Traditional Chinese herbal remedies for Asthma and Food Allergy

Xiu-Min Li, MD
Department of Pediatrics, Mount Sinai School of Medicine, New York, New York, USA

Abstract

The increasing prevalence of allergic diseases in westernized countries is a significant health problem. Curative therapies for these diseases are not available. There are also significant concerns regarding the potential side effects from the chronic use of conventional drugs such as corticosteroids, especially in children. Many patients with chronic allergic conditions seek complementary and alternative medicine (CAM) therapies including traditional Chinese medicines (TCM). This trend has begun to attract interest from the mainstream healthcare providers and scientific investigators, and has stimulated government agencies in the US to provide support and guidance for the scientific investigation of CAM. This effort may lead to improved therapies and better healthcare/patient outcomes. This review presents an update on the most promising Chinese herbal remedies for asthma and food allergy.

Keywords

Asthma; TCM; food allergy-induced anaphylaxis; herbal remedies; CAM; clinical trials; animal study

Introduction

Allergic asthma and food allergy are common and chronic atopic disorders. Many sufferers are frustrated by the lack of curative therapies or have concerns about medicine side effects. Consequently, an increasing number of patients turn to complementary and alternative medicine (CAM).[1-3]

Traditional Chinese medicine (TCM) is the major component of CAM therapies used in the US. TCM is one of the oldest medical practices in the world, and has played an important role in preventing and treating diseases in China and other Asian countries for centuries where it is still used as a monotherapy or in integrated medicine. TCM has a unique system of theory, diagnosis, and treatment,[4] in which acupuncture and Chinese herbal medicines are the major modalities of treatment. TCM and other CAM therapies are increasingly being incorporated into western medical centers in the US.[5;6] However, unlike the situation in China, a role for TCM in mainstream medicine in the US remains to be established. Patients in the US receive TCM therapy mainly from licensed TCM practitioners outside of hospital settings. Chinese herbal medicines under US law are viewed as dietary supplements. This situation contributes to the gap between empirical human use-based practice and scientific evidence-based medicine. It has been suggested that “West meets East” as a means of studying TCM is narrowing this gap[7;8] and may lead to better options and outcomes for patients. In 1998, the NIH established the National Center for Complementary and Alternative Medicine (NCCAM).
to support basic and clinical research on CAM. In view of the unique complexity of natural herbal remedies, and long human use history, the US Food and Drug Administration (FDA) issued “Guidance for Industry Botanical Drug Products” in 2000.[9] This document focuses on investigating the consistency, efficacy and safety of botanical products, making it possible to develop botanical drugs in the US. This review is therefore, not a review of the English literature on TCM studies in general, but rather on observational and experimental studies, concentrating in particular on those herbal remedies that show the most promise for allergic asthma and food allergy, specifically those reported from 2005 to 2007. Since Japanese herbal medicine (Kampo) and traditional Korean medicine are of TCM origin, they are also included in this review.

Part I. Chinese Herbal Remedies for Asthma

Allergic asthma, an increasingly common disease in industrialized countries affecting 15.7 million adults and 6.5 million children in the US alone, is a chronic inflammatory condition of the airways that causes airway hyperresponsiveness (AHR). A Th1-Th2 imbalance has been hypothesized to underlie allergic asthma through a shift in immune responses from a Th1 (IFN-γ) pattern toward a Th2 (IL-4, IL-5, and IL-13) profile. Although corticosteroids (CS), the cornerstone of asthma treatment, improve asthma symptoms they do not alter the progression of or cure the disease. Memory Th2 cells have been suggested to be critical to the chronic nature of asthma. CS withdrawal is often accompanied by increased inflammation in bronchial biopsies and symptomatic disease relapse. This has been suggested to be due to CS mediated-overall suppression of IFN-γ or potentiation of Th2 polarized immunity. In addition, prolonged use of CS causes serious systemic side effects, which have particularly far-reaching consequences for children. This situation has intensified the need to develop alternative therapies for this disorder.

Asthma was recognized in ancient China and there are a number of established, classical formulas used in TCM practice.[10] In the past decade, researchers began to investigate the potential use of some of these formulas and suggested that there is potential for the development of herbal interventions for asthma.[11;12] Since 2005, there have been a number of English-language publications reporting double-blind, placebo-controlled clinical studies investigating the efficacy and safety of herbal products, as well as basic studies aimed at understanding the mechanism of actions at the immunological and molecular levels. The major findings of several promising herbal remedies are summarized below.

1. Anti-asthma Herbal Medicine Intervention (ASHMI)

It is believed that complex interactions between herbal formula constituents produce synergistic effects and reduce possible side effects of some herbs.[4;10] The complexity of traditional Chinese herbal formulas, which commonly contain many chemical constituents, makes standardization of herbal products difficult. Equally challenging is the determination of mechanisms of action and interactions between and among the various constituents. While developing botanical drugs, in an attempt to improve the ease of study and quality control while simultaneously maintaining therapeutic efficacy and safety, we developed a simplified formula for the treatment of allergic asthma.[12] ASHMI, a three-herb anti-asthma formulation (Table I), is derived from a 14-herb formula, MSSM-002[13], which was used to treat asthma in the China-Japan Friendship Hospital in Beijing.[12;13] We found that ASHMI had comparable effects on AHR and eosinophilic inflammation to the classical 14-herb formulation and showed a high safety profile in an animal model of asthma.[13] Consequently, Wen et al.[7] investigated the efficacy and tolerability of this formula on 91 patients in China with moderate-to-severe asthma in a double-blind, randomized, placebo-controlled trial comparing ASHMI to oral prednisone therapy. Subjects in the ASHMI group received oral ASHMI capsules (4
capsules, tid, 0.3 g/cap) and placebo tablets similar in appearance to prednisone. Subjects in the prednisone group received oral prednisone tablets (20mg qd in the morning) and “ASHMI placebo capsules”, for 4 weeks. Treatment was administered daily over 4 weeks, and all subjects, 18-65 years old, remained in the hospital for the duration of the study. No medications other than rescue beta-agonists were allowed. Spirometry measurements, symptom scores, side effects, and serum cortisol, cytokine and IgE levels were evaluated pre- and post-treatment. This study found that post-treatment lung function (FEV1 and PEF values) was significantly improved in both ASHMI (64.9±3.6 to 84.2±5.0, p <.001) and prednisone (65.2±3.7 to 88.4±8.0, p<0.001) treated groups. The improvement was slightly but significantly greater in the prednisone group (P < 0.05). There was a significant and a 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<0.001], and prednisone ([5.0 (4-7)] to [2.0 (0-4)], p<0.001), use of beta 2-bronchodilators [median (range), ASHMI: (4.7 (3.5-5.7) to 0.9 (0.14-2.3), p<0.001] and prednisone:(4.7 (3.5-5.6) to 0.6 (0.3-1.0), p<0.001)], serum IgE levels [median (range), ASHMI: (950 (552-1349) to 476 (73-913) kU/L, p<0.001)] and prednisone: (948 (368-1356) to 310 (60-619) kU/L, p<0.001), and the numbers of eosinophils [(means ± SD, ASHMI: 0.52 ±0.24 to 0.27 ± 0.14 × 10^9/L, p<0.001; prednisone: 0.53 ±0.21 to 0.19 ±0.10 × 10^9/L, p<0.001]. Th2 cytokines IL-5 and IL-13 were significantly reduced in both treated groups (P < 0.001 for each). Strikingly, serum IFN-gamma and cortisol levels were significantly decreased in the prednisone group (P < 0.001), but significantly increased in the ASHMI group (P < 0.001). In addition, ASHMI had no significant effect on body weight (increases in body weight post-therapy 2.8 kg in prednisone group vs 0.8 kg in ASHMI). No significant side effects were observed. All hematological, electrocardiogram and liver and kidney functions were normal in both groups. Thus ASHMI appeared to be effective and well tolerated, and may offer benefits comparable to standard corticosteroid therapy without undesirable side effects. ASHMI has received investigational new drug approval by the US FDA for phase I and II clinical trials for treating asthma (IND 71,526). Unpublished data from the first cohort phase I study showed that ASHMI is well tolerated (Kelly-Pieper et al.).

Research into the mechanisms underlying ASHMI effects is underway. A study by Ko et al. [14] showed that ASHMI significantly suppressed Th2 cytokine, but not Th1 cytokine production by peripheral blood mononuclear cells from patients with asthma and food allergy. Animal studies found that ASHMI exhibits a broad spectrum of therapeutic effects on the major pathogenic mechanisms of asthma, inhibiting airway hyperreactivity (AHR), pulmonary inflammation, and airway remodeling, as well as down-regulating Th2 responses[15] and direct modulation of airway smooth muscle contraction.[16] Recent data also showed that ASHMI completely blocked AHR and markedly reduced eosinophilic inflammation in a chronic severe asthma model. These effects lasted for at least 8 weeks after discontinuing ASHMI treatment, and were associated with sustained specific suppression of Th2 memory responses to antigen re-challenge (Zhang et al., manuscript submitted) suggesting that ASHMI may generate long-term benefit for severe and chronic asthma patients. Although the detailed mechanisms underlying ASHMI’s potent effects on multiple asthma mechanisms are unknown, our recent pharmacological study demonstrated that constituents in ASHMI act synergistically in suppression of eotaxin production by human fetal lung fibroblasts.[17] Isolation and identification of active constituents in ASHMI, currently underway, may lead to better understanding of the mechanisms of ASHMI and a novel alternative or complementary asthma therapy.

2. Modified Mai Men Dong Tang (mMMDT)

In 2005, Hsu et al.[18] reported results of a clinical investigation of a complementary TCM therapy for asthma. This study evaluated the efficacy and safety of a Chinese herbal formula, modified Mai Men Dong Tang (mMMDT) for treatment of persistent, mild-to-moderate
asthma. Modified Mai Men Dong Tang (mMMDT) consists of 5 herbs (Table I). This four-month trial included 100 asthmatics aged 5 to 18. The two active groups received 40 mg mMMDT (40 patients), or 80 mg mMMDT (40 patients). The control group received placebo capsules (20 patients). Western medications as part of standard asthma therapy were provided equally to all groups, although it is unclear if there were adjustments for severity of disease at baseline. Parameters used to evaluate efficacy were changes in FEV1, symptom score, total serum IgE and dust-mite-specific IgE. Safety assessments included complete blood count, and liver and kidney function tests. Relative to baseline, significantly greater increases in FEV1 were demonstrated for both mMMDT-treated groups in comparison with the placebo group (P < 0.05 for both doses of mMMDT). Symptom scores were similarly improved in both mMMDT treatment groups. The serum total IgE for the 80 mg/day dose of mMMDT treatment showed a decreasing tendency but no statistical difference was found. No drug-related adverse effects were reported. Possible efficacy of mMMDT as a monotherapy for asthma has not been tested.

3. Ding Chuan Tang

In 2006 Chan et al.[19] reported that Ding Chuan Tang (DCT), a Chinese herbal decoction, could reduce AHR in stabilized asthmatic children in a randomized, double-blind clinical trial. DCT contains 9 herbs (Table I). This study enrolled children aged 8-15, diagnosed as mild-to-moderate persistent asthma patients. They were randomly allocated to receive 6.0 g DCT or placebo daily for 12 weeks. Self-recorded daily symptom scores, medication scores, and morning and evening peak expiratory flow rates were returned at monthly clinic visits. Pulmonary function testing, methacholine challenge testing, and serum inflammatory mediators were measured before and at the end of the trial. Fifty-two asthmatic children completed the clinical study. 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 PC(20) was significantly improved in the DCT group (0.51 +/- 1.05 mg/ml vs. 0.26 +/- 0.84 mg/ml, p = 0.034). The clinical and medication scores showed improvement in the DCT group (p = 0.004). The authors concluded that more stable airways were achieved with this add-on complementary therapy.

4. STA-1

In 2006, Chang et al.[20] reported results of a clinical evaluation of the Chinese herbal medicine formula STA-1 containing 10 herbs [Table I] and STA-2 in the treatment of allergic asthma in a double-blind, placebo-controlled, randomized trial. STA-1 is a combination of mMMDT and Lui-Wei-Di-Huang Wan (LWDHW). The difference between STA-1 and STA-2 is in the preparation procedure of the six herbs of LWDHW. These six herbs of LWDHW were milled to a powder in STA-1, but all the herbs in STA-2 were extracted by boiling water. In this study, 120 patients between the ages of 5 to 20 years with mild-to-moderate asthma were included. These patients were treated with either STA-1 (44 patients) at a dose of 80 g/kg/day or STA-2 (40 patients) at a dose of 80 g/kg/day, or placebo (16 patients) administered twice daily for 6 months. Completion rate was 88%, 80% and 80% for STA1, STA2 and placebo respectively. The main outcome measures were a daily diary record of symptoms, supplementary bronchodilator and glucocorticoid treatment, changes of pulmonary function (forced expiratory volume in 1 s), changes of total and Dermatophagoides pteronyssinus (DP)-specific IgE and side effects. The results showed a statistically significant reduction of symptom scores, systemic steroid dose, total IgE and specific IgE levels in the STA-1 group. Furthermore, STA-1 improved pulmonary lung function (FEV1) compared with the placebo group. However, STA-2 treatment did not show significant improvement on any of above parameters. The authors suggested that unknown compounds that have anti-inflammatory effect in LWDHW may be heat sensitive. However, chemical analysis is required support this hypothesis. This study also reported that there were no obvious adverse events noted among
the groups during the intervention period. These results suggested that STA-1 may be helpful for the treatment of mild-to-moderate chronic asthma. This same group also published an animal model study which demonstrated that STA-1 could effectively suppress the Der p 5-induced allergic reactions as evidenced by significantly reduced Der p 5-specific IgE, pulmonary inflammation and AHR.[21]

5. Sophora flavescens Ait

In 2007, Hoang et al.[22] reported the impact of a Sophora flavescens Ait (S. flavescens, sophora root) extract with excitatory modulator activity in the management of asthma. An open and selective 3-year follow-up of 14 chronic refractory asthmatics aged 22 to 70 was used. Participants received an extract of Sophora flavescens Ait water-extract powder in capsules with a dose equal to 4g of dried root three times daily for 3 months, and 2 times daily for 6 months and once daily for 27 months thereafter. Medication use, a diary of symptoms and respiratory function were recorded. The quality of life, clinical symptoms and respiratory function measurements were recorded. This study showed that the use of inhaled corticosteroid and beta-agonists were reduced or eliminated. No significant adverse reactions were reported. The authors concluded that the extract of S. flavescens appears to be a safe and may be effective alternative treatment for refractory chronic asthma. Interestingly, Sophora flavescens Ait is one of the major components of ASHMI and has also used in traditional Hawaiian herbal medicine as an anti-asthma medicine.[23;24] We also found, in an animal model of asthma, that Sophora flavescens Ait alone reduced allergic airway responses; however, the dose required was double the amount in the ASHMI formula.[25] The long-term effects of Sophora flavescens Ait in this model have not been investigated.

6. Others

Several preclinical studies published since 2005 reported some effects and mechanisms of action of Chinese herbal medicines on allergic asthma. For example Kim et al.[26] reported that DA-9601, an Artemisia asiatica herbal extract, ameliorated airway inflammation in a murine model of allergic asthma. The data suggest that DA-9601 may be developed as a clinical therapeutic agent for allergic diseases due to the suppressing of airway allergic inflammation via regulation of various cellular molecules involved in the MAP kinases/NF-KappaB pathway. Fang et al.[27] showed that Gyokuheifusan (GHS) administered during sensitization significantly reduced ovalbumin(OVA)-specific IgE, IL-4 and increased IFN-γ production, demonstrating a beneficial immunomodulatory effects of GHS on Th1/Th2 balance in an OVA-induced mouse asthma model. The authors concluded that GHS may inhibit the development and severity of asthma. It would be interesting to see the clinical outcome of administering these herbal remedies to allergic asthma patients.

In summary, studies investigating Chinese herbal medicine effects on asthma are increasing. Five recent clinical trials all reported favorable clinical outcomes, objective lung function measurement improvement and favorable safety results. The treatment durations ranged from 1 month to 3 years. ASHMI also was shown to have beneficial immunoregulatory effects on Th1 and Th2 responses and a beneficial effect on adrenal function. Taken together these findings suggest the potential of TCM for developing effective and safe alternative approach for asthma.

Part II. Potential Traditional Chinese medicine therapy for food-induced anaphylaxis

Unlike asthma and other allergic diseases, food allergy is not described in the TCM literature. Food allergy, particularly peanut allergy, is still rare in China.[28] However, there are TCM
herbal formulas for treating gastrointestinal disorders, the symptoms of which are similar to food allergic reactions. In light of the gastrointestinal symptoms induced by food allergic reactions, and the Th2-dominant responses of food allergy, we developed an herbal formula designated FAHF-1 containing 11 herbs, which combined the traditional herbal formula, **Wu Mei Wan (WMW)** and **Ling Zhi**. WMW was classically prescribed to treat colic, vomiting, and chronic diarrhea or dysentery, or collapse (also translated as syncope) caused by parasitic worms.\[10\] Interestingly, like several other ancient herbal formulas and contemporary prescription drugs, WMW has also been recently reported to be effective for treating several other syndromes, such as drug-induced rash, neurogenic vomiting, asthma,\[29\] chronic gastroenteritis and colitis.\[10\] Ling Zhi has been found to have "anti-inflammatory" and anti-allergy properties\[10\] and immunomodulatory effect on Th1 and Th2 responses.\[30\] We found that FAHF-1 markedly reduced mast cell degranulation and histamine release, and completely blocked PN-induced anaphylactic symptoms, as well as reduced PN-specific serum IgE levels in a murine model of PNA.\[31\] FAHF-1 also significantly reduced lymphocyte proliferation, and IL-4, IL-5 and IL-13, but not INF-γ synthesis in vitro. No toxic effects on liver or kidney functions and no overall immune suppression were observed.\[31\]

To increase ease of standardization of the herbal product and further increase the safety profile, we have attempted to simplify FAHF-1. We eliminated two herbs, **Zhi Fu Zi** (Radix Lateralis Aconiti Carmichaeli Praeparata) and **Xi Xin** (Herba Asari), from FAHF-1 because based on the Traditional Chinese medicine formulation system\[10\] they are not likely to be the principal herbs, and are toxic if incorrectly processed or significantly overdosed. We named the refined formula FAHF-2. A preliminary study \[32\] found that, as with FAHF-1, FAHF-2 also completely blocked peanut-induced anaphylaxis. We then extended the study and found that FAHF-2-treated mice were completely protected from anaphylaxis following challenge for up to 5 wks post-therapy, and that reduced IgE levels remained significantly lower at 5 wks post-therapy. Complete protection was confirmed using several well-established parameters, including anaphylactic symptom scores, decreased core body temperatures, elevated plasma histamine levels\[32\] and vascular leakage.\[33\] This therapeutic effect was associated with immunoregulatory effects on Th1-Th2 responses.\[34\] Furthermore, this formula appears to have a large margin of safety. Mice fed 24 times the effective daily dose showed no signs of acute toxicity, and no evidence of abnormal liver and kidney functions, or abnormal complete blood test or histology of major organs.\[34\] Furthermore, our recent extended studies showed that FAHF-2 completely protects against anaphylactic reactions following multiple peanut re-challenges every 1-2 months for at least 6 months (~1/4 the life expectancy of mice).\[35\] Since FAHF-2 was given to the mice during peanut sensitization in those previous studies, we recently investigated whether FAHF-2 can induce peanut tolerance in mice with well-established PN allergy and found that FAHF-2 can establish tolerance after peanut allergy is established.\[36\] This protection is also persistent (Srivastava et al., unpublished data). The potent and long-lasting protection against peanut allergy by FAHF-2 has not been established by any other therapeutic regime. In addition, we tested the actions of individual herbs in FAHF-2 and several additional simplified formulas derived from FAHF-2. Interestingly, while FAHF-2 provides total protection against peanut allergy, no individual herb or further reduced formula was as effective as FAHF-2 on peanut allergy.\[37;38\] This finding suggests that the herbs in FAHF-2 work synergistically and/or additively to produce the therapeutic effects of the complete herbal formula. (Kattan et al., manuscript submitted). These results indicate that the FAHF-2 formulas, although more complicated, have advantages over individual herbs or formulas with fewer herbs and that FAHF-2 is a candidate for developing a botanical drug for treatment of PNA.

To determine the effect of FAHF-2 on human T-cell responses, purified human peripheral blood mononuclear cells were obtained from peanut allergic subjects and stimulated with crude peanut extract in the presence or absence of FAHF-2. The cells stimulated in the presence of
FAHF-2 showed a decreased antigen-dependent T-cell proliferation response. These cells also demonstrated a dose-dependent decrease in production of the Th2 cytokines, IL-5 and IL-13, with an increase in IFN-\(\gamma\) production.[14] These initial findings suggest that FAHF-2 does not globally suppress cytokine production but rather selectively suppresses Th2-cytokine production to inhibit the Th2-specific response, suggesting that FAHF-2 will likely exert a favorable immunoregulatory response in food allergic subjects.[14]

In summary, given the efficacy and safety profiles in an animal model of peanut allergy and the beneficial immunoregulatory effect in vitro human studies, as well as the long history of safe human use of the herbs in FAHF-2, we hypothesize that FAHF-2 will be safe and effective in preventing food-allergy associated anaphylaxis and/or desensitize food hypersensitivity. Phase I and II clinical trials are planned. Medline searches found no other report of investigation of Chinese herbal medicine for food-induced anaphylaxis.

Conclusion

Traditional Chinese medicine herbs and formulas are now attracting significant interest in the West. The evaluation of efficacy and safety of these herbal remedies is now being approached with the methodologies and clinical trial protocols standard in Western medicine. Published English-language studies investigating TCM herbs and formulas for their anti-allergic effects have been increasing. Controlled clinical trials with anti-asthma TCM formulas such as ASHMI, mMMDT, and DCT, etc., highlight the potential of TCM formulas to be efficacious and safe alternatives or complements to standard western therapy for asthma. FAHF-2, a potential TCM herbal treatment for food allergy, was shown to be remarkably effective against food anaphylaxis in an animal model with the potential to be a long-lasting therapy. Some of these herbal remedies may be available in the near future to allergists for use as botanical drugs for treating allergic asthma and food allergy.

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References


36. Qu C, Srivastava KD, Ko J, Zhang TF, Sampson HA, Li XM. Induction of tolerance after establishment of peanut allergy by the Food Allergy Herbal formula (AFHF)-2 is associated with upregulation of IFN-gamma. Clin Exp Allergy. 2007 in press


**Glossary**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHR</td>
<td>airway hyperresponsiveness</td>
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<tr>
<td>ASHMI</td>
<td>Anti-asthma herbal medicine intervention</td>
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<td>CAM</td>
<td>complementary and alternative medicine</td>
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<td>CS</td>
<td>corticosteroids</td>
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<td>DCT</td>
<td>Ding Chuan Tang, classical formula</td>
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</table>
FAHF-1
Food allergy herbal formula

FAHF-2
Food allergy herbal formula, refined

LWDHW
Lui-Wei-Di-Huang Wan, classical formula

mMMDT
Modified Mai Men Dong Tang, modified classical formula

MSSM-002
Herbal formula

OVA
ovalbumin

PN
peanut

PNA
peanut allergy

RCT
Randomized controlled trial

TCM
traditional Chinese medicine

WMW
Wu Mei Wan, traditional herbal formula
Table 1
Summary of Clinical Studies for Asthma published 2005 to 2007

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<td>Sample size</td>
<td>n = 46 ASHMI (20mg/d)</td>
<td>n = 40 mMMDT 80mg</td>
<td>n = 28 DCTn = 24 Placebo</td>
<td>n = 50 STA-1</td>
<td>n = 14</td>
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<td>Ages (years)</td>
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<td>8-15</td>
<td>8 -15</td>
<td>22-70</td>
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<td>Indication</td>
<td>Moderate-to-severe persistent asthma</td>
<td>Mild-to-moderate persistent asthma</td>
<td>Mild-to-moderate persistent asthma</td>
<td>Mild-to-moderate persistent asthma</td>
<td>Chronic refractory asthma</td>
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<td>Length of Study (basis)</td>
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<td>12 weeks (Outpatient)</td>
<td>6 months (Outpatient)</td>
<td>3 years (Outpatient)</td>
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<td>1 Gang-Cao (Radix Glycyrrhizae)</td>
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<td>1 Gang-Cao (Radix Glycyrrhizae)</td>
<td>1 Gang-Cao (Radix Glycyrrhizae)</td>
<td>1 Ku-Shen (Radix Sophorae Flavescentis)</td>
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<td></td>
<td>2 Ku-Shen (Radix Sophorae Flavescentis)</td>
<td>2 Mai-Men-Dong (Radix Ophiopogonis)</td>
<td>2 Ban-Xia (Tuber Pinellia)</td>
<td>2 Mai-Men-Dong (Radix Ophiopogonis)</td>
<td>2 Ban-Xia (Tuber Pinellia)</td>
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<td>3 Ling-Zhi (Ganoderma)</td>
<td>3 Xi-Yang-Shen (Radix Panacis Quinquefolii)</td>
<td>3 Ying-Xing (GINGKO Bilboae)</td>
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<td>4 Ban-Xia (Tuber Pinellia)</td>
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<td>4 Ma-Huang (Herba Ephedrae)</td>
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<td>5 Unknown (Herba Tridacis procumbentis)</td>
<td>5 Unknown (Herba Tridacis procumbentis)</td>
<td>5 Kuan-Dong-Hua (Flos Tussilaginis Farfarae)</td>
<td>5 Shu-Di-Huang (Radix Rehmanniae Preparata)</td>
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<td>6 Sang-Bai-Pi (Cortex Mori Albae Radicis)</td>
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<td>7 Su-Zi (Fructus Perilla Frutescens)</td>
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<td>8 Xing-Ren (Semen Pruni Armeniacae)</td>
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<td>9 Huang-Qin (Radix Scutellariae Baicalensis)</td>
<td>9 Ze-Xie (Rhizoma Alismatis Orientalis)</td>
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<td>10 Shan-Yao (Radix Dioscoreae Oppositae)</td>
<td>10 Shan-Yao (Radix Dioscoreae Oppositae)</td>
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</table>

*a Randomized, placebo-controlled, double-blind, Clinical Trial

*b The only difference in these two formulas was the method of preparation.

c Gang-Cao (Radix Glycyrrhizae) is the only herb present in all four of the formulas.
Ku-Shen (Radix Sophorae Flavescentis) is present in both herbal remedies.

Ban-Xia (Tuber Pinellia) is used in three of the formulas.

Herba Tridacis procumbentis, which is not in the Materia Medica or Pharmacopeia, was thought to be found only on Taiwan; it has since been found in both North and South America.