

FEATURE ARTICLE

Effects and Mechanisms of Actions of Chinese Herbal Medicines for Asthma

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ABSTRACT Asthma is a chronic inflammatory disorder of airways that affects approximately 300 million adults and children worldwide. Most therapy currently uses bronchodilators and corticosteroids. Systemic side effects from chronic use of these drugs are concern. Chinese medicine (CM) has a long history of human use in China and other Asian countries and well received by the patients. But as one component of Western integrative medicine (WIM), it is required that CM use is supported by scientific evidence. On the other hand, there are also suggestions that Western standardized medicine should consider personalized practice. In recent years there have been an increasing studies to narrow the gap between CM, the personalized medicine and Western medicine, evidence based medicine. This communication reviews several CM studies published in the English language in details by reviewing

the effects and mechanisms of actions on asthma from clinic and experimental studies.

Chinese herbal medicines exhibit broad actions on multiple asthma pathologic mechanisms. These mechanisms may involve antiinflammatory and immunomodulatory effects, inhibiting airway remodeling and normalization of hypothalamus, pituitary and adrenal (HPA)-axis disturbances. However, the mechanisms of actions of Chinese herbal medicines for asthma are not fully understood. More controlled clinical studies are warranted and some anti-asthma CM may be proved to be effective when used as monotherapy or complementary asthma therapies.

KEYWORDS asthma, complementary and alternative medicine, Chinese medicine, Chinese herbal medicine, mechanism of action

Over the past 40 years, modern medicine has made considerable progress in curing and managing diseases, and prolonging life. Over this same time period, chronic and functional illnesses have become a greater problem than in the past. Although new surgical techniques and drugs have improved health, chronic diseases often cannot be treated satisfactorily by conventional therapy. Complementary and alternative medicine (CAM) has played an important role in treating chronic medical conditions such as bronchial asthma, rheumatic diseases, chronic inflammatory bowel disorders and chronic pain⁽¹⁾.

Asthma is a global health problem affecting approximately 300 million individuals of all ages, ethnic groups, and in all countries⁽²⁾, including 7.7% adults and 9.6% children in the United States⁽³⁾. There is no national asthma prevalence data in China. Some regional data showed prevalence asthma between 2000 and 2007 was about 1.05%–1.86% in adult and 0.74%–4.56% in children⁽⁴⁾. Asthma is a

chronic inflammatory disorder of the airways, leading to non-specific bronchial hyperresponsiveness and airflow obstruction. Management is primarily directed towards suppressing airway inflammation with inhaled corticosteroids and relieving bronchoconstriction with bronchodilators. This standard therapy controls symptoms in most but not all asthmatics^(5,6). Relapse after therapy withdrawal is common⁽⁷⁾, and adverse effects of steroids on growth of children, immunosuppression and hypothalamus, pituitary and adrenal (HPA)-axis disturbances, as well as mood

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changes are of some concern⁽⁸⁻¹⁰⁾. Anti-IgE therapy is beneficial for some asthmatics, however its effects are transient and cysteinyl leukotriene inhibitors have shown only limited efficacy^(11,12). Recently, safety concerns regarding both of these therapies have been raised^(13,14). Thus, a safe, effective and long-lasting therapy remains to be established.

Chinese medicine (CM) is a major component of CAM used in Western countries. CM has an independent system of theory, diagnosis and treatment⁽¹⁵⁾. It has a long history of human use in China and other Asian countries, and well received by the patients. Further research into CAM and integrative medicine has been suggested by American Academy of Allergy Asthma and Immunology, Complementary and Alternative Medicine Committee for Allergy Practice (2011 San Francisco annual meeting). The integrative medicine in China is a regular practice for over 50 years and play an important role in treating and preventing diseases including asthma⁽¹⁾. However there is a significant gap between CM practices based outcomes and scientific evidence based Western medicine. In recent years, a small, but increasing number of well-controlled clinical trials of some CM Anti-Asthma Simplified Herbal Medicine Intervention (ASHMI)⁽¹⁶⁾, Dingchuan Decoction (定喘汤, DCD)⁽¹⁷⁾, STA-1⁽¹⁸⁾, provide some evidence of clinical efficacy, including immunomodulatory effects^(16,18). There are also increases in laboratory studies focusing on actions and mechanisms of actions of anti-asthma herbal medicines using *in vitro* and *in vivo* models. This paper reviews English language publications on CM herbal medicines for asthma, evidence-based research into their efficacy and mechanisms underlying efficacy published between 2006 and 2011.

ASHMI

ASHMI, developed by Dr. Li and colleagues is an investigational new drug approved by U.S. Food and Drug Administration for asthma (ASHMI is composed of 3 herbs, Table 1). Previously Wen, et al⁽¹⁶⁾ reported the first double-blind, randomized, placebo-controlled trial (RCT) investigating the efficacy and tolerability of ASHMI compared with oral prednisone therapy in 91 patients with moderate-to-severe asthma. Treatment was administered daily over 4 weeks. This study found that post treatment, lung function [forced expiratory volume in one second (FEV₁)] and peak expiratory flow values (PEF) were

significantly improved in both groups, and clinical symptom scores, use of β 2-bronchodilators and serum IgE levels and Th2 cytokine levels were reduced in both groups. However, in contrast to prednisone, ASHMI significantly increased serum interferon- γ (IFN- γ) and cortisol levels. No significant side effects were observed. Kelly-Piper, et al⁽¹⁹⁾ conducted a double blind, placebo controlled, dose escalation safety trial (phase I) in 18 adult asthma individuals and showed that ASHMI is safe and well tolerated. All subject's laboratory test results were within the normal arrange. Patil, et al⁽²⁰⁾ showed ASHMI *in vitro* treatment of peripheral blood mononuclear cells (PBMCs) from patients with moderate to severe asthma for 72 h significant suppressed interleukin 5 (IL-5) production without affecting IFN- γ and cell viability, and increased IL-10 production to antigen stimulation compared to untreated PBMCs. This *in vitro* study provided direct evidence that ASHMI has immunomodulatory effects.

Zhang, et al⁽²¹⁾ investigated the pharmacological and immunological actions of ASHMI in a murine asthma model. In this study BALB/c mice were sensitized weekly intraperitoneally twice with ovalbumin (OVA) and alum followed by 3 weekly intratracheal challenges with OVA, then 2 consecutive daily challenges 4 weeks later. To determine whether ASHMI affected the progression of chronic asthma, ASHMI was administered intragastrically twice daily for 6 weeks. ASHMI abolished early-phase airway responses, which was associated with significantly reduced plasma and bronchoalveolar lavage fluid (BALF) histamine and leukotriene C4 (LTC4) levels, and decreased plasma OVA-specific IgE levels. It was also showed that late-phase airway responses were prevented, as showed by significantly reduced numbers of BALF eosinophils, decreased collagen content of lungs, fewer goblet cells in the airways, as well as reduced levels of the Th2 cytokines, IL-4, IL-5, IL-13 but increased IFN- γ , IL-10 and transforming growth factor β (TGF- β) levels in BALF. A direct effect of ASHMI on airway constriction was demonstrated by inhibition of acetylcholine induced constriction of murine tracheal rings *ex vivo*. This effect was not mediated by β 2-adrenergic receptor stimulation. ASHMI also increased production of prostaglandins I2 (PGI2), indicating that the potent smooth muscle relaxer PGI2 played a role in ASHMI-mediated airway relaxation.

Although asthma is typically characterized as a childhood onset disease, it also develops later in life, and older asthmatic patients may be at increased risk for corticosteroid adverse effects. Osteoporosis, increased fracture risk, muscle weakness, glucose intolerance, and easy bruising, are of particular concerns in older patients. Therefore, developing non-steroid interventions for late onset asthmatic patients is important. Busse, et al⁽²²⁾ subsequently investigated the effects of ASHMI on characteristics of allergic asthma in an aged mouse model of late onset asthma. In this study ASHMI treatment of young and aged OVA mice resulted in significantly decreased lung inflammation, airway mucous cell metaplasia, and messenger RNA copy numbers of the mucin gene MUC5AC, as well as reduced collagen production.

Srivastava, et al^(23,24) evaluated the persistence of ASHMI beneficial effects following discontinuation of therapy as compared to that of dexamethasone (Dex) in a murine model of chronic asthma and found that ASHMI completely resolved OVA challenge induced airway hyper-reactivity (AHR) and pulmonary eosinophilic inflammation that did not re-occur following OVA re-challenge at up to 8 weeks post-therapy. Decreased allergen-specific IgE and Th2 cytokine levels, and increased IFN- γ levels also persisted at least 8 weeks post-therapy. In contrast, Dex-treated mice that exhibited similarly reduced airway inflammation, Th2 cytokines and OVA-specific IgE levels immediately after 6 weeks therapy and were not protected at 8 weeks post-therapy. IFN- γ levels in BALF, and serum corticosterone levels were reduced by Dex treatment. To determine the contribution of IFN- γ to ASHMI effects, mice were given IFN- γ neutralizing antibody concomitantly with ASHMI. ASHMI effects were eliminated by neutralization of anti-IFN- γ antibody, but not anti-TGF- β antibody during therapy.

Taken together these studies showed that ASHMI was safe and well tolerated in clinical study. ASHMI also showed multiple beneficial effects in allergic asthma. Because ASHMI enhanced IFN- γ , and normalized cortisol levels in a clinical study, future clinical investigations should determine if ASHMI can restore/normal IFN- γ and cortisol levels when used in combination with corticosteroids. Identification of active compounds in ASHMI will enhance our understanding of the pharmacological mechanisms

of ASHMI and may lead to novel drugs for asthma therapy.

Xiaoqinglong Decoction (小青龙汤)

Xiaoqinglong Decoction, known as Sho-seiryu-to (SST) in Japan, is a traditional Chinese herbal formula developed from Shang Han Lun (伤寒论, Table 1). It has been used to treat asthma in Asian countries for centuries. Nagai, et al⁽²⁵⁾ previously investigated anti-allergic activity of SST on airway inflammation in a mouse model. BALB/c mice were sensitized and boosted with OVA and alum at day 0 and 5 days later. Seven days after sensitization, the mice were inhaled to provocation of OVA. SST was orally administered from day 1 to 6 days after OVA inhalation. SST reduced the IL-4 and IL-5 and increased the IFN- γ production by lung CD4⁺ T cells, reduced IL-4 levels in BALF and returned IFN- γ level to the control level. Nerve growth factor (NGF) increased in the BALF and lung cells of OVA-sensitized mice. This overexpression may be at the repair stage of airway inflammation. Oral administration of SST produced 200% higher NGF levels in the sensitized mice. SST may modulate the effect of NGF to enhance the processes of repair. Nagai, et al⁽²⁶⁾ further investigated antiinflammatory effects of SST compared with prednisolone. SST reduced the inflammation in lung tissue, AHR, the number of eosinophils and OVA-specific IgE in BALF. Spectrin, a α/β heterodimer, is a major components of the cortical cytoskeleton that lies beneath the plasma membrane. The expression of spectrin $\alpha 2$ was reduced in the lung tissue of OVA-sensitized mice and SST recovered the expression. Prednisolone in contrast did not reduce OVA-specific IgE antibody levels in BALF and did not restore the expression of spectrin $\alpha 2$ in lung tissue. Pinellac acid, one of the active ingredients in SST reduced BALF OVA-specific IgE antibody levels. The authors speculated the possibility that pinellac acid is related to the different mechanism between SST and prednisolone.

The results showed that SST possessed anti-inflammatory activity and modulated Th1/Th2 balance in the lungs, restored normal expression of spectrin $\alpha 2$, and augmented NGF expression in the lungs. These antiallergic effects of SST may be related to its pharmacological activities.

DCD

DCD, developed during the Ming Dynasty

is composed of 9 herbs (Table 1). Chan, et al⁽¹⁷⁾ conducted a RCT to assess clinical effects of DCD. This study enrolled children diagnosed with mild-to-moderate persistent asthma between 8 and 15 years of age. Patients were randomly allocated to receive DCD or placebo daily for 12 weeks. Both groups received conventional treatment including using inhaled fluticasone therapy during the 12 weeks. DCD reduced the severity of AHR and improved clinical and medication scores compared with placebo. There was no significant difference in serum total IgE, LTC₄, and histamine values between the two groups and after treatment. The authors concluded that the significant improvement of AHR suggested more stable airways were achieved by this add-on complementary therapy. The mechanisms of DCD effects on asthma should be further studied.

STA-1

Chang, et al⁽¹⁸⁾ reported results of a clinical evaluation of STA-1 herbal formulas (Table 1). STA-1 is composed of Maimendong Decoction (麦门冬汤, MMDD, 4 herbs) and Luiwei Dihuang Pill (六味地黄丸, LWDHP, 6 herbs) and was originally formulated by two Chinese physicians ZHANG Zhong-jing (Han Dynasty, 150–219 AD) and QIAN Yi (Song Dynasty, 1035–1117 AD), respectively. The total of 120 patients 5 to 20 years of age with mild-to-moderate asthma were investigated by conducting a RCT. Patients were treated with STA-1 twice daily for 6 months. The results showed a significant reduction of symptom scores, systemic steroid dose, and serum total IgE and dermatophagoides pteronyssinus (Dp)-specific IgE levels in the STA-1 group. Furthermore, STA-1 improved percentage of FEV₁ predicted (FEV₁%) compared with the placebo group. The influx of eosinophils and neutrophils in BALF and Dp-induced AHR were reduced by SST treatment in a murine model⁽²⁷⁾. The result also revealed the 6 herbs in STA-1 when ground into a powder had a greater anti-inflammatory effect than when extracted in boiling water.

San'ao Decoction (三拗汤)

San'ao Decoction (SA), a classical Chinese prescription (Table 1) has been used to treat asthma and cough for thousands of years. Li, et al⁽²⁸⁾ investigated the effects of SA on normal human bronchial epithelium (NHBE) IL-4 induced apoptosis. Fluorescence microscopy and flow cytometry showed

that IL-4-induced NHBE apoptosis was decreased by SA. Reverse transcription-polymerase chain reaction showed little or no expression of eotaxin-3 mRNA by unstimulated NHBE, and that IL-4 induced eotaxin-3 mRNA expression was decreased by SA. Bronchial epithelium plays an important role in the pathogenesis of asthma, through defects in its structure and responses to environment insults (e.g. respiratory viruses, air pollution episodes and exposure to allergens). Specifically, a defect in barrier function and an impaired innate immune response to viral infection may provide the substrate upon which allergic sensitization takes place. Once sensitized, repeated allergen exposure leads to disease persistence. Holgate, et al⁽²⁹⁾ raised the possibility of developing treatments that increase the lung's resistance to the inhaled environment rather than concentrating all efforts on trying to suppress inflammation once it has become established. Li, et al, for the first time, elucidated an important action of Chinese herbal medicine in protecting cytokine damage to NHBE. This finding may lead to development of new therapeutic targets for asthma prevention and treatment.

Shenmai Injection (参麦注射液)

Shenmai Injection (SMI) is composed of *Radix Ginseng Rubra* and *Radix Ophiopogonis* (Table 1). Zhao, et al⁽³⁰⁾ investigated the effect of SMI on human airway smooth muscle cells (HASMCS). Normal human airways were obtained from patients undergoing partial pulmonary resection for carcinomas. The dissociated cells were cultured in medium containing serum from asthma patients. The passively sensitized HASMCs were then incubated with SMI. Expression of proliferating cell nucleus antigen (PCNA) and phosphorylation-extracellular signal regulated kinase1/2 (p-ERK1/2) in HASMCs significantly increased after passive sensitization. SMI significantly decreased both in a dose dependent manner. HASMCs proliferation is an important component of airway remodeling. SMI inhibition of the proliferation of airway smooth muscle cells through lowering the phosphorylation of ERK may be related to action mechanisms of SMI in treating asthma.

Andrographolide

Andrographolide (AP) is one active component in the medicinal plant *Andrographis paniculata*, known as Chuan-xin-lian in China. AP is widely used for treating infections, inflammation, the common cold,

Table 1. Summary of Chinese Herbal Medicine for Asthma (Formula)

Item	ASHMI	Xiaoqinglong Decoction	Dingchuan Decoction	STA-1	Sanlao Decoction	Shenmai Injection
Herbal components	1. <i>Ganoderma lucidum</i> 2. <i>Radix Sophora flavescens</i> 3. <i>Radix Glycyrrhiza uralensis</i>	1. <i>Herba ephedrae</i> 2. <i>Tuber Pinelliae</i> 3. <i>Radix Paeonia lactiflora</i> 4. <i>Zingiber officinale</i> 5. <i>Asiasarum sieboldii</i> 6. <i>Cinnamomum cassia</i> 7. <i>Schisandra chinensis</i> 8. <i>Radix Glycyrrhiza uralensis</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 armeniacae</i> 9. <i>Radix scutellariae baicalensis</i>	1. <i>Radix Rehmanniae</i> <i>Preparata</i> 2. <i>Cortex Moutan Radicis</i> 3. <i>Radix Ophiopogonis</i> 4. <i>Tuber Pinellia</i> 5. <i>Fructus Corni</i> 6. <i>Portia</i> 7. <i>Radix Panacis Quinquefolii</i> 8. <i>Rhizoma Alismatis</i> 9. <i>Radix Dioscoreae</i> 10. <i>Radix Glycyrrhizae</i> RCT	1. <i>Herba ephedrae</i> 2. <i>Gingko bilboae</i> 3. <i>Radix Glycyrrhiza uralensis</i>	1. <i>Radix Ginseng Rubra</i> 2. <i>Radix Ophiopogonis</i>
Clinical study	RCT	N/A	RCT	RCT	N/A	N/A
Animal model	mice	mice	N/A	mice	N/A	N/A
In vitro study	HASMCs PBMCs	N/A	N/A	N/A	NHBE	HASMCs
Outcome measures	RCT study lung function (FEV ₁ , PEF) symptom scores β 2-agonist use serum total IgE, cortisol serum IL-5, IL-13, IFN- γ Animal model: BALF histamine, LTC4, IL-4, IL-5, IL-13, IFN- γ , IL-10, TGF- β serum OVA-IgE, IgG2a, IgG1 cell counts in BALF, lung histology AHR In vitro study: PGI2, PGE2, PGD2, PGF2 α , TxA2 in HASMCs culture IL-5, IL-10, IFN- γ in PBMCs culture	IL-4, IL-5, IFN- γ in lung CD4 ⁺ T cells culture BALF IL-4, IFN- γ cell counts in BALF lung histology spectrin α 2 OVA-IgE NGF	AHR symptom scores medication scores lung function (PEF, FEV ₁ , FVC) serum total IgE serum LTC4, histamine	RCT symptom scores systemic steroid dose lung function (FEV ₁ %) serum total IgE serum Dp-specific IgE Animal model: serum Dp-specific IgE cell counts in BALF AHR	NHBE apoptosis mRNA Eotaxin-3	PCNA p-ERK1/2
Publications	Ref (16,19-24)	Ref (25,26)	Ref (17)	Ref (18,27)	Ref (28)	Ref (30)

Notes: TxA2: thromboxane A2; FVC: forced vital capacity

fever etc⁽³¹⁾. Asthma is an inflammatory lung disorders. Persistent activation of nuclear factor (NF)- κ B is associated with asthma, especially in uncontrolled, severe and moderate asthmatics^(32,33). Bao, et al⁽³⁴⁾ investigated the antiinflammatory effect of AP via inhibiting the NF- κ B activity at the level of inhibitory κ B kinase- β activation. BALB/c mice were sensitized with OVA and alum on days 0 and 14. On days 18, 19, and 20, animals were challenged with OVA aerosol. AP was given by intraperitoneally injections 1 h before and 11 h after each OVA aerosol challenge. AP dose-dependently inhibited OVA-induced increases in BALF total cell count, eosinophil count, and IL-4, IL-5, and IL-13 levels, and reduced serum OVA-specific IgE levels. AP also increased IFN- γ levels in BALF and thoracic lymph node cells cultures. AP attenuated OVA-induced lung tissue eosinophilia and airway mucus production, mRNA expression of E-selectin, chitinases, Muc5ac, and inducible nitric oxide synthase (iNOS) in lung tissues, and AHR to methacholine. In normal human bronchial epithelial cells, AP blocked TNF- α -induced phosphorylation of inhibitory κ B kinase- β , and downstream inhibitory κ B α degradation, p65 subunit of NF- κ B phosphorylation, and p65 nuclear translocation and DNA-binding activity. Furthermore, AP noticeably blocked TNF- α -induced upregulation of IL-6, IL-8 and RANTES mRNA expression. Similarly, AP blocked p65 nuclear translocation and DNA-binding activity in nuclear extracts from lung tissues of OVA-challenged mice. AP inhibition of NF- κ B expression, allergen-induced airway inflammation and AHR was further confirmed by Li, et al⁽³⁵⁾. AP significantly inhibited lipopolysaccharide induced TNF- α and GM-CSF release and expression of mRNA from mouse peritoneal macrophages in a concentration-dependent manner *in vitro*. *In vivo* study, AP significantly inhibited the elevation of BALF levels of TNF- α and GM-CSF and almost completely abolished the accumulation of lymphocytes and eosinophils in BALF of OVA-induced allergic mice⁽³⁶⁾ (Table 2).

Astragalus Membranaceus

Astragalus membranaceus (AM) is an important Chinese herb for supplementing qi in CM. Wang, et al⁽³⁷⁾ explored the effect of AM on Th1 specific transcription factor T-box expressed in T cells (T-bet) expression and Th1/Th2 equilibrium. PBMCs were isolated from patients with moderate to severe asthma and then incubated with AM. The result of RT-PCR

showed that AM could raise the expression of T-bet mRNA. The level of IFN- γ in the supernatants was increased while IL-4 level was decreased after AM intervention. AM also decreased the mean percentage of CD4⁺CCR3⁺ cells and elevated the mean percentage of CD4⁺CCR5⁺ cells, counted by flow cytometry (Table 2).

Shen, et al⁽³⁸⁾ investigated effects of AM injection on the airway lesions as compared to Dex. AM administration significantly decreased inflammatory infiltration and mucus secretion in the lung tissues of allergic mice, and IL-5, IL-13 levels in BALF. AM enhanced OVA induced decreased IFN- γ in BALF. AHR was suppressed significantly in both groups of Dex and AM in allergic mice. But the suppression was greater in the AM group.

Du, et al⁽³⁹⁾ investigated the inhibitory effects of astragaloside IV in a murine model of chronic asthma. Astragaloside IV is primary pure saponin isolated from the root of AM. BALB/c mice sensitized to OVA were chronically challenged with aerosolized OVA for 8 weeks. Astragaloside IV was orally administered during each OVA challenge. Astragaloside IV treatment resulted in significant reduction of eosinophilic airway inflammation, antigen-induced mucus production, AHR, IL-4 and IL-13 levels in BALF, and serum total IgE levels. Furthermore, astragaloside IV inhibited peribronchial fibrosis, reduced peribronchial α -smooth muscle actin (α -SMA) and TGF- β 1 immunostaining.

Ligustrazine

Ligustrazine is an alkaloid isolated from the rhizome of Chuanxiong (*Ligusticum chuanxiong* Hort). Xiong, et al⁽⁴⁰⁾ explored the effect and mechanism of ligustrazine on Th1/Th2 cytokines in a rat asthma model. SD rats were sensitized and challenged with OVA to establish an asthmatic model. The sensitized rat received ligustrazine hydrochloride injection intraperitoneally 30 min before OVA challenge for 14 successive days. The results showed Ligustrazine injection could significantly lower the level of IL-4 in BALF and the expression of GATA-3 protein in lung, and also increase the level of IFN- γ in BALF and expression of T-bet protein in rat asthmatic lungs, while Dex reduced both levels of IL-4 and IFN- γ in BALF, suppressed both GATA-3 and T-bet protein expressions. Furthermore, ligustrazine administration

Table 2. Summary of Chinese Herbal Medicine for Asthma (Single Herbs)

Item	AP	AM	Ligustrazine
Herbal component	AP	AM	Ligustrazine
Clinical study	N/A	N/A	Clinical study
Animal model	mice	mice	rat
<i>In vitro</i> study	normal human bronchial epithelial cells, mouse peritoneal macrophages	PBMCs	N/A
Outcome measures	Animal model: cell counts in BALF BALF IL-4, IL-5, IL-13, IFN- γ BALF eotaxin, TNF- α , GM-CSF mRNA E-selectin, chitinases, Muc5ac, iNOS serum OVA-IgE, IgG2a, IgG1 lung histology, AHR IL-4, IL-5, IFN- γ in thoracic lymph node cells culture nuclear p65, p65 DNA binding activity <i>In vitro</i> study: TNF- α , GM-CSF in mouse peritoneal macrophages culture mRNA TNF- α , GM-CSF I κ B kinase- β , I κ B α , nuclear p65, p65 DNA binding activity mRNA IL-6/IL-8/RANTES in normal human bronchial epithelial cells	Animal model: BALF IL-4, IL-13, IFN- γ serum total IgE, AHR, α -SMA, TGF- β 1 in lung lung histology <i>In vitro</i> study: mRNA T-bet IL-4, IFN- γ in PBMCs culture CD4 ⁺ CCR3 ⁺ cells CD4 ⁺ CCR5 ⁺ cells	Clinical study: lung function (FEV ₁ , FEV ₁ %, PEF) symptom scores β 2-agonist use serum IL-4, IFN- γ Animal model: mRNA GATA-3, T-bet BALF IL-4, IFN- γ cell counts in BALF lung histology
Publications	Ref (31,34-36)	Ref (37-39)	Ref (40,41)

Notes: RANTES: regulated on activation normal T cell expressed and secreted

resulted in a decreased the number total cells, percentage of eosinophils and neutrophil in BALF and ameliorated airway inflammatory cell infiltration. The authors speculated that modulating the expressions of GATA-3 and T-bet might be the mechanism of ligustrazine on Th1/Th2 cytokines (Table 2).

Che, et al⁽⁴¹⁾ evaluated the effect of ligustrazine injection administered by inhalation on serum levels of IL-4 and IFN- γ in patients with mild to moderate asthma. Ligustrazine injection was given by ultrasonic spray inhalation twice a day for 2 weeks. After treatment, scores on clinical condition, frequency of attacks, use of β 2-bronchodilators and serum level of IL-4 and ratio of IL-4/IFN- γ were reduced. Lung function, including FEV₁, FEV₁% and PEF was elevated after treatment. No significant difference was revealed when IFN- γ levels were compared before and after treatment.

Conclusion

In conclusion, Chinese herbal medicines exhibit broad actions on multiple asthma pathologic mechanisms. These mechanisms include anti-inflammatory and immunomodulatory effects,

inhibiting airway remodeling and restoration of HPA-axis disturbances, which is different from that of corticosteroids. These actions of Chinese herbal medicines may be of benefit for treating corticosteroid-resistant asthma. More controlled clinical studies are warranted, and some of the anti-asthma CM may be proved to be effective for asthma therapy when used as monotherapy or complementary therapy.

Authors' Disclosure

Dr. LI Xiu-min, shares a patent for the use of ASHMI (PCT/US05/08600 for ASHMI) and has shares in Herbal Spring LLC. The other authors have no financial interests to disclose.

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