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Minireview

Probiotics in Pediatrics

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The gut microbiota is critically important for development and maturation of the mucosal immune system right from birth till the whole life. The development of the immune system in neonates is especially important because it is not fully matured. However, its growth begins before birth. It depends on various factors like mode of delivery, mother's microbiota, antibiotic consumption, mother's milk, eating habits of infants and other environmental factors. Alterations in gut microbiota (dysbiosis) may disturb the gut homeostasis, and hamper the development of immune system. However, dysbiosis in infants may be averted by administration of probiotics. Mother's milk contains various nutritive components along with some beneficial bacteria, probiotics (lactobacilli and bifidobacteria) which help in the development of gut microbiome of the infant. Probiotics, in particular, serve an important role in sustaining eubiosis in an infant's body. Any dysbiotic condition, particularly in infants, may be associated with a number of diseases/disorders like diarrhea, gastrointestinal problems, and allergic issues. Atopic dermatitis (AD) is one such common allergic problem prevalent in paediatrics. The probiotics serve as modulators of immune response and acts as immunobiotics. AD-related inflammation can be successfully managed by the intervention of probiotics. This review presents the potential of probiotics for proper development of infants' immune system, and for prevention and treatment of various diseases, especially the ever-rising cases of AD.

Keywords: Atopic dermatitis, Bifidobacteria, Dysbiosis, Gut microbiome, Immunobiotics

Introduction

Human gastrointestinal tract (GIT) harbours a wide range of microorganisms that represent a complex microbial ecosystem, and named as gut microbiota[1]. The gut microbiota includes beneficial, harmless and potentially harmful pathogenic microorganisms, which establishes an ecologically balanced interaction with the host, and help maintaining homeostasis[1]. The gut microbiota plays an instrumental role for preventing certain diseases/disorders and supporting overall good human health[2,3]. Alterations in gut microbiota composition (dysbiosis) may lead to aggravation and/or onset of certain diseases/disorders such as autoimmune and allergic diseases, colorectal and other cancer types, gastrointestinal issues, metabolic diseases, bacterial infections and others[4]. Dysbiosis can potentially be averted by the application of probiotics, i.e., administration of good/beneficial microorganisms, thus maintaining eubiosis[4,5].

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Probiotics are defined by the World Health Organization as "live microorganisms, which when administered in adequate amounts confer a health benefit on the host"[3,5]. Probiotic consumption has been associated with a wide range of health benefits such as prevention/treatment of various types of diarrhea, allergies and atopic diseases, alleviation of lactose intolerance, modulation of the immune system, conditioning of gut microbiota and many more[6]. In addition, recent evidences show that probiotics may be beneficial for health-related issues like candidal vaginitis, sexually-transmitted diseases including AIDS, cardiovascular diseases/disorders, hypertension, hypercholesterolemia, diabetes, inflammatory diseases, and various types of cancers[5,7]. Most commonly used probiotics include *Lactobacillus* spp., *Bifidobacterium* spp., and the yeast *Saccharomyces boulardii*, however, a range of microbial spp., viz. *Bacillus*, *Enterococcus*, *Escherichia*, *Propionibacterium*, and several others are under intense investigation as promising probiotic bacterial strains[2,3,6] (Fig. 1).

Fig. 1 — Overall health benefits of probiotics

Probiotics though are vitally important for health and wellbeing of human beings of all ages, but these are considered more significant for infants/children and newborns[8]. Infants are born with an immature immune system, and their GI tract is believed to be sterile, thus, making them more susceptible to distress i.e., diseases/disorders and infections. Recent studies, however, indicated that the fetal intestine might have exposure to microbes through swallowing of amniotic fluid. In any case, however, over a period of time infants build their gut microbiota which strengthens the GI tract barrier function and help evolving a stronger immune system which would provide protection against diseases/infections[8].

In recent years, evidences have established that intestinal gut microbiota may be considered as the measure of health and disease in newborns[2]. Generally sterile at the time of birth, the GIT of the infants is soon colonized by the microorganisms (mainly bacteria) ingested during the process of birth. Various factors have been proposed to affect the early-life development of the microbiota, including the composition of the maternal microbiome, mode of birth, antibiotic usage and, length of gestation[9]. Mother's milk contains various nutritive components along with some beneficial bacteria (lactobacillus and bifidobacteria) which play a very important role in the development of the immune system of an infant[10]. During the first three months of infants' life, the mode of delivery has been reported to be strongly linked with the diversity and colonization patterns of the gut microbiota[11]. Care must be made early during pregnancy to ensure that an individual's gut microbial flora is distributed evenly. Few of the mother's diseases can easily be passed down to the infant. If the mother has a vaginal delivery, beneficial bacteria like *Lactobacillus* can be passed to the newborn[12]. Babies born via caesarean section (CS) had higher abundance and diversity of the phylum Firmicute, and a relatively lower proportion and diversity of the phyla Actinobacteria and Bacteroidetes. *Bifidobacterium*

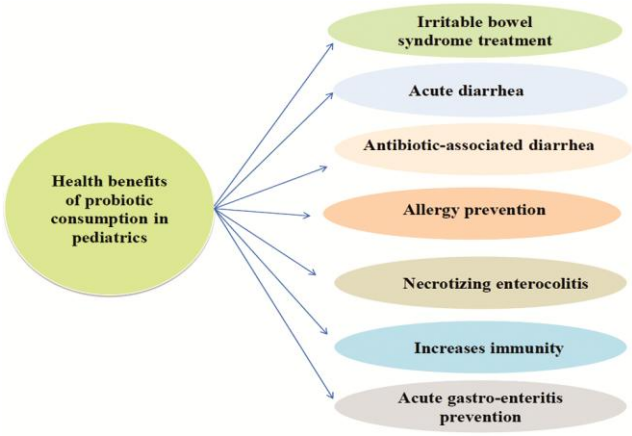

Fig. 2 — Role of probiotics in paediatrics

spp. and *Bacteroides* genera appear to be substantially more common in vaginally delivered infants than in CS delivered infants at the colonization level[13]. The healthy gut microbiota contributes substantially to the growth and maturation of the immune system, whereas an aberrant gut reverses the same, and generally leads to serious gastrointestinal and other infections in children. Other factors such as a child's eating habits, lifestyle, and environment. significantly contribute to the healthy development of the immune system and gut microbiome[14] (Fig. 2).

Studies have established that probiotics' consumption not only helps shaping a healthy gut microbial flora but confers protection against a wide range of diseases, disorders, ailments, metabolic issues, and pathogenic infections[6]. Several clinical trials have shown that the probiotics intervention may help in the treatment and prevention of various infectious disorders. Probiotics are generally given in various food supplements, and several such probiotic foods have been commercialized[15]. Infant nutrition relies heavily on fermented dairy products made with specifically selected lactobacilli and bifidobacteria strains. Acidophilus milk, bifidus milk, yoghurt, kefir, and other infant-feeding products have already been produced and proved to be safe for both healthy and sick babies. Breast milk inadequacy and modified infant formulae have prompted the development of fermented dairy products for infant nutrition[16]. Various studies are available where in the probiotics are investigated as a potential therapeutic tool in the treatment/management of various disorders in paediatrics. Therefore, this review focuses on the benefit of probiotic strains for managing or preventing various pediatric conditions.

Microbes involved during and after pregnancy

The journey of a mother from conception through childbirth is an important one. Countless bacteria are involved in this process. The importance of these microorganisms and their interaction with the mother in the development of the fetus's immune system cannot be overstated. Infants born by Caesarean Section (CS) have different gut microbiota colonization patterns than those born vaginally. During the past two decades, CS has become increasingly popular around the world, and at the same time, more incidences of aberrant gut microbiota are being discovered in infants delivered by CS[13]. If a child is delivered vaginally, they are known to be exposed to microbes such as *Lactobacillus* sp[17] which is significant since it is a key microbe that colonizes the gut and starts the microbiome infrastructure building process[18]. In contrast, if the infant is born via caesarean section, they are more likely to be exposed to bacteria such as *Staphylococcus* and other potential pathogenic spp.[19], which are harmful to the gut development process. Other factors that influence the pattern of infant gut microbiota include the place of birth, maternal vaginal or skin microbiota, type of infant feeding, birth weight, gestational age at birth, hospitalization after birth, antibiotic consumption of mother and, prenatal probiotic therapy[13]. Any vaginal infection or oral infection, such as periodontitis, in the mother can damage the child during pregnancy. In the sense that the microbes found in periodontal plaque are also found in the mother's uterus, there is a clear link between the two. As a result, it is critical to maintain good dental hygiene throughout pregnancy in order to ensure proper microbe seeding from the mother to the foetus.

It is important to ensure that the new-born is fed mother's milk after birth since it is high in *Lactobacillus* and *Bifidobacterium* spp.[20], which consequently may make up to 90% of the gut microbiota. *Lactobacillus* and *Bifidobacterium* spp. constitute a substantial population of microflora, that is transmitted to the neonate endogenously or during breast feeding, which plays an important role in the development and maturation of the infant's immune system. The probiotic bacterial species such as *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* have been isolated from human colostrum samples. It is pertinent to mention that bifidobacteria play a vital role against the adhesion of pathogenic bacteria to an infant gut during the early stages when their immune system is immature[21]. Moreover, the breast milk contains short-chain fatty acids (SCFAs) generated from the fermentation of indigestible food, which acts as nutrient source (prebiotics) for the beneficial bacteria in the infant's GI tract[10]. Also, the sugar in breast milk is a source of oligosaccharide, another prebiotic that significantly contributes towards development of a healthy gut microbiota in the infant's body. Antibiotics should not be taken by the mother during pregnancy because they promote microbial depletion, which is detrimental to both the mother and the baby. Aside from them, the gut microbiome's infrastructure is influenced by factors such as the environment and eating habits[14]. The microbiome of an adult is developed in the first two years of a child's existence, known as the "thousand-day window." This microbiome infrastructure is what determines an individual's immunological condition throughout their lifetime.

Development of immune system in infants

Because of the change in environment from the protective mother's womb to the outside environment, the immune system development of the infant at the time of birth and immediately afterward is critical. The immune system of the infant develops in conjunction with its microbiome[22]. In this sense, the first thousand days are critical for the establishment of the infant's microbiome infrastructure, which is supported by the development of the infant's immune system.

A well-developed eubiotic gut with high microbial diversity at birth aids the development of a resilient and well-functioning immune system in the infant, and it offers a huge number of benefits throughout the life. There are pathogenic bacteria that are not mutualistic in nature even in the eubiotic gut. As a result, as long as these pathogenic bacteria do not cause infection[23], a well-established immune system will be able to tolerate them to a certain level. This tolerance is an immune system feature that is influenced by microbial diversity.

The immune system begins to develop in the womb. The placenta transfers maternal immunoglobulin (IgE) antibodies to the foetus in pregnancy. IgA is transmitted to the foetus via breast milk after delivery, during the first six months, while the infant's immune system is maturing[24]. Secretory

IgA (sIgA) in breast milk not only protects against pathogens but also promotes the development of microbiota in the newborns[25]. The foetus receives immunological support from the mother not only while in the womb, but also during the first six months of pregnancy, when the infant's immune system is developing and maturing. Human milk offers the newborn with many layers of protection against infections, promotes stimulation and maturation of the immune system, intestine development and establishment of the healthy gut microbiome[2] in addition to transmitting IgA. Furthermore, oligosaccharide sugars (prebiotics) available in human milk travel undigested into the infant's gastrointestinal tract and serve as nutrients to support the growth of good or beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* spp. Thus, human milk plays a vital role in the immune system development of infants[10].

For the development of the immune system, exposure to the environment is especially vital throughout the infant's early years. Antibiotics, processed or sugary foods and certain metabolic abnormalities have a negative impact on the baby during pregnancy. The microbial colonisation of the gastrointestinal tract, respiratory tract and skin is negatively affected by these factors. During microbial colonization, the microorganisms release metabolites that influence immunological development in terms of the immune system's organs and cells[11]. Due to the transfer of lactobacilli and other beneficial bacteria from the mother to the child, a vaginal delivery is thought to be a better form of delivery during childbirth. All these variables contribute to the immune system's correct functioning, and healthy life at infant level and older stages of life. On the other hand, if the immune system is not properly formed, a wide range of allergies, and other serious diseases/disorders may be experienced.

Distribution of immune components in the gut

The gut immune system is influenced at three levels: (i) The gut microbiota, which consists of intestinal microbiota and luminal antigens; (ii) The single layer gut epithelial barrier with tight junctions; and (iii) The lamina propria which consists of gut-associated lymphoid tissue.

The intestinal immune system is an integral and potent defense system to regulate commensal tolerance and pathogen elimination[26]. Factors like gut-associated lymphoid tissue and intestinal microbiota are influenced by each other. Immune privilege is developed by the presence of tight junctions and a eubiotic state of the gut lumen. This develops the 'tolerogenic state' in the gut. During the homeostatic interaction between gut microflora and the immune system, the intestinal epithelium plays several protective roles, including acting as a physical barrier for the separation of luminal bacteria from the host tissue. Thereby, an accurate immune development and the immune response is particularly dependent on the regulation by intestinal epithelial cells[26].

Intestinal homeostasis

Intestinal homeostasis is established through dynamic and delicate crosstalk between host immunity and the microbiome. Early infancy is critical for the child's intestinal homeostasis. The gut's tolerogenic state is maintained by a balanced connection among immune system components[27], the intestinal microbiota, luminal antigens and, the epithelial barrier. As a result, colonization with beneficial flora boosts intestinal immunity and the development of immunotolerance in early childhood, resulting in a balanced Th1/Th2 immune response[28]. In the gut, Treg cells maintain homeostasis at steady-state where the cells play an important role in the regulation of inflammation against intestinal microbes[29].

On the other hand, a disruption in homeostasis may result in allergies and several other diseases/disorders. A disruption in homeostasis can alter the microbiota and trigger an allergic reaction, leading to atopy. Cow's milk allergy (CMA) is one of the most common food allergies in early infancy. In particular, the anti-allergic effect of probiotic *Lactobacillus* GG (LGG) on cow's milk allergy (CMA) has been extensively studied and shown to improve the gut microbial balance and allergic symptoms by balanced Th1/Th2 profile[25].

Hygiene hypothesis and Allergy

According to the hygiene theory, early childhood exposure to specific microbes protects against allergy disorders by aiding immune system development[30,31]. The disruption of a balanced microbiome can lead to immunological dysregulation resulting in more susceptibility to diseases such as inflammatory bowel disease (IBD), obesity and, allergic diseases (including asthma and food allergy) in children[32]. If the early childhood exposure to exogenous antigens is

low or non-existent, it may result in poor immune function maturation and loss of immunological tolerance. Due to poor immune tolerance, the Th2/Th1 transition is hampered, and causes increased risk of allergic disorders. Dramatic growth in allergy disorders has been witnessed over the past 5-6 decades (first half of the twentieth century) mainly due to reduced microbial exposure, increased antibiotic usage, and changed lifestyles. As a result, increased incidences of allergy illnesses are encountered in the second half of the twentieth century. Children with one atopic condition, such as eczema, food allergies, rhinitis or asthma, may acquire another atopic condition with the same trigger factor. These allergic reactions could eventually evolve to severe atopic dermatitis. An altered gut microbiome affects microbiota-derived products and metabolites, including pro and anti-inflammatory factors. Protection against microbial invasion is rendered by an intestinal barrier which has multiple lines of defense including commensal bacteria, which competitively inhibit the colonization of pathogenic bacteria, and also produce protective metabolites[32].

There is a well-established link between decreased microbial diversity and an increased risk of allergy disorders. For instance, *Bifidobacterium longum*, *B. breve*, and *Lactobacilli plantarum* were found to possess anti-allergic potential in both animal models and clinical trials[25]. Non-allergic infants have a high microbial diversity in the Shannon diversity index, but allergic infants have a low microbial diversity. Reduced biodiversity in the first month of infancy has been linked to an increased risk of eczema, allergic sensitization, peripheral blood eosinophilia, allergic rhinitis[33], and asthma[34]. At one week of age, fewer bifidobacteria and greater staphylococci and clostridia correlate with a higher allergy risk. Probiotics' application may help in restoring healthy gut microbiota, and a favorable interaction between microbiota and host immune system despite dysbiosis. Furthermore, anti-allergic effects of probiotics coupled with their ability of strengthening the gut barrier function (the intestinal epithelial layer), may help the infants/children to cope with the negative impact of dysbiosis[25].

Role of gut and skin microbiome in regulating immune system

Microbiome plays an important role in the proper functioning of the immune system. Some results of poor microbiome infrastructure include[35]: (i) Poor digestion/frequent diarrhoeal symptoms; (ii) Poor immunity development and high susceptibility to infections; (iii) Antibiotic-associated dysbiosis; (iv) Lactose intolerance; (v) Atopic dermatitis; and (vi) Infantile Eczema.

Not just in the gut, but also in the skin, the microbiome plays a key role in 'Immune Regulation'. One trillion bacteria are present on the skin alone, out of the 100 trillion bacteria found in and on us. Skin microorganisms aid in the maintenance of the skin barrier. It aids wound healing and reduces oxidative damage by minimising allergen and UV radiation exposure.

Immunomodulatory effect of the probiotic is associated with the release of cytokines from the various immune cells including macrophages, lymphocytes, epithelial cells, granulocytes and others. The mechanisms of immune system modulation by probiotics can be either immune-stimulatory or it can be immune-regulatory[36]. The probiotics which are immunostimulatory have the ability to induce IL-12 production which leads to the activation of the natural killer cells and Th1 cells to act against various infections and to fight against cancer cells. Probiotics of this kind can also act against allergies. The probiotics having the immunoregulatory potential have the ability to induce the production of IL-10 and Treg cell, resulting in decreases in allergy, inflammatory responses, inflammatory bowel disease and autoimmune diseases[37]. Several effects of probiotic lactic acid bacteria are mediated via immune stimulation mainly by maintaining the balance between anti-inflammatory and pro-inflammatory cytokines. Various probiotic bacteria are known to down regulate the level of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and up regulate the level of anti- inflammatory cytokines such as IL-10[38]. Dysregulation of pro-inflammatory and anti-inflammatory cytokines results in the inflammatory disorders such as obesity, diabetes and metabolic syndrome leading to the state of chronic inflammation in the human gut and other tissues[39].

Probiotics and Atopic Dermatitis (AD)

Atopic dermatitis (AD) is defined by an aberrant skin barrier caused by several means (e.g., genetic, environmental and immunologic). AD may lead to the development of other atopic disorders such as food allergies, allergic rhinitis, and asthma. The atopic march can be triggered by epithelial dysfunction

linked to the microbiota and immunological dysregulation[32]. Specific allergens sensitise AD patients, and the skin serves as a route for allergen intake. Antigens stimulate the innate response by inducing cytokines in the epithelium. These processes work together to induce Th2 cells[28] from naive-T cells which then secrete IL-4, IL-5, IL-13 and IL-31 as well as produce IgE and activate basophils and mast cells. (Fig. 3)

Among various causes of AD such as hereditary, epidermal barrier dysfunction, environmental, or immunologic, the immunological root cause is the most critical. Additionally, AD patients show increased intestinal permeability and a defective ("leaky") gut barrier, enabling food allergen penetration and sensitization via the gut[32]. The immune system may be corrected with the help of a good site-specific, disease-specific, and strain-specific probiotics or with conventional medicines, the AD can be excellently treated/managed[40]. Exposure of atopic skin to a potential allergen increases the expression of thymic stromal lymphopoietin (TSLP), which is known to activate dendritic cells (DC) in the skin, which is the immunological cause of AD. The activated dendritic cell then drives the development of naive T cells into Th2 and Th17 cells, which are known as mediators of allergic inflammation and dermatological illnesses such as AD.

Probiotics based therapy may potentially be applied for the prevention and treatment of various skin diseases such as eczema, atopic dermatitis, acne, and allergic inflammation or hypersensitivity, and others[41]. Because probiotics regulate skin and stomach homeostasis, which are interconnected, they can be beneficial in the treatment of various skin diseases including especially the AD. Probiotics are known to be effective for the treatment of a variety of skin problems[41]. In order to combat AD, probiotics must be immunobiotic. Oral probiotics function by raising the population of regulatory T cells (Tregs) in the mesenteric lymph nodes, which can help to reduce allergic inflammation. Through lymphatic drainage, these Tregs could migrate to the site of inflammation on the skin, suppressing the Th2 and Th17-mediated allergic response in the skin while also lowering the expression of TSLP. As a result, the AD-related inflammation is kept under control. Thus, the probiotics serve as modulators of immune response.

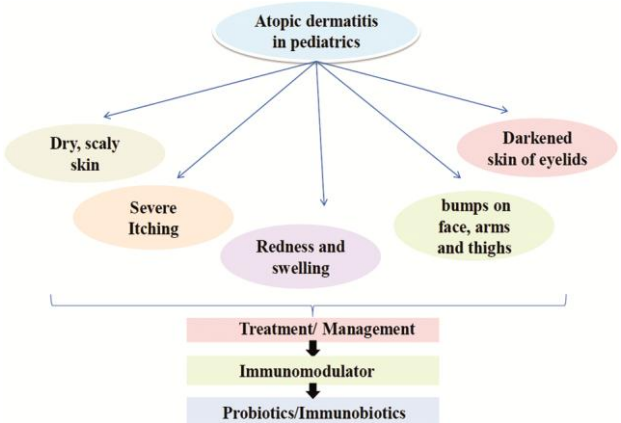

Fig. 3 — Atopic dermatitis in paediatrics and role of probiotics

Clinical trials study

Rising prevalence of infant and childhood allergic diseases especially the atopic dermatitis (AD) has been a cause of great concern. Alterations in the gut microbiota and consequential changes in the immune system regulation have been considered as one of the major reasons for increasing AD incidences[42]. Application of probiotics has been reported to play an important role in prevention and treatment of AD[42, 43, 44, 45].

Several clinical studies have indicated the potential of probiotics for managing ever-rising cases of AD. Meta-analysis of clinical trials involving prenatal and postnatal probiotics' application for prevention/ treatment of pediatric atopic dermatitis showed the mixed results, and a clear conclusion or interpretation could not be drawn[45]. Reduction in the Scoring Atopic Dermatitis (measurement of AD severity) by −6.64 and −8.56 points in the intergroup, and by −1.06, and −1.37 in the intragroup was not that convincing. Thus, the treatment trial was not clinically significant. In contrast, however[43] established the protective effects of probiotics for the treatment of infantile atopic dermatitis in a meta-analysis study of clinical trials. Double-blinded randomized clinical trials were examined to evaluate the efficacy of probiotics (*Lactobacillus* sp.) for the treatment of atopic dermatitis in infants. The overall pooled change in Scoring Atopic Dermatitis index (95% CI) was −5.71 ($P < 0.01$) while in subgroups it was −8.32. The study clearly showed the beneficial effects of probiotics' application for the treatment of atopic dermatitis[43]. Another meta-analysis of randomized controlled studies revealed that the prenatal or postnatal application of probiotics (*Lactobacillus* alone and combined *Lactobacillus* with *Bifidobacterium*) provides protection against AD occurrence ($P < 0.001$). Both general and high risk

population subgroups exhibited protection against AD development[46]. In contrast, however[47] could not establish the beneficial effect of probiotic administration for the treatment of atopic dermatitis especially in infants during meta-analysis of clinical trials.

Another meta-analysis of randomized clinical trials for prevention and treatment of atopic dermatitis in children by the application of mixture of probiotics and prebiotics (synbiotics) was executed [42]. The overall pooled change in SCORAD index was −6.56 (95% CI; P = .008), and heterogeneity was significant (P < 0.001). Subgroup analysis further suggested the significant beneficial effect of synbiotics for treating AD in children[42, 44] conducted a randomized, double-blind study (70 patients, 20 adults and 50 children) having moderate to severe AD. The participants were randomized into control arm (received only conventional therapy) and treatment arm (received conventional and probiotic therapy). SCORAD score analysis revealed that the score was considerably reduced in the case of treatment arm as compared to the control arm indicating the significant effect of probiotics application in the treatment arm. Thus, it was concluded that probiotics administration augments the conventional AD therapy quite effectively (in both adults and children) under moderate and severe condition of the disease[44].

In a recent study based on a post hoc analysis of a clinical trial[48] a correlation has been investigated between the changes in gut microbiota and response to probiotics treatment in AD patients. Administration of a mixed probiotic formulation (*Bifidobacterium* spp. and *Lacticaseibacillus* spp.) in children (4–17 years) with AD showed a significant improvement in SCORAD (scoring atopic dermatitis) index. However, gut microbiota diversity changes were insignificant even after consumption of probiotics. *Bacteroides*, *Ruminococcus*, and *Bifidobacterium* were significantly increased in the probiotic group while the *Faecalibacterium* decreased as compared to the placebo group. The highest presence of *Faecalibacterium* was significantly positively correlated with AD severity (SCORAD index), however, *Abyssivirga*, *Bifidobacterium*, and *Lactococcus* had an inverse correlation. It was concluded that consumption of the probiotic formulation modulates the gut microbiome with significant changes in genera Bacteroides and *Faecalibacterium*. In turn, the improvement in SCORAD correlates with a decrease in *Faecalibacterium* and an increase in *Bifidobacterium*, among others.

Different research reports though shows the protective effects of probiotics for the prevention and treatment of AD[49], however, the positive effects are dependent on several factors viz. type of probiotic strains, administration time, exposure duration, dosage and other parameters. However, despite several studies, strong evidence to establish the role of probiotics for treatment of AD is yet to be established[49].

Conclusion

The gut microbiome plays an important role in health and disease, and probiotics represent a promising modality for prophylactic and therapeutic interventions. In paediatrics, probiotics play a critical role in early immunological development. It aids the child in maintaining a healthy gut. A good probiotic boosts a child's immune system and ensures a higher level of wellness by protecting them from invading bacteria and viruses. Paediatric allergic diseases such as atopic dermatitis (AD) can be successfully managed by the intervention of probiotics. Differences in strain specificity, timing of administration, and length of the therapy are all contributing towards the beneficial effect of probiotics they impart to the host. However, further studies especially the clinical trials of the selected probiotic strains are necessary to establish the role of probiotics in modulating the allergic manifestations. Also the functional mechanism of probiotics in immune modulation, and for providing protective effects in AD or other diseases needs to be investigated.

Conflict of Interest

Authors declare no competing interests.

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