

Review

Immune Homeostasis: Effects of Chinese Herbal Formulae and Herb-Derived Compounds on Allergic Asthma in Different Experimental Models*

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ABSTRACT Allergic asthma is thought to arise from an imbalance of immune regulation, which is characterized by the production of large quantities of IgE antibodies by B cells and a decrease of the interferon- γ /Interleukin-4 (Th1/Th2) ratio. Certain immunomodulatory components and Chinese herbal formulae have been used in traditional herbal medicine for thousands of years. However, there are few studies performing evidence-based Chinese medicine (CM) research on the mechanisms and efficacy of these drugs in allergic asthma. This review aims to explore the roles of Chinese herbal formulae and herb-derived compounds in experimental research models of allergic asthma. We screened published modern CM research results on the experimental effects of Chinese herbal formulae and herb-derived bioactive compounds for allergic asthma and their possible underlying mechanisms in English language articles from the PubMed and the Google Scholar databases with the keywords allergic asthma, experimental model and Chinese herbal medicine. We found 22 Chinese herb species and 31 herb-derived anti-asthmatic compounds as well as 12 Chinese herbal formulae which showed a reduction of airway hyperresponsiveness, allergen-specific immunoglobulin E, inflammatory cell infiltration and a regulation of Th1 and Th2 cytokines *in vivo*, *in vitro* and *ex vivo*, respectively. Chinese herbal formulae and herb-derived bioactive compounds exhibit immunomodulatory, anti-inflammatory and anti-asthma activities in different experimental models and their various mechanisms of action are being investigated in modern CM research with genomics, proteomics and metabolomics technologies, which will lead to a new era in the development of new drug discovery for allergic asthma in CM.

KEYWORDS immune homeostasis, Chinese herbal medicine, allergic asthma, experimental model, database

Chinese medicine (CM) originates from some 2000 years ago. The book *Shen-ntonz's Classic of Materia Medica* (Shen Nong Ben Cao Jing) is one of the earliest records of herbal therapy. However, it was not until the 1800s that pure compounds were isolated from herbs, paving and accelerating the way for drug development and modern pharmaceuticals.⁽¹⁾ In 1887, ephedrine was extracted from the Chinese herb *Ephedra sinica*, which became popular among American physicians for its bronchodilating and decongestant properties in 1924.⁽²⁾ Since then countless examples have been shown about the rich potential of traditional herbal medicine including Chinese herbal medicine therapies of allergic asthma.^(3,4)

Allergy affects more than 25% of the population and, even there are many developed diagnoses and therapies, still often progresses to severe and disabling manifestations such as chronic allergic asthma.^(5,6) Now it is necessary to develop novel

therapies which target allergic asthma from various aspects with the multidisciplinary. CM has been used in Asia for centuries for treatment of allergic disease and is now attracting interest in Western countries as a source of alternative or complementary therapies

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due to its reputed effectiveness, low cost and relative absence of side effects.⁽⁷⁾

Asthma is a common chronic respiratory system disease characterized by bronchospasm edema, airway inflammation, airway hyperresponsiveness (AHR) and airway remodeling.⁽⁸⁾ The allergic immune responses underlying asthma are a loss of the Th1/Th2 equilibrium, increasing production of IgE antibodies by B cells, eosinophilic inflammation, and enhanced airway smooth muscle (ASM) contractility. The loss of such equilibrium has been hypothesized to underlie asthma through a change in immune responses from a Th1 interferon- γ (IFN- γ) pattern towards a Th2 [interleukin-4 (IL-4), IL-5 and IL-13] profile.⁽⁹⁾ In CM, many herbs and herbal formulae are used in the treatment of allergic asthma.^(3,4) But there are only a few evidence-based clinical trials for the treatment of allergic asthma, which could be listed by Li, et al⁽⁴⁾ recently. Thus, it is rational to explore these medicinal herbs as a novel source of immunomodulation. In this article, we aim to review herb-derived immunomodulatory in different experimental models and discuss potential future herbal therapies.

We screened published modern CM research results on the experimental effects of Chinese herbal formulae and herb-derived bioactive compounds for allergic asthma and their possible underlying mechanisms in English language articles from the PubMed and the Google Scholar databases with the keywords allergic asthma, experimental model and Chinese herbal medicine. Totally 561 English articles were found in January 2016. Results of the literature search about experimental studies were screened by reading title, abstract and keywords. Finally, 142 original research articles related to experimental models *in vivo* and *in vitro* on allergic asthma were extracted. For the purpose of researching Chinese herbal formulae and herb-derived compounds related to allergic asthma, we excluded studies with a background of Indian (Ayurveda), Japanese (Kampo) and Korean complementary and alternative medicine theory.

We found 22 CM herb species and 31 herb-derived anti-asthmatic compounds as well as 12 Chinese herbal formulae which showed a reduction of AHR, allergen-specific IgE, inflammatory cell infiltration and a regulation of Th1 and Th2 cytokines *in vivo*, *in vitro* and *ex vivo*, respectively. We screened and listed

the anti-asthmatic herbal compounds and Chinese herbal formulae in the order of research frequency.

Compounds with Immunomodulatory Effects from CM

Herbal medicines are complicated chemical cocktails with therapeutic properties that modern pharmaceuticals cannot reproduce. It is obvious that herbal medicines have the potential to be a rich source of immunomodulation. A wide range of herbs that contain compounds with anti-asthmatic effects are shown in Appendix 1.⁽¹⁰⁻⁴³⁾ Generally, it is more difficult to identify, isolate and explore the underlying mechanisms of the active compounds from complex herbal products. In this review, we focused on the immunomodulatory effects and mechanisms of action of some pure compounds isolated from herbal medicines.

Astragalus membranaceus

Astragalus membranaceus has been used widely in Asia for several hundreds of years for treating asthma with potent immunoregulatory⁽¹⁰⁾ and anti-inflammatory effects.⁽¹¹⁾ Several classes of compounds comprise the pharmacological active constituents of *A. membranaceus* including astragalus saponins, flavonoids, isoflavonoids, polysaccharides, sterols, amino acids and volatile oils. The astragalus saponin, especially astragaloside IV is the major chemical constituent demonstrating biological activity on asthma. Astragaloside IV reduces eosinophilic airway inflammation, AHR and airway remodeling, including subepithelial fibrosis, smooth muscle hypertrophy, collagen deposition, goblet cell hyperplasia and mucus production through the sequential downregulation of total IgE, eosinophilia, IL-4, IL-13, transforming growth factor- β 1 (TGF- β 1) and upregulation of IFN- γ , IL-10, CD4⁺CD25⁺Foxp3⁺ regulatory T cells and Foxp3 mRNA expression.⁽¹²⁻¹⁴⁾ The authors did not show that *A. membranaceus* produced adverse side effects.

Peucedanum praeruptorum Dunn

Coumarins are the main active components in *Peucedanum praeruptorum* Dunn (PPD) and are responsible for its efficacy. Kong LY's and his team demonstrated that coumarins from PPD (CPPD) had potent anti-inflammatory activity in an asthmatic model of ovalbumin (OVA)-challenged mice.⁽¹⁵⁾ The suppressive effects of CPPD on airway inflammation in mice were shown by a marked decrease of AHR and recruitment of inflammatory cells into

bronchoalveolar lavage fluids (BALF) and lung tissue, as well as of the levels of IL-4, IL-5 and IL-13 in BALF, eosinophil peroxidase in lung and allergen-specific IgE in serum, and by a marked increase in the levels of IL-10 and IFN- γ in BALF, and in the ratio of CD4⁺CD25⁺Foxp3⁺ regulatory T cells among CD4⁺ T cells in the spleen. In addition, PPD contains various angular-type pyranocoumarins, such as ($\pm$)-praeruptorin A (PA) and ($\pm$)-praeruptorin B. PA is a pair of coumarin enantiomers isolated from PPD. This research team also reported that PA suppressed airway inflammation, AHR and remodeling, reduced the levels of IL-4, IL-5, IL-13, leukotriene C4 and IgE by inhibiting TGF- β 1/Smad signaling pathway⁽¹⁶⁾ and nuclear factor κ B (NF- κ B) signaling pathway⁽¹⁷⁾ in a murine model of allergic asthma. No observable side effects were attributable to CPPD and PA, and the active ingredients in PPD. The median lethal dose (LD₅₀) of CPPD and PA in mice is over 5.0 and 3.0 g/kg by acute toxicity testing, respectively.

Tripterygium wilfordii

Tripterygium wilfordii has been used to treat autoimmune inflammatory diseases, such as asthma, rheumatoid arthritis, systemic lupus erythematosus and nephritis. Triptolide, the main diterpenoid triepoxide, is a biologically active compound purified from *T. wilfordii*. The immunosuppressive and anti-inflammatory effects of triptolide in OVA-induced asthmatic mice were shown by inhibition of eosinophil infiltration in BALF, airway mucus overproduction, AHR,⁽¹⁸⁾ and by reduction of IL-5, eotaxin in peripheral blood, inflammatory cells expressing eotaxin in lung, and eosinophilopoiesis of the bone marrow, which is associated with a decrease of IL-5 produced by T cells.⁽¹⁹⁾ Furthermore, triptolide also exerts immunomodulatory effect on accessory cells, particularly the professional antigen-presenting cells, such as dendritic cells and macrophages. Recent study has shown that triptolide regulates expression of the IL-12/IL-23p40 gene in mouse peritoneal macrophage (MPM) and human monocyte-derived dendritic cells (MoDCs) stimulated by lipopolysaccharide (LPS). At the transcriptional level, triptolide targets CCAAT/enhancer-binding protein- α (C/EBP α). Further, activation of C/EBP α by triptolide is dependent on upstream kinases extracellular signal-regulated kinases 1 and 2 (ERK1/2) and Akt-glycogen synthase kinase-3 β (GSK3 β).⁽²⁰⁾ This study has uncovered several novel targets of triptolide: C/EBP α ,

ERK1/2, GSK3 β , mitogen-activated protein kinase phosphatase 1 and tumour-suppressor phosphatase with tensin homology. Side effects of triptolide included hematologic abnormalities, gastrointestinal intolerance, infection and infertility.

Chinese Herbal Formulae with Immunomodulatory Effects

The personalized Chinese herbal formulae match the physiologic and psychologic needs of physicians and patients. There are often synergistic interactions when numerous plants or herbs are present in one complex mixture and used together in a multi-compound preparation of Chinese herbal products, to maximize its efficacy and minimize its adverse effects or toxicity.⁽⁴⁴⁾ Chinese herbal formulae modulate several drug targets simultaneously; therefore, it is conceivable to evaluate the chemical mixture in a standard set of *in vivo*, *ex vivo* and *in vitro* asthmatic models.⁽⁴⁵⁾ A summary of Chinese herbal formulae that has been demonstrated to have therapeutic benefit in the treatment of allergic asthma is shown in Appendix 2.⁽⁴⁶⁻⁷²⁾

Xiaoqinglong Decoction

Xiaoqinglong Decoction (小青龙汤, XQL) is used to treat allergic asthma clinically. It contains the extracts of 8 herbs, *Pinelliae ternata*, *Ephedrae sinica*, *Schizandrae chinensis*, *Cinnamomi ramulus*, *Paeoniae lactiflorae*, *Asarum sieboldii*, *Glycyrrhizae uralensis* and *Zingiber officinale*. The immunomodulatory effects of XQL were investigated in a repetitive *Dermatogoides pteronyssinus* (Der p)-challenged chronic asthmatic mice model. Oral administration of XQL (1 g/kg) at one week intervals could reduce bronchial inflammation and airway remodeling.⁽⁴⁶⁾ In addition, the Der p-induced total IgE, Der p-specific IgG1 in serum, IL-10, IL-13, RANTES, eotaxin, monocyte chemoattractant protein-1 mRNA expression in the lung and NF- κ B expression in the nucleus of bronchial epithelial cells were significantly reduced by XQL. LD₅₀ of XQL was estimated to be greater than 8 g/kg with oral single dose toxicity on Sprague-Dawley rats.

Antiasthma Simplified Herbal Medicine Intervention

Antiasthma Simplified Herbal Medicine Intervention (ASHMI), a Chinese herbal formula, was reported to be efficacious in asthmatic patients and murine asthma models by Li XM' team.^(25,49,52,53) It is an aqueous extract of 3 herbs including *Ganoderma lucidum*, *Sophora flavescens* and *Glycyrrhiza*

uralensis. In initial study, they investigated the therapeutic effects and underlying mechanisms of formula MSSM-002, the precursor of ASHMI. *In vivo*, MSSM-002 eliminated AHR, reduced eosinophils in BALF, suppressed inflammation and mucus production by decreasing antigen-specific IgE, IL-4, IL-5, and IL-13 levels without suppressing IgG2a and IFN- γ synthesis in a conalbumin-sensitized and challenged asthmatic mice model.⁽⁴⁷⁾ *In vitro*, MSSM-002 decreased antigen-induced proliferation and IL-4 and IL-5 production, increased IFN- γ production in Th2 polarized splenocytes (Th2-SPCs), suppressed Th2 cytokine secretion, the Th2 specific transcription factor GATA binding protein 3 (GATA-3) mRNA and protein expression and the binding to IL-4 gene promoter and V_A enhancer in TH2 cloned cells, D10 G4.1 (D10) cells.⁽⁴⁸⁾

In 2010, Li XM and her colleagues reported that ASHMI significantly inhibited AHR, pulmonary eosinophilic inflammation, and airway remodeling in OVA-sensitized mice through reducing levels of OVA-specific IgE, Th2 cytokines IL-4, IL-5, IL-13 and increasing IFN- γ secretion.⁽⁴⁹⁻⁵¹⁾ Further work showed that ASHMI inhibits AHR in OVA-sensitized mice and blocks acetylcholine (Ach)-induced tracheal ring constriction via the EP2/EP4 receptor pathway.⁽⁵²⁾ Recently, in a neutrophil-predominant murine model of ragweed asthma, they found ASHMI reduces AHR, mucous production, neutrophilic inflammation, TNF- α , IL-8 and IL-17 levels, and decreases eosinophilic inflammation and Th2 responses.⁽⁵⁴⁾ The authors noted that ASHMI was as effective as oral prednisone without significant side effects.

San'ao Decoction

San'ao Decoction (三拗汤, SA) contains 3 herbs including *Ephedrae sinica*, *Armeniacae communis* and *Glycyrrhiza uralensis*. The immunomodulatory effects of SA were researched in a Der p-induced asthmatic guinea pig model⁽⁵⁵⁾ and in an OVA-sensitized, OVA and LPS-challenged asthmatic mice model.⁽⁵⁷⁾ These studies suggested that SA suppressed the neutrophil infiltration, inhibited the AHR and reduced airway inflammation. Furthermore, SA promoted Th1-type cytokines (IFN- γ) and reduced Th2-type cytokines (IL-4 and IL-5), which led to a Th1/Th2 balance.⁽⁵⁷⁾ The authors did not show that SA had any side effect, but *Ephedrae sinica* could produce adverse effects including exacerbation of hypertension, cardiac arrhythmias, strokes and myocardial infarction.

Role of Herb-Derived Compounds and Chinese Herbal Formulae on Allergic Asthma

Down-regulation of AHR

One of the main characteristics of the allergic asthma is AHR. The definition of AHR is an enhanced sensitivity of airways to bronchoconstrictors.⁽⁷³⁾ AHR can be caused by stimulating ASM contraction by a variety of molecules such as histamine, leukotrienes⁽⁷⁴⁾ which release from IgE-activated mast cells in lung tissue. The main method of evaluating AHR in models of allergic asthma is assessment of airway physiologic parameters through tracheal cannulae combined with whole body plethysmography in conscious and unrestrained animals.⁽⁷⁵⁾ Whole body plethysmography has become popular for assessing lung mechanics mainly owing to its noninvasive approach and ease of use. There are mainly 4 parameters involving enhanced paused (Penh), lung resistance (RL), dynamic compliance (Cdyn) for noninvasive approach and airway pressure time index for invasive approach.

Down-regulation of Allergen-Specific IgE

Allergic asthma is typified by elevated serum IgE levels and inflammation of the airways with high levels of IL-4 and IL-5 in BALF and airways mucosa.⁽⁷⁶⁾ Naive T cells stimulated with allergen in the presence of IL-4 tend to develop into CD4⁺T cells. IL-4 and IL-13, generated by CD4⁺ Th2 effector cells, are essential for Th2 cell differentiation, and are reported to contribute to isotype switching in B cells, from IgG to IgE synthesis.⁽⁷⁷⁾ Early phase airway reaction is triggered by the release of histamine and leukotrienes from IgE-activated mast cells. IgE mediates the allergic response in humans and rodent models of allergic asthma through triggering degranulation of mast cell/basophil and synthesis of leukotrienes after allergen exposure through binding to high-affinity Fc receptors for IgE on mast cells in the bronchial mucosa.⁽⁷⁸⁾ Furthermore, elevated serum IgE levels and eosinophilia are associated with the incidence or severity of asthma.⁽⁷⁹⁾ IgE is a crucial target in anti-asthma strategies and clinical trials, and neutralization of IgE involving diminishing IgE synthesis or inhibiting its action, bring satisfactory effects for asthma patients.⁽⁸⁰⁾

Down-regulation of Inflammatory Cell Infiltration-Eosinophils

The infiltration of inflammatory cells (eosinophils, mast cells and lymphocytes), especially those of eosinophils, is a characteristic of the inflammatory

process of allergic asthma, the severity of which is directly related to the degree of eosinophils.⁽⁸¹⁾ Elevated eosinophil levels are observed in the bone marrow, lung tissues, blood and BALF in these allergen-challenged experimental models. Eosinophils affect the structural changes that occur in the airway of asthma patients, including goblet cell hyperplasia, enlarged submucosal mucus glands and ASM hypertrophy. Of Th2 cytokines, IL-5 is responsible for eosinophil growth, differentiation, migration, recruitment, activation, and survival.⁽⁸²⁾ Eosinophils are mainly derived from the myeloid precursors (CD34⁺ progenitor cells) in bone marrow. There is increasing evidence to suggest that the CD34⁺ progenitor cells expressing IL-5 receptor alpha chain (IL-5R α) may be the eosinophil progenitor cells.⁽⁸³⁾ IL-5R α could not be detected in the lung tissues of the allergen-challenged mice, but from bone marrow.⁽⁸⁴⁾ The migration of eosinophils into lung tissue is a hallmark of allergic asthma. The selective migration of eosinophils from the blood to lung tissues is obtained via specific eosinophil chemoattractants, including eotaxin (CCL11).⁽⁸⁵⁾ CC chemokine receptor 3 (CCR3) is the main chemokine receptor on eosinophils and is an exclusive receptor for eotaxin. Increasing CCR3 expression has been observed in lung and related to the pathogenesis of allergic asthma. The blockade of CCR3 has been shown to result in a reduction of eosinophilic infiltration in animal models of allergic asthma.⁽⁸⁶⁾ Activated eosinophils are also a prominent feature of allergic asthma, which are believed to contribute to the airways damage through releasing a variety of mediators and pro-inflammatory cytokines, including IL-3, IL-4, IL-5, IL-6, TNF- α and granulocyte-macrophage colony-stimulating factor. These mediators and pro-inflammatory cytokines are known to be linked to delayed apoptosis of eosinophils, leading to the accumulation of eosinophils in lung.⁽⁸⁷⁾

Regulation of Th2 and Th1 Cytokines

Allergic asthma is closely related to the imbalance of Th1/Th2 cells and their distinct cytokine profiles. The allergen-induced Th2 response plays an essential role in the mechanism of allergic airway inflammation. The accumulation of Th2 cells in peribronchial and perivascular lung tissues causes inflammatory lesions via the secretion of Th2 cytokines,⁽⁸⁸⁾ such as IL-4, IL-5 and IL-13. In contrast to Th2 cells, Th1 cells play an opposite role. Th1 cytokines, such as IFN- γ and IL-12, are involved in the mediation of cellular immune reaction and antagonism of Th2 immune. Under normal

states, Th1/Th2 cells keep a relative balance via the manner of antagonizing and feedback promotion, with a well-ordered cytokine network.⁽⁸⁹⁾ Th1/Th2 cells imbalance is believed to be the main immunological cause of allergic asthma with up-regulation of Th2 cells in immune response.⁽⁹⁰⁾ Therefore, one of effective therapies for allergic asthma is to stimulate Th1 cells and simultaneously inhibit Th2 immune responses to reverse the ratio of Th1/Th2.

Th2 cytokines play a critical role in the pathogenesis of allergic airway inflammation.⁽⁹¹⁾ Th2 cytokines mediate humoral immune responses and IgE production and recruit eosinophils to airways, thus further inducing the release of histamine and leukotriene. Th1 cells down-regulate Th2-predominant immune responses by secreting interferon IFN- γ . Herbal compounds and Chinese herbal formulae regulate Th1/Th2 cells imbalance by inhibition of Th2 cytokines and elevation of Th1 cytokines. Besides Th1/Th2 imbalance for allergic asthma, the imbalance of Treg/Th2/Th17 in allergic individuals has been researched. Treg and Th17 cells differentiation are cross-regulated. Treg cells are involved in the regulation of Th2-mediated allergic responses through expression of Foxp3, which have an anti-inflammatory role and maintain immune tolerance. On the other hand, Th17 cells, as a pro-inflammatory T cell lineage, could produce IL-17A and recruit neutrophils.⁽⁹²⁾

Future Prospects of CM in Immune Regulation

Herbal formulae are complex mixtures of different herbs which contain a large number of active compounds. Thus, the standardization of herbal formula is full of challenges. Unlike ancient herbal therapy that is based on practice without laboratory research, modern drug development requires chemical, manufacturing and control data in 3 phases (raw herbs, extracts and final products) to ensure quality, efficacy and consistency of the herbal drugs.⁽⁹³⁾

For quality control, standard materials are selected to represent the herbal medicines in herbal formulae and are analyzed by high-performance liquid chromatography (HPLC) fingerprints.⁽⁹⁴⁾ Considering the variation of the standard materials in different batches of herbal formulae, each compound is analyzed from 3 independent batches with triplicate data. In addition, the minimum quantities of standard material in herbal formula should be determined. For identification of

chemical markers of each herb, liquid chromatography coupled with mass spectrometry is performed to confirm the consistency of herbal drugs.⁽⁹⁵⁾ Finally, a standard formula that contains several herbal extracts is developed through a series of biological assays during *in vitro* and *in vivo* screening efforts. These data offer an opportunity for the standardization of herbal therapy and drug development. HPLC fingerprinting was performed as a means of quality control in the research of ASHMI and SA described above.^(47,48,57)

Besides improving the quality control above, understanding the pharmacokinetics and identification of active compound is essential to obtain deep understanding of the mechanisms of action. Herbal products comprise many constituents, but only a few components are responsible for their bioactive characteristics. With the advent of genomics, proteomics and metabolomics and with the huge development in analytical techniques, e.g. surface-enhanced laser desorption ionization time-of-flight mass spectrometry (MS), and with modern chromatographic techniques for isolation and purification, e.g. HPLC with MS and nuclear magnetic resonance and high-throughput screening of bioactive components, there is an unprecedented opportunity to exploit traditional herbal medicines.⁽⁹⁶⁾ It is conceivable to use bioactivity-directed fractionation to confirm immunomodulatory herbs that have potential in the treatment of allergic asthma.

Conclusion

This article reviewed the effects of Chinese herbal formulae and herb-derived compounds on allergic asthma in different experimental models. The elucidation of action mechanisms of herbal medicines and their pharmacological evaluation has paved the way for identification of novel targets in the treatment of allergic asthma. Three classes of phytochemical compounds, non-steroidal alkaloids, polyphenols and terpenes, which have been used frequently to treat allergic asthma in the form of CM herbs and Chinese herbal formulae, have been shown to have immunomodulatory, anti-inflammatory and antiasthma activities in different experimental models using genomics, proteomics and metabolomics technologies, which will lead to a new era in the development of new drug discovery for allergic asthma in CM. We summarized 31 herb-derived anti-asthmatic compounds and 12 Chinese herbal formulae, which could guide

clinical trials and novel therapies for patients with allergic asthma in the near future.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author Contributions

Ma Y conceived and planned the review and modified the manuscript. Liu L carried out the review plan and drafted the manuscript. Wang LP helped to perform the structure of article. He S helped to search the references. All authors read and approved the final manuscript.

Electronic Supplementary Material Supplementary materials (Appendixes 1 and 2) are available in the online version of this article at <http://dx.doi.org/10.1007/s11655-018-2836-2>

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Appendix 1. Herb-derived Anti-asthmatic Compounds/Extracts and Their Mechanisms

Herb species	Compound/extract	Model	Mechanism	Usage and dosage	Reference
<i>Astragalus membranaceus</i>	Astragaloside IV	OVA-sensitized/challenged mice	↓ Eosinophil and IL-4, ↑ IFN- γ , IL-10, CD4 ⁺ CD25 ⁺ Foxp3 ⁺ T cells, Foxp3	20 and 40 mg/kg i.g.	(12)
	<i>A. membranaceus</i> extract	OVA-sensitized/challenged mice	↓ AHR, eosinophils, IL-4, IL-5 and NF- κ B	<i>Astragalus</i> extract	(11)
	Astragaloside IV	<i>In vitro</i> Der p 1 activated human blood eosinophils	↓ CCR3, ICAM-1, IL-1 β , IL-5, TNF- α , GM-CSF and eosinophils	50 μ g/mL	(21)
	Astragaloside IV	OVA-sensitized/challenged mice	↓ AHR, ↑ IFN- γ	50 and 150 mg/kg i.g.	(13)
	<i>A. membranaceus</i> extract	OVA-sensitized/challenged mice	↓ AHR, IL-5 and IL-13, ↑ IFN- γ	10 g/kg i.p.	(10)
	Astragaloside IV	OVA-sensitized/challenged mice	↓ AHR, IL-4, IL-13, IgE and TGF- β 1	50 mg/kg i.g.	(14)
<i>Peucedanum praeruptorum</i> Dunn (PPD)	Coumarins from PPD	OVA-sensitized/challenged mice	↓ AHR, IL-4, IL-5, IL-13 and IgE, ↑ IL-10, IFN- γ and CD4 ⁺ CD25 ⁺ Foxp3 ⁺ T cells	50, 100 and 200 mg/kg i.g.	(15)
	($\pm$)-praeruptorin A	OVA-sensitized/challenged mice	↓ AHR, IL-4, IL-13, IgE, TGF- β 1 and pSmad2/3, ↑ Smad7 and IFN- γ	30, 60 and 120 mg/kg i.g.	(16)
	($\pm$)-praeruptorin A	OVA-sensitized/challenged mice	↓ AHR, eosinophils, IL-4, IL-5, IL-13, LTC4, IgE, eotaxin and NF- κ B activation	30, 60 and 120 mg/kg i.g.	(17)
<i>Tripterygium wilfordii</i>	Tripterygium polyglycosid	OVA-sensitized/challenged mice	↓ Eosinophils, IL-5 and AHR	50 mg/kg i.p.	(18)
	Triptolide	LPS-stimulated MPM and human MoDCs	↓ IL-12p40 gene, ↑ transcription of C/EBP α , C/EBP α phosphorylation at Ser21 and Thr222/226	2.5, 5 and 10 ng/mL	(20)
	Triptolide	OVA-sensitized/challenged mice	↓ Eosinophils, IL-5 and eotaxin	40 μ g/kg i.g.	(19)
<i>Curcuma longa</i>	FLLL31 (Curcumin)	<i>In vivo</i> DRA-challenged mice <i>In vitro</i> LPS-stimulated macrophages	↓ STAT3 phosphorylation, IL-17, iNOS, STAT3, TNF- α , IL-1 β , IL-6, IL-2 and IFN- γ	15 mg/kg i.g. 1, 5 and 10 μ mol/L	(22)
<i>Vitidis fructus</i>	Pyranopyran-1,8-dione	Cockroach allergen-induced mice	↓ eosinophils, IL-4, IL-5, IL-13, eotaxin and IgE	1, 2, and 10 mg/kg i.g.	(23)
<i>Scepstridium ternatum</i>	<i>S. ternatum</i> extract	OVA-sensitized/challenged mice	↓ AHR and Cyslt1, ↑ Th1/Th2	1.935, 9.675 and 19.35 g/kg i.g.	(24)
<i>Glycyrrhiza uralensis</i>	Isoliquiritigenin, 7,4'-DHF, liquiritigenin	<i>In vitro</i> effector memory Th2 cells D10 <i>In vivo</i> OVA-sensitized / challenged mice	↓ IL-4, IL-5, IL-13, GATA-3, Eosinophils and IgE, ↑ IFN- γ	6.0 μ g i.g.	(25)
<i>Sophora flavescens</i>	Trifolirhizin	<i>Ex vivo</i> Ach-induced tracheal rings	↓ ASM contraction	6 μ g/mL	(26)
<i>Ilex chinenses</i>	Protocatechuic acid	OVA-sensitized/challenged mice	↓ AHR, IL-4, IL-5, IL-13, IgE, CCL11, CCR3, ERK, p38 MAPK phosphorylation and NF- κ B activation	5, 15 and 30 mg/kg i.p.	(27)
Ginger	[6]-gingerol, [8]-gingerol, [6]-shogao, [10]-gingerol	<i>Ex vivo</i> tracheas <i>In vitro</i> ASM cell <i>In vivo</i> Mch-challenged mice	↓ ASM contraction and AHR	100 and 200 mmol/L 100 mmol/L	(28)
Legumes	Genistein	OVA-sensitized/challenged mice	↑ Th1/Th2 and T-bet, ↓ GATA-3 and STAT-6	20 and 40 mg/kg i.p.	(29)

(To Be Continued)

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Herb species	Compound/extract	Model	Mechanism	Usage and dosage	Reference
<i>Rheum officinale</i>	Emodin	OVA-sensitized/ challenged mice	↓ Eosinophils, IL-4, IL-5, IL-13, IgE, IgG, IgG1, AMCase, Ym2, MUC5AC and AHR	40 mg/kg i.p.	(30)
<i>Lithospermum erythrorhizon</i>	Shikonin	<i>In vitro</i> OVA/TSLP- induced BM-DCs maturation <i>In vivo</i> OVA-sensitized/ challenged mice	↓ MHC-II, CD80, CD86, CCR7, OX40L, IL-4, IL-5, IL-13 and TNF- α ↓ IL-4, IL-5, IL-13, TNF- α , eotaxin, Eosinophils and AHR	0.03, 0.1, 0.3 μ mol/L 0.45 and 4.5 μ g i.t.	(31)
<i>Anoectochilus formosanus</i>	<i>A. formosanus</i> extract	OVA-sensitized/ challenged mice	↓ Th2 polarization, eosinophils, IgE and AHR, ↑ CD4 ⁺ CD25 ⁺ Treg cells	0.5, 1.0 g/kg i.g.	(32)
<i>Propolis</i>	Caffeic acid phenethyl ester	<i>In vitro</i> LPS or crude mite extract-activated human MoDCs	↓ IL-12 p40, IL-12 p70, IL-10, IP-10 and NF- κ B activation	10 μ mol/L	(33)
<i>Pericarpium citri reticulatae</i>	Alkaloid section: Synephrine stachydrine	<i>Ex vivo</i> Ach-induced guinea pig trachea <i>In vivo</i> histamine- induced guinea pig	spasmolytic effects ↑ latent period of asthma	 1 $\times$ 10 ⁻⁶ mol/L synephrine and 3 $\times$ 10 ⁻⁷ mol/L stachydrine	(34)
<i>Andrographis paniculata</i>	Andrographolide	OVA-sensitized/ challenged mice	↓ AHR and NF- κ B	2 μ g/g i.p.	(35)
<i>Gynostemma pentaphyllum</i>	<i>G. pentaphyllum</i> extract	OVA-sensitized/ challenged mice	↓ AHR and eosinophils, ↑ IFN- γ	i.p.	(36)
<i>Cnidii monnieri</i>	Osthol	<i>In vitro</i> IL-4/TNF- α - stimulated BEAS-2B cells	↓ Eotaxin and STAT6	0.1, 1 and 10 μ mol/L	(37)
<i>Ganoderma tsugae</i>	Triterpenoid-rich extracts	OVA-sensitized/ challenged mice	↓ AHR, eosinophils, IL-4, IL-5, eotaxin and IgG1	5 mg/day i.g.	(38)
<i>Perilla frutescens</i>	Luteolin	<i>Ex vivo</i> precontracted guinea pig trachea	↓ Contractions	1–300 μ mol/L	(39)
<i>Cordyceps sinensis</i>	CS-19-22 fraction	<i>In vitro</i> LPS-activated BALF cells	↓ IL-1 β , IL-6, IL-8, IL-10 and TNF- α , ↑ IL-12 and IFN- γ	100 μ g/mL	(40)
<i>Peganum harmala</i>	(+/-)-vasicine deoxyvasicine (+/-)-vasicinone	Ach and histamine- induced guinea pig	↑ Pre-convulsive time	5, 15 and 45 mg/kg i.g.	(41)
<i>Thuja orientalis</i>	<i>T. orientalis</i> extract	<i>In vitro</i> LPS-stimulated macrophages <i>In vivo</i> OVA-sensitized/ challenged mice	↓ iNOS, IL-6, COX-2, MMP-9, TNF- α , IL-4, IL-5, IL-13, eotaxin, IgE and AHR	30 mg/kg i.g.	(42)
<i>Ligusticum wallichii</i>	Ligustrazine	OVA-sensitized/ challenged mice	↓ Eosinophils, neutrophils, eotaxin, IgE, IL-4, IL-5, IL-13, TNF- α , IL-17, GATA-3 and ROR γ t, ↑ IL-10, T-bet and Foxp3	40 or 80 mg/(kg·day) i.p.	(43)

Notes: OVA: ovalbumin, i.p.: intraperitoneally, i.t.: intratracheally, i.g.: intragastrically, AHR: airway hyperresponsiveness, Der p: *Dermatoglyphus pteronyssinus*, CCR3: CC chemokine receptor 3, TNF- α : tumour necrosis factor- α , GM-CSF: granulocyte macrophage colony stimulating factor, TGF- β 1: transforming growth factor- β 1, LPS: lipopolysaccharide, MPM: mouse peritoneal macrophage, MoDCs: monocyte-derived dendritic cells, C/EBP α : CCAAT/enhancer-binding protein- α , COX-2: cyclooxygenase-2, MMP-9: matrix metalloproteinase-9, DRA: including house dust mite, ragweed, and *Aspergillus* species, s.c.: subcutaneously, i.n.: intranasally, STAT-3: signal transducer and activator of transcription 3, CKA: cockroach allergen, IFA: incomplete Freund's adjuvant, D10 cells: D10 G4.1 cells, CA: conalbumin, GATA-3: GATA binding protein 3, Ach: acetylcholine, ASM: airway smooth muscle, Mch: methacholine, T-bet: Tbox transcription factor, AMCase: acidic mammalian chitinase, Ym2: chitinase 3-like protein 4, TSLP: thymic stromal lymphopoietin, BM-DCs: bone marrow-derived dendritic cells, MHC-II: major histocompatibility complex class II, BEAS-2B cells: human bronchial epithelial cell line, BALF: bronchoalveolar lavage fluids, ↑: increased or up-regulated, ↓: decreased or down-regulated.

Appendix 2. Chinese Herbal Formulae in the Treatment of Allergic Asthma and Their Mechanisms

Chinese herbal formulae	Model	Mechanism and pathway	Usage and dosage	Reference
Xiaoqinglong Decoction	Der p-challenged mice	↓ IgE, IgG1, IL-10, IL-13, RANTES, eotaxin, MCP-1 and NF- κ B	1 g/kg i.g.	(46)
	OVA-sensitized/challenged guinea pigs	↓ Eosinophils and IL-5	0.06 g/mL	(58)
	<i>In vivo</i> OVA-sensitized/challenged guinea pigs <i>Ex vivo</i> carbachol-precontracted guinea pig trachea	↓ Contraction and eosinophils	5 and 10 g/kg i.g.	(59)
	Der p-challenged mice	↓ Eosinophils, ↑ CD8 ⁺ and CD4 ⁺ /CD8 ⁺ T cell	1 g/kg i.g.	(60)
Anti-asthma simplified herbal medicine intervention (ASHMI)	RW-sensitized/challenged mice	↓ AHR, TNF- α , IL-8, IL-17 and eosinophils	i.g.	(54)
	<i>In vivo</i> OVA-sensitized/challenged mice <i>Ex vivo</i> Ach-induced tracheal rings	↓ AHR and constriction via EP2/EP4 receptor pathway	ASHMI i.g.	(52)
	<i>In vivo</i> OVA-sensitized/challenged mice <i>Ex vivo</i> murine tracheal ring <i>In vitro</i> HTSMCs	↓ Histamine, leukotriene C4, IgE, eosinophils, Th2 cytokine and contraction ↑ PGI2	4.5 mg in 0.5 mL water i.g. 100 μ g/mL 31.25, 62.5, 125, 250, 500 and 1000 μ g/mL	(49)
	OVA-sensitized/challenged mice	↓ AHR, eosinophils and IgE, ↑ IFN- γ	9 mg in 0.5 mL water i.g.	(50)
	OVA-sensitized/challenged mice	↓ Eosinophils, MUC5AC, IgE, IL-4, IL-5 and IL-13, ↑ IFN- γ	i.g.	(51)
	<i>In vitro</i> PBMC from asthma patients LPS-stimulated macrophages	↓ TNF- α , p-I κ B α , NF- κ B, AP-1/c-Jun, JNK and p-ERK1/2	0, 2.5, 10, 20 and 40 μ g/mL	(53)
	<i>In vitro</i> CA-stimulated Th2-SPCs from CA-allergic mice; CA-stimulated D10 cells	↓ IL-4, IL-5 and GATA-3, ↑ IFN- γ	1, 5, 50, and 500 μ g/mL	(48)
MSSM-002 (the precursor of ASHMI)	CA-sensitized/challenged mice	↓ AHR, eosinophils, IgE, IL-4, IL-5 and IL-13	1 mL i.g.	(47)
Sanao Decoction	OVA-sensitized/OVA and LPS challenged mice	↓ AHR, IL-4 and IL-5, ↑ IFN- γ	2.2, 4.4 and 8.8 g/kg i.g.	(57)
	Der p challenged guinea pig	↓ Neutrophils	10 g/kg i.g.	(55)
	OVA-sensitized/challenged mice	↓ Eosinophils, ↑ CD4 ⁺ CD25 ⁺ Foxp3 ⁺ T cells and Foxp3	1.8 and 3.6 g/kg	(56)
Buzhong Yiqi Decoction	OVA-sensitized/challenged mice	↓ Eosinophils, IgE, IgG1 and IL-4, ↑ IgG2a and IFN- γ	1000 mg/kg i.g.	(61)
	OVA-sensitized/challenged mice	↓ IgE, histamine, IL-4, IgG1 and IL-2	1.7 and 17 mg i.g.	(62)
	OVA-sensitized/challenged mice	↓ AHR, eotaxin, IL-4, IL-5, IL-13 and eosinophil	0.5 g/kg or 1 g/kg i.g.	(63)
Qingfei Xiaoyan Pill	Histamine /Ach-induced guinea pig	↓ Hsp90, ↑ Serpin	132.5 and 397.5 mg/100 g	(64)
Shengfei Yuchuan Decoction	Der p challenged mice	↓ AHR, IgE, IgG1, IL-4, IL-5, IL-13, TGF- β 1, eotaxin, RANTES and MCP-1, ↑ IFN- γ and IL-12	1 g/kg i.g.	(65)
Danggui Buxue Decoction	OVA-sensitized/challenged mice	↓ AHR, eosinophil and IgE	i.g.	(66)
Shenmai Injection	<i>In vitro</i> passively sensitized HASMCs	↓ PCNA and p-ERK1/2	10, 50 and 100 μ L/mL	(67)
Wuwei Dilong Decoction	OVA-sensitized and challenged guinea pigs	↓ Eosinophils and LTB4, ↑ IFN- γ	6, 12 and 18 g/kg i.g.	(68)

(To Be Continued)

(Continued)

Chinese herbal formulae	Model	Mechanism and pathway	Usage and dosage	Reference
Xiabai Powder	<i>In vitro</i> LPS-treated A549 cells; LPS-treated THP-1 cell	↓ IL-8, ICAM-1, TNF- α , IL-1 β , IL-6 and NF- κ B activation	225 μ g/mL	(69)
Wheeze-relief formula	<i>In vitro</i> GM-CSF/PAF-stimulated human eosinophils; Der p 1 activated PBMC	↓ ECP, CCR3, CD49d, TNF- α and IL-2R α	0.5 and 1 mg/mL	(70)
Bushen Yiqi Decoction	OVA-sensitized/challenged mice	↓ AHR, IL-4, IL-5, IL-17A and eotaxin, ↑ IFN- γ	3.125, 6.25 and 12.5 mg/mL i.g.	(71)
	OVA-sensitized/challenged with RSV infection mice	↓ AHR, eosinophils, neutrophils, IgE, IL-4, IL-5, IL-6, IL-17A, GATA-3, STAT-6 and ROR γ t, ↑ IFN- γ , IL-12 and T-bet	2.5, 5 and 10g/(kg·day) i.g.	(72)

Notes: Der p: *D. pteronyssinus*, i.t.: intratracheally, i.g.: intragastrically, OVA: ovalbumin, i.p.: intraperitoneally, s.c.: subcutaneously, CFA: complete Freund's adjuvant, RW: ragweed, RSV: respiratory syncytial virus, i.n.: intranasally, AHR: airway hyperresponsiveness, TNF- α : tumour necrosis factor- α , i.v.: intravenously, Ach: acetylcholine, HTSMCs: human tracheal smooth muscle cells, CA: conalbumin, Th2-SPCs: Th2 polarized splenocytes, D10 cells: D10 G4.1 cells, GATA-3: GATA binding protein 3, LPS: lipopolysaccharide, IFA: incomplete Freund's adjuvant, HASMCs: human airway smooth muscle cells, PCNA: proliferating cell nucleus antigen, LTB₄: leukotriene B₄, THP1 cells: human myelomonocytic cells, A549 cells: human pulmonary epithelial cells, GM-CSF: granulocyte macrophage colony stimulating factor, PAF: platelet activating factor, PBMC: peripheral blood mononuclear cells, ECP: eosinophil cationic protein, T-bet: Tbox transcription factor, ↑: increased or up-regulated, ↓: decreased or down-regulated.