

Complementary and alternative medicine: Herbs, phytochemicals and vitamins and their immunologic effects

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives

1. To recognize the frequent practice of complementary and alternative medicines.

2. To understand the potential risks and benefits associated with complementary and alternative medicines.

3. To provide a critical review of the literature supporting and opposing the use of alternative medication to treat atopic disorders.

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Complementary and alternative medicines (CAMs) are used in more than 80% of the world's population and are becoming an increasing component of the US health care system, with more than 70% of the population using CAM at least once and annual spending reaching as much as \$34 billion. Since the inception of the National Center for Complementary and Alternative Medicine, there has been an enormous increase in the number of basic science and therapy-based clinical trials exploring CAM. The subspecialty of allergy and immunology represents a particularly fertile area with a large number of CAM therapies that have been shown to affect the immune system. Recent work has uncovered potential biochemical mechanisms involved in the immunomodulatory pathway of many supplemental vitamins (A, D, and E) that appear to affect the differentiation of CD4⁺ cell T_H1 and T_H2 subsets. Other research has shown that herbs such as resveratrol, quercetin, and magnolol may affect transcription factors such as nuclear factor- κ B and the signal transducer and

activator of transcription/Janus kinase pathways with resultant changes in cytokines and inflammatory mediators. Clinically, there have been hundreds of trials looking at the effect of CAM on asthma, allergic rhinitis, and atopic dermatitis. This article reviews the history of CAM and its use among patients, paying special attention to new research focusing on herbals, phytochemicals, and vitamins and their potential interaction with the immune system. (*J Allergy Clin Immunol* 2009;123:283-94.)

Key words: *Complementary and alternative medicine, immunology, herbal medicines, vitamin, NIH—National Center for Complementary and Alternative Medicine, asthma, allergic rhinitis, atopic dermatitis*

Complementary and alternative medicines (CAMs) represent a diverse group of interventions that exist outside the realm of traditional medical therapeutics in that their efficacy and safety have yet to be determined. In the 1998 editorial accompanying an article on alternative therapies to prostate cancer, Marcia Angell, then editor of the *New England Journal of Medicine*, stated that what sets alternative medicine apart from conventional medicine "is that it has not been scientifically tested and its advocates largely deny the need for such testing"¹ and that "alternative medicine also distinguishes itself by an ideology that largely ignores biologic mechanisms, [and] often disparages modern science."¹ (pp 839-40) This is all too often a viewpoint shared by many health care practitioners in the United States, and is also engrained in

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Abbreviations used

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|-----------------|--|
| CAM: | Complementary and alternative medicine |
| FDA: | US Food and Drug Administration |
| NCCAM: | National Center for Complementary and Alternative Medicine |
| NF- κ B: | Nuclear factor- κ B |
| STAT: | Signal transducer and activator of transcription |
| TCM: | Traditional Chinese medicine |

many medical school curriculums. However, to provide a balance, the US Congress in 1991 enacted funding for the National Institute of Health's Office of Alternative Medicine, which in 1998 evolved to become the National Center for Complementary and Alternative Medicine (NCCAM). One year later, Dr Stephen Straus was named as its first director. He focused on discovering the biochemical mechanisms and clinical application of a variety of alternative therapies (Fig 1). Being a member of the National Institute of Allergy and Infectious Diseases, Dr Straus had a particular interest in the immunologic mechanisms surrounding complementary and alternative medicine. This article is a review of the recent advances in CAM on the immune system and its clinical relevance.

The number of researchers publishing general CAM articles has exploded with more than 1700 articles cited in PubMed using "complementary medicine" as a keyword for the year 2007, compared with only 355 in 1990. There has been a similar upswing in the number of articles and the general interest in the effect of CAM on allergy and immunology. The number of articles published every year just using the key words *immunology* and *complementary medicine* has tripled since 1990 (Fig 2).

USE OF CAM

Complementary and alternative medicine encompasses several major categories: alternative medical systems, biologically based therapies, manipulative therapies, mind-body therapies, and energy therapies (Fig 3). The use of CAM in the United States has been increasing at a substantial rate over the past 2 decades from a total of 34% (427 million) to 42% (628 million), which was in excess of the 385 million visits to a primary care physician visits in both 1990 and 1997 combined.²⁻⁴ Because the costs of CAM are mostly paid out-of-pocket, the annual spending for CAM is approximately \$27 to \$34 billion, compared with \$29 billion in out-of-pocket expenditures for all other US physician services.⁴⁻⁶ In a recent report, the use of CAM at least once in a lifetime, including prayer, was as high as 75%. Similarly, the use of CAM in the past 12 months was 62%, with 26% of respondents stating that they used 1 or more CAM modalities at the suggestion of a physician.³ When this is compared to a recent survey of allergists (see letter to the editor by Engler et al in this issue), there are many similarities to the trends noted, except for the large difference among those who have ever used herbal medicines (8% vs 25%; Fig 4).

RISKS OF CAM USE

When evaluating the potential risk of a medication, one must consider intrinsic risks, which consist of predictable and expected adverse reactions (type A) and idiosyncratic reactions (type B).

Type A reactions account for 80% of adverse reactions, whereas type B reactions account for 6% to 10%.⁷ In addition, there are extrinsic risks that are attributed to erroneous handling and manufacturing of the product, resulting in misidentified materials, contamination, substitutions, lack of standardization of the product, adulteration, incorrect preparation of the dose, and incorrect labeling and advertising. Although CAM is viewed as natural, it too runs these same risks.⁸ Unfortunately, unlike pharmacotherapy, there is no comprehensive list of potential or predictable reactions with CAM. Along with the listed intrinsic and extrinsic risks, some additional risks of using CAM involve the interruption of conventional therapies because of to the lack of perceived necessity or direct interference of therapeutic actions and the failure to recognize the precautions of the treatment because of the misassumption that the products are "natural" and hence "safe."⁹ This misconception is alarming if one considers that 18% of people in the United States (equivalent to 2-4 million people in February 2004) are simultaneously using CAM and conventional medical therapies and are thus at potential risk for a herb-drug interaction. However, some relief is offered if one considers that in 2001, a systematic review of herb-drug interactions included 41 case reports and 17 formal clinical trials relating to 5 herbs that seemed to have the most potential for such an adverse interaction. Of the 17 clinical trials, 10 trials involved St John's wort (*Hypericum perforatum*), and the remainder involved garlic (*Allium sativum*), ginseng (*Panax ginseng*), ginkgo (*Ginkgo biloba*), and kava (*Piper methysticum*). Considering the millions of people using CAM, this would suggest that the real risks from the hundreds of medicinal plants is underreported, hypothetical, or still unknown.⁷

Some examples of adverse reactions with herbs are reviewed in this article's Table E1 in the Online Repository at www.jacionline.org. Examples of agents commonly used by patients for allergic and immune disorders include ma huang, a Chinese herb containing ephedra previously used to promote weight loss, which has been associated with cardiovascular events^{10,11} that in 2004 resulted in the US Food and Drug Administration (FDA) banning the sale of dietary supplements with ephedrine alkaloids. Vitamin A, which has some immunopotentiating properties (relative risk), was studied in the Beta-Carotene and Retinol Efficacy Trial,¹² which evaluated the effects of β -carotene and vitamin A on the development of lung cancer in smokers and workers exposed to asbestos. The results showed the intervention group had a higher mortality from lung cancer (relative risk, 1.46) and cardiovascular disease (relative risk, 1.26). A meta-analysis of placebo-controlled trials involving vitamin E, vitamin A, and β -carotene demonstrated increased mortality in the intervention groups.¹³ In addition, a recent study of Ayurvedic preparations showed that more than 20% had been found to be contaminated with potentially toxic levels of heavy metals including lead, mercury, and arsenic.^{14,15} Concerns for the subspecialty of allergy and immunology are the development of allergic responses such as anaphylaxis, asthma, urticaria, contact dermatitis,⁸ and the reports of drug interactions with herbal remedies¹⁶ such as St John's wort because of its ability to interact with cytochrome oxidases, including CYP3A, resulting in alterations in concentrations of fexofenadine, cyclosporine, and antiretroviral agents such as indinavir.^{17,18} Despite the 100-fold rise in reported adverse reactions to traditional Chinese medicine (TCM) in the last 20 years, the number of adverse events is still negligible compared with the number of adverse events reported from conventional medical therapies, although are certainly not to be considered without risk.

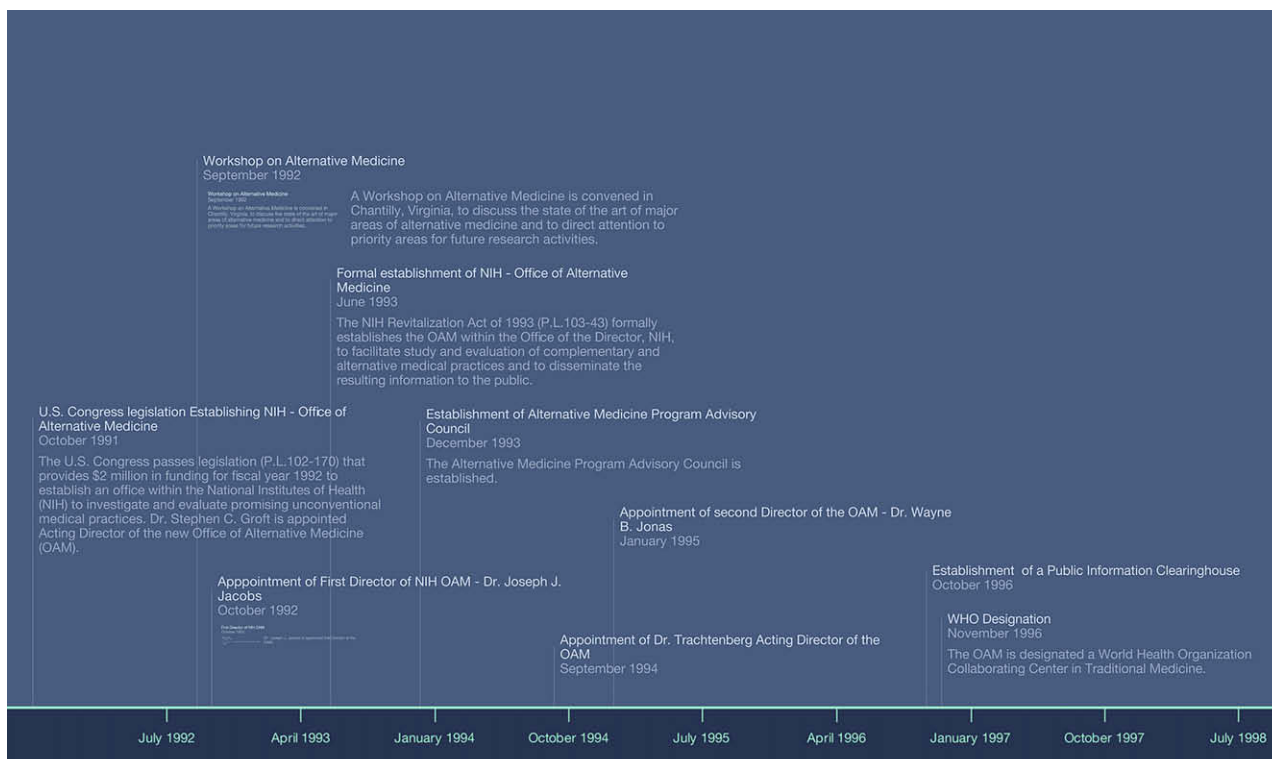


FIG 1. National Institutes of Health NCCAM timeline. A graphical timeline of the events surrounding the formation of NCCAM. *CDC*, Centers for Disease Control and Prevention; *HHS*, Health and Human Services; *NIH*, National Institutes of Health; *OAM*, Office of Alternative Medicine; *WHO*, World Health Organization. (Continued on next page)

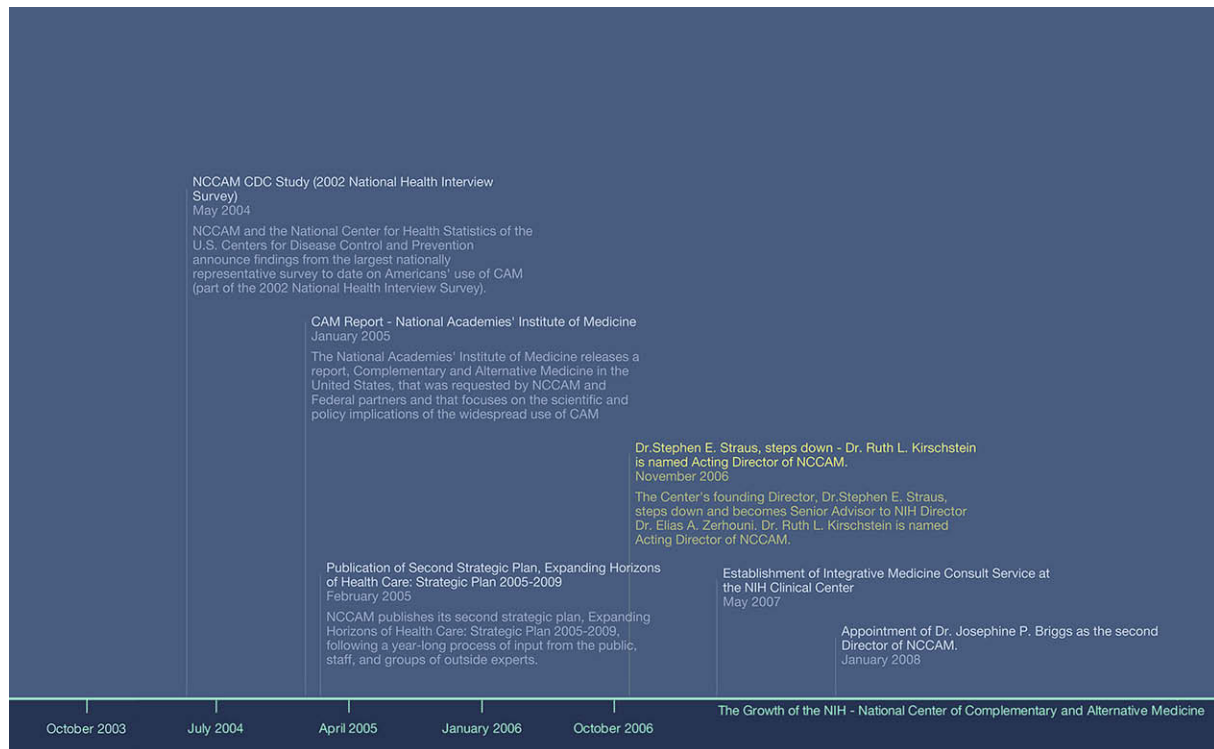


FIG 1. (Continued)

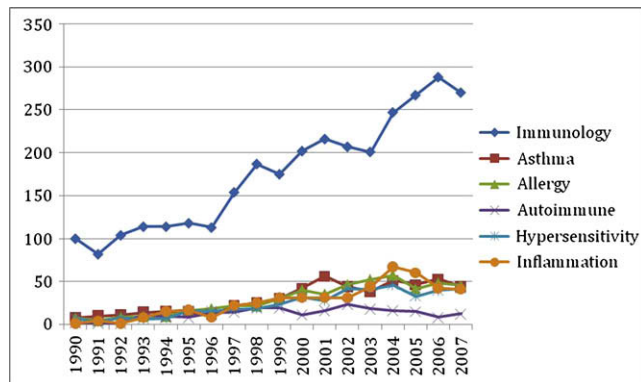


FIG 2. Annual CAM publications related to allergy and immunology. The numbers of articles published and available for search through PubMed using the search terms *complementary medicine* and *immunology*, *asthma*, *allergy*, *autoimmune*, *hypersensitivity*, or *inflammation* are shown.

NCCAM AND CLINICAL TRIALS

In the world of scientific research, randomized controlled trials are accepted as the gold standard when defining the methodologic quality of a clinical trial, especially a double-blind trial. When a clinical trial is designed, attempts are made to minimize bias (placebo effects, observational bias, sampling bias), exclude effects of cointerventions, and prevent the progression of the natural disease course to obtain reliable, reproducible, and generalizable results worthy of recognition. However, some barriers exist that make such scientific designs difficult to achieve and in some cases impossible for researchers investigating complementary and alternative

medical therapies. Examples include finding and randomizing representative CAM sample populations into equal comparison groups. This is challenging as a result of the differing world views regarding CAM, because the motivation to follow the treatment regimen is influenced by the patient's preference. Some have alluded to allocating patients to their preference group and randomizing those who have no preference; however, this suggestion has the potential for biased reporting of a positive response. In another example resulting from ethical implications, some institutions are hesitant to approve clinical trials using CAM when conventional therapies exist that are both effective and evidence-based. As a result, many clinical trials are designed using the CAM intervention as an adjuvant to the conventional therapy, as opposed to being the primary treatment under investigation. Blinding in some CAM therapies is also difficult, especially in mind-body therapies such as tai chi, acupuncture, biofeedback, and other manipulative therapies, because the investigator is critical to the treatment intervention. Similarly, finding a suitable control or placebo for comparison is a hurdle that researchers have tried to overcome using sham interventions, as in the case of acupuncture; however, this attempt has received scrutiny by many, because some claim that sham acupuncture offers some benefits through the process of needling. Because the mechanism of action for most CAM therapies is yet unknown, standardized diagnostic criteria and endpoint measurements to determine the treatment efficacy are lacking, making it difficult to compare multiple study results accurately. Also, some CAM regimens, such as TCM, are individualized and cannot always be standardized for the large groups preferred in conventional randomized controlled trials, which decreases the external validity of the results and increases the likelihood of type II error in these studies. In addition, this form of therapy yields results with less

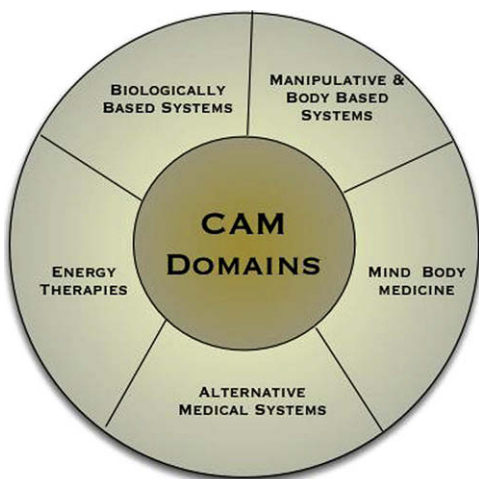


FIG 3. CAM classifications. The alternative medical system involves whole medical systems that are built on other theories and practices including acupuncture, Ayurveda, homeopathic treatment, and naturopathy. Manipulative therapies include chiropractic care and massage. Mind-body therapies use a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms and include biofeedback, meditation, guided imagery, progressive relaxation, deep breathing, hypnosis, yoga, Tai Chi, Qi-gong, Reiki, and prayer. The biologically based therapies use substances found in nature, such as herbs, foods, and vitamins and include megavitamin therapy, various diet-based therapies, folk medicine, chelation therapy, and herbal medicines.³ Energy therapies are essentially made up of biofield therapies that are intended to affect energy fields that purportedly surround and penetrate the human body, whereas bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields.

internal validity than orthodox medical trials because the formulations are often polyherbal and the effectiveness cannot be attributed to any 1 ingredient but rather is a product of the synergistic effect of the formulation as a whole. By the same token, the efficacious results of some Chinese herbal remedies have been linked to contamination by steroids, as in 1 case of atopic dermatitis treated with a topical herbal formula.¹⁹ However, despite the potential for the surreptitious inclusion of glucocorticoids in polyherbal formulations, which can explain the positive outcome, some herbal remedies have withstood rigorous tests disproving the presence of glucocorticoid contamination while demonstrating efficacy.^{20,21} Considering all the obstacles in making a well designed clinical trial, it seems that the best approach is to allow the question under investigation to dictate the methodology of the study design and to take an interdisciplinary approach when determining the therapeutic effectiveness, considering both the qualitative and quantitative data before defining the clinical significance of the results.²² NCCAM has developed a scientifically appropriate support mechanism that has resulted in funding for more than 228 general CAM clinical trials. Many of the initial trials have shown enough promise to warrant further investigations, with several investigating CAM and immunity.

IMMUNE IMPACT OF SPECIFIC HERBS AND VITAMINS

Vitamin D

1 α -25-Dihydroxyvitamin D₃ (vitamin D) is a fat-soluble vitamin necessary in the human diet whose affects include not only

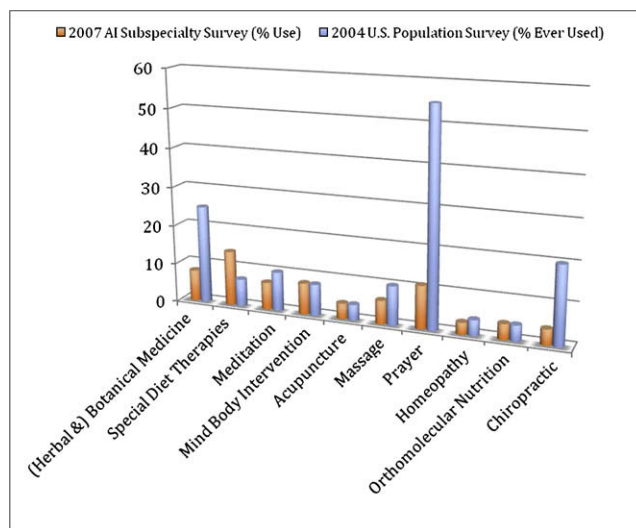


FIG 4. National versus allergist survey. A comparison of the allergy and immunology (AI) subspecialty survey conducted in 2007 compared with the Centers for Disease Control and Prevention survey³ of the US population use of CAM demonstrates an overall similarity in use except for the US population using more prayer, herbal, and chiropractic interventions, whereas the allergy and immunology subspecialty was more inclined to use special diets.

calcium homeostasis and bone metabolism but also immune function. Vitamin D has its actions promoted through binding to the vitamin D receptor (VDR) and translocating to the nucleus. A variety of immune cells express VDR and are under investigation into the effect of vitamin D on autoimmune or infectious diseases.²³ Early studies demonstrated²⁴ that the addition of vitamin D interrupted mitogenesis of T cells because vitamin D appears to suppress preferentially the differentiation of CD4⁺ cells to the T_H1 subtype, with subsequent shifting of the CD4⁺ cells to the T_H2 subtype,^{25,26} and lower levels of vitamin D showing negative effects in both multiple sclerosis and inflammatory bowel disease.^{27,28}

Vitamin E

Vitamin E is a lipid soluble molecule that is known to have at least 8 different isoforms (α , β , γ , and δ -tocopherols and α , β , γ , and δ -tocotrienols), all with a chromanol nucleus surrounded by different lipophilic side chains. Vitamin E intercalates itself into lipid membranes of cells, and it can help in halting peroxidation of lipid molecules. The activity of vitamin E in gene expression and transcription in mast cells has been described recently as affecting the activation of protein kinase C, protein phosphatase 2A, and protein kinase B in mast cells,²⁹ with inhibition of protein kinase C halting the proliferation of mast cells *in vitro*,³⁰ and other studies showing inhibition of eosinophilic infiltration of mucosal surfaces.³¹

Vitamin A

Using the theory that high levels of vitamin A shift the immune system from a predominantly T_H1 to a T_H2 paradigm,³² vitamin A deficiency appears potentially to ameliorate experimental asthma, whereas supplementation with vitamin A increases bronchial hyperreactivity, levels of IL-4 and IL-5, and pulmonary eosinophilia. The effect of vitamin A on shifting the immune response toward a T_H2 phenotype and increasing antibody production has also

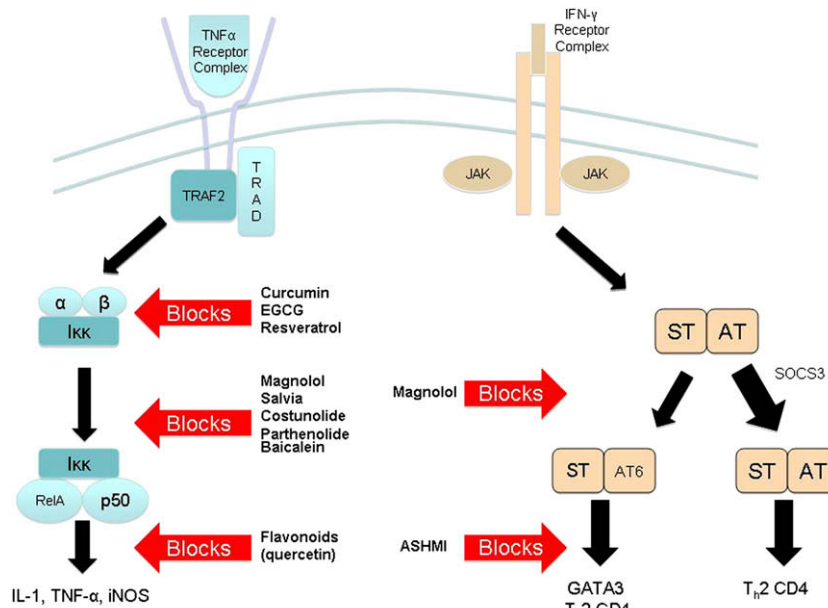


FIG 5. Herbal medicines and potential mechanisms of action. NF- κ B is an enzyme that is at the center of an evolutionarily conserved proinflammatory cascade. Initiation of the NF- κ B system begins through receptors such as TNF- α and TLR4. The inactivated NF- κ B is complexed with an inhibitory protein, I κ B, which, after activation of cell membrane receptor, is a target of phosphorylation and ubiquitination. This allows NF- κ B to translocate to the nucleus and bind to DNA. This allows transcription of proinflammatory genes for such proteins as TNF- α , IL-1, MMP-9, IL-8, monocyte chemoattractant protein 1 (MCP), macrophage inflammatory protein 1 α (MIP), and inducible NOS. The JAK pathway is initiated with cytokine binding to its receptor, particularly the IFN- γ cytokine. The receptor then dimerizes and turns on a member of the STAT family, of which 7 have been described in human beings. This enzyme then translocates to the nucleus and begins transcribing proteins such as IFNs, IL-2, IL-4, and IL-12. Of interest, one of the regulators of the STAT pathway is the suppressor of cytokine signaling family (SOCS), and the SOCS3 enzyme has been implicated in the propagation of allergic responses with increased expression of SOCS3, resulting in greater T_H2 differentiation.¹⁰⁵⁻¹⁰⁷ A final biochemical pathway for the JAK/STAT pathway includes the GATA transcription family. Activation of STAT6 leads to expression of GATA-3, which in turn will transform naive CD4⁺ T cells into the T_H2 subtype. This activation of the GATA-3 pathways has been implicated in asthma and other allergic disorders independent of the SOCS pathway.^{108,109} *ASHMI*, Antiasthma herbal medicine intervention; *EGCG*, epigallocatechin gallate; *TRAD*, TNF- α receptor associated domain; *TRAF*, TNF- α receptor associated factor; *RelA*, reticuloendotheliosis viral oncogene homolog A; *STAT*, signal transducers and activators of transcription protein; *NOS*, nitric oxide synthase.

been demonstrated in the successful seroconversion of children vaccinated in areas known to be vitamin A-deficient with vitamin supplementation.³³ The effect of vitamin A on cytokine production and shifting the body to a T_H2 state has implications in common variable immunodeficiency. Two studies have shown that supplementation with vitamin A improved antibody production.^{34,35}

Vitamin C

Vitamin C is an antioxidant necessary in some species that have lost the ability to synthesize it on their own. The implication that vitamin C is an important mediator of the immune response with an effect on ameliorating the common cold is an idea that stretches back decades, although early studies^{36,37} never demonstrated an effect on the duration or intensity of the common cold in patients supplemented with vitamin C. The connection between vitamin C and asthma has also been of interest to researchers; however, the results have not shown much effect of vitamin C on the pathogenesis of asthma.^{38,39} In a large study by Fogarty et al,⁴⁰ supplementation with vitamin C and magnesium had no effect on asthma symptoms. This was borne out by a recent review⁴¹ of clinical trials looking at vitamin C supplementation and asthma, with most trials showing no benefit.

HERBAL MEDICINES AND POTENTIAL MECHANISMS OF ACTION

The potency of different herbal remedies will ultimately be related to their individual mechanisms of action that have been scrupulously explored over the past decade. A primary focus has been on their ability to interact with transcription factors: the nuclear factor- κ B (NF- κ B) pathway, the JAK/signal transducer and activator of transcription (STAT) pathway, and the GATA-3 pathway (Fig 5).

Magnolol

One of the many plant polyphenols that are present in herbal remedies and have been shown to have action against NF- κ B is magnolol, a constituent of the Chinese herb Hou p'u (*Magnolia officinalis*).^{42,43} By using an elegant assay that monitors the production of NF- κ B transcriptional products through activation via TNF- α , Chen et al⁴² have shown that magnolol suppresses inhibitor of nuclear factor- κ B kinase β subunit activity, and thus decreases degradation of the inhibitor of κ B enzyme. In another study, the researchers showed that magnolol has effects beyond the IKKB activity and in fact can inhibit activation of the STAT3/JAK pathway in IL-6-treated cells.

Quercetin

Quercetin is a ubiquitous flavonoid found in a variety of foods, from raspberries and apples to onions and capers. In a 2003 article, Cho et al⁴⁴ showed that Quercetin reduces LPS-mediated cytokine production through NF- κ B and in particular in the I κ B degradation pathway. This is similar in nature to the cascade suppression previously shown in curcumin and magnolol.⁴⁵ Of interest, Quercetin has also been shown to have antiangiogenic effects *in vitro*,⁴⁶ as well as effects in preventing IL-1-mediated mast cell release of IL-6 without degranulation.

Antiasthma herbal medicine interventions

As opposed to a single herbal intervention, antiasthma herbal medicine interventions Mt Sinai School of Medicine formula 02 and food allergy herbal formula, refined 2, are proprietary formulas containing anywhere from 3 to 14 different herbs. In a randomized clinical trial published in 2005, Wen et al⁴⁷ showed that antiasthma herbal medicine interventions produced significant improvement in FEV₁, peak expiratory flow, self-reported symptoms, and β -agonist use, and was not associated with either adrenal dysfunction or IFN- γ suppression. In a study in 2004,⁴⁸ a group studying Mt Sinai School of Medicine formula 02 showed similar results with a decrease in IL-4 and IL-5 production, without a decrease in IFN- γ , thus suggesting that these herbal formulas can help switch individuals from a predominantly T_H2 to a T_H1 phenotype through the potential suppression of GATA-3.

Resveratrol

Resveratrol is a phytoalexin found in large amounts in the traditional Japanese and Chinese medicinal herb *Polygonum cuspidatum*, as well as in grape skin extracts and red wine. Resveratrol is synthesized in plant cells whenever stress (particularly fungal invasion) or nutrient depletion occurs. Interest in resveratrol as a nutritional supplement grew when an article published in *Science* in 1997⁴⁹ showed that resveratrol has potent cancer chemoprotective activity with remarkable ability to inhibit COX-1 and COX-2. Two later studies published in *Nature*^{50,51} further increased interest because resveratrol supplementation demonstrated an increased lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster*. In 2000, the activity of resveratrol at NF- κ B was discovered to block NF- κ B reporter gene activation through inhibition of phosphorylation of p65.⁵² No activity at inhibitor of κ β subunit α was found. Subsequent studies have shown that resveratrol blocks the TIR-domain-containing adapter-inducing INF- β (TRIF) pathway, not the MyD88 pathway, in Toll-like receptor (TLR)-dependent NF- κ B activation.⁵³

Ma huang (*Ephedrine sinica*)

Ephedrine sinica has been used for >5000 years in the form of teas in TCM to treat respiratory conditions such as asthma. In the United States, however, it was being used for weight reduction, energy boosting, and enhancement of physical performance by athletes. Because of its sympathomimetic properties on α -adrenergic and β -adrenergic receptors, it became popular as an illicit street drug with amphetamine-like effects and was abused in the form of "ecstasy." Ma huang is composed of 6 ephedrine alkaloids, although the indications for its use in the United States were not described in TCM, despite a meta-analysis in 2003 by the FDA demonstrating its short-term effectiveness in promoting

weight loss. In 2003, this agent was removed from the market after >3000 cases were reported to the FDA, of which 30% resulted in serious adverse events (chest pain, hypertension, myocardial infarctions, strokes, arrhythmia, psychiatric disturbances, and death), and many involved young healthy individuals. The safe use of this herb for decades in Chinese medicine compared with its use in the United States was thought to be a result of the differences in the indications for its use and the careful combination of ma huang with synergistic herbs in Chinese herbal concoctions, namely licorice, ginger, honey, cinnamon, and apricot seeds, which also act to reduce its side effects. Others have proposed that extrinsic factors including inadequate chemical analysis of extracts, inconsistent herbal compositions, variations in herb sources, and other idiosyncratic reactions resulted in toxicity despite use at recommended doses, which were determined on the basis of ephedrine content without accounting for the other undefined potent ingredients.⁵⁴ A new assay has since been established that uses reverse-phase HPLC to determine the exact species of *Ephedra* present in a herbal extract.⁵⁵ By chemically fingerprinting in this manner, one can now authenticate ground plant materials and ensure that the active component is the plant extract expected. In this manner, one can prevent surreptitious inclusion of ephedra in unexpected herbal remedies. Because several other herbal remedies have gained popularity in the treatment of atopic diseases, many options are available for those seeking CAM discussed in the Clinical Applications for the Practicing Allergist section below.

CLINICAL APPLICATIONS FOR THE PRACTICING ALLERGIST

To explain the biological mechanisms and provide clinical evidence of the effectiveness of CAM remedies, 3 common atopic disease processes are reviewed.

Asthma

Asthma is a chronic inflammatory disease characterized by bronchial inflammation, bronchial constriction, and increased mucus production. Although effective conventional remedies are available, a large population (as high as 65% among black subjects, poor subjects, less educated parents, and children with persistent symptoms) exists that uses complementary medicines adjunctively to minimize the need for conventional therapies and hence avoid the profound side-effect profiles.^{56,57} These complementary treatments for asthma fall into 1 of 5 main categories: herbal, antioxidants, vitamins, fatty acids, and probiotics.

Although several herbs have reportedly been used for the treatment of asthma, a Cochrane Review recently conducted with 21 herbs showed mixed benefits. For instance, *Tylophora indica* produced improvements in symptom scores >50% from baseline after 1 week^{58,59} and decreased the frequency of attacks by 50%.⁵⁹⁻⁶¹ Unfortunately, these effects were short-lived and were no longer evidenced after 12 weeks of treatment. Similarly, ginger improved symptoms by providing relief from chest tightness,⁶² whereas pulmoFlex, an Ayurvedic polyherbal formulation, provided relief to "patients experiencing deterioration."⁶³ *Eucalyptol* demonstrated a steroid-sparing effect in a single case, although its mucolytic effect has been known for many years.⁶⁴ Contrary to limited subjective reports, objective measures of improvement have been clearly reported with boswellia, a gummy resin of the *Boswellia* tree with a long history of use in Indian herbal medicine,

improving FEV₁⁶⁵ and peak expiratory flow rate (PEFR)⁶⁶ in adults; propolis, a resinous mixture collected by bees from various botanical sources, improved PEFR in adults.⁶⁷ Pycnogenol (Horphag Research, Geneva, Switzerland), a water extract of the bark of the French maritime pine (*Pinus pinaster* ssp *Atlantica*) containing oligomeric proanthocyanidins and bioflavonoids, had similar effects in children.⁶⁸ However, because of the measurements in percent of predicted FEV₁ and PEFR, these improvements equate to only minimal changes in actual FEV₁ and PEFR, and hence their clinical benefit remains undetermined.

The majority of CAM literature associated with allergy and asthma (Fig 2) seems to focus on the effects of antioxidants and probiotics. However, 1 study⁶⁹ on fatty acids reported a 30% to 50% reduction in childhood asthma just by incorporating fish, which is high in ω -3, into the child's regular diet. Although anecdotal, such dramatic results warrant further studies because it is from these anecdotal reports that many of the current studies have found their origin.⁷⁰ As for the antioxidants, although the list is mostly made up of vitamins and minerals (Table E1), there are some vitamins, such as vitamins A and D, that have no antioxidant effects but rather affect immune function. A recent animal model⁷¹ reported that contrary to previous claims that vitamin A negatively correlated with asthma severity,⁷² the excessive intake of vitamin A demonstrated a shift toward T_H2, resulting in pulmonary hyperresponsiveness and more deaths from asthma in the United States compared with Third World countries, where vitamin A deficiency resulted in death from infection.⁷¹ This observation was supported by the decreased IL-4 and IL-5 levels in bronchoalveolar lavage fluid, pulmonary eosinophilia, and suppressed IgE and IgG₁ responses measured in deficient patients. Of the vitamins that have antioxidant properties, vitamin C is the most recognized in regard to asthma. A bivariable analysis of children noted that despite controlling for several potential confounding variables, of the antioxidants, children with asthma lacked vitamin C and α -carotene.⁷³ It is proposed that perhaps the oxidative stress from the generation of reactive oxygen and free radicals causes bronchial inflammation and hyperreactivity, which results in a decrease in the cell's reducing capacity, leading to the development of asthma.^{74,75} Moreover, it seems that although introducing fresh fruits and vegetables after age 1 year reduced the risk of developing asthma, early supplementation within the first 6 months actually increased the child's allergic sensitization to house dust mite on skin prick testing and thereby increased the risk of developing asthma.⁷⁶ This effect was most prevalent among black children.⁷⁷ Finally, in 2007, *Lactobacillus* gained interest as a probiotic with effective therapeutic potential in allergic diseases. Because there are several strains of *Lactobacillus*, conflicting reports of its efficacy exist. Two groups found no objective evidence of beneficial effects with *Lactobacillus* GG given to marathon runners during pollen season⁷⁸ or with *Lactobacillus casei* given to preschool children to decrease the frequency of attacks. However, 2 other groups used mouse models and found significant improvements with live oral *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG, and *Bifidobacterium lactis* (Bb-12). With such mixed data on the subject, further studies are needed to distinguish the mechanisms of action and efficacy of the various probiotic strains before any definitive conclusions can be made. However, one thing is clear: probiotics are vital to the healthy maturation of the immune system after birth,⁷⁹ as has been demonstrated in patients with atopic dermatitis.^{80,81}

Atopic dermatitis

Atopic dermatitis is an inflammatory cutaneous disease characterized by atopic eczema and pruritus and is occasionally complicated by superimposed bacterial skin infections. Like asthma, although many complementary therapies exist for the treatment of atopic dermatitis, only a few have been researched in terms of their efficacy, safety, and mechanism of action. In Table E1, an extensive list of complementary treatments associated with this disease process is presented. However, even with such limited knowledge about these alternative treatments, their popularity is worldwide, and they are being used without inhibition.

Herbal remedies predominate in the literature, whereas of the fatty acids, ω -6 fatty acid and γ -linolenic acid, found in evening primrose (*Oenothera biennis*), is the primary agent to have therapeutic and prophylactic effects in atopic dermatitis,⁸² associated with decreasing the redness, scaling, and itching from the lesions and preventing future exacerbations. Likewise, *Rumex japonicus* *Houtt*⁸³ has been shown to have some efficacy in a hapten-induced mouse model of atopic dermatitis. This herb demonstrated anti-inflammatory, antioxidant, and antibacterial properties. By inhibiting the histological changes in the skin (decreasing the hypertrophy, hyperkeratosis, and infiltration of inflammatory cells in the skin), *R japonicus* *Houtt* decreased the development of eczematous skin lesions, and by decreasing the colonization of the skin by *Staphylococcus aureus*, it decreased scratching behavior and the frequency of exacerbations as well.

A more detailed review of 12 herbs has demonstrated some effect in atopic skin disorders. Butterbur, like montelukast, had no significant effect on either the histamine or allergen-induced cutaneous wheal and flare response compared with fexofenadine.⁸⁴ In an animal model, *Actinidia arguta* improved dermatitis skin lesions in magnesium-deficient hairless rats by decreasing infiltration of the skin by inflammatory cells and preventing histopathological remodeling of the dermis and epidermis while preventing transepidermal water loss.⁸⁵ *Saururus chinensis*, described by the same group,⁸⁶ demonstrated similar anti-inflammatory effects to *A arguta*, resulting in decreased hypertrophy and hyperkeratosis of the dermis and epidermis and decreased itching behavior in the atopic subjects. In addition, they demonstrated a shift toward the T_H1 cell pathway with no effect demonstrated on T_H2. *Mahonia aquifolium* demonstrated contrasting results: in an open-label trial in adults, significant improvements were reported in eczema area, severity index scores, and patient satisfaction on the basis of a post-treatment questionnaire,⁸⁷ whereas a randomized, double-blind, vehicle-controlled, half-side comparison with an herbal ointment containing *M aquifolium*, *Viola tricolor*, and *Centella asiatica* reported no statistical improvement compared with placebo in either primary skin symptoms or secondary assessment of pruritus, effectiveness, and tolerability.⁸⁸ *Lyophyllum decastes* extracted from Hatakeshimeji mushrooms effectively lowered total skin severity scores and serum IgE levels through its inhibitory action on the T_H2 immune response.⁸⁹ Konjac ceramide orally administered favored a shift toward the T_H1 pathway and demonstrated improvements in the Score of Atopic Dermatitis for skin symptoms, decreased skin responses to skin prick testing, and decreased dust mite specific IgE production.⁹⁰ A randomized, double-blind, placebo-controlled monocentric trial of St John's wort cream containing 1.5% hyperforin (the main active ingredient) showed effective anti-inflammatory properties resulting in an improved appearance of the skin in patients with mild-moderate atopic dermatitis in

addition to antibacterial effects with decreased skin colonization by *S aureus*.⁹¹ Persimmon leaf extract was evaluated over a period of 4 weeks by administering 1.5 mg/kg/day of its major flavonoid astragalins. Results showed both prophylactic and therapeutic efficacy in decreasing severity of exacerbations of atopic dermatitis with decreased scratching behavior, decreased transepidermal water loss, and decreased serum IgE, and with prophylactic daily dosing there was a demonstrable decrease in the onset and progression of exacerbations.⁹²

TCM polyherbal remedies have been implicated for the treatment of atopic dermatitis. One such formula containing 5 different herbs was investigated²¹ in children with moderate-severe atopic dermatitis and demonstrated a significant decrease in corticosteroid use by one third and an improvement in the dermatology quality of life score, although no significant difference was noted in the allergic rhinitis score or the Score of Atopic Dermatitis. Zemaphyte (Phytofarm Plc, London, United Kingdom), a Chinese herb, also demonstrated clinical improvements in atopic dermatitis with decreased erythema, decreased surface damage, and decreased itching of the skin with few minor gastrointestinal side effects. Bhu-zong-yi-qi-tang is a polyherbal compound made up of 10 herbs with effectiveness as a prophylactic agent in allergic rhinitis and also therapeutic potential in atopic dermatitis because it decreased serum IgE levels in a mouse model. Finally, BSASM is also a multicomponent preparation with anti-inflammatory effects in atopic dermatitis demonstrated by improvements in pruritus, transepidermal water loss, and eczema area severity index scores. It is thought to act by inducing NF- κ B activation, reducing IL-8 and TNF- α production, and inhibiting IL-2 production in Jurkat T cells, although the true mechanism is still under investigation. One thing is clear: the effectiveness of such polyherbal formulas, whether it is BSASM or bu-zhong-yi-qi-tang, is attributed to the synergistic effects of their individual components, which exemplifies the tenet that the whole exceeds sum of the parts—that is, the synergistic effects of these components, although they are a strong force together (the whole), have only a fraction of the efficacy when tried individually (the parts).

Allergic rhinitis

A large proportion of the literature in CAM and allergy clinical studies has been focused on the impact of multiple herbal remedies on allergic rhinitis² (Table E1).

Butterbur is a perennial shrub whose root contains the active compound petasins. Adult studies showed butterbur proved efficacious compared with placebo in sustaining nasal inspiratory flow while being challenged with a potent nasal congestant, adenosine monophosphate,⁹³ and when compared with fexofenadine, it provided equally significant effective relief from intermittent allergic rhinitis both by subjective patient ratings and by the physician's global assessment.⁹⁴ *Urtica dioica* is a plant whose leaf, flower, seed, and root each contain different chemical constituents, including histamine, thus the common name stinging nettle. Medicinal extracts contain polysaccharides and caffeic malic acid, found in all parts of nettle, which relieved most of the rhinoconjunctivitis symptoms in 58% of subjects and provided greater efficacy than over-the-counter remedies in 48%.⁹⁵ Citrus unshiu powder demonstrated relief from seasonal allergic rhinitis to Japanese cedar pollen with dose-dependent inhibition of histamine and β -hexosaminidase, a marker for mast cell degranulation.⁹⁶ The 3 flavonoids credited for these effects are hesperetin, hesperidin, and nobiletin. Both *Lycopus lucidus* plant

extract⁹⁷ and *Amomum xanthiodes*⁹⁸ have demonstrated antihistamine and anti-inflammatory potential to prevent fatal systemic allergic reactions and IgE-induced passive cutaneous anaphylaxis in mice. Although the objective data are significantly favorable for CAM, one must consider the data in context, keeping in mind that the study of *U dioica* is an open-trial study, and no quantitative data were measured. As for citrus unshiu powder, *L lucidus*, and *A xanthiodes*, *in vivo* trials are needed to determine whether the findings from the rat models can be accurately extrapolated to real clinical practices.

Likewise, dietary products like grape seed extract, tomato extract, dietary spirulina, and cellulose powder have been suggested for the treatment of allergic rhinitis. Unfortunately, no evidence was found to support the efficacy of grape seed extract,⁹⁹ and only an insignificant downward trend in serum-measured eosinophil cationic protein concentrations was seen with tomato extract.¹⁰⁰ However, dietary *Spirulina*, a filamentous blue-green alga, with its main active ingredient C-phycoerythrin, did demonstrate antiallergic effects by inhibiting histamine release from mast cell-mediated allergic reactions and by suppressing IL-4, thereby inhibiting the T_H2 synthesis of IgE.¹⁰¹ Likewise, cellulose powder administered to the nasal mucosa proved beneficial in enhancing the filtration of allergens and irritants from inhaled air, similar to one's normal mucus providing complete resolution of rhinoconjunctivitis in 77% of subjects.¹⁰² Although the trials investigating dietary supplements are designed in a randomized double-blind manner, the data are qualitative, measuring subjective symptom scores and quality of life questionnaires. More objective endpoint measurements and large-scale studies are needed to lend internal and external validity to the conclusions drawn.

Indian Ayurvedic medicine

The 2 most studied regimens in this group include a polyherbal formula called Aller-7 and *Tinospora cordifolia*. Aller-7 has demonstrated anti-inflammatory properties in rat models and has shown improvement in rhinitis and total nasal symptom scores that correlate with objective measurements.¹⁰³ Similarly, *T cordifolia* provided significant relief from sneezing, nasal discharge, nasal obstruction, and nasal pruritus compared with placebo with consistent improvements on examination of the nasal smears and nasal mucosa.¹⁰⁴

TCM

As mentioned, Bhu-zong-yi-qi-tang has shown proven effects in both allergic rhinitis¹⁰⁵ and atopic dermatitis. Another polyherbal formula important to the treatment of allergic rhinitis is biminne, made of 11 constituents, each with anti-inflammatory, antioxidant, and antiallergic properties. Although the mechanism of action is unclear, there are subjective reports of improvement in symptoms that correlate with total serum IgE levels, physician evaluations, and sustained effects after 1 year.¹⁰⁶ Last, Shi-Bi-Lin, a modified form of Cang Er Zi San, has proven to be an effective therapeutic choice with its anti-inflammatory effects on the suppression of IL-4, TNF- α , and IL-6 production.¹⁰⁷ No effect was demonstrated on the messenger RNA sequence for these cytokines, so the mechanism of cytokine modulation remains unknown.

Kampo medicine (Japanese)

Kampo agents Sho-seiryu-to and rosmarinic acid are the main CAM agents used in Japanese culture. Sho-seiryu-to is a

polyherbal formula with evidence of shifting toward a T_H2 response, resulting in decreased IL-4 and allergen-specific IgE production consistent with the improvement in allergen-specific sneezing in mice. No effect was seen on IFN- α .¹⁰⁸ Rosmarinic acid, on the other hand, decreased leukocyte infiltration in the nostrils, demonstrated by subjective improvements in symptoms that correlate with improvements seen by nasal lavage. Polyherbal preparations as seen with Ayurvedic, Kampo, and TCM require carefully designed intricate studies to understand the mechanism of action and the active ingredients responsible for their efficacy. The polyherbal formulas reviewed in this article are all investigated via high-quality randomized trials with reliable reproducible results. Future studies should build on the results of these trials with the aim to follow long-term outcomes via prospective trials.

In conclusion, the data on complementary remedies are extensive but as of yet remain scientifically unclear because there are conflicting results about efficacy, and well controlled trials with reliable data are limited. More independently funded replications of the isolated randomized controlled trials published are needed to confirm the accuracy and validity of the study findings. The National Institutes of Health establishing the National Center for Alternative and Complementary Medicine is a major step forward to unraveling the science of CAM and assisting in integrating those interventions that have passed not just the test of time but also the test of validation. Future trials should include larger studies to account for the subject variations in the extent of allergen exposure and sensitization and disease severity to avoid any confounding variables. Also, better documentation of the methods of randomization and blinding to ensure appropriate allocation concealment will lend strength to the conclusions drawn. Last, reliable subjective and valid objective measurement outcomes are key to confirm the data and conclusions of any study design are trustworthy, even more so in the study of medicine.

Conclusions

- Further studies are required using larger sample sizes, longer study durations, comparable absolute measures, and well constructed study designs that control for biases. Incorporating these changes will increase the power and validity of the results so the validated CAM interventions can be integrated into the general treatment of patients with asthma and allergies.
- Although many herbs are listed in the treatment of atopic disorders, few have actually been investigated with well controlled clinical trials.
- One mechanistic theme that has been found in many of the trials is the suppression of the T_H2 cytokine pathway involving IL-4 and IL-13, which promote IgE synthesis, or enhancing the T_H1 cytokine pathway, increasing IFN- γ synthesis, which inhibits IgE synthesis.
- A major tenet that seems to be true is that the whole exceeds sum of the parts. The synergistic effects of individual components of polyherbal formulations have a concatenate effect together, but may have only a fraction of the efficacy when assessed individually.

What do we know?

- CAM is made up of 5 domains: alternative medical systems, biologically based therapies, manipulative therapies, mind-body therapies, and energy therapies.

- The popularity of CAM among the public sector is rapidly increasing, as evidenced by the increased expenditure on CAM and increased use reported by patients to their physicians.
- Some CAM practices can favorably work in a complementary fashion (not as an alternative) in treating symptoms of allergic and immune disorders.

What is still unknown?

- The true efficacy and safety of CAM therapies
- The efficacy of CAM therapies alone (as alternatives) in the treatment of various disorders
- The individual CAM therapeutic mechanism of effects (some may be multiple)
- The active component of individual CAM therapies.
- The potential drug-drug and drug-herb-phytochemical and vitamin interactions

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TABLE E1. Clinical evidence of CAM safety and efficacy in asthma and allergy

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|--|---|--|---|
| Vitamin A ^{E1,E2} | Immunomodulatory vitamin Deficiency causes decreased serum IgE and IgG ₁ Excess promotes T _H 2 response with pulmonary eosinophilia and increased IL-4 and IL-5 in bronchoalveolar lavage fluid (BAL) | Severe prolonged deficiency causes xerophthalmia | Deficiency in Third World countries causes death from infection Excess in United States causes death from pulmonary hyperresponsiveness and asthma exacerbations Vitamin A has negative correlation with asthma severity Children with asthma have 4× higher risk for vitamin on A deficiency |
| Vitamin C ^{E2-E5} | Antioxidant vitamin found in fresh fruits, vegetables, and whole grains Oxidative stress from the generation of reactive oxygen and free radicals causes bronchial inflammation and hyperreactivity, which results in a decrease in the cell's reducing capacity and the development of asthma | Nausea, vomiting, and diarrhea at high doses | A bivariable analysis of >4000 children showed subjects with asthma had significantly decreased levels of serum vitamin C, α-carotene, β-carotene, and β-cryptoxanthin; after controlling for confounding variables including age, body mass index, socioeconomic status, antioxidant levels, parental asthma, and household smoking, only vitamin C and α-carotene were deficient A case-control study demonstrated subjects with asthma to have a lower level of serum vitamin A and plasma lycopene with no effects noted on vitamin E or β-carotene levels |
| Vitamin B6, B12, and E ^{E6} | Antioxidant vitamin Same mechanism as above | No serious side effect reported | Decreased levels of vitamins B1 and B6 were measured in children with asthma being treated with theophylline with a negative dose-dependent relationship between vitamin B6 and theophylline; no effects were seen on vitamin A, B2, B12, or C |
| <i>Rumex japonicus Houtt</i> ^{E7} | Antioxidant Antiinflammatory Antibacterial Suppresses T _H 2 cells, which in turn decrease serum IL-4 levels and reduce the total IgE levels No effect on IFN-γ or the T _H 1 pathway | None | Anti-inflammatory: prevents histological skin changes of atopic dermatitis (hypertrophy, hyperkeratosis, and infiltration of inflammatory cells) Antibacterial: decreased pruritus and skin colonization by <i>S aureus</i> |
| ω-3 ^{E8} | Fatty acid | No serious events reported | 30% to 50% reduction in childhood asthma just by incorporating fish into child's diet |
| ω-6 ^{E9} | Fatty acid | No serious events reported | Supposed to reduce the severity of atopic dermatitis by decreasing the redness, scaling, and itching of the skin and prevent future exacerbations but has not yet been scientifically confirmed with controlled trials |
| | The oil extracted from the seeds of the evening primrose is applied to the skin as an emollient | | Claims that ω-6-fatty acid is deficient in subjects with asthma are unproven |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|---|---|--|---|
| <i>Lactobacillus</i> ^{E10-E13} | Probiotic Inhibits eosinophil influx to the airway lumen and parenchyma Decreases levels of TNF, monocyte chemoattractant protein 1, IL-5, and IL-13 in bronchoalveolar lavage fluid | None | <i>Lactobacillus</i> GG did not decrease allergic markers like serum eosinophilia, total IgE, or serum eosinophil cationic protein <i>L casei</i> showed no improvement in the frequency of asthma attacks in children but did decrease the annual number of rhinitis episodes Mice with antigen-challenged allergic airway inflammation treated with oral live <i>L reuteri</i> inhibited the T _H 2 pathway, resulting in decreased IL-5 and IL-13 in addition to showing inhibitory effects on proinflammatory chemokines TNF and monocyte chemoattractant protein 1; the killed strain had no effect on eotaxin or IL-10 <i>L rhamnosus</i> GG and <i>B lactis</i> (Bb-12) treatment in newborn mice decreased antigen specific IgE and decreased pulmonary eosinophilia; <i>L rhamnosus</i> also inhibited the T _H 2 response, resulting in decreased IL-4, IL-5, and IL-10 production in addition to increasing the production of TGF- β -secreting CD4 ⁺ CD3 ⁺ cells |
| Butterbur ^{E14-E17} | Inhibits mast cell stimulation, possibly through the leukotriene pathway, causing decreased production and release of histamines and leukotrienes; mechanism is still unclear. Inhibits <i>in vitro</i> synthesis of leukotrienes in human eosinophils, neutrophils, and macrophages Decreases intracellular calcium concentration and mobilization | Unpurified form (pyrrolizidine alkaloid compound) is hepatotoxic and carcinogenic and causes decreased testosterone levels in rats; purified form is safe with unaffected liver biochemistry after 2 weeks of treatment 20% belching 3.8% nausea, abdominal pain | Atopic dermatitis: no significant effect on immediate histamine and allergen cutaneous response in double-blind, double-dummy, cross-over study against placebo, fexofenadine, and montelukast Allergic rhinitis: faster recovery time and less drop in peak nasal expiratory flow scores after nasal adenosine monophosphate challenge with butterbur Butterbur and fexofenadine equally significant, effective relief for seasonal allergic rhinitis based on subjective symptom score and physician's global assessment |
| <i>A arguta</i> ^{E18} | Anti-inflammatory effects on skin Prevents histological remodeling and water loss from the upper skin layers DA-9102 isolated from <i>A arguta</i> showed suppression of T _H 2 cytokine pathway with decreased IL-4 and IL-10 and resulting in decreased IgE synthesis | None | Magnesium-deficient, hairless rats treated with 100 mg/day showed effective resolution of dermatitis by decreasing infiltration of the skin by inflammatory cells, preventing histopathological remodeling of the dermis and epidermis, and preventing transepidermal water loss Flow cytometry showed: <ul style="list-style-type: none"> ● Decreased CD45RA⁺ cells resulting in decreased serum IgE ● Decreased CD11b⁺ cells in the skin and periphery ● Decreased serum nitric oxide and leukotriene B4 ● Decreased T_H2 mRNA expression resulting in decreased IL-4 and IL-10 cytokines and hence decreased IgE synthesis |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|--|---|------------------------------|--|
| <i>S chinensis</i> ^{E19} | Promoted a shift toward the T _H 1 cell response pathway with increased IFN- γ mRNA expression, whereas no effect was seen on IL-4 mRNA associated with T _H 2 | No serious adverse events | Administered subcutaneously 5 days a week \times 8 weeks; showed decreased infiltration of inflammatory cells into the skin, decreased hypertrophy and hyperkeratosis of the dermis and epidermis, and decreased itching behavior in the atopic subjects; objectively decreased serum IgE levels were measured |
| <i>M aquifolium</i> ^{E19-E21} | Topical application | Itching or burning sensation | Open-label trial in adults over a period of 12 weeks demonstrated significant improvements in eczema area and severity index scores with ointment, and posttreatment subjective questionnaire revealed confirmatory reports of improvement in itching, appearance of skin lesions, and effectiveness of the ointment |
| | Not described in the study | | Randomized, double-blind, vehicle-controlled, half-side comparison of ointment containing <i>M aquifolium</i> , <i>V tricolor</i> , and <i>C asiatica</i> showed no statistical improvement in primary outcomes (erythema, edema, papulation, oozing, crust, excoriation and lichenification) or secondary outcomes (pruritus severity and a global assessment of effectiveness and tolerance) |
| <i>L decastes</i> ^{E22} | Extracted from Hatakeshimeji mushrooms Inhibits T _H 2 immune response, IL-4 expression, and hence serum IgE No effect on IFN- γ expression | No serious adverse events | Atopic dermatitis-like skin lesions induced by repeated application of picryl chloride in NC/Nga mice demonstrated lower total skin severity scores and decreased serum IgE after oral herbal treatment |
| Konjac ceramide ^{E23} | Favors the inhibitory T _H 1 cytokine pathway involving increased IFN- γ and IL-12 T _H 2 pathway was notably inhibited with decreased levels of IL-4 and IL-13 | No serious events noted | Konjac ceramide 1.8 mg/day administered orally for 2 weeks to atopic patients with house dust mite allergy demonstrated improvements in the Score of Atopic Dermatitis for skin symptoms, decreased skin responses to skin prick testing, and decreased dust mite specific IgE |
| St John's wort ^{E24} | Anti-inflammatory Antibacterial Main active ingredient = hyperforin | None reported | A randomized, double-blind, placebo-controlled monocentric trial in patients with mild-moderate atopic dermatitis applying St John's wort ointment containing 1.5% hyperforin vs placebo twice a day for 4 weeks showed that the eczematous lesions improved superiorly compared with placebo on all follow-ups day 7, 14, and 28, and it proved to be an effective antibacterial agent by decreasing the skin colonization by <i>S aureus</i> |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|--|--|--|---|
| Persimmon leaf extract ^{E25} | Major flavonoid = astragalin Inhibits histamine release from basophils | None reported | Astragaline 1.5 mg/kg administered for 4 weeks proved demonstrable effects in the treatment and prophylaxis of atopic dermatitis with decreased skin severity including scratching behavior, decreased transepidermal water loss, and decreased serum IgE; daily dosing showed prophylactic effect of decreasing the onset and development of exacerbations |
| Zemaphyte ^{E26} | Antioxidant Not described but may inhibit IL-4 No longer manufactured | No major changes were observed in blood, renal, and liver function tests Minor: dizziness, gastrointestinal discomfort (mild nausea, loose bowels, flatulence), headache, urticaria, photosensitivity, exacerbation of eczema, night diuresis, discoloration of teeth, and both bilirubin and creatinine values outside normal limits | Four randomized clinical trials each lasting 8 weeks were evaluated by Cochrane Review; of these, 3 trials were of a cross-over design, with 2 trials reporting improvements in the eczematous skin lesions measured by decreased erythema and decreased surface damage; 1 trial reported decreased itching; the fourth trial was an open-label trial that compared herbal Zemaphyte with a freeze-dried preparation; both forms demonstrated decreased erythema and skin surface damage, although the 2 forms were not compared against each other |
| TCM polyherbal formula ^{E27} | Consists of 5 herbs (total 9 g of raw herbs): ● <i>Flos lonicerae</i> (Jinyinhua) 2 g ● <i>Herba menthae</i> (Bohe) 1 g ● <i>Cortex moutan</i> (Danpi) 2 g ● <i>Rhizoma atractylodis</i> (Cangzhu) 2 g ● <i>Cortex phellodendri</i> (Huangbai) 2 g | No serious adverse effects | The study trial took place over 12 weeks with treatments of 3 tablets twice a day administered to subjects with moderate-severe atopic dermatitis; every 4 weeks for 4 months, the requirement for topical corticosteroid and oral antihistamine was assessed and values were recorded for Score of Atopic Dermatitis symptoms, Children's Dermatology Life Quality Index, and the allergic rhinitis score; although no significant difference was found in any of the scores between placebo and treatment groups, in the fourth month a significant improvement was reported in the Dermatology Life Quality Index score, and a significant reduction by one third was reported by the treatment group for corticosteroid use |
| Bu-zhong-yi-qi-tang ^{E28,E29} | Composed of 10 herbs: ● <i>Astragalus mongholicus</i> ● <i>Citrus reticulata</i> ● <i>Panax ginseng</i> ● <i>Atractylodes macrocephala</i> ● <i>Angelica dahurica</i> ● <i>Cimicifuga foetida</i> ● <i>Bupleurum chinense</i> ● <i>Zingiber officinale</i> ● <i>Ziziphus jujuba</i> ● <i>Glycyrrhiza uralensis</i> Mechanism of action is not clear | Not addressed | Improved nasal symptom scores in treated group while no change in symptoms with placebo Total serum IgE and IL-4-stimulated prostaglandin E ₂ and leukotriene C ₄ production by polymorphonuclear neutrophilic leukocyte suppressed with Bu-zhong-yi-qi-tang (BZYQT) COX-2 mRNA expression ameliorated with BZYQT Demonstrated the ability to suppress spontaneous atopic dermatitis and decrease serum IgE levels in NC/Nga mice with intractable atopic dermatitis when administered in the oral form |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|---|---|---|---|
| BSASM ^{E30} | Anti-inflammatory Blocks T-cell-mediated immune response Inhibited LPS-induced NF-κB activation Reduced LPS-induced production of IL-8 and TNF-α Inhibited IL-2 production in Jurkat T cells Mechanism of action not yet clearly defined | No serious adverse reactions | Demonstrated a reduction of eczema area severity index score, decrease of pruritus, and decrease of transepidermal water loss both on the antecubital fossa and abdomen |
| <i>U dioica</i> ^{E31} | Polysaccharides stimulate T-lymphocyte activity and complement activation <i>in vitro</i> Polysaccharides and caffeic malic acid demonstrate anti-inflammatory activity <i>in vitro</i> and in animal models via COX and lipoxygenase inhibition | The nettle leaf contains histamine causing erythematous macules and itching. (wheals and flares) | Open trial: 58% relief of most symptoms, 48% greater efficacy than over-the-counter remedies |
| Citrus unshiu powder ^{E32} | Flavonoids hesperidin and nobiletin inhibit histamine and β-hexosaminidase, a molecular marker from mast cell degranulation; hesperidin was the more potent of the 2 Flavonoid hesperidin suppressed phosphorylation of Akt, a serine/threonine kinase and direct effector of PI3-K that is involved in IgE-mediated basophil stimulation Hesperidin showed no effect on mast cell degranulation | Not addressed in study | Decreased histamine release from basophils at 1.6 mg/mL; degree of inhibition is patient-dependent Decreased β-hexosaminidase between 8 mg/mL and 16 mg/mL Histamine and β-hexosaminidase inhibited with 100 μM hesperidin and 500 μM nobiletin Hesperidin had no effect on mast cell degranulation, but it does suppress phosphorylation of Akt, a serine/threonine kinase and direct effector of PI3-K, and thus inhibits IgE-mediated basophil stimulation Hesperidin is absorbed in its intact form and detectable in plasma and urine, whereas hesperidin is metabolized to hesperidin glycoside in the intestinal tract |
| <i>L lucidus</i> plant extract ^{E33} | Inhibits synthetic compound 48/80 causing inhibition of intracellular calcium mobilization and interrupting mast cell degranulation cascade, resulting in inhibition of histamine release Inhibits p38-mitogen-activated protein kinase (MAPK), necessary for expression of inflammatory cytokines, and prevents NF-κB DNA binding, resulting in decreased expression of proinflammatory cytokines TNF-α and IL-6, thereby inhibiting inflammatory cascade | Not addressed in study | Dose-dependent inhibition of 48/80 synthetically induced allergic reaction with inhibition of intracellular calcium mobilization, mast cell degranulation, and histamine release Inhibition of p38-MAPK and prevention of NF-κB DNA binding causing decreased expression of TNF-α and IL-6 inflammatory cytokine |
| <i>Amomum xanthiodes</i> ^{E34} | Inhibits 48/80-induced histamine release from mast cells via inhibition of intracellular calcium resulting in decreased IgE-mediated passive cutaneous anaphylaxis (PCA) reaction and inhibited p38-MAPK and hence decreased TNF-α production | Not addressed in study | Same findings as <i>L lucidus</i> Also decreased IgE-mediated PCA reaction |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|-----------------------------------|--|---|---|
| Grape seed extract ^{E35} | Contains catechins, epicatechins, proanthocyanidins, and polyphenolic bioflavonoid antioxidants Catechin monomers inhibit allergen-induced histamine release in passively sensitized rat peritoneal mast cells | No laboratory abnormalities detected | No significant difference in symptom scores, rhinitis quality of life scores, or use of rescue chlorpheniramine |
| Tomato extract ^{E28} | Contains the polyphenol naringenin chalcone, the main active component responsible for the antiallergic property of tomato extract ECP is an allergy pathway mediator whose production is dependent on the number and activity of eosinophils in the serum Decreased ECP concentrations in the treatment group suggests that tomatoes act by decreasing the number of eosinophils present, thereby decreasing the quantity of histamine released | No serious adverse effects were observed; cold and diarrhea were reported by some but spontaneously resolved during the study and were of questionable relation to the study extract No significant changes noted in urinalysis, blood, or biochemistry in either study group | Significant improvement in total nasal symptom scores (sneezing, rhinorrhea, and nasal obstruction) Sneezing score returned to baseline 1 week after study completion Patient quality of life score improved in treatment group Physician examination showed no significant intergroup difference and no significant difference in serum IgE levels, nasal discharge eosinophil counts, or serum ECP levels, although a downward trend in ECP was noted; ECP is a mediator released from eosinophils in quantities based on the activity and number of eosinophils present |
| Dietary spirulina ^{E36} | Inhibits secretion of IL-4 and thus suppresses the pathway leading to T _H 2-committed cells C-phycoyanin is the active ingredient with COX-2 inhibitory activity and antioxidant effects and acts as free radical scavenger | Not addressed in the study | Dose-dependent (2000 mg) decrease in IL-4 levels by 32%, resulting in suppression of T _H 2 differentiation No change in secretion of T _H 1 cytokines IFN- γ and IL-2 |
| Cellulose powder ¹⁰² | Inhibits bacterial growth Turns into gel in nasal cavity and serves like mucous to filter out allergens from inhaled air to ensure clean air is supplied to the lungs | In week 1 of study, 10% reported uncomfortable sensation in back of throat, which authors think may have been a result of hay fever One person reported itchy eyes and 1 reported sore throat In 1 subject who ran out of cellulose powder, serious hay fever symptoms occurred immediately | Completely relieved hay fever symptoms within minutes to hours of administration with a success rate of 77% of patients as per subjective patient reports on questionnaire |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|----------------------------|---|--|--|
| Aller-7 ^{E37,E38} | <p>Mast cell stabilization</p> <p>Lipoxygenase and hyaluronidase inhibition</p> <p>Antihistamine and antispasmodic activity</p> <p>Antioxidant</p> <p>Anti-inflammatory potential</p> | <p>Proven safety in acute, subacute, subchronic, reproductive, and teratogenic toxicity studies</p> <p>All biochemical and histological parameters remained within normal limits</p> | <p>Aller-7 (250 mg/kg) had greater efficacy than prednisolone (14 mg/kg) in reducing 48/80-induced paw edema in Balb/c mice, 62.55% compared with 44.7%, respectively</p> <p>In Swiss albino mice, Aller-7 showed its most potent anti-inflammatory effect at a dose of 225 mg/kg, compared with 175 and 275 mg/kg</p> <p>In carrageenan-induced paw edema, Aller-7 (120 mg/kg) showed comparative efficacy to ibuprofen (50 mg/kg) with 31.3% inhibition of inflammation compared with 68.1% by ibuprofen</p> <p>Dose-dependent inhibition of arthritis inflammation, although less effective than prednisolone in this case</p> <p>In open trial, noted >40% improvement in sneezing, rhinorrhea, and nasal congestion after 6 weeks with further improvement by 12 weeks</p> <p>In randomized group, improvement in total nasal symptoms at 6 weeks (83.5%) with greater improvement at 12 weeks (91.1%) noted in treated group, whereas placebo had no further improvement after 6 weeks (75% at 6 weeks, 65.2% at 12 weeks)</p> <p>Absolute eosinophil count decreased in treatment group, whereas mucociliary time improved (average 79.4 seconds; Aller-7 at 6 weeks, 75.7 seconds, and 12 weeks, 32.5 seconds)</p> <p>Improved peak expiratory flow rate (average 451 L/min, Aller-7 at 6 weeks 491 L/min, and at 12 weeks, 486 L/min), but not statistically different, perhaps because of normal flow rate at baseline</p> <p>Improved nasal obstruction with peak nasal flow rate increase from 119.3 to 156 L/min correlating with subjective symptom improvement</p> |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|------------------------------------|--|---|--|
| <i>T cordifolia</i> ^{E39} | <p>Immunostimulant because it increases leukocyte counts and ablates neutropenia</p> <p>Immunoprotective because it improves phagocytic and bactericidal capacity of polymorphs; primary target is the macrophages.</p> <p>Anti-inflammatory effects suggested by decreased neutrophils in nasal smears</p> <p>Antiallergic effects indicated by decreased number of goblet cells and eosinophils in nasal smears; previous studies also showed decreased histamine-induced bronchospasms in pigs, decreased capillary permeability in mice, and reduced number of disrupted mast cells in rats</p> | <p>Out of 36 treated patients, 2 had nasal pain and 1 had headache, although they were still able to complete the study</p> | <p>Sneezing significantly relieved in 83% with <i>T cordifolia</i> and 21% placebo</p> <p>Nasal discharge significantly relieved in 69% with TC and 3% placebo</p> <p>Nasal obstruction significantly relieved in 61% with TC and 83% placebo</p> <p>Nasal pruritus significantly relieved in 71% with TC and 12% placebo</p> <p>Total leukocyte count increased significantly in 69% with TC and 11% with placebo</p> <p>Nasal smear in TC group showed decreased neutrophils and eosinophils with absent goblet cells; placebo group showed marginal decrease in eosinophils, neutrophils, and goblet cells</p> <p>Change in nasal mucosa color from blue to pink in 69% treated with TC</p> |
| Biminne ^{E40} | <p>Composed of 11 herbs:</p> <ul style="list-style-type: none"> ● <i>Rehmannia glutinosa</i> ● <i>Scutellaria baicalensis</i> ● <i>Polygonatum sibiricum</i> ● <i>Ginkgo biloba</i> ● <i>Epimedium sagittatum</i> ● <i>Psoralea corylifolia</i> ● <i>Schisandra chinensis</i> ● Pulp of <i>Prunus mume</i> ● <i>Ledebouria divaricata</i> ● <i>Angelica dahurica</i> ● <i>Astragalus membranaceus</i> <p>Mechanism of action is not yet understood but is thought to be attributed to the composition of the mixture and the proportion of each constituent</p> | <p>No adverse events detected</p> <p>As with any herbal medication, possible side effects include nonspecific complaints of nausea, bloating, or skin rash</p> <p>One has to be careful of dose-dependent or allergic reactions to a particular constituent when using polyherbal formulas</p> <p>Also, potential for herb interactions with food, conventional medications, and even other herbs needs to be monitored carefully when administering this form of treatment</p> | <p>Subjective improvements in daily symptoms, overall quality of life, and visual analog scale scores of symptoms</p> <p>Statistically significant improvement in sneezing, itchy nose, and inability to sleep</p> <p>Similar efficacy as antihistamine on physician's overall evaluation and use of relief medication</p> <p>>50% maintained improvement in visual analog scale scores at 1-year follow-up</p> <p>Total serum IgE was decreased</p> |
| Shi-bi-lin ^{E26} | <p>Modulates cytokine production, although the exact mechanism is not yet understood</p> <p>Inhibits nitric oxide synthase and release of thromboxane B2 from endothelial cells</p> <p>Modified form of a 700-year-old herbal formula named Cang Er Zi San</p> <p>Human mast cell line 1 (HMC-1) cells exposed to different concentrations of formula for different lengths of time</p> <p>Composed of 6 raw herbs:</p> <ul style="list-style-type: none"> ● <i>Fructus xanthii</i> ● <i>Radix Angelicae Dahuricae</i> ● <i>Radix Saposhnikoviae</i> ● <i>Flos Magnoliae</i> ● <i>Radix Gentianae</i> ● <i>Herba Verbena</i> | <p>Not discussed</p> | <p>Potent inhibition of IL-4 and TNF-α. Inhibits TNF-α, a potent stimulator of inflammatory markers from airway epithelial cells</p> <p>Stimulates IL-6 at concentration of 0.05 mg/mL in early incubation otherwise inhibitory effect on this cytokine which normally induces IgG, IgM, and IgA secretion and synergistically works with IL-4 as a proinflammatory agent</p> <p>Stimulatory effect on IL-8 at low concentration, but overall no prominent effect</p> <p>No detected effect on cytokine mRNA expression by RT-PCR</p> |

(Continued)

TABLE E1. (Continued)

| Remedy | Mechanism of action | Adverse events | Clinical evidence |
|------------------------------------|--|--|---|
| Sho-seiryu-to ^{E41} | <p>Polyherbal formula with 8 herbs:</p> <ul style="list-style-type: none"> ● Hange (Pinelliae Tuber) ● Kanzo (Glycyrrhizae Radix) ● Keihi (Cinnamomi Cortex) ● Gomishi (Schisandrae Fructus) ● Mao (Ephedra Herba) ● Saishin (Asiasari Radix) ● Shakuaku (Paconiae Radix) ● Kakyo (Zingiberis Siccatum) <p>Of these constituents, mao-containing alkaloids have adrenergic effects that alter the balance of T_H1/T_H2 via the α-adrenergic receptor on CD4 T-cells</p> <p>Modulates cytokine production, although exact mechanism is not yet understood</p> <p>Inhibits nitric oxide synthase and release of thromboxane B2 from endothelial cells</p> | Not discussed | <p>Decreased ovalbumin-induced sneezing</p> <p>Decreased total and ovalbumin-specific IgE levels from T cells</p> <p>Decreased IL-4 producing CD4 T_H2 cells, although no effect on IFN-γ production from T_H1 cells</p> <p>In type 1 allergic reactions, CD86 is upregulated and differentiates naive CD4 T cells (T_H0) into T_H2 cells producing the IL-4-mediated IgE response; decreased CD86⁺MHC class II cells and CD28⁺CD4 T cells seen with Sho-seiryu-to (SST) inhibit this anti-inflammatory effect</p> <p>No effect on CD80 MHCII, CD40 MHCII, and CD154CD4 T cells</p> <p>No effect on B-cell production of cytokine IL-4 or IgE</p> |
| Rosmarinic acid ^{E42,E43} | <p>Extracted rosmarinic acid from <i>Perilla frutescens</i>, a popular Japanese garnish, to evaluate effects on seasonal allergic rhinitis to Japanese cedar pollen</p> <p>A polyphenol phytochemical from the plant genus Lamiaceae; found in various herbs including basil, sage, mint, rosemary, and <i>Perilla frutescens</i></p> <p>Inhibition of locally expressed proinflammatory cytokines and chemokines IL-1b, IL-8, and eotaxin results in inhibition of local PMNL (neutrophils and eosinophils) infiltration</p> <p>Mast cell stabilization</p> <p>Lipoxygenase and hyaluronidase inhibition</p> <p>Antioxidant properties</p> <p>Previous reports suggest antihistaminic activity, although these reports not confirmed in other trials</p> <p>Previous studies have shown inhibitory effects of pollen-specific IgE production from B cells, although this too is controversial</p> | No significant abnormalities were detected by routine blood tests at the end of the study; routine tests included complete blood cell counts, hepatic and renal function tests, total protein and proteinogram, electrolytes, lipids, uric acid, and concentration of creatine phosphokinase | <p>Decreased neutrophils and eosinophils in nasal lavage on days 0 and 3 of treatment</p> <p>Initially the 50-mg dose lost effectiveness over nasal eosinophil infiltration, and by day 21, even the 200-mg dose was not effective at suppressing proinflammatory cytokines that activate the polymorphonuclear leukocytes (PML) infiltration</p> <p>Neither serum IgE nor nasal eotaxin, IL-1β, IL-8 or histamine levels were ever significantly different among the groups</p> <p>Decreased subjective recording of symptoms</p> <p>Decrease number of neutrophils and eosinophils in nasal lavage</p> <p>Both anti-inflammatory and antioxidant effects were noted in the animal model</p> <p>In the animal model, RA treatment produced marked reductions in intercellular adhesion molecule 1, vascular cell adhesion molecule 1, COX-2, and macrophage inflammatory protein 2 (adhesion molecules, chemokine and eicosanoid synthesis)</p> <p>Also in animal models, decreased reactive oxygen radical production was seen with RA treatment measured by decreased thiobarbituric acid reactive substance, lipid peroxide, and 8-hydroxy-2'-deoxyguanosine</p> |

ECP, Eosinophil cationic protein.

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