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IMPACT OF PROBIOTIC SUPPLEMENTATION ON ROSACEA: AN INTEGRATIVE REVIEW

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Abstract: Introduction: Rosacea is a chronic, complex inflammatory disease with varied manifestations and an unclear etiology. Its treatment is varied and includes both oral and topical therapies that target symptoms and exacerbations. **Objective:** To understand the effects of using probiotic supplementation in patients affected by rosacea based on published scientific evidence and to discuss its mechanism of action. **Method:** An advanced search was carried out on the Virtual Health Library (VHL) and PubMed platforms. To optimize the results, the search included a Boolean operator and standardized descriptors using the Descriptors in Health Sciences (DeCS/MeSH). The inclusion criteria were full texts, free of charge and in Portuguese, English or Spanish that aligned with the research question. As an exclusion criterion, duplicate articles and those whose full text did not answer the guiding question were eliminated. Four articles were included in this review. **Results:** 13 different bacteria with applications in rosacea were mentioned. In terms of prevalence, the strains *Bifidobacterium breve* BR03, *Lactobacillus salivarius* LS01 and *Vitreoscilla filiformis* were widely linked to positive disease outcomes. The effect of using probiotics on the skin seems to favor the skin barrier – restoring its hydration, modulating the natural microbiota and reducing inflammatory cytokines. **Conclusion:** Although the use of probiotic strains has received favorable reviews, studies targeting rosacea are still scarce. The quality, quantity and formulation are not a consensus, although their use is already widespread by some dermocosmetic companies in diseases such as atopic dermatitis, psoriasis and acne. **Keywords:** Probiotics. Rosacea. Dermatology. Skin Diseases. Cosmetic Microbiology.

INTRODUCTION

Rosacea is a chronic inflammatory disease of as yet unknown etiology and is common in fair-skinned patients between 30 and 50 years of age, regardless of gender. Its varied phenotypes give this pathology different classifications into four subtypes: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous and ocular rosacea. Consequently, the symptoms generally involve persistent erythema, papules, pustules, telangiectasia, redness, hypertrophy of the sebaceous glands and fibrosis.²⁻⁶

Its manifestation occurs in 4 phases, with the pre-rosacea phase being the characteristic appearance of flushing and uncomfortable burning – which is occasionally triggered by bouts of sun exposure, stress, cold or heat, alcohol, spices, exercise, cosmetics, among others. In the vascular phase, patients develop multiple telangiectasias – probably caused by vasomotor instability. In the inflammatory phase, papules or pustules appear, while in the late phase there is the appearance of cutaneous hyperplasia of the cheeks and nose – called rhinophyma.²

Due to its phenotypical complexity, rosacea receives different treatments, depending on the degree of severity. Thus, in addition to oral and topical treatment, patients require care with moisturizing and photoprotecting the skin – as these are known symptom triggers. Although there is treatment, not all patients achieve complete resolution of symptoms – with relapses or progression to other phenotypes.²

In this sense, new therapeutic approaches have been studied in recent years. One of them – the subject of this review – establishes the relationship between the gut-skin axis concept and also the balance of the skin microbiota in inflammatory diseases – such as atopic dermatitis, psoriasis, acne vulgaris and rosacea – together with the immune system,

through the use of probiotic strains. Since rosacea is caused by external factors such as pathogenic bacteria and/or mites, studies suggest the role of probiotics in improving the skin's natural barrier, since they could favor the production of important peptides that help the tissue's immune response.¹

This review included studies that have addressed the topical and/or oral use of probiotic strains in diseases such as atopic dermatitis, acne and rosacea in recent years. With a focus on rosacea, we sought to understand the mechanism behind the disease and how science evaluates the use of these bacterial products as adjuncts in the treatment of the disease.

METHOD

This is an integrative literature review based on bibliographic data collection. This type of study is based on Evidence-Based Practice (EBP) and its aim is to synthesize results in an orderly, standardized and explicit way, in order to establish a critical evaluation that encompasses relevant studies – different from traditional literature.^{4,7} According to Mendes (2008), “the initial purpose of this research method is to obtain a deep understanding of a particular phenomenon based on previous studies”.

In this sense, this review is based on six fundamental, well-structured points: 1) formulating the research question; 2) searching the literature; 3) categorizing the studies; 4) evaluating the included studies; 5) discussing the results; 6) synthesizing the knowledge.

EBP proposes that teaching or research problems should follow four components that form the acronym **PICO**. For Santos (2007), a targeted research question “maximizes the retrieval of evidence from databases, focuses the scope of the research and avoids unnecessary searches”. The authors came up with the following guiding question: “Is there scientific evidence in favor of probiotic

supplementation for the control of rosacea in patients affected by this condition?”. The process of formulating the research question is best illustrated in **Table 1**.

The literature review was then started. For this, advanced searches of the Virtual Health Library (VHL) and PubMed platforms were used. Using the Health Sciences Descriptors (DeCS/MeSH), the authors established the search terms: “*Probiotics*” and “*Rosacea*”. As a strategy to optimize the results, a Boolean operator was used, such as: “[*Probiotics*] AND [*Rosacea*]”. The initial identification resulted in 43 articles. The inclusion criteria were full texts, free access, in Portuguese, English or Spanish and that aligned with the research question after reading the abstracts. As exclusion criteria, duplicates (n=3) and two (n=2) were eliminated after full reading. Finally, 4 articles were included (t=4), which went on to be filed, summarized and the data interpreted – as follows.

The process of searching for and selecting articles was simplified by the PRISMA 2020 flowchart as illustrated in **figure 1**.

ACRONYM	DEFINITION	DESCRIPTION
P	Patients/Population	Patients with rosacea
I	Intervention/ Exposure	Probiotic supplementation
C	Controls	Not applicable
O	Outcome	Rosacea management

Table 1 - Description of the PICO strategy in formulating the research question.

Source: Faccin, Guido *et al* 2024.

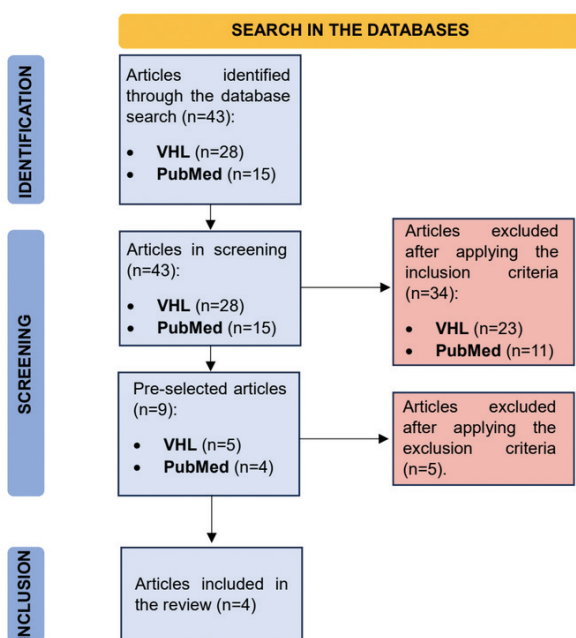


Figure 1 - PRISMA FLOW DIAGRAM 2020/2021 illustrating the process of identification, screening, and inclusion of articles.

Source: Faccin, Guido *et al* 2024.

RESULTS

Following the process, the authors proceeded to collect the data and summarize the information. It is essential to carry out a complete reading, extract the material and summarize it in a clear and objective manner to guarantee the accuracy of the findings and ensure that the transcription is aligned with the research question.⁸ According to Mendes (2008), “the reviewer’s objective at this stage is to organize and summarize the information in a concise manner, forming a database that is easy to access and manage”.

It was therefore decided to list the articles in a table containing the author’s name and the year of publication, country of origin, type of study and the main results, as shown in **Table 2**.

Overall, the studies listed in this review cover the use of the following probiotic strains: *Lactobacillus reuteri* (DMS 17938), *Lactobacillus salivarius* LS01, *Lactobacillus plantarum*, and *Lactobacillus johnsonii*; *Streptococcus*

thermophilus, *Streptococcus epidermidis* and *Streptococcus hominis*; *Bifidobacterium longum reuteri* and *Bifidobacterium breve* BR03; *Escherichia coli* Nissle 1917 (EcN); *Vitreoscilla filiformis*; *Enterococcus faecalis* cell-free supernatant; and *Lactococcus ferment* lysate.

In a quantified analysis, the probiotic strains *Bifidobacterium breve* BR03, *Lactobacillus salivarius* LS01 and *Vitreoscilla filiformis* were cited in 50% of the references. Below are some important considerations based on this analysis.

DISCUSSION

WHAT IS KNOWN ABOUT PATHOPHYSIOLOGY

The pathophysiology of rosacea is still not well understood. Studies suggest that predisposing immunological factors, vascular dysfunction, genetics and aggravating factors are the key to understanding and designing effective therapies to prevent flares.

It is currently believed that the immune system reacts to external stimuli and produces a reaction mediated by mast cells – with the release of pro-inflammatory mediators. These stimuli are commonly bacteria or mites (*Demodex mites* and *Bacillus oleronius*), which act by activating pathogen-associated molecular patterns (PAMPs) and, as a consequence, *Toll-like* receptors (TLRs) - such as TLR-2. The activation of these receptors leads to the stimulation of nuclear factor kappa B and the consequent production of cytokines, chemokines and peptides.⁶

The recruitment of mast cells favors a *positive feedback* mechanism by releasing the cathelicidin LL-37 – since these induce their chemotaxis, degranulation and release of more inflammatory cytokines. The process continues with the release of interleukin 6 (IL-6) and matrix metalloproteinases (MMPs). LL-37 may also be responsible for the pro-in-

Reference	Origin	Type of study	Results
ROZAS <i>et al.</i> , 2021	Belgium	Narrative review	<p>This is a review study on <i>Curibacterium acnes</i> and its relationship with diseases such as acne, atopic dermatitis, rosacea and psoriasis.</p> <p>[I] Two interventional studies evaluated topical bacteriotherapy in acne and atopic dermatitis. The first proposed a mixture of probiotic strains (SLST types: C3, K8, A5, F4) of <i>C. acnes</i> in 14 patients. This open study, without placebo, showed a reduction in inflammation and no adverse effects. The second study (randomized, placebo) investigated the effect of the <i>Lactobacillus Reuteri</i> strain (DMS 17938) in 36 adults with atopic dermatitis. There was no significant improvement in the score.</p> <p>[II] A third study (placebo-controlled) evaluated the application of <i>Streptococcus thermophilus</i> cells to the healthy skin of 20 elderly people. An improvement in hydration was reported (p=0.001).</p> <p>[III] A fourth study (double-blind with placebo) evaluated strains of <i>S. epidermis</i> on the healthy skin of 21 elderly people. A significant reduction in TEWL (unit of water loss), an increase in lipid content and a consequent increase in hydration were observed.</p> <p>[IV] A randomized, placebo-controlled study explored the application of <i>Bifidobacterium longum reuteri</i> in patients with sensitive skin. The group had a positive outcome with decreased sensitivity in subsequent tests.</p> <p>Although the promising results suggest a positive impact - mainly in terms of reducing inflammation - on some skin conditions, the studies are still in the very early stages and mention rosacea very little.</p>
SÁNCHEZ-PELLICER <i>et al.</i> , 2024	Spain	Narrative review	<p>This is a study containing systematic reviews of randomized clinical trials and case reports.</p> <p>[I] An open randomized clinical trial with 57 patients with erythema and papular lesions divided the patients into two groups: standard treatment <i>versus</i> treatment with probiotic administration of <i>Escherichia coli</i> Nissle 1917. After 1 month, 32% of patients in the probiotic group showed recovery and 57% significant improvement; compared to 17% of patients in the control group. Supplementation showed benefit with an increase in beneficial bacteria and a reduction in harmful bacteria such as <i>Klebsiella</i>.</p> <p>[II] A randomized clinical trial of 60 patients with rosacea was established in two groups: treatment with antibiotics, vitamins and antihistamines <i>versus</i> treatment with a mixture of <i>Bifidobacterium</i> and polyoxidonium (immunomodulator) for 3 weeks. In the probiotic group, 57% experienced clinical remission compared to 28% in the control group.</p> <p>[III] A case report showed the efficacy of the combination of oral antibiotic therapy and strains of <i>Bifidobacterium breve</i> BR03 and <i>Lactobacillus salivarius</i> LS01 in a patient with rosacea on the scalp. The patient showed significant improvement in skin and eye symptoms after 6 months.</p> <p>[IV] A clinical trial evaluated the efficacy of a topical dermocosmetic with probiotic fractions of <i>Vitreoscilla filiformis</i>. This product (Vichy Mineral 89 Probiotics) provided benefits in cellular immunity, protection of the skin barrier and control of pathogenic bacteria for the skin.</p>
KNACKS-TEDT; KNACKS-TEDT; GATHERWRIGHT, 2019	United States	Systematic review	<p>This is a systematic review study involving the topical use of probiotics in the treatment of inflammatory conditions such as atopic dermatitis (AD), acne, psoriasis and rosacea.</p> <p>[I] One study showed benefit in combining doxycycline with probiotic therapy.</p> <p>[II] A review including <i>V. filiformis</i>, <i>S. thermophilus</i> BID, <i>E. faecalis</i> cell-free supernatant, <i>B. longum</i>, <i>L. plantarum</i>, <i>S. hominis</i> or <i>S. epidermidis</i> and <i>L. johnsonii</i> was explored and reported by several authors - separately - from 1999 to 2017. <i>johnsonii</i> have been explored and reported by various authors - separately - from 1999 to 2017 and have shown positive results in increasing ceramides, improving hydration, reducing erythema, reducing scaling and itching, reducing acne lesions, reducing sensitivity (<i>B. longum</i>) and restoring the skin barrier.</p> <p>Although these studies show favorable results in conditions such as AD and acne, they are scarce when it comes to establishing connections with conditions such as psoriasis and rosacea. However, as they have shown suggestive effects on inflammatory control and decreased sensitivity, these strains deserve a better analysis aimed at these pathologies.</p>
HABEEBUDDIN <i>et al</i> 2022	Saudi Arabia	Narrative review	<p>This is a narrative review study involving the topical use of probiotics in diseases such as acne, psoriasis and rosacea.</p> <p>[I] The review suggests a benefit linked to the use of <i>Bifidobacterium breve</i> BR03 and <i>Lactobacillus salivarius</i> for rosacea.</p> <p>[II] The review, in two parts, also suggests the potential benefit of <i>Lactococcus</i> (ferment lysate). At another point, the complex <i>Lactococcus</i> (ferment lysate) + associations (<i>Hansenula/Kloeckera/Lacrobacillus/Lactococcus/Leuconostoc/Pediococcus/Saccharomycea</i>) was described with potential benefit in natural defense and susceptible irritation in rosacea situations. The trade names listed for the respective products are, in order: Probiotic + Ds Soothing Serum (Amperna), Columbia Skincare Probiotic Concentrate and LaFlora Probiotic Serum Concentrate.</p> <p>[III] One study showed favorable resolution in scalp rosacea with the use of oral probiotics and doxycycline.</p>

Table 2 - Summary of the studies and their main results.

Source: Faccin, Guido *et al* 2024.

flammatory effects of UV radiation, contributing to the sensitivity of patients affected by this pathology after sun exposure.⁶

BACTERIA AND THE GUT-SKIN AXIS

The gut-skin axis is currently the key to several studies, but there are still uncertainties. It is known, however, that 70% of lymphocytes are found in the intestinal lymphoid tissue, where it has the largest composition of bacterial colonies. One hypothesis about this relationship – based on what is known about other diseases – is that epithelial junctions are compromised and bacteria are translocated into the bloodstream.⁶

According to Pellicer (2023), the increase in PAMPs in the bloodstream and the decrease in butyrate – which produces anti-inflammatory action – can lead to hyperresponsiveness of B cells and impaired differentiation of T cells.

Recent studies have shown positive effects in resolving skin problems (such as atopic dermatitis, psoriasis and acne) with the use of oral probiotics, although rosacea in particular merits further research. With regard to topical probiotics, a clinical trial study explored the efficacy of the product M89PF (which contains probiotic fractions of *Vitreoscilla filiformis*). According to the author, in addition to protecting the skin barrier, the product was able to optimize the immunocellular response and establish protection against pathogenic bacteria. Specifically in this study, there was an improvement in the reduction of *Demodex* mite and facial erythema.⁶

Another study, this time for the treatment of psoriasis, showed that patients affected by the condition had a significant reduction in beneficial microorganisms, such as *Bifidobacterium spp.* Oral administration of probiotics was able to reduce the expression of inflammatory cytokines such as TNF- α , IL-6 and pro-inflammatory cytokines in the IL-23/IL-17 cytokine axis.¹

CONCLUSION

Rosacea is a skin condition that is not yet well understood, but which, according to recent studies, involves inflammation mechanisms mediated by excitatory pathways – such as bacterial agents and mites. Dysbiosis can favor the weakening of protective barriers, both in the intestine and on the skin, with the consequent provocation by pathogens that – when they enter the bloodstream – favor the inflammatory cascade. The hypothesis that probiotics can restore control of the skin is already covered in some pathologies – such as psoriasis – but is still very weak in diseases such as rosacea. Although it may seem discouraging at first, some of the products listed in the studies in this review have shown positive effects in re-establishing the skin barrier, moisturizing and reducing erythema – being positively used as adjuncts in the treatment of rosacea. However, there is no established consensus on specific colonies (to be used) and their respective dosages, as well as the control of formulations – since preservatives can directly influence the viability of the probiotic strain sample. An alternative – not explored in this review – would be the use of prebiotics, favoring the growth of non-pathogenic bacteria that already exist on the skin.

Further studies are needed to select specific strains, as well as to establish their effects – both desirable and collateral – targeted at rosacea. Short and long-term safety studies, as well as the establishment of standardized handling guidelines in the manufacture of dermocosmetics, are crucial to the efficacy of the therapy.

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