



Complementary and alternative medicine for allergic rhinitis: What is the evidence?

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Abstract

Allergic rhinitis is a common chronic disease affecting both adults and children worldwide. Intranasal glucocorticoid is the standard recommended treatment in conventional medicine. A wide range of complementary and alternative medicine (CAM) has been proposed. This review aims to evaluate the evidence of CAM in this aspect. Some methods including acupuncture, immunotherapy and particular herbs have supportive evidence, but the efficacy of many other CAM is mostly controversial. On the other hand, possible side effects of different modalities remain unclear. Most studies regarding the use of CAM are of great heterogeneity, and having low quality in general. Hence further studies are needed to assess the efficacy and safety before they are employed in treating allergic rhinitis.

Keywords: Allergic rhinitis, Alternative medicine, Complementary medicine, Efficacy, Safety

Background

Globally allergic rhinitis is one of most common chronic diseases affecting 10-20% population.¹ In our locality, the prevalence of intermittent rhinitis and persistent rhinitis was estimated to be 13% and 23% respectively, and an overall prevalence of rhinoconjunctivitis estimated as 17.7% among children of 6-7 years old,^{2,3} with an increasing trend in the prevalence.⁴ According to ARIA (Allergic Rhinitis and its Impact on Asthma) guideline 2010 revision, only intranasal glucocorticosteroid in adults is categorised under strong recommendation (over intranasal H1 antihistamines) in treating allergic rhinitis based on high quality evidence. Oral leukotriene receptor antagonist for seasonal allergic rhinitis, intranasal glucocorticoids in children, intranasal chromones and ipratropium bromide, and oral H1-antihistamines are conditionally recommended based on moderate to high level of evidence.¹ Other than conventional medications, different modalities of complementary and alternative medicine have been developed in management of allergic rhinitis but most of them are having low quality evidence and thus not suggested by the ARIA guideline.^{1,5}

Evidence of complementary and alternative medicine for allergic rhinitis

Literature search based on Pubmed was performed in April 2015, using keywords "complementary medicine" OR "alternative medicine" AND "allergic rhinitis". The results were limited to systematic reviews, review, meta-analysis, multicentre study and randomised controlled trials (RCTs), from 2000/01/01 to 2015/05/13 (15 years), and human, without limit on language. A total of 173 publications were retrieved. The following review will be based on, but not limited to, these references.

Acupuncture

Acupuncture has been suggested to have promising effect on allergic rhinitis by multiple clinical trials but the methodology and quality of these studies were questioned by multiple reviews.⁵⁻⁷ A systematic review performed by Roberts et al included seven RCTs⁸⁻¹⁴ (n=459), only two of them were assessed as of high quality,^{9,11} while meta-analysis showed no overall improvements in allergic symptoms or serum IgE level, no recommendation on the use of acupuncture on allergic rhinitis could be made.¹⁵ Lee et al systematically review seven RCTs of high quality^{8,9,11-13,16,17} (n=449), three of them did not prove advantage of acupuncture over sham acupuncture in seasonal allergic rhinitis,^{8,11,13} while two showed acupuncture could have positive

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effect on symptoms relief of perennial allergic rhinitis,^{9,16} with meta-analysis showing superiority over sham acupuncture (n=152; standard mean difference, 0.45; 95% CI, 0.13-0.78; p=0.006).¹⁸ Two RCTs favored acupuncture over conventional medication,^{19,20} but meta-analysis suggested the difference was statistically insignificant (n=193; risk ratio, 1.08; 95% CI, 0.84-1.38; p=0.56).¹⁸ Pfab et al summarised 8 clinical trials on the efficacy of acupuncture on allergic rhinitis,^{9,12-14,16,21-23} among which seven^{9,12,14,16,21-23} of them showed improvement in terms of symptoms, use of rescue medication and/or quality of life, while the remaining one smaller trial¹³ reported no significance difference in symptoms between sham and acupuncture.²⁴

Specifically for ear acupressure, a systematic review revealed general poor quality of the included 5 studies, any benefits reported from the studies were actually uncertain.²⁵ As for summer acupoint application treatment (SAAT), a cross-sectional multicentre study (n=1058) showed efficacy to be directly proportional to the length of treatment course, and SAAT was more effective in treating seasonal allergic rhinitis than non-seasonal allergic rhinitis.²⁶ From the mixed result of reviews, it is concluded that larger scale of controlled trials of higher quality are needed to confirm the efficacy of acupuncture in allergic rhinitis.

Different adjuncts of acupuncture in treating allergic rhinitis have been developed but there is lack of supportive evidence. Ultrasound was thought to have effect on mast cell degranulation and hence anti-inflammatory effect.²⁷ However no reviews or RCTs working on this particular aspect were published. Moustafa et al compared light emitting diode (LED) phototherapy and laser acupuncture in treating allergic rhinitis in 40 paediatric patients, concluded both were effective and safe, while intranasal LED phototherapy gave more long-lasting result at one year, though further comparison with conventional therapy was warranted.²⁸ Adding a Chinese herbal preparation to acupuncture provided no extra benefits to patients with seasonal allergic rhinitis.²⁹

Regarding the cost and effectiveness of acupuncture, a systematic review performed by Kim et al suggested acceptable cost-effectiveness in various conditions, including allergic rhinitis.³⁰ While in Germany, Witt et al showed acupuncture could be cost-effective as supplementary to routine care of allergic rhinitis,³¹ while Reinhold et al proposed that the cost-effectiveness was limited by the resources for healthcare,³² same as noted by Pfab et al.²⁴

Acupuncture has been regarded as a safe procedure. A review of 9 trials including 782 paediatric patients, incidence of side effect was reported as 1.55/100, with puncture redness being most commonly reported. The rate of serious adverse effects (defined as death, hospital admission, or prolongation of hospital stay, resulting in major disability) was estimated at 5.36/10,000 treatments in paediatrics.³³ As for adults, the risk of adverse events of acupuncture, in a general term, was reported as around 9% by 2 reviews. Most of them were bleeding, pain, numbness and headache which were considered as mild.^{18,24}

Jung et al suggested an antiallergic effect as the underlying mechanism of acupuncture in treating allergic rhinitis, based on reducing the expression of substance P, STAT6, NF κ B, and iNOS from studying mice models.³⁴ More studies were advised in this aspect, in both animal and human models.²⁴

As for the prospect of acupuncture in treating allergic rhinitis, three large clinical trials are in progress currently, one by Kim et al in China and Korea, to study the efficacy of acupuncture for perennial allergic rhinitis in 238 patients,³⁵ second by Brinkhaus et al focusing on the effect on acupuncture on seasonal allergic rhinitis in 422 patients,^{31,36} third by Wang et al to compare the efficacy of acupuncture to cetirizine hydrochloride on allergic rhinitis for 240 patients in China.³⁷

Herbs

Variable mechanisms have been suggested to be responsible for immune-modulation activity, including inhibition of release of histamine and down regulation of serum IgE.³⁸ Multiple trials were performed on various formulae or herbal medicines in treating allergic rhinitis, some of them are listed as follows:

1. **Butterbur:** Butterbur (*Petasites hybridus*, butter dock, bog rhubarb, exwort) is one the most commonly studied herbs in treating allergic rhinitis. It contains petasin which was demonstrated to have *in vitro* inhibiting effect on cysteinyl leukotriene synthesis and to reduce level of histamine and leukotriene *in vivo*,³⁹⁻⁴¹ but without significant antihistaminic effect in cutaneous allergic response.^{42,43} A double-blinded RCT (n=125) by Schapowal et al compared the efficacy and tolerability of Butterbur in seasonal allergic rhinitis with cetirizine. It showed similar global improvement by Butterbur and cetirizine (p<0.001), while Butterbur was more tolerable as it has no sedative effect.⁴¹ Another double-blinded RCTs

(n=330) by the same author found both fexofenadine and Butterbur superior to placebo in symptoms improvement intermittent allergic rhinitis ($p<0.001$), while the two treatments had similar efficacy ($p=0.37$).³⁹ Noted both studies were sponsored by the companies of related medication. This supported the finding of another similar trial by Lee et al (n=16),⁴⁴ but was different from a placebo-controlled trial by Gray et al from which no difference in efficacy between placebo and Butterbur was observed.⁴⁵ Schapowal suggested Butterbur could be considered as a safe alternative when the sedating effect of antihistamine is not desired in treating allergic rhinitis,^{39,41} while Gray et al⁴⁵ and systematic review of six double-blinded RCTs^{39-41,44-46} performed by Guo et al⁴⁷ concluded further studies were needed for confirmation for any efficacy. ARIA guideline 2010 revision suggested that butterbur should only be considered as an alternative in selected patients due to the uncertain adverse effects from toxic alkaloids which may be found in non-commercial preparations.¹

2. ***Nigella sativa***: In a review of 4 trials, a total of 140 patients with allergic rhinitis showed significant symptomatic improvement with *Nigella sativa*, but its long term efficacy was unknown;⁴⁸ another clinical trial (n=66) claimed better symptomatic improvement in allergic rhinitis compared with placebo,⁴⁹ but the trial mentioned no randomisation.
3. ***Shi-Bi-Lin (modified Cang-Er-Zi-San)***: It may be effective by inhibiting IL-4 and TNF- α ,⁵⁰⁻⁵² double-blinded RCTs (n=126) showed effective in symptoms relief and improving quality of life compared with placebo ($p<0.05$).⁵¹⁻⁵³
4. Polyherbal formula *Flos Ionicerae* (Jinyinhua) 2 g, *Herba menthae* (Bohe) 1 g, *Cortex moutan* (Danpi) 2 g, *Rhizoma atractylodis* (Cangzhu) 2 g and *Cortex phellodendri* (Huangbai) 2 g (total 9 g of raw herbs): There was no significant difference in total allergic rhinitis scores and symptoms between treated group and placebo group from a randomised, double-blinded, placebo-controlled study.^{50,54}
5. ***Grapeseed extract***: There was no difference in symptoms, quality of life or use of rescue chlorpheniramine outcome compared with placebo in a placebo-controlled RCT in patients with seasonal allergic rhinitis (n=51);⁵⁵ although rare, adverse effects have been reported, including contact dermatitis.⁵⁶
6. ***Rosmarinic acid***: It reduced neutrophils and eosinophils counts in nasal lavage but effect decreased over time; it may be considered in mild allergic rhinitis.^{50,57,58}
7. ***Spirulina***: The dried biomass of blue-green algae *Arthospira platensis*, was shown to promote interferon gamma production and natural killer cell damage,⁵⁹ and reduce IL-4 level by 32% ($p=0.0082$) in a randomised double-blinded controlled trial (n=36) with allergic rhinitis.⁶⁰ In another randomised double-blinded placebo controlled study (n=129) spirulina improved allergic symptoms and physical finding compared with placebo ($p<0.001$).⁶¹ More RCTs were recommended to confirm the efficacy of spirulina in allergic rhinitis.⁶²
8. ***Biminne***: A polyherbal formula made of 11 components, was found to improve sneezing, but not nasal obstruction, with sustained effect at 1 year from a randomised, double-blind, placebo-controlled trial (n=50).⁶³
9. ***Bhu-zhong-yi-qi-tong***: A polyherbal formula made of 10 herbs was suggested to have anti-inflammatory effect (lowered IgE level and IL-4 activity) and symptomatic improvement in a mice⁶⁴ and a human trial (n=60).⁶⁵
10. As many trials resulted in unreliable findings and conflicting efficacy, and adverse effects especially hypersensitivity are common among herbal medicines, multiple reviews and guidelines concluded additional studies, preferably large scale randomised double-blind, placebo-controlled trials are needed to determine the efficacy, before they could be recommended in the treatment of allergic rhinitis.^{1,5-7,50,56,62,66}

Antioxidants

It was proposed that oxidative stress is associated with the development and exacerbation of allergic rhinitis, but supporting evidence is limited.^{7,67} Two RCTs showed no difference to modest improvement by vitamin E supplement compared with placebo in rhinitis symptoms.^{68,69} Cohort studies demonstrated no clear association between reduced maternal intake of antioxidants with allergic rhinitis in childhood.⁶⁷ While evidence of beneficial effects is lacking, systematic review shows synthetic vitamin E supplement may increase mortality,⁷⁰ more data is needed to establish the value of therapeutic antioxidants in allergic rhinitis.

Immunotherapy

Sublingual and subcutaneous routes are two forms of administration of immunotherapy, with the underlying



mechanism proposed as increasing serum IgG4 antibodies which compete with IgE for allergen binding, and by modifying peripheral and mucosal Th2 responses.^{71,72} Sublingual pollens and house dust mites specific immunotherapy in both adult and children were conditionally recommended by the ARIA guideline 2010 based on very low to moderate quality evidence.¹

Calamita et al performed systematic review of sublingual immunotherapy in asthma. Among the 25 RCTs included, 18 involved patients with asthma and coexisting rhinitis and/or rhinoconjunctivitis.⁷³ For the 10 studies giving analysis of asthma symptoms together with rhinitis, the combined standardised mean difference in allergic symptoms following sublingual immunotherapy was -1.18, 95% confidence interval -1.93 to -0.43, though significant heterogeneity among the studies was noted. There was a more remarkable improvement in symptoms and reduction in use of medication when allergy combinations were analysed instead of asthma symptoms alone. As for subcutaneous immunotherapy, another systematic review found 20 out of 20 placebo controlled RCTs showed better efficacy in improving rhinitis symptoms compared with placebo.⁷⁴ The authors suggested that more investigations were needed to identify the particular subgroup of allergic patient benefits from immunotherapy, and future trials should have more standardised methodology and discussion on single and multiple allergen regimens.⁷⁴

Bahceciler et al compared the efficacy of subcutaneous and sublingual immunotherapy in allergic rhinitis,⁷⁵ by reviewing multiple Cochrane meta-analyses. One Cochrane review of 51 trials of subcutaneous immunotherapy including a total of 2871 patients showed reduction in medication use and symptoms improvement in 13 and 15 studies respectively,⁷⁶ though significant heterogeneity was observed, and number of some trials of specific immunotherapy groups (e.g juniperus ashei, Bermuda, cocos) was as small as one. As for sublingual immunotherapy, two meta-analyses involving a total of 32 trials and 1463 paediatric patients showed sublingual immunotherapy was significantly more effective than placebo in terms of symptoms control and rescue medication use.⁷⁷⁻⁸¹ Noted pollen studies demonstrated more variable and negative results, and again, significant heterogeneity existed among the trials.⁷⁵ Moreover, immunotherapies were shown to have long-lasting efficacy after 4 years and 5 years of discontinuation of subcutaneous grass-pollen

therapy⁸² and sublingual mite extract therapy,⁸³ respectively.

More severe systemic complications (asthma, anaphylaxis) have been reported with subcutaneous immunotherapy than sublingual immunotherapy, and were especially more common in patients with asthma, extensive sensitivity, and receiving high dose allergen.^{75,84,85} The risk of fatal reactions in subcutaneous immunotherapy was still rare, estimated to be one in 2-2.5 million doses administered, by the American academy of Allergen asthma and Immunology committee.⁸⁶ As for sublingual immunotherapy, common side effects include oral itchiness, throat irritation and sneezing, with a rate of adverse events estimated to be 2.7 in 1000 doses affecting 12% patients.^{75,84,87} Eleven cases of anaphylaxis have been reported till 2014.⁸⁵

Saline nasal irrigation (SNI)

Nasal irrigation aims at removing allergen and mucus, thus provides symptomatic treatment.⁸⁸ A systematic review of 10 studies with 400 patients revealed reduction in nasal symptoms and use of medication by average of 27% and 62% and an increase in quality of life score by 27%, after use of SNI. Though it was suggested hypertonic saline theoretically can be used to relieve mucosal swelling by osmosis,⁸⁸ isotonic saline was more commonly preferred to hypertonic saline as the later one produced more variable and less improvements in allergic rhinitis (improvements by 19% to 70% vs -67% to 13%).⁸⁹ No adverse events from SNI have been reported so far,^{89,90} thus it may be considered as a safe adjunct in treating allergic rhinitis, though more investigations are required to decide the best form of SNI (spraying vs douching), type (sodium chloride, Emser salt, seawater salt) and concentration of salt.^{89,91}

Homeopathy

Homeopathy utilised diluted form of a substance which provoked the symptoms to treat the disease.⁶ According to a systematic review performed by ARIA,⁵ and another review by Resnick et al,⁷ both including the same 7 trials with good-quality (a total of 623 patients), the efficacy in homeopathy in allergic rhinitis is mixed. Further evidence is needed to recommend homeopathy in this aspect. The first systematic review of all

homeopathic modalities is under progress to evaluate their effectiveness in allergic rhinitis.⁹²

Physical techniques

Phototherapy

Leong reviewed 9 clinical studies on intranasal phototherapy, among which 4 were placebo-controlled and 5 were not. The quality largely varied from Jada score from 0 to 5. Heterogeneity exists and different devices were used in different studies, without comparison with another. Eight out of 9 studies showed symptomatic improvement, but none showed differences in objective parameters such as inflammatory markers or nasal airflow.⁹³ A recent randomised open study showed phototherapy had better efficacy in reducing nasal obstruction in seasonal allergic rhinitis than azelastine, though the subjective measures could be affected by placebo effect and volunteer bias.⁹⁴ The mechanism of phototherapy is still unclear, more research on basic science, clinical efficacy and long term side effects will be needed before it is recommended as a standard treatment.^{1,93,94}

Conclusion

Overall the evidence of efficacy of CAM in allergic rhinitis is mixed. Acupuncture, immunotherapy, some herbs such as butterbur and some polyherbal formula, as well as saline nasal irrigation may have significant efficacy in allergic rhinitis. Yet more high quality evidence is needed before they can be adapted in regular treatment of allergic rhinitis. Otherwise, till now there is not enough clinical evidence to recommend antioxidants, homeopathy, and phototherapy in routine care. There is extensive heterogeneity in methodology and outcome measurements among studies, which make meta-analysis difficult. Many of the trials are of low quality, with small sample size. Some of the studies are funded by relevant pharmaceutical companies so publication bias must be considered in analysing these trials.

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