RESEARCH ARTICLE

The probiotics for the treatment of allergic rhinitis: a systematic review of randomized controlled trials

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ABSTRACT

The goal of this meta-analysis is to comprehensively assess the efficacy of probiotics in treating allergic rhinitis (AR). Two researchers independently screened the literature, extracted data, and assessed the methodological quality of the included studies. Subsequently, they utilized RevMan 5.3 software to perform meta-analysis, aiming to observe the effects of probiotics on various parameters such as RQLQ scores, RTSS, blood eosinophil count, total and antigen specific IgE levels. The pooled risk was calculated using either the fixed- or random-effects model depending on the presence of significant heterogeneity. The meta-analysis encompassed 36 randomized controlled trials, involving a total of 7,400 patients. The results revealed that the RQLQ global scores (mean difference [MD] = -9.43; P < 0.00001), RQLQ nasal scores (MD = -1.52; P = 0.03), and RTSS nasal scores (MD = -1.96; P = 0.02) showed significant enhancements. However, there were no significant differences observed in blood eosinophil count (MD = -0.09; P = 0.82), RQLQ eye scores (MD = -1.45; P = 0.07), RTSS global scores (MD = -2.24; P = 0.26), RTSS eye scores (MD = -0.39; P = 0.31), total serum IgE levels (MD = -0.04; P = 0.7), or antigen-specific serum IgE levels (MD = -0.08; P = 0.81) between the probiotic and placebo groups. Patients with AR who received probiotics saw significant improvements in their quality of life and symptoms when compared to the placebo group. This suggests a new possible application strategy for probiotics in AR.

Key words: Allergic rhinitis; allergy; randomized trial; meta-analysis; probiotics

Introduction

Allergic rhinitis (AR) is a condition affecting the nasal mucosa, triggered by allergic reactions mediated by immunoglobulin E (IgE) (Linton et al., 2021). It occurs when disruption of the epithelial barrier allows allergens to penetrate the mucosal epithelium of nasal passages, inducing a T-helper type 2 inflammatory response and production of allergen-specific IgE (Bernstein et al., 2024). Allergic rhinitis typically presents with symptoms of nasal congestion, rhinorrhea, postnasal drainage, sneezing, and itching of the eyes, nose, and throat (Campbell et al., 2008). The prevalence of AR has been rising over the past few decades, and AR is reported to affect up to 30% of the world population, while its incidence ranges from 10% to 20%, leading to impaired quality of life (Iftikhar et al., 2022). Contemporary medical interventions for AR include allergen avoidance, antihistamines, decongestants, and intranasal corticosteroids. However, these treatments may lead to side effects like dry mouth, drowsiness, and insomnia (Wang et al., 2016).

Numerous studies have highlighted the significant role of the intestinal microbiota in immune and allergic disorder Kim et al. (2018) recently proposed probiotics, for their minimal side effects, as a promising new therapy for allergic rhinitis (AR). Probiotics, living microorganisms found in foods such as yogurt, sauerkraut, and kimchi, have been shown to exert various beneficial effects in AR. These include the inhibition of lung airway inflammation and mast cell degranulation, prevention of airway remodeling, suppression of ovalbumin (OVA)-specific IgE/IgG1 expression, rebalancing of Th1/Th2 immune responses, and promotion of the anti-inflammatory cytokine interleukin (IL)-10 (Juan et al., 2017; Schaefer & Enck, 2019). Certain strains of microorganisms have been shown to have immunomodulatory properties, 4 including certain strains of *Lactobacillus* and *Bifidobacterium.* Furthermore, S*treptococcus* sp.,

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Enterococcus sp., and non-pathogenic strains of *Escherichia coli* have also been found to benefit the host (Sestito et al., 2020).

Dendritic cells, pivotal antigen-presenting cells, are instrumental in steering the differentiation of T helper (Th) cells toward either Th1 or Th2 responses. Probiotics have been demonstrated to stimulate the maturation of dendritic cells, thereby modulating the balance between Th1 and Th2 immune responses. This modulation occurs through the production of cytokines such as interleukin-12 (IL-12) and interferon (IFN), promoting Th1 responses, or by inhibiting Th2 responses through the reduction of key mediators like interleukin-4 (IL-4), specific IgE, IgG1, and IgA, particularly observed in murine models with OVA-induced food allergy (Borchers et al., 2009; Sardar & Hossain, 2022). Furthermore, additional research has indicated that probiotics have the potential to enhance patients' quality of life and decrease the necessity for medication use (Watts et al., 2016).

Presently, the research landscape regarding the efficacy of probiotics in treating allergic rhinitis (AR) yields mixed findings. While some studies have shown improvements in the quality of life questionnaire scores related to rhinitis, others have found no significant effects on total symptom scores, or symptom drug scores associated with rhinitis. Consequently, there remains a lack of consensus regarding the applicability of probiotics in AR treatment (Zajac et al., 2015). Recognizing this uncertainty, the current study rigorously assessed and analyzed existing randomized controlled trials (RCTs) investigating probiotics' role in AR treatment. By doing so, the study aimed to furnish clinicians with robust, evidence-based guidance on the judicious and safe use of probiotics in clinical AR management.

A significant limitation of this review is the absence of demonstrated therapeutic effects of probiotics on allergies and atopic diseases. Research, such as the study conducted by Szajewska & Horvath (2018) has shown that regardless of the timing of administration, probiotics do not lower the risk of eczema. Similarly, another study found that administering a combination of probiotics to preterm infants after birth had no discernible impact on the incidence of allergic diseases or atopic sensitization within the first two years of life (Plummer et al., 2020). Moreover, discrepancies in efficacy have been observed in comparative randomized controlled trials of atopic dermatitis treatment. While one probiotic strain exhibited effectiveness in treating atopic dermatitis, another strain proved to be entirely ineffective. These findings underscore the complexity and variability inherent in probiotic interventions across different allergic and atopic conditions, highlighting the need for further research and cautious interpretation of results (Zajac et al., 2015).

Materials and Methods

We compiled the results of the studies using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Figure 1) and we performed an overview of systematic reviews following the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions (Page et al., 2021).

Search strategy

Four databases (PubMed, EBSCO CINAHL, Web of Science, and Cochrane Library) were searched for randomized controlled trials on probiotics using the following keywords in different combinations: allergic rhinitis, allergy, rhinitis, and probiotics; Boolean operators were also employed. Every search was carried out till February 15, 2024. While we limited the language to English only, there were no restrictions on dates. We also manually searched the gray literature by looking through previously published systematic reviews' references. In addition, we utilized Google Scholar's key phrases to double-check the studies we included.

Study selection

For the deduplication process, the literature management programme EndNote X5 was utilized. Strict adherence to the inclusion and exclusion criteria was observed during the rigorous screening of the literature by two researchers, A. Alam and P. Banerjee, who then cross-checked their findings. The corresponding author, S. Islam, was consulted if there was a disagreement.

Inclusion criteria

1. English-language articles and RCTs involving probiotics as AR treatments in humans.
2. Age and gender were not restricted; all included subjects had a medical history spanning more than a year and had been identified with AR in the experiment using specific IgE and/or skin pricks, including seasonal and perennial AR.
3. The control group was given equivalent dosages of placebo items, while the patients in the experimental group received varying doses of probiotic products (milk, capsules, powder, etc.) containing probiotics.
4. Serum IgE levels, both total and antigen-specific, blood eosinophil count, global and nasal Rhinitis Quality of Life (RQLQ) scores, nasal and ocular RQLQ scores, and total and antigen-specific Rhinitis Total Symptom Scores (RTSS) global and nasal scores are the outcome markers.

Exclusion criteria

1. Controlled, nonrandomized trials.

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2. Case studies and tests with animals.
3. Clinical trials using ambiguous outcome measures.
4. Clinical trials with insufficient data and no author available for cross-checking the original data

Data extraction and quality evaluation

Researcher D. Sardar and researcher S. Islam extracted data and came to a consensus for the final inclusion of RCTs. Observation indicators, experimental findings, number of participants, age, experimental intervention measures, duration of intervention, first author, publication year, author nation, and single- or double-blind RCTs were among the information taken from the literature. Independent evaluations of each study's methodology were conducted in the interim.

The Cochrane Risk of Bias (ROB) was adopted to evaluate the methodological quality of included RCTs. The revised seven-point Jadad scale is used to evaluate studies that meet the inclusion criteria. This scale includes random sequence generation, allocation concealment, participant and staff blinding, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each of these domains was rated as "low," "unclear," or "high." A total quality score of less than four or more denoted good quality, correspondingly. An assessment risk bias graph was created using the results of the evaluation.

Data analysis and synthesis

The P and I^2values were calculated using the heterogeneity analysis between studies. If $I^2 \leq 30\%$ and $P \geq 0.10$ had occurred, which means low heterogeneity, then the fixed effect model would have been applied; if $I^2 > 30\%$ or $P < 0.10$ had occurred, which means statistically significant heterogeneity, then the random effects model would have been applied. RevMan 5.3 software was used for statistical analysis. The effect analysis statistics of enumeration data were expressed by mean difference (MD) or standardized mean difference (SMD), and $P < 0.05$ indicated that the difference was statistically significant.

Results

Search outcome

A total of 350 articles were found through the literature search. Two authors (D. Sardar, S. Islam) independently screened the papers after deleting duplicates of the identified research. The initial stage of screening focused on reading titles and abstracts, followed by full-text screening. Furthermore, after reading the entire paper text, it was filtered using the inclusion and exclusion criteria. Finally, 36 papers were included with about 7400 patients (the specific screening process is shown in Figure 1).

Basic characteristics of the included studies

The exact details of the included literature are shown in Table 1. The treatment time of the probiotics was between 3 weeks and 6 months. All studies described the baseline data of the patient's gender, age, region, and race in detail, whose differences were not statistically significant and comparable. The commonly used observation indicators were RQLQ (seven studies), RTSS (three studies), blood eosinophil count (seven studies), total IgE level (eight studies), and antigen-specific serum IgE levels (seven studies). The outcomes of the 27 studies showed that compared with placebo, probiotics had a therapeutic effect on at least one outcome index and 9 studies showed no therapeutic significance.

Risk assessment for bias in included studies

According to the bias risk assessment method recommended by the Cochrane library, 36 of the included studies had random allocation methods; 33 were double-blind; one was randomized crossover, and only five mentioned the allocation concealment. About 21 studies had lost follow-up data, and five were unclear about the reason for the loss of follow-up. None of the studies showed selective reporting outcomes; however, one research may have additional biases after the assessment. Figure 2 indicates the overall bias risk graph.

Total and antigen-specific serum IgE

The effects of probiotics on total and antigen-specific serum IgE levels were evaluated in eight and seven studies, respectively (Figure 3). The results of the meta-analysis indicated that there was no significant difference between the probiotic group's overall IgE levels and the placebo group's (SMD = −0.04; 95% confidence interval [CI], −0.23 to 0.15; P = 0.70) or antigen-specific serum IgE levels (SMD = −0.08; 95% CI, −0.72 to 0.56; P = 0.81). The meta-analysis of the total IgE level showed I2 = 0%, indicating no statistical heterogeneity between the two groups, using a fixed-effect model and weighted combined analysis. The antigen-specific serum IgE displayed I2 = 85% using the weighted combination analysis and random-effects model, showing a significant difference between the two groups. The Begg and Egger tests revealed no evidence of significant study bias (total IgE, p = 1.0 and p = 0.73, respectively; antigen specific IgE, p = 0.74 and p = 0.65, respectively.

Blood eosinophil count

The impact of probiotics on the blood eosinophil count was assessed in seven studies (Figure 4). The probiotic

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medication was administered to about 206 of the study participants, while the placebo treatment was given to 195 of them. The probiotic group and the placebo group did not vary statistically, according to the findings of a meta-analysis of

Table 1: *Characteristics of the included studies*

Study	Type	Patients (n)	Ages	Intervention (Probiotic strain)	Duration	Outcomes	Results	Jadad scores
Ahmed et al. (2019)	RCT-DB	106	26 ± 16.64 months	*Lactobacillus paracasei* (LP-33)	6 weeks	Change in clinical symptoms	No benefits	6
Aldinucci et al. (2002)	RCT-DB	20	19-44 years	*Lactobacillus acidophilus* and *Bifidobacterium*	4 months	Change in subjective symptoms	Decrease in NSS	3
Cox et al. (2023)	RCT-DB	165	18–65 years	*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51 and *Lactobacillus acidophilus* W55	8 weeks	Change in total symptom severity score	Reduction in symptom severity and reductions in medication use	3
Anania et al. (2021)	RCT-DB	117	10.5±3.1 years (probiotic) and 8.8±3.5 years (placebo)	*Bifidobacterium animalis* Subsp. Lactis BB12 and *Enterococcus faecium* L3	16 months	Change in NSS	Decrease in NSS	5
Chen et al. (2010)	RCT-DB	105	6–12 years	*Lactobacillus gasseri* A5	8 weeks	Change in subjective symptoms, total IgE	Decreased nasal allergic symptoms	4
Ciprandi et al. (2005)	RCT-DB	20	12–15 years	*Bacillus clausii*	3 weeks	Change in RTSS and medication use	No significant difference in RTSS; reduced medication use	3
Costa et al. (2014)	RCT-DB	425	18–60 years	*Lactobacillus paracasei* LP-33	5 weeks	Change in RQLQ, RTSS	Decreased RQLQ; no change in RTSS	4
Dölle et al. (2014)	RCT-DB	34	19–54 years	*Escherichia coli* strain Nissle 1917	6 months	Change in SMS	No benefit	4

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Dennis-Wall et al. (2017)	RCT-DB	81	18-60 years	*Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1, and *Bifidobacterium longum* MM-2	8 weeks	Change in MRQLQ and the total IgE	Decease in MRQLQ; no change in the total IgE	6
Giovannini et al. (2007)	RCT-DB	49	2-5 years	*Lactobacillus casei*	12 months	Change in time free from and number of episodes of asthma/rhinitis, total IgE	Decrease in annual rhinitis episodes; no change in total IgE	5
Han et al. (2023)	RCT-DB	20	18-60 years	*Lactobacillus plantarum*	4 weeks	Change in TNSS,TNNSS and RCAT compared to baseline	Change in sub-symptom score of rhinorrhea, itching, sneezing, and tearing; markedly decreased IgE level	4
Harata et al. (2017)	RCT-DB	14	36.9 ± 6.9 years (probiotic) and 36.5 ± 6.1 years (placebo)	*Lactobacillus rhamnosus* GG and *L. gasseri* TMC0356	10 weeks	Change in gut microbiota composition and blood lipid levels	With beneficial effects on the blood lipid levels and gut microbiota composition	4
Helin et al. (2002)	RCT-DB	15	14-36 years	*Lactobacillus rhamnosus*	5.5 months	Change in RTSS, respiratory and eye symptoms, and use of medications scores	No benefits	4
Ishida et al. (2005)	RCT-DB	49	34.0 ± 3.4 years (probiotic) and 36.9 ± 3.0 years (placebo)	*Lactobacillus acidophilus* L-92	8 weeks	Change in SMS, total IgE, antigen specific IgE	Improvement in nasal symptom-medication scores, no change in total IgE or antigen-specific IgE	3
Jan et al. (2011)	RCT-DB	98	8.1 ± 4.4 years (probiotic) and 8.0 ± 4.3 years (placebo	*Lactobacillus rhamnosus*	12 weeks	Change in SSS and the total IgE	No benefits	4

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Jerzynska et al. (2016)	RCT-DB	20	5-12 years	SLIT-*L. rhamnosus* GG	5 months	Change in symptom medication score	Decease in symptom-medication scores.	4
Kawase et al. (2009)	RCT-DB	40	20–57 years	*Lactobacillus* GG and *L. gasseri* TMC0356	10 weeks	Change in mean symptom score, mean symptom-medication score, total IgE, antigen-specific IgE	Decreased nasal blockage and medication score for nasal blockage; no change in total or antigen specific IgE	4
Lin et al. (2013)	RCT-DB	199	6–12 years	*Lactobacillus salivarius*	12 weeks	Change in SSS, SMS, total IgE	Reduction in nasal, eye, medication scores; no change in total IgE	4
Lue et al. (2012)	RCT	63	7–12 years	*Lactobacillus johnsonii* EM1	24 weeks	Changes in RTSS and PRQLQ	Decreased RTSS; no change in PRQLQ	3
Meng et al. (2019)	RCT	2	33.34 ± 3.21 years (probiotic) and 29.33 ± 4.13 years (placebo)	OM85-Broncho-Vaxom	8 weeks	Change in TNSS	Reduction in the total nasal symptom scores, itching score, nasal rhinorrhea score, and sneezing score; no change in nasal congestion score.	4
Schaefer et al. (2023)	RCT-DB	125		*Enterococcus faecalis*	6 weeks	Change in SMS, RQLQ and TNSS	Improved SMS; significantly stronger effects for TNNS and RQLQ	4
Nishimura et al. (2009)	RCT-DB	45	33.8 ± 2.0 years (high dose probiotic), 36.7 ± 1.2 years (low dose probiotic), 36.5 ± 2.8 years (placebo)	*Tetragenococcus halophilus* Th221	8 weeks	Change in disease severities, TNSS, total IgE, antigen specific IgE	Decreased total nasal symptom scores at high dose only; no change in sneezing rhinorrhea, or antigen specific IgE	4

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Nagata et al. (2010)	RCT-DB	55	18–27 years	*Lactobacillus plantarum* No. 14	6 weeks	Change in SMS, total IgE, antigen specific IgE	Decreased SMS and itchy eyes; no effect on medication intake	3
Nembrini et al. (2015)	RCT-DB	63	18-65 years	*Lactobacillus paracasei* NCC 2461	8 weeks	Change in symptoms scores, quality of life, and the specific IgE levels	No benefits	5
Ouwehand et al. (2009)	RCT-DB	47	4–13 years	*Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* BI-04	4 months	Change in subjective symptoms	No benefits	4
Peng & Hsu (2005)	RCT-DB	30	16.07 ± 2.11 years (live-probiotic); 14.50 ± 1.78 years (heat-killed probiotic); and 16.60 ± 2.02 years (placebo)	*Lactobacillus paracasei* 33	30 days	Change in modified PRQLQ	Decease in PRQLQ and bothersome symptoms and reduction in the frequency and dosage required for medical treatment.	5
Perrin et al. (2014)	RCT-DB	15	18-35 years	*Lactobacillus paracasei* NCC2461	4 weeks	Change in objective and subjective clinical symptoms	Decrease in nasal pruritus; no benefit on nasal congestion.	6
Singh et al. (2013)	RCT-DB	20	20-65 years	*Bifidobacterium lactis* NCC2818	8 weeks	Change in TNSS	Reduction in total nasal symptom scores	4
Sadeghi-Shabestari et al. (2020)	RCT	14	12.08 ± 34.15 years (probiotic) and 12.32 ± 29.64 years (placebo)	Kant's 10^9 CFU probiotics	8 weeks	Change in clinical symptoms	No benefits	4
Tamura et al. (2007)	RCT-DB)	120	39.3 ± 8.0 years (probiotic) and 39.5 ± 10.9 years (placebo	*Lactobacillus casei* Shirota	8 weeks	Change in SMS	No benefit	4

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Wang et al. (2004)	RCT-DB	80	15.87 ± 1.53 years (probiotic) and 14.00 ± 1.90 years (placebo)	*Lactobacillus paracasei*-33	30 days	Change in modified PRQLQ	Decreased PRQLQ (decreased frequency, level of bother)	4
J. Z. Xiao et al. (2006)	RCT-DB	40	23–61 years (probiotic) and 24–55 years (placebo)	*Bifidobacterium longum* BB536	14 weeks	Change in subjective symptoms	Decreased eye symptoms; no benefit in other symptoms	4
J. Z. Xiao et al. (2007)	RCT-DB	44	26–57 years (probiotic) and 22–48 years (placebo)	*Bifidobacterium longum* BB536	13 weeks	Change in subjective symptoms	Decreased symptom scores for rhinorrhea, congestion, and composite scores	4
J. Xiao et al. (2006)	RC	24	41.0 ± 8.0 years (placebo 1st) and 37.6 ± 7.5 years (probiotic 1st)	*Bifidobacterium longum* BB536	4 weeks	Change in subjective symptoms	No change in nasal symptom score; reduced throat and ocular symptoms	3
Yonekura et al. (2009)	RCT-DB	116	20–50 years	*Lactobacillus paracasei* KW3110	3 months	Change in RQLQ, antigen specific IgE	Improved quality of life when pollen scattering low.	4
Xu et al. (2016)	RCT-DB	44	25/26 years(median)	SIT with *Clostridium butyricum*	6 months	Change in NSS, medication scores, serum specific IgE levels and recurrence of clinical symptoms	Decrease in NSS, medication scores, serum specific IgE levels, and recurrence of clinical symptoms; maintained at least for 12 months.	4

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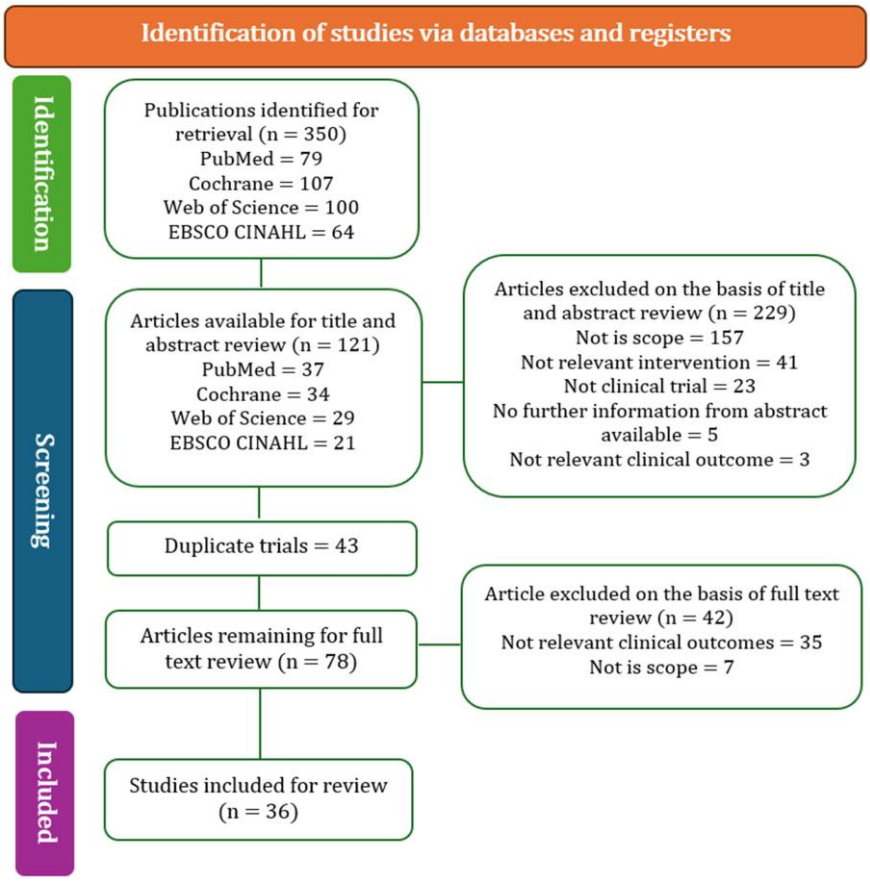

Figure 1. *PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow chart of literature searching and screening.*

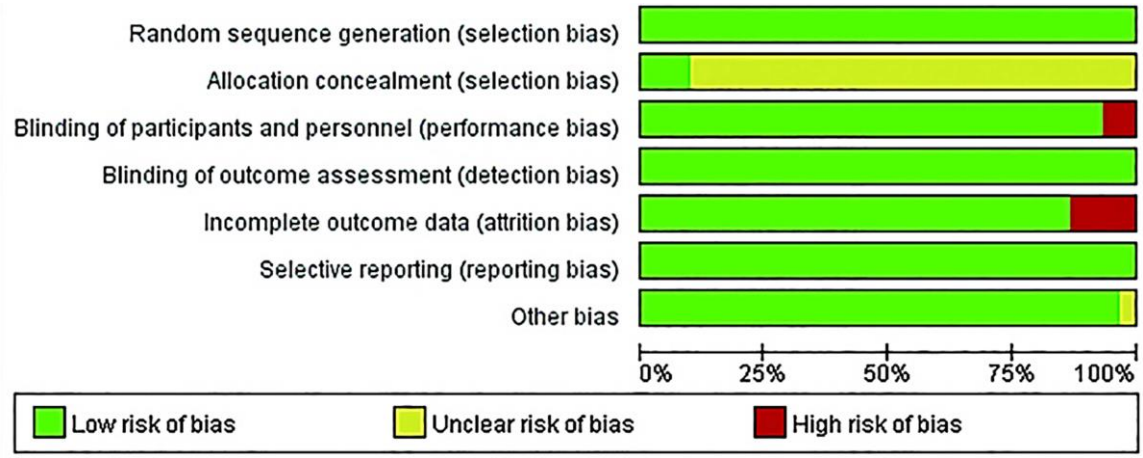

Figure 2. *Quality assessment of the included randomized controlled trials using the Cochrane Collaboration tool for assessing risk*

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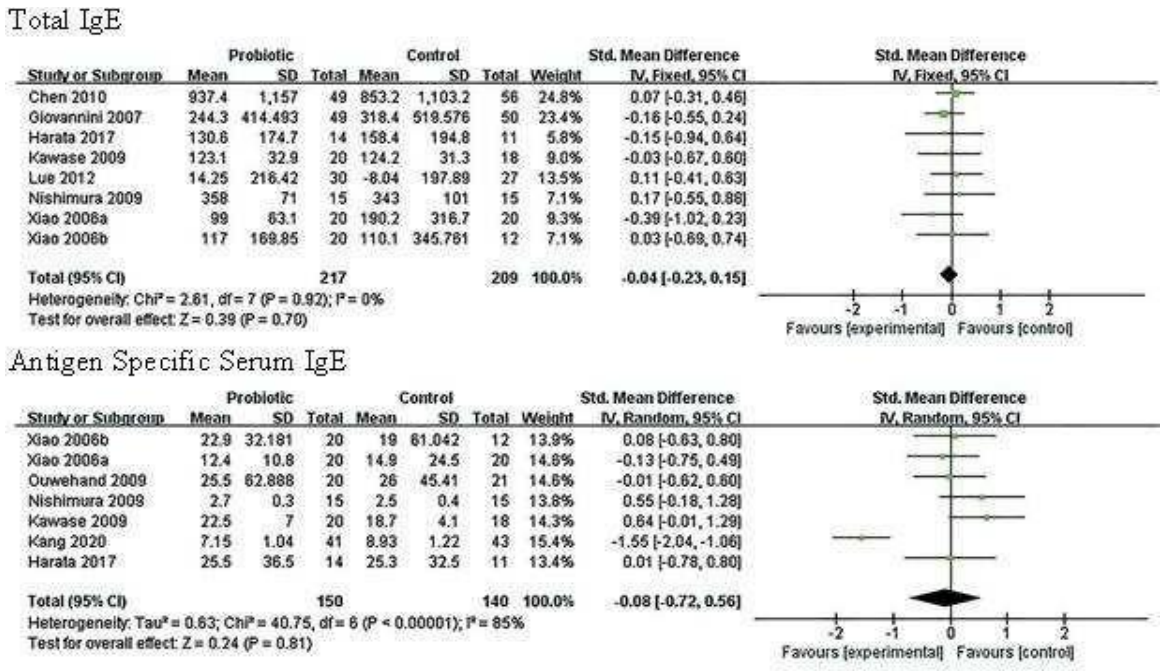

Figure 3. *Forest plot showing the comparison of probiotic versus placebo outcomes in the total and antigen specific IgE.*

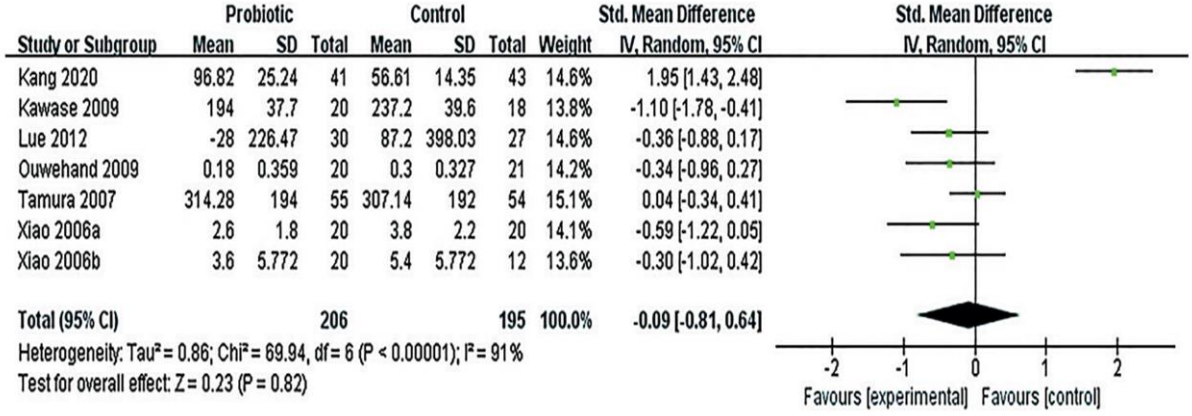

Figure 4. *Forest plot showing the comparison of probiotic versus placebo outcomes in the blood eosinophil count*

blood eosinophil levels (SMD = −0.09; 95% CI, −0.81 to 0.64; P = 0.82). There appears to be no heterogeneity between the two groups, as indicated by the I2 = 91% of the weighted combined analysis and the random-effects model.

Rhinitis quality of life questionnaire (RQLQ)

RQLQ is a popular and well-researched quality of life questionnaire that assesses how well rhinitis affects a patient's ability to go about their everyday life (Juniper et al., 1999). This specific metric was developed to evaluate the functional issues (physical, emotional, social, and vocational) related to AR. Of the seven studies that employed RQLQ, six of them permitted meta-analysis and direct comparison of descriptive data (Figure 5). These six studies' data comprised

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389 patients who received a placebo and 434 patients who received probiotic medication. The results of the meta-analysis demonstrated that the probiotic group's RQLQ overall scores (MD = −9.43 (95% CI, −11.71 to −7.15) and RQLQ nasal symptoms (MD = −1.52 (95% CI, −2.89 to −0.15); P = 0.03) were considerably better than those of the placebo group. The study findings indicated no statistical significance, but there was a trend of improvement in RQLQ eye symptoms (MD = −1.45 (95% CI, −3.04 to 0.14); P = 0.07). An I^2 of >50%, indicating significant heterogeneity, was found in a meta-analysis of RQLQ global scores and nasal and ocular symptom scores using a random-effects model and weighted combination analysis.

The Begg and Egger tests were used to statistically evaluate the risk of bias. It was found that neither test was significant (p = 0.16 and 0.09, respectively). Using the Begg and Egger tests, the risk of bias was evaluated quantitatively. At p = 0.16 and p = 0.09, respectively, neither test was statistically significant. The effect revealed in this meta-analysis, however, may be at least partially attributable to confounding variables and variations among trials, given the relatively low p values and high heterogeneity. The fact that the two larger, more recent studies found either a tiny difference or no difference between groups, whereas the two older, smaller studies demonstrated a pretty significant difference between placebo and probiotic, serves as evidence for this.

Rhinitis total symptom score (RTSS)

The primary indicators of AR patients' symptoms, both nasal and nonnasal, are measured by RTSS. For this meta-analysis, seven trials with adequate quantitative data utilizing the RTSS were considered (Figure 6). They comprised 253 patients who received a placebo and 260 patients who received probiotic medication. The probiotic group's RTSS global scores and RTSS eye symptom scores did not differ substantially from those of the placebo group, according to the results of the meta-analysis (MD = −2.24; 95% CI, −6.15 to 1.68; P = 0.26; and MD = −0.39; 95% CI, −1.13 to 0.36; P = 0.31). On the other hand, the probiotic group significantly outperformed the placebo group in the meta-analysis of RTSS nasal symptom scores, and this difference was statistically significant (MD = −1.96; 95% CI, −3.61 to −0.32; P = 0.02). With the random-effects model and weighted combination analysis, a meta-analysis of RTSS global scores and nose and eye symptom scores revealed an I^2 of >50%, indicating significant heterogeneity. According to the results of the Begg and Egger tests, there was no discernible study bias (p = 0.77 and0.47, respectively).

Adverse events

Adverse events included vomiting, diarrhoea, conjunctival itching, sublingual itching, and abdominal pain in seven of the included studies. These symptoms have no connection to probiotic intervention and could go away on their own in a short amount of time. Some trials recorded

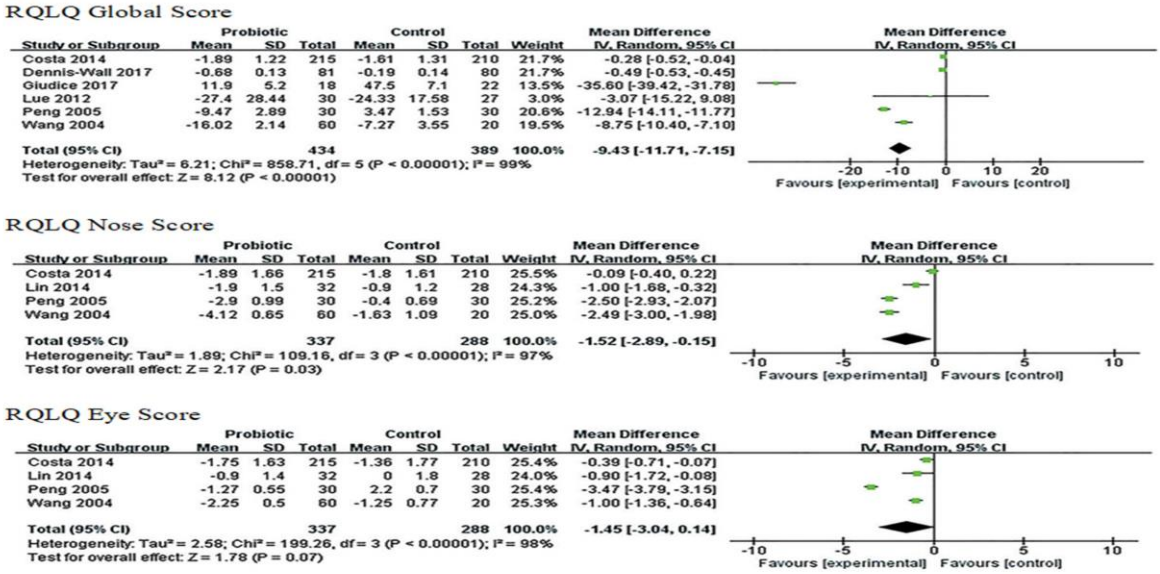

Figure 5. *Forest plot showing the comparison of probiotic versus placebo outcomes in the Rhinitis Quality of Life Questionnaire*

cases of flatulence; however these cases usually reflected the placebo group. No patients needed further care or intervention, and there were no major or potentially fatal adverse effects. Merely two patients failed to finish the study out of the 36 included trials, mostly as a result of an adverse event (flatulence).

Discussion

This systematic review and meta-analysis represent the most up-to-date and extensive examinations of probiotics' efficacy in addressing allergic rhinitis (AR) available to date.

When comparing probiotics to a placebo, the majority of trials showed at least some therapeutic effect. Both the RTSS nasal scores and the RQLQ global and nasal scores showed statistically significant improvements in the probiotic group. However, antigen-specific serum IgE levels, RQLQ eye scores, RTSS global and eye scores, and total IgE are not impacted by probiotics.

The concept of probiotics was first presented by Lilly et al. in early 1965 (Lilly & Stillwell, 1965). It has been demonstrated that taking probiotic supplements helps patients with a range of inflammatory conditions. For instance, a review paper looking at the therapeutic potential of probiotics for irritable bowel syndrome discovered that probiotic administration improved symptoms in almost two-thirds of controlled clinical trials (Watts et al., 2016). Oral probiotic delivery has shown demonstrated benefits in the management of atopic dermatitis and food allergies (Kim et al., 2018). It has even been demonstrated that probiotics can prevent liver cirrhosis patients from developing hepatic encephalopathy (Enaud et al., 2020).

According to Yamanishi & Pawankar (2020), the imbalance in the inferior turbinate nasal mucosal microbiota, which includes an increase in Staphylococcus aureus and a decrease in Propionibacterium acnes, was linked to an increase in total IgE levels in patients with AR. This suggests that environmental allergens, alterations in the body's response to allergic inflammation, and microbial changes in particular areas may all contribute to the pathophysiology of AR (Juniper et al., 1999). Probiotic strains that exhibit strong Th2 inhibitory activity can modify the intestinal microbiota's composition and the host immune system. They regulate the formation of tolerant dendritic cells, stimulate Toll-like receptors, and promote the lineage of immunosuppressive regulatory T cells (Watts et al., 2016). According to the

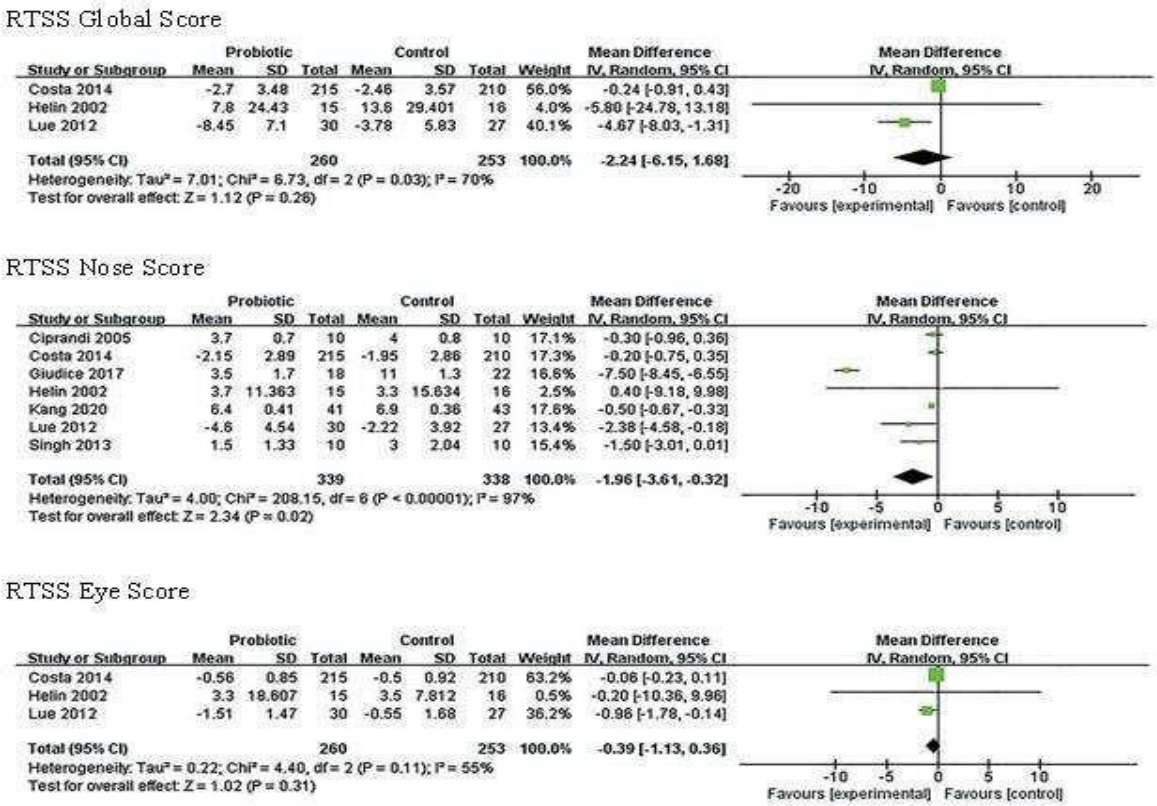

Figure 6. *Forest plot showing the comparison of probiotic versus placebo outcomes in the Rhinitis Total Symptom Score.*

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papers included in this meta-analysis, Lactobacillus and Bifidobacterium are the two main probiotics now utilized to treat illnesses. As this review summarizes, numerous RCTs have now also shown promise in the treatment of AR using probiotics.

We still don't fully understand how probiotics could affect atopic disorders. Probiotics have been shown in animal models to decrease Th2 responses and enhance T helper type 1 (Th1) immunity (Nishimura et al., 2009). Probiotic administrations significantly modify the gut microenvironment by encouraging alterations in the local microflora and cytokine secretion. It may also modify enterocytes' Toll-like receptors and proteoglycan recognition proteins, which in turn activates dendritic cells and elicits a Th1 response. Th2 responses may be inhibited by the subsequent activation of Th1 cytokines (Tang et al., 2015). According to other data, probiotics may change the gut microflora's composition, which could lead to an increase in the prevalence of regulatory T cells (Tregs) (Torii et al., 2007). They discovered that probiotics boost IL-10 and TGF-b levels via promoting Treg cell function while suppressing the Th2 response and the production of IL-4, IL-5, and IL-13 cytokines (Wang & Wang, 2015). Treatment with B. longum strains IM55, IM76, or their probiotic blend (PM) significantly reduces allergic nasal symptoms induced by ovalbumin (OVA), as well as OVA-induced increases in mouse blood IgE levels, and IL-4 and IL-5 levels in nasal tissue and bronchoalveolar lavage fluid (BALF). However, OVA-induced inhibition of IL-10 levels is increased, and the disrupted composition of gut microbiota, specifically Proteobacteria, Bacteroidetes, and Actinobacteria, is restored by this treatment. These findings suggest that B. longum strains IM55 and IM67 can alleviate allergic rhinitis by addressing Th2/Treg imbalance and disturbances in intestinal microbiota (Kim & Leung, 2018). Additionally, examination of BALF and draining lymph node samples from mice treated with L. plantarum strains CJLP133 and CJLP243 revealed a reduction in immune cell counts and the secretion of Th2 cytokines (IL-4, IL-5, and IL-13). However, there was an observed increase in Th1 cytokine secretion (IFN-γ), suggesting that this probiotic mixture can rebalance Th1/Th2 responses by bolstering the Th1 immune response and alleviating symptoms of allergic rhinitis triggered by birch pollen in mice (Choi et al., 2018). Holzapfel et al. (2001) discovered that the supernatant produced by lactic acid bacteria can dampen the activation of various immune cell subtypes triggered by S. aureus superantigens, including CD4+, CD8+, mucosal-associated invariant T cells, and natural killer (NK) cells. The probiotic mixture containing Lactobacillus inhibits the proliferation and degranulation of these cells, indicating that probiotics may modulate autoimmunity by influencing regulatory T cells (Treg) and T helper 17 cells (Th17) (Dipankar et al., 2022) However, much remains unclear regarding the role of probiotics in the human immune response. As a result, future study must dive further into the possible mechanisms of gut immunity in order to better understand and exploit probiotics' therapeutic potential in allergic rhinitis.

The present study suggests that probiotics hold promise in modifying the severity of disease, alleviating symptoms, and improving the quality of life for individuals with allergic rhinitis (AR). Most studies reported positive outcomes with no significant adverse effects. This systematic review and meta-analysis encompassed 36 studies involving 7,400 patients. However, due to incomplete data in some studies, the analysis was limited, and additional studies could not be included. The term "probiotic" is broad, and the effectiveness of specific formulations varies depending on factors such as geographical location, dietary habits, and the existing gut microbiota. This variability is reflected in the current study, where certain strains (e.g., L. paracasei 33) were found to be effective in treating grass pollen allergies, while others (e.g., Escherichia coli strain Nissle 1917) were not effective.(Costa et al., 2014; Perrin et al., 2014) Similar variations in effectiveness have been observed in other atopic disorders; in a comparative RCT, one probiotic strain was found to be beneficial for treating atopic dermatitis, while another proved to be totally worthless in the same condition (Wickens et al., 2008). Despite certain limitations, current study yields several key findings. Firstly, there are variations in probiotic composition, outcome measures, and intervention durations across the studies. Nonetheless, the majority of randomized controlled trials (RCTs) suggest that probiotics can enhance at least one outcome measure. Secondly, the research findings indicate significant improvements in RQLQ global and nasal scores, as well as RTSS nasal scores, within the probiotic group, demonstrating a statistically significant difference. However, no significant effect was observed on RQLQ eye scores. While RTSS global and eye scores in the probiotics group suggest relief from nasal symptoms in patients with AR, the effect on eye symptoms is less evident. These results may be attributed to the strengthening of the connection between intestinal microbes and lung diseases via the "lung-intestine axis" (Enaud et al., 2020). The respiratory system includes the nose, whereas the ocular system does not. Second, allergen accumulation in the conjunctiva, blockage of the nasolacrimal duct, and naso-ocular reflex are potential mechanisms of AR linked to symptoms related to the eyes.

However, the probiotics could not have complementary targets, meaning they can't treat ocular issues. Of course, further information on the precise mechanism will be needed in the future. There aren't many patients with problems in the majority of the included research. Lastly, there is no significant difference found between the probiotic and placebo groups in terms of total, antigen-specific serum IgE, or blood eosinophil count. This suggests that probiotics can enhance quality of life and that clinical symptoms are not significantly correlated with the regulation of these parameters. This finding is consistent with a study by Tamura et al. (2007) that found probiotics may alleviate subjective symptoms even in cases where there was no difference in immunological parameters such as allergen specific IgE level or Th1/Th2. It's interesting to note that, in contrast to earlier animal research, there was a tendency towards a decrease in antigen-specific blood IgE in the placebo group (Dennis-Wall et al., 2017; Meng et al., 2019). This would imply that probiotics' potential modulatory influence on IgE levels may not be connected to the physiological effects of the supplement on humans.

Probiotics have demonstrated beneficial effects in various inflammatory and immunologic conditions. The current systematic review indicates that they could potentially yield similar benefits in allergic rhinitis (AR), although the precise mechanism and duration of this effect remain uncertain. Future studies must address the limitations observed in existing randomized trials, particularly the inconsistencies in study designs and probiotic formulations, which hinder direct comparisons between studies. While recommending probiotics as a standalone therapy for AR is premature, they might ultimately emerge as a valuable adjunctive therapy for managing stubborn AR in specific patient groups.

Conclusion

Despite the heterogeneity in probiotic formulations, study designs, and outcome measures among the included randomized controlled trials (RCTs), this systematic review and meta-analysis suggest that probiotics exhibit a discernible effect in treating allergic rhinitis (AR). Presently, probiotics cannot be recommended as a standalone treatment for AR, but as a promising new therapy, they are anticipated to serve as an adjunctive therapy in AR management. Consequently, more large-scale studies with consistent outcome measures and high-quality prospective randomized controlled trials are warranted to furnish more robust evidence-based support for AR treatment.

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