Efficacy and safety of Chinese medicines for asthma
A systematic review protocol

Qi Shi, PhD, Dongxu Si, PhD, Haipeng Bao, PhD, Yue Yan, PhD, Yanhua Kong, PhD, Chunlei Li, PhD, Wenfeng He, MD, Dashzeveg Damchaaperenlei, PhD, Mingxia Yu, MD, Youlin Li, PhD

Abstract
Background: Asthma is a complex disease associated with many factors such as immunologic, environmental, genetic, and other factors. Common medicines used to treat asthma include β-agonist and glucocorticoid. However, in the long-term treatment, the effect of the above-mentioned drugs is not satisfactory, so many patients choose oral Chinese medicines instead of western medicines. The introduction of Chinese medicines therapies, a rapid proliferation of the literature on management of asthma in general, call for novel ways of evidence synthesis in this area. This systematic review is to systematically summarize and evaluate a large number of evidences for Chinese herbal interventions for asthma. Evaluate the efficacy and safety of Chinese medicines in the treatment of asthma and inform a decision aid for the clinical encounter between patients and clinicians. In addition, it helps to establish a future research agenda.

Methods: Five English databases (PubMed, Web of science, EBASE, Springer Cochrane Library, and WHO International Clinical Trials Registry Platform) and 4 Chinese databases (Wanfang Database, Chinese Scientific Journal Database, China National Knowledge Infrastructure Database, and Chinese Biomedical Literature Database) will be searched normatively according to the rule of each database from the inception to the present. The literature screening, data extraction, and quality assessment will be conducted by 2 researchers independently. Data will be synthesized by either the fixed-effects or random-effects model according to a heterogeneity test. Asthma control test symptom score will be assessed as the primary outcome. The curative effect of single symptom and sign; Withdrawal and reduction of western medicines in a course of treatment, including: time, type, and quantity; Maintenance of western medicines after the course of treatment, including: type, quantity; Asthma Quality of Life Questionnaire; laboratorial efficacy indexes as the secondary outcome. General physical examination; routine examination of blood, urine, and stool; electrocardiogram; liver and kidney function examination; possible adverse reactions and related detection indicators as the security indexes. Meta-analysis will be performed using RevMan5.3.5 software provided by the Cochrane Collaboration.

Results: This study will provide high-quality synthesis based on current evidence of Chinese medicines treatment for asthma in several aspects, including asthma control score, side effects and laboratory examination such as lung-function test, serum total immunoglobulin, and so on.

Conclusion: The results of this study will provide updated evidence for whether Chinese medicines is an effective and safe intervention for asthma.

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1. Introduction

Asthma, affecting 1% to 18% of the population in different countries, is a complex disease associated with many factors such as immunologic, environmental, genetic, and other factors. It usually characterized by chronic airway inflammation and defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[11] Chronic inflammation of the airways recognized to be controlled by the T-helper 2 (Th2) lymphocytes, which secrete cytokines to increase the production of immunoglobulin (IgE) by B cells.[2] Eosinophils (EOS) is one of the most important cells involved in the pathogenesis of chronic airway inflammation in asthma.[3]

Asthma can be divided into acute and nonacute attack period. Acute attack period, clinicians advocate the use of Western medicines (such as bronchodilators,[4] monoclonal antibodies,[5,6] corticosteroids,[7,8] the combination of inhaled corticosteroid and long-acting β2-agonist,[9] and others[10]), even bronchial thermoplasty[11] symptomatic supportive treatment to relieve symptoms. Most patients may benefit from these treatments. Nonacute attack period, also known as chronic duration, refers to the patient although there is no acute attack of asthma, but in a considerable period of time still have different frequency and different degrees of wheezing, coughing, chest tightness, and other symptoms. Thus, due to the persistence of symptoms in chronic duration asthma, and the above-mentioned drugs treatment is not satisfactory, Patients’ conditions were not effectively controlled and their quality of life was not improved. In addition, some patients were unable to tolerate the above drugs[12–14] or show side effects, such as gastrointestinal, cardiovascular, metabolic, and bone-related complications that have been reported from long-term use of the above-mentioned medications.[15–17] Therefore, many patients choose Chinese medicines, with relatively few side effects, to treat asthma. Traditional Chinese medicine (including Chinese medicines,[18,19] acupuncture,[20] massage, acupoint sticking therapy,[21] acupoint catgut embedding therapy,[22] diet therapy,[23] and other physical interventions) is widely applied for asthma.

Among the above treatment measures, Patients often choose oral Chinese medicines to treat asthma. Many clinical and experimental studies have confirmed the effectiveness of Chinese medicines in the treatment of asthma, such as Wengtong decoction could accelerate EOS apoptosis, reduce asthma inflammation, and alleviate the disease through regulating and controlling the factors related to the anti-apoptosis and pro-apoptosis[3]: Yupingfeng San could inhibit NOD-like receptor family pyrin domain-containing 3 inflammassome components to attenuate the inflammatory response in asthma.[24] Many Chinese herbs could inhibit the activation and migration of inflammatory cells, regulate the balance of Th1/Th2 responses, and suppress allergic hyperreactivity through inducing regulatory T cells or attenuating the function of dendritic cells.[25] Pingchuans formula and Bu-Shen-Yi-Qi formulae could improves asthma via restoration of the Th17/Treg balance in a mouse model.[26,27] Although a rapid proliferation of the literature on the introduction of Chinese medicines therapies of asthma in general, few systematic analyses and syntheses are identified. Thus, call for novel ways of evidence synthesis in this area. This systematic review is to systematically summarize and evaluate a large number of evidences for Chinese herbal interventions for asthma. Evaluate the efficacy and safety of Chinese medicines in the treatment of asthma and inform a decision aid for the clinical encounter between patients and clinicians. In addition, it helps to establish a future research agenda.

2. Methods

2.1. Study registration

The protocol of this review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019136074) and has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[28]

2.2. Inclusion criteria for study selection

2.2.1. Types of studies.

Non-RCTs, cohort studies, reviews, case reports, experimental studies, expert experience, the data of the included study is missing or incomplete, and duplicate publications will be excluded.

2.2.2. Types of participants. Asthma participants of all ages will be included in the study regardless of nationality, gender, race, occupation, or education level.

Patients with drug-induced asthma, aspirin intolerance triad, asthma with fixed airflow limitation, asthma with obesity, late-onset asthma will be excluded.

2.2.3. Types of interventions. This study focuses on the clinical trial (RCTs) of asthma with the therapy of Chinese medicines, and the results will provide advice and consultation for clinicians. Therefore, patients in the experimental group were only treated with Chinese medicines, and the types and dosage forms of Chinese medicines prescriptions were not limited. In addition, western medicines and other treatment methods were not combined (except for emergency medical use). Studies that with combination therapy fail to objectively evaluate the efficacy and safety of Chinese medicines will be excluded.
Studies of control groups were treated with western medicines or placebo and other interventions (eg, acupuncture, moxibustion, and other physical interventions).

2.2.4. Types of outcome measures

2.2.4.1. Primary outcomes. Asthma control test\textsuperscript{[29]} symptom score was assessed as the primary outcome. Symptom score: Step 1: accurately record the score of each question; Step 2: add up the scores of each question to get the total score; Step 3: find the meaning of the total score (3 levels: 25 points: total control; 20–24 points: partial control; <20 points: not under control).

2.2.4.2. Secondary outcomes. The secondary outcomes of this review mainly include the following aspects:

(1) The curative effect of single symptom and sign.
(2) Withdrawal and reduction of western medicines in a course of treatment, including: time, type and quantity; maintenance of western medicines after the course of treatment, including: type, quantity.
(3) Asthma Quality of Life Questionnaire.\textsuperscript{[9,10]}
(4) Laboratory efficacy indexes.
   (1) Serum CD4\textsuperscript{+}, CD8\textsuperscript{+} levels, and CD4\textsuperscript{+}/CD8\textsuperscript{+} ratio.
   (2) The Th1, Th2.\textsuperscript{[25]}
   (3) Serum IgE.\textsuperscript{[31]}
   (4) Blood eosinophil count.\textsuperscript{[9]}
   (5) Skin prick test.

2.2.4.3. Security index.

(1) General physical examination (temperature, pulse, respiration, blood pressure).
(2) Routine examination of blood, urine, and stool.
(3) Electrocardiogram.
(4) Liver and kidney function examination.
(5) Possible adverse reactions and related detection indicators.

2.3. Search methods for identification of studies

2.3.1. Electronic searches. Five English databases (PubMed, Web of science, EBASE, Springer Cochrane Library, and WHO International Clinical Trials Registry Platform) and 4 Chinese databases (Wanfang Database, Chinese Scientific Journal Database, China National Knowledge Infrastructure Database, and Chinese Biomedical Literature Database) will be searched normatively according to the rule of each database from the inception to the present.

2.3.2. Searching strategy. The search strategy for PubMed is listed in Table 1, which including all search terms, and other searches will be conducted based on these results. This search strategy will be modified as required for other electronic databases.

2.4. Data collection and analysis

2.4.1. Selection of studies. The basic process of the included literatures will be determined by referring to the Cochrane Collaboration System Evaluator’s Manual (5.1.0). The study name, author, year, database, and whether the study met eligibility criteria and should be included in the review will be recorded using an excel spreadsheet. Reasons for inclusion and exclusion (PICOS) are documented in a spreadsheet during abstract screening and full-text evaluation. The records in this spreadsheet will be used to generate the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig. 1). All the procedures will be carried out by 2 independent reviewers and completed cross-check. If there is any disagreement, the 3rd author will be invited to assist in the discussion and make a decision.

2.4.2. Unit of analysis issues. We will only extract the 1st experimental period data of crossover trials to avoid carryover effects. With multiple intervention groups, we will combine all relevant experimental groups and control intervention groups into a single respectively group to prevent a unit of analysis issue.

2.4.3. Data extraction and management. Two independent reviewers will extract the data of interest from the eligible study and enter the following information in the data extraction sheet: The basic characteristics of each study (1st author, title, source/journal, time of publication, and country); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type of Chinese medicines, randomization, allocation concealment, and blinding methods); comparators (western medicines); outcomes (measures, main outcomes, security indexes, and follow up); if funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer will make a decision.

2.4.4. Data synthesis. RevMan5.3.5 will be used for all statistical analyses. Based on the heterogeneity levels of the included studies, a fixed-effects model will be used if there is no significant heterogeneity of the data ($I^2 \leq 50\%$); a random-effects model will be used if significant heterogeneity existed ($I^2 > 50\%$). The dichotomous data will be analyzed by risk ratio with 95% confidence intervals (CIs), while the continuous data will be analyzed by mean difference (MD) or standard MD with 95% CIs. The meaningful heterogeneity will be explained by any additional assessment included sensitivity analysis or subgroup analysis depended on the data.

2.4.5. Assessment of study quality. A rigorous quality assessment of the literatures included in the study will be conducted using the bias risk assessment tool (RevMan5.3.5) of the Cochrane Collaborative Network System, and high, low, unclear evaluations will be performed for each item. Meanwhile, the STRICTA checklist will be completed. When 2 quality assessors are unable to reach a consensus on the risk assessment by negotiation, the third the third reviewer will make a decision.
2.4.6. Assessment of reporting bias. When 10 or more studies are included in a meta-analysis, we will assess the reporting bias. The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from publication bias, if appropriate.\[32\]

2.4.7. Assessment of heterogeneity. Data analysis will be performed using RevMan5.3.5 software provided by the Cochrane Collaboration. Using the software to obtain forest plots and test the heterogeneity between the included studies. Chi-square test and $I^2$ value will be applied to calculate and present the heterogeneity degree. When $P > .1$, $I^2 < 50\%$, it is considered that there is no heterogeneity between the trials, and the fixed effect model will be used for statistics, otherwise, the random effect model will be adopted to analyze.

2.4.8. Subgroup analysis. When heterogeneity is detected, we will judge the source of heterogeneity through subgroup analysis (eg, different types of Chinese medicines therapies, research quality, publication age, participation population, length of treatment). In addition, we can also observe the relationship between effect values and grouping variables.

2.4.9. Sensitivity analysis. In the case of sufficient trials data, sensitivity analysis is mainly carried out for research characteristics or types such as methodological quality, and the effect on total effects is examined by excluding certain low-quality studies or small-sample sizes of studies. When heterogeneity occurs, we may perform sensitivity analysis by excluding the data one by one.

3. Discussion

Asthma can be divided into acute and nonacute attack period. In the acute exacerbation period, $\beta$-agonist and glucocorticoid are used to symptomatic treatment. Non-acute attack period, due to the persistence of symptoms, and the above-mentioned drugs treatment is not satisfactory. Patients’ conditions were not effectively controlled and their quality of life was not improved. Furthermore, many patients were unable to tolerate the above drugs or show side effects. Therefore, many patients choose oral Chinese medicines instead of western medicines. Although Chinese medicines have a certain unique therapeutic effect on asthma. However, due to the complex composition of Chinese
medicines, potential safety hazards may exist. The purpose of this systematic review is to systematically summarize and evaluate a large number of evidences for Chinese herbal interventions for asthma. Evaluate the efficacy and safety of Chinese medicines in the treatment of asthma and inform a decision aid for the clinical encounter between patients and clinicians. In addition, it helps to establish a future research agenda.

**Author contributions**

**Conceptualization:** Qi Shi, Dongxu Si, Youlin Li.

**Data curation:** Haipeng Bao, Wenfeng He, Dashzeveg Damchaaperen, Mingxia Yu.

**Formal analysis:** Dongxu Si, Haipeng Bao.

**Project administration:** Qi Shi, Dongxu Si, Haipeng Bao.

**Supervision:** Qi Shi, Yue Yan, Yanhua Kong, Chunlei Li.

**Writing – original draft:** Qi Shi, Dongxu Si.

**Writing – review and editing:** Qi Shi, Youlin Li.

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