

Mechanisms of allergic diseases

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Efficacy and mechanisms of action of traditional Chinese medicines for treating asthma and allergy

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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.

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List of Design Committee Members: *Authors:* Xiu-Min Li, MD, and Laverne Brown, MD

Activity Objectives

1. To identify traditional Chinese medicines that may be used in the treatment of asthma and allergic diseases.

2. To understand the possible mechanisms underlying the efficacy of traditional Chinese medical herbal therapy in treating allergic diseases.

Recognition of Commercial Support: This CME activity is supported by an educational grant from Merck & Co., Inc.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: Xiu-Min Li receives grant support from the National Institutes of Health and the Food Allergy Initiative and has provided legal consultation or expert witness testimony in cases related to food allergy. Laverne Brown has no significant relationships to disclose.

Background: Although corticosteroids and β_2 -agonists are effective in managing asthma symptoms, a curative therapy for asthma is lacking. Traditional Chinese medicine (TCM), used in Asia for centuries, is beginning to play a role in Western health care as a complementary and alternative medicine modality. There is increasing scientific evidence supporting the use of TCM for asthma treatment.

Objective: This review article discusses promising TCM interventions for asthma and explores their possible mechanisms of action.

Methods: We first reviewed 5 clinical studies of antiasthma TCM herbal remedies published between 2005 and 2007. We then summarized possible mechanisms underlying their effects on the basis of data in the original articles, published abstracts, and available databases. Possible mechanisms include anti-inflammation, inhibition of airway smooth muscle contraction,

and immunomodulation. Research on TCM herbal therapy for food allergy is rare, and we therefore focused on the effect and mechanism of action of food allergy herbal formula-2 on a murine model of peanut allergy and preliminary clinical study results. **Conclusion:** Evidence from clinical studies supports beneficial effects of TCM herbal therapy on asthma. A number of mechanisms may be responsible for efficacy of these agents. Strong preclinical study data suggest the potential efficacy of food allergy herbal formula-2 for food allergy. (*J Allergy Clin Immunol* 2009;123:297-306.)

Key words: *Complementary and alternative medicine, traditional Chinese herbal medicine, botanical drug, asthma, food allergy, T_H1/T_H1 balance*

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Supported by the National Institutes of Health/National Center for Complementary and Alternative Medicine grant #1P01 AT002644725-01 and #R01 AT001-14, the Food Allergy Initiative, the Rothstein family, and the Cornfield Family Foundation.

Received for publication November 3, 2008; revised December 15, 2008; accepted for publication December 19, 2008.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2008.12.026

Terms in boldface and italics are defined in the glossary on page 298.

Asthma is a chronic respiratory disease that affects 300 million adults and children worldwide, including 15.7 million adults and 6.5 million children in the United States.¹ The prevalence has increased by 50% in the past few decades, particularly in Westernized countries. Although corticosteroids and β_2 -agonists are effective in managing asthma symptoms, there is no curative therapy. There are also concerns regarding the side effects from chronic use of current drugs, particularly by children. The chronic nature of asthma and the lack of preventive and curative therapy are leading patients with asthma in Western societies to seek complementary and alternative medicine (CAM) treatment.^{2,3} Although there are wide variations in the reported use of CAM, a

Abbreviations used

AHR:	Airway hyperresponsiveness
ASHMI:	Antiasthma herbal medicine intervention
CAM:	Complementary and alternative medicine
DCT:	Ding Chuan Tang
FAHF-2:	Food allergy herbal formula-2
FDA:	US Food and Drug Administration
IND:	Investigational new drug
LWDHW:	Lui-Wei-Di-Huang Wan
mMMDT:	Modified Mai Men Dong Tang
NIH:	National Institutes of Health
TCM:	Traditional Chinese medicine

reasonable estimate is that as many as 30% of adults and 60% of children in the United States are currently using some form of CAM to treat their asthma.⁴ Thus, there is a need for defining and developing reliable CAM therapy for patients.

Traditional Chinese medicine (TCM) has a long history of human use and is 1 of the major components of CAM used in the United States. It has a unique (independent) system of theory and diagnosis and treatment tools. The National Center for Complementary and Alternative Medicine at the National Institutes of Health (NIH) defined TCM as a whole medical system.⁵ In the United States, TCM is mainly provided by licensed practitioners and is playing an increasing role in the health care system. Chinese herbal medicines are 1 of the major components in TCM practice and are prescribed in hospitals in China as either

monotherapy or complementary therapy to conventional Western therapy. However, TCM remains to be established as part of mainstream medicine in the United States. Unlike in China and other Asian countries, TCM herbal products are viewed as dietary supplements in the United States, and the cost is not covered by most insurance policies. This may contribute to the gap between scientific evidence-based medicine and human use-based practice (West meets East).^{6,7} The National Center for Complementary and Alternative Medicine/NIH now supports clinical and basic research on CAM. In recent years, the US Food and Drug Administration (FDA) has provided guidance for investigating botanical drug products, including complex formulas containing several ingredients, focusing on efficacy, safety, and consistency.⁸ NIH support and FDA guidelines will foster the development of botanical drugs in the United States. Thus, certain beneficial TCM products currently used as dietary supplements for asthma and allergy may be investigated as new botanical drugs.

In contrast to the long human use history and popularity of TCM herbal medicines for asthma, evidence-based research into their efficacy and mechanisms of efficacy is still in its infancy. Although a number of antiasthma herbal formulas are recorded in TCM textbooks and used in TCM practice,^{9,10} only a few have been studied. Several literature reviews of herbal medicines for asthma have reported that evidence for clinical efficacy is weak, although some herbal preparations induced improvement in asthma symptoms and FEV₁. These early clinical investigations of herbal medicines are far from satisfactory, but the reviews concluded that additional well designed—that is, double-blind,

GLOSSARY

β-HEXOSAMINIDASE, RBL-2H3 CELLS: β-Hexosaminidase is released on degranulation of basophils and thus can be used in basophil release assays as a marker of basophil activation. Rat basophilic leukemia (RBL-2H3) cells are rat basophil leukemia cells that can be used in such assays.

EOTAXIN: Eotaxins are a family of CC chemokines that bind to CCR3 and induce eosinophil trafficking. Eotaxin-1 and eotaxin-2 attract eosinophils to the lung and lower gastrointestinal tract; eotaxin-3 attracts eosinophils to the esophagus.

GATA-3: GATA-3 is a member of the GATA family of transcription factors and increases the transcription of the IL-5, IL-13, and IL-4 genes. The *Gata3* gene is activated by IL-4, and signal transducer and activator of transcription 6, and autoregulated by GATA-3.

HPLC: HPLC is used in botanical drug discovery to separate, identify, purify, and/or quantify small molecules on the basis of retention (via noncovalent interactions) on a stationary phase (usually a silica gel column) relative to a mobile phase. Molecules are separated with respect to relative polarities. Polar molecules have shorter retention times in reverse-phase separations and longer retention times in normal-phase separations.

IFN-γ: IFN-γ is induced in T_H1 cells by IL-12 and the T_H1 transcription factor, T-bet. Decreased IFN-γ is associated with decreased clearance of lower respiratory tract viruses.

IL-4, IL-5, IL-13: IL-13 is involved in mucous production, eosinophilic inflammation, and IgE production in allergic asthma. IL-5 is critical for eosinophilopoiesis. Anti-IL-5 therapy can reduce airway remodeling in patients with asthma. IL-4 increases IgE and IL-5 production. IL-4 and IL-13 bind a common α-chain on their receptors. Pitrakinra, an IL-13/IL-4 antagonist, has showed some benefits on asthma in initial trials.

IL-8: IL-8 is a chemoattractant for neutrophils, is associated with viral-induced and corticosteroid-resistant asthma, can cause airway smooth muscle contraction, and can function as a proangiogenic IL.

LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY: Liquid chromatography uses technology similar to HPLC but on a smaller scale for column diameter and flow rates. Mass spectrometry is used to fragment small molecules into ions such that the mass of molecules can be measured as a mass-to-charge ratio. The combination of liquid chromatography–mass spectrometry technology is used in botanical drug discovery to separate (chromatographically in a liquid form) and then identify small molecules on the basis of the mass of the parent ion and fragmentation patterns.

MEMORY T_H2 CELLS: CD4⁺ T cells that make T_H2 cytokines such as IL-4 and IL-13 that have an activated phenotype and potential for rapid expansion and cytokine secretion; CD45RO can be a marker of memory cells.

NUCLEAR MAGNETIC RESONANCE: Nuclear magnetic resonance spectroscopy determines the structure of organic compounds on the basis of the spin characteristics of the nuclei of elemental isotopes in a magnetic field.

PROSTAGLANDIN E₂: Prostaglandin E₂ is increased in asthmatic airways and can have both proinflammatory and antibronchoconstrictive effects. Prostaglandin E₂ is produced by mast cells, dendritic cells, and airway epithelium and can cause relaxation of smooth muscle. Prostaglandin E₂ acts on 4 separate G-protein-coupled receptor subtypes that involve cyclic AMP, phosphoinositide 3 kinase, and inositol (1,4,5) triphosphate signaling pathways.

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 6: The signal transducer and activator of transcription family of transcription factors become phosphorylated, dimerize, and bind to palindromic DNA elements in response to Janus-activated kinase pathways. Signal transducer and activator of transcription 6 is important for IL-4 and IL-13 signals and activates GATA-3 gene expression.

The Editors wish to acknowledge Seema Aceves, MD, PhD, for preparing this glossary.

TABLE I. Summary of clinical studies for asthma published 2005 to 2007

	TCM formula			
	ASHMI ¹²	mMMDT ¹⁸	Ding Chuan Tang ¹⁹	STA-1 ²⁰
Publication date	2005	2006	2006	2006
No. of herbs	3	5	9	10
Type of study	RCT	RCT	RCT	RCT
Sample size	n = 45 ASHMI n = 46 Prednisone	n = 40 mMMDT 80 mg n = 40 mMMDT 40 mg n = 20 Placebo	n = 28 DCT n = 24 Placebo	n = 50 STA-1 n = 50 STA-2 n = 20 Placebo
Age (y)	18-65	5-18	8-15	8 15
Indication	Moderate-to-severe persistent asthma	Mild-to-moderate persistent asthma	Mild-to-moderate persistent asthma	Mild-to-moderate persistent asthma
Length of study	4 wk	4 mo	3 mo	6 mo
Herbal components ^{9,51}	1. <i>Radix glycyrrhizae</i> 2. <i>Radix Sophorae flavescens</i> 3. <i>Ganoderma</i>	1. <i>Radix glycyrrhizae</i> 2. <i>Radix ophiopogonis</i> 3. <i>Radix panacis quinquefolii</i> 4. <i>Tuber Pinellia</i> 5. <i>Herba tridacis procumbentis</i>	1. <i>Radix glycyrrhizae</i> 2. <i>Tuber Pinellia</i> 3. <i>Gingko bilboae</i> 4. <i>Herba ephedrae</i> 5. <i>Flos tussilaginis farfarae</i> 6. <i>Cortex mori albae radices</i> 7. <i>Fructus Perilla frutescens</i> 8. <i>Semen pruni armeniaca</i> 9. <i>Radix scutellariae baicalensis</i>	Combined formula of mMMDT without the herb #5 with Lui-Wei-Di-Huang Wan (6 herbs) 1. <i>Radix rehmanniae preparata</i> 2. <i>Cortex moutan radices</i> 3. <i>Fructus corni officinalis</i> 4. <i>Sclerotium poriae cocos</i> 5. <i>Rhizoma alismatis orientalis</i> 6. <i>Radix dioscoreae oppositae</i>
Improved FEV ₁	Yes	Yes	Yes	Yes
Improved symptom score	Yes	No	Yes	Yes
Safety and tolerability	Yes	Yes	Yes	Yes

All the herbals are Chinese originals. All formulas contain *Radix glycyrrhizae*. This table is a modification of the table in Li, J Allergy Clin Immunol⁶⁵ with permission. RCT, Randomized, placebo-controlled, double-blind clinical trial.

placebo-controlled—trials of herbal medicines are warranted because of the promising findings and increased popularity of herbal use for asthma. It should be noted that previous reviews included findings from all herbal medication publications, including Chinese, Japanese (Kampo), Indian, Latin American, Hawaiian, and Western herbal medicines. Because herbal medicines used in TCM practice differ, including Japanese and Korean herbal medicines that are derivatives of TCM, separate sections specifically summarizing clinical studies relevant to TCM appear to be more positive. Huntley and Ernst,¹¹ for example, reviewed herbal interventions for asthma, in which 17 controlled studies were included. Six of these studies used traditional Chinese herbal medicines, and 4 reported significantly increased FEV₁ levels ($P < .05-.01$) compared with controls. However, these studies were not double-blind.

Since 2005, several new English language publications have reported results of double-blind, placebo-controlled clinical studies investigating the efficacy and safety of TCM herbal products for asthma. Some publications also provided evidence regarding possible mechanisms underlying the reported clinical efficacy.¹² One of these TCM herbal products is undergoing clinical trials in the United States under an FDA botanical investigational new drug (IND) title. In this review, we focus on the clinical effects of TCM herbal therapy for asthma and the possible underlying mechanisms reported in English language publications since 2005.

The prevalence of food allergy is increasing in Western societies, including the United States. It is now estimated that 6% of children under the age of 3 years and 4% of adults are allergic to food.¹³ Currently there is no definitive treatment for

food allergy. Although research in TCM herbal therapy for food allergy is still very limited, food allergy herbal formula-2 (FAHF-2) has demonstrated excellent efficacy in a murine model of peanut allergy,¹⁴⁻¹⁶ and a clinical trial is ongoing in the United States (IND 77,468). We also review the preclinical efficacy, safety, and mechanisms of FAHF-2 and update information about a FAHF-2 clinical trial.

This review is not a general systematic review and does not address whether herbal medicine studies beginning in the early 1980s demonstrated efficacy. This review discusses promising TCM interventions for asthma and allergy and explores their possible mechanisms of action. In addition, according to FDA guidelines for botanical drug development and the use of advanced chromatographical techniques and available TCM phytochemistry databases,¹⁷ we provide information regarding herbal product quality control and chemical characteristics of botanicals aimed at botanical drug development for asthma and allergy.

EFFICACY AND MECHANISMS OF ACTIONS OF TRADITIONAL CHINESE MEDICINE FOR TREATING ASTHMA

Clinical efficacy of Chinese herbal medicine for asthma

Chinese herbal medicine for asthma as monotherapy. Wen et al¹² reported the first double-blind, randomized, placebo-controlled trial investigating the efficacy and tolerability of an antiasthma herbal medicine intervention (ASHMI, which contains 3 herbs; Table I) compared with oral prednisone therapy on

91 patients 18 to 60 years of age with moderate-to-severe asthma. Subjects in the ASHMI group (45 patients) received oral ASHMI capsules (4 capsules, three times a day, 0.3 g/capsule) and placebo tablets similar in appearance to prednisone. Subjects in the prednisone group (46 patients) received oral prednisone tablets (20 mg every day in the morning) and "ASHMI placebo capsules" for 4 weeks. Treatment was administered daily over 4 weeks. This study found that after treatment, lung function (FEV₁ and peak expiratory flow values) was significantly improved in both the ASHMI (64.9 ± 63.6 to 84.2 ± 65.0; $P < .001$) and the prednisone (65.2 ± 63.7 to 88.4 ± 68.0; $P < .001$) groups. The improvement was slightly but significantly greater in the prednisone group ($P < .05$). There was a significant and similar degree of reduction in clinical symptom scores in both treated groups (median [range], ASHMI, 5.0 [4-8] to 2.0 [0-4]; $P < .001$; prednisone, 5.0 [4-7] to 2.0 [0-4]; $P < .001$), use of β_2 -bronchodilators (median [range], ASHMI, 4.7 [3.5-5.7] to 0.9 [0.14-2.3]; $P < .001$; prednisone, 4.7 [3.5-5.6] to 0.6 [0.3-1.0]; $P < .001$). ASHMI had no significant effect on body weight (increase in body weight posttherapy was 2.8 kg in the prednisone group vs 0.8 kg in ASHMI). No significant side effects were observed in either group. All hematologic, electrocardiographic, and liver and kidney function test results were normal in both groups. Thus ASHMI appeared to be effective and well tolerated, and may offer benefits comparable to standard prednisone therapy for some patients without the undesirable side effects associated with steroid use.

Chinese herbal remedies used as complementary therapy. Three recent controlled studies have been published in English language journals. In those studies, Chinese herbal remedies were used as complementary therapy.

Modified Mai Men Dong Tang. Hsu et al¹⁸ tested modified Mai Men Dong Tang (mMMDT, 5 herbs) for treatment of persistent, mild-to-moderate asthma in children (Table I). This 4-month trial included 100 patients with asthma age 5 to 18 years. The 2 active groups received 40 mg (40 patients) or 80 mg (40 patients) mMMDT for 2 months. The control group received placebo capsules (20 patients). Asthma medications were provided gratis and adjusted in a stepwise fashion equally in all 3 groups as follows: step 1, use of bronchodilator as needed; step 2, regular use of bronchodilator (theophylline or albuterol); step 3, regular use of 2 or 3 drugs (theophylline, albuterol, and cromolyn); step 4, addition of beclomethasone delivered with a metered-dose inhaler or alternate day methylprednisolone; and step 5, addition of oral corticosteroids (> 0.5 mg/kg/day, with tapering). Acute exacerbation of asthma was treated as directed by the child's physician using tapered doses of oral methylprednisolone. The investigators reported that relative to baseline, significantly greater increases in FEV₁ were demonstrated in both mMMDT-treated groups in comparison with the placebo group ($P < .05$ for both doses of mMMDT), but no dose-response effect was found between the 2 mMMDT-treated groups. However, symptom scores were similarly improved in both mMMDT treatment groups. No drug-related adverse effects were reported. Blood tests and liver and kidney function test results were within normal ranges during the study.

Ding Chuan Tang. Chan et al¹⁹ reported that in a randomized, double-blind clinical trial, Ding Chuan Tang (DCT), a 9-herb formula, reduced airway hyperresponsiveness (AHR) in stabilized children with asthma (Table I). This study enrolled children between 8 and 15 years of age diagnosed with mild-to-moderate persistent asthma. Patients were randomly allocated

TABLE II. Summary of *Sophora flavescens* Ait on refractory asthmatics

	4 wk	3 mo	1 y	3 y
Daytime asthma improvement	78	87	94	97
Nighttime	72	85	95	98
Reduction of β_2 -agonist use	45	92	95	97
Reduction of ICS	45	84	92	100 (no patient took ICS)
Mean PEF rate improvement	12	15	18	21
Side effect	None	None	NR	NR

ICS, Inhaled corticosteroid; NR, not reported.

Values are percentages unless otherwise indicated.

to receive 6.0 g DCT or placebo daily for 12 weeks. Fifty-two children with asthma completed the study. Both groups received standard asthma management in a stepwise fashion (5 steps) as outlined in the study by Hsu et al.¹¹ Twenty-eight patients were assigned to the treatment group and 24 to the placebo group. At the end of the treatment period, AHR determined by log PC₂₀ was significantly improved in the DCT group (0.51 ± 1.05 mg/mL vs 0.26 ± 0.84 mg/mL; $P = .034$). Clinical and medication scores showed improvement in the DCT group ($P = .004$). The authors concluded that more stable airways were achieved by this add-on complementary therapy.

STA-1. Chang et al²⁰ reported results of a clinical evaluation of STA-1 and STA-2 herbal formulas (Table I). STA-1 and STA-2 are combinations of mMMDT (10 herbs) and Lui-Wei-Di-Huang Wan (LWDHW, 6 herbs). However, the authors did not specify the specific composition. STA-1 and STA-2 reportedly differ only in the preparation procedures of LWDHW. The 6 herbs in LWDHW were milled to a powder for STA-1 and extracted in boiling water for STA-2. Overall, 120 patients 5 to 20 years of age with mild-to-moderate asthma were included in this study. Forty-four patients were treated with STA-1 at a dose of 80 g/kg/day, 40 were treated with STA-2 at a dose of 80 g/kg/day, and 16 patients received a placebo. Treatment was administered twice daily for 6 months. All patients were provided with asthma medications adjusted in a stepwise fashion as described in the mMMDT study by Hsu et al.¹¹ Completion rates were 88%, 80%, and 80% for STA-1, STA-2, and placebo, respectively. The results showed a statistically significant reduction of symptom scores, systemic steroid dose, and total IgE and specific IgE levels in the STA-1 group. Furthermore, STA-1 improved pulmonary lung function (FEV₁) compared with the placebo group. STA-2-treated patients showed no significant improvement in any parameter. The authors speculated that some as-yet unknown heat-sensitive compounds in LWDHW possess anti-inflammatory activity.

***Sophora flavescens* Ait.** In addition to the multi-herb formulas, Hoang et al²¹ reported the effect of an extract of *S. flavescens* Ait, a traditional Hawaiian antiasthma medicine and a component of ASHMI, on asthma. An open and selective 3-year follow-up of 14 patients with chronic refractory asthma ages 22 to 70 years was used. Participants received an aqueous *S. flavescens* Ait extract with a dose equal to 4 g dried root 3 times daily for 3 months, twice daily for 6 months, and once daily for 27 months. Although this study was not controlled, because it involved unstable subjects with refractory asthma, the reported clinical outcome appears to be remarkable. Table II summarizes the improvement of symptoms, reduction of β_2 -agonist use, reduction in dose of inhaled corticosteroid, and improvement of peak

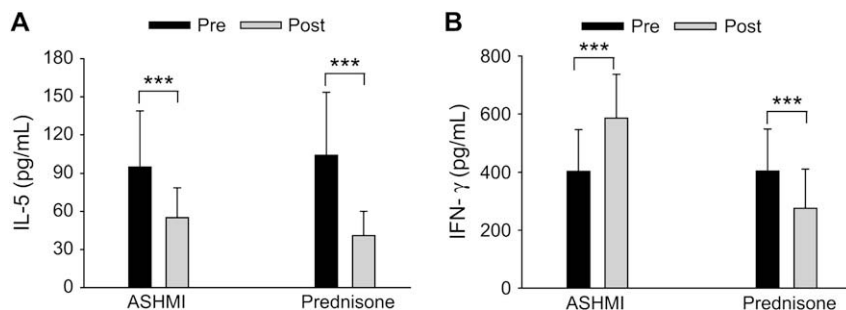


FIG 1. Effect of 4 weeks of treatment with ASHMI or prednisone on serum cytokine levels. All blood samples were drawn between before treatment and 48 hours after treatment. Serum IL-5 (A) and IFN- γ (B) were determined by ELISA. *** $P < .001$. Modified from Li XM. Traditional Chinese herbal remedies for asthma and food allergy. *J Allergy Clin Immunol* 2007;120:25-31⁶⁵ with permission.

expiratory flow from 4 weeks to the third year of treatment. The improvement was greater with longer treatment. Because this study used a prolonged observation, safety data were an important factor. No side effects were detected by clinical examination, hematology, or clinical chemistry.

In summary, these clinical studies show promising results. All reported improvement in lung function, an objective measurement of clinical improvement. Furthermore, all addressed safety and demonstrated that the tested TCM herbal medicines were safe and well tolerated. Although demonstrating significant improvement in asthmatic symptoms compared with the earlier clinical trials of TCM,¹¹ these studies have limitations. ASHMI, mMMDT, and DCT studies were short, and although most studies showed significant improvement in symptoms scores, mMMDT did not, which may be a result of the small sample size in the placebo arm. Dose-dependent effects, except for mMMDT, were not addressed in these studies. Studies of mMMDT, DCT, and STA-1/STA-2 also used conventional therapy based on a stepwise algorithm of asthma management, but not fixed regimens. The DCT and STA-1/STA-2 studies reported a reduction in conventional medication use compared with placebo controls. Thus, it is unlikely that the positive effect of TCM was a result of variations in conventional medications. However, no reduction in conventional medication use was reported in the mMMDT study, and improvements in lung function because of variations in conventional medication use cannot be excluded. The study using *S flavescens* Ait for refractory asthma was a long-term study, but because this study did not include a placebo control arm, a placebo effect cannot be ruled out. Clinical studies of TCM are limited, and there are no previous studies investigating possible persistent effects after discontinuation of treatment. Given the positive preliminary results and safety profiles, and the increased use of TCM for asthma treatment, additional studies of TCM formulations with the goal of botanical drug development should be strongly encouraged. One TCM formulation, ASHMI, has received FDA IND approval (IND 71, 526) for phase I and II clinical trials for treating asthma. A phase I study has been completed that included 20 patients age 18 to 40 years with mild-to-moderate, persistent allergic asthma. This was a double-blind, placebo-controlled dose escalation study. On the basis of clinical and laboratory test results, ASHMI was considered safe and well tolerated (Kelly-Piper et al, unpublished data, January 2009). A phase II study involving 60 patients over a 6-month period is underway.

Mechanism of action of antiasthma TCM herbal remedies

Asthma is a chronic inflammatory condition of the airways that causes airway hyperresponsiveness. T_H1 and T_H2 responses are felt to be mutually antagonistic, such that they normally exist in equilibrium and cross-regulate each other. An optimum T_H1-T_H2 balance has been suggested as necessary to maintain healthy immune homeostasis. Loss of such balance has been hypothesized to underlie allergic asthma through a shift in immune responses from a T_H1 (*IFN- γ*) pattern toward a T_H2 (*IL-4*, *IL-5*, and *IL-13*) profile, which promotes IgE production; eosinophilic inflammation, activation, and survival; and enhanced airway smooth muscle contractility.²² A recent study showed that low IFN- γ production in the first year of life was a predictor of wheeze during childhood.²³ In another study, patients with severe asthma exhibited significantly reduced IFN- γ production in response to allergen compared with control subjects and subjects with resolved asthma.²² It has also been shown that allergen immunotherapy, when effective, results in an increase in antigen-specific T_H1 cells and suppression of T_H2 cytokine production.²⁴ Therefore, a shift in balance of cytokines from a dominant T_H2 response to a strong T_H1 response may help to resolve allergy and asthma. Although corticosteroids improve asthma symptoms, they do not alter the progression of asthma or cure the disease.²⁵ Guilbert et al²⁶ reported that prophylactic administration of a corticosteroid to high-risk children for 1 year did not decrease the rate of asthma development compared with controls. Corticosteroid withdrawal is often accompanied by increased inflammation in bronchial biopsies and symptomatic disease relapse.²⁷ This has been suggested to be a result of corticosteroid-induced overall suppression of both T_H1 and T_H2 responses. Among the 5 antiasthma herbal remedy studies reviewed, some interesting pharmacologic actions have been generated from ASHMI studies. These findings are summarized in the following 4 sections.

Immunomodulation—but not overall immune suppression—data generated from clinical study. To understand the mechanisms underlying ASHMI's clinical effects, we evaluated immunologic responses secondary to treatment. Both ASHMI and prednisone decreased peripheral blood eosinophil, serum IgE, and T_H2 cytokine (IL-5 and IL13) levels (Fig 1, A). Inhibition was greater in the prednisone group. However, unlike prednisone, which suppressed IFN- γ secretion, ASHMI actually increased IFN- γ secretion¹² (Fig 1, B).

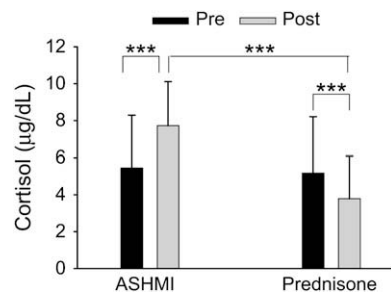


FIG 2. Effect of 4 weeks of treatment with ASHMI or prednisone on serum cortisol levels. All blood samples were drawn between 7:30 and 8:30 AM before treatment and 48 hours after treatment. Serum cortisol levels were determined by RIA. Data are means \pm SDs. *** $P < .001$ (normal level of morning serum cortisol levels are 8–23 $\mu\text{g/dL}$). Modified from Li XM. Traditional Chinese herbal remedies for asthma and food allergy. *J Allergy Clin Immunol* 2007;120:25–31⁶⁵ with permission.

Because ASHMI was used as monotherapy in this study, we investigated whether ASHMI would also enhance IFN- γ production in patients on inhaled steroid. We recently completed a study to determine the safety, tolerability, and immunologic benefits of complementary ASHMI in children 5 to 14 years of age with persistent asthma with or without allergic rhinitis. Subjects were randomly assigned to receive standard inhaled corticosteroid treatment (budesonide (Pulmicort) Turbohaler, Astrazeneca, Wilmington, Del) plus ASHMI as complementary therapy (complementary ASHMI group, $n = 28$) or inhaled corticosteroid treatment plus placebo (standard group, $n = 28$). A total of 51 patients with asthma completed the trial, including 26 patients in the complementary ASHMI group and 25 from the standard group. We found that patients in the complementary ASHMI group showed significantly greater reduction of serum total IgE ($P < .05$) and higher serum levels of IFN- γ after 3 months of treatment than the standard therapy alone group (Wen et al, unpublished data, January 2009).

A clinical study by Chang et al²⁰ also found that total and specific IgE levels were significantly reduced by herbal therapy (STA-1) compared with placebo treatment. However, effects on T-cell responses were not investigated. The clinical studies of mMMDT and DCT did not find a significant reduction of IgE compared with placebo.^{18,19}

ASHMI enhances adrenal functions: data generated from clinical study. Corticosteroid-induced suppression of the hypothalamic-pituitary-adrenal axis, marked by depressed cortisol levels, has been implicated as an adverse side effect of systemic steroid use.^{28,29} In the study by Wen et al,¹² a beneficial effect of ASHMI treatment on adrenal function was found. Pretreatment cortisol levels were slightly below normal (6–23 mg/dL) in both groups (Fig 1, C). After treatment, subjects in the prednisone treatment group showed a significant reduction in serum cortisol levels (5.1 ± 3.0 to 3.7 ± 2.3 $\mu\text{g/dL}$; $P < .001$). In contrast, patients in the ASHMI treatment group showed increased levels of serum cortisol (5.4 ± 2.8 to 7.7 ± 2.3 $\mu\text{g/dL}$; $P < .001$; Fig 2), which is within the normal range. The difference between groups was statistically significant ($P < .001$). Thus, ASHMI restored adrenal homeostasis. This result might be attributed to glycyrrhizin (a component of Gan-Cao), which affects the conversion of cortisol to cortisone, by inhibition of the 11- β -hydroxysteroid dehydrogenase enzyme activity.³⁰ Gan-Cao has been used for adrenal insufficiency.³¹ However, it is also possible that the increase in cortisol levels may be a result of the lack

of suppression of adrenal functions. Further research is required to understand the precise mechanisms.

Broad mechanisms of action of ASHMI in a murine model of asthma. Animal models of asthma are a valuable tool to explore the mechanisms of action of ASHMI and other herbal remedies for treating asthma. There are at least 2 phases of asthmatic reactions after allergen exposure. The first, an IgE-mediated type 1 hypersensitivity response, induces an early-phase airway reaction, usually within 30 minutes after relevant antigen exposure, and is triggered by mast cell-derived bronchoconstrictors such as histamine and leukotrienes.^{32,33} The second phase, a late-phase hypersensitivity reaction, occurs 6 to 12 hours after allergen inhalation and is associated with infiltration of inflammatory cells, primarily eosinophils.^{32,33} Studies using a murine model of asthma found that ASHMI exhibits a broad spectrum of therapeutic effects on the major pathogenic mechanisms of asthma. It blocked an early-phase airway reaction, which was associated with a reduction of histamine and leukotriene release (Zhang et al, unpublished data, January 2009), airway hyperresponsiveness (AHR), pulmonary inflammation, and airway remodeling, which was accompanied by downregulation of T_H2 responses.³⁴ Another murine study found that STA-1 suppressed Der p 5–induced allergic reactions, as evidenced by significantly reduced Der p 5–specific IgE, pulmonary inflammation, and AHR.³⁵ Our initial study of herbal medicine showed that the formula MSSM-002, the precursor of ASHMI (containing more herbs), inhibited the T_H2 specific transcription factor *GATA-3*.³⁶ ASHMI had the same effect on *memory T_{H2} cells*. In addition to anti-inflammatory properties, ASHMI directly modulates airway smooth muscle contraction *ex vivo*, as shown by using myographic techniques with murine tracheal rings.³⁷ ASHMI both decreased airway smooth muscle contractility in response to acetylcholine and increased airway smooth muscle relaxation in response to *prostaglandin E₂*. These effects were not associated with β_2 -adrenergic receptors, but were associated with increased prostaglandin E_2 production.³⁷ Although the detailed mechanisms underlying ASHMI's potent effects on numerous asthma-associated mechanisms are unknown, our recent pharmacologic study demonstrated that constituents in ASHMI act synergistically in suppression of *eotaxin* production by human fetal lung fibroblasts.³⁸

In summary, modulation of T_H1 and T_H2 responses, but not overall immune suppression, and lack of inhibition of adrenal function suggest that ASHMI exhibits different therapeutic mechanisms from corticosteroids. However, more studies are required to understand the exact mechanisms by which ASHMI and perhaps other TCM herbal products modulate T_H1 - T_H2 responses at the molecular level.

DEVELOPMENT OF HERBAL INTERVENTIONS FOR FOOD ALLERGY

Investigation of herbal interventions from TCM for peanut allergy in animal model and human *in vitro* study

Peanut allergy accounts for approximately 80% of fatal and near-fatal anaphylactic reactions to foods.^{39,40} The prevalence of childhood peanut allergy doubled between 1997 and 2002⁴¹ and affects ~1% of the American population.⁴² Although tremendous strides have been made in food allergy awareness, there is no satisfactory therapy to prevent or reverse the disease. Peanut allergy

imparts a significant psychological burden on the allergic individuals and their families.⁴³ An effective treatment would offer a life-altering option for those affected.

There is no TCM herbal product for food allergy. Our group developed a food allergy herbal formula I (containing extracts of 11 herbs)⁴⁴ and then a refined formula FAHF-2, containing 9 herb extracts.¹⁶ Using a well established murine model that clinically and immunologically mimics peanut allergy,⁴⁵ we found that FAHF-2 completely blocked peanut-induced anaphylaxis when administered intragastrically during the development of peanut hypersensitivity (early treatment).¹⁶ We then reported that FAHF-2 also completely blocked peanut anaphylaxis when administered after peanut hypersensitivity was fully established (late treatment protocol).¹⁵ This protection was associated with suppression of histamine release, T_H2 responses (IgE and T_H2 cytokines), and upregulation of T_H1 responses (IgG_{2a} and IFN- γ).¹⁵ FAHF-2 also showed a high safety profile in an acute toxicity study in which mice fed with 24 times the effective FAHF-2 dose did not show any detectable abnormality.¹⁶ Given the potent protection and immunomodulatory effects to food allergens, and given that mice were completely protected for 4 to 5 weeks posttherapy,^{15,16} we investigated the long-term effects of FAHF-2 and the mechanisms underlying its prolonged protection. We found FAHF-2 completely prevented anaphylactic reactions after multiple peanut rechallenges every 1 to 2 months for at least 6 months (~25% of the mouse life span⁴⁶). This was also accompanied by continued suppression of histamine release and IgE production posttherapy.⁴⁶ We then used *in vivo* depletion techniques to explore the mechanisms of persistent protection. IFN- γ neutralization and CD8⁺ T-cell depletion abolished the FAHF-2's suppressive effect on IgE and T_H2 cytokine production, and significantly attenuated FAHF-2's protective effect on peanut anaphylaxis,^{47,48} demonstrating an important role of IFN- γ and CD8⁺ T cells in mediating long-term protection. A similar immunomodulatory effect has also been found on human cells. In this study, PBMCs from children with peanut allergy were cultured in the presence or absence of peanut protein with or without FAHF-2. We found that FAHF-2 significantly suppressed IL-5 production and increased IFN- γ production.⁴⁹ We recently extended our studies to explore additional effects of FAHF-2 on other mechanisms involved in peanut anaphylaxis and found that FAHF-2 inhibited Fc ϵ RI expression on mast cells and basophils *in vivo*, and inhibited mast cell degranulation *in vitro*.⁵⁰ It appears that multiple mechanisms are involved in FAHF-2's potent and persistent protection. In ongoing studies, we found that FAHF-2 is also effective in a mouse model of multiple food allergies in which animals were sensitized to fish and egg, in addition to peanut (Srivastava et al, manuscript in preparation and abstract accepted for AAAAI annual meeting, January 2009).

Clinical investigation of FAHF-2 for food allergy

Given the excellent efficacy and safety profile in animal studies, FAHF-2 appears to be an ideal candidate to treat human food allergy. After IND approval from the FDA and local institutional review board approval were obtained, a FAHF-2 clinical trial was initiated in 2008. This was the first clinical trial of a botanical drug for multiple persistent food allergies, including peanut and/or tree nut, fish, and shellfish allergies, and the first botanical drug trial that included children. A double-blind, dose escalation phase I study was conducted on 12 subjects (8 received

FAHF-2 and 4 received placebo) with peanut and other food allergies. The results showed that FAHF-2 is safe and well tolerated. An extended 6-month phase I open-label study is currently underway. After completion of this study, we will conduct a double-blind, placebo-controlled phase II study.

BOTANICAL DRUG QUALITY CONTROL AND RESEARCH INTO CHEMICAL AND BIOLOGICAL MECHANISMS OF BOTANICALS

Botanical drug quality control and IND

Although TCM has been used for thousands of years, the use of TCM herbal products as investigational botanical new drugs began only recently in the United States. Unlike synthetic drugs that begin with preclinical laboratory studies, botanical drug development from TCM has the advantage of long-term experience in human beings and generally an established safe profile.^{9,10,51} However, standardization of herbal formulas is challenging because the complex mixtures of herbs contain many constituents that have not been clearly defined. An essential requirement for clinical investigation of a botanical drug is an IND approval by the FDA (Title 21 Code of Federal Regulations 312.23 (a)). The most unique section in this IND is the Chemical, Manufacturing, and Control (CMC) Data [21 CFR 312.23(a) (7)] requirement, which differs from that required for synthetic drugs. Given the unique characteristics of herbal mixtures, the FDA frequently relies on a combination of tests when the active chemicals are not well defined. **HPLC** fingerprints, assays of characteristic markers, and biological assays are accepted methods to ensure quality, potency, and consistency of botanical drugs. In accordance with the FDA guidelines, provision of sufficient quality and safety data at 3 levels—raw herbs, extracts (*substance* in FDA terminology), and final product—led to the approval of ASHMI and FAHF-2. The 3-dimensional HPLC fingerprint of FAHF-2 and chemical markers identified by **liquid chromatography** coupled with **mass spectrometry** are shown on the cover of this issue. HPLC fingerprinting was also used as a means of quality control in the studies of mMMMDT, DCT, AST-1, and AST-2, as described.

Research into chemical and biological activities of botanicals

Although selected chemical markers and HPLC fingerprints are accepted by the FDA for botanical quality control purposes in preliminary clinical trials, the FDA encourages identification of active ingredients in herbal products, if feasible, to improve the quality control and to understand the pharmacokinetics of herbal products. Isolation and identification of active constituents are essential to obtain better understanding of the mechanisms of action. This goal depends on biological testing-guided isolation and chemical identification of active ingredients. Although herbal products contain many constituents, only a few compounds are responsible for the physiological effects. The development of modern chromatographic techniques, such as HPLC, together with mass spectrometry and nuclear magnetic resonance, makes isolation and purification of chemical constituents from complex mixtures feasible.⁵²⁻⁵⁴ Recently a phytochemical database of Chinese herbal constituents and bioactive plant components was established.¹⁷ This database shows that the 2 classes of phytochemicals most often represented in TCM are the triterpenes

TABLE III. Summary of herbal components of ASHMI and known chemical constituents

Chinese name	Ling-Zhi	Ku-Shen	Gan-Cao
Synonyms	Reishi	Light yellow sophora root	Licorice root
Pharmaceutical name	Ganoderma	Radix Sophorae Flavescentis	Radix Glycyrrhiza
Plant species information	<i>Ganoderma lucidum</i> Karst	<i>Sophora flavescens</i> Ait	<i>Glycyrrhiza uralensis</i> Fischer
Part used	Fruiting body	Root	Root and rhizome
Family	Polyporaceae	Leguminosae	Leguminosae
Traditional Uses (ref)	General weakness, cough, asthma, insomnia, indigestion	Dysentery, jaundice, pruritis edema, dysuria, eczema	Sore throat, cough
Modern Uses	Nightmares, neurasthenia, coronary heart disease, arrhythmia, asthma, leukocytopenia	Chronic hepatitis B, leukocytopenia	Bronchitis, gastroduodenal ulcers
Chemical constituents	<ol style="list-style-type: none"> Polysaccharides Nucleotide: adenosine, guanosine, ganoderpurine Alkaloid: choline, betains, γ-butyrobetaine, ganoine, ganodine Steroid: ergosterol, ergosta-palmitate, ergosta-7,22-dien-3-one Triterpenoids: Ganoderic acid A, B, C, D, E, C₅, C₆, G, K, Ganoderol A 	<ol style="list-style-type: none"> Alkaloid: matrine, oxymatrine, sophoranol, sophocarpine, anagyrene, d-isomatrine, sophocarpine, sophoridine Flavonoid: kushenol A, B, norkurarinone, kuraridine, kurarinone, maaackiain, trifolirhizin, formonetin 	<ol style="list-style-type: none"> Triterpene saponin: glycyrrhizic acid, glycyrrhetic acid, deoxyglycyrrhetic acid I, deoxyglycyrrhetic acid II, liquiritic acid, glycyrrhetol, glabrolide Flavonoids: liquiritin, isoliquiritin, liquiritigenin, isoliquiritigenin, neo-liquiritin, neoliquiritigenin

(15%) and sesquiterpenes (13%). The remaining classes of phytochemicals include alkaloids (10%), simple phenolics (10%), flavonoids (10%), and monoterpenes (10%). The diterpenes (5%), coumarins (5%), aliphatics (5%), and steroids (5%) are found less often in TCM, and tannins, isoflavonoids, polycyclic aromatics, lignans, and carbohydrates are least common (less than 5% each).^{17,50,55} Of these phytochemical classes, the nonsteroidal alkaloids, polyphenols, and terpenes are constituents of TCMs most frequently used to treat allergy and asthma.⁵⁵ As an example, Table III shows the major known chemical constituents of individual herbs in ASHMI.^{17,56,65} However, most of these compounds identified in TCM are not yet commercially available, and their potential pharmacological actions have not been well established. In recent years, an increasing number of pharmacologic studies of known compounds have been published. As examples, prenylated flavonoids from *S. flavescens* inhibited the release of β -hexosaminidase from cultured *RBL-2H3* cells, suggesting an anti-allergy property.⁵⁷ *Glycyrrhiza uralensis* (Gan-Cao), commonly called licorice, is one of the most commonly used herbs in TCM. The licorice triterpenoid glycyrrhizin and related compounds downregulate production of the inflammatory chemokines *IL-8* and eotaxin-1, and *signal transducer and activator of transcription 6* expression by a human lung fibroblast cell line.^{58,59} However, their effects on asthma have not been reported, and other potential anti-inflammatory constituents in *G. uralensis* have not been fully investigated. Eosinophilic airway inflammation is a major feature of allergic asthma, and eotaxin is involved in recruitment of eosinophils to sites of antigen-induced inflammation in asthmatic airways.⁶⁰ Because human lung fibroblasts are a major source of eotaxin,⁶¹ inhibition of eosinophil recruitment by suppression of fibroblast eotaxin production is a potentially valuable approach to pharmacologic intervention in asthma. Our group has conducted a systematic bioassay-guided purification of *G. uralensis* that yielded 5 flavonoids: liquiritin, liquiritigenin, isoliquiritigenin, 7, 4'-dihydroxyflavone, and isoononin. The structures of the

compounds were established by ¹H, ¹³C nuclear magnetic resonance and liquid chromatography coupled with mass spectrometry. The potential ability of these isolated compounds, and of glycyrrhizin, to inhibit eotaxin-1 secretion by human fetal lung fibroblasts (HFL-1) was tested. *Glycyrrhiza* flavonoids inhibited eotaxin-1 secretion, and liquiritigenin, isoliquiritigenin, and 7, 4'-dihydroxyflavone were more effective than liquiritin, isoononin, and glycyrrhizin (commercially available) in suppressing eotaxin secretion.⁶²

Because most previous phytochemical studies of herbal medicine focused on isolation and identification of new compounds, and because limited amounts of material were isolated, few isolated compounds are commercially available, and studies on pharmacologic actions and mechanisms of action relevant to asthma are limited. Isolation of individual compounds from each individual herb in complex formulas is a major undertaking. Several groups have generated targeted fractions based on the phytochemistry of TCMs.^{63,64} One previous study of a murine model of allergic asthma showed that triterpenoid-rich extracts of *Ganoderma tsugae* exhibited anti-inflammatory effects, decreased airway responses, and attenuated T_H2 responses without causing overall immune suppression.⁶³ Our approach is to generate targeted fractions of ASHMI and its constituent herbs, and by using various *in vitro* models representing pathological asthma mechanisms, determine active fractions for purification into single compounds. We have found that certain triterpene-rich ASHMI fractions are potent suppressors of TNF- α production by macrophages (RAW 264.7 cell line). Other fractions, flavonoid-rich, inhibit IgE production by B lymphocytes (U266 myeloma cell line), and an alkaloid-rich fraction inhibits acetylcholine induced airway smooth muscle contractility (Brown et al, unpublished data, January 2009). These procedures may prove to be an efficient approach to identification of anti-inflammatory and other pharmacologically active compounds in the complex ASHMI formula and other TCM formulas.

Conclusion

Several recent controlled clinical studies have found that some herbal formulas and 1 individual herb improved lung function and reduced symptoms when used as monotherapy, or as a complement to conventional standard therapy for the treatment of asthma. These findings strongly suggest that TCM herbal remedies are of some value for asthma management. ASHMI produced a beneficial immunomodulatory effect in patients with asthma. Other mechanisms in addition to anti-inflammatory activity require further investigation. Given the lack of any alternative food allergy therapies, and the excellent preclinical safety and efficacy data, continued research into FAHF-2 for food allergy is needed. Both ASHMI and FAHF-2 are entering clinical studies in the United States and may prove to be the first generation of antiasthma and food allergy botanical drugs. Additional TCM formulas and individual medicinal herbs as well as purified compounds should be investigated by using state-of-the-art laboratory and clinical methodologies.

We thank Kamal Srivaratava, Ming-Chun Wu, Tengfei Zhang, Chunei Qu, Zhong Mei Zho, Joseph Godthab, Rong Wang, Sylva Wallenstein, Jimmy Ko, Joyce Yu, Meyer Kattan, Sally Noon, Brian Schofield, Julie Wang, and Hugh Sampson for their significant contributions to this work and Sharon Hamlin for her assistance with manuscript preparation.

US Provisional Patent Applications regarding FAHF-2 (reference number 60554775) and ASHMI (PCT/US05/08600) have been filed.

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