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Clinical Applications of Probiotics in Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) remains challenging to manage due to its chronic inflammatory nature, often requiring long-term treatment approaches. While current therapies provide relief for many patients, they can sometimes cause unwanted side effects. This has led to a growing interest in complementary treatment options. Probiotics have gained increasing attention due to their potential to modulate the gut-skin axis, restore microbial balance, and regulate immune responses. Recent clinical trials suggest probiotics may alleviate AD symptoms by correcting gut microbiota dysbiosis and enhancing immunoregulation. However, the efficacy of probiotics is influenced by several factors, including strain specificity, timing and duration of administration, and dosage. Although promising, current evidence remains insufficient to recommend probiotics as standard

treatment for AD. Significant variability in clinical study designs and outcomes highlights the need for more robust, well-controlled clinical trials. This review explores the underlying pathophysiological mechanisms of AD, focusing on the role of microbiota and immune dysfunction, and reviews recent probiotic interventions. It further emphasizes the need to identify specific bacterial strains and optimize probiotic formulations for therapeutic use. Understanding of the roles of gut microbiota in AD pathogenesis could pave the way for developing effective probiotic therapies as part of an integrated management strategy for AD.

Keywords: atopic dermatitis, microbiota dysbiosis, probiotics, immune responses; SDG 3 Good health and well-being

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with complex etiologies that involve genetic predisposition, environmental triggers, immune dysregulation, and psychological factors. Over 200 million people are affected globally, with more than 100 million adults and children respectively [1]. AD is more common in children than adults, making it one of the most prevalent skin conditions in young populations [2]. A systematic review indicated that Western European countries and other high-income regions such as the United Arab Emirates, Iceland, and the United States tend to have the highest prevalence of AD [1].

The clinical hallmarks of AD include xerosis, intense pruritus, and the appearance of eczematous lesions on the skin, which contribute to a cycle of persistent scratching, chronic skin barrier disruption, and secondary infections [3]. The relapsing-remitting course of AD frequently leads to sleep disturbances and significant impairment of quality of life, underscoring its profound psychosocial impact [4]. Current treatments for AD primarily involve topical corticosteroids, calcineurin inhibitors, and systemic immunosuppressants that focus on alleviating symptoms, reducing inflammation, and restoring the skin barrier [5]. However, despite the availability of these treatments, there is still a significant need for more effective long-term management strategies that provide sustained disease control, minimize clinical exacerbations, and ultimately enhance the quality of life for affected individuals.

Recent years have witnessed growing scientific interest in investigating the therapeutic potential of probiotics for AD. Probiotics such as *Lactobacillus rhamnosus*, *Bifidobacterium breve*, and *Lacticaseibacillus casei* exert their beneficial effects through

multiple mechanisms that influence both microbial ecology and immune function [6]. By enhancing intestinal barrier integrity through tight junction protein upregulation and mucin production, these live microorganisms help maintain gut homeostasis while preventing translocation of potential allergens [7]. Furthermore, probiotics modulate systemic immune responses by promoting regulatory T (Treg) cell differentiation and reducing pro-inflammatory cytokine production [8, 9]. This dual action on both the microbiome and host immunity may explain their potential to mitigate allergic sensitization and attenuate the severity of atopic dermatitis manifestations.

A significant gap exists in consolidated evidence regarding the clinical development of probiotics for AD. Interpreting disparate clinical trials to evaluate probiotic efficacy against AD is essential for deriving clinically relevant conclusions. This review provides insights into: (1) the key pathogenic mechanisms underlying AD, (2) the immunomodulatory potential of probiotics in AD management, and (3) recent clinical applications of probiotics for alleviating AD symptoms.

2. Immune dysregulation in AD

AD is characterized by a predominant Th2-skewed immune response, marked with increasing levels of IL-4, IL-5, and IL-13 cytokines, which drive the inflammatory processes and contribute to the chronic nature of the disease. These cytokines drive the chronic inflammatory process by inducing the differentiation and activation of myeloid and dendritic cells, activating B cells, promoting IgE class switching, and recruiting eosinophils. IL-4 exacerbates AD severity by reducing fibronectin production, which impairs wound healing in the dermis [10, 11]. Both IL-4 and IL-13 are known to disrupt the epidermal barrier by reducing the expression of barrier proteins such as filaggrin (FLG), loricrin (LOR), and involucrin (IVL) and impair lipid synthesis in keratinocytes [12]. They also inhibit key lipid-metabolizing enzymes such as fatty acid synthase and serine palmitoyltransferase, decreasing ceramide levels. Barrier proteins and essential lipids like ceramides, free fatty acids, and cholesterol are critical components that function as a barrier to trans-epidermal water loss, external irritants, and electrolyte loss from the skin [13]. While IL-5 is elevated in some AD patients, its direct role remains less defined compared to IL-4 and IL-13. Notably, Mepolizumab, an anti-IL-5 monoclonal antibody, failed to show clinical efficacy in patients with AD [14]. In contrast, Dupilumab, is an FDA-approved monoclonal antibody that blocks both IL-4 and IL-13, significantly improving the signs and symptoms in adults with moderate to severe AD [15].

Thymic stromal lymphopoietin (TSLP) and IL-31 are critical cytokines involved in AD that drive inflammation and pruritus, which are the key symptoms of AD [16]. TSLP, released by epithelial cells in response to environmental irritants, activates dendritic cells, which in turn stimulate the differentiation of naïve T cells into Th2 cells, amplifying the inflammatory cascade [17]. IL-31, secreted primarily by Th2 cells and mast cells, is a key mediator of pruritus. It directly activates sensory neurons via the IL-31 receptor (highly expressed on itch-sensing neurons), transmitting signals to the brain and perpetuating the itch-scratch cycle [18, 19]. The production of IL-31 is strongly upregulated by upstream cytokines, including IL-4, IL-13, and TSLP, leading to enhanced inflammatory response [20]. Nemolizumab, a monoclonal antibody that specifically targets IL-31 signaling, has demonstrated efficacy in reducing pruritus and improving skin lesions in Phase 2 and Phase 3 clinical trials [21]. Tralokinumab, a monoclonal antibody that selectively targets IL-13 and is FDA- and EMA-approved for treating moderate to severe AD [22].

Additionally, IL-22 and IL-17 significantly contribute to the pathogenesis of AD by compromising skin barrier integrity and promoting chronic inflammation. Elevated levels of these cytokines stimulate keratinocytes to release more pro-inflammatory cytokines, leading to the recruitment of neutrophils and other immune cells that sustain the inflammatory cascade. IL-17, produced by Th17 cells, is well recognized for its role in driving chronic inflammation in AD. While IL-22 is mainly secreted by Th22 cells, this cytokine can also be secreted by Th17 cells, Th1 cells, and innate lymphoid cells, exerting dual regulatory effects on keratinocytes [23]. IL-22 prevents the maturation of keratinocytes by down-regulating the expression of several genes involved in keratinocyte differentiation, such as keratin 1, keratin 10, IVL, epidermal FLG, profilaggrin and LOR [24-26]. Additionally, IL-22 stimulates the proliferation and migration of keratinocytes, which can lead to hyperkeratosis (thickening of the skin) seen in chronic stages of AD [27].

The involvement of these cytokines in the JAK/STAT pathway has made JAK inhibitors therapeutic agents for AD. Both FDA-approved JAK inhibitors, Upadacitinib and Abrocitinib exert their effects by selectively inhibiting JAK enzymes (JAK1, JAK2, JAK3 and TYK2), thereby reducing the downstream effects of multiple cytokines involved in the disease. This targeted inhibition leads to improved inflammation control, pruritus reduction, and restoration of skin barrier function. However, long-term safety monitoring remains crucial, given potential adverse effects such as increased risk of infections.

3. The Role of Gut Microbiome in AD

The gut microbiome plays a crucial role in regulating immune homeostasis, especially in early life. Dysbiosis of gut microbiome is characterized by a decrease abundance in beneficial commensals such as *Bifidobacterium* and *Lactobacillus*, along with an increase abundance of pathogenic bacteria such as *Clostridium* and *Staphylococcus*. Gut microbiome dysbiosis further reduces the production of key microbial metabolites, particularly short-chain fatty acids such as butyrate, which exert immunomodulatory effects. Consequently, gut microbiota dysbiosis is associated with the pathophysiology of several inflammatory diseases, such as AD, inflammatory bowel disease and systemic lupus erythematosus [28, 29]. For instance, enrichment of pathogenic sulfidogenic bacteria has been associated with the development of intestinal mucositis in patients [30].

Emerging evidence supports the concept of gut-skin axis, whereby gut microbiota composition significantly affects the skin integrity through immune and metabolic signaling [29]. With gastrointestinal tract being the primary site for pathogen invasion, it is particularly susceptible to intestinal colonization by pathogenic species [31]. Pathogenic colonization disrupts gut health, not only reducing the abundance of beneficial commensals and decreasing the microbiota diversity, but also by releasing toxins and other harmful compounds that damage the intestinal environment [31, 32].

Under healthy conditions, tight junction proteins maintain the integrity of gut epithelial barriers by sealing the paracellular space. However, in the condition where gut microbiota is disrupted, the tight junction proteins are disassembled, resulting in a “leaky gut”, which allows infiltration of pathogenic bacteria and their components, such as lipopolysaccharides, into circulation [31]. The systemic translocation of these microbial products triggers inflammation characterized by the exaggeration of Th2-mediated immune responses that impair skin barrier functions [31]. Additionally, the reduction in short-chain fatty acids production during gut microbiota dysbiosis limits the availability of immune signaling factors to travel in the systemic circulation, further contributing to immune dysregulation [31].

In the relevance of AD, gut dysbiosis is the key factor contributing to the immune dysregulation in AD. In fact, the severity of AD is positively correlated with the increase in leaky-gut-related biomarkers [33]. This provides the rationale for using probiotics as a strategy to restore gut microbiome dysbiosis in AD patients and ameliorate the disease.

4. Probiotic Modulation of Inflammatory Immune Responses in AD

Probiotics are non-pathogenic microorganisms that provide beneficial effects on the health of the host when administered in suitable quantities [34]. Multiple studies have shown that probiotic is a promising therapeutic strategy in several diseases such as depression, obsessive compulsive disorder and intestinal mucositis [30, 35, 36]. The most commonly used bacterial strains for probiotic products belong to the genera *Bifidobacterium* (e.g. *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium lactis*), *Lactobacillus* (e.g. *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*), *Lactococcus* and *Streptococcus* [37]. These probiotics, especially strains like *Lactobacillus* and *Bifidobacterium*, can restore immune balance by reducing levels of pro-inflammatory cytokines such as IL-4, IL-5, and IL-13.

For example, yogurt containing *Lactococcus lactis* 11/19-B1 has shown promising results in treating AD by suppressing Th1, Th2 and Th17 T cell subsets associated with inflammation, although Treg cell levels remained unchanged in the AD mouse model [38]. Similarly, *Lactobacillus plantarum* CJLP133 decreased IL-4 secretion and increased IFN-γ and IL-10 production in draining lymph node cells [39]. Clinical studies suggested that *Lactobacillus rhamnosus GG* ingestion alleviates clinical symptoms of AD in children with increased level of serum IL-10 concentrations, which suggest an increase in Treg activity towards immune regulation [40].

Furthermore, *Lacticaseibacillus paracasei* KBL382-treated mice showed decreased production of Th1, Th2, and Th17 cytokines, including key mediators such as TSLP, thymus, and activation-regulated chemokine, and macrophage-derived chemokine [41]. This was accompanied by increased production of the anti-inflammatory cytokine IL-10 and TGF-β in skin tissue and increased the proportion of Treg cells in mesenteric lymph nodes, which is associated with enhanced immune regulation.

Probiotics have been shown to influence various immune cells, including dendritic cells, macrophages, natural killer cells, and T and B cells. For example, *Bifidobacterium longum* can inhibit the activation of the NLRP3 inflammasome, a key component of the innate immune system, in macrophages, which is associated with the modulation of inflammation in conditions such as ulcerative colitis [42].

Furthermore, the modulation of the gut-skin axis by probiotics has been identified as a crucial factor in controlling the systemic immune response. A recent study has reported the probiotics-mediated activation of the intestinal signaling pathway in stabilizing the gut

microbiota and maintaining barrier function. *Lactobacillus rhamnosus GG* has been shown to activate farnesoid X receptor (FXR) signaling, a nuclear receptor critical for gut homeostasis [43]. Activation of FXR not only contributes to microbial balance and mucosal protection but may also influence systemic immune regulation, which is relevant in AD, where gut dysbiosis and immune dysregulation are key contributing factors. *Lactobacillus rhamnosus GG* can interact with the gut microbiota, influencing gut-associated lymphoid tissue (GALT), which plays a significant role in the development of AD [44]. Probiotic interventions have been shown to ameliorate intestinal mucositis caused by chemotherapy, suggesting their ability to restore mucosal integrity and reduce inflammatory damage across diverse clinical contexts [30]. Supplementation with *Bacillus subtilis* spores restored abnormal behavioral patterns in $Muc2^{+/+}$ mice by modulating mucosal immunity and reducing systemic inflammatory responses [45].

Lactobacillus paracasei KW3110 supplementation significantly reduced the development of AD-like skin lesions, accompanied by less mast cell infiltration and lower plasma IgE levels [46]. It also suppressed immediate hypersensitivity reactions and IL-4 mRNA expression in the auricular tissue, indicating its potential for modulating AD.

Additionally, certain probiotics enhance the production of antimicrobial peptides (AMPs) and the expression of genes and proteins involved in the tight junction signaling, which are essential for maintaining a robust skin barrier [47]. For example, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Bifidobacterium longum*, and *Bifidobacterium breve* produce AMPs that help regulate the skin microbiota by inhibiting the growth of *Staphylococcus aureus* [48], a common skin pathogen associated with AD.

All these findings highlight the diverse immunomodulatory mechanisms of probiotics in influencing both innate and adaptive immune responses relevant to atopic dermatitis. By reducing pro-inflammatory cytokines, promoting Treg cell activity, enhancing gut barrier integrity, and suppressing pathogenic skin microbes such as *Staphylococcus aureus*, probiotics demonstrate significant potential in reducing the symptoms of AD. Beyond dermatological conditions, probiotics have been widely investigated for their potential clinical applications, including in major depressive disorder [35], obsessive-compulsive disorder [36], and as adjunct therapies in Long COVID patients [49]. Probiotics have also been studied in psychiatric therapies, with antidepressants shown to impact the gut microbiome and depression outcomes [50]. These studies support the notion that probiotics can modulate host immunity, microbial balance, and systemic inflammation, underscoring their potential utility in chronic inflammatory conditions, such as AD. These findings provide a strong

foundation for exploring the clinical use of probiotics as a supportive treatment for managing AD. The following section will discuss current clinical evidence and practical applications of probiotics in AD treatment, including dosage strategies, strain-specific effects, and patient outcomes.

5. Application of Probiotics in AD

Probiotics have been shown to aid in improving AD symptoms through the alteration of the gut microbiome. Observational studies conducted regarding the microbiota composition in patients with AD show that bacterial species in the gut microbiome, such as *Bifidobacterium pseudocatenulatum*, *Faecalibacterium prausnitzii*, *Clostridium difficile*, and *Escherichia coli*, were found in excess, compared to healthy controls [51, 52]. Furthermore, studies have also shown that bacterial genera, including *Akkermansia*, *Bifidobacterium*, *Enterococcus*, *Bacteroides*, and *Ruminococcus*, were deficient in the microbiome of AD patients. Notably, studies have also implicated *Ruminococcus gnavus* in driving chronic inflammation linked to inflammatory bowel disease and irritable bowel syndrome [28]. Its enrichment in the gut microbiota of inflammatory disease patients suggests that targeted probiotic interventions aimed at suppressing or balancing this microbe may contribute to therapeutic benefits in AD. A summary of clinical studies involving probiotic interventions for AD, along with the specific components and major findings, is provided in **Table 1**.

5.1. Atopicina®

A real-life observational study conducted in Italy involved 144 AD patients with a mean age of 25.1 ± 17.6 years for 12 weeks [53]. The patients were given a concentration of not exceeding 2.5 x 10^9 active fluorescence units (AFU) of three bacterial strains, *Lactiplantibacillus plantarum* LP14 (DSM 33401), *Bifidobacterium animalis subsp. lactis* BS01 (LMG P-21384), and *Lacticaseibacillus rhamnosus* LR05 (DSM 19739) [53]. There was an improvement in the AD clinical symptoms, such as lesion severity, including reductions in itch, erythema, and edema-papules. This was reflected in an improvement of SCORAD index, a standardized scoring system to assess AD severity based on extent, intensity and subjective symptoms, which decreased from 11.3 at baseline to 2.8 at Week 12 in the probiotic group. The improvement in AD symptoms may be attributed to probiotic-induced modulation of the gut–skin axis, causing the restoration of microbiome balance and Th1/Th2 homeostasis [53]. Therefore, future studies should explore the mechanism of action and the changes in gut microbiomes affected by Atopicina® administration.

5.2. Capsule with probiotic formulation

A clinical study was conducted in Spain that involved 43 children aged 4 to 17 years with moderate AD for 12 weeks [54]. Children were divided into two groups, with one group being given a capsule containing 1 x 10^9 colony forming units (CFU) of 3 probiotics (*Bifidobacterium animalis subsp. lactis*, *Bifidobacterium longum*, and *Lacticaseibacillus casei*) in a 1:1:1 ratio, and the other group receiving a placebo capsule [54]. It was reported that the intake of probiotics mixture had successfully alleviated the AD-associated symptoms in the probiotic group after 12 weeks, with a reduction of 27.0 in SCORAD index as compared to baseline. This probiotics mixture can effectively reduce the use of topical steroids in ameliorating the AD-associated symptoms [54].

It was then discovered that, despite the overall microbiome diversity remained unchanged, the consumption of this probiotic mixture resulted in an improvement in gut microbiota dysbiosis in the probiotic group [54]. Noticeably, the abundance of members of genera *Bacteroides*, *Bifidobacterium*, and *Ruminococcus* increased significantly, whereas the abundance of the members of *Faecalibacterium,* particularly *Faecalibacterium prausnitzii* decreased in the gut microbiome [55]. Importantly, the increase of *Faecalibacterium* correlated positively with AD severity, while *Bifidobacterium* and *Lactococcus* showed an inverse correlation, as measured by the SCORAD index [55]. It was suggested that the increased abundance of *Bacteroides spp.* was associated with the increased abundance of specific exopolysaccharides (EPS)-producing bifidobacteria such as *Bifidobacterium animalis subsp. lactis* and *Bifidobacterium longum* strains that are present in the probiotic mixture [56]. *Bacteroides spp.* helped in the fermentation of complex sugars into short-chain fatty acids such as acetate, butyrate, formate and propionate, suggesting the involvement of butyrate in immunomodulatory effects [55, 56]. Although *Faecalibacterium prausnitzi* is commonly recognized as a beneficial butyrate producer, the decreased abundance of *Faecalibacterium prausnitzi* involved here suggested that it was either a non-butyrate producer strain, or other mechanisms of action were involved [57].

5.3. Lactobacillus acidophilus L-92

A 24-weeks clinical study conducted in Japan involved 50 AD patients aged 16 and above [58]. The patients were divided into two groups, with one group receiving a 20.7 mg tablet of heat-killed and dried *Lactobacillus acidophilus* 92 (L-92) daily, while the other group received a placebo tablet [58]. The results showed a significant decrease in SCORAD index in the probiotic group from 8 weeks onwards, with a reduction of 6.30 observed after 24 weeks compared to baseline [58].

Noticeably, there was also a reduction in IgE and eosinophils in the probiotic group from 8 weeks onwards, whereas the significant reduction in lactate dehydrogenase (LDH) was observed from 16 weeks onwards [58]. The reduction in LDH could directly correlate to the improvement in AD symptoms, as LDH is released when the skin barrier is disrupted due to scratching behaviour in AD patients [59]. Besides that, there was an increased concentration of IL-12 (p70) and TGF-β observed in the probiotic group after 24 weeks of treatment. It was suggested that the increase in TGF-β level can induce Foxp3 expression and facilitate the conversion of naïve Treg cells in the periphery into Treg cells that have immunosuppressive capabilities, which helped alleviate the AD-associated symptoms [60]. The increased production of IL-12 after the intake of *Lactobacillus acidophilus* can further activate Th1 and suppress the activity of Th2, which helps to restore Th1 and Th2 imbalance that causes the progression of AD [58].

5.4. Lacticaseibacillus casei DN-114001

A clinical research trial in Poland was conducted over 12 weeks, involving 40 medium-severe AD patients aged from 6 to 18 months [61]. Patients were divided into two groups, either with dietary supplementation with 1 x 10^9 CFU of *Lacticaseibacillus casei* DN-114001 daily, or a diet with a placebo of a bacterial carrier [61]. It was reported that there was a significant improvement in the SCORAD index of the probiotic group with a reduction of 12.1 after 12 weeks of treatment, suggesting the high efficacy of *Lacticaseibacillus casei* in alleviating the AD severity [61]. The SCORAD index continues to improve even after 5 months of treatment discontinuation, showing a further reduction of 6.4 points, indicating that *Lacticaseibacillus casei* can be a promising treatment for AD [61]. \Despite some gut microbiomes such as *Bacteroides*, *Enterococcus* and *Enterobacteriaceae* being reported to have no changes after probiotic treatment, there was a significant reduction in the abundance of pathogenic *Clostridium* in the probiotic group after 3 months of treatment [61]. It was also reported that there was a steady maintenance level of *Lactobacillus* and *Bifidobacterium* during the treatment period; however, a significant reduction in them was observed after 5 months of treatment discontinuation [61]. This further proved that *Lacticaseibacillus casei* managed to increase the beneficial strains of *Lactobacillus* and *Bifidobacterium*, and decrease the pathogenic strains of *Clostridium* in the gut, therefore reducing the severity of gut microbiota dysbiosis.

5.5. Lactobacillus salivarius LS01

A clinical trial conducted in Italy involved 38 adults aged from 18 to 46 years with moderate to severe atopic dermatitis for 16 weeks [62]. Patients were divided into two groups,

one group received a dose of 1 x 10^9 CFU of *Lactobacillus salivarius* in maltodextrin twice daily, while those in the placebo group received maltodextrin alone [62]. It was discovered that patients in the probiotic group had a significant improvement in their SCORAD index from 27.57 at baseline to 13.14 at Week 16, alongside a decrease in the abundance of *Staphylococci* and a slight increase in the abundance of *Bifidobacteria* in the gut microbiome [62]. These changes to the microbiome have been previously shown to correlate with the severity of AD; therefore, the gut microbiome shift helped in the restoration of a healthy gut microbiome [62]. There was a significant reduction in Th1 cytokines and Th1/Th2 ratio in placebo group, which indicates the increased severity of AD in the placebo group [62]. Despite a significant improvement in SCORAD index in the probiotic group, no changes were observed in the probiotic group on the level of cytokines such as IL-4, IL-5, IL-12 and IFN-γ, implying that *Lactobacillus salivarius* might instead influence the immune modulation by activating Treg cells [62].

5.6. Lactobacillus rhamnosus GG

A randomized, double-blind clinical study conducted in Italy involved 91 children aged 6 to 36 months with AD for 12 weeks [63]. Children were either given a capsule containing 1 x 10^{10} CFU of *Lactobacillus rhamnosus GG*, or an isocolor and isosmell placebo capsule [63]. It was discovered that probiotic supplementation led to significant improvement in AD symptoms, with a significant reduction in the SCORAD index of more than 8.7 was observed after 12-weeks treatment [63]. However, a higher number of subjects in the probiotic group achieved minimal clinically important differences (MCID) in AD symptoms compared to the placebo group (63% vs. 37.8%), indicating the probiotic group had a greater rate of subjects showing SCORAD improvement than the placebo group [63]. It was also noted that LGG successfully elicited a persistent effect on the reduction of rescue medication usage even after 4 weeks of treatment discontinuation [63].

In the study, the improvement of AD clinical symptoms is associated with a parallel shift of balance between microbiomes in the gut-skin axis [63]. There was a significant increase in *Akkermansia* and *Ruminococcus* and a decrease in inflammatory bacteria such as *Porphyromonadaceae*, *Enterobacteriaceae*, and *Haemophilus* in the gut after probiotic treatment [63]. It was observed that the increased butyrate level after probiotics treatment, due to the increase in the abundance of butyrate-producing bacteria, aided in reducing systemic inflammation and further alleviating AD-associated skin symptoms [63]. Furthermore, the restoration of skin health in the AD group was associated with the shift of balance in skin microbiomes, characterized by an increase in *Prevotella* and *Veillonella*, along with the

decrease in *Stenotrophomonas* [63]. This shift contrasts with typical skin microbiomes in AD patients, where they usually have low levels of *Prevotella* and *Veillonella* but high levels of *Stenotrophomonas* [64, 65].

5.7. Mixture of Lactobacilli

A total of 80 mild-to-moderate AD patients aged between 18 to 50 years were involved in a randomized, double-blinded 8-weeks clinical study conducted in Italy. The patients were randomly divided into two groups, with one group being given daily administration of a capsule of 3×10^9 CFU of *Lactobacillus plantarum* PBS067, *Lactobacillus reuteri* PBS072, *Lactobacillus rhamnosus* LRH020 in a 1:1:1 ratio, while another group received placebo capsule [66]. This study reported that the probiotic group had a reduction in SCORAD value from 20.9 at baseline to 13.7 after 8-weeks treatment, along with the improvement of skin health such as smoothness and moisturization, suggesting the beneficial traits of *Lactobacilli* mixture towards AD [66]. Furthermore, it was observed that the level of pro-inflammatory cytokines such as TNF-α, thymus and activation-regulated chemokine (TARC) and TSLP were significantly lowered in the probiotic group after 8 weeks of treatment [66].

This formulation was efficient in alleviating the AD clinical symptoms by improving the cellular antioxidant potential and modulating the inflammatory status [66]. The abundance of *Lactobacilli* in the gut microbiome significantly increased the production of active compounds that can travel to the whole parts of the body through circulation, further increasing the level of anti-inflammatory cytokines [66]. Additionally, the replenishment in skin health of AD patients in the probiotic group positively correlated with the abundance of *Lactobacilli* as a shift of skin microbiome essential in inhibiting the growth of AD-related skin pathogens (*Staphylococcus aureus*, *Staphylococcus epidermis*) and producing B-group vitamins for healthier skin maintenance [66].

5.8. Novel E3 probiotics formula

A clinical trial study involving 41 mild to severe AD patients aged between 18 to 73 years was conducted in Hong Kong for 8 weeks [67]. The patients were categorized into two groups based on the severity, with 17 patients in the mild group and 24 patients in the severe group. All patients were given a daily capsule of novel E3 probiotic formula containing 7 types of highly effective gastro-resistant probiotics including (*Lactobacillus rhamnosus GG*, *Lactobacillus acidophilus GKA7*, *Lactococcus lactis GKL2*, *Lactobacillus casei GKC1*, *Lactobacillus paracasei GKS6*, *Bifidobacterium bifidum GKB2*, and *Bifidobacterium lactis GKK2*) (not less than 2×10^{10} CFU/capsule at the time of production), postbiotic HK-

LP (heat-killed *Lactiplantibacillus plantarum*, 10 mg/capsule), and triple prebiotics containing inulin, Galacto-oligosaccharides (GOS) for 8 weeks [67]. After 8 weeks of treatment, 58.5% of AD patients (14 patients from the mild group and 10 from the severe group) showed an improvement in AD severity as measured by Eczema Area and Severity Index (EASI) [67]. Next, the improvement of AD severity was more prominent in mild AD patients (82.4%) as compared to that in severe AD patients (41.7%) [67]. The higher efficacy of the novel E3 probiotic formula in mild AD patients was likely due to the easier restoration of microbiota balance as mild AD patients had less severity in gut microbiota dysbiosis as compared to severe AD patients [67, 68].

The novel E3 probiotic formula, mainly composed of *Lactobacilli* and *Bifidobacterium*, successfully improved the diversity of gut microbiomes and caused a microbiota shift in gut microbiomes [67]. The successful colonization of *Lactobacilli* in the gut through oral ingestion aided in the increased abundance and colonization of other beneficial strains in the gut, such as *Clostridium*, *Fecalibacterium*, *Romboutsia*, and *Streptococcus*, and a reduction of pathogenic strains such as *Collinsella*, *Bifidobacterium*, *Fusicatenibacter*, and *Escherichia-Shigella* [67]. The microbiota restoration simultaneously reduced inflammation by producing short-chain fatty acids or reducing the expression of pro-inflammatory cytokines [67].

5.9. Probiatop®

A randomized clinical study conducted in Brazil involved 40 mild AD patients aged between 6 months and 19 years for six months treatment period [69]. The participants of the study were randomly divided into two groups, one group received a daily dose of 4×10^9 CFU of *Lactobacillus rhamnosus* HN001, *Lactobacillus acidophilus* NCFM, *Lactobacillus paracasei* Lcp-37, *Bifidobacterium lactis* HN019, while the other group received a placebo sachet [69]. A significant reduction in SCORAD index, with a reduction of 27.69 percentage points and an improvement of AD clinical symptoms was observed in the probiotic group after six months of treatment [69]. However, there was no significant difference reported on the inflammatory and tolerogenic cytokines in the serum, such as IgE, interferon, interleukin, and TNF-α [69]. This finding was inconsistent with a previous study by Yesilova *et al.* that tested on a similar probiotic mixture, as the dosage of probiotics administered in this study was lower than that [69, 70]. Additionally, the level of cytokines was measured in serum for this study while the level of cytokines measured in the study by Yesilova *et al.* was from the plasma [69, 70]. Therefore, the mechanism of action induced by Probiatop® to ameliorate the severity of AD remains unclear. Although the microbiota composition changes were not

elucidated in this study, the formula remains a promising probiotic mixture that can help in the improvement of AD-associated symptoms, as the SCORAD index reduction persisted even 3 months after treatment discontinuation [69].

5.10. SIM03

A 12-weeks clinical trial conducted in Hong Kong involved 20 children aged 1 to 5 years with eczema [71]. Children were given SIM03 twice a day, with each sachet containing a total of 1 x 10^9 CFU of two bacterial strains, *Bifidobacterium breve* and *Bifidobacterium bifidum* [71]. After three months, the consumption of SIM03 showed a significant improvement in the total SCORAD index, from 25.6 at the baseline to 14.6 [71].

Metagenomic sequencing of stool samples revealed relative abundance of *Bifidobacterium breve* and *Bifidobacterium bifidum* increased after one month of SIM03 consumption [71]. High levels of acetate and acetyl-CoA were observed, resulting from increased metabolic activity by *Bifidobacterium breve* and *Bifidobacterium bifidum*. These bacteria are involved in acetylene degradation, N-acetylneuraminate degradation and the superpathway of fermentation of menaquinol-8 biosynthesis III, leading to the production of acerate and acetyl-CoA, which act as the precursor for the synthesis of immunomodulatory butyrate. Additionally, the increase in *Bifidobacterium bifidum* was associated with better sleep quality and an improved pruritus score, while an increase in *Bifidobacterium breve* led to a better SCORAD index [71], suggesting that SIM03 is an effective treatment option for young children suffering from eczema.

Collectively, these clinical trials demonstrate that probiotics, particularly strains from the genera *Lactobacillus* and *Bifidobacterium*, show promising potential in alleviating AD symptoms across different age groups. Improvements in SCORAD index, skin barrier function, cytokine modulation, and gut microbiome composition highlight the therapeutic value of probiotics in managing AD. However, variability in strain specificity, dosage, treatment duration, and individual microbiota profiles suggests the need for more standardized and large-scale clinical trials to confirm their efficacy and treatment guidelines.

Table 1: Summary of probiotic interventions in AD clinical studies.

Name	Components	Dosage	Study Group/Age and gender	Findings	References
Atopicina®	3 probiotic strains *Bifidobacterium animalis subsp. lactis* BS01 *Lacticaseibacillus rhamnosus* LR05 *Lactiplantibacillus plantarum* LP14	A concentration not exceeding 2.5 x 10^9 AFU daily for 12 weeks	n=144 Atopicina®: n=144 Male=66, Female=78 Age group: 25.1 ± 17.6 years	- improvement of SCORAD index in probiotic group after 12 weeks - improvement in lesion severity, including reductions in itch, erythema, and edema-papules after treatment	[53]
Capsule with probiotic formulation	3 probiotic strains *Bifidobacterium animalis subsp. lactis* CECT 8145 *Bifidobacterium longum* CECT 7347 *Lacticaseibacillus casei* CECT 9104	1 x 10^9 CFU in a 1:1:1 ratio daily for 12 weeks	n=43 Capsule with probiotic: n=22 Placebo: n=21 Male=24, Female=26 Age group: 4-17 years	- improvement of SCORAD index in probiotic group after 12 weeks - increased abundance of bacterial genera *Bacteroides*, *Bifidobacterium*, and *Ruminococcus* - decreased abundance of *Faecalibacterium prausnitzii* - contributed to the fermentation of complex sugars into short chain fatty acids such as butyrate - reduced the level of pro-inflammatory cytokines	[54, 55]
***L. acidophilus* L-92**	*Lacticaseibacillus acidophilus* L-92	20.7 mg of heat-killed and dried *Lacticaseibacillus acidophilus* daily for 24 weeks	n=50 L-92: n=24 Placebo: n=26 Male=22, Female=28 Age group: 16-49 years	- improvement of SCORAD index in probiotic group after 24 weeks - reduction in IgE, eosinophils and LDH after 24-weeks - increased level of IL-12p70 and TGF-β and in the probiotic group	[58]
***L. casei* DN-114001**	*Lactobacillus casei* DN-114001	1 x 10^9 CFU daily for 12 weeks	n=40 *L. casei*: n=18 Placebo: n=22 Gender: not stated Age group: 6-18 months	- improvement of SCORAD index in probiotic group after 12 weeks - decreased abundance of *Clostridium* during treatment - decreased abundance of *Bifidobacteria* after treatment discontinuation	[61]

***L. salivarius* LS01**	*Lactobacillus salivarius* LS01	1 x 10^9 CFU twice daily for 16 weeks	n=38 *L. salivarius*: n=19 Placebo: n=19 Male=18; Female=20 Age group: 30.46 ± 1.33 years	- improvement of SCORAD index in probiotic group - decreased abundance in *Staphylococci* - significant decrease in Th1 cytokines and Th1/Th2 ratio in placebo patients	[62]
LGG	*Lacticaseibacillus rhamnosus GG*	1 x 10^{10} CFU daily for 12 weeks	n=91 LGG: n=46 Placebo: n=45 Male=64; Female=36 Age group: 6-36 months	- improvement of SCORAD index in probiotic group after 12 weeks -increase in fecal butyrate levels in probiotic group - Increased abundance in beneficial butyrate-producing bacteria, *Akkermansia* and *Ruminococcus* in gut, *Prevotella* and *Veillonella* on skin - decreased abundance in inflammatory associated bacteria, *Porphyromonadaceae*, *Enterobacteriaceae*, and *Haemophilus* in gut, *Stenotrophomonas* on skin	[63]
Mixture of *Lactobacilli*	3 probiotic strains *Lactobacillus plantarum* PBS067 *Lactobacillus reuteri* PBS072 *Lactobacillus rhamnosus* LRH020	A total of 3 x 10^9 CFU in a 1:1:1 daily ratio for 8 weeks	n=80 Probiotic mixture: n=40 Placebo: n=40 Male=12; Female=68 Age group: 18-50 years	- improvement of SCORAD index in probiotic group after 8 weeks - improvement of skin health in probiotic group - decreased TNF-α, TARC and TSLP in probiotic group - improve the cellular antioxidant potential by producing active compounds - inhibit the growth of skin pathogens *Staphylococcus aureus* and *Staphylococcus epidermis* - produce B-group vitamins for skin health	[66]

Novel E3 Probiotic Formula	7 probiotic strains *Lactobacillus rhamnosus* GG *Lactobacillus acidophilus* GKA7 *Lactococcus lactis* GKL2 *Lacticaseibacillus casei* GKC1 *Lactobacillus paracasei* GKS6 *Bifidobacterium bifidum* GKB2 *Bifidobacterium lactis* GKK2	A daily capsule of not less than 2 × 10^{10} CFU/capsule for 8 weeks	n=41 Mild AD: n=17 Severe AD: n=24 Male=16; Female=25 Age group: 18-73 years	- improvement of SCORAD index in both mild and severe AD groups after 8 weeks - increased abundance in beneficial strains *Lactobacilli*, *Clostridium*, *Fecalibacterium*, *Romboutsia*, and *Streptococcus* - decreased abundance in pathogenic strains *Collinsella*, *Bifidobacterium*, *Fusicatenibacter*, and *Escherichia-Shigella* - reduced inflammation by producing short-chain fatty acids - reduced the expression of pro-inflammatory cytokines	[67]
Probiatop®	4 probiotic strains *Lactobacillus rhamnosus* *Lactobacillus acidophilus* *Lactobacillus paracasei* *Bifidobacterium lactis*	A total of 4 x 10^9 CFU daily in 1:1:1:1 ratio for 24 weeks	n=40 Probiatop®: n=24 Placebo: n=16 Male=16; Female=24 Age group: 6 months-19 years	- improvement of SCORAD index in probiotic group after 6 months - SCORAD index reduction persisted after 3 months of treatment discontinuation	[69]
SIM03	2 probiotic strains *Bifidobacterium breve* *Bifidobacterium bifidum*	1 x 10^9 CFU twice daily for 12 weeks	n=20 SIM03: n=20 Male=8; Female=12 Age group: 1-5 years	- improvement of SCORAD index after 12 weeks - increased abundance of *Bifidobacterium breve* and *Bifidobacterium bifidum* in the probiotic group - Increased level of acetate and acetyl-CoA synthesis in the probiotic group	[71]

6. Discussion

Accumulating evidence supports the fact that gut microbiota dysbiosis plays a critical role in the pathogenesis of AD, signifying the importance of maintaining healthy, balanced gut microbiota for immune homeostasis and skin health. Despite promising preliminary results, translating these mechanisms into consistent clinical outcomes remains challenging due to significant heterogeneity in study designs, probiotic strain selection, dosages, and treatment duration.

This review paper compared the clinical efficacy of various probiotic formulations in AD patients. **Figure 1** demonstrates the reduction in SCORAD index across various probiotic formulations, with probiotic supplementation doses ranging from 1×10^{9} to 2×10^{10} CFU/day and treatment duration ranging from 8 to 24 weeks. The most notable improvement (a 27-point reduction in SCORAD) was observed with a capsule containing three probiotic strains, suggesting the multi-strain formulation may offer synergistic benefits.

Interestingly, single-strain formulations usually made up of *Lactobacillus* elicited a significant improvement of AD after treatment. Among single-strain formulation, *Lactobacillus salivarius* with 16-weeks treatment at 1×10^{9} CFU/day showed greater SCORAD reduction compared to *Lactobacillus casei* at 1×10^{9} CFU/day and *Lacticaseibacillus rhamnosus GG* at 2×10^{10} CFU/day, both given for 12 weeks. This suggests that longer treatment duration, rather than higher dosage may enhance clinical efficacy. Lower SCORAD reductions were also observed for other multi-strain formulations, including SIM03 and Atopicina®, despite high dosage, suggesting that clinical efficacy may not be dose-dependent, but may depend more on strain characteristics and formula composition.

An important finding is that probiotic treatments can modulate the baseline gut microbiota composition of AD patients. The most common and effective bacterial genera incorporated in probiotics formulation are *Bifidobacterium* and *Lactobacillus*. However, it remains challenging to determine which specific bacterial species or strains confer the highest clinical efficacy in treating AD due to the inconsistencies in study design. Clinical studies commonly reported that an increased abundance of beneficial bacteria, such as *Akkermansia*, *Bifidobacterium*, *Lactobacillus*, and *Ruminococcus*, along with a decreased abundance of pathogenic bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermis*, correlates with symptom improvement in AD patients. Moreover, probiotic intervention in AD has been linked to the immunomodulation effect, as evidenced by the significant improvement in the

Th1/Th2 ratio. This signifies the importance of probiotics in suppressing the exaggerated inflammatory responses in AD through the production of butyrate, which decreases pro-inflammatory cytokines and increases the anti-inflammatory cytokines. **Figure 2** illustrates key mechanisms of how probiotics modulate the intestinal immune system to restore gut health, enhance skin barrier integrity and regulate inflammatory cytokines.

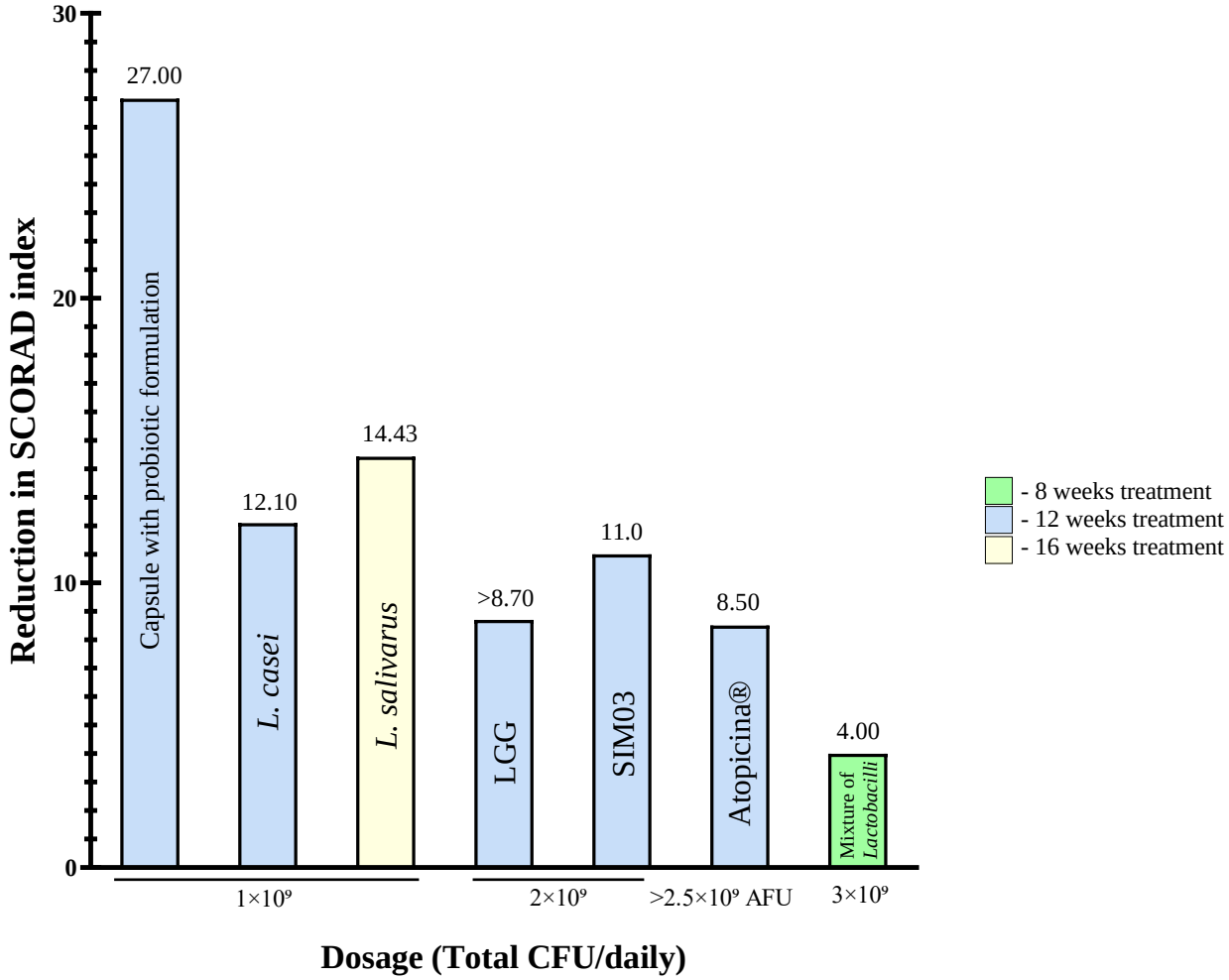

Figure 1. Reduction in SCORAD index following probiotic intervention in AD patients. Probiotic formulations without reported mean reduction in SCORAD index including *L. acidophilus* and Probiatop® were excluded from the analysis. CFU: colony forming unit; AFU: active fluorescence units.

The determinants affecting the effectiveness of a probiotic have long been a subject of discussion. Studies have suggested that multi-strain probiotic formulation resulted in greater reductions in SCORAD index [72, 73]. A meta-analysis by Jiang W, et al. showed that, although remission of AD can be achieved regardless of the type of probiotics offered, multi-strain probiotics were more effective, with a greater treatment effect observed compared to single-strain formulations [72]. In addition, studies with treatment durations longer than 8 weeks showed greater reductions in SCORAD values than those with shorter durations [72].

This finding is consistent with our review, where an 8-week treatment with a mixture of *Lactobacilli* resulted in the smallest reduction in SCORAD compared to other formulations supplemented for 12-16 weeks (Figure 1). These results support that a longer duration of probiotic supplementation may be necessary to enhance clinical improvement in AD symptoms.

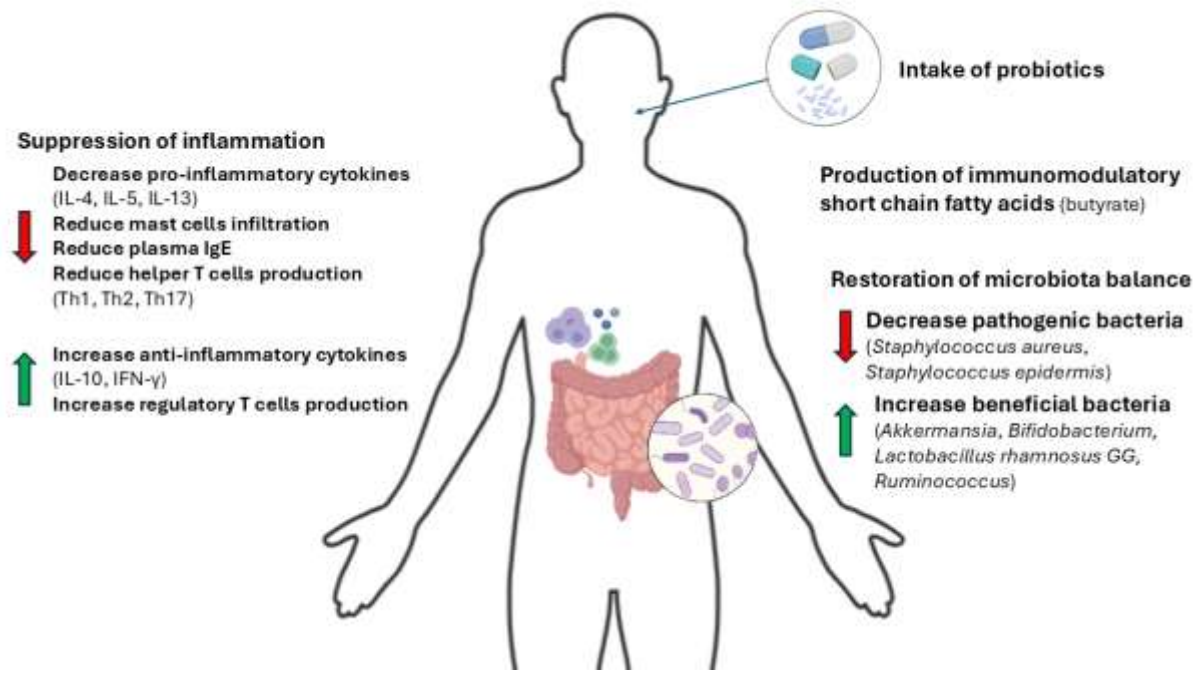

Figure 2. The mechanisms of probiotics in modulating gut microbiota and immune response in AD.

Another important observation is the favorable safety profile of probiotics, as no major adverse effects were reported across the reviewed clinical trials, supporting their suitability for long-term use as a complementary intervention alongside conventional treatment using topical steroids for AD patients. Nevertheless, probiotic strain specificity should be emphasized in the intervention of probiotics. Different strains within the same species may vary in term of the immunomodulatory effects.

Despite the studies reporting an inverse correlation between probiotics treatment and AD severity, current evidence remains insufficient in supporting probiotics as a standard treatment for AD at this stage. This is due to the significant variability across studies, including patient demographics, disease severity, treatment dosage and duration and probiotic strain specificity, making it hard to draw consistent and conclusive outcomes**.** Notably, patient factors such as age and genetic factors might influence the individual response to the probiotic treatment differently. For instance, multi-strain formulation composed of *Bifidobacterium* and *Lacticaseibacillus* appears to be the most promising

probiotic formulation in paediatric population, whereas single-strain probiotic of *Lactobacillus salivarius* has shown the most significant AD clinical improvement in adults. These findings highlight the importance of patient stratification in future studies to clearly investigate the differential effects of probiotics in children and adults, and to personalize the treatment strategies.

The heterogeneity observed in AD probiotic trials is paralleled by similar challenges reported in other diseases, such as psychiatric disorders, where probiotics have demonstrated benefits in depression management through modulation of the gut–brain–immune axis [74]. The variability in clinical outcomes may reflect complex interactions between host factors and microbiome modulation. In addition, reviews on next-generation probiotics highlight the potential of novel engineered or specifically selected strains to overcome current inconsistencies and achieve more reproducible clinical outcomes [75].

Disease severity is another key consideration in study designs, as it significantly affects the baseline gut microbiota composition and immune profile of AD patients, which in turn affects the response elicited after probiotics supplementation. This can be observed in the clinical studies using Novel E3 probiotic formula, where a more significant improvement was observed in the mild-AD group as compared to severe-AD group. However, most studies focused on patients with mild-AD, while the effect of various probiotic strains on severe-AD patients remains largely unexplored. This patient subgroup should be given greater attention, as they may benefit the most from this alternative therapeutic approach. Similar challenges are also reported across other chronic disorders, including autism spectrum disorder and Alzheimer's disease, where gut microbiota plays a central role in disease modulation [76, 77].

Additionally, there is also inconsistency in the clinical assessment tools used, such as SCORAD, EASI, and the validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) further complicates the evaluation and comparison of the effectiveness of probiotic treatments across various studies. Therefore, future studies should focus on the standardization of clinical study designs to investigate the long-term clinical effects and the optimal use of probiotics in AD management.

Overall, a promising solution lies in the potential of probiotics to alleviate AD symptoms through restoration of gut microbiota and modulation of host immune response. However, additional studies are needed to investigate the underlying molecular mechanisms, optimize probiotic formulations, determine effective therapeutic dosages, and assess long-term safety and effectiveness.

7. Conclusions

The effectiveness of probiotics in alleviating AD symptoms is influenced by several factors, including strain specificity, formulation type, dosage, and patient characteristics such as age, genetic factors and disease severity. Multi-strain formulations appear to be more effective than single-strain probiotics, as supported by both clinical trials and meta-analyses. While most studies demonstrated a reduction in SCORAD index and improvement in skin health, inconsistencies in study design, outcome measures, and microbiota analysis hinder direct comparisons and conclusive recommendations.

Despite these limitations, probiotics offer a promising, safe, and well-tolerated complementary approach for AD management through modulation of the gut-skin axis and host immunity. Future research should focus on identifying specific probiotic strains or combinations that can effectively restore gut microbiota balance and regulate immune responses in AD patients. These insights will be essential to guide the rational design of multi-strain probiotic formulations that combine several bacterial genera or species to achieve broader and more consistent therapeutic outcomes. Formulation should be optimized to target key mechanisms such as SCFA production, immune modulation, and skin barrier enhancement. Future clinical trials should also aim to determine optimal probiotic combinations and personalized approaches specific to disease severity and microbiota profiles.

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