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Probiotic based therapy for atopic dermatitis: Outcomes of clinical studies

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ABSTRACT

Atopic dermatitis (AD) is one of the chronic inflammatory skin diseases characterized by conflicts in epidermal barrier and wired immune response. About 10%-20% of the population is affected by AD, especially infants. Topical application of corticosteroids, antihistamines, and antibiotics are used to treat severe AD condition. Recent studies suggest that disturbance in skin and intestinal microbiota is majorly linked to skin diseases. Probiotics are known for the positive alteration of an individual's microbiome and associated with several health benefits. Clinical studies suggest that probiotic and synbiotic supplementation protect infants from a stringent AD to some extent. Reduction in the risk of AD development upon probiotic supplementation was not observed in all studied populations. Further studies are needed to regularize microbiome of skin and intestine in AD patients that may reduce AD severity. Present review summarizes the outcomes from clinical studies on AD using probiotic as an alternative treatment candidate.

1. Introduction

Skin is the principal organ of the human body, which consists of several layers such as skin surface, epidermis, and dermis, and acts as a physical barrier against toxic substances and invading microorganisms. The skin is also considered as an interface of the human system from the external environment[1]. The epidermal layer of the skin is prone to microbial infection, and the skin microbiome is also influenced by the integrity of the epidermal layer[2].

Skin diseases are the fourth leading cause of global disease burden. More than 3 000 skin diseases were recorded with the impact of environmental factors, aging, genetic factors, and skin damages. The economic burden of the skin diseases has been estimated among US population and found that about $75 billion was used for the treatment of skin related diseases. Nearly $887 have been spent by every affected individual for treating skin diseases in the US during 2013[3] .

The typical treatment strategies for the primary skin diseases are metronidazole[4], and antibiotics like tetracyclines for rosacea[5], and retinoids[6,7], erythromycin, and clindamycin[8] for acne treatments. Atopic dermatitis (AD) cannot be controlled or treated with single treatment methods; it requires several clinical procedures to recover the affected individual. The use of effective moisturizer to reduce the dryness of the skin and topical corticosteroids to diminish the immune responses like inflammation is the prescribed first line treatment for AD[9].

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Probiotics (live microbes that confer a health benefit on the host, when administered in adequate amounts) containing foods are considered as functional food, since they promote the health conditions by modulating host defense system, inhibiting the growth of invading microbial pathogens and secreting the bioactive principles such as short chain fatty acids, antioxidants, and vitamins[10]. The species of *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Enterococcus* are frequently used as probiotics[11]. The beneficial effect of probiotic varies among the strains of same species[12], and the impact of probiotic also depends on the consumer's health conditions, gender, age and food habits[13].

It has been reported that the topical use of corticosteroids for the treatment of AD leads to skin atrophy and viral infection[14]. Alternative probiotic based therapies for AD have been reported in recent years with promising results. The present review focused on the clinical outcomes of probiotic-based treatment for AD.

2. AD

AD or atopic eczema is a chronic medical condition that makes the skin inflamed, itchy, and flare frequently. The primary cause of AD is genetic and environmental factors. The children exposed to various antibiotics have disturbed gut microbiome, which facilitates the development of AD, and AD incidence is also closely associated with hygiene practices, the immune system of an individual, *etc*[15]. Children with severe AD have a risk to develop asthma[16–18]. The AD is common in urban areas[15], and prevalence of AD is common in Western countries and now increasing in developing countries[19].

The major symptom of the illness is itching, which affects the quality of AD patient's life. Sweat, skin dryness, physical effort, and stress are the common factors that influence the severity of AD[20,21]. The neck[20], legs and back were the itchiest parts of the body, and the pruritus was increased during night time. A clear mechanism behind the increased itching during night time is not yet revealed[20,21]. The disturbed sleep and itchiness significantly affect the mental health and increase the stress in AD patients[22].

The skin microbiome is disturbed by endogenous factors and external factors like hygiene, use of skin care cosmetics, clothing, and contemporary treatments. A composed skin microflora is a defense measure against various skin infections[23]. About 90% of AD patient skin are residing with *Staphylococcus aureus* (*S. aureus*), and 50% of these *S. aureus* are producing toxin[24]. Rubbing disrupts the skin barrier that enhances the attachment of *S. aureus* to the skin. *S. aureus* can induce flares, which facilitates the spreading of the lesional AD[25]. *S. aureus* can penetrate epidermis layer of the skin and disturb the barrier function by inducing keratinocyte endogenous serine protease production[26]. AD is considered as a risk factor for the methicillin-resistant *S. aureus* invasion and colonization[27]. The intestinal microbiome also influences the development of AD. The use of antibiotics disturbs or prevents the healthy development of intestinal microbiome in infants. For example, excess antibiotic use interrupts *Escherichia coli* colonization in the intestine that disturbs the protective measures against AD[28].

It is known that the disturbance in gut microbiome enables the development of AD, especially in children, along with genetic and environmental factors.

3. Probiotic treatments for AD

The supplementation of *Lactobacillus fermentum* VRI-033 PCC for eight weeks significantly reduced the Scoring of Atopic Dermatitis (SCORAD), and the severity of AD in infants of 6-18 months old[29]. The distinct intervention of *Lactobacillus sakei* KCTC 10755BP (2-10 years old children; 5×10^9 CFU twice a day)[30], and *Lactobacillus plantarum* CJLP133 (1-13 years old children; 0.5×10^{10} CFU per day)[31] for 12 weeks significantly reduced the SCORAD, disease activity, and improved the quality of children with atopic eczema-dermatitis syndrome[30,31].

Two separate studies suggested that the synbiotic preparations can reduce the intensity of AD. The supplementation of *Lactobacillus acidophilus* DDS-1, *Bifidobacterium lactis* (*B. lactis*) UABLA-12, and fructo-oligosaccharide (FOS) to children (1-3 years old) showed the significant reduction in SCORAD (33.7%), Infant Dermatitis Quality of Life (33%), Dermatitis Family Impact (35.2%) scores. The lymphocyte subsets (CD22, CD3, and CD16) were not changed. Whereas CD4 and CD25 counts were decreased, and CD8 count was increased in the AD patients supplemented with symbiotic preparations[32]. The intervention of single strain of *Lactobacillus salivarius* (*L. salivarius*) along with FOS showed a reduction in the severity of AD, SCORAD, eosinophil cationic protein levels, and frequency of medication. The results suggested that the synbiotic supplementation was better than prebiotic treatment for infant AD[33].

The supplementation of proBiotik® pur (a mixture of *L. salivarius*, *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*) to 1-13 years old children showed the predominant reduction in SCORAD, IgE, IL-6, IL-5, and IFN- γ levels while TNF- α, IL-10, IL-2, and IL-4 levels were not affected. The results claimed that the proBiotik® pur was effective against AD[34]. Another report suggested that the intervention of *Lactobacillus fermentum* (2×10^9 CFU) alone, *Lactobacillus paracasei* (2×10^9 CFU) alone, and a mix of both strain (4×10^9 CFU) for three months can reduce the SCORAD, Children's Dermatology Life Quality Index and Family Dermatology Life Quality Index scores, and urine 8-Oxo-2'-deoxyguanosine and eosinophilic protein X, serum IgE and TNF- α levels, thereby improving the clinical status of the AD[35].

Several scientific reports are available on the impact of supplementation of the probiotic formulation to pregnant women with high risk for infant AD. Pregnant women were supplemented with *Lactobacillus rhamnosus* (*L. rhamnosus*) GG (2×10^{10} CFU per day) for 2-4 weeks

before the projected delivery date, and postnatally for six months to the mothers or their infants (same dose). The results showed that the intervention prevents the early atopic disease in their children. The incidence of atopic eczema was reduced during first two years of life, and the protective effect extended up to 4 years[36,37].

L. rhamnosus GG ATCC53103 (2×10^{10} CFU per day) was supplemented to pregnant women prenatally for four weeks and postnatally, *i.e.*, to a newborn baby, for six months. Then the protective effect of the probiotic intervention was assessed after 2, 4 and 7 years. Interestingly, the results suggested that the supplementation of *L. rhamnosus* GG protects the children from the risk of AD even for seven years[38].

Lactobacillus reuteri ATCC55730 (1×10^{8} CFU per day) was supplemented to pregnant women from 36 week until delivery; then the infants were supplemented with same strain (same dose) for 12 months and follow-up study was carried out for one more year. The results suggested that the intervention reduced the risk of development of respiratory allergic disease at a later period of life[39]. Ecologic® Panda (*Lactococcus lactis*, *B. lactis*, and *Bifidobacterium bifidum*; 1×10^{9} CFU of each strain per day) was supplemented to pregnant women from 6 weeks before delivery, continued another 12 months intervention to infants. The clinical assessments recommended that the supplementation of Ecologic® Panda prevents the incidence of eczema in infants up to 2 years[40]. Three subsequent studies with probiotic strains (*Bifidobacterium animalis* subsp *lactis* HN019; 9×10^{9} CFU per day or *L. rhamnosus* HN001; 6×10^{9} CFU per day) on pregnant women and their infants revealed that *L. rhamnosus* HN001 supplementation reduces the SCORAD and incidence of eczema, and also significantly diminishes the risk of infant eczema[41,42] up to the age of six[43].

A mixture of probiotic formula that consisted of *B. lactis* Bb12, and *L. rhamnosus* GG ATCC53103 at the concentration of each 1×10^{10} CFU per day was given to the pregnant women (atopic mothers) from the 1st trimester of pregnancy to the end of exclusive breastfeeding. The probiotic intervention protected the sensitization in high-risk infants effectively compared to placebo control[44]. Another study was conducted with two sets of probiotic formulations (*Bifidobacterium longum* BL999 and *L. rhamnosus* LPR, each 1×10^{9} CFU per day; *Bifidobacterium longum* BL999 and *Lactobacillus paracasei* ST11, each 1×10^{9} CFU per day). The probiotic supplements were given to pregnant women during two months before the delivery and another two months after giving birth. The clinical parameters were evaluated at postnatal 6, 12, and 24 months. The results revealed that both combinations of probiotic interventions were safe and reduced the risk of eczema development in infants[45].

AD is most common among the infants, but some of the adult AD incidences are recorded, and some of the probiotic based clinical trails were conducted in adults. The separate supplementation of *L. salivarius* LS01 (2×10^{9} CFU per day) to 18-46 years old adults (AD patients) for sixteen weeks improved the Dermatology Life Quality Index score, reduced the SCORAD index and *Staphylococci* load. *L. salivarius* LS01 supplementation modulated the Thl/Th2 cytokine profiles. Moreover, *L. salivarius* LS01 supplementation reduced the Th2 cytokines production while the Th1 production level was maintained[46,47]. The intervention of *Bifidobacterium animalis* subsp *lactis* LKM512 (6×10^{9} CFU) along with dextrin, glucose, silicon dioxide, inulin, and skim milk reduced the itching and increased kynurenic acid levels in AD patients. The study claimed that LKM512 supplementation induces the antipruritic effects by accelerating the kynurenic acid production. LKM512 could be a potent therapeutic agent for pruritus[48].

However, not all the probiotic formulations and intervention studies are successful regarding health benefits to human subjects. For example, the supplementation of synbiotic formulation that contains seven probiotic strains and FOS to infants (1-36 months old)[49], and the intervention of *Lactobacillus paracasei* CNCM I-2116 or *B. lactis* CNCM I-3446 to 3-6 months old infants[50] showed no statistical significance in SCORAD scores and other assessed parameters between treated and placebo groups[49,50]. Infants (postnatal period: 48 h) were supplemented with *Lactobacillus acidophilus* LAVRI-A1 (3×10^{9} CFU per day for six months) in maltodextrin and found that the intervention does not prevent the development of AD, significantly[51]. Some of the studies suggested that the supplementation of *L. rhamnosus* GG at different concentrations to infants does not have protective effects against AD[52,53] while supplementation (for four weeks) of *L. rhamnosus* GG (5×10^{9} CFU) showed a reduction in SCORAD score, and the symptoms of AD syndrome in IgE-sensitized infants[54]. Whereas, the cocktail of a probiotic mixture containing *L. rhamnosus* GG, *Propionibacterium freudenreichii* ssp. *shermanii* JS, *Bifidobacterium breve*, and *L. rhamnosus* LC705 along with galactooligosaccharides displayed no impact on the incidence of allergic diseases[55,56], and no allergy-preventive effect[56], but reduced atopic eczema[55] in infants at high risk for allergy.

4. Conclusion

Latest studies have attempted to explain the role of intestinal microbiome and skin in the risk of development of AD. But most of the information is from infants, and the data from the adult AD is limited. It is known that the probiotic supplementation alters the microbiome of an individual. Thus, several clinical studies were conducted to explore the therapeutic property of probiotic formulations against AD. Some of the studies showed positive results and others demonstrated no effect. A particular probiotic strain exhibits the protective act on AD in some group of the population that may not work on another study group. Multi-strain formulations and synbiotic preparations showed better protection from allergic diseases than single-strain or prebiotic interventions. To explain the link between the microbiome and AD development, and the

prevention measures for AD via probiotic supplementation, further intensive study is required in this field.

Conflict of interest statement

All authors declare that there is no conflict of interest.

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