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Efficacy of Probiotic Supplementation for the Treatment of Pediatric Atopic Dermatitis. A Systematic Review and Meta-analysis: Assessment of SCORAD Index, Serum Immunoglobulin-E, and Interleukin-4 Parameters

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ABSTRACT

Background: Atopic Dermatitis (AD) is a chronic, recurring inflammatory skin disease affecting 15-30% of childhood population. Its standard management entails the right skin care, avoidance of triggers, and topical corticosteroid treatment. However, long term topical corticosteroid usage produces significant side effects. Pathogenesis of AD is mainly influenced by the response of one of the main immune cells, type Th2. In AD, a change of intestinal microbiome composition takes place, which influences gut-skin axis. Probiotics are living organisms, which when consumed regularly and in adequate amount, promotes health benefits for the host. Probiotics modulate the immune system and cytokine production, causing a balance in Th1 and Th2 immune responses. This also regulates intestinal and skin microbiome homeostasis in AD. **Methods:** Online database research is conducted in Pubmed-MEDLINE, Cochrane Library, ProQuest, EBSCOhost, and Scopus. Seven articles are included in qualitative analysis (n = 701), between which four (n = 473) are included in quantitative analysis. **Results:** SCORAD Index meta-analysis with random effect model shows heterogenity test of I2 = 73% (p=0.003). Standardized mean difference is found to be -0.42 with CI 95%, -0.76 to -0.08. This shows a significant decrease in SCORAD Index in probiotic group, compared to placebo (p=0.01). Meta-analysis of serum IgE with fixed effect model shows heterogenity test of I2 = 0% (p=0.71). The standardized mean difference of IgE is -0.03 with CI 95%, -0.24 to 0.17. This shows a non-significant decrease on IgE serum in probiotic group, compared to placebo (p=0.74). Meta-analysis of serum IL-4 with fixed effect model shows heterogenity test of I2 = 0% (p=0.76). The standardized mean difference of IL-4 is -0.16, with CI 95%, -0.35 to 0.02. The result shows a greater but statistically non-significant decrease of serum IL-4 in probiotic group, compared to placebo (p=0.09). **Conclusion:** Probiotic supplementation may reduce AD lesion severity, but has no effect on the patient's immunoserological profile.

Keywords: Atopic dermatitis, probiotic, SCORAD, Immunoglobulin-E, Interleukin-4

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Introduction

Atopic dermatitis (AD) is a chronic, recurring inflammatory skin disease with a very complex pathogenesis mechanism. Its incidence has risen significantly in the last few years. AD is found most frequently in childhood, with prevalence around 15-30%. Its ethiopathogenesis consists of mutation of the *Filaggrin* gene, immune dysregulation, as well as skin and intestinal microbiome imbalance. These mechanisms cause disruption in skin and gut mucose barrier integrity, which allows allergens to pass through, provokes the immune system, and triggers the development of AD lesions. AD is mainly caused by Th2 immune response.[1–3]

Skin barrier dysfunction caused by *Filaggrin* (FLG) mutation lowers the production of *Natural Moisturizing Factor* (NMF), hence affecting skin hydration and pH. Immune dysregulation causes a decrease in T-regulators function, making an imbalance of Th1 and Th2 immune responses. Dysbiosis of skin and gut microbiome is known to affect each other in the gut-skin axis. Dysbiosis of skin microbiota is shown by an increase of *Staphylococcus aureus* population, which produces many virulence factors such as α-toxin and exogen protease enzymes, disturbing the keratinocyte integrity. Meanwhile, gut dysbiosis is marked by a decreased number of lactic acid bacteria, which are the commensal organisms in the gut, responsible of producing metabolites that inhibit pathogenic bacteria growth and regulating normal flora ecosystem in the digestive system. [4–6]

Management of AD includes the right skin care, avoidance of triggers, and topical corticosteroid treatment. Long term topical corticosteroid usage produces significant side effects, therefore an effective adjuvant therapy is needed to control AD progression and minimize corticosteroid side effects. [7]

Probiotics as immunomodulators work through balancing Th1 and Th2 immune responses by inducing T-Reg cells activity in mesenteric lymph nodes. T-Reg cells increases Th1 immune response by secreting TGF-β dan IL-10, which are anti-inflammatory cytokines, thus subduing Th2 immune responses. [8]

Probiotics modulates and balances microbiota compositions by producing the metabolite short chain fatty acid (SCFA), Antimicrobial Peptide (AMP), and lactic acid. SCFA inhibits the profileration, migration, and adhesion of inflammatory cells, as well as the production of pro-inflammatory cytokines. Bacteriocins (AMP) work directly to inhibit pathogenic bateria growth. Lactic acid causes a decreased pH, creating a hostile ecosystem for the pathogens. These mechanisms are probiotics function for returning balance of gut microbiome, thus making an optimal intestinal barrier integrity and preventing pathogen and toxin invasion from the digestive system into the skin and causing inflammation on the skin. [4,9]

Material and Methods

Literature Search

The following databases were accessed until data analysis: Pubmed-MEDLINE, Cochrane Library, ProQuest, EBSCOhost, and Scopus. The reference list, conference proceedings, and researchers in the field of eligible studies were searched to identify additional studies.

The following MeSH terms were used for searching: ”Atopic dermatitis or atopic eczema” AND ”Probiotic or probiotics” AND ”children”. The literature search was performed by three reviewers independently using PRISMA flow diagram 2009. Differences in opinion were resolved between all reviewers to reach a consensus.

Inclusion criteria were: clinical trials with randomization method, children with AD based on Hanifin Radjka criteria, age range 1-18 years old, using *Lactobacillus sp. / Bifidobacterium sp.* probiotic supplementation, control group receiving placebo, and outcomes of SCORAD Index, Immunoglobulin E and Interleukin-4 levels.

Exclusion criteria: studies involving subject using oral corticosteroid / immunosuppresive

agents / antibiotics / other probiotics or food supplement containing other probiotics in the research, case report studies, case series, letters, systematic review, and literature review.

Study Selection

Three reviewers conducted the study selection independently. Duplicate articles were removed. Title and abstract, as well as full-text were reviewed for eligibility using the predefined inclusion and exclusion criteria. Differences in opinion were resolved between all reviewers to reach a consensus.

Data Extraction

Data extraction was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only. Differences in opinion during data extraction were resolved between all reviewers, and the consensus was reached.

Assessment of Risk of Bias

Risk of bias assessments were performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only and The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.

Data Synthesis

Meta-analysis of difference in weighted mean was conducted using *The Cochrane systematic review software (Review Manager (RevMan) Version 5.4.1, 2020)*. Where data was not available to enable pooling, a descriptive synthesis was performed.

Results

The search for research articles was conducted based on the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart (Figure 1)

Study Characteristics

The studies were conducted in Korea (57,14%, n=4), followed by Taiwan (14,29%, n=1), Turkey (14,29%, n=1), and Spain (14,29%, n=1). The total samples from seven studies include 701 subjects. All studies are double-blinded, placebo-controlled randomized studies. All studies also include children of age 1-18 years old with AD, based on Hanifin Rajka criteria. All seven studies use LAB probiotic, which are *Lactobacillus sp.* and *Bifidobacterium sp.* One study uses *Lactobacillus pentosus* as probiotic (14,29%), two *Lactobacillus sakei* (28,57%), one *Lactobacillus plantarum* (14,29%), and one with *Lactobacillus paracasei, Lactobacillus fermentum,* and a combination of both (14,29%). One other study uses a combination of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivatorius,* and *Bifidobacterium bifidum* (14,29%), and also one with combination of *Bifidobacterium lactis, Bifidobacterium longum,* and *Bifidobacterium casei* (14,29%). Probiotic was given to be consumed once daily in four studies (57,14%) and twice daily in three other studies (42,86%). The duration of six studies is 12 weeks (85,71%), and one study for eight weeks (14,29%). Characteristics of included studies are included in Table 1.

Result of Qualitative Data Analysis

1. Ahn et al, 2020 [10]

In January to December 2017, the author did a study on children with moderate to severe atopic dermatitis (AD) (SCORAD Index 20-50). The age range was 2-13 years old. The study was a double-blinded, placebo, controlled randomized study. Probiotic group (n=48) got a *Lactobacillus pentosus* dosage of 1.0 x10^{10} CFU, in the form of powder. Placebo group (n=47) got a specimen of similar appearance with color, taste, smell, shape, and administration similar to probiotic group. Both interventions were administered orally twice daily. The study was done for 12 weeks. During study period, the subjects were given topical emollients. All subjects are prohibited from using systemic corticosteroid, antibiotics, antihistamines, and other forms of probiotics. If any flare broke out with severe itching, the subjects were only allowed fluticasone propionate. During every observation, the tubes containing emollient and topical steroid were weighted quantitatively.

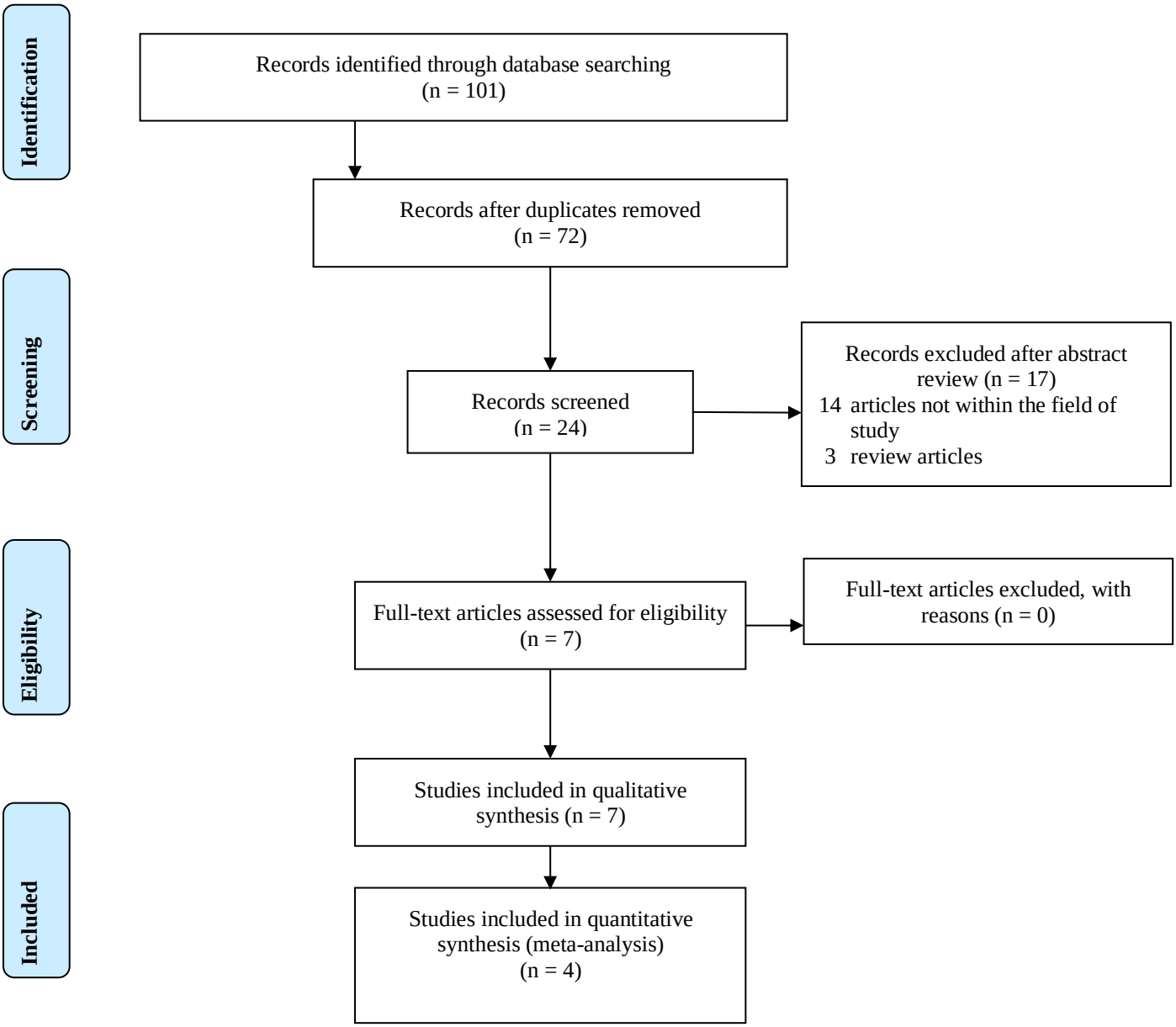

Figure 1. PRISMA Flow Diagram

Table 1. Characteristics of Included Studies

No	Author and Year	Country	Sample Size	Study Population	Interventions		Study Outcome	Frequency	Duration of Intervention
					Probiotic Group	Placebo Group			
1	Ahn et al, 2020	Korea	95	2-13 years	L. pentosus $1.0x10^{10}$ CFU	Identical color, taste, and shape, without active ingredient	SCORAD Total IgE IL-4	Twice daily	12 weeks
2	Woo et al, 2010	Korea	88	2-10 years	L.sakei $5.0x10^{9}$ CFU	Microcrystalline cellulose	SCORAD	Twice daily	12 weeks
3	Rather et al, 2020	Korea	90	3-18 years	L.sakei $1.0x10^{10}$ CFU	Pure microcrystalline cellulose without active ingredient	SCORAD Total IgE	Once daily	12 weeks
4	Han et al, 2012	Korea	118	1-13 years	L. plantarum CJLP133 $0.5x10^{10}$ CFU	Identical color, taste, and shape, without active ingredient	SCORAD Total IgE IL-4	Twice daily	12 weeks
5	Yesilova et al, 2012	Turkey	40	1-13 years	Mixture $2.0x10^{9}$ CFU	Skim-Milk Powder and dextrose	SCORAD Total IgE IL-4	Once daily	8 weeks

6	Wang et al, 2015	Taiwan	220	1-18 years	L. paracasei $2.0x10^9$ CFU; L.fermentum $2.0x10^9$ CFU; Mixture LP+LF $4x10^9$ CFU	Placebo not mentioned in study	SCORAD Total IgE IL-4	Once daily	16 weeks
7	Navarro-Lopez et al, 2018	Spain	50	4- 17 years	Mixture 1.0×10^{10} CFU	Tapioca maltodextrine	SCORAD Total IgE IL-4 levels	Once daily	12 weeks

Mean ± standar deviation (mean ±SD) of SCORAD Index in probiotic group during baseline is 30.4±8.6, and 23.6±11.0 on week-12 (p<0,001). Meanwhile, mean ±SD in placebo group during baseline is 34.3±8.3, and 23.2±9.7 on week-12 (p<0,002). SCORAD Index mean scores on probiotic groups do not differ significantly from placebo group (p=0,254).

Mean ±SD of total serum IgE logarithmic concentration during baseline does not differ significantly in two study groups. Probiotic group is found to be 4.7±15, and in placebo group 4.5±2.0 (p=0.150). Mean ±SD of total serum IgE logarithmic concentration in week-12 is also not significantly different in the two groups, which are 4.9±1.5 on probiotic group and 4.7±1.2 (p=0.563) on placebo group.

Mean ±SD of IL-4 during baseline also does not differ significantly between the two groups, with probiotic group of 0.29±0.26 and placebo group 0.26±0.07 (p=0.479). Mean ±SD of IL-4 on week-12 are also not significantly different in both groups, with probiotic group of 0.25±0.00, and placebo group of 0.25±0.00.

2. Woo et al, 2010[11]

On January 1, 2007 until August 31, 2008, the author did a study on 88 pediatric patients with AD (SCORAD Index >25). Subjects receiving cyclosporin, systemic corticosteroid, topical calcineurin inhibitor or herbal / traditional medicine in three months before the study, were excluded. The subjects were 2-10 years old. The study was a double-blinded, placebo-controlled randomized study. Probiotic group (n=45) received probiotic intervention of freeze-dried Lactobacillus sakei KCTC10755BP with dosage of 5.0×10^9 CFU, with microcrystalline cellulose vehiculum (1,76 gram). Probiotic specimen was kept in alubags in temperature 4ºC up to administration, and is stable for up to six months. Placebo group (n=43) received a preparate of probiotic look-alike, with similar color, taste, and shape with microcrystalline cellulose vehiculum, without active ingredients. Probiotic and placebo were administered per oral twice daily by being dissolved in 2,5 – 5 mL of distilled water. The study was done for 12 weeks. During the course of study, the subjects were instructed to take daily shower with warm water for 5-10 minutes and apply emollients soon after. They were not permitted other topical corticosteroid usage, and only allowed 0,1% prednicarbate if necessary during the study.

Analyzed outcomes were SCORAD Index difference before (pre) and after (post) intervention expressed as mean (range). The study found a SCORAD Index in probiotic group (mean (range) baseline) of 42.6 (26.4-75.7), and on week-12 28.8 (25.1-32.4). Meanwhile, in placebo group, the SCORAD Index was found to be 40.0 (27.2-76.5), and on week-12 35.8 (31.9-39.8). The mean SCORAD Index in probiotic group decreased significantly (p<0,01) on week-12 from baseline, compared to placebo. The mean SCORAD Index in probiotic group was significantly higher at -13.1 (95% confidence interval, -17.5 to -8.6) compared to placebo group which is -5.2 (95% confidence interval, -8.8 to -1.5). Total serum IgE measurements were done using ELISA method (CAP FEIA; Phadia Inc, Uppsala, Sweden) and expressed as mean (range). The values in probiotic group was 2.37 (0.96-3.38) and placebo group 2.31 (1.18-3.06).

3. Rather et al, 2020[12]

The authors conducted the research from June 2014 to February 2016. The study was approved by Ethical Committee of the Chungnam National

University Hospital (IRB No. CNUH 2013-12-020-029), and was registered on Clinical Research Information Service with registration number KCT0003928. The authors did the research on pediatric patients (n=90), with moderate to severe atopic dermatitis (with SCORAD Index 20-50), and subject age range 3-18 years old. The study was a double-blinded, placebo-controlled randomized study. Study randomization was done with SAS system and with block randomization, and the block size was kept confidential until the end of the study. Each of the study materials (probiotics live cells, dead cells, and placebo) was labelled with numbers, according to randomization process. Randomization split the samples into three groups. First group was given Probiotic/live cells (n=30), second group was given heat-killed probiotics/dead cells (n=30), and third group was given placebo (n=30). This study utilized probiotic *Lactobacillus sakei* ProBio65 (live cells); ghost ProBio65 (dead cells / heat killed by autoclaving in the temperature 121^{o}C for 30 minutes) with microcrystalline cellulose vehiculum, and placebo (pure microcrystalline cellulose). Probiotic was administered as freeze-dried probiotic (powder inside 400 mg sachet) with dosage of 1.0 x 10^{10} CFU; 1 sached once daily, 30 minutes after meal. Probiotic or placebo was given orally, once per day. The study was carried on for 12 weeks. During study period, the patient was not allowed to consume antibiotics, corticosteroid, antihistamine, immune-suppresant medicine, herbal medicine, other food supplements, and probiotic (outside of the study) and other fermented food.

The primary outcomes are SCORAD Index on week-6 and week-12 from baseline. SCORAD Index in group one (live cells) on week-6 decreased 6.83±2.20 points (p=0.073) from baseline; and on week-12 decreased 10.72±2.78 points (p=0.0015) from baseline. SCORAD Index in group two (dead cells) was found decreasing 7.30±2.77 (p=0.0154) from baseline on week-6, and 10.51±4.94 (p=0.0017) on week-12. Meanwhile, SCORAD Index in group three (placebo) on week-6 decreased 4.45±1.90 (p=0.0301) from baseline, and on week-12 there was no significant change from baseline. On week-6, there was no significant difference between the two intervention groups; on week-12, SCORAD Index was significantly lower in group one (probiotic live cells) (p=0.0193) and group two (dead cells) (p=0.0242) compared to placebo.

Other outcome analyzed was Investigator's Global Assessment (IGA), the change of skin condition (moisture and sebum levels), and a change in serum profile, including eosinophil count, immunoglobulin-E (IgE) levels, eosinophil cationic protein (ECP), CCL17 (thymus and activation-regulated chemokine [TARC]), CCL27 (cutaneous T cell-attracting chemokine [CTACK]) on baseline and week-12. Measurement of IgE levels didn't find any significant change on week-12 from baseline, for all intervention groups.

4. Han et al, 2012[13]

Han et al conducted a registered study in WHO International Clinical Trials Registry Platform (ICT-RP) with registration number KCT0000358. The study was done in Chung-Ang University Hospital in Seoul. The researchers collected pediatric samples (n=118) with atopic dermatitis (SCORAD Index 20-50), with age range 1-13 years old. The study design was a double-blinded, placebo-controlled randomized study. Randomization was done using computer-generated list of random numbers. A random number list was prepared by an investigator not participating in the study process or assessment, and was stuck on the front of each bag containing intervention material (probiotic and placebo). Probiotic group (n=58) received *Lactobacillus plantarum* CJLP133, with a dosage of 0.5 x 10^{10} CFU. The placebo group (n=60) was given placebo with similar shape and taste. Probiotic and placebo administration was done per oral twice daily. The study began with a period of wash out for the first two weeks, where probiotic and placebo groups were still given placebo. After wash out period,

intervention was conducted for 12 weeks. Measurements of results were done two weeks after intervention period was done. During the study, patients were not allowed to consume any fermented food containing probiotics. The patients were also instructed to shower once daily with warm water, and to apply emollients as often as possible on AD lesions. During study period, patients were allowed topical corticosteroid (prednicarbate 0.25%) if VAS was found to be ≥7 for itch and sleep disturbance, with dosage of the surface area of two palms, 1 fingertip unit. In every observation, the tube containing topical corticosteroid was weighted, to measure the quantitative usage. SCORAD Index measurements were done on week-0, 2, 8, 14, and 16. Serum IgE measurements were conducted on week-2 and 14.

The outcomes assessed were SCORAD Index change with two analysis method, which is pre-protocol (PP) and intention-to-treat (ITT). In PP analysis, SCORAD Index for probiotic group in week-14 was lower than placebo (p=0.022), and the change of SCORAD Index mean value from baseline – week-14 on probiotic group was bigger than placebo (p=0.002). ITT analysis also showed the same results, that SCORAD Index in probiotic group on week-14 was lower than placebo group (p=0.044). During the study period from week-2 to week-14, the mean SCORAD Index decreased significantly in probiotic group compared to placebo (p=0.004). The change of SCORAD Index mean ±SD from baseline, week-2, 8, 14, 16 on probiotic groups were as follows: 30.6±7.7, 27.6±10.0, 23.9±10.3, 20.4±11.8, 21.9±13.2. The changes of mean±SD of SCORAD Index from baseline, week-2, 8, 14, and 16 in placebo groups respectively were as follows: 30.3±6.8, 25.6±9.0, 25.4±9.4, 25.6±11.6, 24.9±10.7.

The outcome of IgE serum levels was expressed in logarithmic expression (total IgE), with mean ±SD baseline value in probiotic group of 5.2±1.7, and placebo group 5.2±1.6. On week-14, there was no significant change in logarithmic total IgE from baseline, in probiotic or placebo groups (p=0.054 and p=0.800).

The outcome of interleukin-4 (IL-4) level was expressed in logarithmic expression. It decreased significantly from baseline in the probiotic group on week-14 (p=0.049), but showed no significant difference in placebo group, from baseline to week-14.

5. Yesilova et al, 2012[14]

In October 2007 to April 2008, the author conducted a study on pediatrics (n=40) with AD of moderate to severe SCORAD index. The researchers included children from the age of 1-13 years. The study was a double-blinded, placebo-controlled randomized study. Randomization was done by the nurses, by distributing samples using closed-envelope method. The researchers took no part in the randomization. Randomization split the samples into two groups, which are probiotic group (n=20) and placebo group (n=20). The probiotic group received a mixed probiotic consisting *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivatorius,* and *Bifidobacterium bifidum* with dosage of 2.0 x 10^9 CFU. Placebo group received a placebo preparate made of skim-milk powder and dextrose. Probiotic and placebo were given orally once per day, for eight weeks.

The analyzed outcome was SCORAD Index difference, total serum IgE, and IL-4 levels before (pre/baseline) and after intervention / week-8 (post). The results was shown in the notation of mean ±SD.

Mean±SD of SCORAD Index in probiotic group during baseline was 35.4±13.4, which became 12.4±7.2 on week-8. SCORAD Index mean± SD in placebo group during baseline was 28.1±6.1, which became 15.3±5.1 on week-8. In the end of study, SCORAD Index decrease in probiotic group was significantly bigger than placebo group, and was also statistically significant (p=0.0015).

Mean ±SD of total serum IgE in probiotic group during baseline was 427 ±500, and decreased

into 281.9±405 on week-8. The score in placebo group was 337.3±298 during baseline, which increased into 347.7±271.3 on week-8. Total serum IgE levels on week-8 in probiotic group was significantly different statistically to placebo group (p=0.0035).

Mean±SD of IL-4 levels in probiotic group during baseline was 31.34±27.96, which then became 25.12±15.16 on week-8. The IL-4 levels in placebo group during baseline was 19.51±17.75, which then became 19.51±17.75 on week-8. The difference of IL-4 levels on week-8 of probiotic group wasn't significantly different compared to placebo group (p=0.67).

6. Wang et al, 2015[15]

On December 2011 to September 2013, the authors did a research on pediatric patients (n=220) with AD of SCORAD Index >15. The authors included children of age 1-18 years old. The study was a double-blinded, placebo-controlled randomized study. Randomization was done using computer-generated four block design lists, and split the sample into four groups, which are probiotic 1 (*Lactobacillus paracasei*) (n=55), probiotic 2 (*Lactobacillus fermentum*) (n=53), probiotic 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum*) (n=51) and placebo group (n=53). Probiotic 1 and 2 groups received probiotic intervention with a dosage of 2.0 x 10^9 CFU, meanwhile group 3 received a probiotic combination of dosage 4.0 x 10^9 CFU. The placebo group received a placebo substance with identical color and shape with protiobitc group, but the ingredient was not mentioned in the journal. Both interventions were given per oral once a day, for 12 weeks. During the study, the subjects were not allowed to consume antibiotics, corticosteroid, calcineurin inhibitor, oral antihistamine and probiotic outside of the study intervention. The subjects were also instructed to apply emollients. Topical corticosteroids allowed for the study was fluticasone propionate during flare and severe itching.

Analyzed outcomes included SCORAD Index difference, total serum IgE, and IL-4 levels before (pre/baseline) and after intervention. The results were expressed in mean ± SD.

SCORAD Index results showed that in the group probiotic 1 (*Lactobacillus paracasei*), the value at baseline was 50.93±19.42, which then became 25.62±22.35 on week-12. In group probiotic 2 (*Lactobacillus fermentum*), the value at baseline was 52.25±16.85, and decreased to 28.38±20.24 on week-12. In group probiotic 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum*), the value at baseline was 51.90±18.90, and 24.17±17.63 at week-12. Meanwhile, in placebo group, the baseline value was 54.08±17.06, and 39.39±18.34 at week-12. The SCORAD Index at week-12 decreased substantially in every group (intra-group comparison p<0.05). SCORAD Index of the three probiotic groups on week-12 were significantly lower than placebo group (inter-group comparison p<0.001).

Total serum IgE of group probiotic 1 (*Lactobacillus paracasei*) during baseline was 1055.11±1219.50, and 868.04±1107.16 on week-12. The baseline value of group probiotic 2 (*Lactobacillus* fermentum) was 923.41±1101.44, and 799.76±1051.19 on week-2. Baseline value of probiotic 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum*) was 1228.78±1524.66, and 927.51±1185.62 on week-12. The placebo group's baseline value was 1443.24±1548.75, and decreased slightly to 1234.78±1237.38 on week-12. The total serum IgE value on week-12 decreased significantly in group probiotic 1 (*Lactobacillus* paracasei) and group 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum*) (p<0.05). There were no significant change in total serum IgE on week-12 among all the probiotic and placebo groups.

IL-4 levels in group probiotic 1 (*Lactobacillus paracasei*) was 0.13±0.17 at baseline, and 0.07±0.13 at week-12. Group 2 (*Lactobacillus fermentum*) was 0.16±0.18, which then became

0.05±0.09 on week-12. Group 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum)* was 0.13±0.16, which became 0.09±0.16 on week-12. The values of placebo group was 0.19±0.21 at baseline and 0.15±0.20 on week-12. The IL-4 values on week-12 decreased significantly in statistic (p=0.04) in all probiotic groups (1, 2, and 3) compared to placebo groups.

7. Navarro-Lopez et al, 2018[16]

The authors did a research from October 2015 to December 2016. The study protocol was approved by Ethics Committee for Clinical Research (CEIC) of the Hospital General Universitario de Alicante, and The Agencia Espanola del Medicamento (Spanish Medicines Agency), as well registered in American Registry of Clinical Trials (Clinical Trial.gov NCT02585986). The authors did the study on pediatric subjects (n=50), with moderate to severe atopic dermatitis aged 4-17 years old. The design was a double-blinded, placebo-controlled randomized study. Randomization was done using computerized randomized which orders had been prepared before by the authors. Randomization split the samples into two groups, probiotic (n=26) and placebo (n=24). Probiotic group received a combination probiotics of *Bifidobacterium lactis* CECT8145, *Bifidobacterium longum* CECT7347, and *Lactobacillus casei* CECT 9104, each with a ratio of 1:1:1, with dosage of 1.0 x 10^9 CFU. Probiotic was administered in the form of gelatine capsules as small as 9.85x16.44 mm, filled with 30 mg freeze-dried probiotics powder, with maltodextrine vehiculum. Placebo group (n-26) received placebo preparate in the form of maltodextrine tapioca, in the same gelatine capsule vessel as the probiotic group. Both treatments were administered per oral once daily for 12 weeks.

Primary outcome analyze were SCORAD Index change on baseline and week-12, and proportion of days of corticosteroid usage for 12 weeks, if any flare happened. The secondary outcome was serum laboratorium marker changes taken from peripheral blood sample to measure IgE, IL-4, IL-5, IL-10, and IL-13 values.

Mean±SD value of SCORAD Index in probiotic group was 33.58±3.38 during baseline. SCORAD Index of placebo group during baseline was 31.64±5.05. Twenty two out of 23 subjects (96%) in probiotic group and 11/24 (46%) in placebo group obtained improvements in SCORAD Index. After 12 weeks of intervention, the mean change of SCORAD Index in probiotic group was -83% (95% CI, -95% to -70%), and in placebo group -24% (95% CI, -36% to -11%). SCORAD Index change from baseline on week-12 in probiotic group was -27.0 (-31.1 to -22.8) and -7.8 (-11.9 to -3.6) in placebo group.

Mean±SD value of serum IgE in probiotic group during baseline was 989±1714. The same value in placebo group was 773±1528. The authors presented the results in the parameter of logarithmic IgE (log IgE) in IU/mL. The *mean difference log IgE* between groups during baseline was -0.019 (-0.129, 0.085) and *mean difference in change log IgE* from baseline was -0.035 (-0.181, 0.129). During 12 weeks of intervention, there were no significant changes in serum IgE, between probiotic and placebo groups.

Mean±SD of IL-4 levels in probiotic group during baseline was 32.19±8.34. The same value in placebo group was 30.11±4.56. The authors presented the result in parameter logarithmic IL-4 (log IL-4) in pg/mL. The *mean difference log* IL-4 between groups during baseline was 0.038 (-0.045, 0.113) and the *difference in change log* IL-4 from baseline was -0.068 (-0.176, 0.041). During 12 weeks of intervention period, there were no significant change in IL-4 values between the probiotic and placebo groups.

Quantitative Data Result (Meta-Analysis)

Meta-analysis of the parameter SCORAD Index with random effect model showed a heterogenity study with I^2=73% (p=0.003). Standardized mean difference was -0.42 with 95% CI, -0.76 to -0.08. This shows that SCORAD Index reduction

was greater significantly in probiotic group compared to placebo group (p=0.01) (Figure 2).

Meta-analysis of IgE levels with fixed effect model showed a heterogenity test with I^2=0% (p=0.71). Standardized mean difference of IgE levels was -0.03 with 95% CI, -0.24 to -0.17. This shows no statistically significant change in IgE serum levels in group probiotic, compared to placebo (p=0.74) (Figure 3).

Meta-analysis of IL-4 levels with fixed effect model showed heterogenity test with I^2=0% (p=0.76). Standardized mean difference of IL-4 levels was -0.16 with 95% CI , -0.35 to 0.02. This shows a bigger change of IL-4 level on probiotic group, but not statistically significant, compared to placebo (p=0.09) (Figure 4).

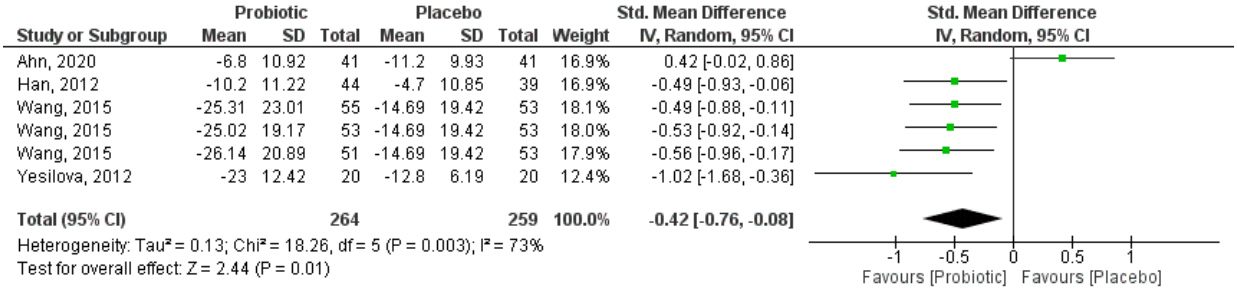

Figure 2. Results of Meta-Analysis on the effectiveness of probiotics supplementation on the parameter SCORAD index

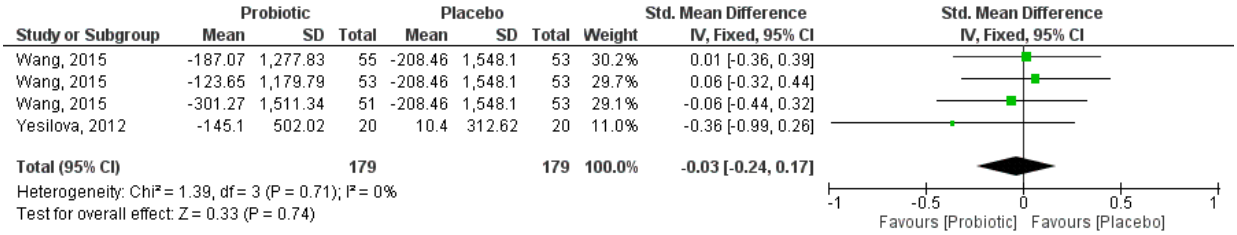

Figure 3. Results of Meta-Analysis on the effectiveness of probiotics supplementation on the parameter Immunoglobulin E levels

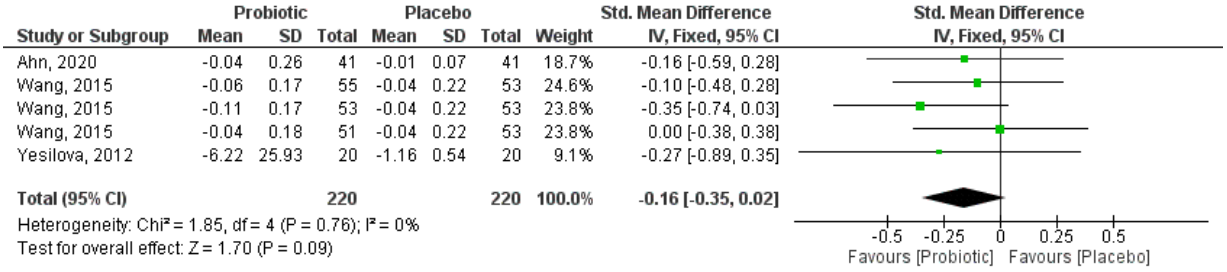

Figure 4. Results of Meta-Analysis on the effectiveness of probiotics supplementation on the parameter Interleukin-4 levels

Risk of Bias in Included Studies

The study articles included in the meta-analysis were four studies, such as Ahn et al, 2020; Han et al, 2012; Yesilova et al, 2012; and Wang et al, 2015; with complete data including mean±SD pre and post intervention. [10,13–15]

SCORAD Index outcome were found in seven articles included in the systematic review. However, only four out of the seven

studies were included in the SCORAD Index meta-analysis, which are Ahn et al, 2020; Han et al, 2012; Yesilova et al, 2012; and Wang et al,

2015, since those studies reported SCORAD Index outcome in the form of mean±SD pre and post intervention. Meanwhile, Woo et al, 2010 reported the SCORAD Index in the form of mean (range), so it's not possible to be converted. Rather et al, 2020 did not report mean±SD of placebo group post intervention on week-12. Navarro-Lopez et al, 2018 showed some data in percentage, therefore making it impossible to convert to mean±SD.

Total IgE levels outcomes were included in six articles included in the systematic review. However, only two of those were included in meta-analysis of total serum IgE, which are Yesilova et al, 2012 and Wang et al, 2015, because they reported the outcome of serum IgE with mean±SD pre and post intervention. Meanwhile Ahn et al, 2020 reported the data in the form of log IgE, hence cannot be used as a comparison. Rather et al, 2020 did not show their data. Han et al, 2012, reported the data in log IgE, therefore not comparable as well. Navarro-Lopez et al, 2018 reported the data in the form of log IgE, and cannot be compared.

IL-4 levels were reported in five articles. Out of those, only three were included in the systematic review, which are Ahn et al, 2020; Yesilova et al, 2012 and Wang et al, 2015, whwo reported IL-4 outcomes in the form of mean±SD pre and post intervention. Meanwhile, Han et al, 2012 and Navarro-Lopez et al, 2018 reported the data in the form of log IL-4, therefore they are not comparable. [11,12,16]

Risk of bias from the study included in the analysis (be it qualitative or quantitative) was assessed using The Cochrane Collecting data - form for RCTs only and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials, including randomization technique, allocation concealment, participant blinding, blinding outcome, and incomplete outcome, choice of outcomes reported, and other biases. (Table 2)

Table 2. Risk of Bias of Included Studies in the Meta-analysis

	Random Sequence Generation	*Allocation Concealment*	*Selective Reporting*	*Other Bias*	*Blinding of Parpicipants and Personnel*	*Blinding of Outcome Assessment*	*Incomplete Outcome Data*
Ahn et al, 2020	?	?	+	+	+	+	+
Woo et al, 2010	?	?	+	+	+	+	+
Rather et al, 2020	+	+	+	+	+	+	−
Han et al, 2012	+	+	?	+	+	+	−
Yesilova et al, 2012	+	+	+	+	+	+	+
Wang et al, 2015	+	+	+	+	+	+	+
Navarro Lopez et al, 2018	+	+	+	+	+	?	+

Discussion

This study is a observational study, with systematic review and meta-analysis to assess the efficacy of probiotic supplementation for the treatment of atopic dermatitis in children, with the parameter of

SCORAD Index, serum IgE, and IL-4 levels. A total of seven studies were included in qualitative

assessment (systematic review) and four studies in quantitative assessment (meta-analysis).

The articles included in the meta-analysis were those reporting complete outcomes in the form of mean±SD (pre/baseline) and post/end of intervention. Meta-analysis of SCORAD Index included four studies, which are Ahn et al, 2020; Han et al, 2012; Yesilova et al, 2012; and Wang et al, 2015. Meta-analysis of serum IgE included two studies, which are Yesilova et al, 2012 and Wang et al, 2015. Meta-analysis of IL-4 levels included three studies, which are Ahn et al, 2020; Yesilova et al, 2012 and Wang et al, 2015. [10,13–15]

Studies included in the systematic review and meta-analysis has a variative age range. Ahn et al, 2020 included subjects of 2-13 years old (mean 4.8±2.3 in probiotic and 5.4±3.0 in placebo). Woo et al, 2012 included subjects age 2-10 years old (mean 6.3 (2.3-9.8) in probiotic group and 5.8 (2.0-9.7) in placebo group). Rather et al, 2020 has an age range of 3-18 years old (mean 9.19±4.97 and 9.18±4.53 in probiotic group, and 10.10±4.49 in placebo groups). Han et al, 2012 has an age range of 1-13 years old (mean 4.6±3.3 in probiotic, and 5.1±3.3 in placebo). Yesilova et al, 2012 included subjects aged 1-13 years old, Wang et al, 2015 1-18 years old (mean 7.86±3.79, 7.55±4.50 and 8.34±3.80 in probiotic groups, and 8.04±3.97 in placebo group). Navarro-Lopez et al, 2018 has an age range of 4-17 years (mean 9.35±3.58 in probiotic group and 8.96±3.94 in placebo group).

Based on literature, AD is a chronic, recurring inflammatory skin disease with a characteristic red itching lesion with dryness of skin, with the highest incidence in childhood. As much as 45% of AD complaints began in the first six months of life, 60% at one year of age, and 85% in year five, and around 70% of all cases will experience spontaneous remission during early adolescence. [17–19]

Efficacy of probiotic supplementation towards SCORAD Index from six studies (Woo et al, 2010; Rather et al, 2020; Han et al, 2012; Yesilova et al, 2012; Wang et al, 2015; Navarro-Lopez et al, 2018) found an increase in SCORAD Index that is greater on probiotic group, compared to placebo group. This aligns with the literature, mentioning that the mechanism of probiotic action is through gut-skin axis. Probiotics consumed orally can modulate microbiome composition and help balance gut microbiome by producing short chain fatty acid (SCFA), antimicrobial peptide (AMP), and lactic acid. SCFA works by inhibiting proliferation, migration, and adhesion of inflammatory cells as well as inhibit proinflammatory cytokine production. Bacteriocins (AMP) work directly by inhibiting the growth of pathogenic bacteria. Lactic acid causes a decrease in pH levels, creating an ecosystem unbenign for the growth of pathogenic bacteria. This has become the basis of thinking that probiotics can return the balance of gut microbiome, which indirectly balance the skin microbiome, thus decreasing the severity of inflammatory lesions on the skin. The improvement of inflammatory lesions on the skin can be seen by an improvement in SCORAD Index, which is a standardized parameter to measure severity of AD lesions.[55] This also aligns with the literature, that probiotic supplementation once to twice daily with a duration of minimum eight weeks can help alleviate severity of AD lesions. [20–22]

One study by Ahn et al, 2020 stated that SCORAD Index improvement in probiotic group is more insignificant than in placebo. This unmatching finding may be caused by subjects' incompliance in each placebo and probiotic group, and also individual varying factors. In the study, it was mentioned that the proportion of topical corticosteroid as a treatment in placebo group was much greater than probiotic group, which can very likely help alleviate AD lesions. [10] Meta-analysis study has shown that SCORAD Index improvement is better in probiotic groups, with statistical significance as well (p=0.01).

The efficacy of probiotic supplementation towards IgE levels, based on Wang et al, 2015, found that total serum IgE on week-12 decreased substantially in group probiotic 1 (*Lactobacillus paracasei*) and group probiotic 3 (combination of *Lactobacillus paracasei* and *Lactobacillus fermentum*) ($p<0.05$). Yesilova et al, 2012's study also found a significantly greater improvement in IgE levels on week-8 in probiotic group, compared to placebo ($p=0.0035$). This aligns with the literature, that probiotic as an immunomodulator works by balancing the immune responses of Th1 and Th2, by inducing T-Reg cells activity in mesenteric lymph nodes. T-Reg upregulates Th1 immune responses by secreting TGF-β dan IL-10, which are anti-inflammatory cytokines, thus subduing Th2 immune responses. The suppression of Th2 immune response activity also reduces IgE production in the serum of AD patients. [8,20,21]

Meanwhile, studies by Ahn et al, 2020; Rather et al, 2020; Han et al, 2012; and Navarro-Lopez et al, 2018 did not find significant serum IgE improvements in the probiotic group compared to placebo group. This unaligned finding may be caused by other factors influencing the production of IgE, be it modifiable or non-modifiable factors. Modifiable factors include allergen exposure (high protein diet such as milk, nuts, eggs, ocean fish and chicken; inhaled allergens), parasite infestation, meanwhile non-modifiable factors include genetics, race/ethnicity, and other immune diseases increasing IgE production. Other than that, according to Kalliomaki et al, cytokine production pattern induced by intestinal microbiome (caused by probiotic supplementation) may be strain-spesific (pattern-recognition receptors), and also aligns with Elazab et al, 2013 who conducted a study supplementing probiotics and assessing IgE levels. Elazab et al found a more significant IgE levels decline on longer periods of time (comparing followup period of two weeks and 24 months). [23,24] Bonita et al, 2017 stated some different factors that may influence varying IgE results after probiotic supplementation, which are individual's sensitivity to probiotics, which are influenced by genetic predisposition towards probiotic response or gene susceptibility coding certain cytokine receptors in an individual. On the other hand, microbiome variation in each individual may influence probiotic colonization in the intestine. [25]

Meta-analysis results showed that decreasing serum IgE in probiotic group is not statistically significant, compared to placebo group ($p=0.74$).

The efficacy of probiotic supplementation towards IL-4 levels from Wang et al, 2015 stated that IL-4 levels decreased more significantly on week-12 ($p<0.05$) in all probiotic groups (1, 2, and 3) compared to placebo group. Han et al, 2012 stated that IL-4 logarithmic levels in probiotic group decreased significantly on week-14 compared to baseline ($p=0.049$). This aligns with the literature, that probiotic as an immunomodulator works by balancing Th1 and Th2 response, by inducing the T-Reg cells activity on mesenteric lymph nodes, therefore suppressing Th2 immune responses. As known before, inflammation or allergic reaction in AD is coordinated by a subset of T lymphocytes, Th2, with the production of its main cytokine, Interleukin-4 (IL-4). [26]

Meanwhile, Yesilova et al, 2012 stated a decrease in IL-4 levels on week-8 in probiotic group, compared to placebo group. However, this change was not statistically significant ($p=0.67$). Ahn et al, 2020 also stated a decrease in IL-4 on week-12 of probiotic group as greater than placebo group, but also not statistically significant. Navarro-Lopez et al, 2018 also found that during its 12 weeks of intervention, there was no significant change in IL-4 levels between the probiotic and placebo groups.

Meta-analysis result shows that IL-4 levels in probiotic groups do improve, but not significantly, compared to placebo ($p=0.09$). This may be caused by the difference of probiotic strains used in every article, therefore even though the numbers improve, they are not statistically significant. Based on literature

written by Rosenfeldt et al and Yang et al, 2013, it was concluded that the duration of probiotic usage and administration of strain-specific probiotics may cause these unaligning results. [7,27] In other literatures, it is also mentioned that the administration of a mixture of several strains of probiotic is more effective compared to single strain probiotic. [8,28,29]

Conclusion

The supplementation of probiotic may decrease AD lesion severity, but does not affect immunoserological profiles significantly (Immunoglobulin-E and Interleukin-4). More studies with bigger sample sizes and longer observational periods are needed to confirm probiotic efficacy in treating atopic dermatitis.

Abbreviations:

AD: Atopic Dermatitis

SCORAD : Scoring Atopic Dermatitis

RCT : Randomized Controlled Trial

Mesh: Medical Subject Headings

PRISMA: Preferred Reporting Items for Systematic Review and Meta Analysis

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