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

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Background: Although corticosteroids and β2-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.

Key words: Complementary and alternative medicine, traditional Chinese herbal medicine, botanical drug, asthma, food allergy, TH1/TH2 balance

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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. 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. In the United States, TCM is mainly provided by licensed practitioners and is playing an increasing role in the health care system. Children in the United States are currently using some form of CAM to treat their asthma. Thus, there is a need for defining and developing reliable CAM therapy for patients.

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, 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. Early clinical investigations and allergy may be investigated as new botanical drugs.

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

- **β-HEXOSAMINIDASE, RBL-2H3 CELLS**: β-Hexosaminidase is released on degradation 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 helper 1 cells by IL-12 and the T helper 1 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, eosinophil 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 shown 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.

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placeto-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 ± 6.3 to 84.2 ± 6.5; P < .001) and the prednisone (65.2 ± 6.3 to 88.4 ± 6.8; 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 β2-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 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.18 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 flavesces Ait.** In addition to the multi-herb formulas, Hoang et al19 reported the effect of an extract of S flavesces 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 flavesces 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 β2-agonist use, reduction in dose of inhaled corticosteroid, and improvement of peak

| Summary of **Sophora flavesces 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 β2-agonist use | 45   | 92   | 95  | 97  |
| Reduction of ICS   | 45   | 84   | 92  | 100 (no patient took ICS) |

Values are percentages unless otherwise indicated.

ICS, Inhaled corticosteroid; NR, not reported.
disorder; therefore, TCM was a result of variations in conventional medications. 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-\(\gamma\)) 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-\(\gamma\) 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-\(\gamma\) production in response to allergen compared with control subjects and subjects with resolved asthma.\(^{24}\) 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.\(^{25}\) 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 al\(^{26}\) 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 IL-13) levels (Fig 1, A). Inhibition was greater in the prednisone group. However, unlike prednisone, which suppressed IFN-\(\gamma\) secretion, ASHMI actually increased IFN-\(\gamma\) secretion.\(^{12}\) (Fig 1, B).

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**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-\(\gamma\) (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;120:25-31.\(^{6}\) 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 al 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 μg/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 μg/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 glycyrhrizin (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 hyper-responsiveness (AHR), pulmonary inflammation, and airway remodeling, which was accompanied by downregulation of Th2 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 Th2 specific transcription factor GATA-3.36 ASHMI had the same effect on memory Th2 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 β2-adrenergic receptors, but were associated with increased prostaglandin E2 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 Th1 and Th2 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 Th1/Th2 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.32 Although tremendous strides have been made in food allergy awareness, there is no satisfactory therapy to prevent or reverse the disease. Peanut allergy...
impacts a significant psychological burden on the allergic individuals and their families. 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) and then a refined formula FAHF-2, containing 9 herb extracts. Using a well-established murine model that clinically and immunologically mimics peanut allergy, we found that FAHF-2 completely blocked peanut-induced anaphylaxis when administered intragastrically during the development of peanut hypersensitivity (early treatment). We then reported that FAHF-2 also completely blocked peanut anaphylaxis when administered after peanut hypersensitivity was fully established (late treatment protocol). This protection was associated with suppression of histamine release, T$_{H2}$ responses (IgE and T$_{H2}$ cytokines), and upregulation of T$_{H1}$ responses (IgG2a and IFN-γ). 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. Given the potent protection and immunomodulatory effects to food allergens, and that mice were completely protected for 4 to 5 weeks posttherapy, 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 span). This was also accompanied by continued suppression of histamine release and IgE production posttherapy. We then used in vitro 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, 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. 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 FceRI expression on mast cells and basophils in vivo, and inhibited mast cell degranulation in vitro. 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 safety profile. 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 mMMDT, 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. Recently a phytochemical database of Chinese herbal constituents and bioactive plant components was established. This database shows that the 2 classes of phytochemicals most often represented in TCM are the triterpenes.
(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.17,50,55

As an example, Table III shows the major known chemical constituents of individual herbs in ASHMI.17,50,55 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 flavescentes* 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 eotaxin production 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 TH2 responses without causing overall immune suppression.65 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.

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

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