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Oral postbiotics derived from *Lactobacillus* sp. in treatment of atopic dermatitis: a meta-analysis

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Abstract

Introduction: The use of postbiotics, which are defined as dead microorganisms and/or their components that provide health benefits to the target host, has been shown to reduce the severity of atopic dermatitis (AD) in several studies.
Methods: A systematic literature review was conducted in Pubmed, the Cochrane Library, Science Direct, Clinicaltrials.gov, and Google Scholar, covering the period from January 2012 to July 2022 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. AD patients of all ages that received oral postbiotics or placebo as treatment were the focus of the study. The main study outcome was the scoring of atopic dermatitis (SCORAD) and other measures, such as extension area, disease intensity, and adverse events. The final data were pooled using a fixed-effect model.
Results: A meta-analysis of three studies found that, compared to placebo, SCORAD was lower in subjects that were given oral postbiotics from *Lactobacillus* sp. (mean difference: −2.90, 95% confidence interval [CI; −4.21, −1.59], $p < 0.00001$). From the comparison of two studies, the differences in disease extension (mean difference: −2.40, 95% CI [−7.67, 2.81], $p = 0.37$) and intensity (mean difference: −0.27, 95% CI [−0.84, 0.30], $p = 0.36$) were not significant.
Conclusions: The administration of oral postbiotics from Lactobacillus sp. has the potential to alleviate the severity of AD as indicated by a reduction in SCORAD scores.

Keywords: atopic dermatitis, oral postbiotic, *Lactobacillus* sp., SCORAD, human health

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Introduction

Atopic dermatitis (AD) is a multifactorial chronic inflammatory skin disease that begins in childhood and is characterized by skin inflammation and itching (1, 2). Atopic dermatitis has a variety of clinical symptoms, with pruritus and eczema being the major complaints. The pruritus in AD may lead to sleep disturbances, and the eczematous condition renders the skin more susceptible to infection (1). AD is often accompanied by asthma or allergic rhinitis, and together they are known as atopic march (3). The majority of AD patients suffer from decreased quality of life due to these conditions (1).

The main therapy for AD involves the use of emollients and avoidance of precipitating factors, followed by the application of topical anti-inflammatory therapy, usually steroids (4, 5). Nevertheless, these treatments are often insufficient for moderate to severe forms of AD. These patients require the help of systemic immunosuppressive therapy. In 40% to 50% of cases, the condition persists for years, with the need for continuous systemic immunosuppressive therapy (6). The most commonly used class of immunosuppressive therapy is systemic corticosteroids, followed by phototherapy, cyclosporine, methotrexate, and azathioprine. Dupilumab, a human monoclonal antibody, is a possible alternative treatment for AD (7). Despite being effective, these immunosuppressive therapies may come with unwanted side effects and toxicity (6). Having a non-immunosuppressive alternative may therefore be beneficial.

Recent studies suggest that the etiopathogenesis of AD consists not only of genetic susceptibility, epidermal barrier dysfunction, immune system disorders, and environmental factors, but also of the microbiota dysbiosis (8). Dysbiosis in microbiota refers to a decrease in the diversity and distribution of bacteria, archaea, fungi, and protists (9, 10). This condition is found not only in the skin of AD patients but also in the gut lining. Normal gut microbiota is rich in various bacteria such as *Bacteroides*, *Prevotella*, and *Ruminococcus* (11, 12). A shift in the diversity of gut bacteria, such as an increase in *Faecalibacterium prausnitzii*, which is found in AD patients, may lead to the release of molecules that can damage the intestinal epithelium and lower levels of butyrate and propionate. Increased proportions of *Clostridium* and *Escherichia* were also found in the intestines of infants with AD compared to healthy controls (11). These changes affect the skin condition through immunological, neuroendocrine, and metabolic pathways, which are hypothesized to induce AD (10, 13).

Microorganisms that demonstrate a beneficial health effect on the host are classified as probiotic (12). The most widely used probiotic is *Lactobacillus*, which has the largest genus among lactic acid bacteria (14). Administration of probiotics may be especially beneficial for patients with moderate to severe AD that require long-term topical corticosteroid application because this has been associated with adverse local effects, including skin atrophy, rebound flares, and rare but severe systemic effects, such as suppression of the hypothalamic–pituitary–adrenal axis, growth retardation, hypertension, and hyperglycemia (15). Effective probiotics are believed to have immunoregulatory properties and mediate immunomodulation. However, the available data remain inconclusive and contradictory (15–17).

Previous studies have suggested that the amount of nonviable

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cells and their components predominate in probiotic therapy, suggesting that the immunomodulatory effects of probiotics may be derived from nonviable bacteria along with their metabolic products (e.g., short-chain fatty acids) and isolated microbial fraction or bacterial components (15, 18, 19). The International Scientific Association of Probiotics and Prebiotics (ISAPP) defines postbiotics as dead microorganisms and/or their components that concur health benefits on the target host (20). Based on this definition, the benefits harvested from probiotics might actually come from the postbiotic component instead.

Postbiotics made from *Lactobacillus* sp., such as heat-killed *Lactobacillus paracasei* (15, 17, 21), heat-killed *Lactobacillus acidophilus* (19, 22), or tyndallized *Lactobacillus rhamnosus* (16), seem to improve AD lesions in both children and adults even when compared to placebo. Adverse effects such as nausea and headache were observed in several studies, with the number being similar between experimental and placebo groups, indicating that the complaints may be coincidental (16, 21). These positive outcomes may suggest that the use of postbiotics may be a safe alternative for AD treatment. However, systematic reviews and meta-analyses are required to support these claims before the use of postbiotics as AD treatment.

Methods

We conducted a systematic review and meta-analysis to determine the role of *Lactobacillus* sp. as an oral postbiotic treatment for AD. The meta-analysis was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (23). To start with, we determined the research question and PICO (population, intervention, comparison, and outcome), followed by the validation of ideas. The research question was to determine the use of oral postbiotics as treatment of AD. The population of the study consisted of children and adults with AD, the intervention of the study was postbiotics, the comparison of the study was placebo, and the outcome was the scoring of AD (SCORAD), as described in Table 1.

The literature search in this study was conducted in five databases: Pubmed, the Cochrane Library, Science Direct, Clinicaltrials.gov, and Google Scholar. The literature search was carried out using PICO (patient/problem, intervention, comparison, outcome)-compliant search terminology. Studies included were those using Hanifin–Rajka or United Kingdom (UK) Working Party diagnostic criteria, which compared oral postbiotics and placebo in treating AD patients with SCORAD as the outcome measure. There were no restrictions on country, patient age, race, and sex. *In vitro* research, non-human subjects, research with non-extractable data, publication in abstract form without full text, case reports, case series, and systematic reviews were excluded from this study. Initial screening was carried out based on inclusion and exclusion criteria by four researchers on the same team.

Table 1 | **PICO (population, intervention, comparison, outcome) of the study.**

P	I	C	O
– Atopic dermatitis	– Postbiotic	– Placebo	– SCORAD
– Atopic eczema	– Paraprobiotic		
– Eczematous dermatitis	– Nonviable probiotic		
	– Heat-killed probiotic		
	– Tyndallized probiotic		
	– Bacterial lysate		

SCORAD = SCORing Atopic Dermatitis, P = patient/problem, I = intervention, C = comparison, O = outcome.

Researchers at this stage manually eliminated duplicates and provided reasons for study exclusion. The full text in the inclusion study was obtained through an open-access journal website or by e-mail to the principal investigator. This stage was also carried out by two or more researchers working individually to determine which studies were to be included in the final analysis. A manual search was also carried out to mitigate bias and identify studies that should have been included but were excluded for various reasons; for example, incorrect keywords. This was done by identifying associated articles from the citations and searching for similar articles in the database. The research data were entered into an Excel table. The quality of the randomized controlled studies was assessed by Cochrane RoB-2 researchers and visualized with RobVis (24). The extracted data were rechecked by the researchers or additional individuals to avoid bias.

We analyzed the qualitative study through a systematic review and the quantitative study through meta-analysis using the Review Manager application. Data were presented in the form of a forest plot and a funnel plot. After the statistical analysis was carried out, the data check was repeated. Research results were written in the following format: introduction, methods, results, discussions, and conclusions. A table of study characteristics containing author names, year of publication, and patient characteristics is attached.

Results

The following PRISMA steps, as shown in Figure 1, identified 413 studies from five resources. The literature excluded before screening was duplicated studies, studies older than 10 years, studies published in languages other than Indonesian and English, *in vivo* studies, *in vitro* studies, reviews, protocols, presentations, and editorials. A total of nine articles were screened based on titles and abstracts. We obtained six articles with postbiotics made from *Lactobacillus* sp. All studies were deemed eligible for systematic review. Only three out of the six studies provided sufficient data for meta-analysis.

All studies selected for systematic review were of the randomized controlled trial (RCT) type. Determination of the level of evidence was based on the inclusion criteria using the Joanna Briggs Institute levels of evidence tools. Level 1C is the level of evidence for RCT in a treatment study.

The characteristics of the studies included are shown in Table 2. Four out of six studies administered oral postbiotics derived from *L. paracasei*, *L. rhamnosus*, or *L. sakei* to children (73.7%), and the rest administered oral postbiotics derived from *L. acidophilus* to adults (24.7%). Topical corticosteroids, emollients, or antihistamines were prescribed as suggested by atopic dermatitis guidelines in all studies except in the study by Rather et al. (25). The total use of topical corticosteroids was not different between experimental and placebo groups, as suggested by D'Auria et al. (15) and Jeong et al. (16). Information regarding additional treatment was not provided by Yamamoto et al. (22).

SCORAD was used to determine the AD severity before and after postbiotic treatment. Only the studies by D'Auria et al., Jeong et al. (16), and Yan et al. (17) provided the necessary data to analyze the effect of postbiotics on AD. Some risk of bias was found, especially in deviation from intended interventions or selection of reported result, as shown in Figure 2. The concerns indicated that the study might be prone to bias, but the possibility of annulling the study results was deemed not strong.

Three studies comparing a total of 121 subjects that were given oral postbiotics made from *Lactobacillus* sp. and 121 subjects that were given a placebo (see Fig. 3) showed a significant SCORAD score difference. The SCORAD value was lower in subjects that were given oral postbiotics made from *Lactobacillus* sp. (mean difference: –2.90, 95% confidence interval [CI; –4.21, –1.59], $p <$ 0.00001) with low heterogeneity (I2 = 0%). The funnel plot in Figure 4 shows that the three studies are symmetrically distributed, whereby the distribution of the research is balanced on the left and right of the center-line boundary. This implies that there is no potential for publication bias.

The adverse effects were stated after administering postbiotics derived from *L. rhamnosus* and *L. paracasei*, as shown in Table 3. The number of adverse effects in the experimental and placebo

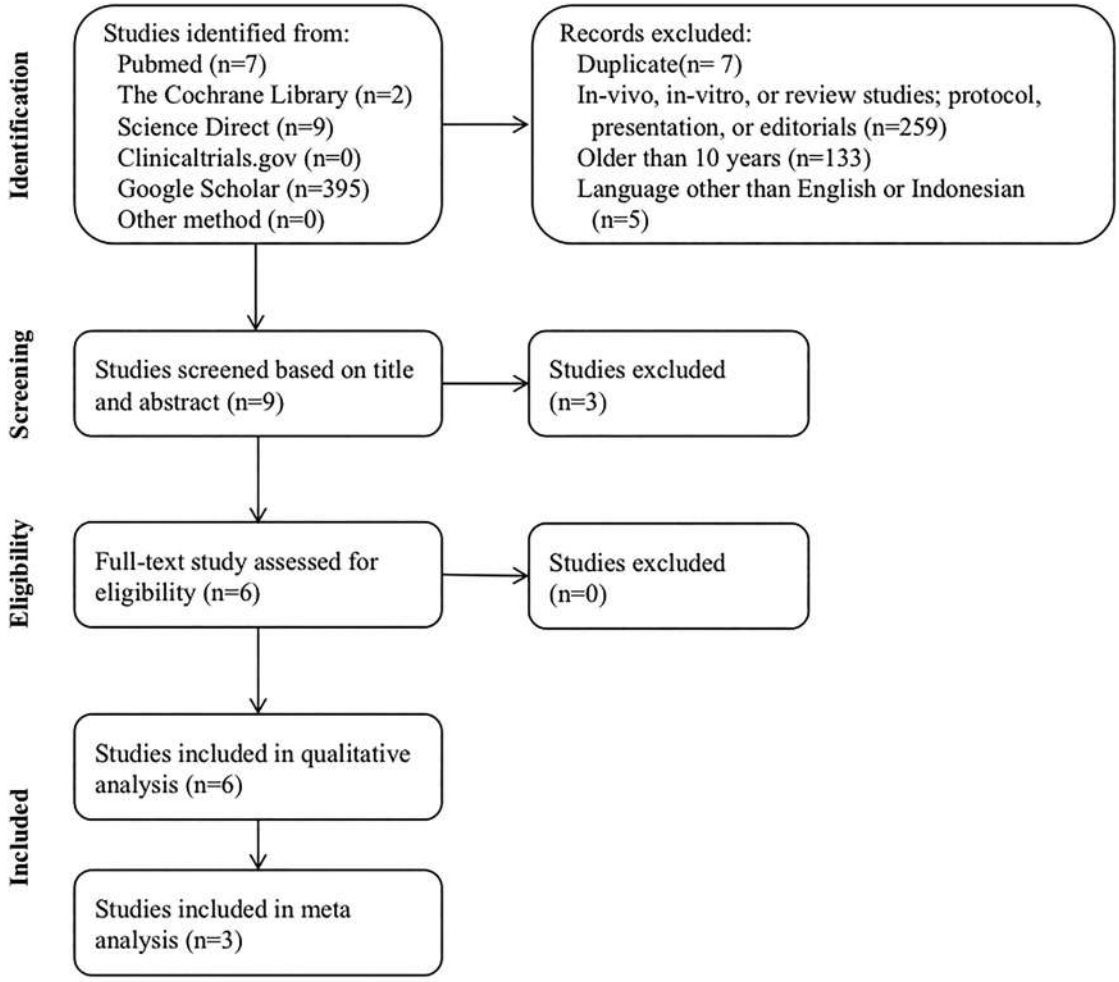

Figure 1 | PRISMA (preferred reporting items for systematic reviews and meta-analyses) steps from five references to find the articles used in the meta-analysis.

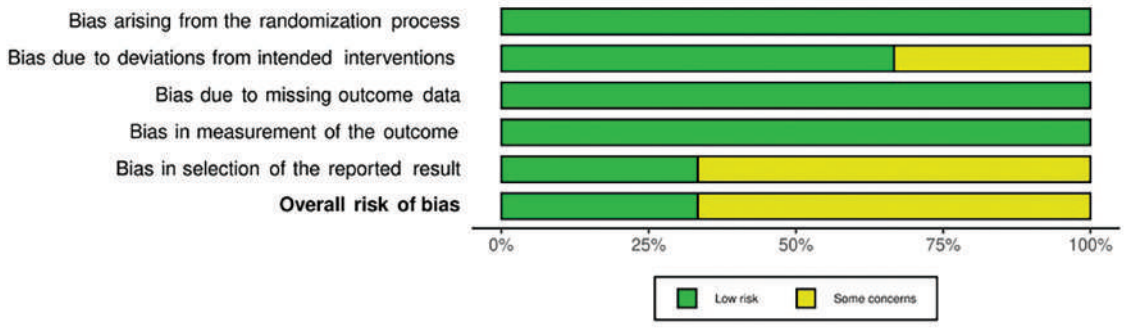

Figure 2 | Risk of bias showing possible deviation from intended intervention.

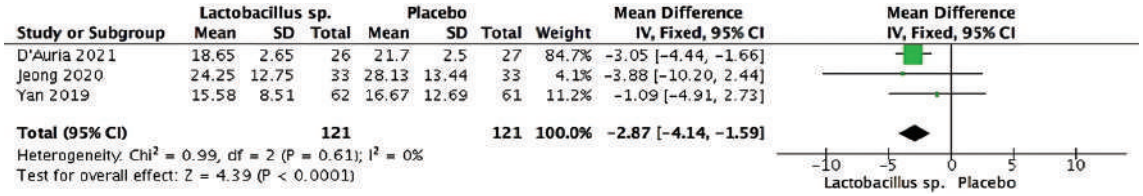

Figure 3 | Forest plot indicating the difference in SCORing Atopic Dermatitis (SCORAD) between placebo and postbiotics.
SD = standard deviation, IV = inverse variance, CI = confidence interval, Chi² = Chi-square test, df = degrees of freedom, I² = I-squared, Z = Z-score.

group was 122 and 130, respectively. The most frequently occurring adverse events were infections, which included upper respiratory tract infections, skin infections, ear infections, and others. The adverse events listed are suspected to be unrelated to the study.

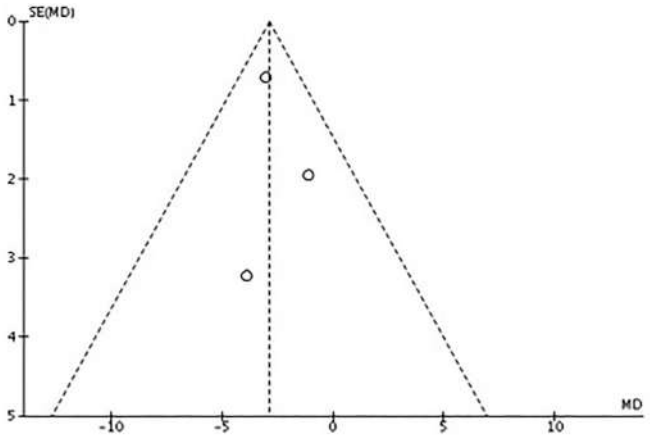

Figure 4 | Funnel plot showing symmetrical distribution.

Discussion

Preclinical data show that postbiotics derived from *Lactobacillus* are effective in reducing contact hypersensitivity reactions and the development of atopic skin lesions (15). Teame et al. (14) proposed that postbiotics produced from *Lactobacillus* consist of various molecules, including proteins, peptides, small molecules, and others, which mediate positive effects on the host, such as immunomodulatory, anti-tumor, antimicrobial, and barrier protective effects. Biological responses to postbiotics made from *Lactobacillus* have also been observed in human trials, in which good safety profiles, longer shelf life, and resistance to mammalian enzymes were obtained (15). Giving postbiotics is expected to limit the amount of corticosteroids needed to treat AD ("sparing effect") (17). Postbiotics may have a longer shelf life and are relatively resistant to heat or an acidic environment (15).

The RCT studies of the efficacy of oral postbiotics in AD patients in the last 10 years were found to be carried out on *L. paracasei* (15, 17), *L. rhamnosus* (16), *L. sakei* (25), and *L. acidophilus* (19, 22), which were mainly killed by heat treatment. Heat treat-

Table 2 | Studies included.

Study	Population	Study design	Intervention and comparison	SCORAD
D'Auria et al., 2021	Children 6–36 months old with moderate to severe AD	Double-blinded RCT study, 12 weeks observation	Heat-killed *L. paracasei* CBA L74 in rice flour (*n* = 26)	W0: 42.5 (38.4–46.6) W12: 18.7 (16.0–21.3)
			Rice flour as placebo (*n* = 27)	W0: 41.5 (37.5–45.5) W12: 21.8 (19.2–24.4)
Jeong et al., 2020	Children 1–12 years old with moderate AD	Double-blinded RCT study, 12 weeks observation	Tyndallized *L. rhamnosus*, 1.0 × 1010 CFU/day (*n* = 33)	W0: 38.15 ± 7.09 W6: 28.70 ± 12.12 W12: 24.25 ± 12.75
			Placebo (*n* = 33)	W0: 36.49 ± 7.20 W6: 29.43 ± 12.75 W12: 28.13 ± 13.44
Yan et al., 2019	Children 4–30 months old with moderate to severe AD	Double-blinded RCT study, 16 weeks observation	Heat-treated *L. paracasei* 1.0 × 1010 CFU/day (*n* = 62)	W0: 30.70 ± 10.27 W4: 24.56 ± 10.22 W10: 20.48 ± 11.95 W16: 15.58 ± 8.51
			Maltodextrin as placebo (*n* = 61)	W0: 30.56 ± 11.17 W4: 23.84 ± 8.87 W10: 20.31 ± 11.42 W16: 16.67 ± 12.69
Rather et al., 2021	Children 3–18 years old with mild AD	Double-blinded RCT study, 12 weeks observation	Heat-killed *L. sakei* (*n* = 22)	(Mean difference) W6: 7.30 ± 2.77 (*p* = 0.0154) W12: 10.51 ± 4.94 (*p* = 0.0017)
			Freeze-dried *L. sakei* (*n* = 16)	W6: 6.83 ± 2.20 (*p* = 0.0073) W12: 10.72 ± 2.78 (*p* =0.0015)
			Placebo (n = 20)	W6: 4.45 ± 1.90 (*p* = 0.0301) W12: No change
Yamamoto et al., 2016	Adults 16 years old or more with mild to moderate AD	Double-blinded RCT study, 24 weeks observation	Heat-killed *L. acidophilus* L-92 (*n* = 24)	W4: −2.60 (−19.5 to 25.90) W8: −4.90 (−20.8 to 17.80) W12: −7.25 (−19.70 to 20.20) W16: −8.50 (−25.30 to 19.50) W20: −9.45 (−24.70 to 16.60) W24: −6.30 (−19.20 to 4.30)
			Placebo (*n* = 26)	W4: −3.60 (−28.1 to 16.80) W8: −0.30 (−16.30 to 14.20) W12: −0.90 (−18.20 to 19.50) W16: −2.00 (−16.40 to 14.40) W20: −1.60 (−17.50 to 17.30) W24: −1.10 (−16.60 to 5.60)
Inoue et al., 2014	Adults 16 years old or more with mild to moderate AD	Double-blinded RCT study, 8 weeks observation	Heat-killed *L. acidophilus* strain L-92 (*n* = 24) Placebo (*n* = 25)	Data in graphic Mean difference in SCORAD when compared between treatments indicated p ‹ 0.01

AD = atopic dermatitis, RCT = randomized controlled trial, W = week, CFU = colony forming unit , SCORAD = SCORing Atopic Dermatitis.

ment involved the use of pasteurization or autoclave to reach a temperature of 70 to 100 °C. Tyndallization is a combination of a lower temperature and incubation period to kill bacteria (26).

Tyndallized *L. rhamnosus* has shown a therapeutic effect on AD in a mouse model with significantly lower mast cell count, serum immunoglobulin E, and interleukin (IL)-4 concentrations in lymph node cells (16). *L. rhamnosus* produces p40 protein, which has an immunomodulating effect in mice. The p75 protein found in *L. rhamnosus* has anti-apoptotic activity. *L. rhamnosus* can form short-chain fatty acids, which are important in increasing acetate and butyrate, and decreasing intestinal permeability and monoamine oxidase in the brain. *L. rhamnosus* can also synthesize conjugated linoleic acid, especially cis-9, tra-11, and tra-10, which can reduce the growth of HT-29 and Caco-2 cancer cells in *in vitro* experiments (14).

L. paracasei has been extensively investigated and has demonstrated beneficial effects in *in vitro* and *in vivo* studies as an inhibitor of pro-inflammatory cytokines and an inductor of T-regulatory cell-like responses (15). *L. paracasei* as a probiotic can reduce SCORAD in children 1 to 18 years old when given for 3 months (17). *L. paracasei* also produces p40 protein, which has an immunomodulating effect in mice. *L. paracasei* was also found to secrete bacteriocin, which was proven to kill *Porphyromonas gingivalis* (14).

Heat-killed *L. acidophilus* L-92 is useful for the treatment of hay fever, allergic rhinitis, and AD (22). *L. acidophilus* can secrete protein aggregation promoting factor, which helps colonization of the gastrointestinal tract. The colonization promotes inhibition of pathogen adhesion by means of exclusion of competition or by coaggregation against pathogens. *L. acidophilus* also synthesizes bacteriocins that can mediate inhibitory effects against pathogens (14). Postbiotics made from *L. sakei* have been shown to treat AD skin conditions and have shown a significant reduction of serum IgE in animal studies (rats) (25).

Demography

Atopic dermatitis is a multifactorial chronic inflammatory disease with an unclear etiopathogenesis. The increased prevalence of AD, especially in industrialized areas, has been linked to the "hygiene hypothesis," whereby excessive hygiene kills beneficial bacteria and reduces their role in educating the host immune system (27). This hypothesis supports the possibility that gut microbial diversity and composition may play a role in the etiopathogenesis of AD (11, 28).

AD-associated features can occur at any age (29). The prevalence of AD is higher in children (10%–20%) than in adults (1%–3%), with a two- to three-fold increase in incidence in recent decades, especially in younger children and in developing countries such as those in Southeast Asia (1, 3). The more severe forms of AD in infancy and early childhood are thought to be associated with an important period in the gut microbiota development (27). Microbial shift in adults may potentially contribute to the reduction of age-related AD by suppressing the growth of *Staphylococcus aureus*. Adult skin commensal bacteria are dominated by *Cutibacterium* and *Corynebacterium*, harboring genes involved in porphyrin metabolism, which could theoretically reduce *S. aureus* infection in *in vitro* and animal studies. Mature skin flora also secretes metabolites with antimicrobial properties, which in turn inhibit the growth of *S. aureus*, as shown in *in vitro* and rat studies (30).

Immunomodulation

The balance in gut microbiota affects brain and skin conditions through immunological, metabolite, and neuroendocrine pathways (27). Gut dysbiosis impairs the production of short-chain fatty acids, which regulate the activation and apoptosis of the immune system, as well as the production of metabolites, which can enter systemic circulation (12). Dysbiosis also causes disruption of the neuroendocrine system directly through tryptophan production and indirectly through regulation of IL-10 and interferon (IFN)-γ, which in turn causes an increase in cortisol (27). These conditions stimulate the formation of pro-inflammatory cytokines, which are proposed to be directly transferred to the skin through systemic circulation, hence inducing the symptoms of AD. A current dominant hypotheses states that AD is caused by allergen penetration in Th2-dominant conditions, which arises from an imbalance between type 1 T helper cells (Th1) and type 2 T helper cells (Th2) (22). Inequality between Th1/Th2 and increased Th2-related cytokines, such as IL-4 and IL-13, have been associated with disease activity (6).

Atopic dermatitis severity

Stalder et al. formulated the SCORAD by adding the values of extension, intensity, and subjective symptoms of AD (31). The severity of AD can be classified according to the SCORAD score into mild (< 25), moderate (25–50), and severe (> 50) (32). The results of a meta-analysis showed that the administration of postbiotics made from *Lactobacillus* sp. to groups of infants and children with moderate to severe AD for 12 to 16 weeks was able to reduce the severity of AD based on the SCORAD index (15–17). A decrease in the severity of AD was also found after the administration of postbiotics made from heat-killed *L. acidophilus* to adults 16 years or older (19, 22). Heat-killed *L. sakei* may reduce the severity of AD in children and adolescents 3 to 18 years old with no significant difference from AD treated with live *L. sakei* (25).

Steroid sparing agent

Conventional management of AD is primarily aimed at restoring the skin barrier function using moisturizers and preventing the disease from worsening through the administration of topical corticosteroids (15). One of the expected postbiotic roles is to reduce the use of steroids; that is, as a steroid sparing agent. A study by D'Auria et al. showed a decrease in steroid use in the postbiotics treatment group compared with placebo (15). In contrast, both the experimental and placebo groups in a study by Yan et al. indicated no significant difference (25).

Adverse effects

The high demand for food and medicine in response to the increasing human population in modern countries increases the need for a well-conducted and standardized quality and safety assessment of these products. Various investigations have provided evidence regarding the beneficial effects of probiotics. The available evidence still does not show definite safety for at-risk groups such as infants, the elderly, or people that are immunosuppressed, for whom probiotics can cause certain side effects such as gastroin-

testinal symptoms, systemic infections, and possible transfer of antibiotic resistance genes from probiotics to normal microbiota (33, 34).

Studies regarding the use of oral postbiotics in AD patients have reported relatively good safety. A study by Rather et al. using live and dead *L. sakei* and a study by Inoue using *L. acidophilus* reported that the occurrence of adverse effects in their studies were similar in both experimental and control groups (25). A study by Yan et al. using *L. paracasei* reported a similar incidence of adverse events in all treatment groups. A total of 71.9% of subjects in the GM080 group and 67.7% in the placebo group had at least one adverse event during the study (17). Only one of the adverse events in the placebo group was classified as (likely) related to therapy. A total of 12.5% of subjects in the GM080 group and 17.7% in the placebo group experienced adverse events related to diaper rash or AD. This led to the dropout of one subject per group (25).

This study is limited to a small number of studies on postbiotics and mainly focused on *Lactobacillus* sp. The limited number of studies included was a consequence of the insufficient published data from a few published studies, some of which were excluded from the final result. To conclude, oral postbiotics derived from heat-treated *Lactobacillus* sp. can reduce AD severity in children, as shown by a decrease in SCORAD when administered daily for 12 to 16 weeks with little to no known side effects. This study is unable to determine whether the use of oral postbiotics can act as a steroid sparing agent.

Table 3 | **The number of adverse effects in the experimental and placebo group.**

	Postbiotics			
	L. rhamnosus	*L. paracasei*	Total	Placebo
Infection	23	39	62	61
Skin and subcutaneous diseases	5	12	17	16
Respiratory disorders	4	7	11	15
Gastrointestinal disorders	3	9	12	6
Systemic complaints		4	4	6
Trauma and procedural complications		3	3	8
Metabolic and nutritional disorders		2	2	4
Blood and lymphatic disorders		2	2	3
Eye disorders	1	1	2	4
Genetic disorders		2	2	1
Reproductive disorders		1	1	2
Nervous system disorders				2
Musculoskeletal disorders	1		1	1
Benign tumors		1	1	1
Psychiatric complaints		1	1	
Anaphylactic reaction	1		1	

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