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VIEWPOINT

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Targeting the gut-skin axis—Probiotics as new tools for skin disorder management?

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Abstract

The existence of a gut-skin axis is supported by increasing evidence, but its translational potential is not widely recognized. Studies linked inflammatory skin diseases to an imbalanced gut microbiome; hence, the modulation of the gut microbiota to improve skin condition seems to be a feasible approach. Today, there is a growing interest in natural products as alternatives to synthetic drugs. In this respect, oral probiotics could be a simple, safe and cheap modality in the therapeutic management of skin inflammation. Unfortunately, very few studies have looked into how probiotic supplementation influences inflammatory skin disorders. The result, though promising, are difficult to implement in clinical practice due to the heterogeneity of the applied supplemental regimen in the different studies. In this Viewpoint, we aim to encourage the conduction of more research in that direction to explore unambiguously the therapeutic potential of oral probiotics in dermatology. We focus on the most common inflammatory skin diseases (atopic dermatitis, psoriasis, rosacea, acne vulgaris) with an associated gut dysbiosis, but we also discuss some less common, but very serious skin pathologies (eg erythema nodosum, pyoderma gangrenosum, hidradenitis suppurativa) that are possibly linked to a disturbed gut flora composition. We dissect the possible mechanisms along the gut-skin axis and highlight novel points where probiotics could interfere in this communication in the diseased state.

KEYWORDS
atopic dermatitis, inflammatory skin diseases, pathogenesis, psoriasis

1 | INTRODUCTION

Research in the past decade highlighted the importance of the gut microbiota to our health. There is a delicate interaction between the host and the microbiota, and the disruption of this balance can compromise the homeostasis and survival of the entire human organism[7] and can contribute to the development of severe pathologies[36] The gut microbiome greatly influences the host immune system by providing protection against exogenous pathogens and by priming immunoprotective responses[60] Hence, an altered gut flora may contribute to the development of autoimmune and inflammatory diseases, even in organs distant from the gut, such as the skin.[60] Indeed, a growing body of evidence supports that intestinal dysbiosis, a state of microbial imbalance, can almost invariably be observed

in common inflammatory skin pathologies, such as atopic dermatitis (AD)[58,91] psoriasis[51,112] rosacea[82] and acne vulgaris.[16] This realization gave rise to the recognition of the gut-skin axis. [62,86] Actually, this notion is not a new one. In 1930, the two dermatologists, John H. Stokes and Donald M. Pillsbury, proposed their groundbreaking theory about an interrelationship between emotional states, the intestinal flora and systemic and skin inflammation,[108] which was later unified as the gut-brain[103] and the gut-brain-skin axis models[4] Most recently, similar crosstalk has also been postulated between the gut microbiome and the lungs (gut-lung axis)[23] or cancer cells (cancer-gut axis).[75]

Although many reports associate the gut microbiota composition with human health and disease, the causative relationships remain to be elucidated. There is a need for manipulation strategies to clarify the involvement of the gut microbiome in diseases. These strategies may be the use of orally administered antibiotics, prebiotics, probiotics and most recently faecal transplantation.[76] Antibiotics are commonly involved in the management of cutaneous inflammation, but their use should be limited, due to the risk of developing resistance. Though the concept of using faecal transplantation for treating abdominal diseases dates back to mediaeval China[45] faecal transplantation maturated into a medically accepted approach only in the recent years as an effective treatment strategy in *Clostridium difficile* infection.[106] Though a promising treatment modality in gastrointestinal disorders associated with a disturbed gut flora and skin symptoms, faecal transplantation is unlikely to enter dermatology and cosmetology clinical practice rapidly. In terms of modulating the gut microbiome with potential beneficial effects on the skin, prebiotics represent an appealing set of compounds. Prebiotics are dietary components fermented by gut microbes, and nutritional elements that support the growth of bacteria. Among others, prebiotics involve fructooligosaccharides, galactooligosaccharides, inulin, polydextrose, lactulose, sorbitol or xylitol.[21]

Probiotics by definition are 'live microorganisms, which, when consumed in adequate amounts, confer a health effect on the host'.[41] Actual health effects have been reported for specific strains of the following genera: *anaerobic microbes: Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, *Escherichia coli; and the aerobic Bacillus strains*.[38] The bacterial probiotic genera demonstrated to exert beneficial effects on skin health after oral application are the *Bifidobacterium* and *Lactobacillus* (for an overview on the subject readers are referred to[97]. In an interesting paper Levkovich *et al*, reports that feeding mice with yogurt containing the probiotic *Lactobacillus reuteri* induces a general 'glow of health' phenotype in the animals, which was characterized by epithelial follicular shift to anagen phase with increased folliculogenesis and sebocytogenesis resulting in thick, radiant fur. The probiotic strain exerted these effects through the modulation of the immune system; the application of the probiotic increased the production of the anti-inflammatory cytokine IL-10 that induced peripheral regulatory T (Treg) lymphocytes and the secretion of health-stimulating hypothalamic hormones leading to improved epithelial integrity and immune tolerance.[63] Unfortunately, the study does not go into detail if the application of the probiotic modulated the composition of the gut microbiota. Nor do we know, whether the observed phenotype can be generalized after probiotic consumption or it is specific for *Lactobacillus reuteri* intake. Nevertheless, it is easy to realize that benefits gained upon probiotic supplementation in mice would be a desirable improvement in human skin health, with obvious implications in the therapy of inflammatory skin conditions.

Currently, the recommendation of oral probiotics as a treatment or adjuvant strategy in skin disorders is not usual. Given that gut dysbiosis is commonly observed in skin pathologies, the crosstalk between gut and skin could offer targetable pathways with obvious therapeutic potential in dermatological practice. However, the molecular mechanism of the crosstalk is not well understood. The gut is considered as a major immune organ, with the gut-associated lymphoid tissue (GALT) being the most complex immune compartment. Parts of the GALT are Peyer's patches that are organized lymphoid tissues known as the primary inductive sites for the mucosal immune response.[3] It has long been demonstrated that dendritic cells of the Peyer's patches synthesize IL-10 and induce the differentiation of T helper cells.[55] Cytokines and primed immune cells from the Peyer's patches may be transported via the circulation to the skin, where they could modulate the immune status and improve defense mechanisms, providing a possible link in the gut-skin communication[9] Reports suggest that probiotics trigger immunomodulation through the components of the GALT, and the Peyer's patches may have special significance.[44] Contributing to our understanding of probiotic action, evidence has been presented that probiotics ameliorate intestinal inflammation by local stimulation of the gut epithelial innate immune responses.[88] The presented mechanism of probiotics involves the improvement of epithelial barrier function, increased production of TNF-alpha by epithelial cells and activation of the NF-kappaB pathway.[88]

Beyond immune modulation, one has to take into consideration that when we are talking about the microbiota of the gut, we are talking about probably trillions of microorganisms that obviously have huge metabolic capacity. The bioactive metabolites produced by bacteria upon interaction with dietary components are the most probable signalling links between the gut microbiota and the host.[28] Faecal and serum metabolomics should be conducted from patients with dermatological diseases to gain insight into the correlation of intestinal bacterial metabolism and skin condition. These analyses could help to better understand probiotic action, and to better design probiotic application.

In this viewpoint essay, we dissect the possible mechanisms and pathways through which the gut and skin may communicate, and we try to shed light on the significance of these pathways in the pathomechanisms of the most common inflammatory skin diseases, and how probiotics may intervene in the gut-skin axis.

1.1 | Atopic dermatitis

Atopic dermatitis (AD) or eczema is a chronic inflammatory skin disease where the initial symptoms commonly occur in the first 5 years of life, that affects about 20% of children in developed countries,[119] and the prevalence of adulthood AD is estimated around 2%-5% across different countries[6] Skin of patients with AD exhibits a significant barrier dysfunction, which is a result of a specific combination of genetic and environmental factors.[22] A well-established genetic determinant of skin barrier impairment is the deficiency of the structural protein filaggrin.[22] Environmental factors, such as the use of hygienic products, may further exacerbate epidermal barrier disruption.[22] Application of soaps and detergents is very frequently associated with the appearance of irritant contact dermatitis on the hands, which can aggravate AD.[73] The negative effect of the use of soaps and detergents on skin is most possibly due to the consequent marked increase (3 U) of skin surface pH that can last for almost two hours,[80] and an elevated pH is detrimental on epidermal barrier function.[34] It is of note that AD-affected patients have a higher skin surface pH than individuals with normal skin.[32] Whether the prevalent cutaneous dysbiosis of AD patients is a cause or a consequence of the elevation of skin pH is not yet clarified. It is interesting though that topical application of a probiotic strain, *Lactobacillus johnsonii*, for 3 weeks was shown to be effective in reducing *Staphylococcus aureus* colonization and improving symptoms of AD patients,[13] and metabolites of Lactobacilli may reduce skin surface pH.

In this context, we have to mention the so-called 'hygiene hypothesis', according to which there is an inverse relationship between AD and an early exposure to microbial agents. Exposure to microbes starts at birth, when the mode of delivery greatly influences both the gut and skin microbiota of the newborn.[29] Vaginally delivered infants harbour bacterial communities resembling their mother's vaginal microbiota, with the dominant species being of the genera *Lactobacillus* and *Prevotella*, while infants born by Caesarian-section acquire microbial species characteristic of the mothers' skin surface, dominated by *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp.[29] Caesarian-section delivery has been associated with an increased risk for immune disorders, such as asthma, allergy and even inflammatory bowel disease.[102] Although there is no clear correlation between Caesarian-section and AD, it is very likely that *Lactobacilli* of vaginal origin play a protective role in the infant by priming the immature immune system against pathogens like *Staphylococcus aureus*, which may have relevance in skin disorders.

No wonder then that several studies point to the importance of an early-life, proper establishment of a diverse gut microbial community in the prevention of AD.[12,85,117] Numerous clinical trials support this hypothesis by demonstrating that very early-life (pre- and postnatal) probiotic supplementation of the children could reduce the risk of developing AD[2,30,56,59,61,83,118] We presume that *Lactobacilli* have pivotal role in protection against AD, since under natural circumstances, *Lactobacilli* are the major microbes transmitted from mother to baby, hence it seems logical to assume that these are the bacteria that serve the baby's immune system the best. Taken together, gut flora composition is probably key in the development of the disease.

The gut flora produces a vast amount of metabolites, which may enter the circulation, travelling throughout the body and affecting distant sites of the organism. This process can reach high levels when the epithelial barrier integrity of the gut is disrupted, leading to increased intestinal permeability, a condition called as the "leaky gut syndrome."[68] When a "leaky gut" develops, the penetration of immunogenic molecules, including dietary antigens, bacterial toxins and pathogens increases. These antigens may accumulate in the skin, may disturb the epidermal barrier, leading to chronic skin inflammation and continuous immune response.[68] For example, the bacterial metabolites, free phenol and para-cresol, are considered as biomarkers of an imbalanced gut flora, since the production of these molecules is triggered by infection of the pathogen *Clostridium difficile* after antibiotic treatment.[24] These metabolites can access the blood stream and accumulate in the skin.[78] Data suggest that phenol and para-cresol can disrupt epidermal barrier integrity by reducing the expression of keratin 10 in keratinocytes.[78] It has been demonstrated that daily intake of the probiotic *Bifidobacterium breve* together with the prebiotic galactooligosaccharide reduced serum total phenol levels and improved skin hydration in healthy adult women.[78] Besides, a randomized double-blind placebo-controlled clinical study demonstrated that oral supplementation with a probiotic *Lactobacillus paracasei* strain decreased skin sensitivity and increased barrier function in the treated group,[49] pointing to the importance of oral probiotics in skin health.

The gut microbiota and their metabolites can affect the intestinal barrier function.[79] Therefore, gut dysbiosis may disturb the intestinal barrier in a way that unwanted immunogens, such as bacterial products, could escape the lumen and influence the state of the skin. We are aware that it is speculative to make direct association between gut dysbiosis, a "leaky gut" and AD. However, there is evidence in the literature that intestinal permeability is increased in AD patients compared to control subjects.[69] We do not know whether it is a consequence of a gut dysbiosis in patients, but there are some suggestive data in the literature.

The short-chain fatty acids (SCFAs), such as butyrate, propionate, acetate and lactate, are products of fibre fermentation by the gut microbiota,[71] and SCFAs are known to promote epithelial barrier integrity of the gut and exert anti-inflammatory effects.[71] Intriguingly, intestinal dysbiosis has been demonstrated in AD patients by the analyses of their faecal samples, and a clear reduction of SCFAs has been detected.[93,107] Therefore, it is tempting to hypothesize that any agent, able to influence gastrointestinal microbiota and the production of SCFAs, might be expected to affect inflammatory responses, which may also affect skin condition. Butyrate is mainly produced by species belonging to the *Firmicutes* phylum, such as *Roseburia intestinalis*, *Faecalibacterium prausnitzii* and *Eubacterium hallii*.[64] Propionate originates mainly from the production by species of the *Bacteroidetes* phylum, involving *Bacteroides uniformis*, *Prevotella copri*, and by *Akkermansia muciniphila* of the

Verrucomicrobia phylum.[64,75] With the use of probiotics, we may restore a healthy gut flora and increase the ratio of SCFA-secreting bacteria in the gastrointestinal tract in AD patients. Indeed, according to a recent report, five doses of a cocktail containing 5 *Lactobacillus* and 5 *Enterococcus* probiotic strains were successful in significantly enhancing the microbial diversity and consequently SCFAs production in the gut.[81] Furthermore, probiotics can also promote epithelial barrier integrity by inducing mucus production [67] and tight junction function.[101]

Among the bacterial metabolites in the colon, secondary bile acids (such as litocholic acid and deoxycholic acid) may also have impact on skin physiology.[77,95] The most important secondary bile acid-producing bacteria belong to the *Bacteroidetes* and *Firmicutes* phyla.[95] It has been reported that a *Firmicutes* species, *Clostridium scindens*, confers resistance against *Clostridium difficile* infection in a secondary bile acid-dependent manner,[18] which affects skin function as it was discussed above. Besides, litocholic acid has been reported to influence adaptive immune response by affecting the activation of Th1 cells.[90] In this fashion, replenishing bacteria capable of the biosynthesis of secondary bile acids may contribute to the maintenance of skin homeostasis. Currently, we do not know bacteria with probiotic characteristics that could do that, but these data could be used to develop targeted probiotics to manipulate intestinal bile acid metabolism.

Diet may affect the development of AD across the gut-skin axis. Dietary gluten can damage the intestinal barrier leading to a leaky gut, even in individuals that do not suffer from coeliac disease.[115] It is of note that both coeliac [11] and non-coeliac[14] gluten sensitivity have been associated with severe cutaneous manifestations resembling AD. Of further importance, gluten sensitivity has been linked to intestinal dysbiosis,[25] and certain probiotics have been found to be able to hydrolyze gluten polypeptides.[25] Therefore, the use of probiotics as an adjuvant therapy in gluten sensitivity-associated AD seems to be an interesting approach.

Another intriguing piece of the puzzle is the demonstration that low vitamin D level seems to correlate with the severity of AD.[5] It is of great significance that the gut microbiota may regulate systemic vitamin D metabolism,[15] and the vitamin D pathway might be an important signalling mechanism between the microbiota and the host.[65] Hence, we might assume that low vitamin D levels observed in these patients may be a consequence of a dysbiosis in their gut. Interestingly, a study performed on cystic fibrosis patients suggests that vitamin D deficiency of patients is associated with alterations in microbiota composition that may promote inflammation and that supplementation with vitamin D has the potential to impact microbiota composition.[57] Moreover, growing body of evidence suggests that probiotics can increase serum levels of vitamin D and expression of vitamin D receptor, protecting against gastrointestinal inflammation.[104] These data definitely warrant investigations on the effects of probiotics on vitamin D homeostasis in case of AD.

The multifaceted interactions between the gut microbiota and AD skin clearly point out that modulation of the gut flora may be utilized as adjuvant therapy in disease management. This is also supported by the growing literature about the beneficial effects of probiotics on AD, overviewed in [91]. In order to better exploit probiotics in AD, better characterization of their gut microbiota composition and metabolome is necessary. Besides, carefully designed clinical investigations are required, because the studies conducted so far with oral probiotics are highly heterogeneous. The enrolled subjects, the probiotic strains used, the formulation of the probiotics, and the timing and duration of the probiotic intervention vary between the studies. Therefore, comprehensive studies are needed to assess clinical applicability.

1.2 | Psoriasis

Psoriasis is an immune-mediated inflammatory skin disease, the pathogenesis of which involves numerous environmental and internal factors.[89] Psoriatic lesions are characteristic of the hyperproliferation of keratinocytes with a consequent keratinocyte hyperplasia.[8] Ample data point to the critical role of the cytokine network of Th17 cells in the pathogenesis of the disease.[66,84] Psoriasis has been associated with gut dysbiosis.[51] It is of note that SCFAs potentially regulate the generation and function of Th17 cells,[87] and the loss or depletion of *Faecalibacterium prausnitzii*, a major source of the protective SCFAs in the gut, is associated with psoriasis,[35] suggesting a link between gut dysbiosis, SCFAs and Th17-mediated inflammation in the pathomechanism of the disease.

The development of psoriasis often accompanies gastrointestinal inflammation, such as inflammatory bowel disease (IBD),[53] the aetiology of which is closely associated with the dysbiosis of the gut.[50] Moreover, the reduction in bacterial diversity of the gut found in psoriatic patients strongly resembles the pattern of dysbiosis observed in cases of IBD.[99] Besides, similarly to AD, psoriasis has also been associated with low vitamin D levels, both in children and adults.[94]

Taken together, these data suggest the significance of the gut-skin axis in the pathophysiology of psoriasis and raises the relevance of the application of oral probiotics in the management of the disease. To date, only three studies have looked into the effects of orally administered probiotics on psoriasis, using three distinct probiotic species affecting distinct pathways of the pathomechanism of psoriasis.[19,48,116] All three studies have shown improvement in the course of the disease. However, as the available data are limited and heterogeneous, it would be difficult to suggest a proper supplementation protocol with probiotics in psoriasis-affected patients.

1.3 | Rosacea

Rosacea is a chronic inflammatory skin disease characterized by erythema and telangiectasia predominantly on the face.[17] An association between gastrointestinal microbial status and rosacea has been postulated, in particular the role of *Helicobacter pylori* infection has long been suggested in the pathogenesis of rosacea.[92] Like psoriasis, rosacea was associated with IBD.[33] However, the pathogenic role of intestinal dysbiosis in rosacea is a debated issue, and comprehensive

studies are missing. A recent Korean metagenomic study observed a link between intestinal microbial alterations and rosacea in a group of 12 Korean women with rosacea[82] Besides, a case study reported an effective treatment of one rosacea affected patient with a combination of orally administered doxycycline and probiotics,[42] which might give us a hint about the potential of oral probiotics in rosacea management.

1.4 | Acne vulgaris

Acne vulgaris is a disease of the pilosebaceous unit, manifesting in non-inflammatory comedones or inflammatory pustules and papules. The pathophysiology of acne is characterized by sebum oversecretion, follicular hyperkeratinization and increased production of pro-inflammatory cytokines.[10] Acne is quite commonly associated with microbial dysbiosis.

One of the most investigated subjects in acne studies is the role of a commensal cutaneous bacterium, C*utibacterium acnes* (*C. acnes*, reclassified from *Propionibacterium acnes* as proposed in [100]) in the pathogenesis of acne, which is still not fully elucidated. *C. acnes* is a predominant species of the skin microbiota and an important producer of SCFAs on skin surface; hence, *C. acnes* is essential in the maintenance of skin homeostasis.[20] Nevertheless, *C. acnes* can also act as an opportunistic pathogen.[96] It was a long-standing theory that an increased sebum and fatty acid production favours the proliferation of *C. acnes* in the hair follicles and associated sebaceous glands, which induces the production of inflammatory mediators.[10] However, the most recent findings on *C. acnes* suggest that it is not the proliferation of the bacterium, rather the presence of certain *C. acnes* phylotypes that determines acne onset,[31] as no quantitative difference of *C. acnes* abundance between acne patients and healthy individuals has been found.[31] Phylotype IA1 was the most strongly associated with acne, while phylotypes IA2, IB and II were less represented in acne-affected skin.[72]

There is a long-standing association between diet and acne. Since the prevalence of acne is noticeably higher in developed countries, it is believed that the high glycemic or Western-type diet triggers acne formation.[74,110] A high glycemic load drives the production of insulin and insulin-like growth factor-1 (IGF-1) that promotes the proliferation of sebocytes and keratinocytes, as well as inducing lipid synthesis in the sebaceous glands.[27]

The gut microbiota has been shown to induce IGF-1.[120] Hypothetically, we may assume that Western diet affects the gut flora in a way that may lead to the increased induction of the IGF-1 pathway. Adding to the picture, a recent study demonstrated that in the gut flora of acne patients the ratio of the phyla *Bacteroidetes* to *Firmicutes* increased,[26] which is consistent with the enterotype of the Western diet.

Interestingly, *C. acnes* has been shown to stimulate the IGF-1/IGF-1-receptor system in the skin,[54] suggesting a dual activation of the IGF-1/IGF-1-receptor pathway by the gut and skin microbiota, which may contribute to the pathophysiology of acne. Whether these mechanisms act independently or are interrelated needs further investigation. However, it is reasonable to assume that the two mechanisms act through a synergistic loop. Gut dysbiosis may induce IGF-1 that may trigger a change in the quantity and/or quality of the lipid-rich sebum,[105] which may favour the colonization of the pilosebaceous unit by distinct *C. acnes* phylotypes,[46] disturbing the tight equilibrium among members of the skin flora. This might be a feasible mechanism for the possible interconnectedness of gut and skin flora.

Other explanations for a possible causation of gut microbial imbalance and inflammatory acne involve the role of lipopolysaccharides (LPS), as LPS biosynthesis pathways have been found to be upregulated in acne patients, which may be a consequence of the increased abundance of the main LPS-producing *Bacteroidetes* species in the intestine of the individuals.[26] In our point of view, these pathways (IGF-1 and LPS pathways) are possibly not independent of each other. Even if there is still no direct evidence that gut dysbiosis contributes to the pathogenesis of acne, the association seems to be clear, and suggest the relevance of a probiotic-based supplemental therapy in acne treatment. Supporting this theory, one study demonstrated that the consumption of the probiotic *Lactobacillus rhamnosus SP1* for 12 weeks resulted in a decreased expression of IGF-1 in the skin, and in an improvement of acne symptoms.[37]

1.5 | Other skin diseases

In addition to those common disorders detailed above, we would also like to draw the readers' attention to some less common, though more serious skin pathologies, including hidradenitis suppurativa (HS), erythema nodosum (EN) and pyoderma gangrenosum (PG). These disorders are frequently associated with intestinal inflammation, such as IBD.[40] Their aetiology is complex, and not fully clarified. So far, a correlation between these diseases and gut dysbiosis has not been made,however, the common association with IBD raises the possibility of the involvement of a disturbed gut microbiome in their pathogenesis. The beneficial effects of probiotics on IBD have been suggested,[1] but data of the effects of probiotics on the occurrence of cutaneous manifestations in IBD patients is missing. The only study evaluating the association between probiotic use and skin lesions in IBD patients has been published very recently, and it demonstrates a negative correlation between the use of probiotics and the occurrence of skin lesions,[98] prompting the importance of research to be made in this direction. In addition, it would be very intriguing to see the gut microbial status of HS-, EN- or PG-affected patients without IBD.

2 | CONCLUSIONS

We outlined here a framework of how an imbalanced gut flora may contribute to the development of inflammatory skin diseases, and we propose a scheme of the benefits of probiotic intervention on these disorders (illustrated on Figure 1). We are aware that inflammatory skin conditions are all multifactorial diseases, the pathophysiology

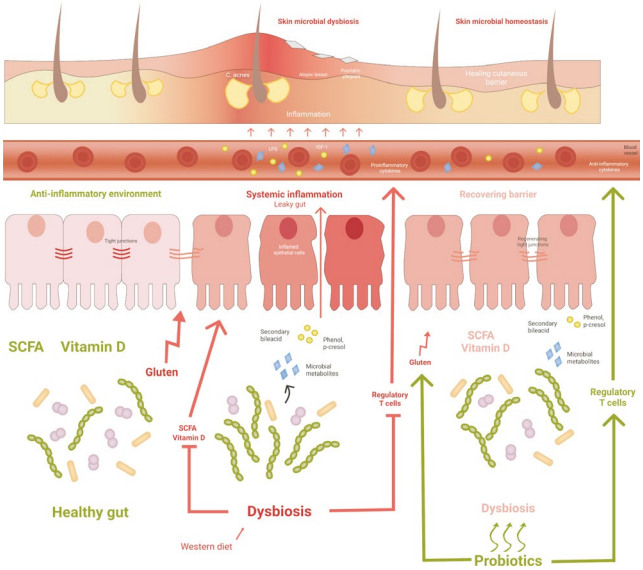

FIGURE 1 A proposed scheme of the contribution of a dysbiotic gut to the onset of cutaneous inflammation, highlighting the potential sites of action of probiotic intervention that may result in the alleviation of the inflammatory condition

of which cannot be simplified solely to the disruption of the gut microbiota. Nonetheless, a disturbance in the homeostasis of the gut flora may contribute to the development and symptoms of these pathologies. As a logical continuation to these, oral probiotics have an obvious translational potential in dermatology. Since adverse effects have not been recorded in relation with the application of oral probiotics, we think that probiotic supplementation could be a cheap and simple modality in the management of skin diseases.

For the sake of completeness of the concept of probiotic application, we have to mention that the concept of probiotics has been re-examined since the now widely adopted definition by the WHO that we also cited in the introduction. In 2013, The International Scientific Association for Probiotics and Prebiotics (ISAPP) organized a panel meeting to define clearer guidelines and standards for using of probiotics, and for the determination of what products can be included in the scope of probiotics.[52] The panel proposed a slight modification of the original 2001 definition, that is, probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'. It is important that this definition differentiates between commensal microorganisms and probiotics. Although probiotics are usually derived from gut commensals, until these strains are properly characterized and their health effects are clearly demonstrated, they cannot be called 'probiotics'.[52] It is important to adopt the criteria defining probiotics to avoid the misleading of consumers and researchers, resulting from the misuse of the term in the absence of proved health effects.

There are many outstanding questions as for the mechanism of action of probiotics yet to be answered. Even though we outlined several pathways where probiotics could interfere with the gut-skin axis modulating host immune and metabolic processes, further studies are required to uncover their exact mechanisms of action.

An issue with probiotic supplementation is that the colonization of probiotic bacteria in the gut is mostly transient as they are only detectable for less than 2 weeks after cessation of intake.[39,43] Researchers tried to answer the question of what may determine the successful colonization by a given species. It has been suggested that it lies with the ability of the probiotic to adapt to the ecosystem of the gut, which is determined by intestinal phylogenetic limiting and resource availability in the individual.[70] The study by Maldonado-Gómez *et al* demonstrated that a certain *Bifidobacterium longum* (*B. longum*) strain was able to persist for over 6 months in a subset of subjects in whom that was originally absent. Moreover, the persistent *B. longum* bacteria enriched the faecal microbiome with functional genes associated with *B. longum*.[70] This study provides an important discovery which can be helpful in the prediction of the outcome of supplementation with a specific bacterial strain, which could be used in the personalized application of probiotics.

Additionally, it also needs clarification whether and how the manipulation of the gut microbiome affects the microbiome of the skin. Given the delicate nature of the interaction between host and the microbiome to maintain the homeostasis of the human organism, we presume that the different microbial communities (eg gut, skin, oral, vaginal) should not be considered as separate, but rather as a complex, interacting ecosystem of the commensals inhabiting distinct body regions. In the above-described skin diseases, bacterial dysbiosis may not be restricted to the gut, but communities at distant body sites could also be affected. Therefore, modulation of the gut microbiota by the application of oral probiotics may impact upon the skin microbiota, as well. In this regard, it is an intriguing issue whether this plausible interaction between the gut and skin microbiota is uni- or bidirectional. Hypothetically, the synthesis of vitamin D in the skin upon UV irradiation might be exploited as adjunctive in case of gastrointestinal inflammation, such as IBD, where vitamin D deficiency occurs.[114] These are fascinating fields of microbial research yet to be explored.

This line of research though has to face many challenges. For one, the skin flora is considered to be highly diverse and variable.[47] There are topographical differences on different body sites that allow only a certain set of microbes to colonize certain skin regions. More importantly, there are many individual-specific factors, including sex, age, occupation, clothing, the usage of hygienic products that determine the variability seen in the cutaneous flora.[47,109] The aforementioned factors create an individual-specific micro-environment on the skin that may require personalized solutions for the management of any skin conditions with oral probiotics.

A major area in this subject, which surpasses the capacity of the current essay, is the translational potential of the use of topical probiotics, oral and topical prebiotics or the combination of pre- and probiotics, called synbiotics, for the manipulation of microbial communities. The use of topical probiotics may have special subclinical significance, for example to improve skin defense with probiotic-containing cosmeceuticals. It has been reported that *B. longum* strains exert pro-differentiating and pro-regenerating effects on primary human epidermal keratinocytes.[111] However,

topical applications of probiotics can create challenges, not only because of the problem of proper formulation, but also the environmental conditions of the skin that may prevent colonization by the probiotic.[113] It seems probable though that using the most suitable oral probiotic strain in combination with topical probiotics and/or prebiotics might help in the individualized design of treatment of skin disorders.

To better exploit the potential within oral probiotics in dermatology, clinical trials should be conducted in order to optimize the intervention protocols involving the determination of the optimal formulation of the most effective probiotic strain or the combination of certain strains, the duration of the supplementation or treatment, and also the inclusion criteria of the subjects in the study.

The described diseases are all common, affecting a substantial proportion of the population of developed countries. Even though their pathomechanisms are getting well characterized, effective and well-tolerated treatment modalities are currently lacking. Oral probiotic supplementation is relatively cheap and if proven to be effective, it could serve as a useful, supportive therapy for the management of microbiome-associated cutaneous disorders. Our opinion is that both gastroenterology and dermatology should better understand the translational potential of the gut-skin axis for the perks of a better therapeutic strategy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Wrote the manuscript: MS, AD, DA, KS, LK, PB. Designed and created the figure: MS. All authors have read and approved the final manuscript.

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