

Allergic Rhinoconjunctivitis: Complementary Treatments for the 21st Century

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Even in the 21st century, some seeds of tradition remain firmly grounded regardless of the technological advancements of humankind. One such “tradition” involves using unconventional means—including mental healing, herbal formulas, and healing hand therapies such as acupuncture—to treat chronic illnesses. Although mental healing is unproven and energy therapy is not completely understood, acupuncture, herbal therapy, and sublingual immunotherapy have been described more extensively with mixed results that lack consistency and high-quality scientific data. Researchers are working to modernize these traditional therapies in the treatment of allergic disorders and using advanced technology to alter what some call “the earth’s natural healing power” in hopes of developing a new, integrative form of medicine.

Introduction

Complementary and alternative medicine (CAM) includes a diverse array of practices, treatments, and products used together with or in place of conventional allopathic medicine. A more encompassing practice is integrative medicine, which combines treatments from conventional medicine and CAM for which some high-quality evidence for safety and effectiveness exists. As per the National Center for Complementary and Alternative Medicine (<http://nccam.nih.gov>), complementary practices can be grouped into four domains: mind–body medicine, biologically based practices, manipulative and body-based practices, and energy medicine.

In the era of Internet cafes, organic foods, and increased health consciousness, it is no wonder that people

are seeking new and innovative treatments for common medical conditions. Allergic rhinoconjunctivitis is no exception, especially considering the rising out-of-pocket costs of medications and the side effects of traditional medical therapies. Despite the advances in medical technology, more people are turning to old-fashioned remedies and in some cases taking old concepts and adapting them to modern times to try to cure their illnesses. By incorporating an in-depth review of the most recent studies, we investigate the various CAM treatments being used in the 21st century and provide a comprehensive, informative literature reference for those seeking information on allergic rhinoconjunctivitis.

Mind–Body Medicine

Many books have been written on the power of the mind and its influence on the quality of human existence. In keeping with this idea, to treat chronic medical conditions, new age therapies have incorporated mental healing, including prayer; self-hypnosis; meditation; and therapies that use creative outlets such as art, music, and dance. This form of treatment is especially popular among people of Hispanic and African descent [1]. No randomized, controlled trials have been published to document the proof of efficacy for this category of treatment; however, those who trust and believe in mental healing have a noted improvement in their symptoms and quality of life [2].

Biologically Based Practices

Biologically based practices include therapies that rely on dietary supplements, vitamins, and organic and herbal products to treat medical illnesses. Of the various forms of CAM available, herbal remedies are one of the most popular means of treating medical illnesses internationally. As they relate to allergic rhinoconjunctivitis, research studies have shown that many herbal remedies exist and that user preferences vary depending on cultural influence [3,4].

Butterbur

Butterbur is a perennial shrub whose root contains the active compound petasins, which has been extracted and

studied for its medicinal properties. Although no pediatric trials have been conducted using this herb to treat rhinoconjunctivitis, several adult studies have been published, with mixed results. Some experts believe butterbur acts like montelukast through the leukotriene pathway rather than through the histamine pathway [5]; however, this idea remains controversial. In one study, butterbur was efficacious compared with placebo in sustaining peak nasal inspiratory flow despite nasal adenosine monophosphate challenge [6]. When compared with fexofenadine, it provided equally significant effective relief from intermittent allergic rhinitis by subjective patient ratings and physician's global assessment [7]. However, another study failed to show significant improvement in symptoms, peak nasal inspiratory flow scores, or disease-specific quality of life [8]. The latter study was flawed by its small sample size with heterogeneity in disease severity between groups and inconsistent allergen exposure throughout the study due to its crossover design.

Urtica dioica

Urtica dioica is a plant whose leaf, flower, seed, and root each contain different chemical constituents with therapeutic potential. Medicinal extracts contain polysaccharides and caffeic malic acid, which are found in all parts of nettle and which relieved most rhinoconjunctivitis symptoms in 58% of patients and provided greater efficacy than over-the-counter remedies in 48% [9].

***Citrus unshiu* powder**

Citrus unshiu powder demonstrated relief from seasonal allergic rhinitis to Japanese cedar pollen with dose-dependent inhibition of histamine and β -hexosaminidase, a well-studied molecular marker for mast cell degranulation [10]. The three flavonoids credited for these effects are hesperetin, hesperidin, and nobiletin.

***Lycopus lucidus* plant extract**

Lycopus lucidus plant extract (LAE) has previously demonstrated potential for preventing fatal systemic allergic reactions and antidinitrophenyl, IgE-induced passive cutaneous anaphylaxis in mice. By dose-dependently inhibiting the synthetic compound 48/80, LAE inhibits the mobilization of intracellular calcium that interrupts the mast cell degranulation pathway and inhibits histamine release. LAE also demonstrated inhibitory effects on proinflammatory cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-6 by inhibiting the activation of p38 mitogen-activated protein kinase, which is essential for the expression of inflammatory cytokines, and by preventing nuclear factor κ B DNA binding. By doing so, TNF- α and IL-6 expression are decreased, and the inflammatory cascade is inhibited [11].

Amomum xanthioides

Amomum xanthioides exhibits an inhibitory mechanism similar to that of LAE by inhibiting compound 48/80–

induced histamine release from mast cells via inhibition of intracellular calcium, demonstrating decreased IgE-mediated passive cutaneous anaphylaxis reactions in murine models, and inhibiting p38 mitogen-activated protein kinase, resulting in decreased TNF- α production [12•].

Grape seed extract

Grape seed extract, one of a variety of dietary products readily available and being marketed, showed no evidence to support its efficacy for treating seasonal allergic rhinitis [13].

Tomato extract

Tomato extract generated interest after the skin of red tomatoes demonstrated antihistamine properties in rats. However, tomato extract containing 0.2% of naringenin chalcone showed no objective evidence of an antiallergic nature compared with placebo [14]. Only an insignificant downward trend in serum-measured eosinophil cationic protein concentrations led the authors to speculate that the antiallergic mechanism works by decreasing the number of eosinophils and thus inhibiting the release of histamine and its subsequent reactions.

Dietary *Spirulina*

Dietary *Spirulina*, a filamentous blue-green algae, appears to have nutritional and immunologic benefits. The main active ingredient is C-phycocyanin with antiallergic effects that inhibit histamine release from mast cell-mediated allergic reactions and prevent the differentiation of T-helper (Th) type 2 cells via cytokine IL-4 suppression. No upregulation was noted in the levels of Th1 cytokines (IL-2 and interferon- γ) [15].

Cellulose powder

Cellulose powder administered to the nasal mucosa enhanced the filtration of allergens and irritants from inhaled air similar to normal mucus. A total of 77% of participants in a questionnaire-based study reported complete resolution of rhinoconjunctivitis symptoms, favoring cellulose powder over conventional over-the-counter remedies [16]. Although anecdotal, similar results were obtained in a double-blind, placebo-controlled, crossover trial of 15 patients using cellulose powder, who showed improvements in rhinitis symptoms (sneezing, itchy nose, runny nose) and decreased extracationic proteins in nasal secretions compared with those taking placebo [17].

Indian Ayurvedic medicine

Aller-7

Aller-7, a polyherbal formula, yielded improvement in rhinitis and total nasal symptom scores in correlation with objective measurements of mucociliary clearance times and peak expiratory and nasal flow rates [18]. The anti-inflammatory activity of Aller-7 was confirmed by its significant effectiveness compared with prednisolone and ibuprofen in reducing paw edema in mice [19].

Tinospora cordifolia

Tinospora cordifolia (TC) was evaluated over 8 weeks [20] and demonstrated significant relief from sneezing, nasal discharge, nasal obstruction, and nasal pruritus compared with placebo. In the TC group, the nasal smear consistently demonstrated an absence of goblet cells and a significant decrease in eosinophil and neutrophil counts, and the nasal mucosa changed from blue to pink. No patients in the TC group required rescue medication, which argues for its therapeutic potential. The placebo group showed only a marginal decrease in eosinophils and neutrophils with persistence of goblet cells in nasal smear.

Traditional Chinese medicine*Biminne*

Biminne is a polyherbal formula of 11 ingredients, each with anti-inflammatory, antioxidant, and antiallergic properties. Although its mechanism of action is unclear, subjective reports of improvement in symptoms correlate with total serum IgE levels, physician evaluations, and sustained effects after 1 year [21].

Bu-Zhong-Yi-Qi-Tang

Bu-Zhong-Yi-Qi-Tang (BZYQT) is a preventive polyherbal formula used prophylactically to treat allergic rhinitis, although the molecular basis for this mechanism is unknown. One study compared BZYQT with a *ping wei san* control group, with BZYQT demonstrating anti-inflammatory effects by decreasing leukotriene C₄, prostaglandin E₂, and cyclooxygenase-2 levels, as well as antiallergic effects with decreased serum IgE levels and symptomatic improvement [22].

Shi-Bi-Lin

Shi-Bi-Lin, a modified form of *Cang Er Zi San*, suppressed cytokine production of IL-4, TNF- α , and IL-6 in vitro, whereas IL-8 was unaffected. Inhibition of IL-4 prevents the allergic inflammatory response, as it normally promotes IgE synthesis, Th2-cell proliferation, and the influx of eosinophils. Further suppression of IL-6 and TNF- α supports the anti-inflammatory effect, as these cytokines work synergistically with IL-4. No effect was demonstrated on the cytokine's messenger RNA sequence; thus, the mechanism of cytokine modulation remains unknown [23].

Kampo medicine (Japanese)*Sho-seiryu-to*

Sho-seiryu-to is a polyherbal formula with preventive therapeutic potential. With *sho-seiryu-to*, CD86 major histocompatibility complex II cells and CD28CD4 T cells were selectively suppressed, shifting the Th1/Th2 ratio toward a Th1 response and resulting in decreased IL-4 and allergen-specific IgE production with no effect on interferon- γ . This was consistent with the improvement in allergen-specific sneezing in mice [24].

Rosmarinic acid

Rosmarinic acid acts by inhibiting polymorphonuclear infiltration in the nostrils as demonstrated by decreased neutrophils and eosinophils in nasal lavage on day 0 and 3 of treatment [25]. This correlated with patients' reports of decreased itchy nose, watery eyes, itchy eyes, and total symptoms. However, by the end of the study, the differences compared with placebo were not statistically significant. Hence, these results speak against the therapeutic efficacy and sustaining power of rosmarinic acid despite the authors' claims to the contrary.

Manipulative and Body-based Practices

Forms of therapy in this category include acupuncture, massage, exercise, and chiropractic/osteopathic manipulations. Acupuncture is the most popular of the four.

Acupuncture

The initial literature review process revealed a vast array of literature investigating acupuncture in the treatment of allergic rhinoconjunctivitis, but only a handful of articles represented high-quality research. Xue et al. [26•,27,28•] have published several articles showing the efficacy and safety of acupuncture and Chinese medical therapies in the treatment of allergic rhinoconjunctivitis. They compared real and sham acupuncture for the treatment of seasonal allergic rhinitis and concluded that the improvement in nasal and nonnasal symptom scores in the real acupuncture group (with no reports of adverse effects) favors the safety and efficacy of acupuncture as an alternative medical treatment [27]. They published another trial incorporating the theories of traditional Chinese medicine to study the effects of acupuncture in perennial allergic rhinoconjunctivitis [26•]. In addition to the three key acupuncture points, one supplementary point was included based on the Chinese medicine known as *syndrome differentiation*. With real acupuncture, the individual and total nasal symptom scores improved from baseline after 8 weeks of treatment, with sustained effects observed at 12 weeks. Similarly, Ng et al. [29] demonstrated that in childhood persistent allergic rhinitis, real acupuncture decreased daily rhinitis symptom scores and increased symptom-free days compared with a sham control, although no improvement was seen in the other measured outcomes.

In contrast, a Swedish trial found acupuncture to be ineffective in treating allergic rhinitis by subjective symptom scores using a visual analogue scale and by objective data such as allergen-specific skin prick reactions and allergen-specific serum IgE levels [30]. The exception was the isolated decreased skin reaction and serum IgE to mugwort, which could be statistical error regression to the mean and would need further evaluation by larger randomized studies before any conclusions could be drawn. Xue et al. [28•] attributed these conflicting results to methodologic flaws by Magnusson et al. [30], namely that their inclusion/exclu-

sion criteria were vague, that they included those who had tried acupuncture previously, and that they did not evaluate the use of relief medications; hence, the data would need further controlled studies before acupuncture could be deemed an ineffective treatment regimen.

As of 2008, the only available new studies on the subject were published in the *Chinese Medical Journal*, in which there is a different focus, with a trend toward studying electroacupuncture, comparisons with oral Western or Chinese medications, and more of an interest in understanding the mechanism of action for the effectiveness of acupuncture rather than subjective improvement.

Energy Medicine

A new category in the field of CAM includes the use of energy and energy fields to rid the body of disease [31]. This therapeutic energy is available in two forms. Type 1 includes biofield therapies such as *Reiki*, *Qigong*, and therapeutic touch [32]. Type 2 consists of bioelectromagnetic therapies, namely pulsed fields, magnetic fields, and alternating or direct current fields (<http://nccam.nih.gov>). Controlled trials of energy medicine for allergic rhinoconjunctivitis are needed to understand its role in treating this chronic disease.

Sublingual Immunotherapy

As one can see, medicine in the 21st century is exciting and full of revolutionary concepts. One such concept is the use of sublingual immunotherapy (SLIT) to treat allergic rhinoconjunctivitis. This concept has stirred great interest and come under the scrupulous microscopes of researchers investigating all aspects, from its cost-effectiveness to its safety and efficacy.

SLIT is being recognized as a new, safe, and patient-friendly alternative to subcutaneous immunotherapy. Although this route of therapy may seem well suited for the treatment of pediatric allergic rhinoconjunctivitis, supporting data for its efficacy in this population are lacking. One review reported that 13 randomized, controlled trials and six systematic reviews (one review pending publication) examined SLIT in pediatric populations [33]. Of these, three were negative, two were positive, and one was inconclusive. With such inconsistencies in opinions, further research is necessary to clarify the risks and benefits before any recommendations can be made in favor of this treatment in children, especially the potential for a life-threatening systemic reaction at home. Surprisingly, to the contrary, the evidence for efficacy in adults is more clear and consistent. One study showed that a daily dose of grass pollen SLIT for 22 months produced a 36% mean reduction in rhinoconjunctivitis symptom scores, a 46% mean reduction in medication score, and that mean rhinoconjunctivitis quality of life was improved by 33% compared with placebo [34]. No serious adverse events were noted, and the treatment was well tolerated.

As for the long-term efficacy of SLIT compared with subcutaneous immunotherapy, the data are mixed and lacking in regard to multiple-allergen SLIT. One study of perennial allergic rhinitis concluded that over a 6-year follow-up period, those treated with subcutaneous therapy fared better than those treated with SLIT in regard to symptom scores, skin prick testing, and nasal allergen challenge scores. They concluded that the sublingual route should be offered as an alternative second-line treatment for those who refuse subcutaneous therapy [35]. Others suggest that SLIT provides notable improvements in symptoms [36,37•], improves quality of life [38], and reduces medication use in adults and children [37•,39]; thus, they argue that it is a revolutionary addition to immunotherapy. However, per Marogna et al. [40], treatment with SLIT was required daily for at least 4 years to maintain effective results on clinical parameters 8 years after discontinuation. SLIT treatment for any less than 4 years showed less effective results years after discontinuation. Because evidence for the sustaining power of SLIT is weak compared with that for subcutaneous therapy, future trials must determine how to make SLIT comparable with its subcutaneous counterpart.

Conclusions

Although supporting evidence for the use of CAM in treating allergic rhinoconjunctivitis is limited, the popularity and demand for these treatment modalities is undeniable. In search of a revolutionary treatment for patients seeking an alternative to pharmacologic therapy, researchers worldwide have attempted to describe the mechanism of action, efficacy, and safety of CAM.

Acupuncture has been used for centuries, most popularly in China, to treat physical complaints of pain from various causes. Acupuncture recently expanded its therapeutic effects to treat other medical conditions, including allergic rhinoconjunctivitis. Although it is described as having few side effects, being relatively safe when performed correctly, and an alternative measure for cases refractory to pharmacologic therapy, few high-quality scientific data are available to support this treatment modality. Most studies lack appropriate standardization of study design, treatments, reporting, or outcome measures. Two major design flaws present in most acupuncture clinical trials are participant selection bias and the inability to design a double-blind study. To overcome the limitation of selection bias, Ng et al. [29] suggested that larger, multicultural trials are needed in the future. However, as acupuncturists performing the real and sham treatments must manually perform different techniques for each group, experimenter bias remains a barrier to producing reliable final results. As with any human intervention under study, researchers can only do their best to carefully design clinical protocols that foresee these potential problems and ensure that blinding is as effective as possible.

Next, no standardization or consistency exists in acupuncture treatment protocols. Until now, no one has been able to scientifically prove and standardize the frequency, intensity (number of treatments), duration of treatment, or selection of acupuncture points necessary to yield effective and sustaining results in allergic rhinoconjunctivitis. However, this information is vital to ensure that the benefits outweigh the risks of the procedure. This idea was best demonstrated by Ng et al. [29], who reported that even in patients receiving acupuncture twice a week for 8 weeks, the treatment effects disappeared only 10 weeks after the procedure. With such short-lived results, it is difficult to believe that parents of children considering undergoing this procedure and adults alike will consider the treatment “effective” or worth the risk involved.

Also, a true control was lacking in all studies. Sham acupuncture has been used as a placebo by inserting needles at nonacupuncture points or incompletely inserting the needles at real acupuncture points. However, as these sites are only 1 to 2 cm away from the real acupuncture points, the sham points have nerve endings and thus serve as partial or weak acupuncture. Also, as Streitberger and Kleinhenn [41] noted, even needles that do not penetrate the skin produce a physical sensation with unspecified effects. To overcome this bias, the placebo group should receive no form of acupuncture. To control for the “white coat placebo effect,” all patients could visit with the physician, with only those in the real acupuncture group being treated.

Lastly, many, including Magnusson et al. [30] and Ng et al. [29], have questioned whether a link exists between subjective symptom improvement and objectively measured outcomes, such as the use of relief medications, serum IgE levels, or nasal and blood eosinophil counts. Both found that despite subjective reports of symptomatic improvement by patients, no significant objective difference was found between the two groups [29,30]. However, an uncontrolled study concluded that a decrease in IgE was seen only in those who reported a decrease in clinical symptoms [42]. Therefore, the first step is to determine which objective markers accurately correlate with clinical symptoms in allergic rhinoconjunctivitis in order to determine the true efficacy of the treatment. As for the argument that “needling” alone can cause a therapeutic effect, a third arm could be included in which needle acupuncture is given at sites far from and unrelated to the sites/nerves that may have an effect on the rhinoconjunctivitis symptoms. By adding this group, the researchers could determine whether the therapeutic effects were due to the effect of the needle or the age-old established acupuncture sites used in the treatment group.

With all the listed gaps in our knowledge of acupuncture at this time, this technique cannot be recommended as an evidenced-based treatment option for rhinoconjunctivitis.

Similarly, the data on herbal remedies are extensive but unreliable. Herbal treatments generally are described

as natural and safe. However, natural and organic does not always translate to being safe. That is not to argue that all herbal therapies are harmful but rather brings to light the need for more knowledge about this growing medicinal family.

In China, India, and Japan, the benefits of herbs are accepted. Herbs are used in their original, holistic, and balanced form—no harsh, isolated components or chemicals are used—so they seem to be well tolerated with minimal if any side effects. The remedies are also less expensive than pharmaceutical medications and more readily available, as no prescription or visit to a physician is required. In addition, the herbal tonic is customizable to incorporate each individual’s comorbidities, as each herb included is placed specifically to carry out a particular function. Each formula is made up of 6 to 20 herbs on average, with each herb picked specifically from among more than 350. Each herb is designed to play a significant role in the formula based on its expected and desired interaction with the other herbs. However, before this can be marketed as new age medicine, one must evaluate the risks and efficacy based on scientific research. Although the studies we reviewed were supportive of biologic treatments, two studies reported questionable results because the objective data did not support the subjective reports of improvement. One showed no evidence of improvement with the herbal treatment [14]. However, critics charge that the lack of effect is attributable to the crossover design, which produced biased results due to the inconsistent pollen counts throughout the duration of the study.

Although the data supporting herbal therapy seem promising, the reliability is questionable. The herbal mixtures must be standardized and clearly defined by the World Health Organization in terms of the method of preparation, the active ingredients, and the percentage of each component comprising the mixture before they can be marketed for use as a medical treatment. At present, we do not have sufficient evidence-based knowledge about the mechanism of action, dosing, efficacy, drug interactions, and safety to support use of these products in real world medicine. Also, unlike conventional medicine, achieving the maximum therapeutic potential with herbal treatments depends on the skill and training of the physician who prepares the mixture and patient dedication to his or her own healing process. This is because it takes 3 months to 1 year on average before a therapeutic effect is seen in the case of chronic illnesses.

Moreover, some limitations to the current data available on herbal treatments include the need for more independently funded replications of the isolated randomized, controlled trials currently published with rigour similar to pharmacotherapy trials. These would confirm the true accuracy and validity of the study findings. Also, better documentation of the methods of randomization and blinding to ensure appropriate allocation concealment will lend strength to the conclusions drawn. Lastly,

the need for reliable subjective and valid objective measurement outcomes is key to confirm that the data and conclusions of any study design are trustworthy, even more so than in the study of medicine.

As for SLIT, literature reviews from 1986 to 2008 have sought the optimal dose to provide the maximum efficacy and safety, as this treatment's effectiveness is dose dependent. More recently, scientific reports have concluded that the optimal sublingual dose would be equivalent to one to two times the effective monthly subcutaneous dose taken daily [43]. Side effects range from minor local reactions, such as oral itching, to more severe reactions, including anaphylaxis, which is seen more in children. Hence, this form of therapy is not without risk. It is under investigation by the US Food and Drug Administration to determine the optimal dosing, dosing schedule, mechanism of action, and adverse reactions.

Some have proposed possible mechanisms of actions based on previous knowledge of subcutaneous immunotherapy. Burastero et al. [44•] reported that subcutaneous immunotherapy induces tolerance to allergen through a cooperative effort by the upregulation of IL-10-producing T cells in response to allergen and the shift toward an increased CD4 Th1 cytokine profile. Exposure to allergen causes increased levels of allergen-specific "blocking" IgG4 antibody that in turn decreases IgE-dependent release of mediators from basophils and mast cells and promotes Th1 cytokines. This effect is also seen in SLIT with increased T-regulatory-cell activity as evidenced by decreased proliferation of allergen-stimulated T lymphocytes, increased IL-10, and transforming growth factor- β transcription and the downregulation of Th2 allergen-specific immune response. Although no rise in IgG4 or decrease in allergen-specific IgE was observed, further studies are needed before any conclusions can be drawn regarding this discrepancy [44•]. Similar results were observed by Savolainen et al. [45].

Considering the mixed evidence available for SLIT, no recommendation can be made at the present time, as more detailed investigational studies are needed. However, with the rising prevalence of allergic rhinitis and the progressively increasing severity of pollen seasons, SLIT seems to offer great potential for the world of immunotherapy and, if approved, will expand the treatment of allergic diseases to reach a greater number of patients. All in all, after the limitations and discrepancies are sorted out by researchers, SLIT will likely become a welcome addition to the field of allergy and immunology.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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