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Impact of the microbiome on skin health - assessing the potential of probiotics in the treatment of rosacea

Gabriela Skórska

https://orcid.org/0009-0008-2197-3414

gabrielaskorska12@gmail.com

Medical University of Silesia, Poniatowskiego 15

Katarzyna Gunia

https://orcid.org/0009-0003-0111-5758

katarzyna.gunia2000@gmail.com

Independent Public Health Care Unit of the Ministry of the Interior and Administration in Katowice, Poland; Collegium Medicum, University of Rzeszow, Poland

Aleksandra Lecnar

https://orcid.org/0009-0001-8254-2414

s82946@365.sum.edu.pl

Medical University of Silesia, Poniatowskiego 15

Ewa Szklarek

https://orcid.org/0009-0002-5063-7942

e.szklarek02@gmail.com

Medical University of Silesia, Poniatowskiego 15

Oliwia Matras

https://orcid.org/0009-0007-7029-2810

oliwiamatras4@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Gabriela Grylowska

https://orcid.org/0000-0002-3796-2487

gabriela.grylowska@gmail.com

5th Military Clinical Hospital with Polyclinic in Krakow, Poland

Anna Paluch

https://orcid.org/0009-0003-3913-0830

aniapaluch1303@gmail.com

5th Military Clinical Hospital with Polyclinic in Kraków

Andrzej Palak

https://orcid.org/0009-0007-5381-8438

andrzej.palak699@gmail.com

Collegium Medicum, University of Rzeszow, Poland; University Hospital in Krakow, Poland

Marcin Rebizant

https://orcid.org/0009-0008-1159-228X

marcin-rebizant@wp.pl

University Hospital in Krakow, Poland

Michał Tryba

https://orcid.org/0009-0009-8363-5397

michau.tryba@gmail.com

District Hospital in Chrzanow, Poland

Abstract

Background: Rosacea is a chronic inflammatory dermatosis characterized by flushing, persistent erythema, telangiectasia, papules, and pustules affecting the facial skin. Increasing evidence suggests that disturbances in the skin and gut microbiota may contribute to disease pathogenesis through the gut–skin axis.

Aim: This study aimed to review current knowledge regarding the role of the microbiome in rosacea pathogenesis and the potential therapeutic significance of probiotics.

Materials and Methods: A narrative literature review was conducted using the PubMed, Cochrane Library, and Google Scholar databases. The following keywords were used: microbiome, rosacea, probiotics, and gut–skin axis. After screening and removal of duplicates, 122 publications were included, comprising original studies, review articles, case reports, and clinical guidelines.

Results: Available evidence indicates a significant association between rosacea and dysbiosis of the skin and gut microbiota. Microbial alterations may contribute to immune dysregulation, epithelial barrier dysfunction, and activation of inflammatory pathways. Microorganisms such as *Demodex folliculorum*, *Bacillus oleronius*, *Staphylococcus epidermidis*, and *Helicobacter pylori* appear particularly relevant. Probiotic supplementation may improve barrier integrity, reduce inflammation, and enhance standard rosacea therapy.

Conclusions: Modulation of the microbiome with probiotics may represent a promising adjunctive strategy in rosacea treatment; however, further clinical studies are required to establish evidence-based recommendations.

Keywords gut microbiome, gut dysbiosis, rosacea, probiotics, skin-gut axis

Introduction

Rosacea is a chronic, recurrent, inflammatory disease of the facial skin. Its characteristic symptoms include recurrent facial flushing, erythema, telangiectasias, and papules and pustules occurring mainly on the cheeks, chin, nose, and forehead. There are four non-mutually exclusive subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular [1]. This dermatosis affects approximately 5% of the global population, with peak incidence occurring between 30 and 50 years of age. It predominantly affects fair-skinned women with Fitzpatrick skin phototypes I or II [2]. Despite numerous studies, the etiopathogenesis of the disease has not been clearly elucidated. It is assumed to involve a network of interrelated factors, including genetic factors, such as single-nucleotide polymorphisms in the BTNL2 and HLA-DR genes and mutations in the glutathione S-transferase gene; immunological factors, including infiltrates of Th1 and Th17 lymphocytes and increased expression of Toll-like receptors; as well as infectious and environmental factors [2,3]. Environmental elements that may trigger or exacerbate rosacea-like lesions include temperature changes, stress, physical exertion, ultraviolet radiation, and diet. Observations indicate a negative impact of alcohol, spicy foods, cinnamon, and food products rich in histamine and formaldehyde, including fruits, vegetables, and nuts [1,2,4]. It should be emphasized that in recent years an increasing number of studies have focused on the potential role of the gut microbiota in the pathogenesis of rosacea. This topic represents a relatively new field of interest among researchers investigating the pathogenetic foundations of this dermatosis. Particular attention has been drawn to the proposed concept of the "skin–gut axis," or, in a broader form, the "gut–brain–skin axis." This concept describes the dependence of skin health on gastrointestinal health through metabolic-hormonal, immune, and nervous system pathways. Evidence supporting the importance of the skin–gut axis is provided by the coexistence of many dermatological conditions with gastrointestinal diseases. This relationship suggests that intestinal dysbiosis, by affecting the immune system, may contribute to the exacerbation of skin lesions, including those characteristics of rosacea. This, in turn, indicates the potential rationale for using probiotics as an adjunctive element to conventional pharmacotherapy in the treatment of rosacea [5]. The aim of this paper was to discuss the current state of knowledge regarding the mechanisms by which the microbiome influences the pathogenesis of rosacea. Emphasis was placed on identifying the systematic names of specific microorganisms and the biochemical basis of the negative biological effects they exert in the host organism. In addition, information concerning the influence of diet and the possible

modulation of the gut microbiota with probiotics, which may benefit patients affected by rosacea, was analyzed and integrated. The PubMed, Cochrane Library, and Google Scholar databases were searched. The search was conducted using the following keywords: microbiome, rosacea, probiotic, and gut–skin axis. After analysis of abstracts and titles, followed by removal of duplicate publications, 122 articles were included in the review. In cases of ambiguity, the authors referred to the full text of the publication. The articles included in this paper comprised original studies, review articles, case reports, and clinical practice guidelines.

Skin Microbiome

The term *microbiome* was first introduced in 2001 by Nobel Prize laureate Joshua Lederberg, who defined it as the collective genomes of all microorganisms inhabiting the human body. In contrast, the term *microbiota* refers to the collection of the microbial cells themselves. The human microbiome consists of approximately 30 trillion bacteria and microorganisms functioning within three compartments: the gastrointestinal (GI), skin, and blood microbiomes [2]. Bacteria, fungi, viruses, and arthropods living on human skin collectively constitute the human skin microbiome. In healthy individuals, numerous commensal species inhabit the body surface, including *Staphylococcus epidermidis* and *Demodex folliculorum*. In patients affected by rosacea, however, the skin flora differs significantly — there is an increased abundance of commensal species accompanied by the presence of pathogenic bacteria [2,6]. All of these microorganisms have been shown to play a role in regulating immune responses. Some may cross the skin barrier and interact with deeper cellular structures. It has been suggested that microorganisms trigger inflammation through activation of pattern recognition receptors (PRRs). PRRs become activated upon contact with pathogen-associated molecular patterns (PAMPs), which are molecular motifs resulting from the structure or metabolism of pathogens. Skin microorganisms not only induce the release of antimicrobial peptides, primarily LL-37, but also regulate components of the complement system and intensify cutaneous inflammation through the accumulation of neutrophils, macrophages, mast cells, and plasma cells, as well as through the production of interleukins [5]. In diseased skin, infiltrates composed of Th1 and Th17 lymphocytes are observed. Increased expression of Toll-like receptor 2 (TLR-2) is detected on epidermal cells and within the dermis, stimulating the release of cytokines and pro-inflammatory peptides. Elevated levels of cathelicidin hCAP18, kallikrein 5 (KLK5), matrix

metalloproteinases 2 and 9 (MMP-2 and MMP-9), and IL-6 have also been reported [2,7,8]. These alterations may lead to several adverse effects, including vasodilation, angiogenesis, and extracellular matrix deposition. Several microorganisms have been identified as potentially contributing to the development of rosacea lesions, including *Demodex folliculorum*, *Bacillus oleronius*, *Staphylococcus epidermidis*, and *Cutibacterium acnes* [3,9]. *Demodex folliculorum* is a commensal mite species inhabiting hair follicles in healthy individuals. In rosacea lesions — particularly in erythematotelangiectatic and papulopustular subtypes — the number of mites increases, which may result in elevated TLR2 receptor expression, decreased Th2 expression, and release of IL-4, IL-5, IL-6, IL-10, and IL-13 [10,11,12]. It has been reported that the density of *D. folliculorum* mites reaches up to 10.8/cm² in rosacea patients compared to 0.7/cm² in control groups [13]. *Bacillus oleronius* is a Gram-negative bacterium residing within the mite organism. Its abundance has been found to increase in patients with rosacea; however, its precise role in disease pathogenesis remains unclear. Reports suggest that bacterial proteins, rather than the mite itself, may trigger the immune response. The proposed mechanism involves TLR activation, enhanced neutrophil degranulation, and cytokine production [14,15]. *Staphylococcus epidermidis* is a non-hemolytic bacterium that, under physiological conditions, inhibits the growth of pathogens such as *Staphylococcus aureus* on healthy skin. In patients with rosacea, increased colonization of this bacterium has been observed within affected skin areas. Moreover, the isolated strain demonstrated β-hemolytic properties and, by stimulating TLR-2, contributed to KLK5 activation and immune dysregulation [2,16,17,18]. These relationships indicate the significant role of infectious factors disrupting the natural skin microbiome in the pathogenesis of rosacea-associated lesions.

Gut Microbiome and the "Gut–Skin Axis"

The human intestines, similarly to the skin, constitute a habitat for an enormous number of microorganisms. Intestinal bacterial species such as *Lactobacillus*, *Escherichia coli*, *Bifidobacterium*, and *Streptococcus thermophilus* contribute to the maintenance of human health, whereas others — including *Clostridioides difficile*, *Campylobacter*, *Enterococcus faecalis*, and *Helicobacter pylori* — are capable of inducing disease. The intestines are considered to exist in a state of symbiosis because they are inhabited by a diverse microbial community, while the host organism tolerates the associated mild antigens. This tolerance is established during ontogenesis and reduces microbiome-dependent inflammatory reactions [5].

The individual gut microbiome is established from birth and is acquired, among other mechanisms, during vaginal delivery and subsequent breastfeeding. Initial colonization plays a significant role in determining the future composition of the gut microbiome as the organism ages. Similar microbiomes are found in the intestines of infants and the vaginal microbiota of their mothers. After approximately 3 years of age, the microbiome composition gradually changes until it becomes relatively stable [19].

The gut microbiome typically includes bacterial groups such as *Bacteroidetes*, *Firmicutes*, *Lactobacillus*, *Enterococcus*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* [20]. It plays an essential role in maintaining systemic homeostasis. Since birth, the gut microbiota has been involved in protection, metabolic activity, and the development and regulation of the immune system. It participates in the metabolism of dietary substances, including the biosynthesis of vitamins B and K, and enhances calcium and magnesium absorption [21,22,23].

Additionally, the gut microbiota prevents colonization of the intestine by pathogenic bacteria, stimulates maturation of immune cells, reduces inflammatory processes, and detoxifies toxins and carcinogens. It maintains the integrity of the intestinal barrier through the conversion of indigestible complex polysaccharides into vitamins, particularly B and K, as well as short-chain fatty acids (SCFAs), mainly butyrate and propionate. Butyrate, the principal SCFA, exerts anti-inflammatory effects by inhibiting the proliferation, migration, and adhesion of inflammatory cells, as well as cytokine production. Disturbances in the gut microbiome contribute to the development of civilization diseases such as obesity, diabetes mellitus, autoimmune diseases, and allergies [24,25,26].

The association between gastrointestinal disturbances and skin diseases was first observed in 1930 by John Stokes and Donald M. Pillsbury [27]. Since then, the term “gut–skin axis” has become increasingly important in understanding the pathogenesis of dermatological disorders. This concept assumes that skin homeostasis depends, among other factors, on gastrointestinal health through complex interactions involving the immune, metabolic, and nervous systems. One of the principal regulators of this bidirectional communication pathway is the gut microbiota [28].

In a population-based cohort study involving 50,000 patients, Alexander Egeberg and colleagues demonstrated an increased prevalence of celiac disease, Crohn’s disease (CD), ulcerative colitis (UC), small intestinal bacterial overgrowth (SIBO), and irritable bowel

syndrome (IBS) among patients with rosacea compared with control subjects [29]. Andrea Parodi and colleagues showed that the likelihood of developing SIBO was 13 times higher in patients with rosacea than in unaffected individuals. Furthermore, eradication of SIBO using rifaximin resulted in significant regression of skin lesions [2,30]. It has been suggested that, in SIBO, circulating cytokines such as TNF-α inhibit IL-17 and stimulate a Th1-dependent immune response [31].

Helicobacter pylori is a microaerophilic Gram-negative bacterium colonizing the stomach and duodenum. Rosacea has been associated with *H. pylori* seropositivity [32]. The bacterium induces chronic cytotoxin-dependent inflammation and gastrin-mediated facial flushing [33,34]. Researchers have identified a strong association between a positive C13 urea breath test and rosacea. It should be emphasized that this test is considered highly diagnostic for *H. pylori* infection [35].

H. pylori may significantly increase the generation of reactive oxygen species (ROS), which exert inflammatory effects on the gastrointestinal tract. Among ROS, nitric oxide (NO) contributes to intestinal mucosal inflammation and alters physiological processes in the skin by inducing vasodilation, flushing episodes, persistent erythema, and inflammation, ultimately leading to the clinical manifestations of rosacea. Another mechanism supporting the role of *H. pylori* in rosacea development involves cytotoxin production, which induces the release of pro-inflammatory cytokines such as TNF-α and IL-8. The release of these mediators results in gastric mucosal inflammation and clinical symptoms associated with rosacea.

Eradication of *H. pylori* has been shown to alleviate both rosacea symptoms and accompanying gastrointestinal complaints [35,36,37,38].

As mentioned previously, butyrate decreases intestinal barrier permeability and strengthens epithelial barrier integrity. The intestinal mucus layer acts as the primary barrier preventing translocation of microorganisms into host tissues. Mucosal defense is mediated by innate immune structures collectively referred to as gut-associated lymphoid tissue (GALT). These structures recognize nonspecific infections and activate both innate and adaptive immune responses through antigen presentation [39].

Defensins exert antibacterial activity by generating pores within bacterial membranes, ultimately leading to cell death. Cathelicidins, including LL-37 in humans, also contribute to

maintaining epithelial barrier integrity. Although their primary mechanism involves disruption of bacterial membranes, they additionally possess immunomodulatory properties [40].

Studies in mice have demonstrated that short-chain fatty acids produced by commensal microorganisms during fermentation facilitate the generation of regulatory T lymphocytes (Treg cells). These cells primarily suppress inflammatory and allergic reactions within the intestines, thereby maintaining intestinal barrier integrity [41]. B lymphocytes synthesize immunoglobulins, including IgA and secretory IgA (SIgA), which, after entering the intestinal lumen, constitute a major component of defense against pathogenic microorganisms by trapping them on mucosal surfaces and preventing their penetration through mucous membranes into the body [42].

However, these mechanisms may fail, resulting in impaired function of the intestinal mucosal layer, disruption of epithelial tight junctions, and translocation of bacteria and/or their toxins into the bloodstream. After reaching peripheral tissues, including the skin, bacterial metabolites may induce alterations in skin physiology, disrupt local immune responses, and ultimately contribute to the development of rosacea symptoms.

Individual studies emphasize that the presence of bacterial DNA in the bloodstream may participate in the course of rosacea and other dermatological diseases, including psoriasis, atopic dermatitis, and hidradenitis suppurativa. Research conducted by Yun et al. demonstrated the presence of *Chromatiaceae*, *Fusobacteriaceae*, and *Rheinheimera* species in the blood of patients with rosacea [43]. It is believed that lipopolysaccharides produced by the Gram-negative bacterium *Rheinheimera* may activate Toll-like receptors and contribute to acne development [44].

Another theory suggests that intestinal dysbiosis activates the plasma kallikrein–kinin system (PKKS), thereby inducing further inflammation. In a study by Arthur Kendall, PKKS overactivation was confirmed in both patients with inflammatory bowel disease and individuals with rosacea [45].

Using next-generation sequencing (NGS), Chen et al. observed reduced diversity of the colonic microbiome accompanied by increased colonization by *Rabdochlamydia*, *Bifidobacterium*, *Sarcina*, and *Ruminococcus*, alongside reduced abundance of *Lactobacillus*, *Megasphaera*, *Acidaminococcus*, *Haemophilus*, *Roseburia*, and *Clostridium* species [46]. Conversely, Nam

et al. reported increased colonization by *Acidaminococcus*, *Megasphaera*, and *Lactobacillus*, together with lower abundance of *Peptococcaceae* and *Methanobrevibacter* species.

A Korean study demonstrated an association between gut microbiota composition and rosacea in a group of 12 affected women. Although the overall abundance of microbiota was comparable between rosacea patients and healthy controls, the microbial composition differed significantly [47].

It has been proposed that the composition of the fecal microbiome may be associated with sulfur metabolism and the transport of carbohydrates and cobalamin. Imbalance of thiol compounds in serum may predispose rosacea patients to oxidative stress [48].

The "Gut–Brain–Skin Axis"

In the first half of the 20th century, dermatologists John H. Stokes and Donald M. Pillsbury were the first to suggest that the intestines and skin also communicate with the central nervous system. They hypothesized that emotional states, such as depression and anxiety, may modulate the microflora, leading to increased intestinal barrier permeability and the development of systemic inflammation [49]. The coexistence of psychiatric disorders, gastrointestinal disturbances, and chronic dermatological diseases has, in recent years, led to the emergence of specialized research groups focusing on psychodermatology and neurodermatology. Studies indicate that chronic psychological stress slows intestinal transit time, thereby promoting bacterial overgrowth and consequently weakening the intestinal barrier [50]. SIBO remains strongly correlated with anxiety and depression, and anxiolytic treatment improves emotional well-being in patients affected by bacterial overgrowth. It should be recalled that SIBO is 10 times more prevalent in individuals with rosacea compared with control groups, and its treatment leads to improvement in skin condition [51,52,53].

Moreover, it is known that a diet deficient in omega-3 fatty acids not only increases the risk of gut microbiome disturbances but is also associated with depressive symptoms and acne manifestations [54,55,56]. The amount and reactivity of bacterial lipopolysaccharide (LPS) endotoxins in the bloodstream increase in acne through a mechanism involving enhanced intestinal permeability [57]. Other studies have shown that LPS derived from *Escherichia coli*induces depression-like behavior in animals [58]. Manipulation of the bacterial flora through orally administered probiotics affects mechanisms regulating mental health. Such supplementation increases peripheral blood tryptophan levels and alters serotonin and

dopamine metabolism within the frontal cortex and limbic system [59]. Increased neuronal resilience and reduced apoptotic processes under conditions of experimental physiological stress have also been observed [60]. Probiotics enhance the synthesis of omega-3 fatty acids in tissues, which are essential for maintaining proper mood regulation [61]. The presence of *Bifidobacteria* — beneficial commensal bacteria — attenuates stress responses by maintaining high levels of brain-derived neurotrophic factor (BDNF). BDNF levels decrease in depression, whereas gastrointestinal inflammation in animals reduces its production and induces anxiety [62,63]. Oral administration of *Bifidobacteria* protects against systemic lipid peroxidation, decreases brain monoamine oxidase activity, and thereby improves synaptic neuronal communication [64].

An important communication pathway within the gut–brain–skin axis is substance P. Experimental alterations in gut microflora may increase the release of this compound within the nervous system and promote anxiety-related behavior, depression, or aggression [65,66]. Individuals responding to antidepressant pharmacotherapy experience mood improvement that correlates with decreased serum levels of substance P [67].

Another mechanism linking probiotics, mental health, and acne involves glycemic control. Studies investigating the effects of a diet rich in carbohydrates, low in fiber, and characterized by a high glycemic index demonstrated its influence on acne risk. Blood test results indicative of insulin resistance were also associated with an increased risk of depressive symptoms [68,69,70]. Oral supplementation with probiotics containing *Bifidobacterium lactis* may beneficially influence fasting insulin levels and glucose turnover rates [71]. Loss of these microorganisms, among others, as a consequence of poor dietary choices increases intestinal permeability, facilitates penetration of LPS endotoxins into the bloodstream, and consequently leads to inflammation, oxidative stress, insulin resistance, and depressive symptoms [72,73].

Psychological stress alone, or in combination with an inadequate diet, alters intestinal motility and the microbiota profile. Loss of the normal bacterial biofilm increases intestinal permeability, allowing endotoxins to gain systemic access. This results in inflammatory burden and oxidative stress, increased levels of substance P, and reduced insulin sensitivity due to endotoxemia. In genetically predisposed individuals, these mechanisms contribute to the development of rosacea symptoms. Both probiotics and antimicrobial agents may play a role in interrupting this cycle at the intestinal level.

The Role of Diet and Probiotics in the Treatment of Rosacea

Qualitative and quantitative disturbances of the gut microbiome observed in the course of rosacea have become a rationale for incorporating bacteria into the therapeutic process. Probiotics — selected live cultures of beneficial bacteria or yeasts which, when consumed in appropriate amounts, help restore microbiome balance — have therefore found application in treatment [74]. Oral probiotics administered to patients with rosacea significantly support standard pharmacological therapies. Several probiotic strains have demonstrated beneficial effects on skin condition. *Lactobacillus paracasei* CNCM-I 2116 was shown to induce faster regeneration of barrier function following impairment by sodium lauryl sulfate in an ex vivo skin organ culture model [75]. Three weeks of high-dose administration of this strain significantly reduced transepidermal water loss (TEWL) in a murine model of dinitrochlorobenzene-sensitized skin [76]. A randomized, double-blind, placebo-controlled clinical trial demonstrated that supplementation with this strain for two months reduced skin sensitivity and enhanced skin barrier recovery [77]. In a reconstructed human epidermis model, lysate of *Lactobacillus reuteri* DSM 17938 increased levels of laminin A and B, important extracellular matrix proteins, suggesting a beneficial effect on the skin barrier [78]. A randomized, double-blind, placebo-controlled clinical trial showed that oral administration of *Lactobacillus plantarum* HY7714 at a dose of 10^{10} CFU daily for 12 weeks inhibited TEWL in facial and forearm skin while simultaneously increasing tissue water content [79]. The same research group demonstrated in an observational study that healthy volunteers receiving this probiotic strain exhibited changes in gut microbiota composition, including increased abundance of *Bifidobacterium* and reduced levels of *Proteobacteria*, accompanied by decreased plasma concentrations of MMP-2, MMP-9, zonulin, and calprotectin, all of which are associated with skin and intestinal permeability [80]. Furthermore, oral treatment with *L. plantarum* HY7714 at a dose of 10^{9} CFU daily for eight weeks in hairless mice reduced UV-induced epidermal thickening and inhibited TEWL [81]. In a mouse study, supplementation of drinking water with *Lactobacillus reuteri* improved epidermal thickness, increased folliculogenesis, lowered skin pH, and enhanced production of sebum-producing epithelial cells. Consequently, mice receiving probiotic-supplemented water exhibited shinier and thicker fur compared with control animals [82,83]. In another experiment, administration of *Lactobacillus johnsonii* to mice demonstrated therapeutic effects in restoring UV-induced skin damage [84].

A beneficial role of probiotics in rosacea therapy has also been demonstrated clinically. Manzhalii et al. conducted an open-label randomized clinical trial involving 57 patients presenting with erythema and papulopustular lesions, among whom 36% were diagnosed with papulopustular rosacea (the remaining 22% and 57% were diagnosed with acne and seborrheic dermatitis, respectively). Patients were divided into two groups, one of which received standard topical therapy consisting of tetracyclines, corticosteroids, and retinoids. The second group received the same therapy supplemented with oral administration of the probiotic strain *Escherichia coli* Nissle 1917. After one month of observation, 32% of patients in the probiotic group demonstrated complete recovery and 57% showed significant improvement, compared with 17% and 39%, respectively, in the control group. Furthermore, patients receiving probiotics demonstrated improved quality-of-life questionnaire scores. Stool cultures performed after treatment showed that therapy with *E. coli* Nissle 1917 increased the growth of *Lactobacillus* and *Bifidobacterium* species while reducing *Staphylococcus*, yeasts, *Bacteroides*, *Proteus*, *Citrobacter*, and *Klebsiella* species [85].

Buianova et al. published another randomized clinical trial in 2018 involving 60 patients with rosacea. Participants were divided into two groups. Thirty patients were treated for one week with oral antibiotics, vitamins, antihistamines, and topical permethrin. The remaining 30 patients received a mixture containing *Bifidobacterium* strain 5×10^7 CFU three times daily together with polyoxidonium (an immunomodulator) for three weeks. In the probiotic group, 57% of patients experienced complete clinical remission compared with 28% in the control group. Moreover, stool cultures at the end of treatment revealed increased abundance of *Lactobacillus* and *Bifidobacterium* species in patients from the probiotic group [86].

Fortuna et al. described a case of rosacea involving the scalp, characterized by papules and pustules localized on the face and scalp accompanied by intermittent erythema, burning sensation, blepharitis, and conjunctivitis. The patient was successfully treated for eight weeks with low-dose doxycycline (40 mg/day) combined with oral probiotics (*Bifidobacterium breve* BR03 and *Lactobacillus salivarius* LS01, 10^9 CFU twice daily), followed by probiotic monotherapy. During six months of follow-up, no recurrence or exacerbation of the disease was observed. Significant improvement occurred in both cutaneous and ocular symptoms [87].

Factors influencing gut microbiota composition include mode of delivery, diet, age, stress, and antibiotic use. It is also noteworthy that the host may additionally provide beneficial substrates for probiotic bacteria through the consumption of prebiotics and synbiotics (a combination of

probiotics and prebiotics). The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines prebiotics as substrates selectively utilized by microorganisms that confer health benefits to the host [88]. They are present in food products or supplements rich in specific saccharides such as fructose, glucose, galactose, inulin, lactulose, sorbitol, or xylitol. Galactooligosaccharides (GOS), one of the principal components of human breast milk, may be fermented into SCFAs by *Bifidobacterium* species. This has been demonstrated by decreased concentrations of human milk oligosaccharides (HMOs) in stool samples accompanied by increased abundance of *Bifidobacterium* genera. Utilization of HMOs by *Bifidobacterium* spp. may therefore be regarded as a prebiotic effect on the infant gut microbiome [89].

Similarly, GOS have been used for decades in the treatment of dermatological conditions associated with photoaging. In one study, a combination of GOS and *Bifidobacterium* reduced transepidermal water loss (TEWL/TWL) and prevented skin erythema. Atopic dermatitis and eczema have also been treated using GOS [90]. Another metabolite derived from prebiotics (carbohydrates), sodium butyrate, is commonly used in the treatment of hyperproliferative skin diseases, including psoriasis, through modulation of key cellular processes such as differentiation, proliferation, and apoptosis [91]. Sodium butyrate influences the cell cycle, proteolytic enzymes, and transforming growth factor beta (TGF-β). Apoptosis in keratinocyte (HaCaT) cells may be induced by sodium butyrate through upregulation of the Fas receptor (death receptor) together with activation of caspases 8 and 3 [92].

Dietary habits, through modulation of gut microbiota, may positively or negatively affect skin condition. This applies not only to daily diet but also to all natural or synthetic substances consumed routinely. The effects of antibiotics constitute perhaps the best example of the relationship between the gut microbiome and skin microbiota. Although antibiotics are primarily used to eliminate infectious pathogens, they may also be useful in treating noninfectious skin diseases because of their anti-inflammatory and immunomodulatory properties [93].

With regard to diet, several food products may significantly contribute to deterioration of skin condition in patients with rosacea through their influence on the gut microbiome. These include trans fatty acids, which induce increased growth of harmful microorganisms such as *Desulfovibrionaceae* and *Proteobacteria* while simultaneously suppressing populations of beneficial bacteria including *Bacteroidetes*, *Lachnospiraceae*, and *Bacteroidales* [94]. Refined

and hydrogenated oils, including soybean, sunflower, safflower, rapeseed, corn, and vegetable oils, induce intestinal inflammation, which may subsequently affect facial skin condition. Skin healing processes may additionally be delayed by high-fat diets and alcohol consumption, both of which intensify cutaneous inflammation and oxidative stress [95].

High-fat diets reduce intestinal microbial diversity and induce production of elevated concentrations of lipopolysaccharides. This results in impaired colonic epithelial integrity and barrier function, reduced mucus layer thickness, and increased release of pro-inflammatory cytokines, ultimately promoting systemic inflammation [96]. Individuals affected by rosacea should also avoid excessively high-protein diets. Excess amino acids, through metabolism by commensal bacteria, lead to synthesis of indoxyl sulfate (IS) and trimethylamine N-oxide (TMAO) [97]. These toxins are implicated in several dermatological conditions, including peripheral arthritis and psoriasis [98,99].

Conversely, diets rich in collagen peptides, which contain large amounts of microorganisms, may protect the skin against aging and support wound healing [100]. The abundance of commensal intestinal bacteria such as *Lactobacillus* and *Bifidobacterium* increases following consumption of diets containing whey and pea protein extracts, while levels of pathogenic *Bacteroides fragilis* and *Clostridium perfringens* decrease. Concentrations of SCFAs within the intestinal mucosa also increase with pea protein consumption, which is critical for maintaining mucosal barrier integrity [98].

The beneficial effects of dietary fiber on the gut microbiome are well documented. As a product not digested within the human gastrointestinal tract, fiber is metabolized by bacteria inhabiting the colon. This process stimulates the growth of multiple bacterial groups. Consumption of foods rich in dietary fiber, particularly whole-grain products, markedly increases populations of *Bifidobacteria* and *Lactobacillus/Enterococcus* groups [101]. Products containing complex dietary carbohydrates may be converted into SCFAs, including propionate, acetate, and butyrate, through fermentation by the gut microbiome [101,102]. SCFAs mediate the development of regulatory T lymphocytes (Treg cells) within the colon, thereby influencing mucosal immunity by enhancing epithelial barrier function [102]. Regulation of Treg development and function occurs through expression of Foxp3 (Forkhead box P3 protein) [103,104]. By strengthening intestinal integrity, SCFAs prevent the development of inflammatory disorders and inhibit accumulation of potentially harmful metabolic byproducts such as D-lactate. Their anti-inflammatory effects are additionally supported by G protein-

coupled receptor 43, TGF-β, and/or IL-10 [105]. Within the skin, anti-inflammatory effects may be mediated by resident Treg cells, which become less abundant in certain inflammatory dermatoses [102]. SCFAs derived from intestinal fiber fermentation may also influence the occurrence of specific groups of skin microorganisms, thereby affecting skin defense mechanisms. By preventing proliferation of harmful bacteria on the skin and reducing inflammation, the skin microbiome may cooperate with the immune system to promote cutaneous homeostasis [106].

Another therapeutic option apart from oral probiotics involves topical probiotics. Topical application of probiotic bacteria may improve the natural skin barrier by exerting direct effects at the site of application. To date, few clinical studies have evaluated the efficacy of topical probiotics in rosacea treatment. In January 2023, results of a clinical study by Leonardo Berardesca and colleagues were published, assessing the efficacy of a product containing mineralizing volcanic water combined with the probiotic fraction *Vitreoscilla filiformis*, hyaluronic acid, niacinamide, and tocopherol in patients with rosacea. Topically applied *V. filiformis* extract demonstrates beneficial properties including optimization of cellular immunity, protection against pathogenic skin bacteria, and improvement of skin barrier function. In this clinical study, 20 rosacea patients were randomly assigned to receive either the tested product or standard non-medicated cosmetic skincare on opposite halves of the face for 30 days. Treatment significantly improved skin hydration by reducing TEWL, decreasing *Demodex* density, reducing erythema severity (measured using a chromameter), and improving skin tightness and dryness [107]. Moreover, a study by Benedusi et al. using the same cosmetic product demonstrated that it protected against skin barrier damage induced by UV and ozone exposure [108].

Contraindications to Probiotic Use

In 2011, the Agency for Healthcare Research and Quality published a report stating that existing clinical studies had not demonstrated risks associated with the safe use of probiotics. However, the report also emphasized the insufficient level of knowledge currently available to definitively exclude potential adverse effects [109]. The World Health Organization(WHO), together with the Food and Agriculture Organization (FAO), identified four theoretical groups of side effects: systemic infections, harmful metabolic effects, excessive immune system stimulation in susceptible individuals, and gene transfer [110].

There are a limited number of case reports describing infections corresponding to the strains contained in administered probiotics. These most commonly involve fungemia associated with the presence of *Saccharomyces cerevisiae* and *Saccharomyces boulardii*; however, cases of bacteremia caused by *Lactobacillus casei* and *Lactobacillus acidophilus*have also been reported [111,112,113,114]. Cases of overt sepsis, infective endocarditis, and liver abscess formation have likewise been described [115,116,117].

The PROPATRIA clinical trial raised concerns regarding the safety of probiotic administration. Two groups of patients with severe acute pancreatitis were studied, one of which received a multispecies probiotic preparation to evaluate its usefulness in preventing infection. Patients assigned to the probiotic group experienced increased mortality related to intestinal ischemia. It was postulated that the metabolic effects of probiotics may have increased oxygen demand within the intestinal mucosa or triggered inflammatory reactions at this site [118].

Another metabolic adverse effect associated with probiotic use is acidosis resulting from D-lactate synthesis by probiotic strains. One case report of this complication has been described in a patient with short bowel syndrome [119].

Excessive stimulation of the immune system currently remains a theoretical concern that has not yet been confirmed in clinical studies. The demonstrated effects of probiotics on innate and adaptive immunity, cytokine function, and dendritic cell activity raise concerns regarding potential overstimulation, particularly in susceptible individuals, which requires further investigation.

Another emerging issue is the possibility of gene transfer. Lactic acid bacteria possess plasmids encoding resistance genes to numerous antibiotics, including tetracycline, erythromycin, lincosamides, chloramphenicol, and others. Gene transfer between lactic acid bacilli and endogenous bacteria may occur within the intestines of animals. Despite this theoretical route of genetic information transfer, no clinical evidence confirming its occurrence has been observed to date, which appears particularly important considering the widespread concomitant use of probiotics and antibiotics [120,121,122].

Summary and Conclusions

Clarifying the pathophysiological mechanisms underlying the development of rosacea remains an evolving area of research. Current theories focus on explaining the role of the skin and gut microbiome in the formation of inflammatory lesions. The findings presented in this paper, based on the results of existing studies and observations, provide sufficient evidence supporting the existence of the skin–gut axis. The coexistence of dermatological diseases with gastrointestinal disorders, as well as the efficacy of probiotics in the treatment of skin lesions, further supports this relationship.

A deeper understanding of this bidirectional interaction is necessary in order to establish new evidence-based recommendations and develop more effective therapeutic strategies in the future. At the same time, there is a need to direct further research toward dietary supplements, particularly probiotics and prebiotics, that support microbiome homeostasis and may in the future serve as complementary elements in rosacea therapy.

Disclosure

Authors' contribution:

Conceptualization: Gabriela Skórska, Katarzyna Gunia, Ewa Szklarek, Oliwia Matras, Aleksandra Lecnar, Methodology: Gabriela Skórska, Katarzyna Gunia, Aleksandra Lecnar, Andrzej Palak

Software: Anna Paluch, Marcin Rebizant

Check: Gabriela Skórska, Katarzyna Gunia, Ewa Szklarek, Oliwia Matras, Gabriela Grylowska

Formal analysis: Aleksandra Lecnar, Anna Paluch

Investigation: Gabriela Skórska, Katarzyna Gunia, Ewa Szklarek, Marcin Rebizant

Resources: Aleksandra Lecnar, Andrzej Palak, Michał Tryba

Data curation: Ewa Szklarek, Oliwia Matras, Anna Paluch, Marcin Rebizant

Writing - rough preparation: Gabriela Skórska, Ewa Szklarek, Oliwia Matras, Gabriela Ziółkowska, Aleksandra Lecnar, Andrzej Palak

Writing - review and editing: Gabriela Skórska, Katarzyna Gunia, Oliwia Matras, Michał Tryba

Visualization: Gabriela Grylowska, Michał Tryba

Supervision: Aleksandra Lecnar, Gabriela Grylowska

Project administration: Gabriela Skórska, Katarzyna Gunia, Oliwia Matras

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