Next-Gen Biotherapeutics: A Systematic Review and Network Meta-Analysis on Postbiotics as Treatment For Pediatric Atopic Dermatitis

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April 17, 2023

Abstract

Background: Due to the recency of the postbiotic field, there are no head-to-head postbiotic studies investigating its biotherapeutic potential for atopic dermatitis (AD). No network meta-analysis (NMA) has yet been conducted to synthesize relevant studies to compare postbiotic interventions for AD. **Objective:** To assess the comparative efficacy and safety of postbiotic strains for treating pediatric AD. **Methodology:** This is an NMA of randomized controlled studies that evaluate postbiotics in treating pediatric AD. Systematic search of databases and registers from inception to November 30, 2022. Three authors independently performed the search, screening, appraisal using the Cochrane risk of bias tool version 2 and data extraction. Data analysis was done using STATA14 software. **Results:** There were 9 studies that evaluated 8 postbiotic preparations. *Lactobacillus rhamnosus* IDCC 3201 (LR) ranked highest in the efficacy outcome. Compared to placebo, LR may be effective in reducing symptoms of atopic dermatitis both in the main analysis (SMD -0.53, 95%CI -1.02 to -0.04) and sensitivity analysis involving studies that used SCORAD (MD -5.52, 95% CI -10.46 to -0.58), based on low-certainty evidence. Based on moderate-certainty evidence, LR probably does not increase the risk of adverse events (RR 0.97, 95% CI 0.79 to 1.21). Although *Lactobacillus paracasei* GM080 (LP2) ranked highest in the safety outcome, it may not reduce AD symptoms compared to placebo (SMD -0.03, 95% CI -0.37 to 0.32) based on low-certainty evidence. **Conclusion:** LR showed significant benefits for children with AD, based on low-certainty evidence. Further investigation on LR is recommended.

INTRODUCTION

Atopic dermatitis (AD) is the most common skin disorder among children. As a chronic inflammatory disorder, it is considered a psychologically burdensome pediatric concern and affects 15 to 20% of children worldwide.[1-3] Probiotics are live microbial agents that have been increasingly used for various disease conditions over the past two decades.[4] While its effect on AD has been studied extensively, concerns about the safety of administering live microbes in children instigated further research for alternative approaches in AD management.[1]

Recent studies show increasing interest in the potential clinical application of postbiotics to prevent and treat AD.[5-13] Postbiotics are defined as "preparations of inanimate microorganisms and/or their components that confer a health benefit on the host".[14] Aside from mutually benefiting hosts, another similarity between probiotics and postbiotics is their high strain-specificity. In postbiotics, exopolysaccharides and lipoteichoic acid production are strain-specific behavior.[15.]

Postbiotics are promising alternatives to probiotics since these eliminate the risk of using live microbial strains, especially among individuals with weakened immune systems, and address product longevity

concern[14,16]. Several randomized controlled trials (RCTs) have been conducted on this topic, with conflicting evidence. As of the writing of this paper, no systematic review and meta-analysis that evaluate the efficacy of postbiotic therapy for atopic dermatitis in children have been conducted. This network meta-analysis (NMA) aims to synthesize all available evidence and determine the efficacy and safety of various postbiotics preparations in treating pediatric AD.

METHODOLOGY

This SR/NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (PRISMA) incorporating the Extension Statement for Reporting of Systematic Reviews incorporating Network Meta-analysis of Health Care Interventions.[17]

Eligibility criteria

RCTs from the earliest record to November 30, 2022, that evaluated postbiotics in pediatric patients with AD were included. The intervention should involve postbiotics compared to other postbiotic preparations or placebo. No restrictions were made on the strain type, dose, and treatment length.

The primary outcome was a relief of AD symptoms which may be reported using several scoring systems such as SCORAD, EASI, POEM, Pruritus-NRS, TIS, IGA, and SASSAD.[18-22] While scoring systems attribute different weights for various symptoms, lower scores always indicate less severe AD. The secondary outcome was the adverse event occurrences (AEO), defined as any untoward medical condition observed among study participants during postbiotic administration.

Studies where participants had concomitant diseases were excluded. Quasi-randomized trials and observational studies were excluded.

Information sources and search strategy

Three reviewers independently searched the databases PubMed, Cochrane Library, Science Direct, Ovid, Springer Link, Google Scholar, and ClinicalTrials.gov (https://clinicaltrials.gov). The search algorithm includes: (((((((Postbiotics) OR (Paraprobiotics)) OR (Ghost probiotics)) OR (Parapsychobiotics)) OR (Tyndallized probiotics)) OR (Metabiotics)) OR (Bacterial lysates)) AND (Atopic dermatitis). Some studies involve postbiotics but may not explicitly mention this term or its related terms; instead, they may only describe its inanimation process and the specific microorganism used. Thus, individual probiotic strains reported in the SR on the probiotics of Tan-Lim *et al.,* [23] were also used as search terms for the PubMed database. Search for additional references cited in the screened full-text papers was also performed.[24] Search for unpublished articles was done by correspondence with content experts in the field.

Study selection

Three authors independently reviewed studies from six databases, resolving conflicts with a 4th author. The PICO (Population, Intervention, Comparison, Outcome) framework was used to evaluate titles and abstracts of initially selected studies. A narrowed number of studies that met eligibility criteria were selected for full-text review. The same process was used for data extraction, quality assessment, and manual search. Study consolidations were done manually using Microsoft Excel.

Data collection process

Data including study author(s), country of publication, sample size (n), age range, microorganism(s) of interest, treatment dosage, mode, and treatment length, and results for both the experimental and placebo groups were tabulated in an Excel sheet. Three reviewers independently assessed the risk of bias assessment using the Cochrane risk of bias tool version 2.0. The outcome for efficacy and safety were tabulated by three authors and independently reviewed by the 4th author. Original investigators were contacted via email to seek unreported or underreported information.

Data items

The primary outcome, relief of symptoms, was measured as a continuous variable as change in AD severity score from baseline to end of treatment. Safety outcomes based on AEO were reported as rates/counts; information whether these were intervention-related was also noted.

This study employed the intention-to-treat principle in order to minimize type-1 error.[25] Missing data were not imputed. The outcome measures reported at the end-of-treatment were used for analysis. Probable effect modifiers may stem from the population and intervention characteristics, including age and dosage.

Review of network geometry

Each postbiotic strain was represented in the network geometry as a node. The placebo was also represented as a node. The nodes' links represent studies comparing the postbiotic strain with a different strain or placebo.

Risk of bias within individual studies

The revised Cochrane risk-of-bias tool for randomized trials (RoB-2) was used for independent appraisal of included studies by three authors.[26] Issues were resolved through collaborative discussions to achieve consensus. The risk-of-bias assessment of the individual studies was done for both efficacy and safety outcomes.

Summary measures

Effect sizes for the efficacy outcome were summarized using Standardized Mean Difference (SMD) and 95% confidence interval (CI) since studies used different AD relief indices. Safety data was summarized using relative risk (RR) and 95% CI. Interval plots were generated to visualize the efficacy and safety effect estimates for the different postbiotic preparations compared to placebo. Forest plots were generated to inspect the relative effects of each strain-specific treatment.

A league table was generated for the outcomes, showing NMA summary estimates with 95% CI. Ranking of interventions was assessed using cumulative ranking probabilities and SUCRA values.

Data analysis

Comparisons of postbiotic preparations using direct and indirect evidence for efficacy and safety was to be conducted. In trials where postbiotics were administered at different doses, the main analysis used the results of the higher dose group to avoid the generation of an auto-loop. Sensitivity analysis on the dose-response was conducted to determine if there was a difference in results when used as high- or low-dose.

STATA 14 software was used for data analysis and synthesis, employing the frequentist approach using random effects model incorporated in STATA 14. Heterogeneity of studies was measured quantitatively using the software Review Manager 5.4.

For studies with missing summary statistics, the study authors were contacted. If they were unresponsive, the guide for data collection in section 5.5.8 of the Cochrane Handbook for systematic reviews of interventions was followed.[27] Data from figures reported in journal articles[28] was electronically extracted using WebPlotDigitizer. Missing means and/or SD were derived from the available data in the studies following the section on data extraction for continuous outcomes in the Cochrane Handbook (Higgins*et al.,* 2022), the formula derived by Wan *et al.,* [29] and using MedCalc Comparison of Means Statistical Software (www.medcalc.org/calc/), as appropriate.

Sensitivity analysis was conducted with studies that reported the efficacy outcome using SCORAD. Results were reported as mean difference with 95% CI. This sensitivity analysis was done to facilitate ease of interpretation of results in the clinical setting since SCORAD has an established minimal clinically important difference (MCID) at 8.7 points.

Publication bias was to be assessed using comparison-adjusted funnel plots.

Assessment for NMA Assumptions

Directness

The PICO of the included studies was qualitatively assessed for directness with the research question.

Heterogeneity

Heterogeneity was assessed qualitatively by evaluating the similarity of studies for each pairwise comparison and quantitatively using the inconsistency statistic ($\mathbf{I^2}$) and the chi-square test. Heterogeneity was considered significant for $\mathbf{I^2}$ >50% and p-value <0.10.

Transitivity

Assessment of transitivity was done qualitatively by analyzing similarity of the PCO of adjacent edges to ensure the validity of the indirect comparisons.[28]

Coherence

Coherence was assessed qualitatively by analyzing similarity of interventions of direct and indirect links. Quantitative assessment of coherence was to be done by assessing loop inconsistency through node splitting (if with closed loops) and design inconsistency (if with multi-arm studies).

Rating strength of evidence through GRADE CoE

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used for the assessment of certainty of evidence (CoE). The GRADE approach considers five domains, namely: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Intransitivity and inconsistency were also considered in the rating of certainty of evidence.[30]

RESULTS

Study selection

A total of 434 studies from six databases were identified through electronic and manual searches. Nineteen duplicate studies were excluded, and 371 studies did not pass the title and abstract screening. From 44 studies eligible for full-text assessment, 36 were excluded due to deviation from the PICO, of which two papers were excluded due to the study subjects having concomitant diseases and allergies.[31-32] One study was a duplicate, and the full-text of one study could not be retrieved despite maximal efforts. An additional 3 studies were identified through manual search of relevant articles. Finally, nine studies were included in this SR/NMA (Figure 1).

Presentation of Network Geometries

Efficacy of postbiotic strains on AD

The network geometry for the efficacy outcome at the strain-specific level is shown in Figure 2a. There were seven postbiotic preparations evaluated, which were all compared to placebo. Six were supported by one study and one (comparison of MV1 and placebo) was supported by two studies.

Safety of postbiotic strains on AD

Of the seven postbiotic preparations that were compared to placebo, the link between MV1 and placebo is the thickest, with two studies supporting the comparison. The rest each have one study to support the comparison (Figure 2b).

Characteristics of Included Studies

This SR includes nine RCTs with a total of 793 children with AD, whose ages ranged from four months to 18 years old. The main characteristics of the nine eligible studies are summarized in Table 1. Of the nine RCTs, five reported the efficacy outcome using SCORAD, and four used SASSAD. Eight studies reported the safety outcome. Five studies administered the interventions orally and four intradermally.

Risk of bias within studies

Figure 3a displays risk of bias assessment for the efficacy outcome in nine studies. Three had low overall risk of bias, three were high, and three were unclear. Randomization processes were adequate in all studies, but only four followed the intended interventions for the participants. Two studies had high risk of bias due to intervention deviations for failure to report the analysis used to estimate the effect of assignment to intervention and failure to analyze participants in the group to which they were randomized. Three had unclear risk of bias for not reporting blinding or possible deviations.

One study did not report the reason for missing outcomes. Two studies may have used inappropriate outcome measurement methods. Three studies had unclear risks due to selective reporting and insufficient result detail.

Figure 3b shows bias risk for safety outcomes in eight studies. Three had low overall bias risk, three high, and two were unclear. Unclear and high risks were due to intended intervention deviations, missing outcome data, inappropriate outcome measurement, and selective reporting of results.

Synthesis of Results

Efficacy of strain-specific postbiotic administration on relief of AD symptoms

All nine studies reported the reduction of AD symptoms. However, only eight were included in the network meta-analysis as one study provided insufficient data to allow pooling. This study reported that SCORAD values were significantly lower at 6 months of treatment using Mix postbiotic preparation (median 11.4 points for Mix, 19.4 points for placebo; p=0.02) but not at 9 months of treatment (median 9.5 points for Mix, 14.8 points for placebo, p=0.08).[9]

Figure 4a shows the interval plot containing the SMD and 95% CI of each postbiotic strain compared to placebo. LR had the most favorable effect with SMD -0.53 (95% CI of -1.02 to -0.04), indicating statistically significant reduction in symptoms compared to placebo. MV2 had the least favorable effect with SMD= 0.03, indicating possible increase in symptoms. However, MV2, LP1, LP2, LS, MV1, and MV3, have wide CIs which preclude definite conclusions from being made.

The league table, ranking probabilities and SUCRA values are in the Supplementary File. LR was the highest-ranked while MV2 was the lowest-ranked strain for the efficacy outcome.

Adverse effects of strain-specific postbiotic administration for AD

Figure 4b shows the interval plot containing the RR and 95% CI of seven postbiotic preparations compared with placebo. LP2 had the lowest RR for adverse events; however, the 95% CI is wide and precludes definite conclusions from being made (RR 0.32, 95% CI 0.01 to 7.78). MV3 and MV2 had statistically significant increase in adverse events (MV3 RR 25.77, 95% CI 1.63 to 406.64; MV2 RR 3.37, 95% CI 2.48 to 4.58). LR showed no significant difference with placebo (RR = 0.97 95% CI 0.79 to 1.21).

LP2 was the highest-ranked while MV3 was the lowest-ranked strain for the safety outcome.

Assessment of NMA Assumptions

Directness

All included studies were direct. All trials involved the administration of postbiotics compared to placebo among pediatric patients with AD and reported reduction in AD symptoms.

Heterogeneity

Only the pairwise comparison between MV1 and placebo had more than one study contributing evidence. Qualitative assessment showed that the PICO and effect modifiers in the two studies comprising the edge had no substantial variation. Quantitative assessment also showed no heterogeneity, with I^2=0% and p-value=0.33.

Transitivity

All postbiotic preparations were compared to placebo. The population and outcomes reported were similar; thus, there was no violation of the transitivity assumption.

Inconsistency

There is no source of loop and design inconsistency in this network.

Results of GRADE CoE Assessments

The CoE assessments for the efficacy and safety outcomes are presented in Table 2. Compared to placebo, LR may reduce the symptoms of AD based on low CoE, and does not cause a significant increase in adverse events based on moderate CoE.

Results of Additional Analyses

Sensitivity analysis

In the sensitivity analysis including only studies that used SCORAD, 3 postbiotic strains (LP, LR, LS) were evaluated in four studies. The network geometry is shown in Supplementary Figure 5a and the interval plot is shown in Supplementary Figure 5b. Compared to placebo, LR decreased the SCORAD value by 5.52 points (95% CI –10.46 to –0.58). Although statistically significant, results were not clinically significant since the mean difference (MD) was smaller than the MCID of 8.7 points. LS and LP had negative MD values indicating reduction in AD symptoms; however, the 95% CI are wide and inconclusive.

One dose-response-controlled trial was included in this NMA. Sensitivity analysis found no difference in results when using data from the low-dose and high-dose groups in reducing AD severity.[7]

Publication bias

Comparison-adjusted funnel plot was not generated given the limited number of studies supporting each pairwise comparison.

DISCUSSION

This NMA synthesizes evidence on the efficacy and safety of various postbiotic strains for treatment of pediatric AD. Only LR showed significant benefit compared to placebo. Evidence suggests LR may reduce AD symptoms, but CoE is low. LR had a statistically significant effect in reducing SCORAD values in the sensitivity analysis, but results did not reach clinical significance. The MD and upper limit of the 95% CI were less than the MCID. A reduction of least 8.7 points in SCORAD is considered clinically significant. [33]

Effectiveness is a crucial factor in clinical decision-making, but other factors including safety and cost-effectiveness are also important.[34] In this study, there was no significant difference in adverse events between LR and placebo, based on moderate certainty of evidence. Although LP2 was the highest-ranked postbiotic strain in terms of safety, it only ranked 6$^{\text{th}}$ (out of 7 postbiotic preparations) in the efficacy outcome and did not demonstrate significant benefit when compared to placebo.

MV2 and MV3 demonstrated significant harm, which may be explained by the route of administration since *Mycobacterium vaccae* was administered intradermally. The other postbiotic species were administered orally. Injection site reactions such as induration and erythema were common and dose-related.[7-8]

Only one study that tested a mixed preparation of postbiotics was included in the review. However, it was not included in the NMA due to inadequate data. Their study showed favorable effect on AD at 6 months of treatment, with no major safety concerns. This finding is similar to the NMA of Tan-Lim *et al. 2020* that compared probiotic preparations for the treatment of pediatric AD, three of the six mixed probiotic preparations demonstrated significant reduction in AD symptoms. This effect was hypothesized to be due to the synergistic activity of the bacteria included in the mix.[23]

Furthermore, of the 17 probiotic preparations included in the NMA of *Tan-Lim et al. 2020* , probiotic Mix 1 (ProbioMix1;*Bifidobacterium animalis* subsp. *lactis* CECT 8145,*Bifidobacterium longum, CECT 7347, Lactobacillus casei CECT 9104*) had the most favorable effect in reducing AD symptoms (SMD = -1.94 (95% CI of -2.65 to -1.94). None of the strains included in this Mix1 were included in this NMA on postbiotics. ProbioMix1 had MD_{SCORAD} of -19.2 (95% CI of -24.76 to -13.64) compared to placebo, which was clinically significant. In this NMA on postbiotics, LR had the most favorable effect in reducing AD symptoms, but results were not clinically significant.

In the Tan-Lim *et al. 2020* study, *Lactobacillus rhamnosus*MP 108 also showed significant benefit in reducing AD symptoms (SMD –0.62, 95% CI –1.12 to –0.13).[23] Although the LR postbiotic evaluated in this NMA consists of a different strain (*L. rhamnosus* IDCC 3201), the *L. rhamonsus* species seem to have a promising effect on atopic dermatitis both in probiotic and postbiotic form.

There is one study that evaluated the effect of live and heat-inactivated *Lactobacillus rhamnosus* GG (LGG) compared to placebo,[31] but this was not included in this NMA since participants had concomitant cows' milk allergy. This trial showed significant benefit only with the viable LGG supplementation. The authors emphasized the importance of including the safety variable for future research on heat-inactivated LGG, as adverse gastrointestinal symptoms were observed.

One of the main limitations of this study is the limited number of studies supporting each pairwise comparison and the absence of direct evidence providing head-to-head comparisons of the postbiotic strains. Multiple treatment comparisons could not be performed for the interventions. The imprecise results found in most pairwise comparisons may be due to the limited available data. However, this is expected given the recentness of the postbiotic field. Consensus on the naming and defining the concept of 'killed microorganism that benefits its host' was only recently established.[14]A recent convention attended by foremost experts in the field was organized last December 2022 for further discussion[35]. Nevertheless, the study sheds light on postbiotic treatments' potential benefits and safety concerns for AD management.

Impact in Healthcare

The specific strain RHT3201, here known as LR, may potentially confer benefits to pediatric patients with AD to relieve symptoms, based on low certainty of evidence. Although the effect did not reach clinical significance, further research on the optimal dose and duration of treatment using LR may be explored. LR showed favorable safety outcomes based on moderate certainty of evidence. As the age of the participants in the trials included for this study are considerably broad, suggestions on the optimal age for postbiotic administration in AD treatment cannot be made.

Impact on microbiological research

Exploration of the effects of postbiotics on different AD phenotypes and endotypes, as well as patients' ages and immune mechanisms, is essential for better understanding of their role in AD treatment. Future studies on LR compared with other postbiotic preparations could enrich the quality of evidence. Evaluating LR as part of a mixed postbiotic preparation is also a potential research interest. Using a standard reporting method and common scoring system is recommended for easier pooling and interpretation of data.

ACKNOWLEDGMENTS

Our gratitude is extended to Ms. Micah Dispo, Mr. Jeno Rey Pagaduan, and Asst. Prof. Jhunas Paul Viernes for their valuable contributions in this study.

IMPACT STATEMENT

Concerns on the long-term efficacy and safety of current treatments for pediatric AD have propelled the search for therapeutic alternatives, including postbiotics. This study compares the efficacy and safety of different postbiotic preparations for treating pediatric AD. This NMA shows biotherapeutic potential of inanimate *Lactobacillus rhamnosus*. Our findings may assist healthcare professionals in making evidence-based decisions for pediatric AD patients and enrich our current microbial research focusing on *biotics* .

REGISTRATION

This study was registered through the Science Research Center (SRC) of the University of the Philippines Baguio with registration number 04032023152822. The review protocol and study data may be accessed upon request with the corresponding author. There were no protocol amendments.

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TABLES

Table 1. Characteristics of included studies.

Study	Country	N (experimental, control)	Age range	Postbiotic intervention	Dosage	Mode of administration	Treatment length	Control group	Outcome
Arkwright 2001	United Kingdom	41 (21, 20)	5 – 18 y	MV3 (Heat-killed *Mycobacterium vaccae* SRL 172)	0.3 mL	Intradermal	3 mo	Placebo	SASSAD index, adverse events
Arkwright 2003	United Kingdom	56 (29, 27)	2 – 6 y	MV1 (Heat-killed *Mycobacterium vaccae* SRP 299)	10 mg/mL	Intradermal	6 mo	Placebo	SASSAD index, adverse events[§]
Berth-Jones 2006	United Kingdom, Croatia	101 (52, 49)	5 – 16 y	**High dose MV1 (Heat-killed *Mycobacterium vaccae* SRP 299)** [+] Low dose (Heat-killed *Mycobacterium vaccae* SRP 299)	**1 mg** 0.1 mg	Intradermal	12 wk	Placebo	SASSAD index, adverse events[++]

Study	Country	N (experimental, control)	Age range	Postbiotic intervention	Dosage	Mode of administration	Treatment length	Control group	Outcome
Study	**Country**	**N (experimental, control)**	**Age range**	**Postbiotic intervention**	**Dosage**	**Mode of administration**	**Treatment length**	**Control group**	**Outcome**
Bodemer 2017	France	179 (93, 86)	6 months – 7 years	Mix (Lyophilized *Haemophilus influenzae, Streptococcus pneumoniae, S. aureus, S. viridans, S. pyogenes, Klebsiella ozaenae, K. pneumoniae, Neisseria catarrhalis*)	3.5 mg	Oral	9 mo	Placebo	Adverse events^{+}
Brothers 2009	New Zealand	124 (61, 63)	5 – 16 years	MV2 (Heat-killed *Mycobacterium vaccae* AVAC)	250 µg/mL	Intradermal	6 wk	Placebo	SASSAD index, adverse events

Study	Country	N (experimental, control)	Age range	Postbiotic intervention	Dosage	Mode of administration	Treatment length	Control group	Outcome
D'Auria 2020	Italy	58 (29, 29)	6 – 36 mo	LP1 (Heat-killed *Lactobacillus paracasei* CBA L74)	8 g	Oral	12 wk	Placebo	SCORAD index
Jeong 2020	South Korea	66 (33, 33)	1 – 12 years	LR (Tyndallized *Lactobacillus rhamnosus* IDCC 3201)	10^{10} CFU/day	Oral	12 wk	Placebo	SCORAD index, adverse events
Study	**Country**	**N (experimental, control)**	**Age range**	**Postbiotic intervention**	**Dosage**	**Mode of administration**	**Treatment length**	**Control group**	**Outcome**
Rather 2021	South Korea	42 (22, 20)	3 – 18 years	LS (Heat-killed *Lactobacillus sakei pro-Bio65*)	400 mg	Oral	12 wk	Placebo	SCORAD index, adverse events
Yan 2019	Taiwan	126 (64, 62)	4 – 30 months	LP2 (Heat-treated *Lactobacillus paracasei* GM-080)	10^{10} CFU/day	Oral	16 wk	Placebo	SCORAD index, adverse events^{+}

Bold = *Only dose used in the analysis*

$^{+}$*related to treatment*

$^{++}$*serious adverse events*

§*adverse effects*

Table 2. GRADE Certainty of evidence assessments for network meta-analysis estimates.

Efficacy outcome		
Comparison	**Standardized Mean Difference (95% CI)**	**Certainty of Evidence**
LR and Placebo	-0.53 (-1.02, -0.04)	Low [a]
LS and Placebo	-0.33 (-0.94, 0.27)	Low [a]
LP1 and Placebo	0.33 (-0.84, 0.19)	Moderate [d]
LP2 and Placebo	-0.03 (-0.37, 0.32)	Low [a]
MV1 and Placebo	-0.12 (-0.44, 0.19)	Low [a]
MV2 and Placebo	0.03 (-0.32, 0.37)	Low [a]
MV3 and Placebo	-0.28 (-0.90, 0.33)	Very low [a]
Safety outcome		
Comparison	**Relative Risk (95% CI)**	**Certainty of Evidence**
LR and Placebo	0.97 (0.79, 1.21)	Moderate [d]
Mix and Placebo	1.39 (0.24, 8.09)	Low [e]
LS and Placebo	0.91 (0.02, 43.99)	Very low [c]
LP2 and Placebo	0.32 (0.01, 7.78)	Very low [b]
MV1 and Placebo	0.72 (0.15, 3.58)	Very low [b]
MV2 and Placebo	3.37 (2.48, 4.58)	Low [f]
MV3 and Placebo	25.77 (1.63, 406.64)	Low [a]

[a] Downgraded due to risk of bias and imprecision.

[b] Downgraded due to risk of bias and very serious imprecision.

[c] Downgraded due to very serious risk of bias and imprecision.

[d] Downgraded due to imprecision.

[e] Downgraded due to very serious imprecision.

[f] Downgraded due to very serious risk of bias.

FIGURES

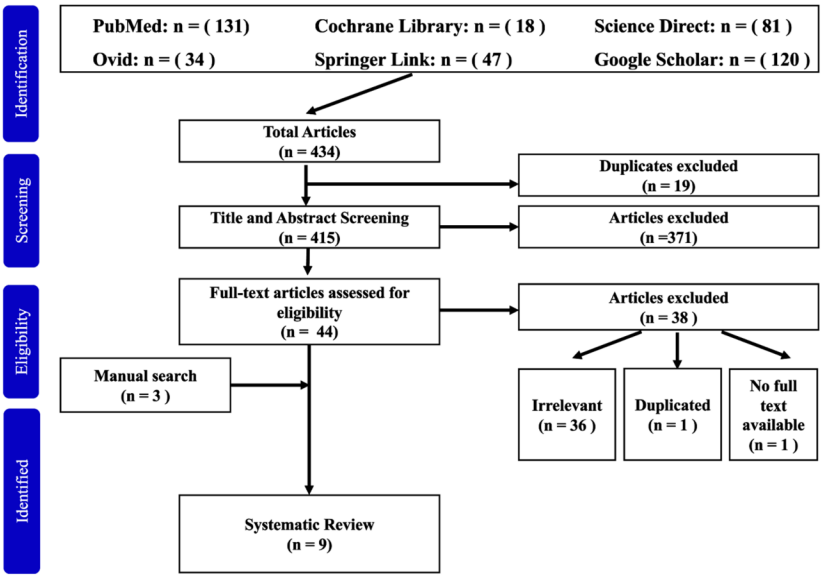
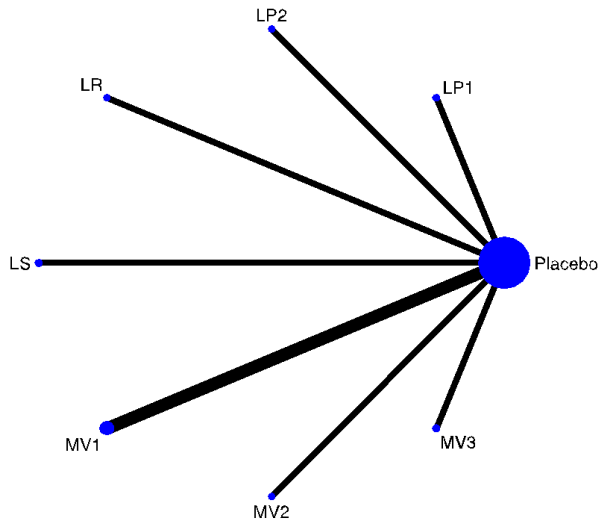


Figure 1. Search flow diagram for the systematic review and network meta-analysis of Postbiotics as Treatment for Pediatric Atopic Dermatitis. The diagram summarizes the number of articles identified during the initial search, screening, retrieval, and inclusion in the meta-analysis.



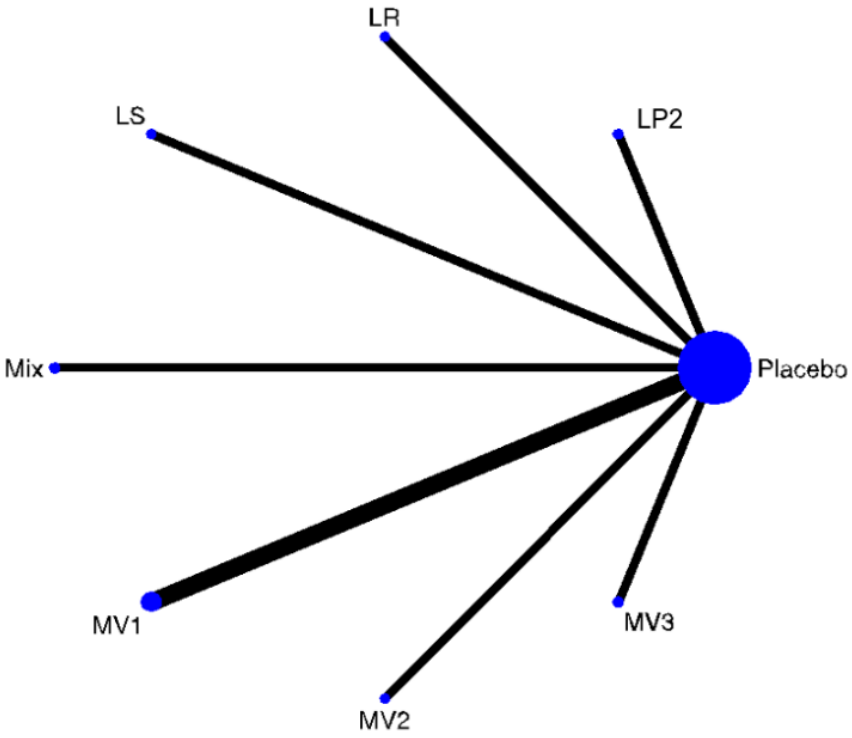


Figure 2a Figure 2b

Figure 2. Network geometry for the efficacy outcome (a) and safety outcome (b). Each node represents one strain-specific intervention. The size of the node is proportional to the number of participants randomly assigned to the intervention, and the thickness of the lines is proportional to the number of trials comparing the two interventions. The largest node is placebo, with a total of 303 patients for the efficacy outcome and 370 patients for the safety outcome across all studies.

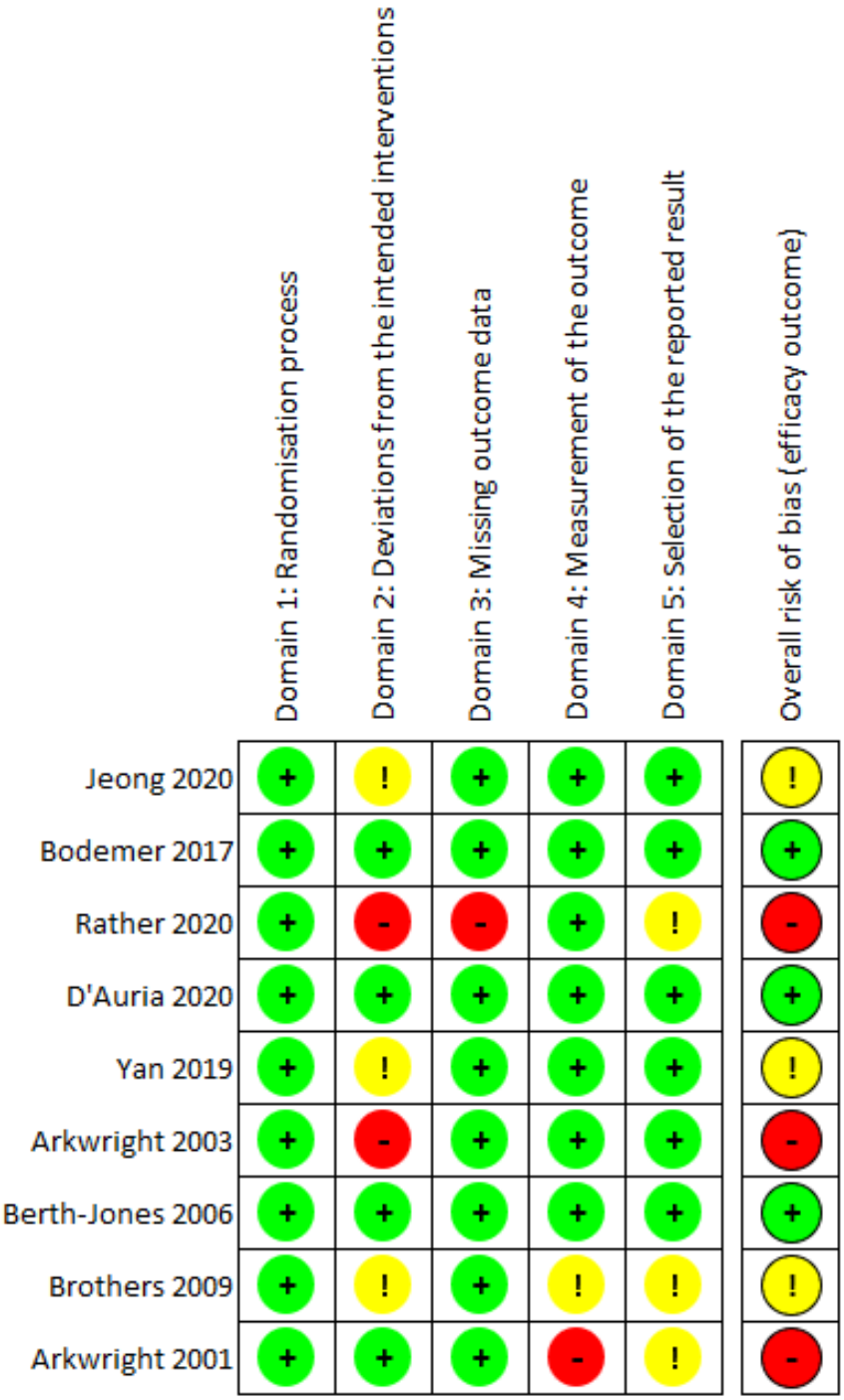
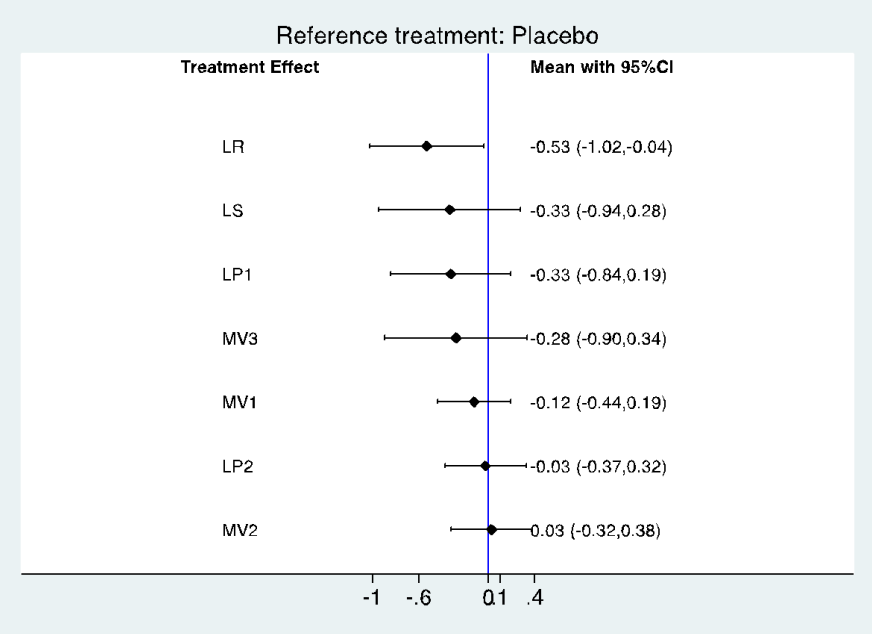


Figure 3a Figure 3b

Figure 3. Risk of bias summary for efficacy outcome (a) and safety outcome (b). Review authors' judgments about the risk of bias in all included studies. Positive signs indicate low risk. Exclamation marks indicate unclear risk. Negative signs indicate high risk.



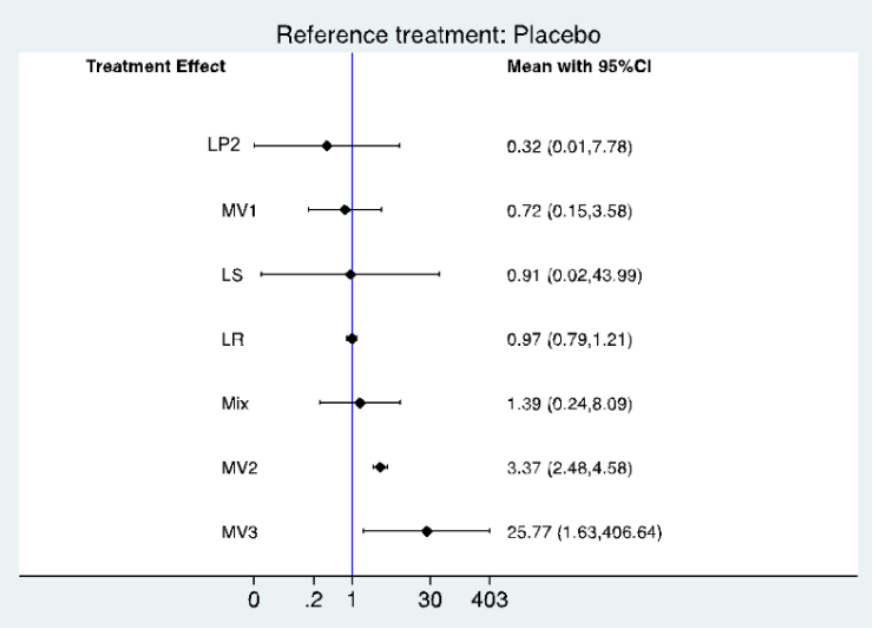


Figure 4a Figure 4b

Figure 4. Interval plot of postbiotic strains compared to placebo for the efficacy outcome in standardized mean difference (SMD) (a) and safety outcome in relative risk (RR) (b). The plot shows the strain-specific SMD for efficacy and RR for safety and their respective 95% confidence interval. For SMD, comparisons with negative treatment effect estimates at the left of the no-effect line (SMD = 0) favor the postbiotic strain, whereas positive treatment effect measures at the right favor the reference treatment, placebo. Relative risk and 95% CI less than 1 is indicative of the superiority of the intervention

over placebo in terms of safety, whereas relative risk and 95% CI greater than 1 indicate that the treatment intervention is inferior to placebo.