Review Article

Probiotics in Dermatology: An Evidence-based Approach

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Abstract

Probiotics are viable microorganisms that confer health benefits when administered to the host in adequate amounts. Over the past decade, there has been a growing demand for the use of oral and topical probiotics in several inflammatory conditions such as atopic dermatitis, psoriasis, acne vulgaris, etc., although their role in a few areas still remains controversial. The objective of this article is to shed light on understanding the origin and implications of microbiota in the pathophysiology of these dermatological conditions and the effect of probiotic usage. We have conducted a comprehensive search of the literature across multiple databases (PubMed, EMBASE, MEDLINE, and Google Scholar) on the role of probiotics in dermatological disorders. Commensal microbes of the skin and gastrointestinal tract play an important role in both health and disease. Increased use of probiotics has asserted a good safety profile, especially in this era of antibiotic resistance. With the advent of new products in the market, the indications, mechanism of action, efficacy, and safety profile of these agents need to be validated. Further studies are required. Oral and topical probiotics may be tried as a treatment or prevention modality in cutaneous inflammatory disorders, thus facilitating decreased requirement for topical or systemic steroids and antimicrobial agents. Tempering microbiota with probiotics is a safe and well-tolerated approach in this era of antimicrobial resistance.

Keywords: *Acne vulgaris, atopic dermatitis, gut microbiome, probiotics*

Introduction

A microbiota refers to the amalgamation of microorganisms that are present within a specific environment. Both the skin and gut, with their large interphase, are characterized by highly diverse microbiota that have immuno-modulatory shielding effects at distant sites.[1] The skin surface of the neonate is immensely colonized with both environment and maternally acquired bacterial strains. The normal microbial composition of the individual is affected by some pathological factors such as age, diet, or antibiotic consumption, which is known as dysbiosis. The microbial diversity acquired during early life has long-lasting health implications, especially in the development of immune tolerance. During early childhood, adaptive immunity of the skin develops and the neonatal skin, populated by regulatory T cells (Treg), is prejudiced towards anti-inflammatory responses.[2] Possession of one's intestinal microbiota is greatly favored by the genetic constitution of the newborn, maternal pathogens acquired during birth, type of feeding, use of antibiotics, and stressful or inflammatory conditions affecting the mother.[1] The intestinal microbes are essential for the development of the immune system, as evidenced by poorly formed T and B cell subsets, IgA-producing plasma cells, and decreased $CD4^+$ cells that are inclined towards a type 2 helper T cell (Th2) configuration, in germ-free mice.[1]

Probiotics are viable microorganisms that provide health benefits to the host when administered in adequate amounts. Prebiotics are nondigestible food ingredients that selectively stimulate the growth and/or activity of colonic bacteria [Figure 1]. A symbiotic is an optimal synergetic combination of both prebiotic (s) and probiotic (s). The most widely used probiotics are *Lactobacillus* and *Bifidobacteria* containing formulations available as drinks, powders, tablets, and fermented dairy products. There are various dermatological conditions in which probiotics play an important role. This article sheds light on the recent findings

How to cite this article: Gowda V, Sarkar R, Verma D, Das A. Probiotics in dermatology: An evidence-based approach. Indian Dermatol Online J 2024;15:571-83.

Received: 09-Aug-2023. **Revised:** 24-Dec-2023. **Accepted:** 24-Dec-2023. **Published:** 24-May-2024.

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Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_614_23

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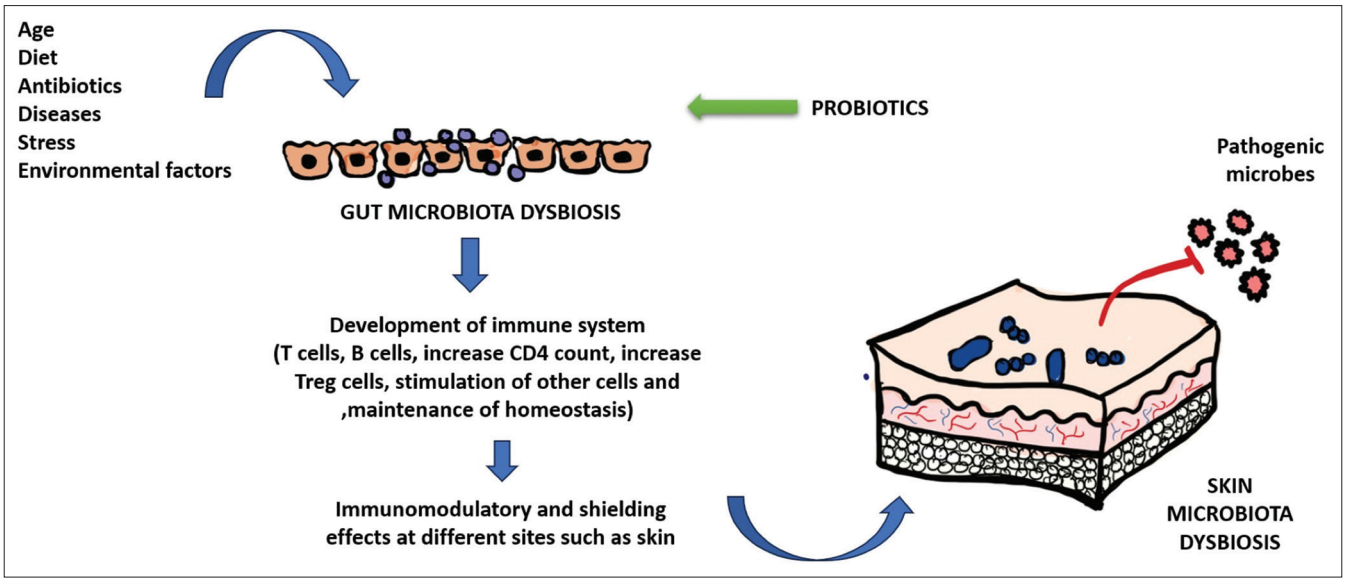

Figure 1: Gut microbial composition is influenced by multiple factors such as diet, age, antibiotics, and other environmental factors, which lead to the activation of innate and adaptive immune systems. It leads to immunomodulatory and shielding effects on other sites such as skin. Probiotics stimulate the growth of gut microbes and, hence, have immunomodulatory and anti-inflammatory effects

that are of importance, along with areas in which further research could unravel their benefits, as their use has been slightly controversial. Their levels of evidence as per "Oxford Centre for Evidence-Based Medicine-Levels of Evidence (LOE), March 2009"[3] have been mentioned in Table 1.

Atopic Dermatitis (AD)

AD is a common, pruritic, chronic inflammatory skin condition driven by a complex multifactorial etiology, affecting all age groups. This chronically relapsing disease most commonly begins during early infancy and childhood with 80% of the affected children below 5 years of age as recapitulated in a recent nationwide Norwegian study.[4] Affected individuals suffer from a genetic predisposition to mutations in the filaggrin gene, resulting in the disruption of skin barrier integrity and increased transepidermal water loss. Another change is the strong Th2-mediated immunological response, which increases the levels of immunoglobulin E (IgE) and interleukins (IL)-4, 5, 9, 10, and 13.

The primary modality of treatment comprises righteous use of moisturizers, antihistamines, topical and systemic steroids, other immunomodulators, and antibiotics assessed on a case-to-case basis. Recent research has thrown light on the disarray in intestinal barrier function of AD individuals with disruption of homeostasis of various cell populations including the regulatory and helper T cells (Th1 and Th17), thus propagating a type 2 inflammatory pathway.[1] Hence, the role of gut microbiota has come into play as a vital aspect in influencing immunological tolerance. Atopic children have numerous coliforms and clostridia, while fewer *Bifidobacteria* and *Lactobacilli* constitute their gut flora, subsequently mediating a Th2 polarization. Therefore, the role of nonpharmacological agents like probiotics as a replenisher of microflora and thereby, a probable supplement in the prevention and treatment of AD has been evaluated.[5] Their role could also be linked to the hygiene hypothesis in AD, which suggests that a lack of exposure to microbes early in life can affect immune system development and increase susceptibility to allergies.

Probiotics upregulate the production of Tregs and anti-inflammatory cytokines, which are dispensed to the sites of inflammation. The other mechanisms of action of probiotics are stimulation of intestinal epithelial mucin production, competitive inhibition of pathogenic bacteria by molecular mimicry,[47] upscaling of the production of antigen-specific secretory IgA,[48] a transfiguration of proteoglycan recognition proteins, and toll-like receptors causing activation of dendritic cells and in turn, a skew toward Th1 immune response.[49]

Though probiotics display promise in halting the inception of atopic march, there are conflicting reports in their therapeutic effects.[50] Navarro-Lopez *et al*.[5] suggested that probiotic supplementation can improve moderate to severe AD in treatments spanning more than 8 weeks. The study was conducted over a period of twelve weeks, wherein a capsule preparation containing freeze-dried powder with 10^9 total colony-forming units (cfu) of the probiotic strains *Bifidobacterium lactis (B Lactis), Bifidobacterium longum (B longum)*, and *Lactobacillus casei (L casei)* was administered daily. A mean reduction in SCORing atopic dermatitis (SCORAD) and an appreciable reduction in the use of topical steroids during flares were noted. They also noted that after the first year of life, there was a superior response and a mixture of probiotics had an

Table 1: Important studies on probiotics in dermatology

	Name and year of the study	Disease studied	Probiotic used	Result	Level of evidence	Grade
1.	Mohn CH *et al.* 2018[4]		**	**	2c	B
2.	Navarro-López V *et al*. 2018[5]	Atopic dermatitis	*Bifidobacterium lactis CECT 8145, Bifidobacterium longum CECT 7347, and Lactobacillus casei CECT 9104* and *maltodextrin*	Greater reduction in SCORAD index in the probiotic arm with a significant decrease in the use of topical steroids to treat flares, after 12 weeks in patients with moderate AD	1b	A
3.	Wu YJ *et al*. 2017[6]	Atopic dermatitis	*Lactobacillus rhamnosus*	Decrease in the symptoms of AD after 8 weeks by *L rhamnosus*, with a reduction in all the components of SCORAD	1b	A
4.	Prakoeswa CRS *et al*. 2017[7]	Atopic dermatitis	*Lactobacillus plantarum*	Levels of IFN-γ, IL-4, and IL-17 and SCORAD were significantly decreased in the probiotic arm with no significant change in the IgE levels between the two groups	1b	A
5.	Viljanen M *et al*. 2005[8]	Atopic dermatitis	*Lactobacillus GG (LGG)*	In infants with IgE-sensitization, LGG group displayed a greater decrease in SCORAD after 4 weeks	1b	A
6.	Van der Aa LB *et al*. 2010[9]	Atopic dermatitis	*Bifidobacterium breve M-16V* and *a galacto-/ fructooligosaccharide mixture (Immunofortis)*	At 12 weeks, infants with IgE-associated AD showed improvement in SCORAD with the symbiotic mixture	1b	A
7.	Blanchet-Réthoré S *et al*. 2017[10]	Atopic dermatitis	*Lactobacillus johnsonii* NCC 533	Application of HT La1 to the lesional surface for 3 weeks controlled *S. aureus* colonization and was associated with clinical improvement	1b	A
8.	Myles IA *et al*. 2018[11]	Atopic dermatitis	*Roseomonas mucosa*	Treatment with R. mucosa significantly decreased severity of the disease, need for topical steroids and *S. aureus* load	1b	A
9.	Nakatsuji T *et al*. 2017[12]	Atopic dermatitis	*Antimicrobial peptides* produced by coagulase-negative Staphylococcus (*CoNS*) species	CoNS strains with antimicrobial activity directly suppressed S. aureus colonization in AD	1b	A
10.	Jung GW *et al*. 2013[13]	Acne vulgaris	*Lactobacillus acidophilus* (5 billion CFU)/ capsule), *Lactobacillus delbrueckii* subspecies *bulgaricus* (5 billion CFU/ capsule), and *Bifidobacterium biftdum* (20 billion CFU/capsule)	Probiotic supplementation with minocycline resulted in significant improvement in lesion count at 8 and 12 weeks. Probiotics alone resulted in a decrease of the lesion count at 4-weeks, thus making it a therapeutic option in acne vulgaris as well as an adjunct along with antibiotics	1b	A
11.	Fabbrocini G *et al*. 2016[14]	Acne vulgaris	*Lactobacillus rhamnosus SP1* (LSP1)	LSP1 at a dose of 75 mg/day resulted in a 32% reduction in cutaneous expression of insulin signaling genes in the acne areas of back and improved the lesions at 12 weeks	1b	A
12.	Kim J *et al*. 2010[15]	Acne vulgaris	Lactoferrin-enriched fermented milk containing probiotics (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*)	Lactoferrin group decreased inflammatory and total lesion count as well as acne grade by 12 weeks Triacylglycerols and free fatty acids (FFA) were decreased as well	1b	A

Contd...

Table 1: Contd...

	Name and year of the study	Disease studied	Probiotic used	Result	Level of evidence	Grade
14.	Craft N. 2017[16]	Acne vulgaris	*B244* strain of ammonia oxidizing bacteria	4 pumps of the spray administered twice daily over the entire face for 12 weeks in mild to moderate cases of acne vulgaris was found to bring about a reduction in the lesional count	1b	A
14.	Wienholtz N *et al*. 2021[17]	Rosacea	**	Eradication of small intestinal bacterial overgrowth with Rifaximin 200 mg 3 times a day for 3 days, improves papulopustular symptoms of rosacea	4	C
15.	Drago F *et al*. 2016[18]	Rosacea	**	A 10-day rifaximin treatment brought about a remission of rosacea in 64.5% of subjects, followed up for 3 years, by decreasing SIBO	2b	B
16.	Fortuna MC *et al*. 2016[19]	Rosacea	*Bifidobacterium breve BR03*, *Lactobacillus salivarius LS01 1*×10^9 CFU/dose	Once a day doxycycline 40 mg and twice daily probiotic therapy successfully resolved scalp rosacea by 8 weeks	4	C
17.	Navarro-López V *et al*. 2019[20]	Psoriasis	*Bifidobacterium longum CECT 7347, B. lactis CECT 8145* and *Lactobacillus rhamnosus CECT 8361* with a total of 1×10^9 CFU per capsule, formulated on maltodextrin	At 12-week follow-up, 66.7% of the patients in the probiotic arm showed a reduction in Psoriasis Area and Severity Index of up to 75%. On the Physician Global Assessment index, 48.9% of individuals in the probiotic arm reached a score of 0 or 1. A lower risk of relapse after the intake of the probiotic mixture was seen at 6 months follow-up	1b	A
18.	Reygagne P *et al*. 2017[21]	Seborrheic dermatitis	*Lactobacillus paracasei* NCC2461 ST11	Consumption of a sachet of ST11 (1×10^9 CFU) on a daily basis for 56 days, improved free and adherent dandruff, scalp seborrhea, erythema and global clinical score of moderate to severe dandruff	1b	A
19.	Priya K *et al*. 2021[22]	Seborrheic dermatitis	*Lactobacillus rhamnosus, Enterococcus faecalis* and *Enterococcus faecium*	Isolates demonstrated a maximum zone of inhibition of 7 mm in in-vitro studies and were found to be enriched with antifungal components, which could be used to target against *Malassezia furfur*	2b	B
20.	Zareie E *et al*. 2020[23]	Seborrheic dermatitis	Triphala	Two months of treatment with 1 gm of Triphala, resulted in a decrease of scalp sebum secretion.	1b	A
21.	Xie HY *et al*. 2017[24]	Vulvovaginal candidiasis.	*Lactobacillus fermentum RC-14, Lactobacillus fermentum B-54*	Probiotics as an adjuvant therapy increased the rate of short-term clinical cure and mycological cure and decreased the relapse rate at the end of one month, without increasing the risk of adverse events	1a	A
22.	Russo R *et al*. 2019[25]	Vulvovaginal candidiasis	*Lactobacillus acidophilus; Lactobacillus rhamnosus; Bovine lactoferrin*	Treatment with probiotics and lactoferrin as adjuvant to topical clotrimazole significantly improved itching and discharge at the end of 3 and 6 months, thus is was considered a safe and effective adjuvant for decreasing symptoms and recurrences of recurrent vulvovaginal candidiasis	1b	A

Contd...

Table 1: Contd...

	Name and year of the study	Disease studied	Probiotic used	Result	Level of evidence	Grade
23.	Gaziano R *et al*. 2020[26]	Vulvovaginal candidiasis	**	**	5	D
24.	Bisanz JE *et al*. 2020[27]	Bacterial vaginosis	*Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14*	Probiotic administration ensued a temporary increase in the vaginal *Lactobacilli, although there was no* improvement in Nugent score. They were also found to have an immune-modulatory response, effects on pattern recognition receptors and also epithelial barrier function	1b	A
25.	Bradshaw CS *et al*. 2020[28]	Bacterial vaginosis	*Lactobacillus acidophilus vaginal-probiotic containing oestriol*	A combination of oral metronidazole with an extended course of vaginal-L. acidophilus, did not reduce recurrence of bacterial vaginosis	1b	A
26.	Yu Y CS *et al*. 2020[29]	Wound healing	**	**	5	D
27.	Knackstedt *et al*. 2020[30]	Wound healing	**	**	5	D
28.	Jones M *et al*. 2012[31]	Wound healing	N*itric oxide gas (gNO)-producing probiotic patch*	A wound healing gNO-producing probiotic patch, containing lactic acid bacteria in an adhesive gas permeable membrane was applied to ischemic and infected dermal wounds which resulted in increased wound closure over 21 days. The wound closure rate was 2·52 times more than the control patch	1b	A
29.	Huseini HF *et al*. 2012[32]	Wound healing	Kefir	At the end of the two weeks, the percentage of closure of Pseudomonas infected wounds was highest in the group administered with kefir 96 h gel along with a decrease in inflammation and high rates of epithelization	1b	A
30.	Satish L *et al*. 2012[33]	Wound healing	*Lactobacillus plantarum*	Application of *L. plantarum* decreased the severity and the duration of pseudomonal infection. Probiotic therapy-depleted Type I collagen mRNA and total collagen accumulation thus reducing scarring	1b	A
31.	Zoccali G *et al*. 2012[34]	Wound healing	Cream containing probiotic-derived active principles	Cream applied postoperatively to patients treated with fractional CO2 laser twice a day for 2 weeks, demonstrated faster resolution of erythema and swelling as compared to the patients on antibiotic and hyaluronic acid cream	1b	A
32.	Satoh TV *et al*. 2015[35]	Photoaging	*Bifidobacterium breve B-3*	Oral administered B. breve B-3 (2×10^9 CFU/mouse/day) for 7 weeks suppressed transepidermal water loss, interleukin-1β production; increased skin hydration and epidermal thickening, and decreased the damage by chronic UVB irradiation	1b	A
33.	Im AR *et al*. 2016[36]	Photoaging	*Lactobacillus acidophilus*	Orally administered tyndalized *L. acidophilus* decreased the expression of MMP-1 and MMP-9 and inhibited wrinkle formation	1b	A

Contd...

Table 1: Contd...

	Name and year of the study	Disease studied	Probiotic used	Result	Level of evidence	Grade
34.	Kimoto-Nira H 2018[37]	Photoaging	**	**	5	D
35	Rezazadeh A *et al*.[38]	Urticaria	**	**	3b	B
35.	Nabizadeh E *et al*. 2017[39]	Urticaria	**	**	3b	B
36.	Atefi N *et al*. 2021[40]	Urticaria	Symbiotic mixture containing -*Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium breve, Lactobacillus bulgaricus, Bifidobacterium longum, Streptococcus thermophilus* and prebiotic- fructooligosaccharides	66% reduction of Urticaria Activity Score in the antihistamine and probiotic combination group was seen, although no statistically significant difference in its efficacy was noted as an adjuvant to antihistamine when compared to antihistamines alone	1b	A
37.	Rinaldi F *et al*. 2020[41]	Alopecia areata	*TR-PRP plus-Celsi*	Significant improvement of SALT score at 2 months	1b	A
38.	Park DW *et al*. 2020[42]	Alopecia areata	*Kimchi and Cheonggukjang*	Improvement in hair count and thickness at 1 and 4 months along with reversal of hair loss	2b	B
39.	Xie W *et al*. 2019[43]	Alopecia areata	Fecal microbiota transplantation (FMT)	six rounds of FMT promoted the regrowth of a solitary patch of alopecia	5	D
40.	Friedrich AD *et al*. 2019[44]	Skin cancer	*lipoteichoic acid (LTA) from Lactobacillus rhamnosus GG*	LTA overcomes UV-induced immunosuppression by modulating the expression of dendritic cells. They significantly reduced the growth of established skin tumors on discontinuation of UV radiation, thus demonstrating its therapeutic benefit, apart from its antitumor effect	1b	A
41.	Nakatsuji T *et al*. 2018[45]	Skin cancer	*Staphylococcus epidermidis*	6-*N*-hydroxyaminopurine (6-HAP) produced by *S. epidermidis* inhibited DNA polymerase and proliferation of tumor clones. Intravenous injection of 6-HAP suppressed the growth of melanoma in mice without causing systemic toxicity	2b	B
42.	Zhong L *et al*. 2014[46]	Colorectal cancer	**	**	5	D

** – Not applicable

augmented effect, especially combinations of *Lactobacilli* and *Bifidobacteria*. Wu *et al*.[6] noted a significant reduction of disease severity over a period of 8 weeks, in the probiotic group administered with 350 mg *Lactobacillus rhamnosus (L rhamnosus)* among children aged between 4 and 48 months. Prakoeswa *et al*.[7] noted a decline in AD severity and inflammatory markers (IL-4, IFN-γ, and IL-17) with 10^{10} cfu/day of microencapsulated *Lactobacillus plantarum (L plantarum)* 17 pa twice daily for 12 weeks.

However, studies also indicate that the effects of probiotic supplementation *(L rhamnosus GG (LGG)* 5×10^9 cfu for 4 weeks) are more enhanced in patients with an allergic milieu due to IgE-channelled hypersensitivity reactions in the pathogenesis of AD.[8] The occurrence of subtle gastrointestinal symptoms in children with AD is termed atopic gastroenteropathy and has been observed more commonly in those with an allergic background. A similar inference was obtained in another study where there was a significant reduction in SCORAD and IgE levels in infants on the administration of symbiotics *(Bifidobacterium breve M-16V* and a *galacto-/fructooligosaccharide* mixture for 12 weeks).[9]

Some studies, on the other hand, have not noted any significant improvements in SCORAD, inflammatory parameters, serum IgE levels, and sensitization in the probiotic group.[51,52] These discrepancies could be attributed to differences in age, genetic and cultural backgrounds, dietary factors, disease severity, concomitant allergies, and study designs. It could also be due to the various mechanisms of action of probiotics, the dosages,

and combination of different strains, as the effects are strain specific.[50]

Recent studies have shed light on the correlation between disease severity and *Staphylococcus aureus (S. aureus)* colonization, which has in turn led to the research on the use of topical probiotics in AD. Administration of a cosmetic lotion containing 0.3% heat-treated *Lactobacillus* johnsonii (HT La1) twice daily for 3 weeks resulted in its adherence to the keratinocytes and inhibition of *S. aureus* attachment.[10] HT La1 can alter the gene expression and increase the synthesis of antimicrobial peptides (β-defensin 2), levels of which are deranged in AD.[10] Similar studies have shown reduced disease activity by topical *Roseomonas mucosa* and *Lactobacillus reuteri*.[11] Nakatsuji *et al*.[12] noted that autologous transplantation of *Staphylococcus hominis* and *Staphylococcus epidermidis (S. epidermidis)* reduced the burden of *S. aureus.*

As far as the preventive role of probiotics in AD is concerned, a recent meta-analysis has shown a significantly lowered rate of incidence of AD among healthy children and a decrease in SCORAD levels in children with AD, on administration of probiotics. Mixed strains of probiotics were found to be more efficacious than single strains due to their synergistic effect. Introducing these agents to both pregnant mothers and infants, and pregnant mothers alone, was found to be superior to incorporating them in only infants in lowering the occurrence of AD, as the preliminary target of developing immune factors within the fetus maximizes the effects of probiotics.[53]

Acne Vulgaris

Acne is frequently allied with anxiety, depression, aggressive behavior, and other psychological conditions. These individuals are also more likely to encounter gastrointestinal symptoms. As we know, the physiologic integrity of the intestinal microbes plays an important role in liaising both emotional behavior and cutaneous inflammation. Alterations in the microflora increase intestinal permeability, which sparks off systemic as well as local inflammation in the skin. The intestinal microbiota, cutaneous inflammatory elements like acne, and psychological conditions, such as depression and anxiety, are all amalgamated physiologically through the "gut-brain-skin" axis. This is where the role of probiotics come into play, which act by regulating intestinal permeability and impeding the production of proinflammatory cytokines.[54]

Reports indicate small intestinal bacterial overgrowth (SIBO) is about 10 times more extensive in those with acne compared to healthy controls; the rectification of which leads to an evident clinical improvement.[55] Probiotics are also found to minimize the gastrointestinal adversities of antibiotic treatment and act synergistically thereby encouraging patient adherence. Jung *et al*.[13] found that twice-daily administration of a combination containing *Lactobacillus acidophilus (L. acidophilus)* 5 billion cfu/capsule, *Lactobacillus delbrueckii* 5 billion cfu/capsule, and *Bifidobacterium biftdum)* 20 billion cfu/capsule, with minocycline over 12 weeks, resulted in an improvement of acne and quality of life, as both these agents exhibit anti-inflammatory and immunomodulatory actions. Probiotics prevent inflammation by kindling $CD4^+$ T cells and regulatory dendritic cells, which in turn result in B and helper T cell hyporesponsiveness, along with a restraint in proinflammatory cytokines production. Probiotics also prevent the detrimental effects of interferons and TNF-α on the intestinal epithelium. Thus, through these mechanisms, probiotics act independently as well as in harmony with antibiotics.[13]

Recent studies have demonstrated that increasing levels of serum insulin-like growth factor-I stimulate sebaceous lipogenesis and acne, especially in postadolescent women. Probiotics improve the insulin signaling pathway as demonstrated by the antihyperglycemic effects of LGG (1×10^8 CFU) for 13 weeks in diabetic animal models.[56] Fabbrocini *et al*.[14] evaluated the role of *L rhamnosus* (3×10^9 cfu/day) as monotherapy in adult acne for 12 weeks and observed consequential improvement in the back acne lesions.

Kim *et al*.[15] have shown the role of Lactoferrin-enriched fermented milk-containing probiotics (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) in reducing inflammatory acne lesions. Even the intake of plain fermented milk brought about a decrease in sebum, free fatty acids, and total lesion count, thus reprising the role of probiotics.

Streptococcus, Lactococcus, and *Lactobacillus* species produce bacteriocins that inhibit the growth of *Propionibacterium acnes (P. acnes)*, while *Bifidobacterium* species are antimicrobial. *S. epidermidis* directly inhibits the growth of *P acnes* by its action on glycerol fermentation. *Streptococcus thermophile*s elevate the production of ceramides helping in the retention of water. Likewise, several strains of probiotics have been used in accordance as well as discordance, which demonstrate a beneficial role in acne by targeting various pathways in its pathogenesis.[57] As the integrity and immunomodulatory effects of intestinal microbiota are of utmost importance in the prevention of lesions of acne, probiotics may prevent skin eruptions.

Not much research has been carried out in the field of topical probiotics for acne. A new clinical trial has shown the use of *Nitrosomonas eutropha* through the application of four pumps of the spray twice daily over the entire face for 12 weeks in mild to moderate cases of acne vulgaris in reducing the Investigator's Global Assessment of acne severity.[16] Topical probiotics can also comprise bacteriophages that are viruses that play a role in both skin health and disease by regulating the melange and motion of

bacterial community (*P. acnes)* phages on the pilosebaceous unit act through their antiviral mechanisms by bringing about lysis of acne-associated phylotypes and, hence, determining the *P. acnes* populations.[58] Hence, topical probiotics or their lysates demonstrate a potential role in acne prevention. In those with acne, they have been reported to improve the lesions, erythema, as well as bacterial load in addition to enhancing the barrier function. As acne involves overgrowth of *P. acnes*, treatment with probiotics can help restore the commensal microflora, improving the lesions without systemic adverse effects.[59] Certain phylotypes of *P. acnes* are more commonly associated with acne, whereas others with healthy skin. Deploying congruent species of bacteria that partake in a similar ecological niche could lead to a systematic approach to treating acne over other cutaneous or systemic microbes, thus resulting in more protracted results.[29]

This is as for the preventive role of topical probiotics is concerned, however, very few human clinical trials are available with respect to these formulations and there is no regulatory system for these as well.[59]

Rosacea

SIBO may precipitate rosacea (especially papulopustular lesions) by elevating the levels of circulating cytokines, particularly TNFα, and a significantly higher prevalence of SIBO is seen in these patients. Reduction or modification of the intestinal flora is shown to improve the cutaneous symptoms.[17,18]

Reduced intestinal transit time ameliorates the symptoms, showcasing the fact that hastened passage of food permits excessive fermentation, and diminution of the bacterial population would benefit the same.[60] Therapy with *Bifidobacterium breve (B. breve)* and *Lactobacillus salivarius* (1×10^9 CFU/dose) twice daily along with low-dose antibiotics have been shown to improve papulopustular rosacea as well as ocular symptoms over 8 weeks.[19]

As stress is one of the triggers of rosacea reiterating the role of the gut–brain–skin axis, supplementing patients with probiotics during these times might prove beneficial. However, it is unclear whether SIBO and altered microbiota metabolism are precursors of inflammation or arise as an offshoot of alterations in the skin microbiome. More data is necessary when it comes to supplementing rosacea patients with probiotics as it may require tailor-made treatment for each patient due to interpersonal differences in the skin and gut microbiota.[53]

Psoriasis

Various microbes are known to activate the innate immune system in psoriasis. Predominantly *streptococci* followed by *staphylococci, corynebacterium*, and *propionibacterium* are found in the psoriatic skin, blood, and throat. Bacterial peptidoglycans (PG), antigen-specific T cells that recognize PG, and mutations in the PG recognition receptor genes, PGRP-3 and PGRP-4, have been found in the psoriatic skin.[61]

The polymerase chain reaction has demonstrated that *Lactobacillus pentosus* strains decrease psoriatic lesions and levels of proinflammatory cytokines.[62] Another study has shown administration of equal proportions of *Bifidobacterium longum (B. longum), Bifidobacterium lactis,* and *L. rhamnosus* (with a total of 1 × 109 CFU per capsule, formulated on maltodextrin), for 12 weeks significantly lowers the severity of disease and relapse after 6 months when administered along with topical. There was a waning of troublesome *Micromonospora* and *Rhodococcus* and a waxing of positive microbes *Collinsella and Lactobacillus*, thus suggesting a role in prevention as well.[20]

However, the role of probiotics in psoriasis still has scope for plenty of research as only little is known about it to date.

Seborrheic Dermatitis (SD)

SD is a chronic, recurrent, inflammatory dermatosis that primarily involves the scalp, producing flaking of the skin and pruritus. The pathophysiology is complex and includes elevated sebum levels, stress, hormonal and environmental milieu, increased individual sensitivity, and immune response to free fatty acids generated by *Malassezia spp (Malassezia restricta, Malassezia furfur*, and *Malassezia globosa*).[63]

The relationship between SD and gut dysbiosis has not been elucidated, yet intake of *Lactobacillus paracasei* (1×10^9 CFU) on a daily basis for 56 days has shown a promising improvement in its severity.[21] *L. rhamnosus, Enterococcus faecium*, and *Enterococcus faecalis* are noted to have an inhibitory effect against *M. furfur*, by yielding acidic metabolites. Hence, incorporation of these agents into antidandruff formulations could be beneficial and less harmful than conventional medications.[22] Oral herbal polyphenol-rich prebiotic Triphala (1 g) was found to be effective in bringing down sebum secretion over 2 months.[23] Also, there have been studies demonstrating the relationship of bacteria (especially Staphylococcus species) with SD being stronger than that of fungi.[64] This may justify the role of probiotics in SD. As there are isolated studies demonstrating the therapeutic benefits of probiotics in SD, their preventive role is still debated.

Vulvovaginal Candidiasis (VVC) and Bacterial Vaginosis (BV)

VVC and BV occur due to disparity in the normal vaginal flora, with a decrease in protective Lactobacilli and a concurrent overgrowth of other bacterial and Candida species. The treatment for VVC is primarily antifungals. However, a concomitant increase in antifungal resistance and recurrence

of VVC have forced us to look at other therapeutic options. Probiotics help in sustaining and recuperating the normal vaginal microbiota and have the potential to brave fungi by preventing their adhesion, colonization, and invasion. Probiotics (*Lactobacillus fermentum (L. fermentum), L. rhamnosus,* and *L. acidophilus*), administered through various routes – oral, intravaginal, or both, are quite effective and safe in urogenital infections.[24]

As per a Cochrane review, administration of a fusion of antifungal and probiotic regimens in nonpregnant women with VVC promoted clinical and microbiological cure rates within 14 days and relapse at one month but not that of long term.[24] However, in another study demonstrating the efficacy of oral *L. acidophilus, L. rhamnosus,* and bovine lactoferrin along with topical clotrimazole on recurrent VVC, there was a pronounced amelioration of discharge and itching at 3 and 6 months.[25] A 2015 German guidelines on the treatment of VVC has encouraged future studies on *Lactobacillus*-containing probiotics.[65]

The use of lactobacilli-containing probiotics helps in reducing the reliance on antifungals, especially in pregnant women through inhibition of Candida species, thus forestalling recurrences and reducing vaginal inflammation. As VVC recurrences are more common in pregnant women due to reduced cell-mediated immunity and elevated levels of estrogen and vaginal mucosal glycogen, risk of premature rupture of membranes, VVC-induced chorioamnionitis, and fetal death exist. The use of probiotics may help in preventing these adverse events.[66]

Recent interest is, however, neighboring around the need for yeast-based probiotics as they provide safety against the development of antibiotic resistance, and also because they can be securely administered in patients on antibiotic therapy. In this context, *Saccharomyces cerevisiae (S. cerevisiae)* has been propitious in the treatment and prophylaxis of VVC.[26] The live forms inhibit secretory aspartyl proteinase gene expressions, which play a pivotal role in the pathogenesis of VVC, thereby reducing inflammation. They also influence the host immune response by escalating the antimicrobial activity of polymorphonuclear cells through increased production of reactive oxygen species and also enhancing their killing activity.[26]

BV is characterized by a reduction of *Lactobacilli* and immoderate growth of *Gardnerella vaginalis, Prevotella* species, *Mycoplasma hominis*, and other anaerobic bacteria. In BV, probiotics elevate *Lactobacilli* thereby conferring protective effects.[27] There have been contradictory studies reporting no effect of *L acidophilus* in combination with oral metronidazole in reducing the recurrence of BV.[28]

Wound healing

Protracted inflammation and disturbance of the skin microbiome delays the process of wound healing. Probiotics may enhance this process by modifying inflammation and normalizing the commensals.[30] Several strains of *Pseudomonas aeruginosa* inactivate beta-lactam antibiotics by producing beta-lactamase enzymes, thus rendering them resistant to topical antimicrobial agents.[67] Wounds contaminated by resistant bacteria add to the financial burden of the patient along with associated morbidity and mortality.[68] Application of antibiotics appears to be less efficacious than before, thus leading to the advent of the use of probiotics and prebiotics. Nesting probiotic cells in polymeric particles like sodium alginate and chitosan could stabilize them. Hence, the mode of delivery – gels, hydrogels, ointments, or films – and stability of the probiotics play an important role in the prevention of infection and promotion of wound healing.[69] The roles of *L. plantarum, L. fermentum*, and *S. cerevisiae* have been investigated in infected and noninfected wounds, diabetic ulcers, and thermal injuries and were found to facilitate the formation of granulation tissue, elevating collagen levels, and stimulating angiogenesis.[30]

Jones *et al*.[31] have shown the use of *L. fermentum* between tegaderms in escalating the rates of wound closure over 21 days. Kefir gel (probiotic mixture of bacteria and yeasts) improved the healing in experimentally induced burn wounds with superadded Pseudomonas infection.[32] *L. plantarum* has been noted to deplete the severity and duration of pseudomonal infections, substantially reduce Type I collagen mRNA levels and protein aggregation in both infected and healthy wounds, thus reducing scarring.[33]

Probiotics have also been found to reduce erythema and swelling following CO2 laser therapy and improve skin hydration and ceramide concentration.[34]

Photoaging

Photoaging mainly occurs due to cumulative exposure to ultraviolet (UV) radiation. *B. breve* was found to remarkably decrease transepidermal water loss, modulate epidermal thickening, minimize the damage to the basement membrane and tight junctions, and deteriorate interleukin-1β production induced by chronic UV irradiation.[35] This study demonstrated the protective role *B breve* B-3 (2×10^9 cfu/day) for 7 weeks in the prevention of UV-induced skin damage. Tyndalized *L. acidophilus* promotes the effacement of fine wrinkles by stimulating collagen and decreasing the expression of matrix metalloproteinases, proving to be a potential agent in preventing photoaging.[36] *Lactobacillus lactis* has been found to improve the skin status of Japanese women by antioxidant activity and regulation of intestinal microbiota and immune response.[37]

Urticaria

Chronic urticaria (CU) is characterized by the periodic appearance of wheals lasting for six or more weeks, with or without angioedema. The protective effects of

Lactobacilli and *Bifidobacteria* against CU could be due to the induction of Treg cells and their potential to create an anti-inflammatory environment.[38]

Rezazadeh *et al*.[38] found mean folds of *Bifidobacterium* and *Lactobacillus* in the stool samples of healthy controls to be much higher than CU patients. Another study demonstrated the concentrations of *Clostridium leptum, Akkermansia muciniphila*, and *Faecalibacterium prausnitzii* were significantly higher in healthy controls and, thus, noted a protective effect of these bacteria.[39] In a Randomised control trial (RCT) evaluating the efficacy of probiotics as an adjuvant to antihistamines in CU, there was a 66% reduction in Urticaria Activity Score, with 9%, 58%, and 33% of patients in the intervention group experiencing mild, significant, and absolute responses, respectively.[40] This study used a symbiotic – a combination of probiotic (*L. rhamnosus, L. casei, L. acidophilus, B. breve, Lactobacillus bulgaricus, Bifidobacterium longum, Streptococcus thermophilus)* and *prebiotic (fructooligosaccharides)* – twice daily for 8 weeks in addition to antihistamines to demonstrate the above results. In conjunction with antihistamines, symbiotics reduced the rate of itch and number of lesions demonstrating their greater therapeutic efficacy in the prevention and treatment of CU. In cases of CU with underlying autoimmunity, reduction of serum IgE by the action of probiotics is observed which improves the outcome.[40]

Alopecia Areata (AA)

The role of cutaneous microbes has been evaluated in AA with a potential role of *S aureus* superantigens. The efficacy of a topical cosmetic product, containing bioactive peptides and microbial metabolites, known as postbiotics (*plantaricin A* and *Lactobacillus kunkeei*), has been gauged for the treatment of AA over 3 months. These postbiotics possess antioxidant, antimicrobial, and immunomodulatory properties.[41] Probiotics – kimchi (salted and fermented vegetables) and cheonggukjang (*Leuconostoc holzapfelii, Leuconostoc mesenteroides*, and *Lactobacillus sakei*) – in AA benefit the patients by improving blood flow and inhibiting the enzyme 5-α reductase (through action of poly-γ-glutamic acid isolated from *Bacillus subtilis*-used to ferment cheonggukjang) over a period of four months.[42] Fecal transplantation has been tried in AA and alopecia universalis which increased follicular growth, thus emphasizing the role of gut microbiota in immunomodulating autoimmune conditions.[43]

Skin Cancer

Skin cancers are induced by UV damage, chronic skin trauma, chemical agents, or biological causes like Human pappiloma virus infection (HPV) infections. The role of probiotics have been demonstrated, and only those probiotic bacteria that have anticancer activity outside of the majority exhibit this biotherapeutic action. Research has shown that consumption of lactic acid-producing bacteria (LAB) prevents the initiation or progression of carcinogenesis.[44]

It was also observed that lipoteichoic acids of *L rhamnosus* were capable of overcoming the growth of squamous cell carcinoma.[45] Nakatsuji T *et al*. reported strains of *S epidermidis* to generate 6-N-hydroxyaminopurine, which inhibits the activity of DNA polymerase and the proliferation of tumor cell lineages. Intravenous injection of the same impeded the growth of melanoma.[46] LAB such as *L. acidophilus*, *L. casei*, and *B. longum* exert strong antitumor effects by induction of apoptosis along with other chemotherapeutic agents, thus proving their role as efficient adjuvants in anticancer therapy.[70] Thus, by restoring a healthy gut microbiome, one could protect against malignancy.

Conclusion

Momentous knowledge has been acquired during recent years regarding the composition of cutaneous microbiota and their association with inflammatory disorders. Elements that adversely affect microbial diversity and their metabolism are considered to influence host immunological tolerance. Environmental and genetic factors, modern lifestyles, and increased use of antibiotics and antifungals have negatively affected the microbiome metacommunity and increased the risk of autoimmune diseases, allergies, and even some forms of cancers.[1,2] However, the interplay between gut microbiota, host immune response, and the ultimate disease is quite complex, as the same commensals can impact the host either positively or negatively depending on the individual's susceptivity.[1]

There has been a growing interest in the role of oral and topical probiotics in the field of dermatology, over the past decade. With the advent of new products in the market, research continues to evaluate the indications, modus operandi, efficacy, and safety of these agents. As science pursues to dive deep into the various aspects of the gut–skin axis, future studies will elucidate the role of probiotics on various skin disorders and skincare.[38]

The U.S. Food and Drugs Administration (FDA) has arrayed probiotics into foods, dietary supplements, food additives, drugs, and cosmetics. However, there is no stewardship for topical probiotics, and are not currently FDA-approved.[38] Increased use of probiotics has asserted an excellent safety profile, but data on its long-term safety are scarce.[25,39,71] Hence, large-scale trials, indicating their stability and functionality, the most effective strains with their titrated combinations, and treatment duration tailor made for each indication along with their safety and antimicrobial resistance profile, are the need of the hour.[23]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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