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Review Article

Effect of Probiotics as Therapeutical and Preventive Modality for Atopic Dermatitis; Lessons from Clinical Trials

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ABSTRACT

Introduction: *Atopic dermatitis is a chronic relapsing inflammatory skin disease that can significantly impact patients' quality of life. Current therapy for atopic dermatitis is corticosteroids, calcineurin inhibitors, and immunosuppressants, but the recurrence of this disease is still reported, and their long-term use is vicious due to their immunosuppressive side effects; the need to discover a new modality that can be used as a therapeutical and preventive modality for atopic dermatitis. Probiotics have been well known for decades due to their various biological activities, including anti-inflammatory and immune-regulatory activity, that have many potential benefits for some skin diseases, including atopic dermatitis.* ***Method:*** *The method consisted of analyzing and evaluating relevant journal literature published within the past ten years.* ***Result****: Several clinical trials have proven the effectiveness of various species of Lactobacilli in improving clinical outcomes for children with atopic dermatitis. Clinical improvement of atopic dermatitis in children can be achieved not only through the administration of a single probiotic but also by combining different probiotic species.* ***Conclusions****: Based on those studies, probiotics are the potential therapeutical and preventive modality for atopic dermatitis and its primary possible mechanism.*

1. INTRODUCTION

Atopic Dermatitis is a chronic relapsing inflammatory skin disease with a frequently remitting and relapsing course, which manifests as eczema and pruritus and is mostly found in persons with atopic predisposition.[1,2] There are about 15-20% children and 1-3% adults live with atopic dermatitis around the world3. In Indonesia, atopic dermatitis is one of the top ten children's skin diseases and has affected 611 (23,67%) children.[4]

Atopic dermatitis can cause life quality impairment due to its symptoms such as erythematous eczema, crusting, lichenification, excoriation, exudation, and itching, that vary from mild and localized lesions, into severe and widespread lesions, leading to physical appearance disturbances which can follow by mental disorders, including decreased self-esteem, attention deficit, sleep disturbances, headache, hyperactivity, disturbed social life, and increased suicidal ideas.[2,3,5] In addition, serious emergency complications such as eczema herpeticum can also occur in untreated atopic dermatitis cases, resulting in severe sequelae of the eyes and meninx.[6]

The chronicity and recurrence of atopic dermatitis bring the importance of enlarging an effective therapeutic modality in controlling the symptoms and preventing the recurrence to enhance the quality of life for the patients.[1,2] Probiotics are non-pathogenic live microorganisms from various genera and species that has many advantages. Probiotics have been well-known and utilized for decades to treat several health problems, including diarrhea, infectious intestinal disease, and some inflammatory conditions such as inflammatory bowel disease and even atopic dermatitis.[7] Recently, the gut-skin axis has been discovered as a new potential approach for preventing and treating several skin diseases due to some similarity between the gut and the skin, providing the possible mechanism of probiotics benefit in treating several inflammatory skin diseases, including atopic dermatitis.[8] This review aims to provide clinical evidence of probiotics' therapeutical and preventive effects for atopic dermatitis and its immunoregulatory mechanism.

2. IMMUNOPATHOGENESIS OF ATOPIC DERMATITIS

Atopic dermatitis occurs due to a complex interplay of multiple factors, including genetics, skin barrier, skin microbiome, environment, neuroimmunology, and immune dysregulation. Cutaneous inflammation is a significant factor that plays a crucial role in the pathogenesis of atopic dermatitis.[9],[10] Dysregulated T-Helper-2 (Th2) will produce abundant pro-inflammatory cytokines such as IL-4, IL-5, and IL-13, influencing chemokine production, skin barrier dysfunction, antimicrobial peptides suppression, and inflammation. A combination of epidermal barrier dysfunction and environmental factors will stimulate the keratinocytes to produce IL-1β, IL-25, IL-33, Macrophage-Derived Chemokine (MDC), Thymus and Activation-Regulated Chemokine (TARC), and Thymic Stromal Lymphopoietin (TSLP), leading to activation of dendritic and Langerhans cells. After being activated, dendritic and Langerhans cells stimulate Th2 cells to produce IL-4, IL-5, IL-13, and IL-33, resulting in an alteration of keratinocytes proliferation, suppressed production of antimicrobial peptides (AMP) and increased inflammatory reaction. Th2-derived IL-5 will also drive the differentiation of B lymphocytes into IgE, while IL-4 and IL-13 together will activate eosinophil and trigger it to be degranulated, causing an itchy sensation in the patients. Conversely, Th2 can also induce pruritus by secreting IL-31, which produces brain-derived natriuretic peptides. Meanwhile, in chronic

atopic dermatitis, there are high amounts of Th17, Th22, and Th1, which produce IL-17, IL-22, and Interferon-γ (IFN-γ) that contribute to abnormal keratinocyte proliferation and differentiation and increased keratinocyte apoptosis. [9–12]

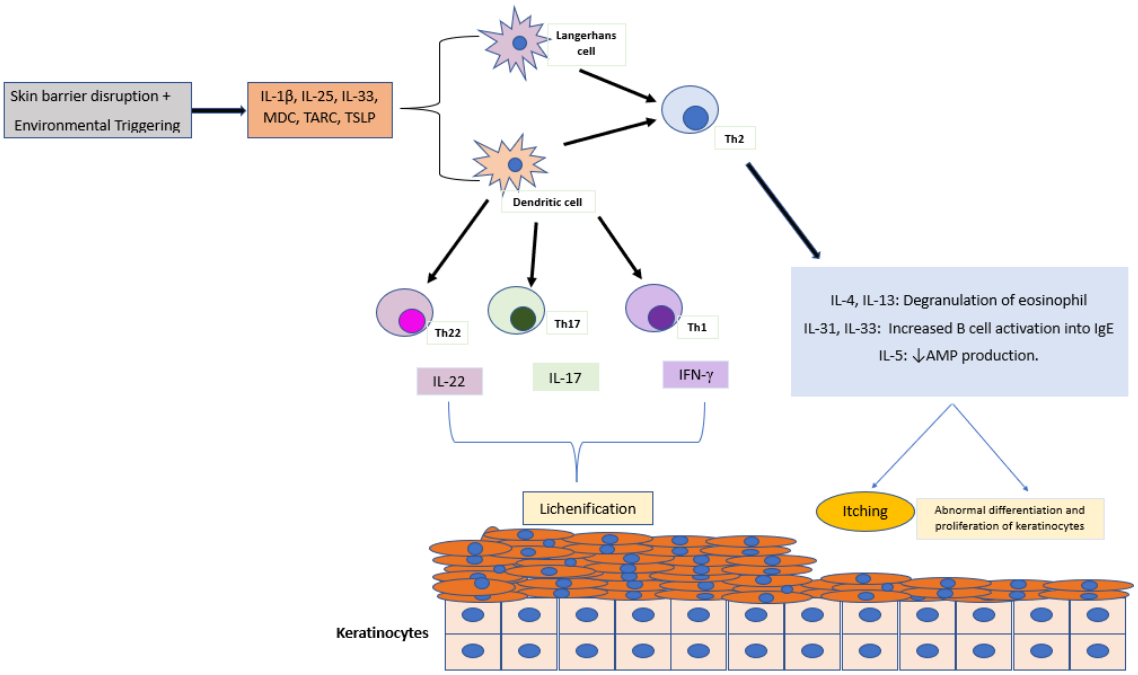

Fig 1. Immuno-pathogenesis of atopic dermatitis[1,9–12]

3. CLINICAL IMPROVEMENT OF ATOPIC DERMATITIS WITH PROBIOTICS SUPPLEMENTATION

Several clinical studies were conducted to determine probiotics' effect in improving patients' clinical conditions with atopic dermatitis. Various species of microbiota were involved in the clinical trials, but Bifidobacteria and Lactobacilli were the two most common bacteria used in the experiments. [13–28]

Several clinical trials have proven the effectiveness of various species of Lactobacilli in improving clinical outcomes for children with atopic dermatitis.[13,14,21–25] In a study by Niccoli et al., it was found that administration of Lactobacillus salivarius (L. salivarius) LS01 to 43 children with atopic dermatitis aged 0-11 years for 16 weeks was effective in improving the clinical symptoms of atopic dermatitis, indicated by reduced Scoring of Atopic Dermatitis (SCORAD) and itch index.[13] Significant clinical outcomes were also found by L. plantarum supplementation for atopic dermatitis children compared to placebo in two randomized double-blinded placebo-controlled trials by Han et al., and Prakoeswara et al.[14,21] Two clinical experiments revealed the ability of L. rhamnosus in providing better clinical outcome for children with atopic dermatitis.[22,23] In a randomized, double-masked placebo-controlled trial by Wu et al., therapy with L. rhamnosus for 8 weeks was found to demote SCORAD score more significantly compared to the placebo group, followed by more considerable decrease in surface area, intensity, and subjective symptoms in the L. rhamnosus group.[22] Jeong et al. also observed a Significantly more remarkable change in SCORAD total score (p=0.0283) in the children who were given oral L. rhamnosus at week 12 compared to the placebo group.[23] Another randomized,

double-blind, placebo-controlled trial was performed by Yan et al. to evaluate the benefit of L. paracasei supplementation for infancy atopic dermatitis. The result showed a more remarkable change in SCORAD value in the L. paracasei group than in the placebo group in the 16th week of the treatment.[24] Ahn et al. also performed a randomized double-blinded placebo-controlled study in order to investigate the effect of treatment with L. pentosus on pediatric atopic dermatitis and found significantly better clinical outcomes, which were evidenced by significantly lower SCORAD value in the children receiving L. pentosus compared to the group that receiving placebo.[25]

Clinical improvement of atopic dermatitis in children can be achieved not only through the administration of a single probiotic but also by combining different probiotic species.[26–28] The effect of L. paracasei and L. fermentum combination in atopic dermatitis was studied by Wang et al. in a randomized, prospective, double-blind, placebo-controlled trial which showed lower SCORAD and DLQI value in the group that received probiotics than in the group that received placebo, indicating the better clinical outcome achieved by supplementation of the combination probiotics.[26] The Benefit of another mixture of Lactobacilli for atopic dermatitis children was studied by Cukrowska et al. in a multicenter randomized, double-blind placebo-controlled study where atopic dermatitis children under 2 years old with SCORAD scores more than ten were randomized into the probiotic group and placebo group. The probiotic group received a combination of L. rhamnosus and L. casei, while the placebo group was given maltodextrin. The study result showed a higher reduction in SCORAD score from the baseline in the probiotic group compared to the placebo group. The number of participants who showed clinical improvement during the third month of intervention and the ninth month of follow-up was also higher in the probiotic group than in the placebo group.[28] Meanwhile, clinical improvement in children with atopic dermatitis was also observed in combination therapy between Bifidobacterium lactis (B. lactis), B. longum, and L. casei. Lopez et al. conducted a randomized, double-masked placebo-controlled trial where the children from the probiotic group were treated with an oral combination of B. lactis, B. longum, and L. casei for 12 weeks, while the placebo group was given maltodextrin orally. By the end of the study, the probiotic group exhibited a significantly greater reduction in the SCORAD index.[27]

The clinical benefits of probiotics for atopic dermatitis were also studied in the adult population.[15–17] In A randomized, double-blind, placebo-controlled trial conducted by Drago et al., administering L. salivarius LS01 twice daily for 16 weeks reduced the SCORAD value significantly ($p<0.001$) compared to the placebo.[15] Better clinical outcome of atopic dermatitis adults was also found with the treatment of other Lactobacillus in a study by Inoue et al. A total of 49 adults with atopic dermatitis were randomized into two groups, L-92 group treated with L. acidophilus L-92, and placebo group that given maltose, starch, vegetable oil, and fat. The study was performed for 8 weeks. At the end of the study, the significant change ($p<0.01$) of SCORAD and its components, including the subjective symptoms, eczema intensity, and area, was reported in the L-92 group. A more significant proportion of respondents that achieved clinical improvement was found in the L-92 group (70.8%) compared to the placebo (44%).[16] Besides Lactobacilli, better clinical outcome for adults with atopic dermatitis was also reported with probiotic therapy with Bifidobacterium animalis subs lactis in a multicenter randomized, double-blind, placebo-controlled study by Matsumoto et al. At

the end of the study, in the 8th week, a significantly better clinical outcome ($p<0.05$) was reported from the probiotic group, including improvement of itch, hurt sensation, sensitive skin symptoms, and tiredness.[17]

Clinical improvement of adults with atopic dermatitis was also reported in several clinical trials using a combination of probiotics species.[18–20] In a randomized, double-blind, placebo-controlled study by Iemoli et al., the clinical improvement of adults with atopic dermatitis was exhibited by a significant reduction of SCORAD index ($p<0.001$) and DLQI ($p=0.024$) in the group that ingested a combination of L. salivarius LS01 and B. breve BR03 compared to the placebo group.[18] Another probiotic therapy with L. plantarum and B. bifidum probiotics was also found to improve the clinical symptoms of adults with atopic dermatitis. Some patients treated with the probiotics experienced a decreased SCORAD index compared to the placebo and oligose group.[19] In a separate clinical study, Drago et al. observed improved clinical outcomes in adults with atopic dermatitis following a one-month treatment with a combination of Lactobacillus salivarius LS01 and Streptococcus thermophilus ST10. This improvement was evidenced by a significantly reduced SCORAD index ($p < 0.0001$) compared to the placebo group.[20]

4. PROBIOTICS AS PREVENTIVE MODALITY FOR ATOPIC DERMATITIS

Several studies have explored the ability of probiotics to prevent atopic dermatitis, as well as their ability to improve the clinical outcome of atopic dermatitis, especially in the pediatric population.[29–31] In a randomized controlled trial, Wickens et al. revealed that administration of either L. rhamnosus HN001 or B. animalis subsp lactis from 35 weeks gestation until 2 years of the infants age was successful to lower the risk of atopic eczema at age of 4 years in the high-risk infants (27.1% in L. rhamnosus group and 33.3% in B. animalis subsp lactis group) compared to placebo group (39.3%).29 Bifidobacterial also exhibited a protective effect against atopic dermatitis development. In a clinical study by Enomoto et al., supplementation of B. longum BB536 and B. breve M-16V combination from 4 weeks before the expected delivery until the first sixth month of the infants was able to reduce the occurrence of atopic dermatitis significantly ($p=0.033$) compared to placebo.[30] Another clinical trial by Marlow et al. also found that L. rhamnosus HN001 and B. animalis subsp lactis HN019 were able to reduce the risk of atopic dermatitis. However, L. rhamnosus exhibited a major reduction compared to B. animalis subsp lactis.[31]

5. IMMUNOREGULATORY EFFECTS OF PROBIOTICS IN ATOPIC DERMATITIS

Atopic dermatitis occurs due to various immune dysregulation involving variable types of leucocytes with their inflammatory cytokines and mediators, both in the acute and chronic phases of the disease. Th2 plays a significant role in the acute phase of atopic dermatitis. Dysfunction of the skin barrier and several environmental triggering factors will provoke the production of certain mediators from epithelial cells that will trigger the dendritic cell to activate the Th2. Various cytokines, including IL4-, IL-5, and IL-13, are then secreted by activated Th2, leading to impaired differentiation of keratinocytes, reduced antimicrobial peptides, and itching.[1,9,10] Several clinical trials have revealed probiotics' ability to regulate Th2-related pro-inflammatory cytokines in the acute phase of atopic dermatitis.[16,19,21,26,32] In a randomized placebo-controlled trial by Wang et al., serum IL-4 levels were found to be reduced after 3 months of treatment with

Lactobacillus plantarum and Lactobacillus fermentum.[26] Another randomized placebo-control study conducted by Fang et al also found downregulation of IL-4 and IL-13 by oral treatment with B. bifidum or L. plantarum.[19] Decreased levels of IL-4 were also observed after 12 weeks of therapy with l. plantarum alone in several randomized, double-masked, placebo-controlled studies.[21,32] Meanwhile, Inoue et al. also stated the ability of L. acidophilus L-92 to downregulate IL-4 in a randomized, double-blind, placebo-controlled study of adults with atopic dermatitis.[16]

In the chronic phase of atopic dermatitis, Th17, Th22, and Th1, together with the cytokines they produce, play a pivotal role in modulating the abnormality of keratinocytes. Th17 and Th22 will release IL-17 and IL-22, which contribute to abnormal proliferation and differentiation of the keratinocytes, while Th1 secretes IFN-γ, leading to apoptosis of the keratinocytes. [1,9,10] Some species of probiotics were found to attenuate certain T-helper and cytokines, which is crucial in the chronic phase of atopic dermatitis. In a randomized placebo-controlled trial by Ro et al., a reduced proportion of Th22 was found in the group that received a combination of L. rhamnosus, B. animalis subsp lactis, and L. acidophilus compared to the placebo.[33] Meanwhile, the level of IFN- γ that plays a role in the chronic phase of atopic dermatitis produced by Th1 and is responsible for keratinocyte apoptosis is significantly reduced after administration of L. plantarum in two randomized, double-blind placebo-controlled studies by either Prakoeswara et al. ($p=0.006$) and Han et al. ($p<0.01$).[21,32] Reduced proportion and activity of several T-cells subsets related to the chronic phase of atopic dermatitis can be linked to the finding that shows the increased T-regulatory cell in cases of probiotics supplementation of L. salivarius and B. breve in a clinical study conducted by Iemoli et al.18 Besides controlling inflammation by downregulating specific pro-inflammatory cells and cytokines; probiotics was also discovered to upregulate IL-10 which is an anti-inflammatory cytokine, as well as found by Fang et al. in a clinical study using B. bifidum and L. plantarum.[19]

Pruritus is a prominent feature of atopic dermatitis, and it is associated with impaired quality of life due to sleep disturbances, attention deficit, and hyperactivity.[3] Several pathways are related to cause itching in atopic dermatitis. The release of IL-5 from Th2 will lead to activation of eosinophil. Meanwhile, IL-4 and IL-13 produced by Th2 will promote B-lymphocyte differentiation into IgE. Increased levels of eosinophil and IgE and the Th2-type cytokines trigger an itchy sensation in atopic dermatitis.[9–12] Several clinical studies have discovered the capability of some species of probiotics to regulate eosinophil and IgE in atopic dermatitis patients.[16,17,21,23,32] In the randomized, double-masked, placebo-controlled trial by Han et al., a significantly lower eosinophil count was detected after 12 weeks of therapy with L. plantarum.[32] The suppressing effect of eosinophil was also found in another species of Lactobacillus. Jeong et al. explored the effect of L. rhamnosus on eosinophil in atopic dermatitis patients in a randomized, double-blind, placebo-controlled study, where 12 weeks of administration of L. rhamnosus was able to decrease the eosinophil count.[23] Furthermore, Prakoeswara et al. also found a decreased IgE with 12 weeks of supplementation of L. plantarum.[21] In another study by Inoue et al., lower IgE was also observed by oral administration of L. acidophilus for 8 weeks.[16] In addition, another antipruritic mechanism of probiotics in atopic dermatitis was also discovered by Matsumoto et al., which shows the ability of the oral administration of B. animalis subsp lactis to increase the levels of kynurenic acid, an antipruritic and antinociceptive metabolite.[17]

Table 1. Clinical and Immunoregulatory Benefits of Various Probiotics Species for Atopic Dermatitis

Probiotics Species	Outcome	Population	References
L. salivarius	Reduced SCORAD	Children	Niccoli et al[13]
		Adult	Drago et al[15]
	Reduced Itch Index	Children	Niccoli et al[13]
L. plantarum	Decreased SCORAD, Lower IFN-γ, Lower IL-4	Children	Han et al[14], Prakoeswara et al[21]
	Reduced eosinophil	Children	Han et al[14]
	Reduced IgE	Children	Prakoeswara et al[21]
L. acidophillus	Reduced SCORAD; improvement of subjective symptoms, eczema intensity and area; lower IL-4 and IgE	Adult	Inoue et al[16]
L. rhamnosus	Reduced SCORAD	Children	Wu et al[22], Jeong et al[23]
	Lower eosinophil	Children	Jeong et al[23]
	Decreased risk of atopic eczema	Children	Wickens et al[29]
L. paracasei	Reduced SCORAD	Infant	Yan et al[24]
L. pentosus	Reduced SCORAD	Children	Ahn et al[25]
B. animalis subps. lactis	Improvement of itchy and hurt sensation, sensitive skin symptoms, and tiredness; increased anti-pruritic substance (kynurenic acid)	Adult	Matsumoto et al[17]
L. salivarius and B. breve	Reduced SCORAD, DLQI, and increased T-Regulatory cell	Adult	Iemoli et al[18]
L. salivarius and S. thermophilus	Reduced SCORAD	Adult	Drago et al[20]
L. paracasei and L. fermentum	Reduced SCORAD, DLQI, Decreased IL-4 and IgE	Children	Wang et al[26]
B. lactis, B. longum, and L. casei	Reduced SCORAD	Children	Lopez et al[27]
B. bifidum or L. plantarum	Reduced SCORAD, Lower IL-4 and IL-13, and Increased IL-10	Adult	Fang et al[19]
L. casei and L. rhamnosus	Reduced SCORAD	Children	Cukrowska et al[28]
B. longum and B. breve	Decreased occurrence of atopic dermatitis	Children	Enomoto et al[30]
L. rhamnosus or B. animalis subsp lactis	Decreased the risk of atopic dermatitis	Children	Marlow et al[31]
L. rhamnosus and B. animalis subsp lactis	Lower Th22 cell	Infant	RØ et al[33]

6. CONCLUSION

Probiotics, with their various species, effectively improve the clinical outcomes for patients with atopic dermatitis, both in pediatric and adult populations. Besides improving the clinical symptoms, probiotics can also prevent the occurrence of atopic dermatitis, especially in pediatric patients. Clinical improvement and preventive properties of probiotics in atopic dermatitis were supported by their ability to regulate several leucocytes and their cytokines that play essential roles in atopic dermatitis, including Th22, eosinophil, IgE, IL-4, IL-13, and IFN-γ. Probiotics can be used as a therapeutical approach to improve the clinical outcomes for atopic dermatitis patients and even prevent the occurrence of atopic dermatitis in high-risk populations. Further research is still needed to determine the best species and combination of probiotics for treating atopic dermatitis.

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.