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Review Article

Review: Probiotics in dermatology

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ABSTRACT

Probiotics are live microbial organisms that are beneficial to the host health when they are administered in adequate amounts. Since its introduction, the concept of probiotics has stimulated much interest and scientific research. Modulation of intestinal microbiota with probiotics is used as a therapeutic modality in many disease conditions. The role of probiotics in dermatological diseases like atopic dermatitis, acne, vaginal infections etc. is not yet established inspite of several studies on the same. As probiotics provide a safe and well-tolerated therapeutic modality in this era of antibiotic resistance and adverse effects, it becomes essential for us to validate the efficacy of its therapeutic supplementation. Herein, an attempt is made to review the current evidence from literature.

Keywords: Probiotics, Atopic dermatitis, Acne, Bacterial vaginosis, Vulvovaginal candidiasis

INTRODUCTION

History

Probiotics have been used for centuries, long before its concept came into being. The use of fermented milk has been mentioned even in the Bible. In ancient Greece and Rome, fermented milk was given to children and convalescents. Elie Metchnikoff, a Russian scientist, in the early 20th century associated the health and longevity of Bulgarian peasants to their generous intake of *Lactobacillus* rich yogurt. The term probiotic (Greek = for life) was introduced by Lilly and Stirwell in 1965.[1]

Gut microbiome (GM)

The human intestine is sterile at birth and is gradually colonized by environmental bacteria. The initial colonization differs according to the mode of delivery. The infants born by cesarean section have lower numbers of *Bifidobacteria* and *Bacteroides* when compared with vaginally born infants. Beyond this phase, the type of feeding influences the GM composition. Breastfeeding stimulates anaerobic bacteria such as *Bifidobacteria* due to the high oligosaccharide content of human milk (bifidogenic effect). Bottle feeding leads to a varied flora consisting of *Bifidobacteria, Escherichia coli,* and *Bacteroides*. When breastfeeding is complemented with bottle feeding, intestinal bacteria becomes similar to that of infants nursed with formula. On cessation of breastfeeding, the microbiota is pushed towards the adult pattern in which most bacterial species are anaerobic (97%) and only 3% are aerobic.

The normal intestinal flora imparts significant metabolic and immune benefits to the host [Table 1].

Intestinal dysbiosis, a state of alteration and imbalance of gut flora has the propensity to induce various lifestyle-related and immune-mediated diseases, including few dermatological conditions [Table 2]. Many of these were found to be benefitted by supplementation of probiotic bacilli.

Probiotics

The United Nations Food and Agricultural Organization define probiotics as "live microorganisms, which, once administered in adequate amounts, confer a health benefit to the host." The most commonly used bacteria as probiotics are the *Lactobacillus* and *Bifidobacteria,* and these are widely available as powders, tablets, drinks, and fermented dairy products. Non-engineered, naturally occurring strains constitute the first generation of probiotics while the second generation ones are genetically engineered and are based on naturally occurring *Lactobacillus* strains.[2]

Modulation of host immunity by probiotics was initially supposed to be by the probiotic bacteria persisting and multiplying in the gastrointestinal system. However, studies have shown that the ingested bacteria last only during periods of dosing or for relatively short periods thereafter and they trigger signaling cascades that activate underlying cells in the lamina propria, either directly or by release of soluble factors. They act through toll-like receptors (TLR) and nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors and modulate key signaling pathways such as nuclear factor-KB and mitogen-activated protein kinase to bring about the desired effect.[3] Probiotics also competitively adhere to the intestinal mucosa and strengthen the gut epithelial barrier.

Table 1: Benefits of intestinal flora[1].

Modulate immune system and reduce risk of allergy
Competitively inhibit pathogenic flora development
Decrease diarrhea episodes
Aid absorption of nutrients and minerals
Synthesis of vitamins B and K
Reduce hypercholesterolemia
Retard development of several pathologic conditions (e.g., Atopic dermatitis)

Table 2: Dermatological conditions in which probiotics have a potential role.

Atopic dermatitis
Acne vulgaris
Bacterial vaginosis
Vulvovaginal candidiasis
Psoriasis vulgaris
Inflammatory bowel disease
Aging
Rosacea
Wound healing
Oral mucositis
Seborrheic dermatitis

Prebiotics and synbiotics

Two terms that need a reference in conjunction with probiotics are the prebiotics and synbiotics. A prebiotic is a nondigestible food ingredient that selectively stimulates the growth and survival of beneficial bacteria in the colon, thereby improving host health. Both inulin and trans-galactooligosaccharides fulfill the standards of prebiotics.[4] Combination of prebiotics and probiotics is referred to as synbiotics. Human milk oligosaccharides exert a prebiotic effect on *Bifidobacteria* and supplementation of similar oligosaccharides in formula feeds reduces the incidence of allergic manifestations.[5]

PROBIOTICS IN DERMATOLOGY

Atopic dermatitis (AD)

AD is a common skin disease of multifactorial etiology driven by a strong type 2 immune response. The onset of the disease occurs early in life and deeply affects the quality of life of both the patient and the family. The increasing prevalence of atopic dermatitis has led to more research on its epidemiology, prevention, and treatment.

In newborns, the immune system is predominated by a Th2 profile, which is usually balanced by the Th1 response induced by intestinal bacteria, especially the *Bifidobacteria*. The lack of normal intestinal microbiota in atopic diseases, particularly during the early phases of mucosal immune system development, pushes the balance towards a Th_2 response. Furthermore, in AD, there is impairment of barrier functions, not only in the skin but also in the intestine resulting in the transfer of exogenous antigens.

A comparative study of the gut microbiota profile of AD children and healthy controls by Sofia *et al*. showed a dysbiotic status in AD patients with a reduction in the presence of short-chain fatty acid (SCFA)-producing bacteria such as *Bifidobacterium, Blautia, Coprococcus, Eubacterium,* and *Propionibacterium*.[6] SCFAs are important for the functioning of cutaneous immune defense mechanisms. Candela *et al*. also found that there is an altered gut microbiota in atopic children and they considered that this inflammogenic microbial consortium contributes to the pathogenesis of the atopic disease.[7] Probiotics favorably alter the GM and modulate the immune response to produce Th1 cytokines and suppress the Th2

response. Furthermore, probiotics such as *Lactobacillus paracasei* have the capability to accelerate barrier recovery functions of the skin.[8]

In this context, much interest has been laid on probiotics as an alternative or adjuvant therapy for atopic disease, and many studies have indicated beneficial effects of probiotics in atopic dermatitis. A pioneering study by Kalliomaki *et al.* selected pregnant women who had a high probability of having atopic children and studied the effect of probiotics in the diet in the last trimester of pregnancy. They found that atopic disease was lower in the neonates of mothers who had taken probiotics in the diet.[9] Gerasimov *et al.* studied the effects of *Lactobacillus acidophilus*, *Bifidobacterium lactis,* and fructo-oligosaccharide in children aged 12–36 months with moderate-to-severe AD. A significant decrease in scoring of atopic dermatitis (SCORAD) index was found in the probiotic group.[10] However, when Gruber *et al.* supplemented *Lactobacillus rhamnosus* in the food of infants with mild-to-moderate AD, they did not find any statistically significant improvement in the supplemented group.[11] It has to be borne in mind that many studies were confounded by concurrent use of medications including oral antibiotics and topical steroids as well as by the effects of elimination diets and use of fermented foods.

The multiple studies with conflicting results stimulated a spate of systematic reviews and meta-analysis [Table 3]. Kim *et al.* reviewed 25 randomized controlled trials (RCTs) on the effects of probiotics in the treatment of AD and found significant differences in SCORAD values favoring probiotics over the control group in children 1–18 years old and in adults, but not in infants less than 1 year.[12] The systematic review and meta-analysis of 13 RCTs conducted by Huang *et al.* on the treatment of atopic dermatitis in children ≤18 years observed that probiotics have the potential to lower SCORAD values in children with AD.[13] Elisabeth *et al.* conducted a systematic review on the role of gut microbiota in atopic dermatitis, which included 44 studies of which 26 were observational and 18 were interventional. Probiotics were found to induce an alteration in GM and decrease the severity of AD only in nearly half of the interventional studies. Review of the observational studies found conflicting results. Hence, they concluded that the role of GM in AD is controversial.[14]

Table 3: Role of probiotics in atopic dermatitis-evidence from reviews and meta-analysis.

S. no	Author	Year	Study design	No. of studies analyzed	Observation
1	Kim *et al.*[12]	2014	Meta-analysis of RCT	25	Significant differences in SCORAD values favoring probiotics in children 1–18 years old and in adults. The effect in <1 year was not established
2	Huang *et al.*[13]	2017	Systematic review and meta-analysis of RCT	13	Probiotics have the potential to lower SCORAD values in children (≤18 years) with AD
3	Elisabeth *et al.*[14]	2018	Systematic review of literature	44	Probiotics alter GM and decrease the severity of AD in nearly ~50% of interventional studies. Observational studies showed conflicting results. Hence, the role of GM in AD is controversial
4	Michail *et al.*[30]	2008	Meta-analysis of RCT	10	Statistically significant reduction in SCORAD, esp. in children with moderately severe AD
5	Lee *et al.*[31]	2008	Meta-analysis of clinical trials	21	Probiotics more efficacious in prevention rather than treatment of pediatric AD
6	Betsi *et al.*[32]	2008	Review of RCT	13	Probiotics effective for prevention of AD in infants. Also found to reduce the severity of AD in children in 50% of RCTs esp. in those with high IgE and food allergy
7	Panduru *et al.*[33]	2015	Meta-analysis of RCT	16	Probiotics protective against the development of AD when given in prenatal and postnatal periods
8	Da Costa *et al.*[34]	2013	Literature review	12	75% of studies indicated a beneficial biological effect of probiotics on AD

GM: Gut microbiome, RCT: Randomized controlled trial, AD: Atopic dermatitis

However, these results should not be generalized due to the considerable heterogeneity in data of the studies in the form of differences in study samples, study populations, and methodological differences as well as by the variations in the genetic predisposition and the microbial exposure of the subjects studied.

Acne vulgaris

Acne vulgaris is a chronic disease of the pilosebaceous unit, mainly seen in adolescents. The lesions along with the resultant pigmentation and scarring produce significant cosmetic impairment leading to depression, anxiety, and other psychological sequelae in many affected individuals. The gut-brain-skin axis proposed by Stokes and Pillsbury in 1930 hypothesized that emotional states would possibly alter the intestinal microflora, increase intestinal permeability and lead on to systemic inflammation and aggravate skin conditions such as acne. Acne patients with deep inflammatory lesions have shown reactivity to *E. coli* lipopolysaccharide endotoxins in the form of microclot formation. However, this reactivity was rarely seen in mild acne and never in controls.[15] The presence of such circulating endotoxins derived from gut microbes indicates the altered gut flora and the abnormal intestinal permeability in acne patients. This intricate relationship between gut microbiota and the skin may also be influenced by diet. A high glycemic load stimulates an increase in insulin/insulin-like growth factor (IGF-1) signaling and favor the pathogenesis of acne. Milk may contribute to the pathogenesis of acne because it contains growth hormones. However, fermented dairy products are not associated with acne, possibly because probiotic bacteria, especially *Lactobacillus,* utilize IGF-1 during fermentation of milk.

Robert H Silver in 1961 found that when probiotics such as *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* were supplemented in 300 acne patients, improvement in acne occurred in 80% of subjects, particularly in those with inflammatory lesions.[16] In another clinical study by Jung *et al*., subjects who were put on oral probiotics in addition to oral minocycline had a significantly greater decrease in total acne count when compared to an antibiotic only control group.[17] Probiotics may also bring down the glycemic load and reduce IGF-1 signaling, thereby decreasing the predisposing factors of acne formation such as keratinocyte proliferation and sebaceous gland hyperplasia. Fabbrocini *et al*. demonstrated that the consumption of *Lactobacillus rhamnosus* for 12 weeks resulted in improvement of adult acne by normalizing the skin expression of genes involved in insulin signaling.[18]

Topical probiotic (*Lactobacillus bulgaricus*) application was also found to be useful in acne as early as in 1912. Kang *et al*. reported that topical *Enterococcus faecalis* produces bacteriocins which act against *Propionibacterium acnes* and its lotion significantly decreased the inflammatory acne lesions like pustules when compared to the placebo lotion.[19]

Vaginal infections

In normal health, the vaginal flora is predominated by lactobacilli. It is believed that these commensals play a major role in protecting against vaginal infections by producing lactic acid, acetic acid, and hydrogen peroxide, which helps in maintaining the vaginal pH around 4.5 or less. The growth of pathogenic bacteria and *Candida albicans* is hampered at this pH, curbing the development of infections. In addition to the lactobacilli, the vaginal microbiota may also contain low proportions of other species such as *Bacteroides*, *Clostridium, Gardnerella, Peptococcus*, *Enterococcus, Streptococcus,* and also *Staphylococcus epidermidis.*

Bacterial vaginosis (BV) is a common vaginal infection which causes significant gynecological and obstetric morbidity. In patients with BV, the vaginal microbiota is predominated by diverse organisms such as *Gardnerella vaginalis, Mycoplasma hominis, Prevotella, Peptostreptococcus, Mobiluncus,* and *Bacteroides* spp., while lactobacilli are seen much less than expected. Lactobacilli have been shown to inhibit the growth of pathogenic bacteria causing BV by producing H2O2, lactic acid, bacteriocins, and also by inhibiting the adherence of *G. vaginalis* to the vaginal epithelium.

A review on the effectiveness of probiotics in the treatment of BV revealed that oral or intra- vaginal administration of lactobacilli can cure and/or reduce the recurrence of BV by increasing the numbers of vaginal lactobacilli and restoring the vaginal microbiota to normal. However, the same review also observed several trials which found no significant effect on BV on intravaginal instillation of lactobacilli.[20] The 2015 guidelines of Center for Disease Control and Prevention (CDC) have not supported any current *Lactobacillus* formulations or other probiotics in the treatment of BV. A meta-analysis of RCTs published in 2017 on the effects of metronidazole combined with probiotics over metronidazole alone for the treatment of bacterial vaginosis found an overall little significance only, necessitating further research efforts.[21]

Vulvovaginal candidiasis (VVC) is characterized by overgrowth of Candida in the vaginal microbiota. This could be a subsequent effect of a reduced number of lactobacilli or due to the presence of a species of lactobacilli not producing H_2O_2. A Cochrane review in 2017 to assess the effectiveness and safety of probiotics for the treatment of vulvovaginal candidiasis in non-pregnant women showed an increase in short-term clinical and mycological cure rates as well as a decrease in relapse rate at 1 month. However, this was not found to increase long-term clinical or mycological cure.[22] A

study done with *Lactobacillus plantarum* P17630 indicated its potential in restoring vaginal microbiome and in view of the frequent recurrences and possibility of antifungal resistance in VVC its role needs to be studied further.[23]

Psoriasis

Psoriasis is a T-cell-mediated chronic inflammatory skin disease resulting from a combination of genetic and environmental factors and can affect all ages. Interestingly, the gut microbiota of patients with psoriasis was shown to have a higher *Firmicutes/Bacteroides* ratio when compared to healthy controls, and this positively correlated with Psoriasis Area and Severity Index (PASI). It is reported that bacteria such as *Firmicutes* are more prone to induce inflammation and hence lead to psoriasis, suggesting that such a shift in GM might be part of the pathogenesis of psoriasis.[24] Another study found that *Akkermansia muciniphila*, which is seen plentiful in health, was significantly reduced in patients with psoriasis.[25] Yet another study by Chen *et al*. showed that oral *Lactobacillus pentosus* significantly reduced erythema and scaling in the skin of topical imiquimod-treated mice by inhibiting the mRNA expression of pro-inflammatory cytokines, including TNF-alpha, IL-6, and the IL-23/IL-17A axis-associated cytokines.[26] A promising outcome in treatment was reported by Vijayashankar and Raghunath, in which a case of pustular psoriasis resistant to steroids, dapsone, and methotrexate responded well to *Lactobacillus Sporogenes* in 2 weeks,[27] justifying future researches in this field.

Other uses

A study in patients with inflammatory bowel disease found an inverse trend between probiotic use and the occurrence of skin lesions suggesting that probiotics may turn out to be an additional tool in the treatment. Research is going on to establish the anti-aging potential of probiotics as they have shown to improve cutaneous elasticity, increase skin hydration, and reverse ultraviolet induced aging. Studies are on the way to elucidate its role in rosacea, wound healing, oral mucositis, seborrhea dermatitis, and other eczemas.

Topical probiotics

Topical probiotics can impede pathogenic flora development by competitive binding at receptor sites and by competitive consumption of nutrients. They also trap pathogens by enhancing mucin and ceramide production and also by modulating host immune responses. They can also prevent biofilm formation and enhance tissue repair. Hence, they may be used to compensate the altered cutaneous flora in conditions such as acne, wound healing, atopic dermatitis, and heat damaged skin. A study of topical *Bifidobacterium longum* lysate application has shown to reduce skin reactivity, dryness, and aging thus attracting much attention to the use of topical probiotics for cosmetological indications.[28]

Potential adverse effects of probiotics

Probiotics have been used safely for many years. However, the joint report by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations in 2002 has put forward four theoretical concerns: Risk of systemic infections, deleterious metabolic activities like d-lactate production and bile salt deconjugation, excessive immune stimulation in susceptible individuals and the risk of gene transfer to other bacteria.[29] Although cases of fungemia, bacteremia, overt sepsis, and endocarditis have been reported after intake of probiotics, studies from Finland and Sweden have shown that there is no change in prevalence of *Lactobacillus* bacteremia in spite of increased consumption of *Lactobacillus* probiotics over the study period. Minor gastrointestinal side effects such as abdominal cramping, flatulence, nausea, diarrhea, and taste disturbances have also been reported.

CONCLUSION

Probiotics are very safe and well tolerated and can be used in even infants and children. However, as theoretical concerns of side effects exist, the safety of probiotics has to be thoroughly investigated before we advocate its widespread use. Research is still ongoing and more evidence in the form of well-designed randomized control trials are required to establish its efficacy and safety. Overall, the future for probiotics looks promising and they may serve as valuable adjuvants or alternatives in the treatment of different dermatological conditions.

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Conflicts of interest

There are no conflicts of interest.

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