Chinese Traditional Medicine Journal

Traditional Chinese Medicine in Asthma – a Systematic Review of their Mechanism of Actions

Lin Ho Wong[1,2]*, Mb BCh BAO, Louisa Tay[2]*, TCM student, Robby Miguel Goh[3], IBSc, Tai Joum Tan[3], IBSc, Ruishu Zhou[2], Adv Dip(Nursing), Aaron Kwun Hang Ho[4], MB BCh BAO, Pang Ong Wong[1,5], PhD in TCM Formula-logy

[1]Ong Fujian Chinese Physician Hall, Singapore, [2]Singapore College of Traditional Chinese Medicine, Singapore, [3]University College London, United Kingdom, [4]Ministry of Health Holdings, Singapore, [5]Chang Chun University of Traditional Chinese Medicine, China

*Wong L.H. and Tay L. are joint first authors

ABSTRACT

Introduction: Asthma is a chronic respiratory condition that results in the inflammation and narrowing of airways. The lack of curative therapies for asthma has led to an increased use of traditional Chinese medicine (TCM) worldwide. This review aims to evaluate the mechanism of action (MOA) of TCM for used for treatment of asthma. **Methods:** A systematic review was conducted in Medline®, Embase®, CENTRAL®, China National Knowledge Infrastructure (CNKI®) and WanFang® for TCM used for asthma, in accordance to the PRISMA checklist. Full-text, articles in English and Chinese language which evaluated the MOA of individual TCM or TCM used as part of a formula for the treatment of asthma were included. The searches were performed between January 2000 and June 2020. A mechanistic guideline for TCM use in asthma was proposed, modelled after Global Initiative for Asthma (GINA) guidelines. **Results:** Of 9260 articles screened, 140 articles were included in the review. Twenty-six individual TCM and sixteen TCM formulas were identified. The most common MOA for individual TCM were multiple monoclonal effects (n=5), β adrenergic agonists (n=5), inhibition of interleukin-14 (n=3) and regulation of T helper cells (n=3). TCM formulas encompassed *Three seeds Combination* and *Zhi Chuan Fang*, For TCM formulas, the most common MOA identified included combination of β adrenergic agonistic, steroid like and/or regulation of T-helper 2 cells. **Conclusion:** The summarized MOA of commonly utilized TCM in asthma from this review will aid TCM practitioners in better educating patients and optimising TCM use to maximise their efficacies and minimize their adverse effects.

Keywords: Asthma; Respiratory Tract Disease; Systematic review; Pharmacology; Traditional Chinese Medicine

INTRODUCTION

The use of traditional Chinese medicine (TCM) has been rising in the recent decades, especially in Asia.[1] Compared to the disease-centric approach employed in Western medicine, TCM utilizes a comprehensive approach in the assessment and treatment of a patient via syndrome differentiation.[1] The basis of TCM centres on key theories related to Yin and Yang energies, five elements as well as concepts regarding meridians and vital energies.[1] The therapeutic benefits of TCM have led to its increased acceptance as an alternative and complementary treatment modality, alongside Western medicine.[2]

Asthma is defined as a heterogeneous disease characterized by chronic, reversible airway inflammation, which culminates in a wide range of presentations, treatment responses and varying course in each patient's lifetime.[3] It affects over 300 million patients globally and is one of the most common chronic respiratory diseases.[3] Its pathogenesis involves 2 key principles: 1) airway inflammation mediated by T helper cells, mast cells and eosinophils; and 2) airway remodelling resulting from airway smooth muscle increase, deposition of matrix in airway wall, angiogenesis and metaplasia of epithelial mucosa. The main classes of therapies used for asthma include inhaled corticosteroids, leukotriene receptor antagonists, short and long acting β-adrenergic agonists.[3] For most asthmatic patients, they are initiated on inhaled corticosteroids and dosages are scaled up with add-on of other therapies such as long acting β-adrenergic agonists depending on the control and severity of asthma.[3] Owing to the lack of curative treatment available and chronicity of asthma, the increased utilization of TCM among asthmatics raises the risk of drug interactions, especially among patients using dual treatment modalities (Western medicine and TCM).[4,5] This is compounded by the poorly elucidated MOA

***Corresponding to:**
Lin Ho Wong (Wong LH), Ong Fujian Chinese Physician Hall, Singapore, Tel: +65 82992667, Email address: nate.wong90@live.com.sg

of a large number of TCM, which may lead to potentially dangerous adverse effects.

As such, the primary objective of this review is to summarize the MOA of commonly utilized TCM and TCM formulas, to enable Western medicine and TCM practitioners to have a better understanding of how TCM work. It is hoped that this will lead to improved patient safety and better treatment outcomes

MATERIALS AND METHODS

The protocol for this systematic review has been pre-registered on Open Science Framework <10.17605/OSF.IO/3SK9B>. Informed consent is not required for this review paper.

We performed a two-phase systematic review in five major literature databases [Medline®, Embase®, Cochrane Controlled Register of Trials (CENTRAL®), China National Knowledge Infrastructure (CNKI®) and WanFang®] in accordance to the PRISMA 2009 checklist. The first phase was to identify commonly prescribed TCM herbs used by TCM practitioners for asthma. The search strategy utilized for this phase was listed in Supplementary File 1 and encompassed key TCM herbs and asthma terms. A senior TCM physician specialising in asthma care assisted in the verification of the list of TCM / TCM formulas. The search period for the initial phase was from January 2000 to April 2020.

In the second phase, a search was performed to evaluate the MOA of identified TCM. The Latin and Mandarin names of the identified were utilized in the search strategy listed in Supplementary File 2. All in-vivo studies which evaluated the MOA of TCM in asthma were included. For inclusion, the studies had to be full-text articles in English or Chinese. Irrelevant reviews, case reports, case series and meta-analyses were excluded. The search period was from January 2000 to June 2020.

For the assessment of risk of bias, the SYRCLE's risk of bias tool was utilized.[6] Regarding both the inclusion of articles and risk of bias for studies, the assessments were performed by two independent reviewers (TJ and L). All discrepancies in the assessments were discussed. When the discrepancies could not be resolved, discussion was made with a third independent reviewer (RS) to achieve a consensus.

The primary outcome of interest is the MOA of TCM/TCM formulas commonly used in asthma. Details related to the names, formulations, MOA, components and adverse effects associated with TCM/TCM formulas, in-vivo model used and indications for different subsets of asthma were extracted into a standardised data collection form.

The TCM and TCM formulas were sorted by their main MOAs. Based on the MOAs identified across studies, a schematic diagram of the TCM and TCM formulas were plotted on the asthma immunological pathway. A mechanistic guideline for the use of TCM and TCM formulas in asthma was also proposed, modelled after Global Initiative for Asthma (GINA) guidelines.[7]

RESULTS

Initial Search for Commonly Utilized Tcm Herbs Used for Asthma

In the first phase of this review to identify relevant TCM/TCM formulas, a total of 128 studies were included from the initial 511,411 records extracted. From the 55 TCM herbs initially identified, 26 herbs were included in the second phase of the review after discussion with the senior TCM physician in the team. [Figure 1]

These included Glycyrrhiza uralensis,[8-20] Prunus armeniaca,[21,22] Pinellia ternate,[23] Asarum sieboldii,[24,25] Pheretima aspergillum,[26-31] Aster tataricus, Fritillaria cirrhosa,[32-35] Lepidium apetalum,[36] Pericarpium Citri Reticulatae,[37-39] Cortex mori,[40-44] Ephedra sinica Stapf,[45-48] Zingiber officinale Roscoe,[49] Tussilago farfara,[50-52] Platycodon grandifloras,[53-56] Fritillaria thunbergii,[57] Paeonia lactiflora,[58,59] Magnolia officinalis,[60-63] Bupleurum chinense,[64,65] Scutellaria baicalensis,[66-72] Anemarrhena rhizoma,[73,74] Gypsum fibrosum, Eriobotryae folium,[75] Cinnamomi ramulus,[76] Zingiberis rhizoma, Schisandrae fructus,[77-79] and Perilla frutescens.[80]

Search Conducted for MOA of 26 Identified Herbs

The second phase of the systematic review yielded 9260 studies, of which 140 met the inclusion criteria [Figure 2]. No studies were found for the herbs *Gypsum fibrosum, Aster tataricus* and *Zingiberis rhizome*.

MOA of Commonly Used TCM Herbs

A summary of the MOA, formulations and adverse effects associated with the TCM were highlighted in Table 1. Majority of the herbs exhibited anti-inflammatory properties (n=23, 88.5%). Based on detailed MOA identified from the studies, the TCM herbs were further divided broadly into beta-adrenergic agonist, steroid-like, anticholinergics, phosphodiesterase antagonist, leukotriene antagonist, herbs with monoclonal effects or those affecting signalling pathways (Table 2). The most common MOA for individual TCM were multiple monoclonal effects (n=5), β adrenergic agonists (n=5), inhibition of interleukin (IL)-14 (n=3) and regulation of T helper cells (n=4). (Table 3)

A schematic representation on how TCM herbs act on the immune-pathological pathways of asthma was depicted in [Figure 3]. The herbs act mainly on IL-4, 5, 13, 17a

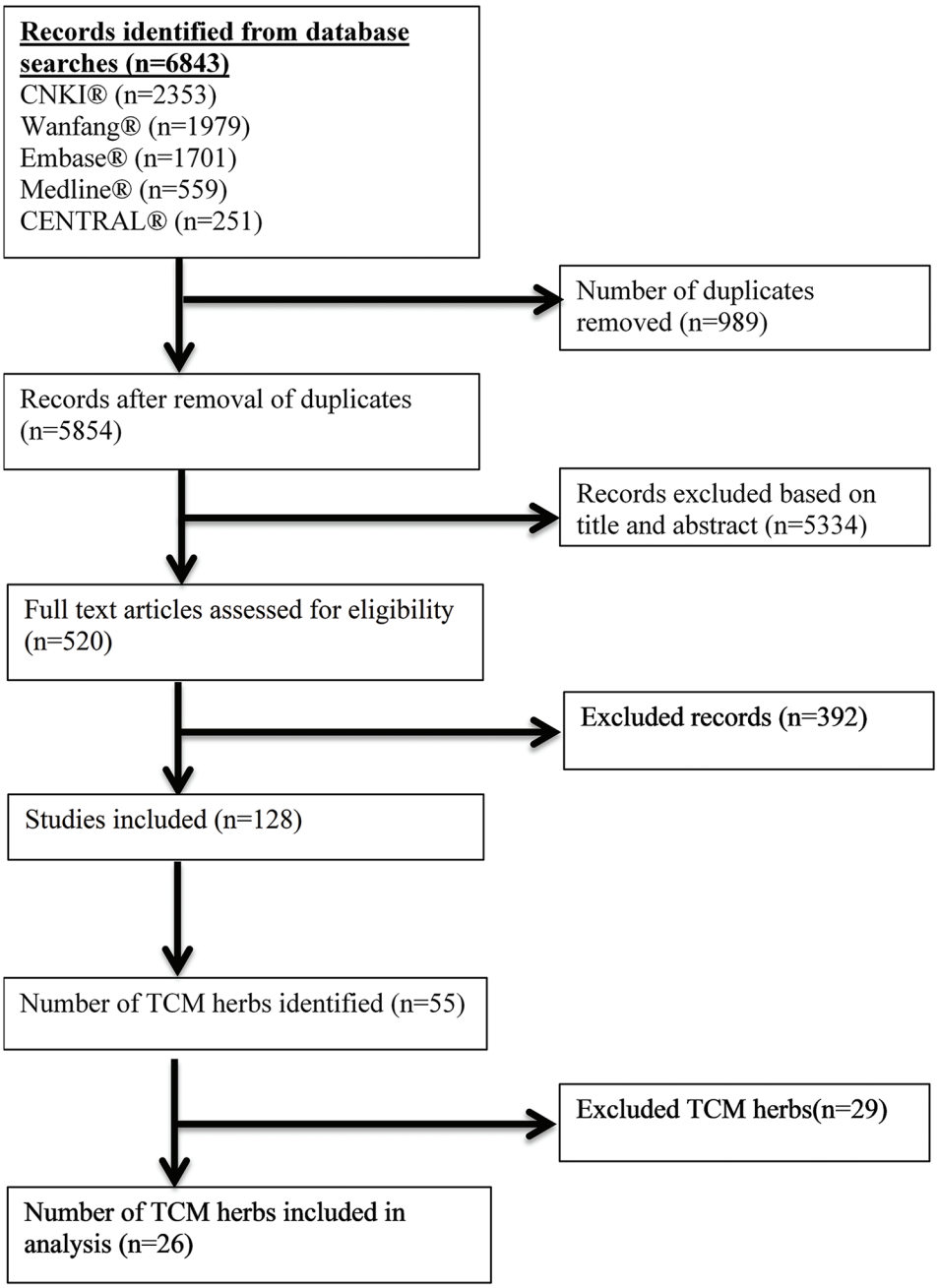

Figure 1: Flowchart of inclusion of articles in initial search.

and T cells on asthmatic pathways, which act to mobilize inflammatory cells, tissue repair and remodelling, causing bronchial hyper-reactivity and induction of chemokines.

Frequently Prescribed TCM Formulas in Asthma

Sixteen formulas comprising of varying combinations of the 26 herbs were identified in this review. (Table 3) Twelve formulas could be used as "stand-alone formulas" (monotherapy) and 4 were utilized as "add-on" formulas during an acute asthmatic exacerbation.[81] Analysis of the MOA of herbs identified in the formulas showed that "stand-alone formulas" had beta-agonist, steroid-like effects or leukotriene antagonist mechanisms, or a combination of beta-agonist and steroid-like effects/leukotriene antagonist. However, "add-on formulas" only had either steroid-like effects, or regulated T helper cells.

Proposed Mechanistic Guidelines for Use of TCM in Asthma

The proposed mechanistic guidelines describe a stepwise approach to treating asthma based on GINA guidelines, where increments in medication are made if existing treatment is insufficient for controlling a patient's symptoms.[7] [Figure 4]

Step 1 involves using a low to moderate dose of beta-2-adrenoreceptor agonist as required. Herbs which work

Table 1: Summary of TCM herbs used frequently in asthma

Latin name of TCM	Formulation	In vivo models	Mechanism of action	Adverse effects	References
Glycyrrhiza uralensis	Oral	Murine Guinea pigs	1) Bronchodilation LPS-induced NO production Attenuates acetylcholine- and carbachol-induced contractions Activate c-GMP and open calcium channels 2) Anti-inflammatory Inhibit T-lymphocytes, eosinophils, IgE, IL-13 and TNF-a Upregulate Caspase-3 and Bax Steroid-like activities Downregulate Bcl-2 3) Mucolytic Inhibit MUC5AC gene expression, production and secretion via regulation of NF-κB, STAT6, and HDAC2	Arrhythmia Bradycardia Edema	8-20
Prunus armeniaca	Oral	Murine	1) Anti-inflammatory Reduce recruitment of eosinophils, macrophages and lymphocytes Inhibit MAPK signalling and IL-4 activation Activate IFN-y	Diarrhoea Giddiness Headache Nausea, vomiting Dyspnoea Palpitation Coma Hypotension	21,22
Pinellia ternate	Oral	Murine	1) Anti-inflammatory Reduce recruitment of eosinophils Reduce IL-4 activation and IFN-y activation	Cough Vomit Hepatotoxcity Haematuria	23
Asarum sieboldii	Oral	Murine	1) Anti-inflammatory Inhibit IL-4 activation and histamine release 2) Signalling pathway regulation Regulate MMP-9 and TIMP-1 signalling	Hypoventilation Arrhythmia Headache, Vomiting Agitation Sweating Opsitotonus Mydrasis Facial flushing, Hyperthermia Risus sardonicus Seizures	24,25

(*Contd...*)

Table 1: (*Continued*)

Latin name of TCM	Formulation	In vivo models	Mechanism of action	Adverse effects	References
Pheretima aspergillum	Oral	Murine Guinea pigs	1) Anti-inflammatory Inhibit IL-4, IL-5, IgE, TNF-a activation Inhibit eosinophil activation Regulate Th1/Th2 balance Inhibit NF-kB activation Inhibit production of NO, PGE2, TNF-a, iNOS, COX-2 Inhibit release of IL-1B and IL-6 Regulate IFN-y, IL-4 and LTB4 production 2) Mucolytic: Decrease collagen deposition Decrease mucin glycogen expression	NA	26-31
Aster tataricus	Oral	NA	None found	NA	-
Fritillaria cirrhosa	Oral	Murine	1) Anti-inflammatory Suppress TH2 cytokines (IL-4, IL-5 and IL-13) Suppress IgE, histamine production Reduce eosinophilic accumulation Increase IFN-y production 2) Block signalling pathways Inhibit ERK/MAPK signalling activation 3) Downregulate NOTCH 2 expression 4) Inhibit MMP-2, MMP-9 and TIMP-1	Mydriasis Hypotension Constipation	32-35
Lepidium apetalum	Oral	Murine	1) Anti-inflammatory Reduce expression of Type 2 cytokines Inhibit differentiation and activation of Th2 cytokines	Bradycardia Polyuria	36
Pericarpium Citri Reticulatae	Oral	Murine Guinea pigs	1) Anti-inflammatory Suppress eosinophil production Downregulate expression of eosinophils and serum IgE, IL-4, and IL-5 levels 2) Bronchodilation Activation of B2-adrenoceptors	Hypertension	37-39
Cortex mori	Oral	Murine	1) Anti-inflammatory Enhancement of CD4(+)CD25(+)Foxp3(+) regulatory T cells and inhibition of Th2 cytokines such as interleukin (IL)-4, -5 and -13 2) Anticholinergic	Hypotension	40-44

(*Contd...*)

Table 1: (*Continued*)

Latin name of TCM	Formulation	In vivo models	Mechanism of action	Adverse effects	References
Ephedra sinica Stapf	Oral	Murine	1) Anti-inflammatory Reduce infiltration of inflammatory cells in the lung Regulate levels of inflammatory factors such as OVA-IgE, IL-4, IL-13, down-regulate the expression of p65 NF-k B protein 2) Bronchodilator Activate a-, B1- and B2-adrenoceptors	Hypertension Insomnia	45-48
Zingiber officinale Roscoe	Oral	Murine	1) Anti-inflammatory Inhibit Th2-mediated immune response 2) Bronchodilation Reduce Ca2+ influx in smooth muscle, promote B-agonist-induced relaxation in human airway smooth muscle by suppressing phosphodiesterase 4D	Hypertension	49
Tussilago farfara	Oral	Murine	1) Anti-inflammatory Regulate IgE, IL-4 and IL-13 levels Downregulate the expression of p65 NF-k B protein Inhibit NO, MAPKs and NF-kB Suppress expression of PGE2, TNF-a and HMGB1 Reduce production of IL-4, IL-5, IL-13, IL-17 Reduce IgE in serum by regulating Th1/Th2 cells Increase HO-1 levels affecting Nrf2/HO-1 pathway 2) Mucolytic Decrease mucin production by regulating NF-kB	Hypertension Tachypnea	50-52
Platycodon grandifloras	Oral	Murine	1) Anti-inflammatory Promote and regulate release of LXA4 Reduce oxygen free radicals Promote secretion of IFN-γ Regulate Th1 / Th2 balance Serum concentrations of NF-κB, MMP-9 and TIMP-1 decreased significantly	Nausea Vomiting	53-56
Fritillaria thunbergii	Oral	Guinea pigs	1) Anti-inflammatory Inhibit PDE, prevent inactivation of cAMP	Mydriasis Hypotension	57
Paeonia lactiflora	Oral	Murine	1) Anti-inflammatory Inhibit IL-22 and IL-13	NA	58,59

(*Contd...*)

Table 1: (***Continued***)

Latin name of TCM	Formulation	In vivo models	Mechanism of action	Adverse effects	References
Magnolia officinalis	Oral	Murine	1) Anti-inflammatory Inhibit IL-4, IL-6 and IL-17 Decrease serum MDA level Increase SOD and GSH-Px/ p-JNK, NF-κB, Caspase-3 and γH2 Ax levels Inhibition of PI3 K/Akt signaling pathway by TLR2 and TLR4 receptors Steroid like activities	Hypotension Reflex tachypnea Tachycardia	60-63
Bupleurum chinense	Oral	Guinea pigs	1) Anti-inflammatory Reduce eosinophil levels Reduce serum levels of IL- 5 and TNF- α	NA	64,65
Scutellaria baicalensis	Oral	Murine	1) Anti-inflammatory Inhibit TGF-β1, α-SMA, decrease p-ERK1/2 Inhibit phosphorylated p38 protein Inhibit IgE, IL-4, IL-5, IL-6, IL-17A Reduce STAT3 protein level Promote expression of FOXP3 protein Increase serum MDA levels Promote expression of FOXP3 protein Inhibit HMGB1 Inhibit protein expression of α-SMA and TLR4 expression of GATA-3, STAT-6 Suppress Th2 response Increase IL-10 levels	NA	66-72
Perilla frutescens	Oral	Murine	1) Anti-inflammatory Suppression of allergen specific Th2 response	NA	80
Anemarrhena rhizoma	Oral	Guinea pigs	1) Anti-inflammatory Reduce serum NO, BALF and ET-1	NA	73,74
Gypsum fibrosum	Oral	NA	None found	NA	-
Eriobotryae folium	Oral	Murine	1) Anti-inflammatory Reduce CD4+ Increase CD 8+ Regulate CD4+/CD8+ dysfunction	NA	75

(*Contd...*)

Table 1: (*Continued*)

Latin name of TCM	Formulation	In vivo models	Mechanism of action	Adverse effects	References
Cinnamomi ramulus	Oral	Murine	1) Anti-inflammatory Inhibition of eosinophils, IFN-γ, IL-4, IgE, histamine and β-hexosaminidase release	NA	76
Zingiberis rhizoma	Oral	NA	None found	NA	-
Schisandrae fructus	Oral	Murine	1) Anti-inflammatory Reduce EOS Increase SOD in serum Reduce MDA Inhibit TNF-α, IL-1β and IL-6 expression Regulate HMGB1 / TLR4 / NF-κB signalling pathway	NA	77-79

similarly include *Pericarpium Citri Reticulatae, Ephedra sinca Stapf, Zingiber officinale Roscoe, Tussilago farfara, and Scutellaria baicalensis*.

Step 2 involves the addition of a low dose of corticosteroids. This can be achieved by adding *Magnolia officinalis* to the existing herbs, or possibly by substituting them with *Glycyrrhiza uralensis* alone.

Step 3 involves increasing the dose of the beta-2-adrenoreceptor agonist to a moderate-high dose and either using a medium dose of corticosteroid, or adding a leukotriene receptor antagonist (LTRA) to the low dose corticosteroid. *Pheretima aspergillum* is an LTRA and could potentially be useful.

Step 4 involves the addition of either an anticholinergic or an LTRA, or increasing to a moderate dose of corticosteroid, whichever was not undertaken during step 3. *Cortex mori* has anticholinergic effects and could have potential use. [Figure 4]

Step 5 involves switching to a high dose of corticosteroid and the addition of drugs with effects such as inhibiting IgE, IL-4, or IL-5, guided by the phenotypic assessment by an asthma specialist. Herbs that may be useful for these purposes include *Asarum sieboldii, Pinellia ternate*, and *Prunus armeniaca* which inhibit IL-4, *Schisandrae fructus* which inhibits IL-17, *Lepidium apetalum*, and *Perilla frutescens* which regulate Th2 helper cell activity, or *Anemarrhena rhizoma, Eriobotryae folium, Platycodon grandifloras, Paeonia lactiflora, Bupleurum chinense*, and *Cinnamomi ramulus* which have a range of effects against multiple targets. (Table 2)

Risk of Bias

Quality assessment was done with SYRCLE's risk of bias tool for animal studies. [6] 20 of the studies were rated as moderate and none were rated as having a high risk of biasness. Frequent reasons cited for having a moderate risk of biasness include, animals were not housed randomly (n=7), caregivers and/or investigators were not blinded (n=17) and the assessors were not blinded (n=19).

DISCUSSION

Despite differences between TCM and Western medicine, this review showed that herbal medicines have similar MOA to conventional pharmacological therapies. Greater understanding of these MOAs of allows for improved characterisation of these herbs and more informed prescriptions adopted by TCM physicians. For example, TCM physicians will be able to better select TCM herbs with beta-agonist effects among patients presenting with acute asthma attacks. The finding from this review also aids in minimising potential drug interactions between TCM herbs and drugs. Of note, recent research showed that up to 33.6% of patients in the United Kingdom consume both herbal and prescription medicine.[82] Potential adverse effects could arise if herbs and drugs with similar MOA were

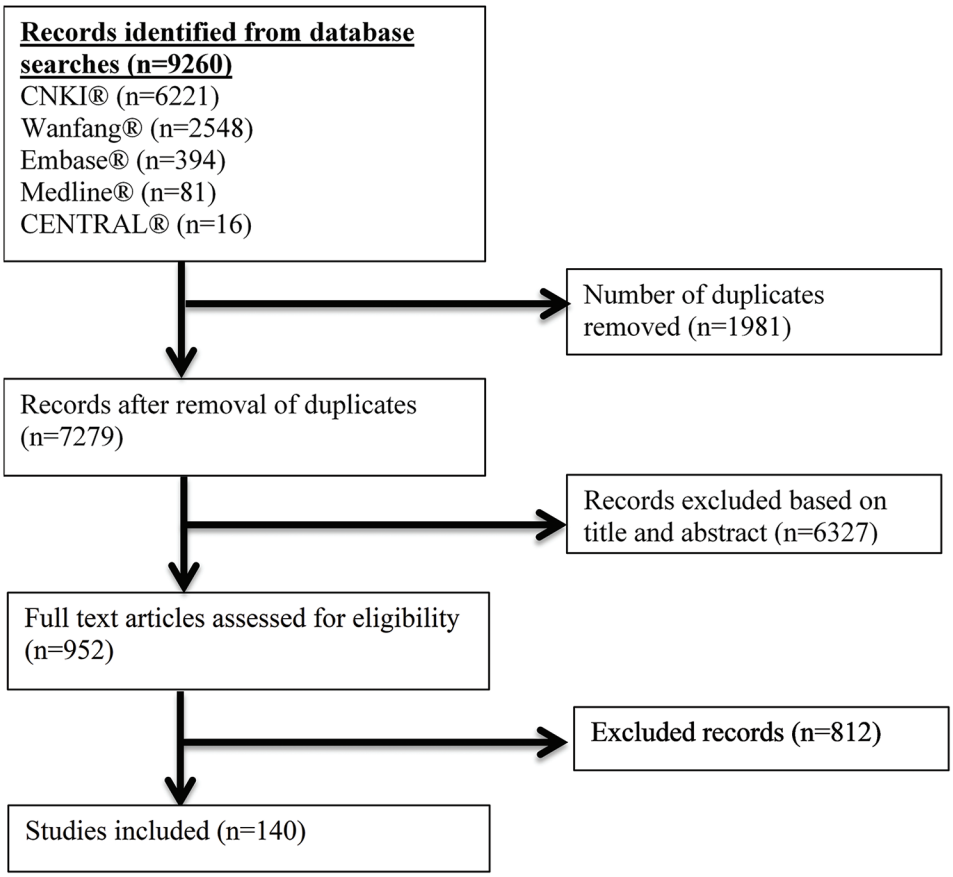

Figure 2: Flowchart of inclusion of articles in final search.

consumed concurrently.[83,84] Importantly, for TCM herbs with unclear MOA such as *Gypsum fibrosum*, *Aster tataricus* and *Zingiberis rhizome*, the concomitant use with Western medicine should be avoided to minimize adverse effects.

In this review, detailed MOA for each individual TCM Herbs were summarized. Some of the TCM herbs were shown to regulate the activity of inflammatory cells and cytokines by acting on particular pathways in the immunopathology of asthma. This information can aid TCM physicians in selecting potential TCM to target varying phenotypes of asthma such as allergen induced asthma. Biologics such as Omalizumab, which target specific cytokines that down-regulate of immunoglobulin E in have been well-studied in the management of allergen induced asthma. TCM herbs with similar effects such as *Tussilago farfara* could potentially be utilized for these subgroups of patients.

TCM Herbs are typically prescribed in various combinations as "TCM formulas", rather than individually.[81] They can be broadly divided into "Stand-alone formulas" which can be used independently for diseases and "Add-on Formulas" which are usually added as adjuvants to "Stand-alone formulas" to enhance their therapeutic effects. Interestingly, the analysis of "Stand-alone Formulas" have shown that despite the differences in herbs used, formulas generally consist of herbs with b-agonist and steroid-like effects.[81] On the other hand, "add-on formulas" consist of herbs with steroid-like effects or assist in the regulation of T helper cells.

It is important to note that some formulas consist of several herbs with the same MOA, which may increase patients' susceptibility to adverse effects. For example, the "Ephedra, apricot kernel, gypsum, and licorice decoction" comprises *Ephedra sinica Stapf* and *Glycyrrhiza uralensis* which exert b-agonistic effects. For patients with underlying cardiac conditions, the use of this decoction could increase their risk of arrhythmias resulting from excessive b-adrenergic activity. Likewise, "Cinnamon Twig Decoction plus Magnolia Bark and Apricot Kernel" comprises Magnolia officinalis and Glycyrrhiza uralensis, which exert steroid-like effects. Its use could result in iatrogenic Cushing Syndrome, a well-documented side effects of steroids especially when administered systemically.[85] Consequently, judicious use of these concoctions should be practised especially among patients with underlying medical conditions.

Overall, TCM physicians generally adopt a "syndrome-based" approach in diagnosing patients which involves reviewing the patient's symptoms, observing patient's tongue and evaluating the pulse's character.[86] The main limitation of this approach is the lack of objective measures which could result in varying diagnosis made by different TCM practitioners.[87] Through better understanding of the MOA

Table 2: Phenotype specific Asthma therapeutic targeting of herbs

Chinese Name	Latin Name	MOA targeting Asthmatic subgroups	Targeted Asthmatic phenotype	References
β adrenergic agonist				
Chen Pi	Pericarpium Citri Reticulatae	• Inhibits IL-5 and reduction of eosinophil 2) inhibits IgE, IL-4	• Idiopathic eosinophilic asthma • Allergen exacerbated asthma	37-39
Ma Huang	Ephedra sinica Stapf	• Inhibits IL-4,13	• Allergen exacerbated asthma	45-48
Sheng Jiang	Zingiber officinale Roscoe	• N/A	• N/A	49
Kuan Dong Hua	Tussilago farfara	• Inhibits IL-4,13, IgE • Inhibits IL-5 • Inhibits IL-17	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	50-52
Huang Qin	Scutellaria baicalensis	• Inhibits IL-4,13, Ig E • Inhibits IL-5 • Inhibits IL-17A	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	66-72
Steroidal effects				
Hou Po	Magnolia officinalis	• Inhibits IL-4,13 • Inhibits IL-5 • Inhibits IL-17A • Inhibits leukotriene release	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma • Aspirin induced asthma	60-63
PDE inhibitor				
Zhe bei	Fritillaria thunbergii	• N/A	• N/A	57
B-adrenergic and Steroidal effects				
Gan Cao	Glycyrrhiza uralensis	• Inhibits IgE and IL13 • Inhibits IL-5 antagonist • Steroidal effects	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	8-20
Anticholinergic				
Sang Bai Pi	Cortex mori	• Inhibits IL-4,13 • Inhibits IL-5	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma	40-44
Leukotriene Antagonist				
Di Long	Pheretima aspergillum	• Leukotriene antagonist • Inhibits IgE and IL-4 • Reduces eosinophils and inhibits IL-5	• Aspirin induced asthma • Allergen exacerbated asthma • Idiopathic eosinophilic asthma	26-31
Inhibition of IL-4				
Xi Xin	Asarum sieboldii	• Inhibits IL-4 and histamine release	• Allergen exacerbated asthma	24,25
Ban Xia	Pinellia ternate	• Inhibits IL-4	• Allergen exacerbated asthma	23
Ku Xing Ren	Prunus armeniaca	• Inhibits IL-4	• Allergen exacerbated asthma	21,22
Inhibition of IL-17				
Wu Wei Zi	Schisandrae fructus	• Inhibits IL-17	• Neutrophilic asthma	77-79
Regulation of T Helper cells				
Ting Li Zi	Lepidium apetalum	• Reduces the expression of Th2 cytokines and inhibits differentiation and activation of Th2 cells.	• Allergen exacerbated asthma	36
Pi Pa Ye	Eriobotryae folium	• Reduction of CD4+, rises CD 8+, alters CD4+/CD8+ dysfunction	• Allergen exacerbated asthma	75

(*Contd...*)

Table 2: ***(Continued)***

Chinese Name	Latin Name	MOA targeting Asthmatic subgroups	Targeted Asthmatic phenotype	References
Multiple Monoclonal effects for asthma				
Zhi Mu	Anemarrhena rhizoma	• Inhibits IL-5, and reduction of eosinophil • Inhibits histamine release, IgE, IL-4,13	• Idiopathic eosinophilic asthma • Allergen exacerbated asthma	73,74
Jie Geng	Platycodon grandifloras	• Inhibits IL-4,13 • Inhibits IL-5 • Inhibits IL-17	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	53-56
Shao Yao	Paeonia lactiflora	• Inhibits IL-4,13 • Inhibits IL-5 • Reduces eosinophil • Inhibits IL-17, reduces neutrophil count	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	58,59
Chai Hu	Bupleurum chinense	• Inhibits IL-4, IgE • Inhibits IL-5 • Inhibits IL-17A	• Allergen exacerbated asthma • Idiopathic eosinophilic asthma • Neutrophilic asthma	64,65
Gui Zi	Cinnamomi ramulus	• Inhibits IgE, IL-4	• Allergen exacerbated asthma	76
Alteration of genetic expression/signaling pathway				
Bei Mu	Fritillaria cirrhosa	NA	NA	32-35

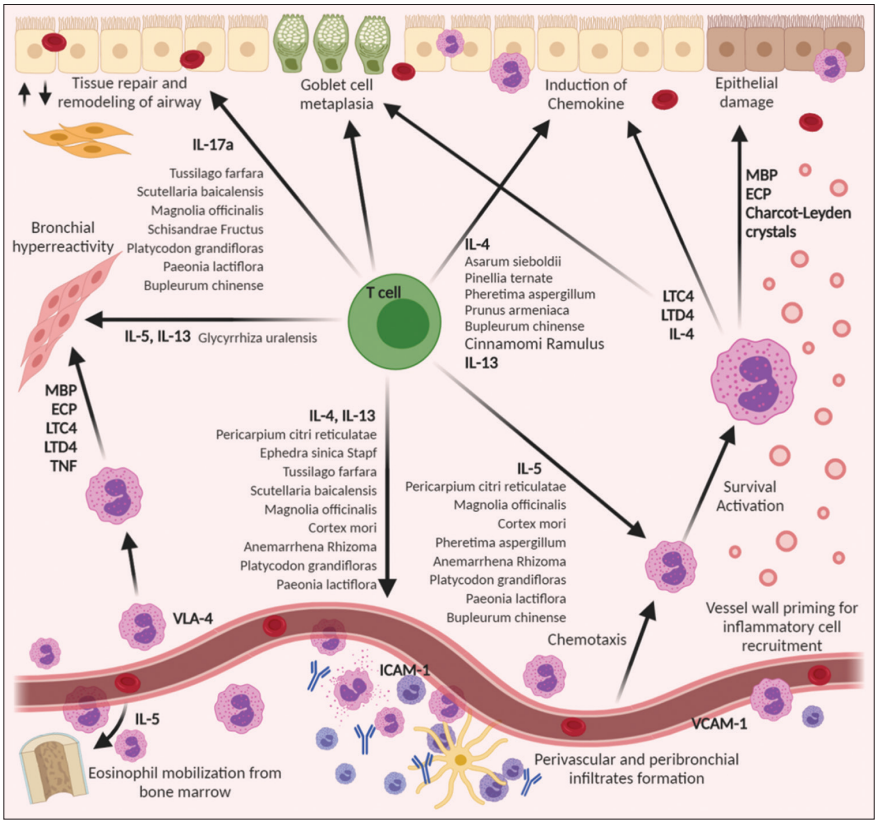

Figure 3: Chinese medicine targeted therapy on immunopathological pathways of Asthma.

Table 3: Analysis of MOA of commonly used TCM formulas

Formula (Chinese)	Formulas	Key ingredients	MOA	Monotherapy / add-on	References
三子养亲汤	Three seeds Combination	Perilla frutescens	Regulation of Th2 Cell	Add on	80
三子汤	Three Seed Decoction to Nourish One's Parents	Lepidium apetalum Perilla frutescens	Regulation of Th2 cell	Add on	36,80
半夏厚朴汤	Pinellia and Magnolia Bark Decoction	Pinellia ternate Magnolia officinalis	Steroid like effects	Add on	23,60-63
桂枝加厚朴杏仁汤	Cinnamon Twig Decoction plus Magnolia Bark and Apricot Kernel	Cinnamomi ramulus Magnolia officinalis Prunus armeniaca Glycyrrhiza uralensis	Steroid like effects	Add on	8-22,60-63, 76
射干麻黄汤	Belamcanda and Ephedra Decoction	Ephedra sinica Stapf Aster tataricus L. f. Pinellia ternate, Schisandrae fructus Asarum sieboldii Tussilago farfara	β agonist	Monotherapy	23-25,45-48, 50-52,77-79
康连智方	Kang Lian Zhi Fang	Ephedra sinica Stapf, Pinellia ternate Asarum sieboldii, Schisandrae fructus	β agonist	Monotherapy	23-25, 45-48, 77-79
董氏治喘基本方	Dong Shi Zhi Chuan Ji Ben Fang	Ephedra sinica Stapf Prunus armeniaca Pheretima aspergillum	β agonist Leukotriene antagonist	Monotherapy	21,22, 26-31,45-48
麻杏石甘汤	Ephedra, Apricot Kernel, Gypsum, and Licorice Decoction	Ephedra sinica Stapf Glycyrrhiza uralensis Prunus armeniaca	β agonist Steroid like effects	Monotherapy	8-22, 45-48
三拗汤	Newly Modified Three-Unbinding Decoction	Ephedra sinica Stapf Glycyrrhiza uralensis Prunus armeniaca	β agonist Steroid like effects	Monotherapy	8-22, 45-48
茯苓杏仁甘草汤	Decoction of Poria cocos, Almond, and Glycyrrhiza	Prunus armeniaca Glycyrrhiza uralensis	β agonist Steroid like effects	Monotherapy	8-22
六君子汤	Six-Gentleman Decoction	Glycyrrhiza uralensis Pinellia ternate Pericarpium Citri Reticulatae	β agonist Steroid like effects	Monotherapy	8-20,23,37-39
治喘方	Zhi Chuan Fang	Ephedra sinica Stapf Asarum sieboldii Glycyrrhiza uralensis Schisandrae fructus Pinellia ternate	β agonist Steroid like effects	Monotherapy	8-20, 23-25, 45-48,77-79
苓桂术甘汤	Linggui Shugan Decoction	Cinnamomi ramulus Glycyrrhiza uralensis	β agonist Steroid like effects	Monotherapy	8-20, 76
小柴胡汤	Minor Bupleurum Decoction	Bupleurum chinense Scutellaria baicalensis Pinellia ternate Glycyrrhiza uralensis	β agonist Steroid like effects	Monotherapy	8-20, 23, 64-72,23,8-20

(*Contd...*)

Table 3: ***(Continued)***

Formula (Chinese)	Formulas	Key ingredients	MOA	Monotherapy / add-on	References
小青龙汤	Minor Bluegreen Dragon Decoction	Ephedra sinica Stapf Paeonia lactiflora Asarum sieboldii Glycyrrhiza uralensis Cinnamomi ramulus Schisandrae fructus Pinellia ternate	β agonist Steroid like effects	Monotherapy	8-20,23-25, 45-48,58,59, 76,77,79
芍药甘草汤	Peony and Licorice Decoction	Paeonia lactiflora Glycyrrhiza uralensis	β agonist Steroid like effects	Monotherapy	8-20, 58,59

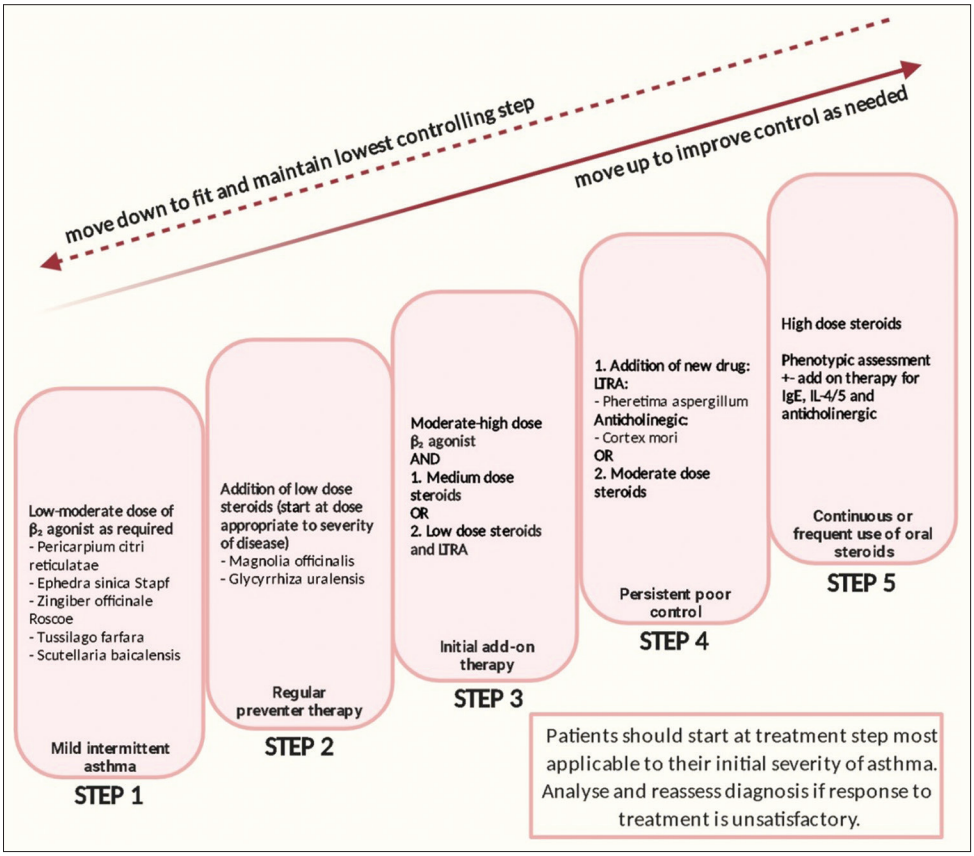

Figure 4: Proposed mechanistic guideline for use of traditional Chinese medicine in asthmatics.

of TCM herbs used in asthma, it is hoped that the proposed mechanistic guideline can aid in greater standardisation in TCM prescription for asthmatic patients and minimize usage of TCM with similar MOAs.

This review is not without limitations. Firstly, only in-vivo studies were included. Future reviews should consider evaluating and summarizing the safety and efficacy of the identified TCMs from studies conducted among asthmatic patients. Secondly, while a relatively comprehensive search strategy was employed, we could not exclude the possibility of excluding potentially relevant articles. To minimize this, the literature search was conducted in five major literature databases.

CONCLUSION

With a rising number of patients seeking TCM, it is paramount for TCM physicians to understand the underlying MOA of herbs. This will aid TCM practitioners in better educating patients and optimising the use of TCM to improve patient outcomes. Further research on *Gypsum fibrosum, Aster tataricus* and *Zingiberis rhizome* to identify their underlying MOA is recommended.

Conflict of Interest

None

Financial Support

No

Authors

All research done by all authors.

Ethical Approval

No ethical approval is required for this review.

REFERENCES

1. Fung FY, Linn YC (2015) Developing Traditional Chinese Medicine in the Era of Evidence-Based Medicine: Current Evidences and Challenges. Evidence-Based Complementary and Alternative Medicine 2015: 425037
2. Lin MH, Chang HT, Tu CY, *et al*. Prevalence of polyherbacy in ambulatory visits to traditional Chinese medicine clinics in Taiwan. Int J Environ Res Public Health 2015; 12:9639–9657.
3. Holgate, S., Wenzel, S., Postma, D. *et al.* Asthma. *Nat Rev Dis Primers* **1,** 15025 (2015)
4. Izzo A, A: Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data. Med Princ Pract 2012;21:404-428. doi: 10.1159/000334488
5. Ching HH, Chun ML, Tung TC. Efficacy and Safety of Modified Mai-Men-Dong-Tang for Treatment of Allergic Asthma. Pediatr Allergy Immunol 2005.doi:10.1111/j.1399-3038.2005.00230.x.
6. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW (2014) SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14: 43-43
7. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2006. Available from: www.ginasthma.com
8. LV XH, Wu T, Qing DY. Effect of Glycyrrhizin on Nitric Oxide and Nitric Oxide Synthase in Mice Model of Bronchial Asthma [J]. Lishizhen Medicine and Materia Medica Research,2009,20(1):40-41. .doi:10.3969/j.issn.1008-0805.2009.01.020.
9. LV XH, Wu T, Qing DY. Gan cao suan dui xiao chuan xiao shu qi dao yan zheng ji lin zhi mei A2 huo xing de ying xiang [J]. Lishizhen Medicine and Materia Medica Research,2007,18(10):2379-2380. doi:10.3969/j.issn.1008-0805.2007.10.024.
10. Zhang WY, Gu YC, Tang Y, *et al*. Effects of glycyrrhizic acid on ERK1/2 and p38 MAPK signaling pathway in a murine model of asthma [J]. Zhonghua yi xue za zh,2018,98(16):1273-1278. doi:10.3760/cma.j.issn.0376-2491.2018.16.017.
11. Wu QZ, Tang Y, Zhang JF, *et al*. Therapeutic Effects of Glycyrrhizic Acid on Airway Inflammation in A Murine Model of Asthma And Its Mechanism [J]. Chinese Medical Journal,[5] 2014,94(42):3338-3344. doi:10.3760/cma.j.issn.0376-2491.2014.42.014.
12. Lv XH, Wu T, Qin DY. Gan cao dui man xing xiao shu xiao chuan mo xing qi dao yan zheng ji wai zhou xue Th1/Th2 shi heng de ying xiang [J]. Zhongguo linchuang yaolixue yu zhiliaoxue, 2006,11(5):532-534. doi:10.3969/j.issn.1009-2501.2006.05.012.
13. Chen W, Ma, Yang LS. Effects of glycyrrhetinic acid on oxidative stress and NF kB signal pathway in bronchial asthma rats [J]. Journal of Zhengzhou University (Medical Sciences),2016,51(6):762-765. doi:10.13705/j.issn.1671-6825.2016.06.018
14. Lin XH, Feng KQ, Zheng SG. Gan cao ci suan dui xiao chuan da shu fei pao guan xi ye bai xi bao ji shu ji xue qing xiang guan yan zheng yin zi de ying xiang [J]. Chinese Journal of Gerontology ,2016,36(11):2613-2614. doi:10.3969/j.issn.1005-9202.2016.11.020.
15. Chen W, Ma L, Yang LS. Gan cao ci suan dui xiao chuan da shu qi dao chong zu ji fei zu zhi Casepase-3Ḅaẋ Bcl-2 biao da de ying xiang [J]. Zhongguo yaoli yu linchuang, 2016,32(4):16-19.
16. Liu B, Wen QS, Zhang JR, *et al*. Antiasthmatic effect of isoliquiritigenin and its mechanism[J]. Chinese Journal of Clinical Pharmacy,2007,16(6):348-352. doi:10.3969/j.issn.1007-4406.2007.06.005.
17. Huang WC, Liu CY, Shen SC, *et al*. Protective Effects of Licochalcone A Improve Airway Hyper-Responsiveness and Oxidative Stress in a Mouse Model of Asthma. Cells. 2019 Jun;8(6). doi: 10.3390/cells8060617.
18. Fouladi S, Masjedi M, Ganjalikhani Hakemi M, Eskandari N. The Review of in Vitro and in Vivo Studies over the Glycyrrhizic Acid as Natural Remedy Option for Treatment of Allergic Asthma. Iranian Journal of Allergy, Asthma, and Immunology. 2019 Feb;18(1):1-11.
19. Hosseinzadeh, H., and Nassiri-Asl, M. (2015) Pharmacological Effects of Glycyrrhiza spp. and Its Bioactive Constituents: Update and Review. Phytother. Res., 29: 1868– 1886. doi: 10.1002/ptr.5487.
20. Liu C, Weir D, Busse P, *et al*. The Flavonoid 7,4'-Dihydroxyflavone Inhibits MUC5AC Gene Expression, Production, and Secretion via Regulation of NF-κB, STAT6, and HDAC2. Phytother Res. 2015;29(6):925-932. doi:10.1002/ptr.5334
21. Wei H, Xu D, Yao DF, *et al*. Ku xing ren gan dui bian yi xing xiao chuan xiaoxiao shu de ying xiang [J]. Shaanxi Journal of Traditional Chinese Medicine, 2016,37(12):1691-1693.
22. Dan LS. Ku xing ren gan tong guo tiao kong MAPK xin hao tong lu yi zhi guo min xing xiao chuan xiao shu de zheng fan ying [A]. Di er shi san ci quan guo er ke Zhong xi yi jie he xue shu hui yi zhi liao hui bian [C]. Chinese Association of Integrative Medicine: ,2019:1.
23. Huang C, Peng W, Wei DN, *et al*. Effect of Pinelliae Rhizoma Praeparatum Cum Alumine Polysaccharides on MUC5AC mRNA in Lung Tissues of Allergic Asthma Model Rats [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2019 ,25(22):15-21. doi:10.13422/j.cnki.syfjx.20192103.
24. Chen H, Cheng Y, Yang LY, *et al*. Xi xin gai shan xiao chuan tun shu xiao qi dao chong su de shi yan yan jiu [J] Journal of Sichuan Traditional Chinese Medicine,2018,36(06):66-68.
25. Chang HC, Gong CC, Chan CL, Mak OT. A nebulized complex traditional Chinese medicine inhibits Histamine and IL-4 production by ovalbumin in guinea pigs and can stabilize mast cells in vitro. BMC Complementary and Alternative Medicine. 2013 ;13:174. doi: 10.1186/1472-6882-13-174.

26. Tang QF, Liu SH, Xu RP, Zhu WS. Effect of earthworm on airway remodeling in the murine model of chronic allergen-induced asthma [J]. Journal of Guangdong Pharmaceutical University,2013,29(05):547-551.
27. Lu WW, Wu GL, Yu GY. Zhong yao zhi liao zhi qi guan xiao chuan zuo yong de ji zhi chu tan [J]. Zhejiang Journal of Traditional Chinese Medicine,2017,52(04):299.
28. Li HC, Xu RE, Yang YN, Wang L. Di long zhu she ye dui wu chen man zhi min qi dao shang pi xi bao TGF-β_1/Smad2 biao da de ying xiang, 2010,45(15):1145-1149.
29. Wang L, Liu Y, Wang F, Li HC. Inhibitory effect of ground dragon on the expression of α-SMA and FN in the lung tissue of mouse with asthma [J]. Chin J Pathophysiol,2009,25(10):1964-1968.
30. Zhou MM, Chu XP, Yang HZ, Kou F, Zhao AH, Jia W. Anti-inflammatory and anti-allergic effects of acidic fraction of Pheratima extract in asthma mice induced by ovalbumin [J]. China Journal of Chinese Materia Medica,2008(19):2249-2252.
31. Huang CQ, Li W, Wu B, *et al*. Pheretima aspergillum decoction suppresses inflammation and relieves asthma in a mouse model of bronchial asthma by NF-κB inhibition. Journal of Ethnopharmacology. 2016 Aug;189:22-30. doi: 10.1016/j.jep.2016.05.028.
32. Wang Y, Feng DP, Sun LB, Zhang BH. Chuan bei dui xiao chuan xiao shu Notch2 de biao da ji yan zheng fan ying de ying xiang [J]. Progress of Anatomical Sciences,2019,25(05):583-585+589.
33. Zhang YF, Xu HN, Huang W, Ren GP, Li HZ. Chuan bei mu dui xiao chuan mo xing xiao shu qi dao yan zheng ji ERK/MAPK xin hao tong lu de ying xiang [J]. China Pharmacy,2018,29(03):343-348.
34. Li HZ, Gao ZY, Huang W, Ren GP, Xu HN, Zhang X, Fu H, Zhang YF. Zhong yao chuan bei mu dui mo xing xiao chuan xia shu MMP-2,MMP-9 he TIMP-1de ying xiang [J]. China Journal of Chinese Materia Medica,2017,42(21):4180-4186.
35. Yeum HS, Lee YC, Kim SH, *et al*. Fritillaria cirrhosa, Anemarrhena asphodeloides, Lee-Mo-Tang and cyclosporine a inhibit ovalbumin-induced eosinophil accumulation and Th2-mediated bronchial hyperresponsiveness in a murine model of asthma. Basic & Clinical Pharmacology & Toxicology. 2007 Mar;100(3):205-213. doi: 10.1111/j.1742-7843.2007.00043.x.
36. Kim SB, Seo YS, Kim HS, *et al*. Anti-asthmatic effects of lepidii seu Descurainiae Semen plant species in ovalbumin-induced asthmatic mice. Journal of Ethnopharmacology. 2019 Nov;244:112083. doi: 10.1016/j.jep.2019.112083.
37. Cai ZQ, Dai Y, Yuan HY. Chen pi hui fa you de yao xiao xue shi yan yan jiu [J]. China Pharmaceuticals,2006(13):29-30.
38. Fu M, Zou B, An K, *et al*. Anti-asthmatic activity of alkaloid compounds from Pericarpium Citri Reticulatae (Citrus reticulata 'Chachi'). Food & Function. 2019 Feb;10(2):903-911. doi: 10.1039/c8fo01753k.
39. Shi Q, Liu Z, Yang Y, *et al*. Identification of anti-asthmatic compounds in Pericarpium citri reticulatae and evaluation of their synergistic effects. Acta Pharmacologica Sinica. 2009 May;30(5):567-575. doi: 10.1038/aps.2009.36.
40. Sui ZY, Wang AJ, Li Q. Effect of Crude and Honeyed Mori Cortex on Serum NO, LPO, IL-4 and IFN-γ in Asthmatic Rats [J]. Chinese Journal of Experimental Traditional Medical Formulae,2015,21(07):95-98.
41. Qin XZ, Li LC, Yan GH, Li GZ. Sang bai pi shui ti wu dui xiao chuan mo xing xiao shu zhi qi guan fei pao guan xi ye zhong yan xing xi bao de ying xiang [J]. Journal of Medical Science Yanbian University,2011,34(02):93-95.
42. Wei YY, Xu F, Chen XW, Chen X, Zhang GG. Sang bai pi huang tong ping chuan zuo yong shi yan yan jiu [J]. Shizhen China,2009,20(11):2743-2745.
43. Ma F, Liao DJ, Lei Y. Effect and mechanism of PDE-4 inhibitor moracin M extracted from cortex mori radicis in mice with asthma [J]. International Journal of Respiration,2018,38(7):485-489. doi:10.3760/cma.j.issn.1673-436X.2018.07.002.
44. Kim HJ, Lee HJ, Jeong SJ, *et al*. Cortex Mori Radicis extract exerts antiasthmatic effects via enhancement of CD4(+)CD25(+)Foxp3(+) regulatory T cells and inhibition of Th2 cytokines in a mouse asthma model. Journal of Ethnopharmacology. 2011 Oct;138(1):40-46. doi: 10.1016/j.jep.2011.08.021.
45. Huang L, Wang YN, Wu SY. Zhong yao ma huang yao li zuo yong yan jiu jin zhan [J]. China Foreign Medical Treatment Magazine,2018,37(07):195-198.
46. Li HY, Lv XH, Ding RG, Zhang TH, Zhao J. Effects of Ephedrine isomers and cholic acid analogs, used alone or in combination, against histamine induced constriction of guinea pig tracheal in vitro [D]. Academy of Military Medical Sciences,2008.
47. Li ZY, Deng J, Xiong B, Xiong Y, Wang SP. Effect of ephedrine on expression of eotaxin in human bronchial epithelial cells stimulated by tumor necrosis factor-α [J]. Chongqing Yixue,2016,45(08):1016-1018.
48. Xu JH, Cao HR, Chen YX. Effect of Herba Ephedrae or Honey-fried Herba Ephedrae Alone on Airway Inflammation of Asthmatic Rats [J]. Journal of New Chinese Medicine,2014,46(12):197-199.
49. Q. Q. Mao *et al*., Bioactive compounds and bioactivities of ginger (zingiber officinale roscoe). Foods. 8 (2019). doi:10.3390/foods8060185.
50. Duan YH. The Effects and Mechanism of Total Sesquiterpenes from Tussilago Farfara L. on OVA-sensitized Asthma Model in Rats [D]. Shanxi University China,2019.
51. Y. K. Kim *et al*., Tussilagone inhibits the inflammatory response and improves survival in CLP-Induced septic mice. International Journal of Molecular Sciences. 18 (2017), doi:10.3390/ijms18122744.
52. J. Li *et al*., Metabolomics reveal the protective effect of Farfarae Flos against asthma using an OVA-induced rat model. RSC Advances. 7, 39929–39939 (2017).
53. Wang L, Du WN, Guo ST, Yan H, Zhang HN, Ma R, Wang LP. Effects of Platycodon grandiflorum on bronchial remodeling in asthmatic rats [J]. Chin J School Doctor,2018,32(11):854-856.
54. Yu WY, Zhu HJ. Jie geng zhi liao zhi qi guan xiao chuan de yao li zuo yong ji zhi yan jiu [J]. Acta Chinese Medicine and Pharmacology,2012,40(03):38-40.
55. H. Y. Lee, G. H. Lee, H. K. Kim, H. J. Chae, Platycodi Radix and its active compounds ameliorate against house dust mite-induced allergic airway inflammation and ER stress and ROS by enhancing anti-oxidation. Food and Chemical Toxicology. 123, 412–423 (2019).
56. Y. Xie, H. Pan, H. Sun, D. Li, A promising balanced Th1 and Th2 directing immunological adjuvant, saponins from the root of Platycodon grandiflorum. Vaccine. 26, 3937–3945 (2008).
57. Zhang YH, Wang J, Yuan HL, Pi HF, Wu JZ. Effect of Verticinone and Its Derivatives on Cyclic Adenosine Monophosphate of Bronchus Smooth Muscle of Guinea-pig. [J]. Chinese Archives of Traditional Chinese Medicine,2007(12):2484-2485.

58. Chen X, Huang Y. Shao yao ti quwu dui xiao chuan mo xing da shu IL-22 he IL-13shui ping de ying xiang [J]. Journal of Military Surgeon in Southwest China,2013,15(06):659-661.
59. Xin QQ *et al*. A review for the anti-inflammatory effects of paeoniflorin in inflammatory disorders. Life Sciences (237) 116925. doi: 10.1016/j.lfs.2019.116925.
60. Qin C, Dai X, Yang XQ, Wang RL, Wang X, Li GP. Intervention effect of honokiol on inflammatory response in lung tissue of asthma mice and its mechanism [J]. Journal of Jilin University (Medicine Edition),2020,46(02):214-220+431.
61. Liu N, Li N, Zhu L, Shi CC. Effect of honokiol on PI3K/Akt signaling pathway in asthmatic mice and its effect on TLR2 and TLR4 expression [J]. Chinese Traditional and Herbal Drugs,2019,50(06):1407-1412.
62. Shen JL, Man KM, Huang PH, Chen WC, Chen DC, Cheng YW, L PL, Chou MC, Chen YH. Honokiol and Magnolol as Multifunctional Antioxidative Molecules for Dermatologic Disorders. Molecules (Basel, Switzerland). 15. 6452-65. doi: 10.3390/molecules15096452.
63. Luo HY, Wu HW, Yu XK, Zhang X, Lu YQ, Fan JW, Tang LY, Wang ZJ. A review of the phytochemistry and pharmacological activities of Magnoliae officinalis cortex. Journal of Ethnopharmacology(236): 412-442. doi: 10.1016/j.jep.2019.02.041
64. Ou EX. Chai hu zao gan d zhi liao bian yi xing xiao chuan de shi yan yan jiu [J]. Hunan Journal of Traditional Chinese Medicine,2016,32(06):172-174.
65. Bui TT, Piao CH, Song CH, Shin HS, Chai OH. Bupleurum chinense extract ameliorates an OVA-induced murine allergic asthma through the reduction of the Th2 and Th17 cytokines production by inactivation of NFκB pathway. Biomed Pharmacother. 2017;91:1085-1095. doi:10.1016/j.biopha.2017.04.133
66. Han C, Yang L, Zhang QL, Liang HL, Xu J. Correlation Study on Baicalin's Anti-Asthmatic Effects and HMGB1/TLR4 Signal Pathway [J]. World Chinese Medicine,2019,14(06):1402-1407.
67. Han C, Yang L, Zhang QL, Pan JQ, Xu J. Effect of baicalin on airway remodeling of bronchial asthma [J]. Chinese Journal of Clinical Pharmacology and Therapeutics,2017,22(07):749-754.
68. Han C, Yang L, Zhang QL, Pan JQ, Xu J. Huang qin gan dui xiao chuan da shu p38MAPK xin hao tong lu ying xiang chu tan [J]. Guangzhou Yi Yao,2016,47(04):5-9
69. Wang P. The Effect of Baicalin on the Imbalance of Th17/Treg Respone in Mice with Allergic Asthma [D]. YanBian University website. 2016. Accessed May 11, 2020. http://new.oversea.cnki.net/KCMS/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201701&filename=1016213672.nh&uid=WEEvREcwSlJHSldTTEYzVDhUSFJQQkRyUjRNNzhFUitZdU45SzE5eFl4ND0=$9A4hF_YAuvQ5obgVAqNKPCYcEjKensW4IQMovwHtwkF4VYPoHbKxJw!!&v=MTA4MjR1eFlTN0RoMVQzcVRyV00xRnJDVVI3cWZZK1Z2Rnl6bVc3dkFWRjI2R0xHNUhkZkxyWkViUElSOGVYMUw=
70. Huang F, Tong XY, Deng HM, Nie H, Zhang RH, Cai Y. Huang qin gan tiao jie xiao chuan mo xing xiao shu Th1/Th2 fan ying ji zhi chu tan [J]. Zhong YaoCai,2009,32(09):1407-1410.
71. Xing R, Guo F, Tian JX, Kong JJ, Gao HB, Song W, Shi GX. Huang qin dui da shu zhi qi guan xiao chuan fa bing ji zhi ying xiang de yan jiu [J]. Chinese Archives of Traditional Chinese Medicine,2003(12):2097-2098.
72. F. Liu *et al*., Herbal medicines for asthmatic inflammation: From basic researches to clinical applications. Mediators of Inflammation. 2016 (2016), , doi:10.1155/2016/6943135.
73. Ding JS, Li JH, Liu XL. Zhi mu dui tun shu xiao chuan de yu fang zuo yong ji qi nei pi su he yi yang hua dan de ying xiang [J]. Chinese Journal of Traditional Medical Science and Technology,2007(02):89-90+64.
74. Lee YC, Kim SH, Seo YB, Roh SS, Lee JC. Inhibitory effects of Actinidia polygama extract and cyclosporine A on OVA-induced eosinophilia and bronchial hyperresponsiveness in a murine model of asthma. International Immunopharmacology. 2006 Apr;6(4):703-713. doi: 10.1016/j.intimp.2005.10.007.
75. Wei Y, Tang HQ, Li XH, Zhu XY. Pi pa ye zhushe ye dui xiao chuan mo xing xiao shu Tlin ba ya qun de ying xiang [J]. Journal of Emergency in Traditional Chinese Medicine,2013,22(07):1151-1152.
76. Wu ZQ. Study on the Anti-allergic Effect and Mechanism of Different Extraction from Ramulus Cinnamomi [D]. Chengdu University of T.C.M. website. 2015. Accessed May 17, 2020. http://new.oversea.cnki.net/KCMS/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201601&filename=1016045917.nh&uid=WEEvREcwSlJHSldTTEYzVDhUSFJQQkRyUjRNNzhFUitZdU45SzE5eFl4ND0=$9A4hF_YAuvQ5obgVAqNKPCYcEjKensW4IQMovwHtwkF4VYPoHbKxJw!!&v=MjA2NTdJUjhlWDFMdXhZUzdEaDFUM3FUc1dNMUZyQ1VSN3FmWStWdkZ5emhWYjNCVkYyNkdMTzhHOWpOcUpFYlA=
77. Lv X, Xu GY, Wang CM, Li H, Cao LJ, Chen JG, Sun JH. Ji yu wang luo yao li xue shai xuan wu wei zi zhong zhi liao xiao chuan de ba bian ji huo xing cheng fen [J]. Journal of BeiHua University (Natural Science),2020,21(02):175-178.
78. Wang DR, Wang YT, Hua S, Fan XY. Wu wei zi yi su dui xiao chuan xiao shu fei bu yanzheng de ying xiang ji qi ji zhi yan jiu [J]. AnHui Medical University,2019,54(05):735-740.
79. Chen X, Feng J. Wu wei zi ti qu wu dui xiao chuan mo xing da shu xue ye kang yang hua huo xing de ying xiang [J]. China Pharmaceuticals,2013,22(23):25-27.
80. HM Ahmed. Ethnomedicinal, Phytochemical and Pharmacological Investigations of Perilla frutescens (L.) Britt. Molecules. 2019 Jan; 24(1): 102. doi: 10.3390/molecules24010102.
81. Zhang JA, Li JY, An XD, Miao Q, Ma YZ. Gu jin zhong han xiao chuan ming yan fang fen xi [J]. Chinese Journal of Information on Traditional Chinese Medicine,1997(08):34-35.
82. Agbabiaka T. B., Spencer N. H., Khanom S. and Goodman C. Prevalence of drug–herb and drug–supplement interactions in older adults: a cross-sectional survey. *Br J Gen Pract* 2018; 68 (675): e711-e717. DOI: https://doi.org/10.3399/bjgp18X699101
83. Lim, JW, Chee, SX, Wong, WJ, He, QL, Lau, TC. Traditional Chinese medicine: herb-drug interactions with aspirin. Singapore Med J. 2018;59(5):230–239.
84. Chua, Y, Ang, X, Zhong, XM. Interaction between warfarin and Chinese herbal medicines. Singapore Med J. 2015;56(1):11–18.
85. Raveendran A.V. Inhalational Steroids and Iatrogenic Cushing's Syndrome. Open Respir Med J 2014; 8: 74-84.
86. Cheng F, Wang X, Song W, Lu Y, Li X, Zhang H, Wang Q. Biologic basis of TCM syndromes and the standardization of syndrome classification. Journal of Traditional Chinese Medical Sciences. 2014;1:92-97.
87. Jiang L, Liu B, Xie Q, Yang S, He L, Zhang R, Yan S, Zhou X, Liu J. Investigation into the influence of physician for treatment based on syndrome differentiation. Evid Based Complement Alternat Med 2013; 2013: 587234.

SUPPLEMENTARY FILE 1. DETAILS OF INITIAL SEARCH STRATEGY

1. Pubmed

S/No		Theme		Search terms
1		Asthma		(“asthma”[MeSH Terms] OR “asthma”[All Fields]) OR “asthmas”[All Fields]) OR “asthma s”[All Fields])
2		Traditional Chinese Medicine		(“tcm”[All Fields])) OR ((((“medicine, chinese traditional”[MeSH Terms] OR ((“medicine”[All Fields] AND “chinese”[All Fields]) AND “traditional”[All Fields])) OR “chinese traditional medicine”[All Fields]) OR ((“traditional”[All Fields] AND “chinese”[All Fields]) AND “medicine”[All Fields])) OR “traditional chinese medicine”[All Fields])) OR ((((“complementary therapies”[MeSH Terms] OR (“complementary”[All Fields] AND “therapies”[All Fields])) OR “complementary therapies”[All Fields]) OR (“alternative”[All Fields] AND “medicine”[All Fields])) OR “alternative medicine”[All Fields]) OR “herbal medicine”[MeSH Terms] OR (“herbal”[All Fields] AND “medicine”[All Fields]) OR “herbal medicine”[All Fields] OR “herbalism”[All Fields] OR “herbal”[All Fields] OR “herbals”[All Fields] OR “common herbs”[All Fields])

Search: #1 and #2

2. Embase

S/No		Theme		Search terms
1		Asthma		(‘asthma’/exp OR asthma)
2		Traditional Chinese Medicine		(tcm OR ‘traditional chinese medicine’/exp OR ‘traditional chinese medicine’ OR (traditional AND (‘chinese’/exp OR chinese) AND (‘medicine’/exp OR medicine)) OR ‘alternative medicine’/exp OR ‘alternative medicine’ OR (alternative AND (‘medicine’/exp OR medicine) OR ‘herbal’/exp OR (common AND ‘herb’/exp)

Search: #1 and #2

3. Cochrane Controlled Register of Trials (CENTRAL)

S/No		Theme		Search terms
1		Asthma		“Asthma”
2		Traditional Chinese Medicine		“TCM” OR “Traditional Chinese Medicine” OR “alternative medicine”

Search: #1 and #2

4. CNKI

S/No		Theme		Search terms
1		Asthma		“Asthma”
2		Traditional Chinese Medicine		“TCM” OR “Traditional Chinese Medicine” OR “alternative medicine”

Search: #1 and #2

5. Wanfang

S/No		Theme		Search terms
1		Asthma		“Asthma”
2		Traditional Chinese Medicine		“TCM” OR “Traditional Chinese Medicine” OR “alternative medicine”

Search: #1 and #2

SUPPLEMENTARY FILE 2. DETAILS OF FINAL SEARCH STRATEGY

1. Pubmed

S/No	Theme	Search terms
1	Asthma	(“asthma”[MeSH Terms] OR “asthma”[All Fields]) OR “asthmas”[All Fields]) OR “asthma s”[All Fields])
2	Relevant Traditional Chinese Medicine	((“glycyrrhiza uralensis”[MeSH Terms] OR (“glycyrrhiza”[All Fields] AND “uralensis”[All Fields])) OR “glycyrrhiza uralensis”[All Fields]) OR ((“prunus armeniaca”[MeSH Terms] OR (“prunus”[All Fields] AND “armeniaca”[All Fields])) OR “prunus armeniaca”[All Fields])) OR ((((“pinellia”[MeSH Terms] OR “pinellia”[All Fields]) OR “pinelliae”[All Fields]) AND “ternate”[All Fields])) OR ((“asarum”[MeSH Terms] OR “asarum”[All Fields]) AND “sieboldii”[All Fields])) OR (“Pheretima”[All Fields] AND ((“aspergillu”[All Fields] OR “aspergillus”[MeSH Terms]) OR “aspergillus”[All Fields]))) OR (((((“aster plant”[MeSH Terms] OR (“aster”[All Fields] AND “plant”[All Fields])) OR “aster plant”[All Fields]) OR “aster”[All Fields]) OR “asters”[All Fields]) AND “tataricus”[All Fields])) OR ((((“fritillaria”[MeSH Terms] OR “fritillaria”[All Fields]) OR “fritillarias”[All Fields]) OR “fritillariae”[All Fields]) AND (“cirrhosa”[All Fields] OR “cirrhosae”[All Fields]))) OR ((“lepidium”[MeSH Terms] OR “lepidium”[All Fields]) AND “petaluma”[All Fields])) OR (((“pericardium”[MeSH Terms] OR “pericardium”[All Fields]) OR “pericardiums”[All Fields]) AND “Citri”[All Fields] AND “Reticulatae”[All Fields])) OR (((“cortex”[All Fields] OR “cortex s”[All Fields]) OR “cortexes”[All Fields]) AND “mori”[All Fields])) OR ((“ephedra sinica”[MeSH Terms] OR (“ephedra”[All Fields] AND “sinica”[All Fields])) OR “ephedra sinica”[All Fields])) OR (((“ginger”[MeSH Terms] OR “ginger”[All Fields]) OR (“zingiber”[All Fields] AND “officinale”[All Fields])) OR “zingiber officinale”[All Fields])) OR (((“tussilago”[MeSH Terms] OR “tussilago”[All Fields]) OR (“tussilago”[All Fields] AND “farfara”[All Fields])) OR “tussilago farfara”[All Fields])) OR (((“platycodon”[MeSH Terms] OR “platycodon”[All Fields]) OR “platycodons”[All Fields]) AND “grandiflora”[All Fields])) OR ((((“fritillaria”[MeSH Terms] OR “fritillaria”[All Fields]) OR “fritillarias”[All Fields]) OR “fritillariae”[All Fields]) AND “thunbergii”[All Fields])) OR (((“paeonia”[MeSH Terms] OR “paeonia”[All Fields]) OR “paeoniae”[All Fields]) AND “lactiflora”[All Fields])) OR (((“magnolia”[MeSH Terms] OR “magnolia”[All Fields]) OR (“magnolia”[All Fields] AND “officinalis”[All Fields])) OR “magnolia officinalis”[All Fields])) OR (((“bupleurum”[MeSH Terms] OR “bupleurum”[All Fields]) OR “bupleurums”[All Fields]) AND ((((“asian continental ancestry group”[MeSH Terms] OR (((“asian”[All Fields] AND “continental”[All Fields]) AND “ancestry”[All Fields]) AND “group”[All Fields])) OR “asian continental ancestry group”[All Fields]) OR “chinese”[All Fields]) OR “chineses”[All Fields]))) OR ((“scutellaria baicalensis”[MeSH Terms] OR (“scutellaria”[All Fields] AND “baicalensis”[All Fields])) OR “scutellaria baicalensis”[All Fields])) OR ((“perilla frutescens”[MeSH Terms] OR (“perilla”[All Fields] AND “frutescens”[All Fields])) OR “perilla frutescens”[All Fields])) OR (((“anemarrhena”[MeSH Terms] OR “anemarrhena”[All Fields]) OR “anemarrhenae”[All Fields]) AND ((((“rhizomae”[All Fields] OR “rhizomas”[All Fields]) OR “rhizome”[MeSH Terms]) OR “rhizome”[All Fields]) OR “rhizoma”[All Fields]))) OR (((((“calcium sulfate”[MeSH Terms] OR (“calcium”[All Fields] AND “sulfate”[All Fields])) OR “calcium sulfate”[All Fields]) OR “gypsum”[All Fields]) OR “gypsums”[All Fields]) AND “fibrosum”[All Fields])) OR (((“eriobotrya”[MeSH Terms] OR “eriobotrya”[All Fields]) OR “eriobotryae”[All Fields]) AND (((“plant leaves”[MeSH Terms] OR (“plant”[All Fields] AND “leaves”[All Fields])) OR “plant leaves”[All Fields]) OR “folium”[All Fields]))) OR (“Cinnamomi”[All Fields] AND “ramulus”[All Fields])) OR (“Zingiberis”[All Fields] AND ((((“rhizomae”[All Fields] OR “rhizomas”[All Fields]) OR “rhizome”[MeSH Terms]) OR “rhizome”[All Fields]) OR “rhizoma”[All Fields]))) OR (((“schisandra”[MeSH Terms] OR “schisandra”[All Fields]) OR “schisandrae”[All Fields]) AND ((“fruit”[MeSH Terms] OR “fruit”[All Fields]) OR “fructus”[All Fields])))

Search: #1 and #2

2. Embase

S/No		Theme		Search terms
1		Asthma		(‘asthma’/exp OR asthma)
2		Relevant Traditional Chinese Medicine		(‘glycyrrhiza uralensis’ OR ‘prunus armeniaca’ OR ‘pinellia ternate’ OR ‘asarum sieboldii’ OR ‘pheretima aspergillum’ OR ‘aster tataricus’ OR ‘fritillaria cirrhosa’ OR ‘lepidium apetalum’ OR ‘pericarpium citri reticulatae’ OR ‘cortex mori’ OR ‘ephedra sinica’ OR ‘zingiber officinale’ OR ‘tussilago farfara’ OR ‘platycodon grandifloras’ OR ‘fritillaria thunbergii’ OR ‘paeonia lactiflora’ OR ‘magnolia officinalis’ OR ‘bupleurum chinense’ OR ‘scutellaria baicalensis’ OR ‘perilla frutescens’ OR ‘anemarrhena rhizoma’ OR ‘gypsum fibrosum’ OR ‘eriobotryae folium’ OR ‘cinnamomi ramulus’ OR ‘zingiberis rhizoma’ OR ‘schisandrae fructus’) AND ‘asthma’)

Search: #1 and #2

3. Cochrane Controlled Register of Trials (CENTRAL)

S/No		Theme		Search terms
1		Asthma		“Asthma”
2		Traditional Chinese Medicine		(“Glycyrrhiza uralensis” OR “Prunus armeniaca” OR “Pinellia ternate” OR “Asarum sieboldii” OR “Pheretima aspergillum” OR “Aster tataricus” OR “Fritillaria cirrhosa” OR “Lepidium apetalum” OR “Pericarpium Citri Reticulatae” OR “Cortex mori” OR “Ephedra sinica” OR “Zingiber officinale” OR “Tussilago farfara” OR “Platycodon grandifloras” OR “Fritillaria thunbergii” OR “Paeonia lactiflora” OR “Magnolia officinalis” OR “Bupleurum chinense” OR “Scutellaria baicalensis” OR “Perilla frutescens” OR “Anemarrhena rhizoma” OR “Gypsum fibrosum” OR “Eriobotryae folium” OR “Cinnamomi ramulus” OR “Zingiberis rhizoma” OR “Schisandrae fructus”)

Search: #1 and #2

4. CNKI

S/No	Theme	Search terms
1	Asthma	哮喘
2	Traditional Chinese Medicine	“甘草” OR “苦杏仁” OR “半夏” OR “细辛” OR “地龙” OR “紫菀” OR “贝母” OR “葶苈子” OR “陈皮” OR “桑白皮” OR “麻黄” OR “生姜” OR “款冬花” OR “桔梗” OR “浙贝” OR “芍药” OR “厚朴” OR “柴胡” OR “黄芩” OR “苏子” OR “知母” OR “石膏” OR “枇杷叶” OR “桂枝” OR “干姜” OR “五味子”

Search: #1 and #2

5. Wanfang

S/No	Theme	Search terms
1	Asthma	哮喘
2	Traditional Chinese Medicine	“甘草” OR “苦杏仁” OR “半夏” OR “细辛” OR “地龙” OR “紫菀” OR “贝母” OR “葶苈子” OR “陈皮” OR “桑白皮” OR “麻黄” OR “生姜” OR “款冬花” OR “桔梗” OR “浙贝” OR “芍药” OR “厚朴” OR “柴胡” OR “黄芩” OR “苏子” OR “知母” OR “石膏” OR “枇杷叶” OR “桂枝” OR “干姜” OR “五味子”

Search: #1 and #2

Supplementary Table 3: Quality assessment of included animal studies using SYRCLE's risk of bias tool for animal studies

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
吕小华. *et al*	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	low
吕小华. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
张吴越. *et al*	Y	Y	Y	NA	Y	Y	N	Y	Y	Y	low
吴巧珍. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
吕小华 *et al*	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	low
陈伟. *et al*	Y	Y	Y	NA	N	Y	NA	Y	Y	Y	low
林香花. *et al*	Y	Y	Y	Y	N	Y	NA	Y	Y	Y	low
陈伟. *et al*	Y	Y	Y	Y	N	Y	NA	Y	Y	Y	low
刘斌. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
Huang WC. *et al*	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	low
Yang N. *et al*	Y	Y	Y	N	Y	Y	NA	N	Y	N	moderate

(*Contd...*)

Supplementary Table 3: ***(Continued)***

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
卫昊. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
单丽沈. *et al*	Y	Y	Y	NA	NA	Y	NA	Y	Y	Y	low
黄聪. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
陈慧. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
Chang HC. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
唐秋凤. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
卢雯雯. *et al*	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	low
李怀臣. *et al*	Y	Y	Y	NA	Y	Y	N	Y	Y	Y	low
王莉. *et al*	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	low
周明眉. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
Huang CQ. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low

(*Contd...*)

Supplementary Table 3: ***(Continued)***

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
王燕. *et al*	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	low
张羽飞. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
李厚忠. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
Yeum HS. *et al*	Y	Y	Y	NA	Y	Y	NA	Y	Y	Y	low
Kim SB. *et al*	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	low
蔡周权. *et al*	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	low
Fu M. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low
Shi Q. *et al*	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	low
隋在云. *et al*	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	low
秦向征. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low
韦媛媛. *et al*	Y	Y	Y	NA	Y	Y	N	Y	Y	Y	low
马飞. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low

(*Contd...*)

Supplementary Table 3: ***(Continued)***

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
Kim HJ. *et al*	Y	Y	Y	NA	NA	Y	N	Y	Y	Y	moderate
黄玲. *et al*	Y	Y	Y	NA	Y	Y	N	Y	Y	Y	low
李红宇. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
李中燕. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
许杰红. *et al*	Y	Y	Y	NA	NA	Y	N	Y	Y	Y	low
段亚辉. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
Y. K. Kim. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
J. Li. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low
王磊. *et al*	Y	Y	Y	NA	Y	Y	N	Y	Y	Y	low
于维颖. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
H. Y. Lee. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low

(*Contd...*)

Supplementary Table 3: ***(Continued)***

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
Y. Xie. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
张勇慧. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
陈霞. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low
秦超. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
刘楠. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
藕二祥. *et al*	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
Bui TT. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
韩超. *et al*	Y	Y	Y	NA	N	Y	N	Y	Y	Y	moderate
韩超. *et al*	Y	Y	Y	NA	N	Y	N	Y	Y	Y	moderate
韩超. *et al*	Y	Y	Y	NA	N	Y	Y	Y	Y	Y	low
Wang P	Y	Y	Y	Y	N	Y	N	Y	Y	Y	moderate
黄丰. *et al*	Y	Y	Y	NA	N	Y	N	Y	Y	Y	moderate

(*Contd...*)

Supplementary Table 3: ***(Continued)***

Article	1. Was the allocation sequence adequately generated and applied?	2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random for outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?	Overall assessment of bias in each study
邢嵘. *et al*	Y	Y	Y	NA	N	Y	NA	Y	Y	Y	low
丁劲松. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
Lee YC. *et al*	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	low
韦祎. *et al*	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	low
Wu ZQ. *et al*	Y	Y	Y	NA	N	Y	N	Y	Y	Y	moderate
王定荣. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low
陈霞. *et al*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	low