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REVIEW ARTICLE

Herbal medicine for adults with asthma: a systematic review

Johannah L. Shergis, PhD[1], Lei Wu, MD[2], Anthony L. Zhang, PhD[1], Xinfeng Guo, PhD[2], Chuanjian Lu, PhD[2,3], and Charlie C. Xue, PhD[1,2]

[1]China-Australia International Research Centre for Chinese Medicine, School of Health and Biomedical Sciences, RMIT University, Melbourne, Australia, [2]Guangdong Provincial Hospital of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, China, and [3]Guangdong Provincial Key Laboratory of Clinical Research on Traditional Chinese Medicine Syndrome, Guangzhou, China

Abstract

Background: Many people with asthma use herbal medicines to help reduce symptoms and improve asthma control. *Objective*: To update the systematic review and meta-analysis of randomised controlled trials of herbal medicine for adult asthma. *Data Sources*: Nine English and Chinese databases were searched (PubMed, Embase, CINAHL, CENTRAL, AMED, CBM, CNKI, CQVIP, Wanfang). *Study Selections*: Herbal medicines combined with routine pharmacotherapies compared with the same pharmacotherapies alone or placebo. Cochrane Risk of Bias Tool and GRADE Summary of Findings tables were used to evaluate methodological quality. *Results*: Twenty-nine (29) studies involving 3,001 participants were included. Herbal interventions used multi-ingredients such as licorice root, crow-dipper, astragali, and angelica. Compared with routine pharmacotherapies alone, herbal medicines as add-on therapy improved lung function (FEV1: MD 7.81%, 95% CI 5.79, 9.83, $I^2 = 63\%$; PEFR: MD 65.14 L/min, 95% CI 58.87, 71.41, $I^2 = 21\%$); asthma control (MD 2.47 points, 95% CI 1.64, 3.29, $I^2 = 55\%$); reduced salbutamol usage (MD −1.14 puffs/day, 95% CI −2.20, −0.09, $I^2 = 92\%$); and reduced acute asthma exacerbations over one year (MD −1.20, 95% CI −1.82, −0.58, one study). Compared with placebo plus pharmacotherapies herbal medicines as add-on therapy improved lung function (FEV1: MD 15.83%, 95% CI 13.54, 18.12 and PEFR: MD 55.20 L/min, 95% CI 33.41, 76.99). Other outcomes were not reported in these placebo studies. Included studies were low to moderate quality. Adverse events were rare. *Conclusions*: Herbal medicines combined with routine pharmacotherapies improved asthma outcomes greater than pharmacotherapies alone. Included studies did not blind participants therefore more studies that address such weaknesses are warranted.

Keywords

Adult asthma, herbal medicine, Chinese medicine, systematic review, meta-analysis

History

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Introduction

While clinical managements for asthma have improved over recent years, yet asthma continues to be poorly controlled in some patients. These patients may benefit from additional treatment options such as herbal medicines. Asthma has long been treated using herbs in multiple traditional medicine systems in Europe, the Middle East and China [1]. Recent reports indicate up to 80% of adults with asthma use some form of complementary medicine, commonly herbal medicine, despite international guidelines not extending any recommendations for use [2–4]. Therefore, it is important to evaluate these treatments to ensure they do not adversely harm patients and ideally have some demonstrable effectiveness.

The physiological effects of herbal medicines are varied due to multiple compounds within one formulation. This complexity is not fully understood but experimental evidence does suggest measurable effects on reducing airway inflammation, hyper-responsiveness, broncho-relaxation and mucus accumulation [5–8]. Screening 12 herbs *in vitro* showed inhibition of pro-inflammatory cytokines and broncho-relaxation in rat trachea, providing preliminary evidence of effects for asthma [8]. In mice models of chronic asthma, Ginkgo biloba and ginseng reduced changes in the lungs that are common in chronic asthma, such as thickening of epithelium and increased goblet and mast cell numbers, resolving pathological changes in the lungs [5,6]. In another study, a herb extract, ginsan, also reduced airway inflammation and hyper-responsiveness in a murine asthma model [7]. The result was likely due to COX gene regulation and notably the anti-inflammatory effects were comparable to the corticosteroid dexamethasone [7]. If these physiological effects are correct it may account for herbal medicines positive effects in the clinical setting in terms of improving lung function, asthma control, quality of life and reducing exacerbations.

Previous systematic reviews indicate herbal medicines have promising effects for asthma. However the evidence is limited by poor methodological quality of the included studies [9,10].

Correspondence: Charlie C. Xue, School of Health and Biomedical Sciences, RMIT University, P.O. Box 71, Bundoora, VIC 3083, Australia. Tel: +613 99257360. Fax: +613 99256539. E-mail: charlie.xue@rmit.edu.au

The aim of this review is to provide an up-to-date analysis of evidence for use of herbal medicines for adult asthma and determine if new research has addressed the methodological shortfalls previously identified. We also focus on Chinese herbal medicine, which was not fully evaluated in the previous reviews [9,10].

Methods

Studies

Studies were randomised controlled trials with parallel or cross-over design.

Participants

Participants were adults with an asthma diagnosed according to the Global Initiative for Asthma (GINA) or equivalent, such as the Experts Consensus of Chinese Medicine Diagnosis and Treatment of Asthma published by the Chinese Medical Association [2,11]. Cough-variant, medication induced and children with asthma were excluded. Studies evaluating acute exacerbations of asthma were also excluded.

Interventions

Interventions included oral herbal medicine combined with pharmacotherapy (add-on therapy) for at least one month. Herbal medicine was defined as plants, animals or minerals or their parts, root, bark, stem, flower, fruit etc; but not plant extracts or constituent compounds derived from plants. Control interventions included placebo or active control (pharmacotherapies) routinely used for asthma, such as corticosteroids and or bronchodilators. The pharmacotherapy in the intervention and active control groups matched.

Outcomes

Studies must include at least one of the pre-defined outcome measures. Primary outcomes are lung function; forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR). Secondary outcomes included asthma control measured with the Asthma Control Test (ACT), use of rescue medication, number of acute exacerbations of asthma, and health related quality of life measured with the Asthma Quality of Life Questionnaire (AQLQ). Type and number of adverse events were also analysed.

Search strategy

English and Chinese databases were searched from inception to May 2014. English databases included PubMed, Embase, CINAHL, CENTRAL, and AMED. Chinese databases included CBM, CNKI, CQVIP and Wanfang. Restrictions were not applied. The search included terms for asthma, herbal medicine and randomised controlled trials. Reference lists of published reviews and clinical trial registries (clinicaltrials.gov, EU Registry, Chinese Registry, Australian New Zealand Registry) were also searched.

Data collection and extraction

Two independent reviewers (JS and WL) performed data search, screening and extraction. Data included: type of study, location, setting, diagnostic criteria, duration of asthma, sample size, interventions, treatment duration, follow-up duration, and outcomes. Any disagreement was discussed with a third reviewer (AZ). Authors were contacted when published reported did not provide sufficient information.

Data analysis

End of treatment between group differences were analysed. Analyses were performed in Review Manager (RevMan). Continuous data are reported as mean difference (MD) with 95% confidence intervals (CI) and dichotomous data as risk ratio (RR) with 95% CI. We planned to combine results from parallel and cross-over trials if data were available and in an appropriate form. If cross-over trials did not include paired analysis results were presented descriptively. Baseline balance and change for each group were also assessed. Evaluation of within group mean change ensured consistency with known effects of the active controls and showed any add-on benefit of the herbal medicines.

There were two main meta-analyses: (1) herbal medicine plus pharmacotherapy versus pharmacotherapy; and (2) herbal medicine plus pharmacotherapy versus placebo plus pharmacotherapy. Statistical heterogeneity was calculated using the I^2 statistic and greater than 50% was considered to be substantial. Subgroup analyses were performed to explore heterogeneity and a random-effects model applied.

Planned subgroup analyses (dependent on available data) included study duration, herbal administration type (e.g. decoction, tablets, and powder), pharmacotherapy drug class (e.g. corticosteroids, bronchodilators, or their combinations). Sensitivity analysis was also planned by removing studies that did not report an appropriate randomisation sequence generation method.

Risk of bias and publication bias

The Cochrane Collaboration's Risk of Bias Tool was used to assess bias [12]. Seven domains of risk were assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias (baseline balance and funding/conflict of interest). Risk was assessed as low, high, or unclear by two independent reviewers. Disagreements were resolved by discussion with a third reviewer. Publication bias for meta-analysis of ten or more studies was assessed using funnel plots and Egger's test.

GRADE summary of findings

To summarise the quality and strength of evidence the Cochrane Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used [13]. Quality of evidence was evaluated against five factors: (1) limitations in study design, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision, and (5) publication bias. Two summary of findings tables were produced (Tables 1 and 2). These tables align with the pre-defined groupings,

Table 1. Summary of findings: herbal medicines plus pharmacotherapy versus pharmacotherapy.

Patient or population: Adult asthma
Setting: Outpatients and inpatients
Intervention: Herbal medicines plus pharmacotherapy
Comparison: Pharmacotherapy

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with pharmacotherapy	Risk difference with herbal medicines plus pharmacotherapy		
Lung function (FEV1%) follow up: median 3 months	The mean lung function was 73.6%	The mean lung function in the intervention group was 7.81% higher (5.79 higher to 9.83 higher)	1782 (14 RCTs)	⨁⨁◯◯ LOW[a,b]
Lung function (PEFR L/min) follow up: median 3 months	The mean lung function was 311.8 L/min	The mean lung function in the intervention group was 65.14 L/min higher (58.87 higher to 71.41 higher)	1037 (7 RCTs)	⨁⨁⨁◯ MODERATE[a]
Asthma control (ACT)[d] follow up: median 3 months	The mean asthma control was 20.1 points	The mean asthma control in the intervention group was 2.47 points higher (1.64 higher to 3.29 higher)	561 (5 RCTs)	⨁⨁◯◯ LOW[a,b]
Rescue bronchodilator use (puffs per day) follow up: median 3 months	The mean rescue bronchodilator use was 2.5 puffs/d	The mean rescue bronchodilator use in the intervention group was 1.14 puffs/d fewer (2.2 fewer to 0.09 fewer)	194 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]
Acute exacerbations of asthma follow up: 1 year	The mean acute exacerbations of asthma was 4.3 exacerbations	The mean acute exacerbations of asthma in the intervention group was 1.2 exacerbations fewer (1.82 fewer to 0.58 fewer)	143 (1 RCT)	⨁⨁◯◯ LOW[a,c]
Quality of life (AQLQ)[e] follow up: median 3 months	The mean quality of life was 154.81 points	The mean quality of life in the intervention group was 2.22 points higher (2.6 lower to 6.74 higher)	142 (1 RCT)	⨁⨁◯◯ LOW[a,c]
Adverse events follow up: median 3 months	Four studies reported no adverse events occurred. Three studies reported events however group and number of cases was not reported. Adverse events included discomfort in the throat, hoarseness, fungal infection in the throat, discomfort in the stomach and abdomen, palpitation and tremor of the hands.			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval.
GRADE Working Group grades of evidence High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[a]Lack of blinding of participants and personnel.
[b]Considerable statistical heterogeneity.
[c]Small sample size limits certainty of results.
[d]Asthma Control Test (ACT): 5–25 points. Higher scores indicate more controlled asthma.
[e]Asthma Quality of Life Questionnaire (AQLQ): 32 items, range: 32–224 points. Higher scores indicate better quality of life.

that is, herbal medicine plus pharmacotherapy versus pharmacotherapy and herbal medicine plus pharmacotherapy versus placebo plus pharmacotherapy. To rate the quality of evidence a panel was formed according to GRADE recommendations [13]. The panel included the review authors, research methodologists, Chinese medicine practitioners, and Western medicine physicians.

Results

Study design

Search of English and Chinese databases found 1437 potentially relevant studies. After reviewing full-text, 29 RCTs were included (Figure 1) [14–32]. A total of 3001 participants were evaluated and mean sample size was 103 (range: 16–552). Participants' mean age was 43 years old, they had asthma for 1–29 years and about half were male ($n = 1495$). We planned to only include studies with adults aged 18 years or over. One included study enrolled participants aged 14 years or older. For the purposes of this review the participants aged 14–18 years were considered to be adults. All studies were randomised using parallel design except one that was cross-over [32]. Three were placebo controlled [32–34]. Eleven used an appropriate randomisation method and the others did not state their randomisation method. Studies were performed in China or Japan and two were published in English [22,32]. Recruitment was from hospital inpatients and outpatients and all were diagnosed according to GINA, American Thoracic Society or the Asthma Guideline published by the Chinese Medical Association [2,11].

Interventions

Interventions included combinations of herbs or single herbs. All included studies used herbs from Chinese material medica.

Table 2. Summary of findings: herbal medicines plus pharmacotherapy versus placebo plus pharmacotherapy.

Patient or population: Adult asthma
Setting: Outpatients and inpatients
Intervention: Herbal medicines plus pharmacotherapy
Comparison: Placebo plus pharmacotherapy

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo plus pharmacotherapy	Risk difference with herbal medicines plus pharmacotherapy		
Lung function (FEV1%) follow up: median 1 months	The mean lung function was 72.4%	The mean lung function in the intervention group was 15.83% higher (13.54 higher to 18.12 higher)	214 (1 RCT)	⨁⨁⨁◯ MODERATE[a]
Lung function (PEFR L/min) follow up: median 6 months	The mean lung function was 142.8 L/min	The mean lung function in the intervention group was 55.2 L/min higher (33.41 higher to 76.99 higher)	48 (1 RCT)	⨁⨁⨁◯ MODERATE[a]
Asthma control – not reported				
Rescue bronchodilator use – not reported				
Acute exacerbations of asthma – not reported				
Quality of life – not reported				
Adverse events – not reported				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval.
GRADE Working Group grades of evidence High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[a]Small sample size limits certainty of results.

Other herbal medicines from Ayurvedic, European and South American materia medica were found however these studies did not meet the inclusion criteria; because they used extracts or compounds derived from herbs, they did not combine herbal medicine with pharmacotherapy (add-on therapy) or treatment duration was less than 4 weeks. The included studies used different herb combinations except two studies that used *Bu zhong yi qi tang* [17,35] and another two used *Zhi bai di huang wan* plus *Jin shui liu jun jian* [36,37]. Twenty-one studies used a traditional combination of herb ingredients and seven used a self-designed formula.

Combinations included on average ten ingredients and despite differences individual constituents were similar. The most common were *Glycyrrhiza uralensis* (Licorice root, pinyin: *gan cao*), *Pinellia ternata* (Crow-dipper, *ban xia*), *Astragalus membranaceus* (Astragali, *huang qi*), and *Angelica sinensis* (Angelica, *dang gui*), all used in 10 or more studies. Twenty-one studies (75%) administered the herbs as decoction, three as tablets, four as powdered granules and one as paste. All administration types were typical of herbal prescriptions and in appropriate dosages according to recommendations [38]. Interventions was given for 1–12 months (mean duration: 3 months) and four studies included a follow-up of 1 month, 6 months or 1 year [14,16,17,22].

Pharmacotherapies in the intervention groups matched the active control groups. Six studies did not state specific drugs but mentioned routine pharmacotherapies were selected based on individual participant needs [17,18,21,39–41]. Fluticasone/salmeterol was used in 10 studies [14,15,20,23,24,26,27,29,31,35]. Three studies used inhaled corticosteroids (ICS) [36,37,42] and three used ICS plus a short-acting beta-agonists (SABA) [19,22,30]. Two studies used SABA alone [28,43], another two used a beta-2 agonist and theophylline [16,32] and one used ICS, SABA and theophylline [25]. Two studies included placebo combined with theophylline or budesonide/formoterol [33,34] and the cross-over study used placebo during one phase [32].

Outcomes

Lung function outcomes were reported in 26 studies; FEV1% (15 studies), FEV1 litres (10 studies) and PEFR (14 studies). Secondary outcomes were seldom reported; asthma control measured with the ACT (5 studies), use of rescue medication (3 studies), acute exacerbations of asthma (2 studies), and health related quality of life measured with the AQLQ (2 studies).

Adverse events

Eight studies reported adverse events [14,15,19,21,27–29,32]. Of these, five reported no events occurred. In the other three studies events in both groups were pooled and could not be attributed to intervention or control. After taking *Jin shui bao jiao nang* and/or fluticasone/salmeterol participants reported discomfort in the throat, hoarseness and fungal infection in the throat [29]. After *Ling zhi bu fei tang* plus budesonide and/or fluticasone/salmeterol participants reported discomfort in the stomach and abdomen [27], and after a self-designed decoction and/or beclomethasone and terbutalin participants reported

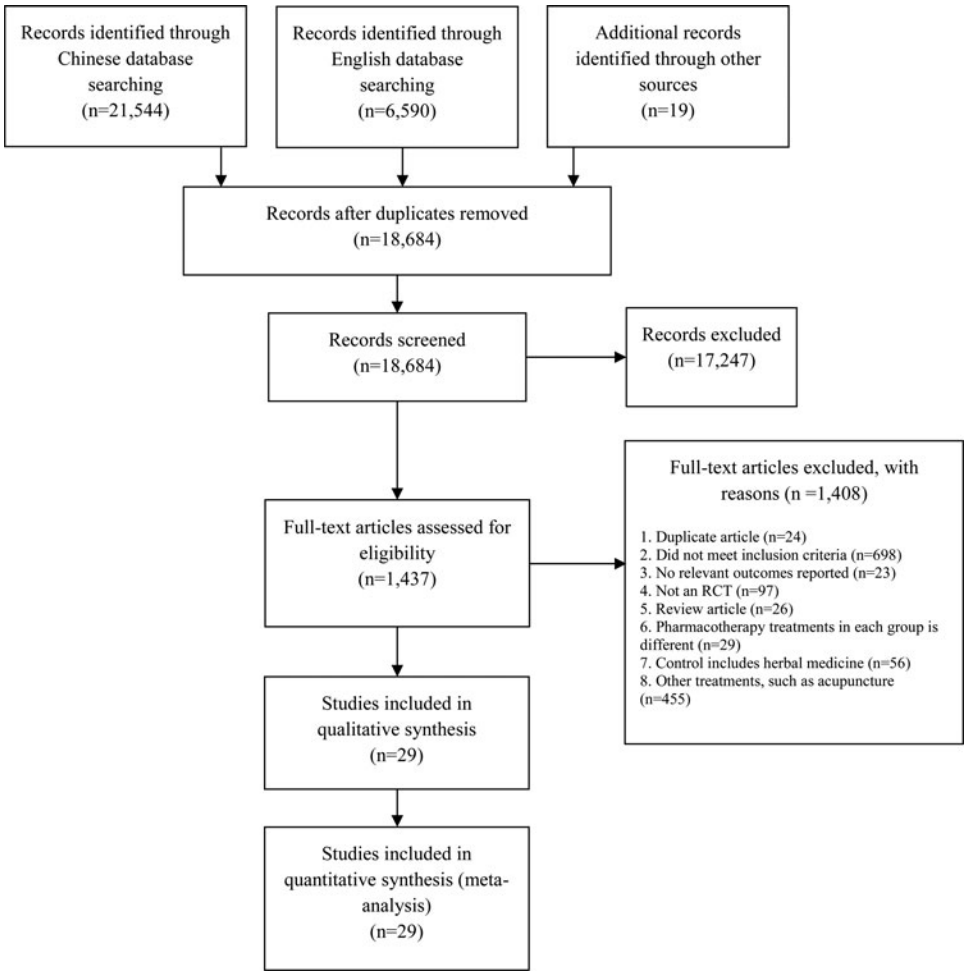

Figure 1. Flow diagram of study selection.

hoarseness and fungal infection in the mouth and palpitation and tremor of the hands [19]. Most of the adverse events are known side effects of the pharmacotherapies.

Risk of bias

The active controlled studies were low quality and placebo controlled studies were moderate quality (Table 1 and 2). Evaluation of risk of bias was overall limited by insufficient details in the published reports. Risk of bias summary is presented in Table 3. Only 11 studies (39%) appropriately described sequence generation method [14,18,22,26,29,31,34–37,41] and one reported concealment by central allocation [26]. All studies used active control and blinding of participants and personnel was assessed as high risk of bias, except in three studies that used placebo – blinding was at low risk of bias [32–34]. Blinding of outcome assessors was rated as high or unclear risk, except in four studies [33,34,42,43].

Withdrawals were adequately reported, except in six studies [25,26,28,29,37,42]. Outcome reporting was mostly at low risk of bias, two studies were judged as unclear because they did not pre-define outcomes [22,23]. Two studies were at high risk because they did not report the results of pre-defined outcomes [24,27]. Other bias including baseline balance was at low risk. Funding/conflicts of interest was at low risk in eight studies [22,24,26,27,31,36,37,41] and the others did not provide sufficient information to permit a judgement.

Publication bias

Publication bias was measureable in one meta-analysis of 14 studies. For FEV1%, the funnel plot was symmetrical and publication bias was not detected. Egger's test $t = -0.22$, 95% CI −1.9 to 1.5, $p = 0.83$.

Effects of interventions: herbal medicines plus pharmacotherapy versus pharmacotherapy

All pre-defined primary and secondary outcomes were reported in at least one study. The Summary of findings table presents the results and quality of evidence (Table 1). Results were low to moderate quality. Adverse events were reported in seven studies and herbal medicines plus pharmacotherapy appeared to be safe for adults with asthma.

Lung function

FEV1

A meta-analysis of 14 studies (1782 participants) showed a significant improvement in FEV1% predicted in favour of herbal medicines plus pharmacotherapy: mean difference (MD) 7.81%, 95% confidence interval (CI) 5.79–9.83 (Figure 2) [15,17,19–21,23,24,26,27,29,36,40,42,43]. Results are limited by substantial heterogeneity ($I^2 = 63\%$). Individual subgroup analysis by study duration, administration type, pharmacotherapy drug class or removal of studies with unclear

Table 3. Study characteristics.

Author, year	Participants I/C	Herbal medicine, preparation type (No. of ingredients)	Control*	Treatment duration	Risk of bias#	Outcomes
Wang, 2013	20/20	Self-designed, decoction, 14	Fluticasone/salmeterol	3 months	U, U, H, H, L, U, U	FEV1%
Yao, 2013	30/29	Self-designed, decoction, 8	Fluticasone/salmeterol	1 month	L, U, H, H, L, L, L	FEV1L, ACT
Yang, 2009	32/32	Liu jun zi & He che da zao, pills, NS	Budesonide and salbutamol	9 months	U, U, H, H, L, L, U	Exacerbations
Xiang, 2013	100/100	Jin shui bao, capsules, NS	Fluticasone/salmeterol	12 months	L, U, H, H, U, L, U	FEV1%, ACT
Wen, 2012	277/275	Ling zhi bu fei, decoction, 3	Mild asthma:Budesonide; Moderate asthma: Fluticasone/salmeterol	3 months	U, U, H, H, L, H, L	FEV1%, PEFR
Wang, 2013	45/45	Self-designed, decoction, 8	Fluticasone/salmeterol	1 month	U, U, H, H, L, H, L	FEV1%, PEFR
Qing, 2007	67/64	Bu zhong yi qi, pills, NS	Adjusted as needed	6 months	U, U, H, H, L, L, U	FEV1L, PEFR
Lu, 2010	34/67	Chuan xiong ping chuan he ji, decoction, NS	Fluticasone/salmeterol	3 months	U, U, H, H, L, L, H	FEV1%, PEFR
Li, 2013	31/32	Jie jing qu feng, decoction, 8	Fluticasone/salmeterol	1 month	L, U, H, H, L, L, U	ACT
Li, 2012	30/30	Qu feng zhi jing, powder, NS	Adjusted as needed	2 months	U, U, H, L, U, L, U	FEV1%, usage
Jin, 2013	30/30	Bu zhong yi qi, pills, 8	Fluticasone/salmeterol	6 weeks	L, U, H, H, L, L, U	FEV1L
Huang, 2013	48/48	Gu ben ping chuan, decoction, 15	Adjusted as needed	3 months	L, U, H, H, L, L, L	FEV1L, PEFR, ACT
Guo, 2013	49/47	Chuan su ting, powder, 15	Adjusted as needed	40 days	U, U, H, H, L, L, U	PEFR
Dong, 2012	107/107	Xiao ping yi hao, decoction, 11	Placebo and budesonide/formoterol	1 month	L, U, L, L, L, L, H	FEV1%
Cui, 2008	29/26	Zhi bai di huang & Jin shui liu jun jian, Pills & decoction, NS	Budesonide	3 months	L, U, H, H, U, L, L	FEV1L, PEFR, AQLQ, usage
Cui, 2006	20/20	Zhi bai di huang & Jin shui liu jun jian, Pills & decoction, 2	Budesonide	12–14 weeks	L, U, H, H, L, L, L	FEV1%, PEFR
Cao, 2006	24/24	Zhi mu, powder, 1	Placebo and aminophylline	6 months	U, U, L, L, L, L, U	PEFR
Su, 2013	50/50	Self-designed, decoction, 10	Adjusted as needed	3 months	U, U, H, H, L, L, U	FEV1%
Huang, 2003	8/8	Lei gong teng jia su, decoction, NS	Salbutamol	1 month	U, U, H, L, L, L, U	FEV1%, ACT
Hong, 2013	45/45	Ping chuan, decoction, 9	Adjusted as needed	6 weeks	U, U, H, H, L, L, U	FEV1%, PEFR
Shen, 2007	40/40	Self-designed, decoction, 10	Beclomethasone and terbutalin	3 months	U, U, H, H, L, L, U	FEV1%
Wu, 2000	25/25	Self-designed, decoction, 11	Terbutalin	3 months	U, U, H, H, U, L, U	FEV1L, PEFR
Wang, 2013	72/72	Qing fei ping chuan bu shen, powder, 14	Fluticasone/salmeterol	3 months	L, L, H, H, U, L, L	FEV1%, AQLQ, usage
Qiu, 2013	35/35	Based on diagnosis**, decoction, varied	Adjusted as needed	1 month	L, U, H, H, L, L, U	FEV1L, PEFR
Ou, 2007	50/48	Ping chuan ding qi, decoction, 11	Procaterol and theophylline	6 weeks	U, U, H, H, L, L, U	FEV1L, PEFR
Tang, 2014	74/69	Self-designed, paste, 18	Budesonide, salbutamol, and aminophylline	60 days	L, U, H, U, L, U, L	ACT, exacerbations
Wang, 2011	30/30	Fang xiao yin, decoction, 10	Budesonide, beclomethasone, and salbutamol	1 month	U, U, H, H, U, L, U	FEV1L, PEFR
Su, 2010	72/68	She gan ma huang, decoction, 15	Fluticasone/salmeterol	2 months	U, U, H, H, L, L, U	FEV1%, PEFR
Urata, 2002	33/33	Saiboku-to TJ-96, powder, 10	Placebo and B2Agonist and theophylline	1 month	U,U, L, U, L, L U	FEV1L, FEV1%

*The same pharmacotherapy was used in the intervention group as in the control group.
**In this study, participants were given herb medicines based on individual diagnosis. A set group of herbs was not given.
#U: unclear risk of bias; H: high risk of bias; L: low risk of bias. Each initial relates to the seven domains of risk of bias. These are; 1. sequence generation; 2. allocation concealment; 3. blinding of participants and personnel; 4. blinding of outcome assessors; 5. incomplete outcome data; 6. selective reporting; 7. other bias (baseline balance and funding/conflict of interest).

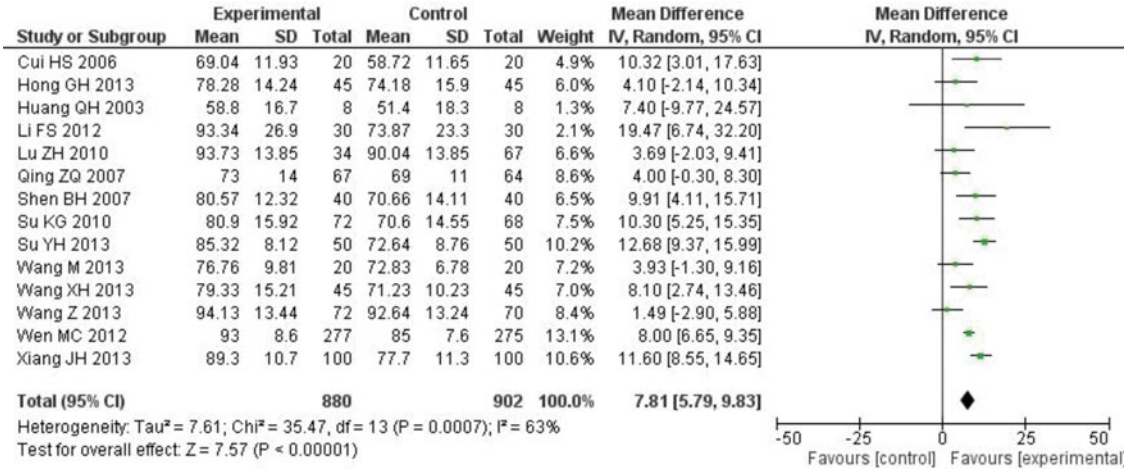

Figure 2. Herbal medicine plus pharmacotherapy versus pharmacotherapy: lung function FEV1% predicted.

risk of bias for sequence generation did not reduce heterogeneity. The best estimate of intervention effect came from a subgroup of four homogeneous studies conducted for less than 3 months and administering a herbal decoction; FEV1%, MD 7.92% (95% CI 4.80, 11.03), $I^2 = 0\%$ [20,24,40,43]. The positive effect of herbal medicines plus pharmacotherapies was also evident in terms of change from baseline. The intervention groups showed a difference in FEV1% of 16.72% compared to a difference of 8.53% in the control groups.

Herbal medicines plus pharmacotherapy improved FEV1 litres compared with pharmacotherapy in eight homogeneous studies; MD 0.37 L (95% CI 0.31, 0.43), $I^2 = 18\%$ (Figure 3) [16,18,25,28,31,35,37,41]. The effect met the minimal clinically important difference (MCID) of 0.23 litres [44]. Five studies were at low risk of bias for sequence generation and they showed an effect similar to the larger pool; MD 0.27 L (95% CI 0.13, 0.42), $I^2 = 34\%$ [18,31,35,37,41].

PEFR

There was a significant increase in PEFR L/min in a pool of seven studies (1,037 participants); MD 65.14 L/min (95% CI 58.87, 71.41), $I^2 = 21\%$ (Figure 4) [16,20,25,27,28,37,41]. The result exceeded the MCID of 18.8 L/min [44]. Only two studies were at low risk of bias for sequence generation [37,41]. Five studies reported PEFR% predicted (434 participants) [15,17,39,40,43]. Herbal medicines plus pharmacotherapy significantly improved PEFR%; MD 4.48% (95% CI 0.99, 7.98), $I^2 = 40\%$. However the confidence interval was wide and the MCID of 5.39% was not met [44]. All studies used different pharmacotherapies and were at unclear risk of bias in terms of sequence generation. Change from baseline showed similar differences between intervention and control groups, 15.45 and 12.07%, respectively; indicating improved lung function after either treatment.

Asthma control

Asthma control was improved in a pool of five studies [14,22,29,31,41]. Results of the ACT showed statistically significant improvements after herbal medicines plus pharmacotherapies, MD 2.47 points (95% CI 1.64 to 3.29) (Figure 5). The result did not meet the MCID of three points [45]. All studies were at low risk of bias in terms of sequence generation however heterogeneity was moderate ($I^2 = 55\%$). Subgroup analysis by duration of treatment and administration type did not reduce heterogeneity. Grouping by control type, fluticasone/salmeterol, reduced heterogeneity and represents the best pool, three studies, MD 2.21 (95% CI 1.78, 2.65). $I^2 = 0\%$ [14,29,31].

Use of rescue medication

Two pooled studies showed a significant reduction in use of rescue medication (salbutamol); MD −1.14 puffs/day (95% CI −2.20, −0.09) [26,37]. The result met the MCID of −0.81 puffs/day [44]. Both studies used decoction for 3 months and were at low risk of bias in terms of sequence generation, yet

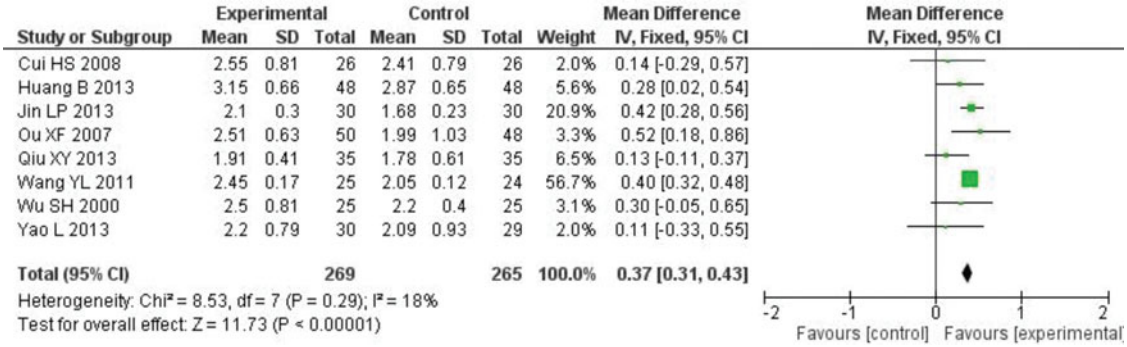

Figure 3. Herbal medicine plus pharmacotherapy versus pharmacotherapy: lung function FEV1 litres.

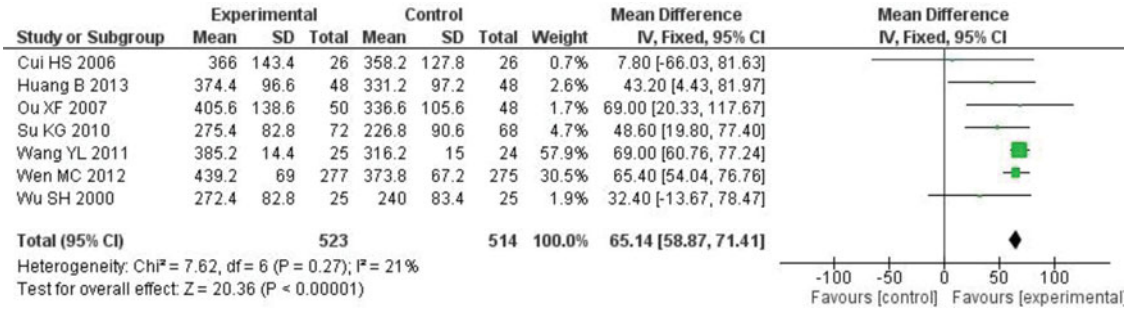

Figure 4. Herbal medicine plus pharmacotherapy versus pharmacotherapy: lung function PEFR L/min.

they were heterogeneous, $I^2 = 92\%$. Heterogeneity could not be explored therefore this result should be interpreted with caution.

Acute exacerbations of asthma

Exacerbations were reported in two studies comparing herbal medicines plus ICS and SABA to ICS and SABA alone. One study reported number of acute exacerbations per month over 9 months [30] and the other reported number over 1 year follow-up [22]. Over 9 months participants in the intervention group had 2.20 fewer exacerbations compared with control (95% CI −2.70, −1.70) [30]. Over 1 year, exacerbations were also reduced; MD −1.20 (95% CI −1.82, −0.58) [22]. Exacerbations were defined as increased shortness of breath, coughing and chest tightness needing additional medication such as SABA and/or emergency hospitalisation.

Health-related quality of life measured with the AQLQ

Two studies reported AQLQ and only one studies' results could be analysed [26]. The other study reported irregular data and authors did not respond to requests for further information [37]. In the single study, herbal medicine plus pharmacotherapy was no different to pharmacotherapy alone, MD 2.22 points (95% CI −2.30, 6.74) [26].

Effects of interventions: herbal medicines plus pharmacotherapy versus placebo plus pharmacotherapy

Three studies used a placebo control and reported lung function results [33,34]. The summary of findings table presents the results and quality of evidence (Table 2). In one study herbal medicine plus budesonide/formoterol improved FEV1% predicted compared to placebo plus budesonide/formoterol; MD 15.83% (95% CI 13.54, 18.12) [34]. The result met the MCID of 10% [46]. The study was conducted for 1 month and was moderate quality (Table 2). The other study showed herbal medicine plus theophylline significantly increased PEFR L/min after 6 months compared to placebo plus theophylline; MD 55.20 L/min (95% CI 33.41, 76.99). The result was greater than the MCID of 18.8 L/min [44]. In the study that used a cross-over design un-paired analysis results could not be pooled with other studies. In the 32 participants lung function (FEV1L and %) was improved after the intervention phase compared with the placebo phase [32]. The result was not greater than the MCID. Evaluation of change from baseline showed intervention groups improved FEV1% predicted 24.11% compared to 9.0% in control groups and PEFR L/min 1.05 L/min compared to 0.17 L/min. Other outcomes including adverse events were not reported.

Discussion

Comprehensive search found 29 randomised controlled trials evaluating herbal medicines for adults with asthma. Herbal medicines combined with pharmacotherapies improved lung function (FEV1, PEFR), asthma control (ACT), reduced acute exacerbations, and reduced the use of bronchodilator medication, compared with pharmacotherapies alone. Quality of life was similar between intervention and control groups. In the three studies that used placebo control, herbal medicines combined with pharmacotherapies improved lung function (FEV1, PEFR) compared with placebo and pharmacotherapies. Other outcomes were not reported in the placebo studies.

Positive clinical effects of the herbal medicines may be related to the anti-inflammatory actions of the individual herbs [47]. The most commonly used herb in the randomised controlled trials was licorice root (*gan cao*). In pre-clinical studies, its active compound glycyrrhizinic acid lessened inflammation in the lungs of asthmatic mice and another constituent compound, liquiritin apioside, had anti-tussive effects in guinea pigs [48,49]. The second most common herb, astargali (*huang*

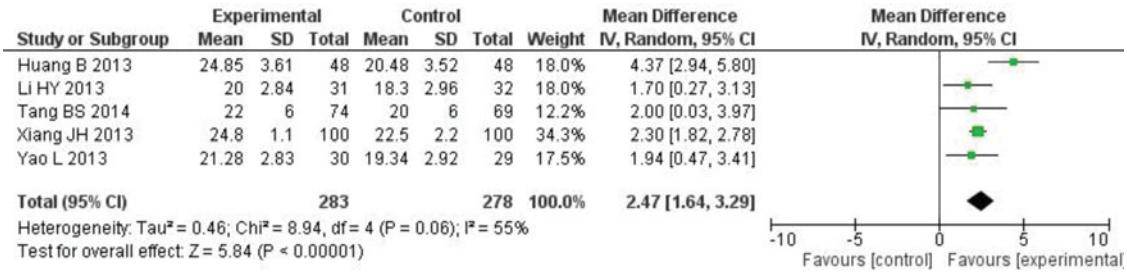

Figure 5. Herbal medicine plus pharmacotherapy versus pharmacotherapy: asthma control test.

qi), also possesses anti-inflammatory effects. In asthma mouse models it reduced airway hyper-responsiveness, eosinophils, cytokines, and mucus secretion by reducing goblet cell hyperplasia [50,51]. These pre-clinical studies demonstrate herbal medicines bioactive effects on typical inflammatory processes observed in asthma inflammation and lend themselves to biological plausibility for herbal medicines effects in the clinical setting.

Combining herbal medicines with pharmacotherapies for asthma showed improvements greater than pharmacotherapies alone. Pharmacotherapies are known to be effective therefore improvements greater than the active control are clinically important. In addition, most asthmatics take pharmacotherapies therefore combining them with herbal medicines means these results are generalisable to the clinical environment. The effects of herbal medicines may also be important in assisting patients stepping down from pharmacotherapies. It is common for asthmatics to experience increased symptoms and reduced quality of life when stepping down from drugs such as long-acting beta2-agonists [52]; herbal medicines may have a role to play limiting the impairment during this period.

Overall the quality of the evidence was low. Blinding of participants and personnel was at high risk of bias in all studies, except three that used a placebo control and pooled results were low quality due to statistical heterogeneity and small sample sizes for some outcomes (rescue bronchodilator use, acute exacerbations of asthma and quality of life). Studies in this review only assessed treatments for 1–3 months and the evidence could have been improved if studies were conducted for at least 6 months as asthma symptoms are known to be variable.

This review differs somewhat from Arnold and Clark's reviews in 2008 and 2010 [9,10]. We were able to identify new randomised controlled trials not previously presented in a systematic review. The studies included Chinese herbs compared with Ayurvedic and European herbs. These non-Chinese herb studies were excluded from this review because they investigated herb compounds/extracts, or did not combine herbal medicine with pharmacotherapy or had treatment durations for less than 4 weeks. Although we identified a new group of studies they have similar methodological shortfalls as those identified by Arnold and Clark. Despite positive effects for lung function, asthma control, reduction in exacerbations and reduced medication usage we could not establish a strong evidence base for herbal medicine for adult asthma. Our data may also be limited by poor reporting of baseline demographics and potential confounding in terms of severity of asthma, cause of asthma, undescribed triggers, and comorbidities including chronic obstructive pulmonary disease.

Herbal medicines appear safe for adults with asthma and adverse events are few and mild. Most adverse events could not be attributed to the herbal interventions but are known side effects of pharmacotherapies (corticosteroids, bronchodilators), such as, throat discomfort, fungal infections, hoarseness, palpitations and tremor of the hands. Overall, we did not identify any noteworthy risks of taking herbal medicines in this group of participants.

Conclusions

Herbal medicines are frequently used by adults with asthma even though existing evidence is not high quality. In this up-to-date systematic review, we identified a new group of studies investigating herbal medicines combined with pharmacotherapies. Such combinations have been reported to be associated with improved lung function, asthma control, and exacerbations but there was no clear difference in terms of quality of life. Caution should be taken with regard to the lower quality of the included studies. As herbal medicines are frequently used by large numbers of asthmatics more research is needed to improve clinical practice and potentially expand their role in appropriate clinical situations.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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