



Role of Probiotics in Patients with Allergic Rhinitis: A Systematic Review of Systematic Reviews

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Abstract

Introduction Allergic rhinitis (AR) is estimated to affect up to 30% of the world population. With the rise in cases, newer treatment modalities have been explored. Probiotics have shown to reduce symptoms of AR and improve quality of life. A few systematic reviews have been published aiming to assess the role of probiotics in AR.

Objectives To consolidate the recent evidence with an overview of systematic reviews by extracting data regarding subjective outcomes (from quality of life questionnaires, the Total Nasal Symptom Score, the Total Ocular Symptom Score, the Daily Total Symptom Score, the incidence of AR, and the Rhinitis Total Symptom Score) and objective outcomes (levels of antigen-specific immunoglobulin E [IgE], total IgE, interleukin 10 [IL-10], interferon gamma [IFNG], eosinophil, and the T helper 1/T helper 2 [Th1/Th2] ratio).

Data Synthesis We conducted a literature search on the PubMed, EBSCO CINAHL, EBSCO Dentistry & Oral Sciences Source, and Cochrane Library up to April 14, 2020. The qualitative assessment was performed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool. A total of 419 titles were screened, and 3 systematic reviews met our eligibility criteria. Probiotics in the treatment of AR have been shown to improve quality of life, the total nasal and ocular symptom scores, the daily total symptom scores and Th1/Th2 ratio. No difference was ascertained for rhinitis total symptom score, and the rates of antigen-specific IgE, total IgE, IL-10, IFNG and eosinophil.

Conclusion The present review showed that there is considerable evidence that probiotics are useful in the treatment of AR. Further randomized trials targeting the limitations of the currently-available evidence can help ascertain the usefulness of probiotics in cases of AR.

Keywords

- ▶ allergic rhinitis
- ▶ probiotics
- ▶ nasal symptom score
- ▶ quality of life
- ▶ rhinosinusitis

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Introduction

The prevalence of allergic rhinitis (AR) has been rising over the past few decades,¹ and AR is reported to affect up to 30% of the world population,² while its incidence ranges from 10% to 20%,³ leading to impaired quality of life (QoL).⁴ These increasing cases are attributed to the “hygiene hypothesis,”⁵ which causes skewing of the T helper 1/T helper 2 (Th1/Th2) ratio toward the Th2 lineage,^{6,7} leading to an increase in serum Th2 mediated cytokines and interleukins (ILs), such as IL-3, IL-4 and IL-13.⁸ Subsequently, it causes induction of immunoglobulin (Ig) E and tissue infiltration by eosinophils.⁸ Some authors⁹ believe that childhood infections have less to do with AR, but this may be attributed to changes in modern practices. These may have in turn led to changes in gut microbiota that predispose an individual to develop allergies later in life, giving rise to the “microbial hypothesis.”⁹ Hence, it is postulated that the introduction of microbiota may have an immunomodulatory role.⁴

Probiotics are live microorganisms that, when administered in adequate amounts, provide a health benefit to the host.¹⁰ They are naturally found in food products such as dark chocolate, pickles, miso, and, famously, in yogurt.¹¹ Probiotics are thought to act on the gut-associated lymphoid tissue⁸ by causing dendritic cell maturation, which, in turn, causes a shift towards Th1 response.⁶ They cause dendritic cell maturation, which, in turn, causes a shift toward Th1 response.⁶ This either takes place through generation of interferon gamma (IFNG) and IL-12, or by downplaying the Th2 response by reduction of IgG1, IL-4 and IgA.^{6,8} Certain strains of microorganisms have been shown to have immunomodulatory properties,⁴ including certain strains of *Lactobacillus* and *Bifidobacterium*. Furthermore, *Streptococcus sp.*, *Enterococcus sp.*, and non-pathogenic strains of *Escherichia coli* have also been found to benefit the host.⁶

A few clinical trials have reported improvements in allergic respiratory disease with the use of probiotics. Similarly, the administration of probiotics has been shown to be beneficial in reducing the risk of developing eczema. However, there are trials that have not shown any significant benefit with use of probiotics. This has led to the performance of various systematic reviews published in recent years which have had some conflicting findings. Therefore, we aimed to conduct an overview of systematic reviews with particular attention to the use of probiotics in the treatment of patients with AR to shed light on their usefulness.

Review of the Literature

We conducted an overview of systematic reviews in accordance with the methods described by the Cochrane Handbook for Systematic Reviews of Interventions.¹² We reported the outcomes of the studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement¹³ (► Fig. 1).

Literature Search

We conducted a literature search on four databases (PubMed, EBSCO CINAHL, EBSCO Dentistry & Oral Sciences Source, and

Cochrane Library) using the following keywords in various combinations: *allergic rhinitis*, *allergy*, *rhinitis*, and *probiotics*; we also used Boolean operators. All searches were conducted until 1 April 14, 2020. There were no date restrictions; however, we restricted language to English only. We also performed a manual search of the gray literature by reviewing the references of previously-published systematic reviews. Furthermore, we also used key terms on google scholar to cross-check our included studies.

Study Selection

The inclusion criteria were as follows: systematic reviews conducted only on adult human subjects to assess the efficacy of probiotics on AR. The exclusion criteria were reviews on asthma along with AR, narrative reviews, or any study design other than systematic reviews, studies that did not explicitly report details on the qualitative assessment of the included trials, and systematic reviews not including randomized controlled trials.

All titles and abstracts were reviewed by two authors independently. As a first step, duplicates were removed. This was followed by full-text reading of the remaining titles. Any disagreement between the two authors was resolved through discussion. In case of further disagreement, a third author was sought. The included studies are listed in ► Table 1 and the excluded studies, in ► Table 2. A total of 419 titles were screened, and 3 systematic reviews met the inclusion criteria, the ones by Zajac et. al.¹¹ (2015), Peng et. al.⁴ (2015), and Güvenç et. al.¹⁴ (2016). Güvenç et. al.¹⁴ and Zajac et. al.¹¹ used the Jadad scale to assess quality, while Peng et. al. used the Cochrane Handbook.

Data Collection

Data was independently collected by two authors (HI and MOA) according to a preprepared data extraction sheet. The data extracted was as follows: year of publication, authors, journal title, number and types of studies included, number of studies screened, and number of trials included in each systematic review. We also collected data for the tool used to assess the quality of each trial, such as the types of probiotics used, the outcomes in terms of QoL, the nasal and ocular symptom scores, and the assessment of hematological markers, which included the levels of antigen-specific IgE, total IgE, IL-10, IFNG, eosinophil, and the Th1/Th2 ratio.

We reported the mean differences along with confidence intervals (CIs) for the outcomes. In case of any outcome that was not included in the meta-analysis, we reported it in our paper in the same way it was reported in the original paper, to avoid the risk of omitting any significant component of AR. Both reviewers cross-checked the studies to eliminate any duplication or mistaken addition for the final data extraction.

Assessment of the Quality of the Reviews

Two authors independently assessed the quality of the systematic reviews. Again, any discrepancy was resolved through discussion. To assess the risk of bias of the included systematic

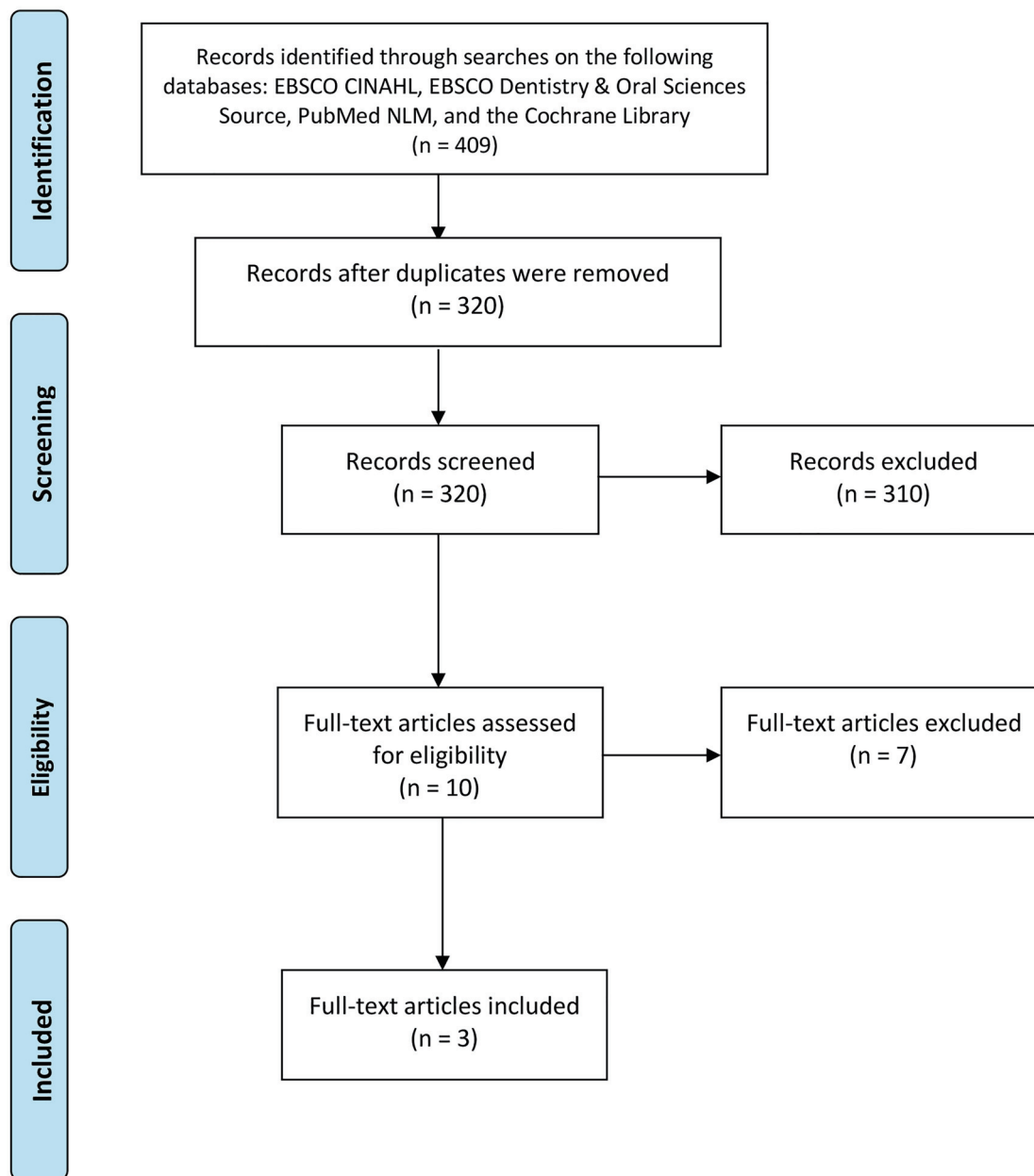


Fig. 1 Flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

reviews, we used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool,¹⁵ which is composed of sixteen components graded as yes, partial yes, and no according to given guidelines (► **Table 3**).

Evidence Synthesis

Data was extracted by both reviewers according to a data extraction sheet. We reported the outcomes as they had been described in the individual systematic reviews, including the

Table 1 Characteristics of the included systematic reviews

Authors	Year	Country	Journal	Quality Assessment	No. of Studies Screened	No. of Trials Included
Güvenç et. al. ¹⁴	2016	Turkey	<i>American Journal of Rhinology and Allergy</i>	Jadad scale	451	22
Peng et. al. ⁴	2015	China	<i>American Journal of Rhinology and Allergy</i>	Cochrane Handbook	496	11
Zajac et. al. ¹¹	2015	United States	<i>International Forum of Allergy & Rhinology</i>	Jadad scale	153	23

Table 2 Studies excluded from the present review

Authors	Year	Country	Journal	Reason for exclusion
Vliagoftis et al.	2008	Canada and Greece	<i>Annals of Allergy, Asthma & Immunology</i>	Contained trials on asthma
Du et al.	2019	China	<i>Allergy and Asthma Proceedings</i>	Contained trials on asthma, wheeze
Das et al.	2013	India	<i>BioMed Research International</i>	Contained data about asthma as well
Batchelor et al.	2010	United Kingdom	<i>Clinical and Experimental Dermatology</i>	Review of atopic eczema
Du et al.	2019	China	<i>Allergy and Asthma Proceedings</i>	Study of respiratory tract allergies, essentially asthma
Melli et al.	2015	Brazil	<i>Allergologia et Immunopathologia</i>	Overall change in allergic diseases
Zuccotti et al.	2015	Italy	<i>European Journal of Allergy and Clinical Immunology</i>	Evaluated atopic disease in infants

mean differences, CIs, and *p*-values of the groups who received probiotics and the control groups.

Outcome Measurements

The outcome measurements were divided into two groups: subjective outcomes (QoL questionnaires, the Total Nasal

Table 3 Risk of bias of the included systematic reviews as per the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool

	Güvenç et. al. ¹⁴	Peng et al. ⁴	Zajac et al. ¹¹
Item 1	Yes	Yes	Yes
Item 2	No	No	No
Item 3	Yes	No	No
Item 4	Yes	Partial Yes	No
Item 5	Yes	No	Yes
Item 6	Yes	Yes	No
Item 7	Yes	No	No
Item 8	Partial Yes	Partial Yes	Partial Yes
Item 9	Yes	Yes	Yes
Item 10	No	No	No
Item 11	No	Yes	No
Item 12	No	No	No
Item 13	No	Yes	No
Item 14	No	Yes	Yes
Item 15	Yes	No	Yes
Item 16	Yes	Yes	Yes

Symptom Score, the Total Ocular Symptom Score, the Daily Total Symptom Score, the incidence of AR, and the Rhinitis Total Symptom Score [RTSS]) and objective outcomes (levels of antigen-specific IgE, total IgE, IL-10, IFNG, eosinophil, and the Th1/Th2 ratio) (► **Tables 1, 4,5,6**).

Quality of Life

We used QoL questionnaires were used in all three systematic reviews^{4,11,14} analyzed in this study. Güvenç et. al.¹⁴ reviewed three studies,^{16–18} with a total of 308 patients, which analyzed nasal QoL scores before and after treatment, and determined that the use of probiotics improved the scores by a significant margin compared with the scores of patients receiving placebo (standardized mean difference [SMD]:2.30; 95%CI: -3.93 to -0.67; *p* = 0.006). In addition to these, Güvenç et. al.¹⁴ also analyzed the total QoL scores of five studies^{16–20}, with a total of 793 patients, which were also found to be significantly lower in patients who were administered probiotics compared with patients taking placebo (SMD: -1.84; 95%CI: -2.94 to -0.74; *p* < 0.001).

Güvenç et. al.¹⁴ also analyzed the QoL scores of patients who were administered a specific strain of probiotic called *Lactobacillus paracasei* (LP-33), which was used in two studies^{16,17} assessing nasal and ocular QoL scores, which were found to significantly decrease in comparison to those of the placebo group (SMD: -2.96; 95%CI: -3.38 to -2.55; *p* < 0.001; and SMD: -4.03; 95%CI: -6.23 to -1.83; *p* < 0.001, respectively). In addition to this, three studies,^{16,17,19} with a combined sample of 595 patients, also reported significant improvements in nasal QoL scores (SMD: -2.31; 95%CI: -4.43 to -0.27; *p* = 0.026) and ocular QoL scores, in the intervention group compared to the placebo group (SMD: -3.33; 95% CI:

Table 4 Effect of probiotics on objective outcome measures in allergic rhinitis

Authors	Antigen-specific IgE	Total IgE	Rhinitis Total Symptom Score	IL-10	IFNG	Th1/Th2 Ratio	Eosinophil
Güvenç et. al. ¹⁴	No	No	No	No	No	Yes	No
Peng et. al. ⁴	Yes	No	No	Yes	Yes	Yes	Yes
Zajac et. al. ¹¹	Yes	Yes	Yes	No	No	No	No

Abbreviations: IFNG, interferon gamma; IgE, immunoglobulin E; IL-10, interleukin10; Th1/Th2, T helper 1/T helper 2.

Table 5 Effect of probiotics on subjective outcome measures in allergic rhinitis

Author	Quality of life	Total Nasal Symptom Score	Total Ocular Symptom Score	Daily Total Symptom Scores	Incidence of allergic rhinitis
Güvenç et. al. ¹⁴	Yes	Yes	Yes	Yes	No
Peng et. al. ⁴	Yes	Yes	No	No	Yes
Zajac et. al. ¹¹	Yes	No	No	No	No

Table 6 Strain of probiotics studied in the systematic reviews

Author	Study design	<i>Lacto bacillus</i>	<i>Bifido bacterium</i>	<i>E. coli</i>	<i>Tetragenococcus</i>	<i>Streptococcus</i>
Güvenç et. al. ¹⁴	Randomized double-blinded trial	Yes	Yes	Yes	Yes	No
Peng et. al. ⁴	Randomized double-blinded trial	Yes	Yes	No	No	Yes
Zajac et. al. ¹¹	Randomized double-blinded trial ²¹ and randomized cross-sectional study ²	Yes	Yes	Yes	Yes	No

-5.97 to -0.69; $p = 0.013$). As for the total QoL scores, these three studies^{16,17,19} concluded that the use of LP-33 significantly decreased the scores of the intervention group compared with the placebo group (SMD: -2.70; 95%CI: -4.90 to -0.49; $p = 0.016$). Peng et. al.⁴ included two trials^{16,17} that used QoL questionnaires to analyze the effects of probiotics in AR. These two trials^{16,17} had a total sample of 140 patients, with 90 patients receiving intervention and 50 patients receiving placebo. They did not observe differences in QoL scores between the two groups in terms of frequency (SMD: -5.60; 95%CI: -16.92 to 5.72; $p = 0.33$) and severity (SMD: -4.40; 95%CI: -9.84 to 1.04; $p = 0.11$). However, a combined analysis of the nasal symptom and QoL scores in both these trials determined that the intervention group had improved scores (SMD: -2.97; 95%CI: -4.77 to -1.16; $p = 0.001$). Zajac et. al.¹¹ included four studies^{16,17,19,20} with a total sample of 622 patients (intervention group 335 patients; control group: 287 patients). Significant improvements were observed in the intervention group regarding the total QoL scores (SMD: -2.23; 95%CI: -4.07 to -0.40; $p = 0.02$) and nasal QoL scores (SMD: -1.21; 95%CI: -1.42 to -0.99; $p < 0.00001$); however, no significant differences observed in ocular QoL scores between the two groups (SMD: -1.45 95%CI: -3.04 to 0.15; $p = 0.08$).

Total Nasal Symptom Score

The Total Nasal Symptom Score was evaluated in two systematic reviews.^{4,14} Güvenç et. al.¹⁴ pooled a total of 10 studies,^{16-18,20-26} with a total of 801 AR. Out of these ten, two studies^{17,21} assessed one type of probiotics each and were therefore included in this pooled analysis: Peng et. al.¹⁷ evaluated heat-killed and live forms of LP-33, while Nishimura et. al.²¹ assessed low and high doses of *Tetragenococcus halophilus* Th221. The analyses of these 10 studies revealed a significant drop in nasal symptom scores in the intervention groups versus the placebo groups (SMD: -1.23; 95%CI: -1.84 to -0.62; $p < 0.001$). Güvenç et. al.¹⁴ also performed a subgroup analysis of patients diagnosed with seasonal AR (SAR) and perennial AR (PAR). They found 5 studies^{18,22,23,25,26} that

included a total of 286 SAR patients, which reported lower nasal symptom scores in the intervention group (SMD: -0.62; 95%CI: -0.93 to -0.31; $p < 0.001$). Peng et. al.⁴ included two trials^{16,17} that evaluated nasal symptom scores, with a total of 140 patients (90 in the intervention and 50 in the placebo group), and found no differences in both groups in terms of frequency (SMD: -0.96; 95%CI: -3.78 to 1.96; $p = 0.51$) and severity (SMD: -1.11; 95%CI: -3.38 to 1.17; $p = 0.11$). However, a combined analysis of the nasal symptom and QoL in both these trials determined that the intervention group had significantly improved scores (SMD: -2.97; 95%CI: -4.77 to -1.16; $p = 0.001$).

Total Ocular Symptom Score

The Total Ocular Symptom Score was only evaluated by Güvenç et. al.¹⁴ through 7 studies^{16-18,20,24-26} with a total sample of 692 patients. They found that the score was significantly decreased in the intervention group compared with the placebo group (SMD: -1.84; 95%CI: -2.83 to -0.84; $p < 0.001$). Güvenç et. al.¹⁴ also performed subgroup analysis of SAR and PAR patients. The SAR subgroup included 3 studies^{18,25,26} with a total of 226 patients, and the Total Ocular Symptom Scores of the intervention group were significantly reduced (SMD: -0.39; 95%CI: -0.67 to -1.11; $p = 0.006$). And the PAR subgroup included 4 studies^{16,17,20,24} with a total of 470 patients, and the scores of the intervention group were significantly reduced (SMD: -2.78; 95%CI: -4.27 to -1.29; $p < 0.001$).

Daily Total Symptom Score

The Daily Total (nasal and ocular) Symptom Score was only assessed by Güvenç et. al.¹⁴ The Daily Total Nasal Symptom Scores were analyzed in 8 studies,^{18,20-26} with a total of 631 patients, and an improvement in AR in the intervention group was observed (SMD: -0.67; 95%CI: -1.15 to -0.19; $p = 0.007$). And the ocular symptoms were assessed in 4 studies,^{20,24-26} with a total of 384 patients, and were found to be significantly reduced in the intervention group (SMD:

-0.70; 95%CI: -1.81 to -0.45; $p < 0.001$). Güvenç et. al.¹⁴ also included 3 studies^{18,21,22} (total sample of 227 patients) that used the Japanese guidelines for AR²⁷ to evaluate the Daily Total Nasal Symptom Scores, and observed a significant drop in the scores of the intervention group (SMD: -0.34; 95% CI: -0.62 to -0.07; $p = 0.015$).

Incidence of Allergic Rhinitis

Only Peng et. al.⁴ evaluated the incidence of AR as an outcome measure. They included 5 trials²⁸⁻³² with a total of 758 cases and 769 controls, and observed no significant differences between the groups (odds ratio [OR]: 1.07; 95% CI: 0.81 to 1.42; $p = 0.64$).

Rhinitis Total Symptoms Score

The RTSS was only assessed by Zajac et. al.,¹¹ and they were divided into eye and nose symptoms, and the global scores. The meta-analyses for the eye and nose symptoms included 3 studies^{19,33,34} (513 patients, 260 cases and 253 controls). No difference was found between the two groups regarding eye symptoms (SMD: -0.10; 95%CI: -0.26 to 0.07; $p = 0.25$) and nose symptoms (SMD: -0.82; 95%CI: -2.41 to 0.78; $p = 0.32$). The RTSS global scores were analyzed through 4 studies^{19,33-35} (270 cases and 263 controls), and no significant differences were found between the groups (SMD: -0.36; 95% CI: -0.83 to 0.10; $p = 0.13$).

Antigen-Specific IgE

Antigen-specific IgE was evaluated as an outcome measure in two systematic reviews.^{4,11} Peng et. al.⁴ analyzed a total of three different articles^{25,26,36} with had a total sample of 105 patients (56 cases and 49 controls), and found no significant differences between the groups (SMD: 0.10; 95%CI: -0.29 to 0.49; $p = 0.62$). Zajac et. al.¹¹ evaluated antigen-specific IgE in 7 studies^{18,21,22,25,26,36,37} with a total sample of 359 patients (185 cases and 174 controls), and observed differences between the two groups that were not significant, but noted that there was a trend toward decreasing antigen-specific IgE levels (SMD: 0.20; 95%CI: -0.01 to 0.41; $p = 0.06$).

Total IgE

Total IgE was only evaluated by Zajac et al.¹¹ through 8 studies^{21,22,25,26,36-39} with a total sample of 446 patients (224 cases and 222 controls), and found not significant differences between the groups (SMD: 0.01; 95%CI: -0.18 to 0.19; $p = 0.94$).

IL-10

The levels of IL-10 were only assessed by Peng et. al.⁴ through 2 studies^{25,26} with a total sample of 72 patients (40 cases and 32 controls), and they found no significant differences between the groups (SMD: 0.43; 95%CI: -0.05 to 0.90; $p = 0.08$).

IFNG

The levels of IFNG were also evaluated by Peng et. al.⁴ through the same 2 studies^{25,26} that analyzed IL-10 levels, and neither did the found significant differences between the groups (SMD: 0.15; 95% CI: -0.32 to 0.62; $p = 0.53$).

Th1/Th2 Ratio

This outcome measure was included in two systematic reviews.^{4,14} Peng et. al.⁴ evaluated the Th1/Th2 ratio through 2 studies^{36,37} with a total sample of 82 patients (41 cases and 41 controls), and found no significant differences between the two groups (SMD: 0.39; 95%CI: -0.05 to 0.83; $p = 0.08$). And Güvenç et. al.¹⁴ analyzed it through 5 studies,^{18,22,36,37,40} and found that the Th1/Th2 ratio was significantly lower in the intervention group (SMD: -0.78; 95%CI: -1.53 to -0.02; $p = 0.045$).

Eosinophil Rates

Eosinophil rates were used as an outcome measure by Peng et. al.,⁴ who analyzed them through 3 studies^{25,26,37} with a total sample of 121 patients (65 cases and 56 controls), and found no significant differences between the groups (SMD: -0.39; 95%CI: -0.95 to 0.17; $p = 0.18$).

Qualitative Assessment

We used AMSTAR-2 to evaluate the quality of the evidence of the systematic reviews, which, overall, was moderate to low. The most common flaw was the lack of a list of the reasons for exclusion of certain studies. There was no significant methodological flaw in any of the studies, except one which did not explicitly explain the eligibility criteria using the Population, intervention, comparison and outcome (PICO) process.

None of the studies included in the present systematic review mentioned the source of funding. Similarly, no justification was provided regarding how different study parameters were pooled for the meta-analyses. This was imperative, as different trials used different probiotics and assessed outcomes at different intervals.

Discussion

Probiotics have been used clinically to treat a variety of inflammatory disorders such as food allergies^{41,42} and atopic dermatitis.⁴³ Their use has also been reported to improve symptoms in approximately two thirds of irritable bowel syndrome patients in a controlled trial,⁴⁴ as well as to decrease the incidence of hepatic encephalopathy in liver cirrhosis patients.⁴⁵ While their exact mechanism of action may still elude us, evidence indicates that probiotics are useful in the treatment of inflammatory disorders, including AR, as shown in the present review. The use of probiotics in the treatment of AR can offer improved quality of life. Zajac et. al.¹¹ reported no serious adverse effects and no instances of patients requiring additional intervention following probiotic therapy. The few adverse effects reported in the intervention group included flatulence, abdominal pain, and diarrhea, and they were essentially similar to the adverse effects reported among the control group. In fact, in the 23 studies reviewed by Zajac et. al.,¹¹ only 1 patient out of ~2,000 dropped out due to an adverse effect.

The present review reports significant improvements after the use of probiotics by AR patients in most of the subjective outcomes, the including QoL questionnaires, The Total Nasal Symptom score, the Total Ocular Symptom score,

and the Daily Total Symptom Score. However, two subjective outcome measures (the incidence of AR and the RTSS) were not found to be significantly altered. Zajac et al.¹¹ noted that this may be due to the low number of patients incorporated in most of the studies that were included in their systematic review. None of the objective outcomes reported in the present study were found to be statistically significant, except for the Th1/Th2 ratio in Güvenç et al.¹⁴ The authors noted that the decrease in the Th1/Th2 ratio was the first time, to their knowledge, that an immunological parameter had been shown to significantly change with the use of probiotics in AR patients. This finding indicates that the use of probiotics for the treatment of AR may yield significant objective evidence in addition to subjective evidence.

A limitation of the present study was related to the wide variability of factors within the data. An example of this is the wide range of probiotics used in different studies. The species of probiotics used ranged from *Lactobacillus*, *E. coli*, *Bifidobacterium*, *Tetragenococcus*, and *Streptococcus*. This wide range of probiotics, as well as the differences in the dosages used and the times at which they were administered may have had an impact on the outcomes measured and therefore altered the results. This limitation can be addressed by conducting a large, controlled trial that uses identical doses and administration methods.

Final Comments

The present review showed that there is considerable evidence that probiotics are useful in the treatment of AR. Further randomized trials targeting the limitations of the evidence currently available can help ascertain the usefulness of probiotics as a therapeutic agent for AR, with regards to both subjective and objective measures.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

- Bousquet J, Khaltaev N, Cruz AA, et al; World Health Organization GA(2)LEN Allergen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and Allergen). *Allergy* 2008;63(Suppl 86):08–160
- Pawankar R, Canonica GW, Holgate ST, Lockett RF, Blaiss MS. WAO white book on allergy. Milwaukee: WI World Allergy Organ; 2011;3:156–157
- Small P, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol* 2011;7(1, Suppl 1):S3
- Peng Y, Li A, Yu L, Qin G. The role of probiotics in prevention and treatment for patients with allergic rhinitis: A systematic review. *Am J Rhinol Allergy* 2015;29(04):292–298
- Strachan DP, Warner J, Pickup J, Schweiger MPH, Stanwell-Smith R, Jones M. The hygiene hypothesis. *BMJ* 1989;299:1259–1260
- Borchers AT, Selmi C, Meyers FJ, Keen CL, Gershwin ME. Probiotics and immunity. *J Gastroenterol* 2009;44(01):26–46
- Christodoulou P, Cameron L, Durham S, Hamid Q. Molecular pathology of allergic disease. II: Upper airway disease. *J Allergy Clin Immunol* 2000;105(2 Pt 1):211–223
- Özdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol* 2010;160(03):295–304
- Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? *Nat Rev Microbiol* 2009;7(12):887–894
- Ouweland AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. *World J Gastroenterol* 2009;15(26):3261–3268
- Zajac AE, Adams AS, Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis. In: *International forum of allergy & rhinology*. Wiley Online Library; 2015:524–532
- Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol. 5. The Cochrane Collaboration; 2009
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700
- Güvenç IA, Muluk NB, Mutlu FŞ, et al. Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis. *Am J Rhinol Allergy* 2016;30(05):157–175
- Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008
- Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. *Pediatr Allergy Immunol* 2004;15(02):152–158
- Peng G-C, Hsu C-H. The efficacy and safety of heat-killed *Lactobacillus paracasei* for treatment of perennial allergic rhinitis induced by house-dust mite. *Pediatr Allergy Immunol* 2005;16(05):433–438
- Yonekura S, Okamoto Y, Okawa T, et al. Effects of daily intake of *Lactobacillus paracasei* strain KW3110 on Japanese cedar pollinosis. *Allergy Asthma Proc* 2009;30(04):397–405
- Costa DJ, Marteau P, Amouyal M, et al. Efficacy and safety of the probiotic *Lactobacillus paracasei* LP-33 in allergic rhinitis: a double-blind, randomized, placebo-controlled trial (GA2LEN Study). *Eur J Clin Nutr* 2014;68(05):602–607
- Lin W-Y, Fu L-S, Lin H-K, Shen C-Y, Chen Y-J. Evaluation of the effect of *Lactobacillus paracasei* (HFA00232) in children (6–13 years old) with perennial allergic rhinitis: a 12-week, double-blind, randomized, placebo-controlled study. *Pediatr Neonatol* 2014;55(03):181–188
- Nishimura I, Igarashi T, Enomoto T, Dake Y, Okuno Y, Obata A. Clinical efficacy of halophilic lactic acid bacterium *Tetragenococcus halophilus* Th221 from soy sauce moromi for perennial allergic rhinitis. *Allergol Int* 2009;58(02):179–185
- Kawase M, He F, Kubota A, et al. Effect of fermented milk prepared with two probiotic strains on Japanese cedar pollinosis in a double-blind placebo-controlled clinical study. *Int J Food Microbiol* 2009;128(03):429–434
- Singh A, Hacini-Rachinel F, Gosoni ML, et al. Immune-modulatory effect of probiotic *Bifidobacterium lactis* NCC2818 in individuals suffering from seasonal allergic rhinitis to grass pollen: an exploratory, randomized, placebo-controlled clinical trial. *Eur J Clin Nutr* 2013;67(02):161–167
- Lin T-Y, Chen C-J, Chen L-K, Wen S-H, Jan R-H. Effect of probiotics on allergic rhinitis in Df, Dp or dust-sensitive children: a randomized double blind controlled trial. *Indian Pediatr* 2013;50(02):209–213
- Xiao JZ, Kondo S, Yanagisawa N, et al. Effect of probiotic *Bifidobacterium longum* BB536 [corrected] in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar

- pollinosis during the pollen season. A randomized double-blind, placebo-controlled trial. *J Investig Allergol Clin Immunol* 2006;16(02):86–93
- 26 Xiao J-Z, Kondo S, Yanagisawa N, et al. Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial. *Clin Exp Allergy* 2006;36(11):1425–1435
 - 27 Okubo K, Kurono Y, Fujieda S, et al; Japanese Society of Allergology. Japanese guideline for allergic rhinitis. *Allergol Int* 2011;60(02):171–189
 - 28 Dotterud CK, Storrø O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010;163(03):616–623
 - 29 Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361(9372):1869–1871
 - 30 Kuitunen M, Kukkonen K, Juntunen-Backman K, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009;123(02):335–341
 - 31 Kukkonen AK, Kuitunen M, Savilahti E, Pelkonen A, Malmberg P, Mäkelä M Airway inflammation in probiotic-treated children at 5 years. *Pediatr Allergy Immunol* 2011;22(02):249–251
 - 32 West CE, Hammarström M-L, Hernell O. Probiotics in primary prevention of allergic disease—follow-up at 8–9 years of age. *Allergy* 2013;68(08):1015–1020
 - 33 Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, *Lactobacillus rhamnosus* (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. *Allergy* 2002;57(03):243–246
 - 34 Lue K-H, Sun H-L, Lu K-H, et al. A trial of adding *Lactobacillus johnsonii* EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7–12 years. *Int J Pediatr Otorhinolaryngol* 2012;76(07):994–1001
 - 35 Ciprandi G, Vizzaccaro A, Cirillo I, Tosca MA. *Bacillus clausii* effects in children with allergic rhinitis. *Allergy* 2005;60(05):702–703
 - 36 Nagata Y, Yoshida M, Kitazawa H, Araki E, Gomyo T. Improvements in seasonal allergic disease with *Lactobacillus plantarum* No. 14. *Biosci Biotechnol Biochem* 2010;74(09):1869–1877
 - 37 Ishida Y, Nakamura F, Kanzato H, et al. Clinical effects of *Lactobacillus acidophilus* strain L-92 on perennial allergic rhinitis: a double-blind, placebo-controlled study. *J Dairy Sci* 2005;88(02):527–533
 - 38 Chen Y-S, Jan R-L, Lin Y-L, Chen H-H, Wang J-Y. Randomized placebo-controlled trial of *Lactobacillus* on asthmatic children with allergic rhinitis. *Pediatr Pulmonol* 2010;45(11):1111–1120
 - 39 Giovannini M, Agostoni C, Riva E, et al; Felicita Study Group. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing *Lactobacillus casei* in pre-school children with allergic asthma and/or rhinitis. *Pediatr Res* 2007;62(02):215–220
 - 40 Tamura M, Shikina T, Morihana T, et al. Effects of probiotics on allergic rhinitis induced by Japanese cedar pollen: randomized double-blind, placebo-controlled clinical trial. *Int Arch Allergy Immunol* 2007;143(01):75–82
 - 41 Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997;99(02):179–185
 - 42 Kirjavainen PV, Gibson GR. Healthy gut microflora and allergy: factors influencing development of the microbiota. *Ann Med* 1999;31(04):288–292
 - 43 Rosenfeldt V, Benfeldt E, Nielsen SD, et al. Effect of probiotic *Lactobacillus* strains in children with atopic dermatitis. *J Allergy Clin Immunol* 2003;111(02):389–395
 - 44 Santos AR, Whorwell PJ. Irritable bowel syndrome: the problem and the problem of treating it - is there a role for probiotics? *Proc Nutr Soc* 2014;73(04):470–476
 - 45 Xu J, Ma R, Chen L-F, Zhao L-J, Chen K, Zhang R-B. Effects of probiotic therapy on hepatic encephalopathy in patients with liver cirrhosis: an updated meta-analysis of six randomized controlled trials. *Hepatobiliary Pancreat Dis Int* 2014;13(04):354–360

