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

Haissan Iftikhar1  Muhammad Ozair Awan2  Muhammad Sohail Awan2  Khawaja Mustafa2  Jai K. Das3  Shahzada Khuram Ahmed4

1 Department of Otolaryngology, Rawal Institute of Health Sciences, Islamabad, Pakistan
2 Department of Surgery, Aga Khan University Medical College, Karachi, Pakistan
3 Division of Women and Child Health, Aga Khan University, Karachi, Pakistan
4 Department of Otolaryngology, Queen Elizabeth Hospital, Birmingham, United Kingdom

Address for correspondence Haissan Iftikhar, FCPS, MRCS, MSc, Department of Otolaryngology, Rawal Institute of Health Sciences, Plot No. 6, PIES Complex, Park Road, Chak Shahzad, Islamabad, Pakistan (e-mail: haissaniftikhar@gmail.com).

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.
Introduction

The prevalence of allergic rhinitis (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 (QoL). These increasing cases are attributed to the “hygiene hypothesis,” which causes skewing of the T helper 1/T helper 2 (Th1/Th2) ratio toward the Th2 lineage, leading to an increase in serum Th2 mediated cytokines and interleukins (ILs), such as IL-3, IL-4 and IL-13. Subsequently, it causes induction of immunoglobin (Ig) E and tissue infiltration by eosinophils. Some authors 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.” Hence, it is postulated that the introduction of microbiota may have an immunomodulatory role.

Probiotics are live microorganisms that, when administered in adequate amounts, provide a health benefit to the host. They are naturally found in food products such as dark chocolate, pickles, miso, and, famously, in yogurt. Probiotics are thought to act on the gut-associated lymphoid tissue by causing dendritic cell maturation, which, in turn, causes a shift towards Th1 response. They cause dendritic cell maturation, which, in turn, causes a shift toward Th1 response. 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. Certain strains of microorganisms have been shown to have immunomodulatory properties, 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.

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. We reported the outcomes of the studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (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. (2015), Peng et al. (2015), and Güvenç et al. (2016). Güvenç et al. 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
reviews, we used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool, 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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Journal</th>
<th>Quality Assessment</th>
<th>No. of Studies Screened</th>
<th>No. of Trials Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Güvenç et. al.</td>
<td>2016</td>
<td>Turkey</td>
<td>American Journal of Rhinology and Allergy</td>
<td>Jadad scale</td>
<td>451</td>
<td>22</td>
</tr>
<tr>
<td>Peng et. al.</td>
<td>2015</td>
<td>China</td>
<td>American Journal of Rhinology and Allergy</td>
<td>Cochrane Handbook</td>
<td>496</td>
<td>11</td>
</tr>
<tr>
<td>Zajac et. al.</td>
<td>2015</td>
<td>United States</td>
<td>International Forum of Allergy &amp; Rhinology</td>
<td>Jadad scale</td>
<td>153</td>
<td>23</td>
</tr>
</tbody>
</table>
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 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) (\( \ast \) 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:...
-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: -0.96; 95% CI: -3.78 to 1.96; \( p = 0.51 \)) 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; \( p = 0.001 \)).

### 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.\(^{15}\) 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; \( p = 0.006 \)). 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 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: -0.49; 95% CI: -0.80 to -0.18; \( p < 0.001 \)).
-0.70; 95% CI: -1.81 to -0.45; p < 0.001). Güvenç et al. also included 3 studies (total sample of 227 patients) that used the Japanese guidelines for AR 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. evaluated the incidence of AR as an outcome measure. They included 5 trials 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., and they and 5 studies with 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 (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. Peng et al. analyzed a total of three different articles with 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. evaluated antigen-specific IgE in 7 studies 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. through 8 studies with a total sample of 446 patients (224 cases and 222 controls), and found no 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. through 2 studies 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. through the same 2 studies that analyzed IL-10 levels, and neither did the studies find 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. Peng et al. evaluated the Th1/Th2 ratio through 2 studies 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. analyzed it through 5 studies 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., who analyzed them through 3 studies 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 and atopic dermatitis. Their use has also been reported to improve symptoms in approximately two thirds of irritable bowel syndrome patients in a controlled trial, as well as to decrease the incidence of hepatic encephalopathy in liver cirrhosis patients. 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. 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. 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. 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. 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.

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