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Sanfu acupoint herbal patching for stable asthma: A systematic review and meta-analysis of randomised controlled trials

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Abstract

Background—*Sanfu* acupoint herbal patching (SAHP) is extensively used in people with stable asthma in China. However, the evidence available is scarce. This systematic review aims to evaluate the preventive and therapeutic effect and safety of SAHP in people with stable asthma.

Methods—We searched seven electronic databases for randomised controlled trials (RCTs). The Cochrane risk of bias tool was utilised to evaluate the methodological quality of the included studies and RevMan 5.3 and GRADEpro 3.6.1 were applied to perform data analyses.

Results—A total of 34 RCTs involving 3313 participants were included. The overall methodological quality of the trials was of high risk of bias. SAHP plus conventional therapy (CT) decreased the mean frequency (times per year) of asthma exacerbations compared with CT alone (MD: -1.42; 95% CI: -2.19 to -0.65; 7 RCTs), and similar effect was found for SAHP versus sham SAHP (MD: 0.42; 95% CI: 0.26–0.69; 1 RCT). For lung function (including PEF%, FEV₁% and FEV₁/FVC), SAHP plus CT showed better effect than CT alone, and so did SAHP versus sham SAHP on PEF and PEF%. Adverse effects in the SAHP groups were reported to be mild and well tolerated.

Conclusions—SAHP alone or combined with CT appears to be more effective than sham SAHP or CT on reduction of asthma exacerbations, improving lung function, and SAHP seems to be safe.

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Author contributions

Conceived and designed the review: F Zhou and JP Liu; Searched studies: F Zhou and N Liang; Appraised trials: F Zhou, N Liang and JP Liu; Extracted data: F Zhou and N Liang; Synthesized and analyzed data: F Zhou and JP Liu; Wrote the paper: F Zhou, JP Liu and M Maier.

Conflict of Interests

None declared.

However, the findings should be interpreted with caution due to limitations in trial quality. Further, rigorously designed, large-scale trials are warranted for robust evidence.

Keywords

Stable asthma; Acupoint herbal patching; *Sanfu*; Traditional Chinese medicine; Systematic review; Randomised controlled trials

1. Introduction

Asthma is defined as a chronic airway inflammation with variable expiratory airflow limitation and a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity.¹ The prevalence of asthma in adults was estimated to be 4.3%, ranging from 0.2% in China to 21.0% in Australia.² It's still increasing in many parts of the world from 300 millions up to 400 million by 2025.³ The burden of asthma is similar to that of diabetes or Alzheimer disease when calculating disability-adjusted life years.⁴ Moreover, when the asthma symptoms are uncontrolled, or one or more severe exacerbation happened in last 12 months, this could increase the risk of recurrence of the next exacerbation.^{5,6} This vicious circle might increase the risk of asthma related death.⁷ Therefore, treatment and management of stable asthma to prevent acute exacerbation are critical.

Currently, conventional therapy (CT) for stable asthma includes pharmacological and non-pharmacological interventions. Pharmacological medications mainly include corticosteroids, beta₂-agonists, leukotriene receptor antagonist and sustained-release theophylline for control and relief of asthmatic symptoms. However, inappropriate use of inhaler technique⁸ and poor adherence⁹ are the major problems. On the other hand, besides the avoidance of exposure to allergens and air pollution, non-pharmacological interventions are often used including allergen immunotherapy, bronchial thermoplasty and vaccines. However, it should take into account the risk of adverse effects, the inconvenience and cost of the prolonged course of the therapy.¹

In China, the use of acupoint herbal patching (AHP, also called as acupuncture point application therapy) in asthma management was first recorded in *Zhang Shi Yi Tong* in Qing Dynasty (1644–1912),¹⁰ and is still in popular use nowadays. As a traditional Chinese medicine (TCM) technique, *Sanfu* AHP (SAHP) is the external application of processed medicinal herbal preparations directly to specific acupuncture points (acupoints), only during the *sanfu* period to produce preventive and/or therapeutic effects. According to the Lunar calendar, *fu* refers to the hottest period of the year between mid-July to mid-August, lasting 30 to 40 days. Each ten days is called one *fu*, and three *fus* are called as *sanfu*. SAHP is a comprehensive intervention that comprises percutaneous absorption of applied herbal extracts, stimulation and regulation of meridians and acupoints.

According to TCM theory, usually, asthma is attributed to lung obstructed by long-retained phlegm.¹¹ When exogenous pathogenic, improper diet, emotional disturbance, over strain attack patient could make asthma recurrence.¹¹ TCM also believe lung, spleen and kidney are related to immunology functions; while AHP might regulate these three organs (*Zangfu*)

through herbs absorption and meridians stimulation.^{12,13} AHP contains herbs with acrid-warm and penetrating flavor which might warm the lung, remove phlegm, facilitate *qi* flow, dissolve masses, dredge the collaterals. Additionally, because *sanfu* is of special significance in TCM when *yang* (a moral connotation of light)¹⁴ in human body is the strongest,¹² it is considered as most effective when AHP is applied during *sanfu* period. A study found that SAHP could reduce the IL-4, and increase IFN- γ significantly which might be the one of the mechanisms of asthma management.¹⁵ A systematic review of six trials published in 2015 showed a positive effect of AHP only on immune outcomes for children with asthma.¹⁶ Another review of 16 RCTs published recently with insufficient searches and mainly focusing on pulmonary function showed encouraging but inconclusive effect.¹⁷

For this review, we included much larger number of trials (34 RCTs), and evaluated the preventive and therapeutic effect and safety of SAHP alone or in combination with CT for stable asthma, using patient related outcomes such as asthma exacerbations.

2. Methods

This review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁸

2.1. Protocol and registration

The protocol registration number was CRD42015019337 (<http://www.crd.york.ac.uk/Prospero>).

2.2. Eligibility criteria

We included randomised controlled trials (RCTs) (parallelgroup, cross-over or cluster) using SAHP in stable asthma regardless of blinding, publication type or language. Quasi-randomised trials were excluded. Participants included both children and adults with stable asthma (not during exacerbation) regardless of gender, etiology, ethnic, and course of the disease. Interventions included all types of SAHP alone or in combination with conventional therapy (CT) and/or biological agents. CT means that prevention and treatment of stable asthma is based on the Global Strategy for Asthma Management and Prevention (GINA) guidelines¹ or its predecessor documents. No restrictions were applied to the herbal regimen used, acupoints selected, number of SAHP sessions or treatment course. The controls included no treatment, sham SAHP, or CT alone. In addition, co-intervention(s) were also included as long as they were applied in both arms.

RCTs had to assess at least one of the following outcomes: frequency of asthma exacerbations during follow-up (primary outcome); asthmatic symptoms by validated instruments (including symptom scores, Likert scale, visual analogue scale); lung function (peak expiratory flow (PEF), predicted peak expiratory flow (PEF%), predicted forced expiratory volume in one second (FEV₁%), FEV₁/FVC (forced vital capacity)) by spirometry; quality of life measured by a validated asthma-specific or generic instruments; numbers of participants experiencing each adverse events.

2.3. Search methods

We searched for published studies in seven electronic databases from their inception to June 2015: PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, China National Knowledge Infrastructure (<http://oversea.cnki.net/kns55/default.aspx>), Chinese Biomedical Literature Database (www.sinomed.ac.cn), Chinese Science and Technology Periodical Database (<http://en.cqvip.com>), and Wan fang Database (www.wanfangdata.com). In order to identify unpublished studies, we searched five major trial registries (Supplementary file. S1).

Moreover, we also hand-searched the reference lists of all retrieved papers for additional relevant reports. A filter was applied to limit to humans. Details of the search strategies are available from Supplementary file 1.

2.4. Study selection and data collection process

Extracted data included participants (age, gender), interventions (herbal preparations, herbal regimen, acupoints selected, frequency, duration and co-interventions if any), controls (type, frequency, and duration), outcomes (measures and time points) and study design (randomisation, allocation concealment, blinding and etc.). If required information was not reported, we tried to request it from the corresponding author of the studies.

2.5. Risk of bias in individual studies

The methodological quality of RCTs was assessed according to the risk of bias tool described in the Cochrane Handbook for Systematic Reviews of Interventions.¹⁹ Six quality elements were assessed: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, free of selective reporting, and baseline balance bias.

Study selection, data extraction and risk bias assessment were conducted by two authors (Zhou F, Liang N) independently; in case of discrepancy consensus were reached by discussion with a third party (Liu JP).

2.6. Data analysis

Statistical analyses were performed using RevMan 5.3 software. Dichotomous outcomes were analyzed by pooled risk ratio (RR) with 95% confidence interval (CI) to present effect estimate; Continuous data were presented as mean difference (MD) with 95% CI. If different measurement scales for continuous data were reported, standardised mean difference (SMD) was performed for data analyses. For the meta-analysis of non-significant heterogeneity, we applied a fixed-effect model (FEM), otherwise, we used randomeffect model for the one of significant heterogeneity (I^2 value greater than 50%).¹⁹ Subgroup analyses were conducted for different comparisons (SAHP vs no treatment, Sham SAHP, CT, or SAHP plus CT vs CT). Summary of findings table was developed using GRADE pro 3.6.1 software. Funnel plots were generated to detect publication bias if more than 10 trials were identified to report on the same outcome. The results of meta-analyses were visualized in forest plots.

3. Results

3.1. Study selection

A total of 1615 records were identified through searching of seven electronic databases. After excluding 710 duplicates, 905 remaining titles and 244 abstracts were screened and 66 full-text articles were read. The reasons for exclusion during full-text review were “other stage of asthma” (n = 19), “other outcomes” (n = 11), and “other treatment” (n = 3), “other design” (n = 2). After contacted author, one RCT was excluded due to non randomisation (Fig. 1). Finally, 34 RCTs were included in the descriptive analysis and *meta*-analysis.^{20–49}

3.2. Characteristics of included RCTs

All studies originated from and were published in China, of which 23 were journal articles (76.67%), one was published in conference proceedings (3.33%)³⁰ and six were dissertations (20%).^{31,36,37,40,41,45} There were 26 RCTs with two arms, three RCTs with three arms,^{23,28,39} and one trial with two subgroups.³⁶

The 34 RCTs involved 3313 participants, varying from 40⁴⁷ to 265³³, with a median of 72 participants per trial. Thirteen trials included children exclusively with age from 1 to 14 years old, three trials included adolescents and adults,^{30,33,44} 13 trials included adults. One trial did not mention the age of the group.⁴⁸ The mean age of participants ranged from 3.3 to 55.6 years, with a median age of 34.8 years. Regarding gender, 49.3% participants were female (data not available in two trials). The majority of trials used Chinese national criteria for diagnosis of asthma; only one trial applied the international diagnostic criteria.³⁰

Six RCTs described the details of the SAHP which were prepared by the hospital pharmacy^{23,25,42,45,47} or by a pharmaceutical company,³⁸ whereas the remaining trials failed to report. The CT used included oral or inhaled corticosteroids, beta₂-agonists, leukotriene receptor antagonist, sustained-release theophylline, thymopeptide enteric-coated tablets, and BCG –polysaccharide nucleic acid injection. The duration of treatment ranged from 1 to 3 years, while the treatment frequency ranged from 3 to 9 sessions (Table 1).

Although some of the ingredients of SAHP were not completely the same among the included trials (that might be the main reason of potential heterogeneity), majority of the herbal patches' formulae had same treatment principle, that is, to warm yang and to dispel cold; and the main properties and flavor of the herbs were consistent: acrid-warm and penetrating. Besides, in this review, we took SAHP as a unique TCM therapy and to evaluate its clinical effectiveness rather to look at each herbal formula against its placebo. Hence, we considered SAHP as the therapy in a whole and pooled the data of the same outcome measure from different trials.

None of included studies reported the data collection methods for adverse event. However, based on our clinical observation, we could speculate they evaluate adverse events by regular checks in each *fu* when participants come back for next session of SAHP. And none of the trials reported the reproducibility of spirometry. In addition, the evaluation time points of each RCT varied from 3 months to 12 months, however, the follow up was at least 6 months since the first session of SAHP finished.

3.3. Risk of bias of the included trials

Although all trials reported “randomisation” in the text, only 12 RCTs described the procedure of randomisation, using random number table^{21,26,27,29,33,34,39,41,42,48} or software.^{35,45} Two RCTs applied opaque envelopes to conceal the allocation.^{30,45} Eight RCTs showed low risk of performance bias by using double blinding,^{20,21,29,30,33,35,37,45} and one RCT used assessor blinding.²³ Three of 30 RCTs reported the number of dropouts,^{26,36,39} and none of them applied the intention to treat analysis (Fig. 2).

3.4. Effect estimates

3.4.1. Frequency of asthma exacerbations (times per year)—Thirteen RCTs reported outcome of asthma exacerbation. Two meta-analyses revealed decreased mean frequency of exacerbation from SAHP compared with no intervention (MD: -1.13; 95% CI: -2.01 to -0.26; FEM; $I^2 = 31\%$; 2 RCTs),^{28,31} and SAHP plus CT compared with the same CT (MD: -1.42; 95% CI: -2.19 to -0.65; REM; $I^2 = 98\%$; 7 RCTs).^{22,24,36,40,43,46} Similar effect was found for SAHP when compared with sham SAHP (MD: -1.85; 95% CI: -2.33 to -1.37).²¹ However, a meta-analysis showed no significant difference between SAHP and CT (MD: -0.49; 95% CI: -1.27 to 0.29; REM; $I^2 = 94\%$; 3 RCTs) (Supplementary Fig. S1 in the online version at DOI: <http://dx.doi.org/10.1016/j.ctim.2016.11.007>).^{28,38,44} Xie’s RCT compared SAHP with thymopeptide enteric-coated tablets found statistical difference on frequency of asthma exacerbations favouring SAHP (MD: -1.39; 95% CI: -1.96 to -0.82).⁴²

One RCT reported the asthma exacerbation recurrence rate, showing improvement from SAHP compared with sham SAHP (MD: 0.42; 95% CI: 0.26–0.69).³³ Another RCT, comparing SAHP with no treatment, did not find a significant difference for the duration of asthma exacerbation (MD: 35.76 min.; 95% CI: -49.57 to 121.09).³⁰

3.4.2. Asthmatic symptom improvement (scores)—Eight RCTs evaluated the mean scores in asthmatic symptoms. A meta-analysis found no significant difference between real and sham SAHP (SMD: -0.94; 95% CI: -2.36 to 0.48; REM; $I^2 = 95\%$; 3 RCTs),^{21,37,45} while the other meta-analyses found beneficial effects of SAHP compared with CT (SMD: -0.43; 95% CI: -0.71 to -0.16; FEM; $I^2 = 0\%$; 3 RCTs).^{34,41,49} Similar for the effects of SAHP plus CT compared with CT alone (SMD: -1.22; 95% CI: -1.55 to -0.88; REM; $I^2 = 0\%$; 2 RCTs).^{26,48} Because of reverse direction of evaluation scores, one RCT was not included into the meta-analysis and showed no effect of SAHP compared with sham SAHP (MD: 0.43; 95% CI: -0.16 to 1.02) (Supplementary Fig. S2 in the online version at DOI: <http://dx.doi.org/10.1016/j.ctim.2016.11.007>).⁴⁵

3.5. Lungfunction

Compared with sham SAHP, Shi’ RCT showed beneficial effect on PEF% (MD: 11.23; 95% CI: 4.04–18.42).³⁵ However, when compared with CT, Hu’s RCT did not find statistical difference on PEF (MD: -11.94 L/min.; 95% CI: -36.17 to 12.29).²³

One meta-analysis, comparing SAHP with sham SAHP, found a beneficial effect on PEF (MD: 35.37 L/min; 95% CI: 1.03 to 69.71; REM; $I^2 = 79\%$; 2 RCTs),^{23,33} while the other two

meta-analyses with the same comparison showed no significant difference on FEV₁% (MD: 2.45; 95%CI: -16.72 to 21.61; REM; $I^2 = 89\%$; 2 RCTs)^{35,45} and on FEV₁/FVC (MD: 7.29; 95%CI: -7.29 to 22.37; REM; $I^2 = 93\%$; 3 RCTs)^{29,35,45} (Supplementary Figs. S3–S6 online version at DOI: <http://dx.doi.org/10.1016/j.ctim.2016.11.007>).

Comparing SAHP with CT, one single RCT and two meta-analyses showed no statistical difference on FEV₁/FVC (MD: -2.88; 95%CI: -13.07 to 7.31)³⁹; while two meta-analyses showed no statistical difference on PEF% (MD: 2.02; 95%CI: -6.52 to 10.56; REM; $I^2 = 64\%$; 2 RCTs),^{22,23,39} and FEV₁% (MD: 4.11; 95%CI: -0.41 to 8.63; 2 RCTs).^{22,39}

Comparing SAHP plus CT with CT alone, two meta-analyses and a single trial revealed effects on PEF% (MD: 8.74; 95%CI: 3.53–13.96; REM; $I^2 = 98\%$; 2 RCTs),^{39,49} FEV₁% (MD: 8.57; 95%CI: 5.01–12.13; REM; $I^2 = 97\%$; 3 RCTs),^{36,39,48} and FEV₁/FVC (MD: 11.68; 95%CI: 1.41–21.95).³⁹

3.5.1. Quality of life (scores)—Three RCTs reported on quality of life using Asthma Quality of Life Questionnaire (AQLQ).⁵⁰ A Meta-analysis showed that SAHP was better than sham SAHP (MD: 6.45; 95% CI: 3.42 to 9.48; FEM; $I^2 = 0\%$; 2 RCTs).^{29,45} Shen's trial compared SAHP with CT, showing better effect from SAHP (MD: 13.66; 95% CI: 2.91 to 24.41)³⁴ (Supplementary Fig. S7 in the online version at DOI: <http://dx.doi.org/10.1016/j.ctim.2016.11.007>).

A summary of finding table presented the main findings of SAHP plus CT versus CT for stable asthma, and provided key information about the quality of evidence, and a summary of important statistical results on mean frequency of asthma exacerbations, asthmatic symptoms and lung function outcomes (Table 2).

3.6. Safety

Of 30 trials, only 9 trials (30%) reported on adverse events: two of them reported that no adverse events occurred^{20,25} While seven trials demonstrated that adverse events were mild, and well tolerated, including skin itch (11/202 in 5 trials^{37,38,40,41,47}), skin blister (1/31, 3.23%)⁴⁰ and allergy (1/30, 3.33%).²⁷

4. Discussion

4.1. Summary of main findings

Thirty four RCTs were included in this review, SAHP as adjuvant therapy with CT seems to be more effective than CT alone for alleviating asthma on both subjective and objective outcomes. Compared with sham SAHP, SAHP alone seems to be effective for preventing asthma exacerbation, and for improving lung function and quality of life SAHP as adjuvant therapy with CT seems to be more effective than CT alone for alleviating asthma on both subjective and objective outcomes. Compared with sham SAHP, SAHP alone seems to be effective for preventing asthma exacerbation, and for improving lung function and quality of life. However, we could not draw conclusion due to the included studies with high or unclear risk of bias. To evaluate safety of SAHP, the more wide study inclusion criteria (including other study designs) is desirable. Hence, although no serious adverse events were reported in

included RCTs, we could not reach firm conclusion on its safety due to lack of evidence from non-randomised studies.

4.2. Comparison with previous systematic review

The previously published systematic review, which focused on AHP (no matter during *sanfu* or not) versus any comparator without AHP, found evidence that AHP improves the immune outcomes for childhood asthma on the basis of 6 RCTs published up to 2014¹⁶; The other one only involved one Chinese database and included 16 RCTs, found encouraging and not conclusive evidence of the AHP (also no matter during *sanfu* or not) efficacy on pulmonary functions and asthmatic symptoms, however, this systematic review missed to evaluated the prevention effectiveness of AHP on asthma and quality of life.¹⁷

4.3. Internal and external validity

In general, the risk of bias in the included studies was high or unclear. First, allocation concealment is a valid measure to avoid selection bias. However, there were only two RCTs which reported on allocation concealment. Further, the chances for performance bias and detection bias would increase because 73.53% RCTs did not apply blind to participants and personnel. Last, few trials provided adequate information on incomplete outcome data, which may contribute to potential attrition bias. Therefore, the potential for various biases strongly limit the interpretability of results.

Participants involved in this systematic review have three characteristics, 1) all the 3313 asthma patients were from China, 2) patients' age range covered children, adolescents, adults and elderly people, and 3) the sex ratio was almost half to half. Hence, this diversity shows that SAHP has a good applicability and acceptance rate in the real world at least in China. However, for other ethnicities different from Chinese, the effectiveness of SAHP is still unknown. In addition, all included trials did not mention co-interventions, the main reason might be the purpose of stable asthma treatment is mainly prophylactic.

4.4. Strengths and weaknesses

This review, to the best of our knowledge, is the first one comparing SAHP plus CT versus CT alone and evaluating the preventive and therapeutic effectiveness of SAHP on stable asthma. The strengths of this review mainly include the comprehensive literature search without language restrictions, the high number of RCTs involving children (56.67%, 17/30) and the subgroup analyses to assess the SAHP's effects in different combinations and scenarios. On the other hand, the poor methodological quality of the studies included is one of the limitations in this review. Secondly, all included studies were conducted in China, which restricts the generalizability of the findings due to the context in terms of tradition and culture. Lastly, most of the *meta*-analyses in this review showed high heterogeneity. Heterogeneity might be partly related to differences of the acupoints selected, the SAHP formula selected and various conventional treatments applied. Although this limits our quantitative analyses, it also reflects asthma management in the real clinical world in China.

4.5. Implications for clinical practice

Compared with sham SAHP, real SAHP alone seems to be effective for preventing asthma exacerbation, and for improving lung function and quality of life. This could carefully be interpreted as a hint on the therapeutic effects of SAHP alone. Furthermore, the similar effects of SAHP and CT interventions could be cautiously interpreted as the effectiveness of SAHP alone.

For the SAHP intervention, the most critical aspects are the herbal patching's regimen and the acupoints selected. Based on our review, the four major herbs of the patching regimens are *Semen Sinapis*, *Rhizoma Corydalis*, *Radix et Rhizoma Asari*, *Radix Kansui*, while the basic four acupoints are *Tian tu* (CV 22), *Dan zhong* (CV 17), *Da zhui* (GV 14), *Fei shu* (BL 13). Until now, there are some pre-clinical studies reported that using these herb on these acupoints could regulate the immune mechanism and decrease the inflammation.^{51–53} However, considering the high risk of bias all the conclusions should be interpreted with caution.

4.6. Implications for further research

The use of rigorous research methods, including pretrial sample size calculation, appropriate randomisation, strict allocation concealment, blinding at least for outcome assessors and statisticians, and intention-to-treat analysis, should be ensured in future RCTs. Scientific reporting according to the consolidated standards of reporting trials (CONSORT) statement⁵⁴ is also critical for future RCTs.

In addition, it is worth noting that the sham SAHP used in the included studies seems to be easily recognized by both physicians and patients. A perfect sham SAHP should look exactly like true SAHP. A sham SAHP without herbs is unlikely to simulate the same color and smell as true SAHP. Hence, the preparation of good sham SAHP is also a challenge for future RCTs.

5. Conclusion

SAHP alone or combined with CT appears to be more effective than sham SAHP or CT on reduction of asthma exacerbations, improving lung function, and SAHP seems to be safe. However, the findings should be interpreted with caution due to limitations in trial methodological quality. Further, rigorously designed, large-scale trials are warranted for stronger evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Flow diagram of study searches and selection.

Fig. 2. Risk of bias summary. Presentation of the risk of bias summary of the review author's judgments about each risk of bias item for each included trials.

Table 1

Characteristics of included RCTs.

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Cai 2010	60/60C:60/60	T:3–14/6.96/40C:3–14/6.77/43.33	SAHP vs Sham	Relieving asthma treatment when asthma exacerbation	Ointment; .Semen Sinapis, .Herba Ephedrae, .Lignum Santali Albi, GV 14, EX-B1, BL 13, BL 20, BL 23; 1 sanfu, once per 10 days for 30 days	NR; same usage with SAHP	12 months	Adverse event
Chang 2013	75/75C:68/68	T:19–65/37.21/52C:18–64/38.91/63.24	SAHP vs Sham	None	Paste; I: .Semen Sinapis, Radix et Rhizoma Asari, Rhizoma Corydalis, Radix Kansui, Radix .Saposhnikoviae, Fructus Schisandrae Chinensis, Borneolum .Syntheticum; II: .Semen Sinapis, Radix et Rhizoma Asari, Rhizoma Corydalis, Radix Kansui, Cortex Cinnamomi, Rhizoma Zingiberis, Herba Epimedii, Borneolum .Syntheticum; I GV 14, EX-B1, BL 12, BL 13, CV 22, HBL 13, BL 43, BL 20, BL 23, CV 17; 1	Flavoring, flour, vaseline, pigment and distilled water; same usage with SAHP	12 months	Frequency of asthma exacerbation, symptoms score, adverse event

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Deng 2012	80/80C:80/80	T:5-14/7.59/40C:5-14/7.86/43.75	SAHP + CT vs CT	None	<i>sanfu</i> , once per 4 days for 32 days, I and II herbal formula and acupoints selected used in alternation Paste; Semen Sinapis, Radix et Rhizoma Asari, Radix Kansui, Rhizoma Corydalis; I GV 14, EX-B1, BL 12, BL 13, CV 22, HBL 13, BL 43, BL 20, BL 23, CV 17; 1 <i>sanfu</i> , once per 10 days for 30 days	Seretide, 1 puff, twice a day, 1 year	12 months	Frequency of asthma exacerbation, FEV ₁ %, FEV ₁ /FVC%, PEF%
Hu 2005*	27/27C:30/30	T:Children/8.22/30.04C:Children/7.91/30	SAHP vs Sham	None	Paste; <i>Semen Sinapis, Fructus Gleditsiae, Rhizoma Corydalis, Radix et Rhizoma Asari</i> ; EX-B1, BL 13, BL 20; 1 <i>sanfu</i> , once per 10 days for 30 days	Vaseline	12 months	PEF
Jin 2011	T:27/27C:30/30 T:21/21C:33/33	T:Children/8.22/30.04C:Children/8.35/36.67 3-6/5.29/35.19	SAHP vs CT SAHP + CT vs CT	None None	See Hu 2005 NR; <i>Radix et Rhizoma Asari, Rhizoma Pinelliae, Radix Kansui, Rhizoma Corydalis, Cortex Cinnamomi</i> ,	Budesonide, 200-600 Budesonide, 100-200 µg	12 months 12 months	PEF Frequency of asthma exacerbation

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Li 2010	T:30/30C:30/30	T:3–8,2/4.78/46.67C:3.2–8.5/4.65/53.33	SAHP vs CT		<i>Semen Sinapis</i> , BL 11, BL 13, BL 12, BL 14, BL 15, CV 17, BL 23; NR; once per 10 days for 30 days Paste; <i>Semen Sinapis</i> , <i>Radix et Rhizoma Asari</i> , <i>Herba Ephedrae</i> , <i>Bombyx Baryticus</i> ; CV 22, CV 17, GV 14, BL 13, BL 17; 1 <i>sanfu</i> ; once per 10 days for 30 days	BCG – polysaccharide nucleic acid injection 0.5 mg, 1 per 2 two days for 30 days	12 months	Adverse event
Li 2012	T:60/60C:60/60	T:3–14/6.96/40C:3–14/6.77/43.33	SAHP vs Sham	Relieving asthma treatment when asthma exacerbation	Ointment: <i>Semen Sinapis</i> , <i>Herba Ephedrae</i> , <i>Lignum Santali Albi</i> ; GV 14, EX-B1, BL 13, BL 20, BL 23; 1 <i>sanfu</i> ; once per 10 days for 30 days	NR; same usage with SAHP	12 months	Adverse event
Li 2015	T:31/30C:31/30	T:NR/64.5/56.67C:NR/60.83/56.67	SAHP + CT vs CT	None	NR; <i>Semen Sinapis</i> , <i>Radix et Rhizoma Asari</i> , <i>Radix Kansui</i> , <i>Rhizoma Corydalis</i> ; EX-B1, BL 13, BL 43; 1 <i>sanfu</i> ; once every 2 days for 30 days	Salmeterol and fluticasone propionate, 1 puff once, 2 per 1 day for 6 months	6 months	Symptoms improvement
Liu 2003 *	T:60/60C:60/60	1–12/6.5/NR	SAHP vs CT	None	NR; <i>Herba Ephedrae</i> , <i>Praeparata cum Melle</i> , <i>Semen</i>	Ketotifen, 0.5–1 mg, 2 per day for 2 months	6 months	Frequency of asthma exacerbation

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Lu 2011	T:35/35C:35/35	1–12/6.5/NR	SAHP vs No treatment	Relieving asthma treatment when asthma exacerbation	<i>Sinapis, Radix et Rhizoma Asari, Fructus Gleditsiae</i> ; EX- B1, BL 13, BL 20; 1 <i>sanfui</i> ; once per 10 days for 30 days	No treatment	6 months	Frequency of asthma exacerbation
					NR; <i>Herba Ephedrae Praeparata cum Melle, Semen Sinapis, Radix et Rhizoma Asari, Fructus Gleditsiae</i> ; EX- B1, BL 13, BL 20; 1 <i>sanfui</i> ; once per 10 days for 30 days	Powder of red rice, black rice and corn; same usage with SAHP	After treatment finished	FEV ₁ %, FEV ₁ /FVC%, QoL
Luo 2007	T:60/60C:60/60	T:18–66/54.62/38.33C:19–68/55.63/51.67	SAHP vs No treatment	None	Pills; <i>Radix Codonopsis, Radix Astragali, Semen Sinapis,</i>	No treatment	After treatment finished	Symptoms improvement

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Luo 2008	T:25/25C:25/25	T: 18–65/54.62/44C: 19–65/55.63/48	SAHP vs No treatment	None	<i>Rhizoma Corydalis, Radix et Rhizoma Asari, Radix Kansui, Rhizoma Pinelliae</i> ; CV 22, GV 14, BL 13, BL 20, BL 23; 2 <i>sanfir</i> , once per 10 days for 30 days (in 2 years)	No treatment Pills; <i>Radix Codonopsis, Radix Astragali, Semen Sinapis, Rhizoma Corydalis, Radix et Rhizoma Asari, Radix Kansui, Rhizoma Pinelliae</i> ; CV 22, GV 14, BL 13, BL 20, BL 23; 2 <i>sanfir</i> , once per 10 days for 30 days (in 2 years)	After treatment finished	Frequency of asthma exacerbation
Luo 2011	T:166/126C:160/121	T: 13/44,58/55.6C: 13/46,58/56.2	SAHP vs Sham	None	Ointment; <i>Semen Sinapis, Rhizoma Corydalis, Radix Kansui, Praeparata, Radix et Rhizoma Asari, Raw Herba Ephedrae, Radix Aconiti Lateralis Praeparata, Cortex Cinnamomi,</i>	Flour, red rice, black glutinous rice; same usage with SAHP	7 days, 3 months, 6 months	Length of asthma exacerbation, FEV ₁ %, FVC %, FEV ₁ /FVC, PEF%

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Lv 2014	T:144/144C:121/121	T:12–75/37/48.15C:14–74/36/48.65	SAHP vs Sham	None	<i>Flos</i> <i>Caryophylli</i> , GV 14EX-B1, BL 13, GV 12, BL 43, BL 23, GV 4; 1 <i>sanfu</i> ; once per 10 days for 30 days	Adhesive plaster without herbal medicine; same usage with SAHP	3 months, 6 months, 12 months	Proportion of asthma exacerbation, PEF
Shen 2014	T:36/36C:36/36	T:NR/46/69.44C:NR/48/72.22	SAHP vs CT	None	Paste; <i>Radix</i> <i>Morindae</i> <i>Officinalis</i> , <i>Fructus</i> <i>Psoraleae</i> , <i>Radix</i> <i>Aconiti Lateralis</i> <i>Praeparata</i> , <i>Herba Ephedrae</i> , <i>Fructus Evodiae</i> , <i>Flos</i> <i>Caryophylli</i> , <i>Cortex</i> <i>Cinnamomi</i> , CV 22, GV 14; 1 <i>sanfu</i> ; twice per	Salmeterol and fluticasone propionate, 1 puff once, 2 per 1 day for 30 days	After treatment finished	Syptoms scores, QoL

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Shi 2014	T:46/46C:46/46	T:3–14/4.8/41.3C:2.8–14/4.9/45.65	SAHP vs Sham	None	7 days for 90 days NR; <i>Semen Sinapis, Radix et Rhizoma Asari, Radix Kansui, Rhizoma Corydalis, Radix Saposhnikovia;</i> BL 13, BL 15, BL 17; NR; once per 10 days for 30 days	Powder of red rice, black rice and corn; same usage with SAHP	12 months	FEV ₁ %, FEV ₁ % ₁ FVC, PEF %
Wang 2008 [#]	T:30/30C:30/28 T:30/29C:30/30	T:18–65/43.26/46.67C:18–65/40.9/60 T:18–65/46.6/53.33C:18–65/45.46/43.33	SAHP + CT vs CT SAHP + CT vs CT	Relieving asthma treatment when asthma exacerbation See Wang 2008	Ointment; <i>Semen Sinapis, Rhizoma Corydalis, Radix et Rhizoma Asari, Rhizoma Pinelliae, Radix Kansui, Moschus, GV 14, BL 13, BL 43; 2. <i>sanfus</i>; once per 10 days for 30 days (in 2 years) See Wang 2008</i>	Salmeterol and fluticasone propionate, 1 puff once, 2 per 1 day for 30 days See Wang 2008	3 months 3 months	Frequency of asthma exacerbation, FEV ₁ %, PEF % Frequency of asthma exacerbation, FEV ₁ %, PEF %
Wang 2012	T:90/90C:90/90	2–12/6.3/NR	SAHP vs CT	None	Paste; <i>Herba Ephedrae, Radix et Rhizoma Asari, Semen Sinapis, Fructus Trichosanthis, Poria, Rhizoma Pinelliae Praeparatum;</i> EX-B1, BL 12, GV 14, BL 13, BL 20, BL 23; 1 <i>sanfu</i> ; once per 1 day for 3 days, then stop two	Montelukast Sodium Chewable Tablets, 4 mg (2–5 years old), 5 mg (6–12 years old) for 90 days	6 months	Frequency of asthma exacerbation, adverse event

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Wang 2013	T:30/30C:30/30	T:18–65/39.73/46.67C:18–65/40.10/50	SAHP vs Sham	None	weeks and then 1 per day for 3 days Pills; <i>Semen Sinapis</i> , <i>Rhizoma Corydalis</i> , <i>Radix Asari</i> , <i>Radix Kansui</i> ; EX-B1, BL 13, BL 23, EX-HN14; 1 <i>sanfu</i> , once per 10 days for 30 days	Flour of soybean; same usage with SAHP	6 months	Symptoms scores, adverse event
Wu 2011	T:31/31C:29/29	T:2–14/NR/29.03C:2–14/NR/17.24	SAHP + CT vs CT	None	Ointment; <i>Semen Sinapis</i> , <i>Cortex Cinnamomi</i> , <i>Radix Kansui</i> , <i>Fructus Evodiae</i> , <i>Radix et Rhizoma Asari</i> , <i>Rhizoma Corydalis</i> , RN 22, EX-B1, BL 13, BL 43; 1 <i>sanfu</i> , once per 10 days for 30 days	Montelukast Sodium Chewable Tablets, 4 mg (2–5 years old), 5 mg (6–14 years old) for 30 days	6 months	Frequency of asthma exacerbation, adverse event
Wu 2012*	T:30/30C:30/26 T:30/30C:30/29	T:2–14/7.3/46.67C:2–14/7.9/46.67 T:2–14/7.3/46.67C:2–14/7.6/50	SAHP vs CT SAHP + CT vs CT	None See Wu 2012	Pills; <i>fried Semen Sinapis</i> , <i>Radix et Rhizoma Asari</i> , <i>Rhizoma Corydalis</i> , <i>Radix Kansui</i> ; BL 13, BL 15, BL 17; 1 <i>sanfu</i> , once per 10 days for 30 days See Wu 2012	Fluticasone propionate, 1 puff once, 2 per 1 day for 30 days See Wu 2012	12 months 12 months	Proportion of asthma exacerbation, FEV ₁ %, FEV ₁ /FVC, PEF% Proportion of asthma exacerbation, FEV ₁ %, FEV ₁ /FVC, PEF%

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Xie 2008	T:30/30C:30/30	T:22–65/34.80/50C:20–63/34.21/46.67	SAHP + CT vs CT	None	Ointment; <i>Semen Sinapis</i> , <i>Herba Ephedrae</i> , <i>Radix et Rhizoma Asari</i> , <i>Lignum Santali Albi</i> , <i>Rhizoma Zingiberis</i> , <i>Receus</i> , GV 14, RN 22, EX-B1, BL 13, BL 23; 1 <i>sanfu</i> , once per 10 days for 30 days	No treatment	6 months	Symptoms scores
Xie 2014	T:45/45C:42/42	T:21–65/34.80/44.44C:20–63/34.21/52.38	SAHP + CT vs CT	None	Paste; <i>Semen Sinapis</i> , <i>Radix Kansui</i> , <i>Rhizoma Corydalis</i> , <i>Radix et Rhizoma Asari</i> , <i>Camphora</i> ; BL 13, BL 20, BL 23, EX-B1, GV 14, CV 17; 2 <i>sanfu</i> , once per 10 days for 30 days (in 2 years)	Thymopeptide enteric-coated tablets, 30 mg, 2 per 1 day for 90 days (in 2 years)	NR	Frequency of asthma exacerbation, FEV ₁ %
Xiong 2014	T:46/46C:46/46	T:1–9/5.87/45.65C:2–10/5.95/47.83	SAHP + CT vs CT	None	Paste; <i>Semen Sinapis</i> , <i>Radix Kansui</i> , <i>Rhizoma Corydalis</i> , <i>Radix et Rhizoma Asari</i> ; BL 13, BL 15, BL 17; 1 <i>sanfu</i> , once per 3 days for 14 days	Convention treatment	NR	Frequency of asthma exacerbation
Yang 2014	T:46/46C:45/45	T:16–71/NR/56.52C:14–70/NR/51.11	SAHP vs CT	Relieving asthma treatment when asthma exacerbation	NR; <i>Semen Sinapis</i> , <i>Rhizoma Corydalis</i> , <i>Radix et Kansui</i> , <i>Radix et</i>	Aminophylline, 0.1 g, 2 per 1 day, per os	NR	Frequency of asthma exacerbation

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Yu 2009	T:33/33C:17/17	T:23–68/47.91/76.47C:26–69/43.53/57.58	SAHP vs Sham	None	<p><i>Rhizoma Asari</i>, <i>Cortex</i> <i>Cinnamomi</i>, <i>Rhizoma</i> <i>Zingiberis</i> <i>Receus</i>, CV 22, CV 17, BL 13, BL 43, BL 23, ST 36; 1 <i>sanfu</i>, once per 10 days for 30 days</p> <p>NR; <i>Fructus</i> <i>Piperis</i>, <i>Semen</i> <i>Sinapis</i>, <i>Radix et</i> <i>Rhizoma Asari</i>, <i>Radix Angelicae</i> <i>Daluriacae</i>, <i>Semiliquidambar</i> <i>cathayensis</i> <i>Chang</i>, <i>Rhizoma</i> <i>Zingiberis</i> <i>Receus</i>, I GV 14, BL 23, BL 13, BL 20, IICV 22, CV 17, CV 6, CV 4, ST 36; 1 <i>sanfu</i>, once per 3–4 days for 28 days, I and II acupoints selected used in alternation</p>	Flour, red rice, black glutinous rice, ginger juice; same usage with SAHP	NR	Symptoms scores, QoL, FEV ₁ %, FEV ₁ /FVC%, adverse events
Yu 2011	T:100/100C:100/100	T:1–7/3.31/40C:2–12/6.78/33	SAHP + CT vs CT	Relieving asthma treatment when asthma exacerbation	<p>Paste; <i>Semen</i> <i>Sinapis</i>, <i>Radix et</i> <i>Rhizoma Asari</i>, <i>Radix Kansui</i>, <i>Rhizoma</i> <i>Corydalis</i>, <i>Rhizoma</i> <i>Zingiberis</i> <i>Receus</i>, BL 13, BL 20, BL 17, CV 22, CV 17, BL 12, EX-B1; 3</p>	NR	After treatment finished	Frequency of asthma exacerbation

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures
Zhao 2012	T:21/21C:21/19	T:18–65/46.89/66.67C:18–65/47.33/63.16	SAHP + CT vs CT	None	<i>sanfu</i> ; once per 10 days for 90 days (in 3 years) NR; <i>fried Semen Sinapis, Fructus Piperis Longi, Radix et Rhizoma Asari, Herba Ephedrae, Rhizoma Acori Jatarinowii</i> ; BL 13, BL 15, BL 17; 1 <i>sanfu</i> , once per 10 days for 30 days	NR	6 months	Frequency of asthma exacerbation, symptom scores, PEF%, QoL, adverse event
Zhu 2011	T:50/50C:50/50	NR	SAHP + CT vs CT	None	Ointment: <i>Semen Sinapis, Mylabis</i> ; 1 EX-B1, BL 13, CV 22, HBL 23, ST 36, GV 12; 1 <i>sanfu</i> , once per 10 days for 30 days	Seretide, 1 puff, twice a day, 3 months	3 months	Symptom scores, FEV ₁ %
Zhu 2012	T:36/36C:36/36	T:18–65/39.8/42.22C:18–65/39.6/50	SAHP vs CT	None	Ointment: <i>Semen Sinapis, Praeparata cum Melle, Rhizoma Corydalis, Radix Kansui, Radix et Rhizoma Asari, Herba Ephedrae, Rhizoma Pinelliae, Zingiberis Recens</i> , CV 22, CV 17, GV 14, LU 1, BL 12, BL 13, BL 17, EX-HN14; 2–3 <i>sanfus</i> , once per 10 days for 90	β ₂ receptor agonist, 8 mg, twice a day,	NR	Symptom scores

RCT ID	No. of participants (R/A)	Age range, years/mean age, years/female, %	Comparison type	Cointervention	SAHP Intervention Herbal preparation type; components; Acupoints Selected; Duration; frequency of SAHP	Control Interventions	Evaluation time points	Outcome measures

days (in 2–3 years)

R:number subjects randomized; A: number subjects analyzed; T:treatment group; C: control group; NR:not reported.

CT: conventional therapy; BCG:Bacillus Calmette – Guerin; PEF%:predicted peak expiratory flow; FEV 1%: predicted forced expiratory volume in one second; FVC: forced vital capacity;

* : this trial has three arms;

: this trial has two subgroups and data can't be pooled together.

Table 2

Summary of finding table of SAHP plus conventional therapy versus conventional therapy for stable asthma.

SAHP plus Conventional Therapy compared to Conventional Therapy for Stable asthma				
Patient or population: Patients with Stable asthma Settings: Hospital ^a Intervention: SAHP plus Conventional therapy Comparison: Conventional therapy				
Outcomes	Illustrative comparative risks* (95% CI)	No of Participants RCTs)	Quality of the evidence (GRADE)	Comments
	Assumed risk Conventional therapy			
Mean frequency of asthma exacerbations patient report Follow-up: 1–12 months	The mean frequency of asthma exacerbations ranged across control groups from 1.21–8.16 times	683 (7 RCTs)	⊕⊕⊕⊕ low ^{b,c,d}	
Mean difference in asthmatic symptoms patient report Follow-up: 3–6 months	The mean difference in asthmatic symptoms in the control groups was 1.8–6.73 scores	160 (2 RCTs)	⊕⊕⊕⊕ very low ^{e,f}	
Mean difference of PEF% Spirometer Follow-up: 3–12 months	The mean difference of PEF% ranged across control groups from 78.42–82.3% ^g	172(3 RCTs)	⊕⊕⊕⊕ low ^{h,i}	
Mean difference of FEV ₁ % Spirometer Follow-up: 3–12 months	The mean difference of FEV ₁ % ranged across control groups from 77.4–80.74% ^g	272 (4 RCTs)	⊕⊕⊕⊕ low ^{c,i}	
Mean difference of FEV ₁ /FVC% Spirometer Follow-up: mean 12 months	The mean difference of FEV ₁ /FVC% in the control groups was 79.86%	55 (1 RCT)	⊕⊕⊕⊕ low ^{e,j}	
Mean difference in quality life ^k – not reported	See comment	Not estimable ^k	–	See comment

* The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (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: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aNone of included trials were conducted in community or clinics.

^bSeven of the eight trials did not report the randomization method.

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^cNone of these eight trials reported allocation concealment and blinding of participants and personnel.

^dThe I^2 equaled to 98%, showing considerable heterogeneity.

^eOne trial could not allow to judge inconsistency of results, indirectness of evidence, imprecision and publication bias.

^fThe I^2 equaled to 88%, showing considerable heterogeneity.

^gThe percentage of predicted value.

^hThree of trials didn't report allocation concealment and blinding of participants and personnel.

ⁱThe I^2 equaled to 97%, showing considerable heterogeneity.

^jThis trial didn't report allocation concealment and blinding of participants and personnel.

^kNo trials reported.