Health Supplements for Allergic Rhinitis: A Mixed-Methods Systematic Review

J. Pellow
A. Nolte
A. Temane
E. M. Solomon

Abstract

Allergic rhinitis is a chronic inflammatory condition caused by an exaggerated response of the immune system to common allergens. Most pharmacological therapies tend to be palliative and in some cases are associated with adverse effects. There is a growing tendency for people to self-medicate with health supplements as they are generally considered safe, however clinical studies relating to their efficacy and safety are limited. This mixed-methods systematic review aims to synthesise the available evidence relating to the treatment of allergic rhinitis with a variety of health supplements. A total of 57 062 articles were derived from searching seven online databases and evidence from 48 RCTs and 10 observational studies were reviewed for methodological quality and risk of bias. No qualitative studies meeting the inclusion criteria could be found, therefore only a quantitative review was performed. Promising evidence for the following single supplements were found: apple polyphenols, tomato extract, spirulina, chlorophyll c2, honey, conjugated linoleic acid, MSM, isoquercitrin, vitamins C, D and E, as well as probiotics. Combination formulas may also be beneficial, particularly specific probiotic complexes, a mixture of vitamin D_3, quercetin and *Perilla frutescens*, as well as the combination of vitamin D_3 and *L. reuteri*. Owing to the paucity of good quality evidence, recommendations pertaining to the use of health supplements for allergic rhinitis should involve a shared decision-making process between the healthcare provider and the patient, taking into account their efficacy, safety and cost. Further good quality clinical studies and qualitative research would further our understanding of the role these health supplements may play in future treatment protocols.

Keywords: health supplements, hay fever, allergic rhinitis, mixed-methods systematic review

1. Introduction

Allergic rhinitis is a common condition affecting around 20-30% of adults and up to 40% of children worldwide. Characteristic symptoms of this condition include sneezing, rhinorrhoea, nasal congestion and nasal pruritus. While not considered to be life threatening, this condition has a significant impact on quality of life, and is linked to increased rates of absenteeism from work and school, poor cognitive performance and rising healthcare costs. Conventional treatment options include a variety of pharmacotherapy options, such as antihistamines, corticosteroids and decongestants, which tend to be palliative and may be associated with adverse effects. Specific immunotherapy (SIT) is considered a viable option in the long-term management of allergic rhinitis, as it has a modulating effect on the immune system, however it can be costly and time-consuming [1]. Health supplements have a nutritional physiological effect on the body and may be used to supplement the person's diet; they include probiotics and prebiotics, vitamins, minerals, amino acids, animal extracts, fatty acids, carotenoids, bioflavonoids, and enzymes [2]. Easy access, relatively low cost, dissatisfaction with

conventional treatment and a desire to have control over their own healthcare are just some of the reasons why people may choose to self-medicate with health supplements for their chronic conditions [3,4]. This mixed-methods systematic review aims to provide a comprehensive synthesis of the evidence relating to the treatment of allergic rhinitis with a variety of health supplements.

2. Materials and Methods

2.1 Study Procedure

The mixed-methods systematic review was conducted according to the guidelines stated in the Joanna Briggs Institute (JBI) Reviewers' Manual [5], and was accomplished using the segregated methodology described by Sandelowski et al. [6], whereby individual, single method reviews were conducted according to the type of evidence, and the findings then combined in a 'mixed-methods' synthesis.

2.2 Inclusion and exclusion criteria

Published research evaluating the treatment of allergic rhinitis using health supplements were considered eligible. Randomised controlled trials (RCTs), non-controlled trials (cohort, case reports, case-control and case series studies) and qualitative studies were included. Clinical studies comparing these interventions with placebo and/or conventional treatment were considered. Studies where conventional medicines were allowed as 'rescue medication' were also eligible for inclusion. Filters for date and language were not applied.

2.3 Types of participants

Participants of all age groups suffering from acute and/or chronic allergic rhinitis, whether previously diagnosed or included based on presenting symptoms and history.

2.4 Types of interventions

Health supplements administered orally as either liquid, tablets, capsules or powders, or through nasal inhalation, or intravenously, as either a single medicine or combination product.

2.5 Outcome measures

Primary outcomes included: an improvement (severity and/or duration) of condition-specific symptoms recorded in validated questionnaires, e.g. a symptom diary, visual analogue scales (VAS), quality of life (QoL) scales, or individual symptom scores. Secondary outcomes included: adverse events/aggravations requiring conventional 'rescue' medication (frequency and quantity), and objective measures (peak nasal inspiratory flow rate (PNIF), the appearance of nasal mucosa, immunoglobulin E (IgE) levels and other allergy and inflammatory serum or nasal markers).

2.6 Sources of information

Published journal articles were sourced from seven online databases, namely PubMed, Science Direct, Springer Link, Scopus, Academic Search Complete, MEDLINE, and CINAHL. A final search update was performed on the 1st of December 2018.

2.7 Search strategy

The search strategy included free text and MeSH terms, and combinations of these (A + B) were used to conduct the online search (Table 1). Lastly, additional studies were identified from the reference lists of previously found articles.

2.8 Assessment of methodological quality

After duplicate studies were excluded, potentially relevant studies were identified based on their title and abstract. Full-text articles were assessed independently by two reviewers for eligibility, methodological quality, reliability and validity prior to inclusion into the review using the Mixed-Methods Appraisal Tool (MMAT). The MMAT consists of five sections, each relating to a specific study type (qualitative, RCTs, non-randomised studies, descriptive and mixed-methods studies). Each study was rated using descriptors and the criteria used to determine the score varies by design. The overall methodological quality score is calculated as a percentage [7]. Risk of bias was assessed in RCTs by means of the Cochrane Collaboration's tool [8]. The risk of bias tool covers six domains of bias, namely selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other' sources of bias. Within each domain, the risk of bias was rated as low, high or unclear. The RTI item bank was used to assess the quality of observational studies (case-control, case series/reports and cohort studies), and consists of 13 items that assess the risk of bias and confounding [9]. In order to establish confidence in the findings of the qualitative studies, the ConQual approach was utilised, which assesses quality based on the dependability and credibility of the findings [10].

2.9 Data extraction and synthesis

Data extraction forms [5, 11] were used to systematically extract study data, including the year of publication, author, setting, population/sample, the aim, study design/methodology, analysis, findings, limitations and conclusions. Information on outcome measures from quantitative studies and the author-derived themes from qualitative studies were extracted. A mixed-methods synthesis was conducted, where all studies were first synthesised according to their design (that is, qualitative versus quantitative), followed by an overarching synthesis across methodologies [11]. For the quantitative synthesis, the number and quality of studies regarding each condition were assessed, and common associations between studies were summarised as themes. The data were collected and graphically represented via tables.
For the qualitative studies, a thematic synthesis was conducted, which involved an iterative process of the coding of text; the development of descriptive themes; and the generation of analytical themes which formed the conclusions. Finally, an aggregative mixed-methods synthesis was conducted whereby the quantitative synthesis was converted into qualitative themes, and these were combined with the findings of the initial qualitative synthesis [5].

3. Results

A total of 57 062 articles were derived from the search strategy (Table 2), and after duplicate records were removed and the articles evaluated for relevance, 48 RCTs and 10 observational studies were included in the review (Figure 1). No qualitative studies meeting the inclusion criteria could be found, therefore only the quantitative review was conducted.

The studies were methodologically heterogeneous, making use of a variety of means of implementing treatment strategies and assessing clinical outcomes. The results of these studies are summarised in Table 3 and the MMAT and risk of bias results are presented in Tables 4 and 5. The majority of these studies investigated the effects of single health supplement preparations, while combination formulas were investigated in nine studies. Fourteen studies received a 100% MMAT rating, indicating good methodological quality. While eight RCTS and two observational studies received a high risk of bias rating, a low

risk of bias rating was awarded to six RCTs and five observational studies. The remaining studies were deemed to have an unclear risk of bias. Rater agreement was 85.1% between the two reviewers, and a third reviewer was consulted when necessary to resolve disagreements.

3.1 Synthesis of related studies

Apple polyphenols

Apples are a rich source of polyphenols, most notably flavan-3-ols, hydroxycinnamic acids, flavonols, dihydrochalcones and anthocyanidins. Apple polyphenols have various physiological functions and pre-clinical studies have demonstrated its anti-allergic effects, primarily through its ability to inhibit the release of histamine from mast cells and basophils [13, 70, 71]. Enomoto et al. [12] conducted a four-week RCT to investigate the effect of a drink containing apple polyphenols (50mg or 200mg daily) on the clinical symptoms of patients with persistent allergic rhinitis. Significant improvements in nasal symptoms and signs occurred, particularly sneezing attacks, nasal discharge and swelling of the nasal turbinates. Only minor adverse effects were noted. The study by Kishi et al. [13] further supports these findings. In this study, patients with Japanese cedar pollinosis who consumed 500mg of apple polyphenols before and during the pollen season were shown to have a significant reduction in sneezing attacks.

Chlorophyll c2

Sargassum horneri (*S. horneri*) is a brown macroalgae that is a rich source in the chlorophyll derivative, chlorophyll c2, as well as other active compounds such as polyphenols, flavonoids, terpenoids, sterols, and sulfated polysaccharides. These compounds exhibit diverse biological activities particularly anti-allergic, anti-inflammatory and antioxidant effects [72]. Pre-clinical studies have demonstrated that S. horneri inhibits degranulation of mast cells and basophils and reduces nasal symptoms in allergy-induced mice [73]; however human clinical studies are limited. Fujiwara et al. [14] conducted a twelve-week RCT which showed that use of chlorophyll c2 extract significantly reduces the need for 'rescue' medications such as antihistamines, in adults with allergic rhinitis. Although this study received a high risk of bias rating due to a high attrition rate, it received a low rating in all other domains.

Conjugated linoleic acid (CLA)

CLAs are naturally occurring fatty acids derived from fatty tissues of ruminant animals. Most commercially available CLAs are however produced by the alkaline isomerization of plant oils, such as sunflower oil, and tend to contain a mixture of 9- and 10-CLAs as well as other CLA isomers. Animal studies have demonstrated that CLA has immune-modulating effects, with the ability to affect both humoral and cellular immune responses, indicating that it may be of benefit in allergic conditions [74]. Only one clinical study could be found relating to its use for allergic rhinitis, which demonstrated that consuming CLA before and during the birch pollen season improves sneezing and induces a feeling of wellbeing in patients. It also appears to produce modest anti-inflammatory effects, reducing specific inflammatory and allergy markers [15].

Honey

Honey has been used as a medicine since ancient times, and remains a popular food worldwide. Its nutritional composition is affected by several factors such as floral source, geographical location and season; however its main constituents include sugars, vitamins,

minerals, amino acids, proteins, enzymes, organic acids, volatile substances, and polyphenols. Honey's many health properties include antioxidant, anti-inflammatory and immune-modulating effects [75], however there is contradictory evidence regarding its use for the treatment of allergic rhinitis. Rajan et al. [17] showed that consuming one tablespoon of either unpasteurised or pasteurised honey daily was not beneficial in reducing nasal symptoms, while more recently Asha'ari et al. [16] demonstrated that honey actually further improves allergic rhinitis symptoms when used as an adjunct to loratadine rather than the use of the antihistamine alone. Also, Saarinen et al. [18] showed that patients with birch pollen allergy who consumed honey containing birch pollen prior to the onset of the pollen season, had positive clinical changes, namely a significant improvement in symptoms and reduction in the use of antihistamines. Both Rajan et al [17] and Saarinen et al. [18] received a high risk of bias rating; the former due to a high attrition rate and the latter as it was a single-blinded trial design.

Isoquercitrin

Quercetin supplements are widely used for their various health benefits and have been known to have anti-inflammatory and anti-allergic properties. Despite its poor bioavailability, pre-clinical studies have shown that this flavonoid has the ability to suppress mast cell activation, inhibiting the release of several inflammatory and allergy-related chemical mediators, such as histamine, leukotrienes and prostaglandins. Quercetin glucosides such as isoquercitrin have been shown to exhibit similar therapeutic effects *in vivo* as quercetin itself, and appear to have better bioavailability [76]. Both Hirano et al. [19] and Kawai et al. [20] performed clinical studies assessing the effect of enzymatically modified isoquercitrin on patients with Japanese cedar pollinosis. Significant improvements in ocular symptoms and certain inflammatory markers were found in both studies, however little difference in nasal symptoms occurred.

Methylsulfonylmethane (MSM)

MSM is a naturally occurring organosulfur compound whose anti-inflammatory properties have been validated in both *in vitro* and *in vivo* studies. MSM is well-tolerated in dosages of up to 4g a day in adults, with few adverse effects being reported [77]. Clinical studies relating to its efficacy for allergic rhinitis are however limited. Barrager et al. [21] conducted a multi-centre observational study which showed that use of 2,6g daily for one month significantly reduces symptoms of seasonal allergic rhinitis, while the clinical trial by Hewlings and Kalman [22] demonstrated that a daily dose of 3g for two weeks appears most effective in relieving rhinitis symptoms and nasal obstruction. The study by Barrager et al. [21] received 100% rating on the MMAT and a low risk of bias rating.

Probiotics

Commercially available probiotics are sold worldwide and usually contain one or more beneficial bacterial genera, such as *Lactobacillus*, *Bifidobacteria* or *Bacillus*; yeast strains such as those of the *Saccharomyces* genus have also demonstrated health promoting effects. Probiotic micro-organisms play a significant role in balancing the gut microbiome, which in turn promotes immunological tolerance in allergic-related conditions [78]. Various different types of probiotics have been investigated as a treatment option for allergic rhinitis, and will be discussed according to bacterial genus.

Bacillus: The addition of *Bacillus claussi* (*B. claussi*) to antihistamine treatment was shown to significantly reduce nasal eosinophils and the need for antihistamines in children [24].

Bifidobacteria: Use of *Bifidobacterium longum* (*B. longum*) strain BB536 was shown to improve ocular symptoms and reduce the need for 'rescue' medication in patients with Japanese cedar pollinosis in three separate trials [51-53], one of which received a low risk of bias rating [51]. Another study showed that the probiotic *B. lactis* NCC2818 significantly lowers nasal symptom scores, IL-5 and IL-13, as well as percentages of activated CD63 expressing basophils in patients with seasonal allergic rhinitis [45].

Clostridium: In a twelve-month RCT, six-month use of *Clostridium butyricum* (*C. butyricum*) was found to enhance the efficacy of specific immunotherapy (SIT) for house dust mite-sensitive patients, reducing nasal symptoms, the need for 'rescue' medication, and modulating serum allergy markers. This effect was maintained in the six-month observation period [54].

Enterococcus: In one good quality observational study with a low risk of bias, lysed *Enterococcus faecalis* (*E. faecalis*) FK-23 use significantly reduced nasal symptoms, signs and serum eosinophils in house dust mite-sensitive patients [44].

Escherichia: One RCT showed that use of *Escherichia coli* strain Nissle 1917 for six months was not superior to placebo in relieving symptoms of allergic rhinitis [27].

Lactococcus: Supplementation with *Lactococcus lactis* subsp. cremoris YRC3780 (1g, 0.1g or 0.01g) for a period of twelve weeks has a tendency to decrease the need for 'rescue' medication and thymus- and activation-regulated chemokine (TARC) levels in patients with birch pollinosis [47].

Lactobacillus: Several studies relating to the use of *Lactobacillus* (*L.*) strains have been conducted, many with positive findings. In one study, consumption of milk fermented with *L. acidophilus* L-92 was shown to improve the symptoms of Japanese cedar pollinosis and reduce the need for 'rescue' medications [29], while *L. johnsonii* EM1 use in combination with levocetirizine proved more effective than the antihistamine alone in relieving symptoms in children; this amelioration continued for at least three months after discontinuation of the probiotic [36]. Both these studies received a high risk of bias rating due to insufficient blinding in their study designs. Seven studies investigated the effects of *L. paracasei* specifically. In 2004, Wang et al. [48] reported that children sensitised to house dust mite who consumed yogurt containing live *L. paracasei*-33 (LP-33) for one month had a significantly improved quality of life. Similar results were shown for heat-killed LP-33 [42].

Costa et al. [25] showed that LP-33 use for seven weeks produced a significant improvement in quality of life and ocular symptoms in patients sensitive to grass pollen, who were using an oral antihistamine (loratadine), while the *L. paracasei* strain KW3110 also appears to have some benefits in improving rhinitis control in patients allergic to cedar pollen [55]. In another study, four-week consumption of *L. paracasei* ST11-fermented milk resulted in significantly lower nasal congestion and pruritus scores after a nasal provocation test, and down-regulated IL-5 and allergen-specific IgG4 in grass pollen-sensitive patients [49].

Nagata et al. [38] performed two six-week RCTs on female students allergic to Japanese cedar pollen and found that *L. plantarum* LP14 taken daily significantly improves ocular symptoms and induces the gene expression of Th1-type cytokines. Similarly, consumption of *L. plantarum* YIT 0132 also significantly improves symptoms, quality of life and reduces eosinophils in patients with Japanese cedar pollinosis [28]. This study received a high risk of bias due to its single-blinded design. Lastly, one good quality RCT showed that *L. salivarius* PM-A0006 taken for twelve weeks significantly reduces allergic rhinitis symptoms and 'rescue' medication use in children with perennial allergic rhinitis [34].

Despite these positive results, several *Lactobacillus*-related studies did not show statistically significant results. Use of *L. casei Shirota* failed to provide clinical benefit to seasonal allergic rhinitis sufferers [30, 46], while *L. rhamnosus* use for twelve weeks does not appear to further improve symptoms in children [31]. Lastly, *L. paracasei* strain NCC 2461 and HF.A00232 do not provide additional therapeutic benefits to patients using conventional treatment, however the latter strain may continue to induce improvements in symptoms after discontinuation of antihistamine therapy [35, 39].

Tetragenococcus: Consumption of *Tetragenococcus halophilus* (*T. halophilus*) Th221 in a daily dose of either 20.4mg or 60mg for eight weeks does not appear to produce a significant therapeutic benefit, however participants receiving the higher dose in this trial showed trends for improvement over time [40].

Probiotic complex: Probiotic supplements found on the market typically consist of a combination of two or more bacterial genera or strains. A number of good quality, low risk of bias studies relating to specific complexes were found. The probiotic complex containing *L. acidophilus* NCFM (ATCC 700396) and *B. lactis* BI-04 (ATCC SD5219) was shown to reduce nasal eosinophilia and modulate rhinitis symptoms [41]. Perrin et al. [43] however found that use of *L. paracasei* NCC2461 on its own produced superior results to a blend of *L. acidophilus* ATCC SD5221 and *B. lactis* ATCC SD5219 in a crossover trial; while no effect was observed on nasal congestion, four weeks of treatment with NCC2461 was shown to significantly decrease nasal pruritus, reduce nasal leukocytes and IL-5, and enhance serum IL-5, IL-13 and IL-10 levels. In the RCT by Dennis-Wall et al. [26], daily use of a complex of *L. gasseri* KS-13, *B. bifidum* G9-1, and *B. longum* MM-2 for eight weeks was shown to significantly improve rhinoconjunctivitis-specific quality of life during the allergy season, while the combination of *B. bifidum* W23, *L. acidophilus* W55, *L. casei* W56, *L. salivarius* W57, and *L. lactis* W58 was shown to significantly improve symptoms and quality of life when taken over a two-month period [50]. In a RCT by Kawase et al. [32], the complex of *Lactobacillus* GG and *L. gasseri* TMC0356 taken daily for ten weeks, significantly improved nasal obstruction, reduced the need for 'rescue' medication and modulated cytokine production.

In another RCT, consumption of yoghurt fortified with *L. rhamnosus* GR-1 and *B. adolescentis* 70007-05 had little clinical benefit; it did however produce potentially desirable effects on the cytokine profile [33]. In a four-month observational study, use of dietary yoghurt containing *L. acidophilus* and *Bifidobacterium* improved muco-ciliary transport time and symptom scores, highlighting its potential benefits for allergic rhinitis sufferers [23]. The latter two studies received an unclear risk of bias due to insufficient methodological reporting.

Spirulina

Spirulina (*Arthrospira platensis*) is a microscopic filamentous cyanobacterium extensively consumed as a health supplement for its nutritional content and health promoting benefits. It contains essential amino acids, minerals, essential fatty acids, vitamins, and carotenoids. Spirulina has been shown to modulate the immune system by inhibiting the release of histamine from mast cells and lowering cytokine IL-4 levels, however there is a paucity of human clinical trials [79, 80]. In a six-month RCT by Cingi et al. [56], daily consumption of spirulina tablets for six months was shown to improve both symptoms and signs of allergic rhinitis, with positive patient feedback received regarding perceived effectiveness and satisfaction with treatment.

Tomato extract

The tomato fruit of the Solanaceae family is a popular food source worldwide. It is rich in bioactive compounds, most notably carotenoids (lycopene, β-carotene and lutein), vitamins and phenolic compounds (flavonoids, phenolic acids and tannins), to which its antioxidant and anti-inflammatory properties are attributed [81]. Studies on the use of tomato extract in the treatment of allergic rhinitis are limited however promising results were found in one RCT, which showed its potential to significantly decrease nasal symptoms and improve quality of life of patients allergic to house dust mite [57].

Vitamin C

Vitamin C, also known as ascorbic acid, is a water-soluble antioxidant with immune-modulating effects. Allergy sufferers tend to produce a variety of reactive oxygen species (ROS) from the cells lining the airways, resulting in a weakened antioxidant defence mechanism and pathological inflammatory changes of the nasal mucosa. These changes include lipid peroxidation, heightened sensitivity and reactivity of the mucosa, production of chemoattractant molecules, and increased vascular permeability [82]. It is therefore possible that supplementing with antioxidants may provide clinical benefits to allergic rhinitis sufferers, and epidemiological studies have shown that increased intake of vitamin C is associated with fewer symptoms in children [83, 84]. Case studies conducted in the 1940s provided conflicting anecdotal evidence regarding the use of oral vitamin C in the treatment of allergic rhinitis [58, 59, 61], two of which received a high risk of bias rating as they failed to report on adverse effects [58, 59]. More recently, an RCT conducted by Podoshin et al. [60] showed that two-week use of nasal applications of ascorbic acid reduces nasal oedema, mucous secretions and nasal obstruction, while Vollbracht et al. [62] demonstrated that high doses of intravenous vitamin C had positive clinical benefits for patients with both acute and chronic allergic rhinitis. The study by Vollbracht et al. [62] scored 100% on the MMAT and was deemed to have a low risk of bias.

Vitamin D

Vitamin D deficiency is common worldwide and may be an important environmental risk factor in the development of allergic disease. Epidemiological studies have found an association between low serum vitamin D levels and the incidence of allergic disorders [85]. Vitamin D exists in two main forms, namely ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). It exerts its immunomodulatory effects through vitamin D receptors which are found on a variety of immune cells such as B and T cells, dendrites and macrophages, thereby influencing the allergy-related inflammatory response [86]. Clinical evidence of its use for allergic rhinitis is unfortunately limited. Jerzyńska et al. [63] demonstrated the results of a RCT on the effects of five-months of vitamin D supplementation in children with grass pollen-related allergic rhinitis, and found a significant reduction in symptoms, the need for 'rescue' medication, as well as an immune-modulating effect. Although the study by Jerzyńska et al. [63] was of good methodological quality, it received a high risk of bias rating due to its high attrition rate. High dosages of vitamin D given orally have been demonstrated to enhance symptomatic relief in patients with asthma and allergic rhinitis undergoing pollen specific immunotherapy [65]. Furthermore, the RCT by Malik et al. [64] showed that allergic rhinitis sufferers deficient in vitamin D who receive supplementation have a highly significant improvement in nasal symptoms.

Two health supplement complexes containing vitamin D have been studied. A proprietary complex containing vitamin D3, as well as quercetin and the medicinal plant *Perilla frutescens*, was shown to significantly reduce allergic rhinitis symptoms when used for one month in a good quality observational study. Use of the complex decreased the need for 'rescue' medication [66]. *Perilla frutescens*, of the Lamiaceae family, is a rich source of anti-allergic and anti-inflammatory constituents, including rosemarinic acid and quercetin, as well as omega-3, -6, and -9 polyunsaturated fatty acids [87]. The benefits of quercetin for allergic conditions have been previously mentioned. In a single-blinded, non-randomised controlled study by Ciprandi and Varrichio [67], adjunctive use of a food supplement containing vitamin D3 800iu and *Lactobacillus reuteri* (*L. reuteri*) DSM 17938) for one month, together with specific immunotherapy for Parietaria pollinosis, improved the perceived effectiveness of SIT by reducing symptom severity and antihistamine use.

Vitamin E

The vitamin E family refers to eight distinct isoforms, namely four tocopherols and four tocotrienols. Vitamin E plays a significant role in immune system functioning however there are currently conflicting reports regarding its role in the treatment of allergic diseases [88, 89]. A clinical study by Shahar et al. [69] reported that supplementation with vitamin E in addition to conventional anti-allergy medication for two months, further improves nasal symptoms in patients with seasonal allergic rhinitis, while Montaño Velázquez et al. [68] demonstrated no clinical benefits for perennial allergic rhinitis sufferers taking this supplement.

4. Discussion

Mixed-method systematic reviews are designed to address the issue of synthesising evidence related to a particular topic and provide a reliable basis for clinical decision-making as they are replicable, reduce bias and resolve controversy between conflicting findings [8, 11].Very few reviews on the use of health supplements for the treatment of allergic rhinitis have been previously conducted. In one review, Tian & Cheng [85] found clinical evidence supporting low serum vitamin D levels with an increased risk for developing allergic rhinitis, however

recommended further research be conducted with regards to using vitamin D as a treatment option. Yang et al. [90] concluded that probiotics may play an important role in the prevention and treatment of allergic rhinitis, the benefits of which are dependent on the type of bacterium administered and the dosage regimen used. Newman [91] conducted a systematic review on the use of unpasteurised honey in the treatment of allergic rhinitis, and found contradictory results from the two studies that were reviewed; therefore, no definitive recommendations could be made.

Health supplements are widely available in pharmacies, health shops, and other retail outlets, and are usually brought to market without the foundation of clinical trials. There is a growing tendency for people to self-medicate with these products, seldom seeking advice from a qualified healthcare practitioner. Although the intake of dietary supplements is generally considered safe, the potential risk when used inappropriately is significant, as they can exert a physiological and pharmacological effect [92]. This current review found promising evidence for the use of several health supplements; namely apple polyphenols, tomato extract, spirulina, chlorophyll c2, honey, CLA, MSM, isoquercitrin, vitamins C, D and E, as well as various probiotics. Of these, probiotics appears to be the most widely studied with several different micro-organism strains showing promising results, such as *B. claussi*, *B. longum* BB536, *B. lactis* NCC2818, *C. butyricum*, *E. faecalis*, *Lactoccus lactis* subsp. cremoris YRC3780, *L. acidophilus* L-91, *L. johnsonni* EM1, and several *L. paracasei* strains, *L. plantarum* LP14 and *L. salivarius* PM-A0006. Specific health supplement combinations also may be beneficial, however only a few studies relating to these could be found.

One of the main limitations of this review is the limited evidence available for each supplement. Also, of those studies that were reviewed, many made use of a small sample size, which may have had an impact on the statistical validity of the findings. Another major challenge encountered was the difficulty in accurately rating the methodological quality and risk of bias of included studies, owing to insufficient reporting in many of the research articles reviewed. This was more evident with older publications, and led to a high number of studies being rated as having an unclear or high risk of bias. There are a number of validated checklists available for authors to use when publishing the results of their studies, and these are helpful to ensure standardisation in reporting. Examples of these include the Consolidated Standards of Reporting Trials (CONSORT) for randomised controlled trials [93]; the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for epidemiological studies [94]; and the Guidelines for Conducting and Reporting Mixed Research for Counselor Researchers for mixed-methods designs [95].

Qualitative research forms a vital cornerstone in informing healthcare practices as it provides valuable insights into patients' experiences, values and healthcare needs [96]. There were unfortunately very few eligible qualitative studies regarding the use of health supplements for allergic rhinitis, and this highlights a research gap that requires further investigation.

On a positive note, very few adverse effects of the evaluated health supplements were reported overall, and these interventions could possibly be considered as low-risk treatment options if used appropriately. Ideally, recommendations pertaining to the use of these interventions should involve a shared decision-making process between the healthcare provider and the patient, and potential efficacy, risks and benefits, and financial implications of their use should be taken into account. Further large-scale studies are warranted to fully understand the role health supplements may play in managing this condition.

5. Conclusion

This mixed-methods systematic review provides a complete and fair representation of the currently available evidence derived from 48 RCTs and 10 observational studies on the use of various health supplements in the treatment of allergic rhinitis. A number of individual health supplements were identified as having a beneficial effect on this condition, such as probiotics, CLA, MSM, spirulina, chlorophyll c2, honey, plant-based extracts (apple polyphenols, tomatoes and isoquercetrin) and vitamins C, D and E. Various health supplement combinations were also investigated and found to have promising results, particularly specific probiotic complexes, a mixture of vitamin D_3, quercetin and *Perilla frutescens*, as well as the combination of vitamin D_3 and *L. reuteri*. Future research on the use of these interventions is warranted in order to verify their efficacy and safety as potential treatment options to address patients' needs and preferences.

Data Availability

The data that supports the findings of this study is available from the University of Johannesburg but restrictions apply to the availability of this data, which was used under license for the current study, and so is not publicly available. Data is however available from the authors upon reasonable request and with permission from the University of Johannesburg.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

This work was financed and supported by the University of Johannesburg.

Acknowledgments

The authors would like to thank the University of Johannesburg for the support of this research, and specifically Antonet Sandelowitz in the library postgraduate centre for her assistance in obtaining the data.

References

[1] F. C. L. Hoyte and H. S. Nelson, "Recent advances in allergic rhinitis," *F1000Research*, 7: F1000 Faculty Rev-1333, 2018. doi:10.12688/f1000research.15367.1.

[2] MCC (Medicines Control Council), "Complementary medicine- discipline-specific safety and efficacy," Available from: http://www.mccza.com/documents/8b57b09c7.01_CMs_SE_DS_Jun16_v3.pdf. Accessed 16/10/2019.

[3] S. Eardley, F. L. Bishop, P. Prescott, et al., "A systematic literature review of complementary and alternative medicine prevalence in EU," *Forschende Komplementärmedizin,* vol. 19, Supplement 2, pp. 18-28, 2012.

[4] N. Corp, J. L. Jordan, and P. R. Croft, "Justifications for using complementary and alternative medicine reported by persons with musculoskeletal conditions: A narrative literature synthesis," *PloS one*, vol. 13, no. 7, e0200879, 2018, doi:10.1371/journal.pone.0200879.

[5] The Joanna Briggs Institute, "Joanna Briggs Institute Reviewers' Manual: 2014 edition. Methodology for JBI mixed methods systematic reviews," The University of Adelaide, Australia, 2014, http://joannabriggs.org/assets/docs/approach/Levels-of-Evidence-SupportingDocuments.pdf.

[6] M. Sandelowski, C. I. Voils, J. and Barroso, J, "Defining and designing mixed research synthesis studies," *Research in the Schools*, vol. 13, p. 29, 2006.

[7] P. Pluye, E. Robert, M. Cargo et al., "Proposal: A mixed methods appraisal tool for systematic mixed studies reviews," 2011, Available from: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/84371689/MMAT%202011%20criteria%20and%20tutorial%202011-06-29updated2014.08.21.pdf.

[8] J. Higgins, S. Green, "Cochrane handbook for systematic reviews of interventions. Part 2: general methods for Cochrane reviews," 2011, Available from: http://handbook.cochrane.org/.

[9] M. Viswanathan, N. D. Berkman, D. M. Dryden, and L. Hartling, "Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank," Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Aug. Report No.: 13-EHC106-EF. AHRQ Methods for Effective Health Care, 2013.

[10] The Joanna Briggs Institute, "Establishing confidence in qualitative evidence," 2017, Available from: https://health.adelaide.edu.au/jbi/current-students/resources/ establishing-confidence-in-qualitative-evidence-presentation-notes.pdf.

[11] A. Pearson, H. White, F. Bath-Hextall, S. Salmond, J. Apostolo, and P. Kirkpatrick, "A mixed-methods approach to systematic reviews," *International Journal of Evidence Based Healthcare*, vol.13, issue 3, pp. 121-131, 2015.

[12] T. Enomoto, Y. Nagasako-Akazome, T. Kanda, M. Ikeda, and Y. Dake, "Clinical effects of apple polyphenols on persistent allergic rhinitis: a randomized double-blind placebo-controlled parallel arm study," *Journal of Investigational Allergology & Clinical Immunology,* vol. 16, pp. 283-289, 2006.

[13] K. Kishi, M. Saito, T. Saito et al., "Clinical efficacy of apple polyphenol for treating cedar pollinosis," *Bioscience, Biotechnology and Biochemistry*, vol. 69, no. 4, pp. 829-832, 2005, doi: 10.1271/bbb.69.829.

[14] T. Fujiwara, N. Nishida, J. Nota et al., "Efficacy of chlorophyll c2 for seasonal allergic rhinitis: single-center double-blind randomized control trial," *European Archives of Oto-Rhino-Laryngology*, vol. 273, no. 12, pp. 4289-4294, 2016.

[15] A. M. Turpeinen, N. Ylönen, E. von Willebrand, S. Basu, and A. Aro, "Immunological and metabolic effects of cis-9, trans-11-conjugated linoleic acid in subjects with birch pollen allergy," *British Journal of Nutrition*, vol. 100, no. 1, pp. 112-119, 2008, doi: 10.1017/S0007114507886326.

[16] Z. A. Asha'ari, M. Z. Ahmad, W. S. Jihan, C. M. Che, and I. Leman, "Ingestion of honey improves the symptoms of allergic rhinitis: evidence from a randomized placebo-controlled trial in the East coast of Peninsular Malaysia," *Annals of Saudi Medicine*, vol. 33, no. 5, pp. 469–475, 2013, doi:10.5144/0256-4947.2013.469.

[17] T. V. Rajan, H. Tennen, R. L. Lindquist, L. Cohen, and J. Clive, "Effect of ingestion of honey on symptoms of rhinoconjunctivitis," *Annals of Allergy, Asthma & Immunology*, vol. 88, no. 2, pp. 198-203, 2002.

[18] K. Saarinen, J. Jantunen, and T. Haahtela, "Birch pollen honey for birch pollen allergy--a randomized controlled pilot study," *International Archives of Allergy & Immunology*, vol. 155, no. 2, pp. 160-166, 2011, doi: 10.1159/000319821.

[19] T. Hirano, M. Kawai, J. Arimitsu et al., "Preventative effect of a flavonoid, enzymatically modified isoquercitrin on ocular symptoms of Japanese cedar pollinosis," *Allergology International*, vol. 58, no. 3, pp. 373-382, 2009, doi: 10.2332/allergolint.08-OA-0070.

[20] M. Kawai, T. Hirano, J. Arimitsu et al., "Effect of enzymatically modified isoquercitrin, a flavonoid, on symptoms of Japanese cedar pollinosis: a randomized double-blind placebo-controlled trial," *International Archives of Allergy & Immunology*, vol. 149, no. 4, pp. 359-368, 2009, doi: 10.1159/000205582.

[21] E. Barrager, J. R. Veltmann Jr., A. G. Schauss, and R. N. Schiller, "A multicentered, open-label trial on the safety and efficacy of methylsulfonylmethane in the treatment of seasonal allergic rhinitis," *Journal of Alternative & Complementary Medicine*, vol. 8, no. 2, pp. 167-173, 2002.

[22] S. Hewlings and D. S. Kalman, "Evaluating the impacts of methylsulfonylmethane on allergic rhinitis after a standard allergen challenge: randomized double-blind exploratory study," *JMIR Research Protocols*, vol. 7, no. 11, e11139, 2018, doi: 10.2196/11139.

[23] C. Aldinucci, L. Bellussi, G. Monciatti et al., "Effects of dietary yoghurt on immunological and clinical parameters of rhinopathic patients," *European Journal of Clinical Nutrition*, vol. 56, pp. 1155–1161, 2002.

[24] G. Ciprandi, A. Vizzaccaro, I. Cirillo, and M. A. Tosca, "Bacillus clausii effects in children with allergic rhinitis," *Allergy*, vol. 60, no. 5, pp. 702-703, 2005, doi: 10.1111/j.1398-9995.2005.00722.x.

[25] D. J. Costa, P. Marteau, M. Amouyal, et al. "Efficacy and safety of the probiotic Lactobacillus paracasei LP-33 in allergic rhinitis: a double-blind, randomized, placebo-controlled trial (GA2LEN Study)," *European Journal of Clinical Nutrition*, vol. 68, pp. 602–607, 2014.

[26] J. C. Dennis-Wall, T. Culpepper, C. Nieves Jr., et al. "Probiotics (Lactobacillus gasseri KS-13, Bifidobacterium bifidum G9-1, and Bifidobacterium longum MM-2) improve rhinoconjunctivitis-specific quality of life in individuals with seasonal allergies: a double-blind, placebo-controlled, randomized trial," *American Journal of Clinical Nutrition*, vol. 105, no. 3, pp. 758-767, 2017, doi: 10.3945/ajcn.116.140012.

[27] S. Dölle, J. Berg, C. Rasche, and M. Worm, "Tolerability and clinical outcome of coseasonal treatment with Escherichia coli strain Nissle 1917 in grass pollen-allergic subjects," *International Archives of Allergy & Immunology*, vol. 163, pp. 29–35, 2014, doi: 10.1159/000356328.

[28] N. Harima-Mizusawa, T. Iino, N. Onodera-Masuoka, et al. "Beneficial effects of citrus juice fermented with Lactobacillus plantarum YIT 0132 on Japanese cedar pollinosis," *Bioscience of Microbiota and Food Health*, vol. 33, no.4, pp. 147-155, 2014, doi: 10.12938/bmfh.33.147.

[29] Y. Ishida, F. Nakamura, H. Kanzato, et al. "Effect of milk fermented with Lactobacillus acidophilus strain L-92 on symptoms of Japanese cedar pollen allergy: a randomized placebo-controlled trial," *Bioscience, Biotechnology & Biochemistry*, vol. 69, no. 9, pp. 1652-1660, 2005.

[30] K. Ivory, A. M. Wilson, P. Sankaran, et al. "Oral delivery of a probiotic induced changes at the nasal mucosa of seasonal allergic rhinitis subjects after local allergen challenge: a randomised clinical trial," *PLoS One*, vol. 8, no. 11, e78650, 2013, doi: 10.1371/journal.pone.0078650.

[31] R-H. Jan, C-J. Chen, L-K. Chen, S-H. Wen, and T-Y. Lin, "Is the effect of probiotics on allergic rhinitis confined to Dermatophagoides farinae, Dermatophagoides pteronyssinus, or dust-sensitive children? A randomized prospective double-blind controlled trial," *Tzu Chi Medical Journal*, vol. 23, no. 2, pp. 51-54, 2011.

[32] M. Kawase, F. He, A. Kubota, et al. "Effect of fermented milk prepared with two probiotic strains on Japanese cedar pollinosis in a double-blind placebo-controlled clinical study," *International Journal of Food Microbiology*, vol. 128, no. 3, pp. 429-34, 2009, doi: 10.1016/j.ijfoodmicro.2008.09.017.

[33] T. Koyama, P. V. Kirjavainen, C. Fisher, et al. "Development and pilot evaluation of a novel probiotic mixture for the management of seasonal allergic rhinitis," *Canadian Journal of Microbiology*, vol. 56, no. 9, pp. 730-738, 2010, doi: 10.1139/w10-061.

[34] T. Y. Lin, C. J. Chen, L. K. Chen, S. H. Wen, and R. H. Jan, "Effect of probiotics on allergic rhinitis in Df, Dp or dust-sensitive children: a randomized double blind controlled trial". *Indian Pediatrics*, vol. 50, pp. 209–213, 2013.

[35] W. Y. Lin, L. S. Fu, H. K. Lin, C. Y. Shen, and Y. J. Chen, "Evaluation of the effect of Lactobacillus paracasei (HF.A00232) in children (6-13 years old) with perennial allergic rhinitis: a 12-week, double-blind, randomized, placebo-controlled study," *Pediatrics & Neonatology*, vol. 55, no. 3, pp.181-188, 2014 doi: 10.1016/j.pedneo.2013.10.001.

[36] K-H. Lue, H-L. Sun, K-H. Lu, et al., "A trial of adding Lactobacillus johnsonii EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7–12 years," *International Journal of Pediatric Otorhinolaryngology*, vol. 76, no.7, pp. 994-1001, 2012.

[37] M. Miraglia Del Giudice, C. Indolfi, M. Capasso, et al., "Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M - 16V) treatment in children with seasonal allergic rhinitis and intermittent asthma," *Italian Journal of Pediatrics*, vol. 43, p. 25, 2017.

[38] Y. Nagata, M. Yoshida, H. Kitazawa, E. Araki, and T. Gomyo, "Improvements in seasonal allergic disease with Lactobacillus plantarum No. 14," *Bioscience, Biotechnology & Biochemistry*, vol. 74, no. 9, pp. 1869-1877, 2010.

[39] C. Nembrini, A. Singh, C. A. De Castro, and A. M. S. Nutten, "Oral administration of Lactobacillus paracasei NCC 2461 for the modulation of grass pollen allergic rhinitis: a randomized, placebo-controlled study during the pollen season," *Clinical and Translational Allergy*, vol. 5, 2015, doi: 10.1186/s13601-015-0085-4.

[40] I. Nishimura, T. Igarashi, T. Enomoto, et al., "Clinical efficacy of halophilic lactic acid bacterium Tetragenococcus halophilus Th221 from soy sauce moromi for perennial allergic rhinitis," *Allergology International,* vol. 58, no. 2, pp. 179-185, 2009, doi: 10.2332/allergolint.O-08-548.

[41] A. C. Ouwehand, M. Nermes, M. C. Collado et al., "Specific probiotics alleviate allergic rhinitis during the birch pollen season," *World Journal of Gastroenterology*, vol. 15, no. 26, pp. 3261–3268, 2009, doi: 10.3748/wjg.15.3261.

[42] G-C. Peng and C-H. Hsu, "The efficacy and safety of heat-killed Lactobacillus paracasei for treatment of perennial allergic rhinitis induced by house-dust mite," *Pediatric Allergy and Immunology*, vol. 16, no. 5, pp. 433–438, 2005.

[43] Y. Perrin, S. Nutten, R. Audran et al., "Comparison of two oral probiotic preparations in a randomized crossover trial highlights a potentially beneficial effect of Lactobacillus paracasei NCC2461 in patients with allergic rhinitis," *Clinical & Translational Allergy*, vol. 4, p. 1, 2014, doi: 10.1186/2045-7022-4-1.

[44] T. Shimada, L. Cheng, T. Enomoto et al., "Lysed Enterococcus faecalis FK-23 oral administration reveals inverse association between tuberculin responses and clinical manifestations in perennial allergic rhinitis: a pilot study," *Journal of Investigative Allergology & Clinical Immunology*, vol. 14, no. 3, pp. 187-192, 2004.

[45] A. Singh, F. Hacini-Rachinel, M. L. Gosoniu 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," *European Journal of Clinical Nutrition*, vol. 67, no.2, pp. 161-167, 2013, doi: 10.1038/ejcn.2012.197.

[46] M. Tamura, T. Shikina, T. Morihana et al., "Effects of probiotics on allergic rhinitis induced by Japanese cedar pollen: randomized double-blind, placebo-controlled clinical trial," *International Archives of Allergy and Immunology*, vol. 143, no. 1, pp. 75–82, 2007.

[47] K. Uchida, H. Motoshima, N. Katano et al., "Effect of Lactococcus lactis subsp. cremoris YRC3780 on birch pollinosis: a randomized, double-blind, placebo-controlled clinical trial," *Journal of Functional Foods*, vol. 43, pp.173-179, 2018.

[48] M. F. Wang, H. C. Lin, Y. Y. Wang, and C. H. Hsu, "Treatment of perennial allergic rhinitis with lactic acid bacteria," *Pediatric Allergy and Immunology*, vol. 15, no. 2, pp. 152–158, 2004.

[49] J. Wassenberg, S. Nutten, R. Audran et al., "Effect of Lactobacillus paracasei ST11 on a nasal provocation test with grass pollen in allergic rhinitis," *Clinical & Experimental Allergy*, vol. 41, pp. 565–573, 2011.

[50] A. M. Watts, A. J. Cox, P. K. Smith et al., "A specifically designed multispecies probiotic supplement relieves seasonal allergic rhinitis symptoms," *Journal of Alternative & Complementary Medicine*; vol. 24, no. 8, pp. 833-840, 2018, doi: 10.1089/acm.2017.0342.

[51] J. Z. Xiao, S. Kondo, N. Yanagisawa et al., "Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial," *Clinical & Experimental Allergy*, vol. 36, no. 11, pp. 1425-35, 2006.

[52] J. Z. Xiao, S. Kondo, N. Yanagisawa 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," *Journal of Investigational Allergology & Clinical Immunology*, vol. 16, no. 2, pp. 86-93, 2006.

[53] J. Z. Xiao, S. Kondo, N. Yanagisawa et al., "Clinical efficacy of probiotic Bifidobacterium longum for the treatment of symptoms of Japanese Cedar Pollen allergy in subjects evaluated in an environmental exposure unit," *Allergology International*, vol. 56, no.1, pp. 67-75, 2007.

[54] L. Z. Xu, L. T. Yang, S. Q. Qiu et al., "Combination of specific allergen and probiotics induces specific regulatory B cells and enhances specific immunotherapy effect on allergic rhinitis," *Oncotarget*, vol. 7, no. 34, pp. 54360-54369, 2016, doi: 10.18632/oncotarget.10946.

[55] S. Yonekura, Y. Okamoto, T. Okawa et al., "Effects of daily intake of Lactobacillus paracasei strain KW3110 on Japanese cedar pollinosis," *Allergy & Asthma Proceedings*, vol. 30, no. 4, pp. 397-405, 2009, doi: 10.2500/aap.2009.30.3256.

[56] C. Cingi, M. Conk-Dalay, H. Cakli, and C. Bal, "The effects of spirulina on allergic rhinitis," *European Archives of Otorhinolaryngology*, vol. 265, no. 10, pp. 1219-23, 2008 doi: 10.1007/s00405-008-0642-8.

[57] M. Yoshimura, T. Enomoto, Y. Dake et al., "An evaluation of the clinical efficacy of tomato extract for perennial allergic rhinitis," *Allergology International*, 56(3):225-230, 2007.

[58] S. Friedlander and S. M. Feinberg, "Vitamin C in hay fever: therapy and blood levels," *The Journal of Allergy & Clinical Immunology*, vol. 16, no. 3, pp. 140–145, 1945, doi: https://doi.org/10.1016/0021-8707(45)90353-4.

694 [59] H. N. Holmes and W. Alexander, “Hay fever and vitamin C,” Science; vol. 96, p. 497,
695 1942.

696 [60] L. Podoshin, R. Gertner and M. Fradis, “Treatment of perennial allergic rhinitis with
697 ascorbic acid solution,” *Ear Nose Throat Journal*, vol. 70, no. 1, pp. 54-5, 1991.

698 [61] S. L. Ruskin, “The use of cevitamic acid in the symptomatic and coseasonal treatment of
699 pollinosis,” *Annals of Allergy,* vol. 7, no. 1, pp. 65-70, 1949.

700 [62] C. Vollbracht, M. Raithel, B. Krick, K. Kraft, and A. F. Hagel, “Intravenous vitamin C
701 in the treatment of allergies: an interim subgroup analysis of a long-term observational
702 study,” *Journal of Internal Medicine Research*, vol. 46, no. 9, pp. 3640-3655, 2018, doi:
703 10.1177/0300060518777044.

704 [63] J. Jerzyńska, W. Stelmach, B. Rychlik et al., “Clinical and immunological effects of
705 vitamin D supplementation during the pollen season in children with allergic rhinitis,”
706 *Archives of Medical Science*, vol. 14, no. 1, pp. 122-131, 2018, doi:
707 10.5114/aoms.2016.61978.

708 [64] A. Malik, B. Menon, Y. Dar et al., “Placebo controlled trial of vitamin D
709 supplementation in allergic rhinitis,” *European Respiratory Journal*, vol. 46, suppl. 59,
710 PA2559, 2015, doi: 10.1183/13993003.congress-2015.PA2559.

711 [65] B. Z. Rappaport, C. I. Reed, M. L. Hathaway, and H. C. Struck, “The treatment of hay
712 fever and asthma with viosterol of high potency,” *Journal of Allergy*, vol. 5, no. 6, pp. 541-
713 553, 1934.

714 [66] R. Ariano, “Efficacy of a novel food supplement in the relief of the signs and symptoms
715 of seasonal allergic rhinitis and in the reduction of the consumption of anti-allergic drugs,”
716 *Acta Biomedica*, vol. 86, no. 1, pp. 53-58, 2015.

717 [67] G. Ciprandi and A. Varricchio, “Vitamin D3 plus Lactobacillus reuteri DSM 17938 as
718 adjuvant for allergen immunotherapy: A preliminary experience,” *Jacobs Journal of Allergy*
719 *& Immunology*, vol. 2, no. 2, p. 014, 2015.

720 [68] B. B. Montaño Velázquez, K. Jáuregui-Renaud, C. Bañuelos Arias Adel et al., “Vitamin
721 E effects on nasal symptoms and serum specific IgE levels in patients with perennial allergic
722 rhinitis,” *Annals of Allergy, Asthma & Immunology*, vol. 96, no. 1, pp. 45-50, 2006.

723 [69] E. Shahar, G. Hassoun, and S. Pollack, “Effect of vitamin E supplementation on the
724 regular treatment of seasonal allergic rhinitis,” *Annals of Allergy, Asthma & Immunology*,
725 vol. 92, no. 6, pp. 654-658, 2004.

726 [70] M. C. Denis, A. Furtos, S. Dudonné, et al., “Apple peel polyphenols and their beneficial
727 actions on oxidative stress and inflammation,” *PloS One*, vol. 8, no. 1, e53725, 2013.
728 doi:10.1371/journal.pone.0053725.

729 [71] J. Wruss, P. Lanzerstorfer, S. Huemer et al., “Differences in pharmacokinetics of apple
730 polyphenols after standardized oral consumption of unprocessed apple juice,” *Nutrition*
731 *Journal*, vol 14, p. 32, 2015, doi:10.1186/s12937-015-0018-z.

[72] S. R. Yende, U. N. Harle, B. B. Chaugule, "Therapeutic potential and health benefits of Sargassum species," *Pharmacognosy Reviews*, vol. 8, no. 15, pp. 1–7, 2014, doi:10.4103/0973-7847.125514.

[73] H. Yoshioka, M. Ishida, K. Nishi et al., "Studies on anti-allergic activity of Sargassum horneri extract," *Journal of Functional Foods*, vol. 10, no. 2014, pp. 154-160, 2014, https://doi.org/10.1016/j.jff.2014.06.002.

[74] S. Benjamin, P. Prakasan, S. Sreedharan, A. D. Wright, and F. Spener, "Pros and cons of CLA consumption: an insight from clinical evidences," *Nutrition & Metabolism*, vol. 12, p. 4, 2015, doi:10.1186/1743-7075-12-4.

[75] M. G. Miguel, M. D. Antunes, and M. L. Faleiro, "Honey as a complementary medicine," *Integrative Medicine Insights*, vol. 12, 1178633717702869, 2017, doi:10.1177/1178633717702869.

[76] J. Mlcek, T. Jurikova, S. Skrovankova, and J. Sochor, "Quercetin and its anti-allergic immune response," *Molecules*, vol. 21, no. 5, p. 623, 2016, doi:10.3390/molecules21050623.

[77] M. Butawan, R.L. Benjamin, and R. J. Bloomer, "Methylsulfonylmethane: applications and safety of a novel dietary supplement," *Nutrients*, vol. 9, no. 3, p. 290, 2017, doi:10.3390/nu9030290.

[78] P. Markowiak and K. Śliżewska, "Effects of probiotics, prebiotics, and synbiotics on human health," *Nutrients*; vol. 9, no. 9, p. 1021, 2017, doi:10.3390/nu9091021.

[79] A. Finamore, M. Palmery, S. Bensehaila, and I. Peluso, "Antioxidant, immunomodulating, and microbial-modulating activities of the sustainable and ecofriendly spirulina," *Oxidative Medicine and Cellular Longevity*, vol. 2017, 3247528, 2017. doi:10.1155/2017/3247528.

[80] P. D. Karkos, S. C. Leong, C. D. Karkos, N. Sivaji, and D. A. Assimakopoulos, "Spirulina in clinical practice: evidence-based human applications," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, 531053, 2011. doi:10.1093/ecam/nen058.

[81] A. Raiola, M. M. Rigano, R. Calafiore, L. Frusciante, and A. Barone, "Enhancing the health-promoting effects of tomato fruit for biofortified food," *Mediators of Inflammation*, vol. 2014, 139873, 2014, doi:10.1155/2014/139873.

[82] B. Chauhan, M. Gupta, and K. Chauhan, "Role of antioxidants on the clinical outcome of patients with perennial allergic rhinitis," *Allergy & Rhinology (Providence, R.I.)*, vol. 7, no. 2, pp. 74–81, 2016, doi:10.2500/ar.2016.7.0163.

[83] H. M. Seo, Y. H. Kim, J. H. Lee et al., "Serum zinc status and its association with allergic sensitization: The Fifth Korea National Health and Nutrition Examination Survey," *Scientific Reports*, vol. 7, no. 1, p. 12637, 2017, doi:10.1038/s41598-017-13068-x.

[84] Y-Y. Han, B. Blatter, J. M., Brehm et al., "Diet and asthma: vitamins and methyl donors," *The Lancet. Respiratory Medicine*, vol. 1, no. 10, pp. 813-822, 2013, doi:https://doi.org/10.1016/S2213-2600(13)70126-7.

[85] H. Q. Tian and L. Cheng, "The role of vitamin D in allergic rhinitis" *Asia Pacific Allergy,* vol. 7, no. 2, pp. 65-73, 2017, doi: 10.5415/apallergy.2017.7.2.65.

[86] H. Mirzakhani, A. Al-Garawi, S. T. Weiss, and A. A. Litonjua, "Vitamin D and the development of allergic disease: how important is it?," *Clinical and Experimental Allergy*, vol. 45, no. 1, pp. 114–125, 2015, doi:10.1111/cea.12430.

[87] M. Asif, "Health effects of omega-3,6,9 fatty acids: Perilla frutescens is a good example of plant oils," *Oriental Pharmacy and Experimental Medicine*, vol. 11, no. 1, pp. 51–59, 2011, doi:10.1007/s13596-011-0002-x.

[88] A. L. Caraffa, G. Varvara, E. Spinas et al., "Is vitamin E an anti-allergic compound?," *Journal of Biological Regulators & Homeostic Agents*, vol. 30, no. 1, pp. 11-15, 2016.

[89] C. A. Stone Jr., J. Cook-Mills, T. Gebretsadik et al., "Delineation of the individual effects of vitamin E isoforms on early life incident wheezing," *The Journal of Pediatrics*, vol. 206, pp 156-163.e3, 2019. doi: 10.1016/j.jpeds.2018.10.045.

[90] G. Yang, Z. Q. Liu, and P. C. Yang, "Treatment of allergic rhinitis with probiotics: an alternative approach," *North American Journal of Medical Science*, vol. 5, no. 8, pp. 465-468, 2013, doi: 10.4103/1947-2714.117299.

[91] T. J. Newman, "Local, unpasteurized honey as a treatment for allergic rhinitis: a systematic review," *School of Physician Assistant Studies*, Paper 462, 2014.

[92] M. Ronis, K. B. Pedersen, and J. Watt, "Adverse effects of nutraceuticals and dietary supplements," *Annual Review of Pharmacology and Toxicology*; 58: 583–601, 2018, doi:10.1146/annurev-pharmtox-010617-052844.

[93] K. F. Schulz, D. G. Altman, and D. Moher, "CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials," *BMJ*, vol. 340, pp. 698–702, 2010, doi: 10.1136/bmj.c332.

[94] E. von Elm, D. G. Altman, and M. Egger, "The strengthening the reporting of observational studies in epidemiology (STROBE) statement. guidelines for reporting observational studies," *Epidemiology*, vol. 18, pp. 800–804, 2007, doi: 10.1136/bmj.39335.541782.AD.

[95] N. L. Leech, and A. J. Onwuegbuzie, "Guidelines for conducting and reporting mixed research in the field of counseling and beyond," *Journal of Counseling & Development*, vol. 88, pp. 61–69, 2010, doi: 10.1002/j.1556-6678.2010.tb00151.x.

[96] R. Chafe, "The value of qualitative description in health services and policy research. Valeur de la description qualitative dans la recherche sur les politiques et services de santé," *Healthcare Policy = Politiques de sante* vol. 12, issue 3, pp. 12–18, 2017.