factors, proteases, lipids, and extracellular matrix components. Dermatological disorders can be promoted by senescence. The gut microbiota influences cellular senescence through the secretion of microbial metabolites **[4-8]**.

Furthermore, metabolomics can be used to identify and quantify metabolites involved in senescence. Furthermore, new anti-senescence therapeutics are warranted due to the poor safety profiles of current pharmaceutical drugs. Probiotics and prebiotics may be effective alternatives, considering the relationship between the microbiome and healthy aging. However, further research on the composition of the senescent gut is needed to develop immunomodulatory therapies **[4,5]**.

In this context, the microbiota compositions of diseased lesional skin have been found to show distinct differences compared to healthy skin. 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 impaired skin barrier function. Modulating the composition of the skin microbiota to restore host microbiota homeostasis may be a future strategy for treating or preventing disease **[7-12]**.

In this sense, the presence of bacteria in the gut is mandatory for the development of various digestive system functions. Furthermore, the gut microbiota is essential for activating the immune system, particularly *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA for antigen removal through a non-inflammatory pathway and increasing T and B lymphocytes. In other words, in the absence of gut microbiota, the gut's motor function is compromised. 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 vitamin synthesis **[13-18]**.

Therefore, this study analyzed the main scientific evidence on the relationship between gut microbiota and skin, emphasizing the importance of gut health through probiotics and exosomes for aesthetically healthy skin.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: July 23, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: July 23, 2025.

Data Sources and Search Strategy

The literature search process was conducted from May to July 2025 and was based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used: "Skin. Gut microbiota. Healthy skin. Exosomes. Probiotics," and the Boolean expression "and" was used between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent articles were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size), using Cohen's d test.

Results and Discussion

Summary of Literature Findings

A total of 127 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated, and a further exclusion was performed, removing articles that did not address the topic of this article, resulting in 79 articles. A total of 52 articles were evaluated in full, and 18 articles were included and developed in the present systematic review (Figure 1). Considering the Cochrane risk of bias tool, the overall assessment resulted in 7 studies with a high risk of bias and 20 studies that did not meet GRADE and AMSTAR-2 criteria. Most studies presented homogeneity in their results, with X^2=88.9%>50%.

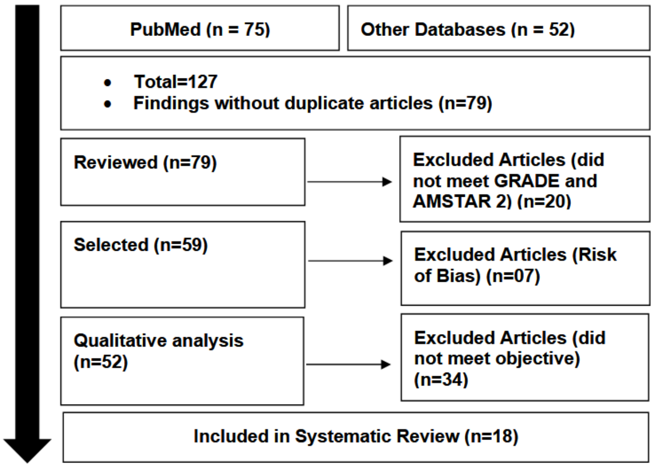

Figure 1. Flowchart showing the article selection process. Source: Own authorship.

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 d Test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), which are shown at the bottom of the graph, or among studies with large sample sizes, which are shown at the top.

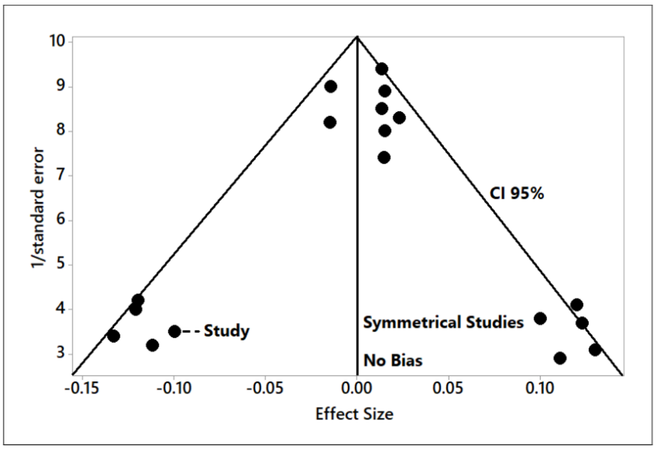

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small-sample studies shown at the bottom of the graph. High-confidence and highly recommended studies are shown above the graph (n=18 studies). Source: Own authorship.

Major Results

The skin and gut microbiome are often compared in terms of purpose and function. Both act as the body's primary interfaces with the external environment and, therefore, must be maintained in homeostasis. The physical barrier, as well as the commensal microbiota present in the skin and gut, are essential components for proper maintenance. The skin is particularly vulnerable to damage from frequent exposure to environmental factors such as air pollution, tobacco smoke, nutrition, and personal care products. As a result, premature skin aging can occur, accompanied by undesirable aesthetic indications and impaired skin function. This disruption to skin health can result in systemic damage. Indeed, previous research suggests that the skin is the primary source of serum inflammatory markers **[1-5]**.

Cell-free wound repair, notably the use of exosomes, has made significant progress in recent years. In addition to their relatively low toxicity, nonspecific immunogenicity, and excellent biocompatibility, exosomes also contain bioactive molecules such as proteins, lipids, microRNAs (miRNAs), and messenger RNAs (mRNAs). Their bioactive compounds have anti-inflammatory properties and can accelerate wound healing **[19]**.

Authors Haykal et al. (2025) **[20]** evaluated the potential benefits and limitations of exosomes in improving skin health and aesthetics for indications such as skin rejuvenation, hair restoration, and pigmentation disorders. The authors highlighted the potential of exosomes in skin rejuvenation through extracellular matrix production and matrix metalloproteinase (MMP) inhibition, as well as in hair restoration by stimulating follicular cell activity and modulating inflammation. Despite these benefits, challenges remain, including inconsistent isolation methods, source variability, and the need for clinical trials to confirm long-term safety and efficacy. Furthermore, a rapid increase in cytokine levels in the skin and serum was observed after acute disruption of the epidermal permeability barrier. Furthermore, a significant reduction in inflammatory markers in the epidermis and serum was found after correction of epidermal functional abnormalities with topical treatment. More recent research has extended the investigation to elderly humans with epidermal barrier disruption. Treatment with a lipid-based dermatologic agent successfully reduced circulating cytokine levels, specifically IL-1β and IL-6, to levels comparable to young controls. An increase in these proinflammatory cytokines is associated with chronic disorders of aging, including cardiovascular disease, Alzheimer's disease, and diabetes. Therefore, considering the epidermal dysfunction that accompanies aging and its apparent relationship with systemic inflammation, the skin may play a role in the pathogenesis of age-related chronic diseases **[21-23]**.

In this sense, the gut microbiota and its metabolites that enter the circulation can travel throughout the body and affect distant organs and tissues, including the skin. It is important to note that there is a bidirectional communication pathway between the gut microbiome and the integumentary system, known as the gut-skin axis. Indeed, several skin pathologies have been shown to co-occur with gastrointestinal disorders, with disruption of the gut microbiota associated with inflammatory dermatoses. Increased intestinal permeability resulting from dysbiosis can lead to the accumulation of bacterial metabolites (e.g., aromatic amino acid phenols) in the skin and compromise epidermal differentiation and skin integrity. This circulation of metabolites gives rise to an association between skin diseases and metabolic or cardiovascular dysfunctions **[24,25]**.

In particular, a bidirectional relationship has been found between psoriasis and obesity, with psoriasis predisposing individuals to obesity and vice versa. Similar alterations in the gut microbiota of psoriasis patients and obese individuals are observed, as well as a shared pathophysiology, including an increase in microbial byproducts (i.e., adipocytes). Furthermore, patients with severe psoriasis have an increased risk of death from cardiovascular disease, malignancies, diabetes, kidney disease, and other systemic diseases **[2,4,26]**.

In this regard, senescent cells commonly accumulate in the skin, triggering inflammation through the senescence-associated secretory phenotype and contributing to various types of skin dysfunction. The unique interaction between the gut and skin presents an opportunity to target senescent skin cells in the hope of simultaneously resolving skin breakdown and associated metabolic disruption. Suppressing the senescence-associated secretory phenotype pathway may improve skin health and help restore microbial imbalance through gut-skin communication pathways. Similarly, directly modulating the gut microbiome is a promising approach for treating skin diseases **[1,2,27]**.

Thus, prolonged underlying inflammatory responses induce keratinocyte apoptosis, contributing to the distinct skin manifestations of these disorders. Current therapeutic approaches are either 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. However, more clinical evidence is needed to support their routine use in medical practice. Similarly, probiotics that protect keratinocytes from oxidative stress or induce skin re-epithelialization may be invaluable for non-healing wounds **[14,20,27]**.

In this context, 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 gut-skin axis. Thus, 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. Metabolites from the diet or microbiota 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 **[4,23]**.

Furthermore, a low-glycemic diet, rich in plant fiber and low in processed foods, has been associated with an improvement in acne, possibly through gut changes or attenuated insulin levels. While there is much interest in the human microbiome, much more remains unknown, especially along the skin axis. Collectively, the evidence suggests that approaches such as plant-based foods and supplements may be a viable alternative to the current first-line standard of care for moderate acne, which typically includes antibiotics. Although patient adherence to major dietary changes is likely much lower than with medications, it is a treatment avenue that deserves further study and development **[8,24]**.

Finally, probiotics and prebiotics are microorganisms that can improve gut health. They target gastrointestinal effects through 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. Given the importance of these approaches to public health, it is timely to reiterate factual and supportive information on their clinical application and use for skin treatments. For example, 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-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. 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 **[9,25,28]**.

Limitations

Additional research is needed to address existing gaps and explore the full therapeutic potential of exosomes in dermatological applications.

Conclusion

It was concluded that exosomes and the gut microbiota directly impact skin regenerative processes. Despite the challenges, their complexity and versatility reinforce their potential in the development of personalized skin health strategies. To achieve aesthetically healthy skin, it is imperative to manipulate the gut microbiota to achieve balance. Therefore, treatments that elevate or repair the gut are essential as adjunctive therapy in the management of inflammatory skin diseases, potentially contributing to the effectiveness of standard dermatotherapy.

CRediT

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