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Systematic Review

The use of gut microbiota probiotics in the management of atopic dermatitis in children: systematic review

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ABSTRACT

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases, affecting more than 20% of the population at some time in their lives. Currently, corticosteroids are generally used for the treatment of AD, although these drugs have the potential to cause more serious side effects. Objective of the study was to find out the role of probiotics in the management of atopic dermatitis in children through a review of previous research. A PubMed search was carried out with the keywords 'atopic dermatitis' and 'probiotic' from databases for the last 10 years (2014-2023). Researchers present the results in narrative form and in table form. A total of 10 articles were included in this study. The research comes from several different countries with the research time being from 2017 to 2022. Each study describes the author, year of study, total sample, type of probiotic, duration of treatment, results and side effects. Giving probiotics to pediatric patients with atopic dermatitis has an impact on reducing SCORAD in evaluation after 2-3 months (8-12 weeks). No significant side effects were found in the included studies.

Keywords: Probiotics, Microbes, Atopic dermatitis, Children

INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases, affecting more than 20% of the population at some time in their lives. This is usually the first manifestation of atopic disease in infancy. Although the pathogenic mechanisms underlying AD are still not completely understood, two of its hallmarks are immune dysfunction resulting in IgE sensitization to allergens and damage to the epithelial barrier.[1-3]

T-helper type 2 (Th2) immune responses result in an immunological imbalance that can lead to the development of AD; increased IgE and interleukins are important in this process. The integrity of the skin barrier also makes an important contribution to the development of AD. The main clinical symptoms associated with AD are erythema, exudate, excoriation, lichenification, edema, and papules.[3] Currently, corticosteroids are generally used for the treatment of AD, although these drugs have the potential to cause more serious side effects. Therefore, there is an urgent need to explore new alternative ways to prevent and treat AD. This study aims to determine the role of probiotics in the management of atopic dermatitis in children through a review of previous research.

METHODS

Search strategy and eligibility criteria

A PubMed search was carried out with the keywords 'atopic dermatitis' and 'probiotic' from databases for the last 10 years (2014-2023). Other keywords used to assist the search were 'Probiotic, 'gut microbe', 'gut microbiota', 'randomized control trial', 'medication', 'atopic dermatitis, 'treatment', 'children, 'atopic dermatitis management', 'supplementation' 'oral administration probiotic' 'atopic eczema' 'childhood'. All articles identified by this search were reviewed if the article text was available in English. The inclusion criteria used were accessible full papers,

articles in English, using a randomized controlled trial method, researched within the last 10 years (2014 to 2023). Exclusion criteria were papers in the form of abstracts or preliminary trials, studies in the form of reviews, cross-sectional, cohort, or case reports, and studies on animals or tests on cells. A total of 663 articles were found in searches using the keywords mentioned previously. Based on these results, the author carried out data collection and obtained 25 references that met the previous inclusion criteria. A total of 638 references were excluded, of which 567 articles were not randomized controlled trials, and 59 articles were published more than 10 years, and 13 articles were research conducted on adults (more than 18 years). Of the 24 references, 11 articles were not found in the full paper, so they were not included in the research analysis.

Data synthesis and analysis

Each case: author, year of study, total sample, type of probiotic, duration of treatment and side effects are tabulated in Table 1. All times are presented in 'years' including year of study and age of sample. In the results section, the article is further divided based on the type of probiotic given to the patient, duration of therapy and side effects. Researchers present the results in narrative form and in table form.

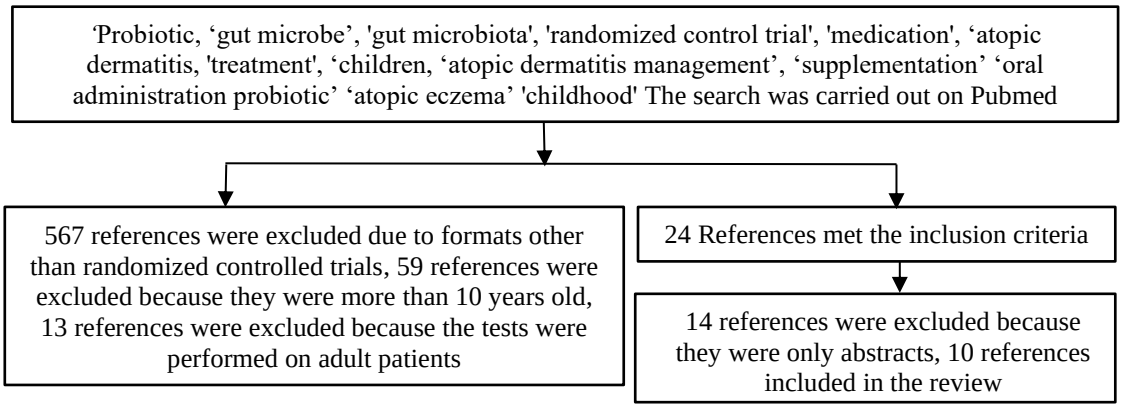

Figure 1: Reference review and selection flowchart.

RESULTS

A total of 10 articles were included in this study. This research comes from several different countries, namely South Korea, Iran, Indonesia, China, Taiwan, Poland, Italy, and Spain.[4-13] The research period was from 2017 to 2022. The data for each study is depicted in Table 1. All studies were randomized clinical trials that examined types of probiotics in children with atopic dermatitis (AD).

Function of probiotics in atopic dermatitis

Probiotics have several functions based on previous research. Rather et al mention *Lactobacillus you said* proBio65 isolated from kimchi was found to have immunomodulatory or immunosuppressive effects by producing immunomodulatory substances. This function was shown to have an effect on reducing allergen-induced skin inflammation by reducing serum levels of IgE and interleukin 4 based on animal models. Wu et al stated that probiotics were shown to be well tolerated, and resulted in gut microbiota colonization and beneficial clinical effects in AD, indicating that probiotic supplementation may be a useful adjunctive therapy for treating AD.

Effectiveness of probiotics against atopic dermatitis

Rather et al stated that giving probiotics was effective in treating atopic dermatitis based on a decrease in SCORAD and improvement in skin cells as assessed by an increase in sebum cells and skin moisture after 12 weeks. Research by Aldaghi et al, Wu et al, Jeong et al, Yan et al, and Navarro-Lopez et al also showed reduced SCORAD results in synbiotic administration after 2 months of treatment compared with controls. In the research of Yan et al and Carucci et al, apart from a reduction in SCORAD, there was also a reduction in itching complaints and an increase in quality of life with infants' dermatitis quality of life index. Based on research by Cukrowska, it was found that there was no significant difference in SCORAD after 9 months but this research was only carried out on patients under 2 years of age. Studies by Carucci et al and Navarro-Lopez et al also added a reduction in the need for topical steroids in patients given probiotics.

Side effects of probiotics

Side effects from administering probiotics still show conflicting results in several studies. Research by Rather et al and Carucci et al stated that no allergic reactions or significant side effects were found when administering probiotics for 12 weeks. Similar results were also found in studies by Wu et al, Jeong et al, and Navarro-Lopez et al. In research by Aldaghi et al, mild abdominal pain was found in 4 cases of synbiotic administration. Research by Yan et al found that there were side effects in the form of: napkin dermatitis associated with probiotic administration. Research by Ahn et al and Prakoeswa et al did not mention any side effects from administering probiotics.

Table 1: Research, sample size, research methods, type of treatment, duration, side effects, research results.

S. no	Author, year, and place	Total sample	Age	Method	Types of probio-tics	Durat-ion of therapy	Side effects	Results
1	Rather et al, 2021, South Korea[4]	90	3-18 years	Education randomized double-blind, placebo-controlled in group *L. sakei* proBio65 live cells, *L. sakei* proBio65 dead cells, or placebo	*L. sakei* proBio65	12 weeks	There were no serious reactions related to clinical trial products	Skor total SCORAD (SCORing atopic dermatitis) decreased in the live cell (p=0.0015) and dead cell (p=0.0017) groups from baseline after 12 weeks, whereas there was no significant change in the placebo group when compared with baseline. Skin sebum content increased in both the live cell group (p<0.0001) and the dead cell group (p<0.0001), indicating a potential increase in skin barrier function. Current data show a positive improvement in the reduction of atopic dermatitis (AD) symptoms after oral administration *L. sakei* proBio65 whether in living or non-living form
2	Aldaghi et al, 2022, Iran[7]	81	1-24 months	Education double blind, randomized clinical trial in children comparing the administration of synbiotics, vitamin D3, and usual care	By Symbiote (PediLact ®)	2 months	Treatment was well tolerated among the three groups and there were no untoward side effects; only four episodes of mild abdominal pain in the synbiotic group were observed	Based on multivariable regression analysis, the mean SCOARD score decreased drastically in the synbiotic (bxy: -13.90, 95% CI, -20.99, -6.81; p<0.001) and vitamin D3 (bxy: -12.38, 95% CI, -19.33) groups -5.43; p=0.001) group compared with the control group at the end of two months. In addition, there was no significant difference regarding the mean SCOARD scores between the vitamin D3 group and the synbiotic group (p=0.661)
3	Wu et al., 2017, China[9]	66	4-48 months	Two-center, double-blind, randomized, and placebo-controlled study with two parallel groups to evaluate the efficacy and safety profile of *L. rhamnosus* in children aged 4–48 months with atopic dermatitis	Com-Prob (*L. rhamnosus*)	2 months	No side effects were found in each group	The mean change in SCORAD from baseline at Week 8 was −21.69±16.56 in the *L. rhamnosus* group and −12.35±12.82 in the placebo group for the intention-to-treat population (p=0.014). For the per-protocol population, the mean change in SCORAD from baseline was −23.20±15.24 in the *L. rhamnosus* group and −12.35±12.82 in the placebo group (p=0.003). Significant differences were demonstrated between groups at week 8 in terms of intensity in both the intent-to-treat and per-protocol populations.
4	Prakoeswa et al, 2017, Indonesia	22	2-10 years	Randomized double-blind placebo controlled trial comparing probiotics *L. plants* IS-	*L. plants* IS-10506	2 months	Not written down	SCORAD and IL-4, IFN-γ, and IL-17 levels were significantly lower in the probiotic group than in the placebo group, whereas IgE levels did not change significantly. The Foxp3+ to IL-10 ratio

Continued.

S. no	Author, year, and place	Total sample	Age	Method	Types of probio-tics	Durat-ion of therapy	Side effects	Results
	(Surabaya)[8]			10506 and placebo in pediatric patients with mild and moderate AD, assessed using SCORAD				was significantly higher in the probiotic group than in the placebo group. Supplementation with the probiotic *L. plantarum* IS-10506 offers a potential treatment for children with AD
5	Jeong et al, 2020, South Korea[5]	66	1-12 years	A study randomized, double-blind, placebo-controlled parallel conducted at the Department of Pediatrics, Ajou University. One hundred children aged 1–12 years diagnosed with moderate AD, defined as a SCORAD score between 25 and 50, were included in the study	*Lactobacillus rhamnosus* IDCC 3201 tyndallizate (RHT3201)	12 weeks	All were common conditions that were temporary in children or caused by concurrent allergic diseases, which were "certainly unrelated" to the medications studied	The change in SCORAD total score at 12 weeks (primary outcome) from baseline was significantly greater in the RHT3201 group (−13.89±10.05) compared with the control group (−8.37±9.95). Eosinophil cationic protein (ECP) and interleukin (IL)-31 levels showed a decreasing trend in the RHT3201 group and a significant reduction in subgroup analysis in AD for ≥50 months
6	Yan et al, 2019, Taiwan[10]	126	4-30 months	Multicenter clinical trials, randomized, double-blind, parallel-group, placebo-controlled it was conducted at five centers in Taiwan from July 2014 to September 2016. Infants aged 4–30 months at the time of inclusion, with moderate or severe AD and SCORAD ≥20	GM080 (*L. paracasei*)	16 weeks	Only one of the AEs in the placebo group was classified as related (probably) to treatment. 12.5% of subjects in the GM080 group and 17.7% in the placebo group experienced AEs related to diaper rash or AD	SCORAD, objective SCORAD, itching, and IDQOL decreased significantly ($p<0.001$) during the treatment period in both treatment groups. A slight decrease (ns) was noted in TEWL of lesioned and unaffected skin and CCL17 levels
7	Ahn et al, 2020, South Korea[6]	82	2-13 years	Study double-blinded, placebo-controlled, randomized. Subjects with mild to moderate AD (2–13 years) recruited from the Department of Pediatrics, Korea University Anam Hospital between January and September 2017 were included	*Lactobacillus pentosus* from kimchi	12 weeks	Not mentioned	Clinical severity decreased significantly over time in both groups, with no significant differences between the two groups. In both groups, there were no significant differences in cytokine levels, microbial diversity, or relative abundance of gut microbiota at week 12 compared with corresponding baseline values. The mean subjective score of SCORAD index after intervention in the probiotic group was significantly lower than that in the placebo group in IgE-sensitized AD ($p=0.019$)

Continued.

S. no	Author, year, and place	Total sample	Age	Method	Types of probio-tics	Durat-ion of therapy	Side effects	Results
8	Cukrowska et al, 2021, Poland[11]	101	<2 years	This is a study randomized, double-blind, placebo-controlled, parallel-group, which was conducted at four centers in Poland	*Lactobacillus casei* and *Lactobacillus rhamnosus* (Latopic®)	9 months	Reports of side effects were sporadic (in both study groups) most often involving changes in stool consistency	The percentage of children showing improvement was significantly higher in the probiotic group than in the placebo group (odds ratio (OR) 2.56; 95% confidence interval (CI) 1.13–5.8; p=0.012) after three months. Probiotics induced improvements in SCORAD especially in allergen-sensitized patients (OR 6.03; 95% CI 1.85-19.67, p=0.001), but this positive effect was not seen after nine months
9	Carucci et al, 2022, Italy[12]	91	6-36 months	The ProPAD study was a randomized, double-blind, placebo-controlled trial aimed at evaluating the efficacy of 12-week treatment with the probiotic LGG in children with AD aged 6–36 months.	Lacticasei bacillus rhamnosus GG	12 weeks	No side effects were reported during the study period.	The rate of subjects achieving the minimum clinically important difference (MCID) at week 12 and week 16 was higher in the LGG Group ($p<0.05$), and remained higher at week 16 ($p<0.05$). Number of days without rescue medication was higher in group LGG. IDQOL increased at week 12 in the LGG group ($p<0.05$). Beneficial modulation of the gut and skin microbiome was only observed in group LGG patients
10	Navarro-Lopez et al, 2018, Spanish[13]	50	4-17 years	A 12-week randomized, double-blind, placebo-controlled intervention trial, from March to June 2016, at the Centro Dermatológico Estético de Alicante outpatient hospital, Alicante, Spain. Observers were blind to patient grouping.	*Bifidobacterium lactis* CECT 8145, *B is long* CECT 7347, dan Lactobacillus casei CECT 9104	12 weeks	There were no relevant side effects associated with the use of the drug or placebo	After 12 weeks of follow-up, the mean decrease in the SCORAD index in the probiotic group was 19.2 points greater than in the control group (mean difference, −19.2; 95% CI, −15.0 to −23.4). Relatively, we observed changes of −83% (95% CI, −95% to −70%) in the probiotic group and −24% (95% CI, −36% to −11%) in the placebo group ($p<0.001$). A significant reduction in the use of topical steroids to treat flares was found in the probiotic group (161 of 2084 patient days [7.7%]) compared with the control group (220 of 2032 patient days [10.8%]; odds ratio, 0.63 ; 95% CI, 0.51 to 0.78)

DISCUSSION

Atopic dermatitis is a homeostatic disorder caused by an imbalance in the Th1-Th2 response due to exposure to allergens, causing mild to severe clinical symptoms. This imbalance process begins in the neonatal phase. The neonatal immune system shifts toward a Th2 response, and exposure to a variety of common allergens after birth causes the maturation of Th1, Th2, Th17, and Treg cells. Gut microbiota plays an important role in mucosal immune system signaling, and gut dysbiosis alters immune regulation and precedes allergic diseases.[12] Changes in the gut microbiota resulting from probiotic administration are expected to be an effective way to prevent the occurrence of AD. However, the therapeutic effect on AD is still inconclusive.[6] Carucci et al mentioned the potential involvement of parallel modulation of gut and skin microbiomes, as also suggested by others. 36 intestinal and skin dysbiosis has been described in patients with AD. The possibility of modulating intestinal colonization through probiotic supplementation in childhood has long been proposed.

The explanation regarding probiotics for atopic dermatitis is still widely debated. There is some evidence that intestinal inflammation and impaired intestinal barrier function are involved in the pathogenesis of AD. Probiotics have been shown in a number of studies to relieve intestinal inflammation. Species *Lactobacillus* showed the most potent inhibitory activity against growth *Staphylococcus aureus*, which was found to be one of the causes of AD exacerbation. Therefore, probiotics may have a beneficial role in the treatment of AD due to their inhibitory effect on *S. Aureus*.[9]

Research by Prakoeswa et al shows that probiotic therapy improves the clinical symptoms of AD. Symptom scores decreased significantly whereas total IgE did not; This may be caused by a pathological process in the form of an allergic reaction in target cells where histamine receptors H1, H2, and H3 mediate the production of mast cell degranulation. Allergic reactions occur due to interactions between allergens, mast cells, and specific IgE allergens that result in mast cell degranulation.[8]

Another study by Cukrowska et al in children less than 2 years old with the average age in both study groups was under nine months. This age range was chosen based on the assumption that probiotics are most effective during early development, when the composition of the gut microbiota begins to take shape (this process is usually completed by 2-3 years of age) and the immune system is being programmed for the future.[11] Therefore, similar results were found after 9 months in both groups in this study.

The increase in SCORAD scores and all symptoms noted in studies by previous studies can be caused by various reasons such as the dose and strain of synbiotic product used, duration of intervention, characteristics of study subjects, differences in study design, and sample size.

In the study by Rather et al, a slight but significant increase in skin moisture was observed in the dead cell group, whereas a higher prevalence and significant increase in skin sebum content was observed in the live and dead cell groups. It is known that in AD patients, lipid deficiency on the skin surface significantly affects the skin barrier, causing the appearance of dry skin. It has also been reported that skin sebum content is significantly lower in AD patients compared with healthy controls. Sebum plays an important role in providing lubrication to the skin to protect against friction and trap moisture; it also delivers antimicrobial lipids and antioxidants to the skin's surface. Impaired skin barrier function will weaken the skin's defences, thereby increasing the skin's vulnerability to invasion by pathogens and allergens.[4,14]

CONCLUSION

Based on the findings in this systematic review, it was found that probiotics provide immunomodulation or immunosuppression by producing immunomodulatory substances. Giving probiotics to pediatric patients with atopic dermatitis had an impact on reducing SCORAD in an evaluation after 2-3 months (8-12 weeks) but the results were found to be insignificant after an evaluation of 9 months. No significant side effects were found in the included studies so it could be a therapeutic recommendation for administering probiotics to children with atopic dermatitis.

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REFERENCES

1. D'Auria E, Panelli S, Lunardon L, Pajoro M, Paradiso L, Beretta S, et al. Rice flour fermented with Lactobacillus paracasei CBA L74 in the treatment of atopic dermatitis in infants: A randomized, double-blind, placebo- controlled trial. Pharmacol Res. 2021;163.
2. Wang IJ, Wang JY. Children with atopic dermatitis show clinical improvement after Lactobacillus exposure. Clin Exp Allergy. 2015;45(4):779-87.
3. Fang Z, Lu W, Zhao J, Zhang H, Qian L, Wang Q, et al. Probiotics modulate the gut microbiota composition and immune responses in patients with atopic dermatitis: a pilot study. Eur J Nutr. 2020;59(5):2119-30.
4. Rather IA, Kim BC, Lew LC, Cha SK, Lee JH, Nam GJ, et al. Oral Administration of Live and Dead Cells of Lactobacillus sakei proBio65 Alleviated Atopic Dermatitis in Children and Adolescents: a Randomized, Double-Blind, and Placebo-Controlled Study. Probiotics Antimicrob Proteins. 2021;13(2):315-26.

5. Jeong K, Kim M, Jeon SA, Kim YH, Lee S. A randomized trial of Lactobacillus rhamnosus IDCC 3201 tyndallizate (RHT3201) for treating atopic dermatitis. Pediatr Allergy Immunol. 2020;31(7):783-92.
6. Ahn SH, Yoon W, Lee SY, Shin HS, Lim MY, Nam Y Do, et al. Effects of Lactobacillus pentosus in Children with Allergen-Sensitized Atopic Dermatitis. J Korean Med Sci. 2020;35(18).
7. Aldaghi M, Tehrani H, Karrabi M, Abadi FS, Sahebkar M. The effect of multistrain synbiotic and vitamin D3 supplements on the severity of atopic dermatitis among infants under 1 year of age: a double-blind, randomized clinical trial study. J Dermatolog Treat. 2022;33(2):812-7.
8. Prakoeswa CRS, Herwanto N, Prameswari R, Astari L, Sawitri S, Hidayati AN, et al. Lactobacillus plantarum IS-10506 supplementation reduced SCORAD in children with atopic dermatitis. Benef Microbes. 2017;8(5):833-40.
9. Wu YJ, Wu WF, Hung CW, Ku MS, Liao PF, Sun HL, et al. Evaluation of efficacy and safety of Lactobacillus rhamnosus in children aged 4-48 months with atopic dermatitis: An 8-week, double-blind, randomized, placebo-controlled study. J Microbiol Immunol Infect. 2017;50(5):684-92.
10. Yan DC, Hung CH, Sy LB, Lue KH, Shih IH, Yang CY, et al. A Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Oral Administration of a Heat-Treated Lactobacillus paracasei Supplement in Infants with Atopic Dermatitis Receiving Topical Corticosteroid Therapy. Skin Pharmacol Physiol. 2019;32(4):201-11.
11. Cukrowska B, Ceregra A, Maciorkowska E, Surowska B, Zegadło-Mylik MA, Konopka E, et al. The Effectiveness of Probiotic Lactobacillus rhamnosus and Lactobacillus casei Strains in Children with Atopic Dermatitis and Cow's Milk Protein Allergy: A Multicenter, Randomized, Double Blind, Placebo Controlled Study. Nutrients. 2021;13(4).
12. Carucci L, Nocerino R, Paparo L, De Filippis F, Coppola S, Giglio V, et al. Therapeutic effects elicited by the probiotic Lacticaseibacillus rhamnosus GG in children with atopic dermatitis. The results of the ProPAD trial. Pediatr Allergy Immunol. 2022;33(8).
13. Navarro-Lopez V, Ramirez-Bosca A, Ramon-Vidal D, Ruzafa-Costas B, Genoves-Martinez S, Chenoll-Cuadros E, et al. Effect of Oral Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical Steroids in Young Patients With Moderate Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2018;154(1):37-43.
14. Shi VY, Leo M, Hassoun L, Chahal DS, Maibach HI, Sivamani RK. Role of sebaceous glands in inflammatory dermatoses. J Am Acad Dermatol. 2015;73(5):856-63.

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