Preventive and therapeutic effectiveness of Sanfu acupoint herbal patching for chronic obstructive pulmonary disease at stable stages: a systematic review and Meta-analysis


OBJECTIVE: To evaluate the preventive and therapeutic effects of Sanfu acupoint herbal patching (SAHP) in adjuvant treatment in patients with stable chronic obstructive pulmonary disease (COPD).

METHODS: We had searched eight electronic databases and six major trial registries from their inception to July 2017 for randomized controlled trials (RCTs). We utilized RevMan 5.3 to evaluate the methodological quality and to perform data analyses.

RESULTS: A total of 28 RCTs involving 1615 records were included in the descriptive analysis, and 25 RCTs were performed for Meta-analysis. Lung function such as forced vital capacity rate of one second FEV1/predicted%, forced vital capacity (FVC) % found no significant difference. The results of Meta-analysis showed that SAHP plus conventional therapy (CT) in the treatment of stable COPD were better than CT, in second sessions’ data of FEV1, in third sessions’ data of FEV1/FVC, in three sessions’ data of SGRQ, in third session’s data of Modified Medical Research Council and 6MWT. The symptoms of SAHP’s adverse reactions seem to be mild and the incidence of that seems to be low. Descriptive analysis shows that SAHP with CT seems to improve clinical effective rate and had a certain preventive effect on acute exacerbation of COPD, which the curative effect may be better with the increase of treatment course.

CONCLUSION: SAHP with CT appears to be more effective than CT or CT plus placebo only on improving the quality of life, but the effect on lung function is not obvious. Improve clinical effective rate and preventive effect is uncertainty. SAHP with CT may be used in any Grade to safely treat patients with stable COPD. The more exactly clinical effect still needs to be proved by more high-quality, large sampling, multilingual RCTs.
Keywords: Pulmonary disease, chronic obstructive; Acupoint sticking therapy; Randomized controlled trials; Systematic review

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation, that is due to airway and (or) alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The prevalence of COPD in Chinese population aged 40 years and over in 1990-2014 was 9.9%. COPD is the fourth largest cause of death in the world, because of the risk factors of prolonged exposure and the aging population, morbidity and mortality increase of COPD has caused serious economic and social burden. Patients with stable COPD often suffer from recurrent symptoms and pulmonary function deterioration due to abandoning treatment, or progress to severe COPD because of not diagnosis and treatment timely, which affects the quality of life and increases the mortality rate. Acute exacerbation of COPD is the main cause of the patient’s admission to hospital, and the mortality rate was 22% within 1 year. Therefore, preventing acute exacerbation and reducing the mortality of stable COPD are the keys to treat the disease. Currently, conventional therapy (CT) for stable COPD includes pharmacological and non-pharmacological interventions. Pharmacological medications mainly include inhaled corticosteroids, β2-agonists, methylxanthines and anticholinergics, which are used to control and relieve the symptoms. However, there is no clinical evidence that the current drug treatment can alleviate the long-term decline in COPD lung function. On the other hand, non-pharmacological interventions mainly include oxygen therapy, pulmonary rehabilitation, self-management, integrative care, ventilatory support and interventional therapy. However, it should take into account the risk of adverse effects, the inconvenience and cost of the prolonged course of the therapy.

Sanfu acupoint herbal patching (SAHP) is a common Traditional Chinese Medicine (TCM) technique in China. It can be traced back to Zhang Shi Yi Tong in 1695. SAHP is the external application of processed medicinal herbal preparations directly to specific acupoints, only during the Sanfu period to produce preventive and 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 d. Each 10 d is called one fu, and three fus are called as Sanfu. Due to the low price, rapid and convenient use, SAHP has been extensively used to treat stable COPD, prevent acute attacks and displayed favorable effects in clinics. According to the theory of TCM, COPD pathogenesis is Qi deficiency and stagnation, stagnation of phlegm and blood stasis, and deficiency of spleen and kidney for a long time. During the Sanfu period, Yang in human body is the strongest and meridian is unobstructed, SAHP can play the best effect during this period. SAHP contains herb with acrid-warm and penetrating flavor which might to penetrate the skin into the meridians, and then to tonify and active Qi, promote blood flow, eliminate phlegm and dredge collaterals of lung, and regulate the viscera function of the lung, spleen and kidney through the role of meridians. The pathogenesis of COPD remain largely unknown. Recent studies have found that the treatment of immune regulation at stable COPD can delay the damage of lung function, reduce the degree of disease and improve labor tolerance. SAHP can regulate the body immune mechanism, improve respiratory immunity, prevent repeated infection, so as to prevent further deterioration caused by repeated infection. A study found that SAHP could reduce the IL-4, and CRP significantly which might be the one of the mechanisms. A recent Meta-analysis of 11 trials published in 2016 showed a more positive effect of SAHP plus CT than CT on treatment efficiency, FEV1/FVC, SGRQ and BODE with stable COPD. It also evaluated the safety of SAHP which reported have no side-effect to liver and kidney. Because of its small number and low quality of studies with some methodological defects, the evidence is insufficient. For our review, we included much larger number of trials (28 RCTs) in qualitative synthesis and 24 RCTs in quantitative synthesis (Meta-analysis). In addition, we evaluated the preventive and therapeutic effect of SAHP combination with CT or CT plus placebo in three years to provide more powerful evidence.

METHODS

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

Protocol and registration

The protocol registration number was CRD42017072224 (http://www.crd.york.ac.uk/Prospero).

Eligibility criteria

All the RCTs (parallel-group, cross-over or cluster) that research the preventive and (or) therapeutic effects of SAHP combined with CT for the treatment of stable COPD were included regardless of blinding, publication type or language. Quasi-randomized trials were excluded. COPD should be diagnosed according to the diagnostic criteria of the existing guidelines. Patients must be aged at least 18 years old with stable COPD. No restrictions were applied to the herbal regimen used, acupoints selected, number of SAHP sessions or treatment course. CT include: Beta2-agonists, anticho-
linergics, methylxanthines, phosphodiesterase-4 inhibitors, inhaled corticosteroids, oral glucocorticoids, phosphodiesterase-4 inhibitors, antibiotics, mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine), nedocromil, leukotriene modifiers, oxygen therapy. The above drugs or measures can be used alone or combined in the treatment. Dosage and course of treatment are not limited. CT means that prevention and treatment of stable COPD are based on the Global Strategy for Global Initiative for Chronic Obstructive Lung Disease (GOLD) or Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised Edition 2013) guidelines, or their predecessor documents. CT include: Beta2-agonists, anticholinergics, methylxanthines, phosphodies-
terase-4 inhibitors, inhaled corticosteroids, oral glucocorticoids, phosphodiesterase-4 inhibitors, antibiotics, mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine), nedocromo-
il, leukotriene modifiers, oxygen therapy. The above drugs or measures can be used alone or combined in the treatment. Dosage and course of treatment are not limited. The control group received CT or CT plus placebo, and treatment group was on the basis of it plus SAHP. No restrictions were applied to the herbal regi-
men used, acupoints selected, number of SAHP ses-
sions or treatment course. RCTs had to assess at least one of the following outcomes: clinical effective rate; quality of life (COPD assessment test, St. George’s respiratory questionnaire, chronic respiratory questionnaire, CAT, etc.); dyspnea [borg scale, visual analog dyspnea scale, Modified Medical Research Council (mMRC, etc.); exercise capacity (6-min walking test, shuttle walking test, etc.); lung function (FEV1, FVC, FEV1/FVC, TLC, RV, etc.); frequency of acute exacerbation; adverse effects.

Search methods
We searched for published studies in eight electronic databases from their inception to July 2017: Pubmed, EMBASE (include MEDLINE), the Cochrane Central Register of Controlled Trials, ovid [Journals @ Ovid Full Text and Ovid MEDLINE (R)], China National Knowledge Infrastructure, Chinese Biomedical Literature Database, Chinese Science and Technology Periodical Database, and Wanfang Database. In order to iden-
tify unpublished studies, we searched six major trial registries: Current Controlled Trials, the World Health Organization International Clinical Trials Registry Platform, Clinical Trials.gov trials registry, The Australian New Zealand Clinical Trials Registry, Centre Watch, and Chinese Clinical Trial Registry. Moreover, we also hand-searched the reference lists of all retrieved papers for additional relevant reports. A fil-
ter was applied to limit to humans. There was no re-
striction on languages of publication. The retrieval for-
mula of PubMed database is as follows:
1 # "Transdermal Patch" (MeSH) or "Transdermal Patches"
2 # "Patch, Transdermal"
3 # "Tianjiu Therapy"
4 # "Point Application"
5 # "Acupoint*" or "Acupoint Application"
6 # "Sticking*"
7 # "Acupuncture Point Paste"
8 # "Acupoint Herbal Patching"
9 # "External Application"
10 # "Emplastrum Therapy"
11 # Or/1#10
12 # "Sanfu"
13 # "Dog?Days" or "Canicular?Days" or "Summer"
14 # "Treating The Winter’s Disease In Summer"
15 # Or/12#14
16 # 11 And 15
17 # "Pulmonary Disease, Chronic obstructive" (MeSH)
18 # "COPD" or "Chronic Obstructive Pulmonary Disease"
19 # "Obstructi* lung disease"
20 # "Obstructi* airway disease"
21 # "COAD"
22 # "Airflow Obstruction", Chronic"
23 # "Chronic Airflow Limitation"
24 # "Chronic Airflow obstruction*"
25 # "Chronic respiratory disease"
26 # "Respiratory Tract Diseases"
27 # Or/17#26
28 # 16 And 27
29 # Randomized controlled trials (pt)
30 # Controlled Clinical Trials (pt)
31 # Randomized (tiab) or Randomly (tiab)
32 # Placebo (tiab)
33 # Trial (tiab)
34 # Groups(tiab)
35 # Or/29#34
36 # 28 And 35

Study selection and data collection process
Extracted data included participants (age, sex, stable stage classification, course of disease), interventions (herbal composition, acupoints selection, and frequency), controls (type, measures, frequency, and duration), outcomes (frequency and duration, evaluation time points and outcome measures) and study design (randomization, allocation concealment, blinded and etc.). If required information was not reported, we tried to request it from the corresponding author of the studies.

Risk of bias in individual studies
The methodological quality of RCTs was assessed ac-
cording to the risk of bias tool described in the Co-
chrane Handbook for Systematic Reviews of Interven-
tions. Six quality elements were assessed: random se-
quence generation, allocation concealment, blinding

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reporting, and other bias. Study selection, data extraction and risk bias assessment were conducted by two authors independently; in case of discrepancy consensus were reached by discussion with a third party.

**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, standardized mean difference (SMD) was performed for data analyses. For the Meta-analysis of non-significant heterogeneity, we applied a fixed-effect model (FEM); If heterogeneity were significant ($I^2 > 50\%$), we would determine the heterogeneous source by sensitivity analysis and subgroup analysis; If not found, random effect model (REM) would be selected by sensitivity analysis and subgroup analysis; If not significant heterogeneity, we applied a fixed-effect model (FEM). For meta-analysis, we used pooled odds ratio (OR) with 95% confidence interval (CI) to present effect estimate.

**RESULTS**

**Study selection**

Through the retrieval of 9 electronic databases, a total of 1615 records were identified. 1 ongoing trial was retrieved from 6 main stream registers. After excluding 714 duplicates, screening 660 remaining titles and abstracts, 139 articles were read in full text. The reasons for exclusion during full-text review were "Reviews" ($n = 3$), "Incomplete randomized trials" ($n = 17$), "Not in the period of Sanfu" ($n = 55$), "Papers or meeting or Conference Abstracts" ($n = 1$), "Other treatment" ($n = 16$), "Other stage of disease" ($n = 4$), "Other outcomes" ($n = 2$), "Other design" ($n = 8$), "Duplicate publication" ($n = 4$), "No diagnostic criteria and no author contact information" ($n = 1$), The 28 RCTs of which ultimately qualified for inclusion in our descriptive analysis. Although all trials meet our inclusion criteria, 3 RCTs were excluded due to incomplete data and 25 RCTs were performed for Meta-analysis (Figure 1).

**Characteristics of included RCTs**

All studies were published in China, 24 of them were journal articles (85.71%), and 4 were dissertations (14.29%). Both 28 RCTs arms were studied. All of them are two arm trials. 28 RCTs involved 2425 participants, ranging from 25 to 105, with a median of 86 participants in each trial. 18 trials included elderly patients from 30 to 85 years old, and 2 trials included 18 to 80 years of age in COPD patients, 8 trials did not mention the age range of patients included. The mean age of patients in the 26 trials ranged from 45.57 to 84.77, and 2 trials did not mention the average age of the patients. 80 in terms of gender, 41.04% participants were female (one trial without sex data). Most of the trials were used the Chinese national standards

![Flow Diagram](image-url)
for COPD to diagnose; 8 trials used the international diagnostic criteria. 15,24-27,37-41 12 trials mentioned in stable stage classification; 3 trials from grade one to grade two, 15,36,38 5 trials from grade one to grade three, 15,32,27,40,45 One trial from grade one to grade four, 44 one trial from grade two to grade three, 39 2 trials from grade two to grade four. 37-41

Frequency of acute exacerbation is the indicator that reflects preventive effect of treatment measures, and the others reflect therapeutic effect mainly. 13 trials assessed the preventive and therapeutic effect, 15,21,24,28,30,31,36,38,45,46 and 14 trials assessed the therapeutic effect. 15,20,23,27,28,32,33,37,40,42,45 one trial assessed the preventive effect. 29 For the preventive effects, 7 trials provided only partial data and statistical results, 24,25,31,36,38,39 and one trial only mentioned but did not provide data. 31 Fifty RCTs reported the SAHP were prepared by the pharmacy or pharmaceutical company in detail, the rest of the trials did not report. CT adopted inhaled corticosteroids, β-agonists, sustained-release theophylline, Expectorant and oxygen therapy, the treatment time ranged from 1 to 34 h, most of them were 1-6 h. The treatment time for the annual Sanfu, namely, Chu Fu, Ambush, Mofu, lasted for 30-40 d each year, each RCT follow-up evaluation time points are from 3 months to 3 years. However, the follow up evaluation time points was at least 6 months since the first session of SAHP finished.

Most of the SAHP properly contained semen Brassicae, Asarum and Ephedra, which had the function of pungent divergence. In addition, there were other Chinese herbal medicines, for example, Euphorbia kansui which could remove phlegm and dispel water, Rhus neonata Corydalis which was to promote blood and circulate Qi, etc. The major sticking points are Zhongfu (LU 1), Dingchuan (EX-B 1), Feishu (BL 13), Geshu (BL 17) and Xinshu (BL 15), to expel phlegm and relieve cough, ventilate lung Qi (Table 1). Although Chinese herbal medicine and sticking points are not the same, it may become the main cause of potential heterogeneity.

Risk of bias of the included trials

The risk of bias was assessed for each of the trials, and randomized trials were included in all the trial reports. 11 trials only refer to “random”, and not specifically describe the stochastic process. 12 trials mentioned the use of “random number table”, but only one trial 3 specified specifically described the process of using random number table. 3 trials were multicenter studies, 37,39,42 Two trials applied double-blinding method. 37,41 Other trials didn’t mention about blinding, but 8 trials of them used placebo regard as single-blinding method (only for participants). 37,32,24,39,47,40,41,44 Allocation concealment (selection bias), blinding of outcome assessment (detection bias) both not be mentioned, they might existence risk of bias. 3 trials 28,30,34 showed high risk of bias and 6 trials 34,36,39,43,45 were unclear risk of bias due to incomplete data or not provide data. 6 trials failed to report all pre specified major outcome measures. Among them, 3 trials 30,24, 32 were only mentioned but did not provide FVC, 2 trials 43,45 reported incomplete FVC’s and FEV1’s data, one trial 11 did not report frequency of acute exacerbations, there were high risk of bias (Figures 2, 3).

Clinical effective rate

A total of 16 RCTs 15,20,23,27,30,36,37,39,42,44 assessed clinical effective rate. Since the definitions of the clinical effective rates were various across studies, Meta-analysis was abandoned for descriptive analysis. Among them, the definition of 3 studies 28-30,44 was based on “the criteria of diagnosis and curative effect of TCM symptom patterns in 1994 edition”; 26 One study 22 was in accordance with the “Guiding principles for clinical research of new Chinese medicine in 1993 edition” and 9 studies 15,20,23,30,33,39,42,45 were based on “Guiding principles for clinical research of new Chinese medicine in 2002 edition”, 26 Three studies 21,22,38 were unclear. 14 studies 15,20,23,30,31,33,36,42,44 illustrated the definition of clinical effective rate and all the definitions contain evaluation of clinical symptoms or symptom scores. The definition of 5 studies 20,23,29,35 were not clear, and no specific symptoms were further explained; The remaining 9 studies 15,20,23,30,31,33,36,37,42-44 assessed symptoms including cough, expectoration, wheezing; The definitions of 3 studies 21,22,31 contained assessments of lung function (FEV1, FVC, FEV1/FVC) and 3 studies 21,22,31 included assessments of the frequency of acute exacerbation; 2 studies 21,22 did not describe the definition. All the studies showed that the clinical effective rate of the experimental group was higher than control group, and the difference was statistically significant (P < 0.05 or P < 0.01, Table 2).

Lung function

Seven RCTs used the FEV1 as the measurement. Among them, 1 RCT reported the annual measurements of 2 years, 21 and 1 RCT reported the annual measurements in 3 years. 31 The heterogeneity among the studies in 2 years were significant (I² = 92%), through the forest map and sensitivity analysis, Tao et al. 30 was the main cause of heterogeneity and could explain the heterogeneity of 59% (Figures 4, 5), so the data were merged after elimination. Compared with CT, We didn’t find statistical difference between SAHP plus CT and CT on FEV1 in 1 year (MD: 0.02; 95% CI: 0.04 to 0.07; I² = 0%; P = 0.61, 3 RCTs), and in 3 year (MD: 0.20; 95% CI: 0.11 to 0.51; I² = 53%; P = 0.21, 2 RCTs). There were statistical difference in 2 year (MD: 0.12; 95% CI: 0.04 to 0.20; I² = 33%; P = 0.002; 4 RCTs) (Figure 5).

Eight RCTs reported outcome of FEV1/PR%. There were 1 RCT reported the annual measurements of 2 years 20 and 1 RCT reported the annual measurements in 3 years. 41 The heterogeneity were significant in 1 year(I² = 64%) and 2 years (I² = 97%), Zhang et al. 30 and Tao et al. 30 were the main cause of heterogeneity which
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects randomized, analyzed (C/T)</th>
<th>Stable stage classification</th>
<th>Gender (M/F)</th>
<th>Mean age (years)</th>
<th>Comparison type</th>
<th>Acupoints selected</th>
<th>Pasting time</th>
<th>Frequency and duration of SAHP</th>
<th>Evaluation time point</th>
<th>Outcome measure</th>
<th>Evaluation of effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li ZY et al 2017&lt;sup&gt;21&lt;/sup&gt;</td>
<td>40/40, 37/39</td>
<td>I II</td>
<td>C: 20/17, T: 23/16</td>
<td>C: 548±4903, T: 567±1117</td>
<td>CT+P vs CT+SAHP</td>
<td>Tiantu (CV 22), Zhongfu (LU 1), Dingchuan (EX-B1), Feishu (BL 13)</td>
<td>First day of each fu</td>
<td>Once per fu, 6-8 h, 1 sanfu</td>
<td>3 months</td>
<td>①③⑤⑦</td>
<td>Preventive and therapeutic effects</td>
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<td>Zhang R et al 2017&lt;sup&gt;20&lt;/sup&gt;</td>
<td>43/43</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>CT vs CT+SAHP</td>
<td>Dazhui (GV 14), Tiantu (CV 22), Geshuang (BL 43), Feishu (BL 13), Ge (BL 17), Xinshu (BL 15)</td>
<td>The first three days of each fu</td>
<td>Third per fu, 2-4 h, 1 sanfu</td>
<td>1 year</td>
<td>①③⑤</td>
<td>Therapeutic effect</td>
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<tr>
<td>Ding RM et al 2016&lt;sup&gt;11&lt;/sup&gt;</td>
<td>33/34</td>
<td>I II III</td>
<td>C: 16/17, T: 18/16</td>
<td>C: 6273±862, T: 6348±871</td>
<td>CT+P vs CT+SAHP</td>
<td>Feishu (BL 13), Geshu (BL 17), Xinshu (BL 15)</td>
<td>First day of first fu, then once ten days</td>
<td>Third per sanfu, 6 h, 2 sanfu</td>
<td>2 years</td>
<td>①②⑤⑦</td>
<td>Preventive and therapeutic effects</td>
</tr>
<tr>
<td>Jü QX et al 2016&lt;sup&gt;22&lt;/sup&gt;</td>
<td>30/30</td>
<td>-</td>
<td>C: 16/12, T: 18/12</td>
<td>C: M(636±62), F(567±69), T: M(621±53), F(591±67), C: 669±1261, T: 725±1226</td>
<td>CT vs CT+SAHP</td>
<td>Dazhui (GV 14), Dingchuan (EX-B 1), Feishu (BL 13), Shenshu (BL 23), Zusanli (ST 36), Fengleng (ST 40)</td>
<td>During the sanfu</td>
<td>Tenth per sanfu, 2-4 h, 3 sanfu</td>
<td>3 years</td>
<td>①③⑤</td>
<td>Therapeutic effect</td>
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<tr>
<td>Liu MY et al 2016&lt;sup&gt;23&lt;/sup&gt;</td>
<td>110/110,101/105</td>
<td>-</td>
<td>C: 53/57, T: 62/48</td>
<td>C: 5992±809, T: 5602±799</td>
<td>CT vs CT+SAHP</td>
<td>Feishu (BL 13), Geshu (BL 17), Xinshu (BL 15)</td>
<td>First day of each fu</td>
<td>Third per fu, 6-8 h, 2 sanfu</td>
<td>2 years</td>
<td>①②⑤⑩</td>
<td>Therapeutic effect</td>
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<tr>
<td>Yuan ZY et al 2016&lt;sup&gt;24&lt;/sup&gt;</td>
<td>73/73</td>
<td>-</td>
<td>C: 39/34, T: 40/33</td>
<td>C: 5992±809, T: 5602±799</td>
<td>CT+P vs CT+SAHP</td>
<td>Feishu (BL 13), Geshu (BL 17), Pishu (BL 20), Shenshu (BL 23), Zusanli (ST 36), Fengleng (ST 40)</td>
<td>The first fu (from july 19th), the second fu (from july 29th), the last fu (from august 18th)</td>
<td>Third per sanfu, 34 h, 2 sanfu</td>
<td>2 years</td>
<td>②⑦⑩</td>
<td>Preventive and therapeutic effects</td>
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<td>Yao SQ et al 2016&lt;sup&gt;11&lt;/sup&gt;</td>
<td>35/35, 34/33</td>
<td>I II III</td>
<td>C: 21/13, T: 19/14</td>
<td>C: 5993±1016, T: 6213±925</td>
<td>CT vs CT+SAHP</td>
<td>Feishu (BL 13), Pishu (BL 20), Shenshu (BL 23)</td>
<td>First day of each fu</td>
<td>Once per fu, 2-4 h, 1 sanfu</td>
<td>3 months</td>
<td>①②⑤⑥</td>
<td>Therapeutic effect</td>
</tr>
<tr>
<td>Zhang Y et al 2015&lt;sup&gt;25&lt;/sup&gt;</td>
<td>30/30</td>
<td>-</td>
<td>C: 16/14, T: 15/15</td>
<td>C: 6323±789, T: 6297±821</td>
<td>CT vs CT+SAHP</td>
<td>First group of acupoints: Dingchuan (EX-B 1), Feishu (BL 13), Tiantu (CV 22); Second group of acupoints: Shenshu (BL 23), Pishu (BL 20), Zusanli (ST 36), Fengleng (ST 40), deficiency of vital energy add Zusanli (ST 36)</td>
<td>First day of each fu</td>
<td>Once a week, 4 weeks</td>
<td>1 month</td>
<td>①③⑤</td>
<td>Therapeutic effect</td>
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Table 1 Characteristics of included RCTs (continued)

<table>
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<tr>
<th>Study</th>
<th>Number of subjects randomized, analyzed (C/T)</th>
<th>Stable stage classification</th>
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<th>Acupoints selected</th>
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<th>Outcome measure</th>
<th>Evaluation of effects</th>
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<tr>
<td>Li ZY et al 2015(^{26})</td>
<td>60/60, 55/57</td>
<td>I II</td>
<td>C: 30/25, T: 31/26</td>
<td>C: 557±382, T: 562±798</td>
<td>CT vs CT+SAHP</td>
<td>Feishu (BL 13), Geshu (BL 17), Pishu (BL 20), Shenshu (BL 23)</td>
<td>From the first day of first fu, then once every ten days</td>
<td>Third every year, 8-12 h, 3 Sanfus</td>
<td>3 years</td>
<td>⑥⑨ Therapeutic effect</td>
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<tr>
<td>Huang PF et al 2014(^{26})</td>
<td>30/30</td>
<td>I II III</td>
<td>C: 22/8, T: 20/10</td>
<td>C: 575±772, T: 609±628</td>
<td>CT vs CT+SAHP</td>
<td>Feishu (BL 13), Dazhui (GV 14), Tianfu (CV 22), Yunmen (LU 2), Gao-huang (BL 43)</td>
<td>From the first day of first fu, then once every 5 days in per fu</td>
<td>Third every year, 8 h, 1 Sanfu</td>
<td>1 month</td>
<td>⑧⑨ Therapeutic effect</td>
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<tr>
<td>Liu J et al 2014(^{28})</td>
<td>30/30, 28/28</td>
<td>–</td>
<td>C: 19/9, T: 18/10</td>
<td>C: 6825±306, T: 6668±519</td>
<td>CT+P vs CT+SAHP</td>
<td>Tiantu (CV 22), Fengmen (BL 12), Dingchuan (EX-B 1), Feishu (BL 13)</td>
<td>From the first day of each fu</td>
<td>Once per fu, 4 h, 3 Sanfus</td>
<td>1 year</td>
<td>⑦ Preventive effect</td>
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<td>Mao LN et al 2014(^{28})</td>
<td>28/25</td>
<td>–</td>
<td>C: 15/13, T: 14/11</td>
<td>C: 6379±8779, T: 6432±8859</td>
<td>CT vs CT+SAHP</td>
<td>Tianfu (CV 22), Dazhui (GV 14), Dingchuan (EX-B 1), Feishu (BL 13)</td>
<td>From the third day after the summer solstice has lasted for 40 days</td>
<td>Third every year, 4-6 h, 2 Sanfus</td>
<td>2 years</td>
<td>①⑦ Preventive and therapeutic effects</td>
<td></td>
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<tr>
<td>Li YN et al 2014(^{28})</td>
<td>38/38</td>
<td>–</td>
<td>C: 20/18, T: 22/16</td>
<td>C: 5985±408, T: 6004±429</td>
<td>CT vs CT+SAHP</td>
<td>Tiantu (CV 22), Fengmen (BL 12), Dingchuan (EX-B 1), Feishu (BL 13)</td>
<td>During the sanfu, 10 times for a course of treatment</td>
<td>Once every 2-3 d, 3 Sanfus</td>
<td>3 years</td>
<td>①③⑤⑦ Preventive and therapeutic effects</td>
<td></td>
</tr>
<tr>
<td>Zhang BH et al 2014(^{28})</td>
<td>30/30</td>
<td>–</td>
<td>C: 18/12, T: 19/11</td>
<td>/</td>
<td>CT vs CT+SAHP</td>
<td>Xingfu (BL 15), Geshu (BL 17), Shenshu (BL 23), Feishu (BL 13), Dazhui (GV 14), Dingchuan (EX-B 1), Gao-huang (BL 43), according to the symptoms to select: Xingfu (BL 15), Geshu (BL 17), Shenshu (BL 23), Pishu (BL 20), Dingchuan (EX-B 1), Feishu (BL 13), Pishu (BL 20), Geshu (BL 17), Dazhui (GV 14), Tiantu (CV 22), Dazhui (CV 17)</td>
<td>During the sanfu, 5 times in total</td>
<td>Once every 7-10 d, 4-6 h, 3 Sanfus</td>
<td>3 years</td>
<td>① Therapeutic effect</td>
<td></td>
</tr>
<tr>
<td>Xie Y et al 2013(^{28})</td>
<td>25/25</td>
<td>–</td>
<td>C: 15/10, T: 16/9</td>
<td>C: 6375±777, T: 6498±801</td>
<td>CT vs CT+SAHP</td>
<td>Feishu (BL 13), Geshu (BL 17), Pishu (BL 20), Shenshu (BL 23), Feishu (BL 13), Dazhui (GV 14), Tiantu (CV 22), Dazhui (CV 17)</td>
<td>First day of each fu</td>
<td>Once every 3-5 d, 2-6 h, 2 Sanfus</td>
<td>2 years</td>
<td>①②③⑤ Therapeutic effect</td>
<td></td>
</tr>
<tr>
<td>Tao HQ et al 2013(^{28})</td>
<td>50/50</td>
<td>–</td>
<td>C: 33/17, T: 35/15</td>
<td>C: 549±67, T: 557±65</td>
<td>CT vs CT+SAHP</td>
<td>Xingfu (BL 15), Geshu (BL 17), Shenshu (BL 23), Feishu (BL 13), Pishu (BL 20), Dingchuan (EX-B 1), Feishu (BL 13), Pishu (BL 20), Geshu (BL 17), Dazhui (GV 14), Tiantu (CV 22), Dazhui (CV 17)</td>
<td>During the sanfu, 5 times in total</td>
<td>Once every 3-5 d, 2-6 h, 2 Sanfus</td>
<td>2 years</td>
<td>①②③⑤ Therapeutic effect</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Number subjects randomized, analyzed (C/T)</td>
<td>Stable stage classification</td>
<td>Gender (M/F)</td>
<td>Mean age (years)</td>
<td>Comparison type</td>
<td>Acupoints selected</td>
<td>Pasting time</td>
<td>Frequency and duration of SAHP</td>
<td>Evaluation time point</td>
<td>Outcome measure</td>
<td>Evaluation of effects</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>Wang CL et al 2013</td>
<td>47/41, 35/35</td>
<td>I II III IV</td>
<td>C: 32/3, T: 27/8</td>
<td>C: 6497 ± 595, T: 6480 ± 722</td>
<td>CT+CT</td>
<td>Feishu (BL 13), Dinghuan (EX-B 1), Shenshu (BL 23)</td>
<td>During the sanfu</td>
<td>Twice every week, 4-8 h, 6 weeks</td>
<td>3 months, 6 months</td>
<td></td>
<td>Preventive and therapeutic effects</td>
</tr>
<tr>
<td>Li GQ et al 2012</td>
<td>71/71, 59/59</td>
<td>II IV</td>
<td>C: 39/22, T: 39/25</td>
<td>C: 6556 ± 939, T: 6275 ± 802</td>
<td>CT+P vs CT+SAHP</td>
<td>Feishu (BL 13), Xinshu (BL 15), Guanyuanshu (BL 26), Tiantu (CV 22), Zusanli (ST 36)</td>
<td>During the sanfu, 3 times in total</td>
<td>Once every 10 d, 6 h, 2 sanfu</td>
<td>1 year, 2 years</td>
<td></td>
<td>Preventive and therapeutic effects</td>
</tr>
<tr>
<td>Wu GC et al 2012</td>
<td>42/42</td>
<td>-</td>
<td>C: 32/8, T: 30/10</td>
<td>C: 64, T: 65</td>
<td>CT+CT</td>
<td>Feishu (BL 13), Fengmen (BL 12), Pishu (BL 20), Shenshu (BL 23), Geshu (BL 17)</td>
<td>During the sanfu</td>
<td>Once per fu, 4-6 h, 3 sanfu</td>
<td>3 years</td>
<td></td>
<td>Preventive and therapeutic effects</td>
</tr>
</tbody>
</table>
| Li XM et al 2012 | 43/43 | - | C: 23/21, T: 24/20 | C: 6278 ± 1102, T: 6395 ± 1075 | CT+CT | Feishu (BL 13), Pishu (BL 20), Shenshu (BL 23), Zhongwan (CV 12), Lili- 
que (LU 7); Second groups of acupoints: Da-zhui (GV 14), Geshu (BL 17), Yiming (EX-HN 14), Zusanli (ST 36), Tiantu (CV 22), Danzhong (CV 17) | During the sanfu, 5 times in total | Once every 5-7 days of per fu, 2-3 h, 3 sanfu | 3 years | | Therapeutic effect |
| Tan GB et al 2011 | 31/32 | I II | C: 22/9, T: 21/11 | C: 5751 ± 782, T: 609 ± 627 | CT+CT | First group of acupoints: Feishu (BL 13), Pishu (BL 20), Shenshu (BL 23), Zhongwan (CV 12), Lili- 
que (LU 7); Second groups of acupoints: Da-zhui (GV 14), Geshu (BL 17), Yiming (EX-HN 14), Zusanli (ST 36), Tiantu (CV 22), Danzhong (CV 17) | During the sanfu | Once every 5 d, 8 h, 3 sanfu | 3 years | | Preventive and therapeutic effects |
<p>| Yang YZ et al 2011 | 63/62 | - | C: 30/33, T: 32/30 | C: 6738 ± 1167, T: 6527 ± 235 | CT+CT | First day of each fu, 3 times in total | Once per fu, 2-8 h, 3 weeks | 3 weeks | | Preventive and therapeutic effects |
| Tian Y et al 2011 | 25/25, 20/30 | I II III | C: 12/8, T: 19/11 | C: 6555 ± 846, T: 6497 ± 738 | CT+P vs CT+SAHP | Feishu (BL 13), Xinshu (BL 15), Geshu (BL 17) | From the first day of first fu, 3 times in total | Once every 10 d, 6 h, 1 sanfu | 3 months, 6 months | | Therapeutic effect |
| Wu RH et al 2011 | 71/71, 63/63 | II IV | C: 39/24, T: 41/22 | C: 6556 ± 939, T: 6275 ± 802 | CT+P vs CT+SAHP | Feishu (BL 13), Shenshu (BL 23), Geshu (BL 17) | During the sanfu, 3 times in total | Once every 10 d, 6 h, 3 sanfu | 12 months, 1 year, 2 years, 3 years | | Preventive and therapeutic effects |
| Zhang HS et al 2011 | 32/32 | - | C: 20/12, T: 18/14 | C: 6023 ± 424, T: 6005 ± 438 | CT+CT | Dazhui (GV 14), Feishu (BL 13), Fengmen (BL 12), Shenshu (BL 23), Zusanli (ST 36), Luoque (CV 8) | During the sanfu (40 days) | Once every day, 24 h | 3 years | | Therapeutic effect |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Mean age (years)</th>
<th>Stable stage classification</th>
<th>Comparison type</th>
<th>Accupoints selected</th>
<th>Pasting time</th>
<th>Evaluation time point</th>
<th>Frequency of acute exacerbations (times per year)</th>
<th>Outcome measure</th>
<th>Therapeutic effect</th>
<th>Other bias</th>
</tr>
</thead>
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<tr>
<td>Zhu XL et al. 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>-</td>
<td>65±6, 60±6</td>
<td>①③⑤⑦</td>
<td>CT vs CT + SAHP</td>
<td>Pishu (BL 13), Pishu (BL 13), Pishu (BL 13), Pishu (BL 13)</td>
<td>③⑤⑦</td>
<td>1 year</td>
<td>1.7±0.8</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
</tr>
<tr>
<td>Wang HF et al. 2009&lt;sup&gt;29&lt;/sup&gt;</td>
<td>-</td>
<td>62±7</td>
<td>②⑤⑥</td>
<td>CT + SAHP vs CT</td>
<td>Guanyuan (BL 40), Zusanli (ST 36), Guanyuan (BL 40), Zusanli (ST 36)</td>
<td>②⑤⑥</td>
<td>1 year</td>
<td>2±0.8</td>
<td>②⑤⑥</td>
<td>②⑤⑥</td>
<td>②⑤⑥</td>
</tr>
<tr>
<td>Guan QH et al. 2006&lt;sup&gt;34&lt;/sup&gt;</td>
<td>-</td>
<td>53±8</td>
<td>①③⑤⑦</td>
<td>CT vs SAHP</td>
<td>Danzhong (CV 12), Qihai (BL 16), Qihai (BL 16), Qihai (BL 16)</td>
<td>①③⑤⑦</td>
<td>1 year</td>
<td>1.3±0.6</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
</tr>
<tr>
<td>Huang PF et al. 2014&lt;sup&gt;32&lt;/sup&gt;</td>
<td>-</td>
<td>65±9</td>
<td>②⑤⑥</td>
<td>CT vs SAHP</td>
<td>Shenshu (BL 23), Shenshu (BL 23), Shenshu (BL 23), Shenshu (BL 23)</td>
<td>②⑤⑥</td>
<td>1 year</td>
<td>1.3±0.6</td>
<td>②⑤⑥</td>
<td>②⑤⑥</td>
<td>②⑤⑥</td>
</tr>
<tr>
<td>Yu SQ et al. 2018&lt;sup&gt;30&lt;/sup&gt;</td>
<td>-</td>
<td>56±8</td>
<td>①③⑤⑦</td>
<td>CT vs CT + SAHP</td>
<td>Danzhong (CV 12), Qihai (BL 16), Qihai (BL 16), Qihai (BL 16)</td>
<td>①③⑤⑦</td>
<td>1 year</td>
<td>1.3±0.6</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
<td>①③⑤⑦</td>
</tr>
</tbody>
</table>

Notes: CT: control group; CT +: treatment group; CT: conventional therapy; SAHP: Sanhi acupuncture herbal patching; P: placebo; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HRCT: high-resolution computed tomography; O2: oxygen; %: percentage; SGRQ: St George Respiratory Questionnaire; mMRC: modified Medical Research Council; 6MWT: six-minute walk test; FEV1/FVC: ratio of forced expiratory volume in one second to forced vital capacity; FEV1/FEV1(F); FEV1/FVC; mFVC; mFVC%. Other: The trial provided partial data or no data.
could explain the heterogeneity of 55% and 97% respectively (Figures 6, 7). It demonstrated no significant difference in this comparison on FEV1/FEV0 1% in 1 year (MD: 0.51; 95% CI: −0.88 to 1.90; 12 = 9%; P = 0.47; 5 RCTs), in 2 years (SMD: 0.01; 95% CI: −0.24 to 0.26; 12 = 0%; P = 0.93, 2 RCTs) and in 3 years (MD: 2.38; 95% CI: −1.76 to 6.53; 12 = 0%; P = 0.26, 2 RCTs) (Figure 7).

Two RCT reported the FVC%, showing no significant difference from SAHP plus CT compared with CT (MD = 2.33, 95% CI: −1.97 to 6.64; 12 = 14%; P = 0.29, 2 RCTs) (Figure 8).

Fourteen RCTs evaluated the FEV1/FVC. Ding’s 11 and Li’s 12 trials reported 2 years’ data. Wu’s trial 10 reported 3 years’ data. The heterogeneity in 1 year (12 = 64%) and 2 years (12 = 97%) were significant, Qi et al 11 and Tao et al 15 were the main cause of heterogeneity and could explain the heterogeneity of 64% and 91% respectively (Figures 9, 10). A Meta-analysis found no significant difference between SAHP plus CT and CT in 1 year (SMD: 0.11; 95% CI: −0.03 to 0.25; 12 = 0%; P = 0.12, 8 RCTs), 2 years’ (SMD: 0.13; 95% CI: −0.44 to 0.30; 12 = 6%; P = 0.15, 4 RCTs) and the 3 years’ (SMD: 0.26; 95% CI: 0.01 to 0.51; 12 = 0%;
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P = 0.04, 3 RCTs). Meta-analyses found beneficial effects of SAHP plus CT compared with CT (Figure 10).

George respiratory questionnaire
Seven RCTs reported on quality of life using St. George Respiratory Questionnaire (SGRQ). Li's trial reported two years' data. Wu's trial compared sanfu SAHP plus CT with CT after 1 year, 2 years and 3 years respectively. The heterogeneity in 3 year ($I^2 = 74\%$) were significant, Wu et al. was the main cause of heterogeneity which the heterogeneity of 74% could

Figure 4 Heterogeneity among the studies of FEV1.
FEV1: forced vital capacity rate of one second.

Figure 5 FEV1 of SAHP plus CT vs CT or CT plus placebo.
FEV1: forced vital capacity rate of one second; SAHP: Sanfu acupoint herbal patching; CT: conventional therapy.

$P = 0.04$, 3 RCTs). Meta-analyses found beneficial effects of SAHP plus CT compared with CT (Figure 10).

George respiratory questionnaire
Seven RCTs reported on quality of life using St. George Respiratory Questionnaire (SGRQ). Li's trial reported two years' data. Wu's trial compared sanfu SAHP plus CT with CT after 1 year, 2 years and 3 years respectively. The heterogeneity in 3 year ($I^2 = 74\%$) were significant, Wu et al. was the main cause of heterogeneity which the heterogeneity of 74% could
be explained (Figures 11, 12). 7 trials showed significant difference the SGRQ after first session (MD: $-2.73; 95\%\ CI: -4.14$ to $-1.33; I^2 = 4\%; P = 0.0001$, 6 RCTs), two session (MD: $-8.40; 95\%\ CI: -13.09$ to $-3.71; I^2 = 37\%; P = 0.0004$, 2 RCTs) and third session (MD: $-2.62; 95\%\ CI: -4.88$ to $-0.36; I^2 = 0\%; P = 0.02$, 2 RCTs) (Figure 12).

mMRC

Three RCTs reported on mMRC score. These trials...
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**Six-Minute Walk Test (6MWT)**

Six trials examined the 6MWT. Wu’s trial\(^1\) reported three sessions’ data of 6MWT. The heterogeneity in 1 year \(I^2 = 85\%\) and 3 years \(I^2 = 69\%\) were significant. The main reason for the heterogeneity in 1 year is the random effect model chose for data merging. Li et al.\(^2\) was the main cause of heterogeneity in 3 years and could explain the heterogeneity of 62% (Figures 14, 15). No significance were found between the comparisons after first session \(SMD: 11.54; 95\% CI: -6.73\) to 29.81; \(I^2 = 85\%; P = 0.22\, 3\) RCTs). But the improvement was observed after the third session \(MD: 19.76; 95\% CI: 15.09\) to 24.43; \(I^2 = 7\%; P < 0.0001\, 2\) RCTs) (Figure 15).

**Frequency of acute exacerbation**

Frequency of acute exacerbation is an indicator that reflects preventive effect of treatment measures. 13 trials evaluated frequency of acute exacerbation, only 6 studies of them provided complete data, other studies, however, provide part of the data.\(^2,13,14,15,16,17,18,19\) one trial\(^1\) only mentioned but did not provide data, So we give up the Meta-analysis and the descriptive analysis were performed (Table 3).

Six trials provided the data of the course of 1 year, 3 trials\(^2,4,5,16,17\) showed that the treatment group was significantly reduced, and the difference was statistically significant; 5 trials\(^2,3,13,15,16\) provided the data of 2 years, the reduction was statistically significant compared with the course for 1 year; 3 trials\(^1,5,16\) counted for the data of 3 years, the reduction was statistically significant compared with 2 years. In the above studies, the control group did not show significant preventive effect on acute exacerbation of COPD.

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### Table 2: Comparison of SAHP and Control for Frequency of Acute Exacerbation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SD</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMD: -11.54</td>
<td>95% CI: -6.73 to 29.81</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>I^2 = 85%</td>
<td>P = 0.22, 3 RCTs)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>SMD: 11.54</td>
<td>95% CI: -6.73 to 29.81</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>I^2 = 85%</td>
<td>P = 0.22, 3 RCTs)</td>
<td>16</td>
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<tr>
<td></td>
<td>SMD: 11.54</td>
<td>95% CI: -6.73 to 29.81</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>I^2 = 85%</td>
<td>P = 0.22, 3 RCTs)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>SMD: 11.54</td>
<td>95% CI: -6.73 to 29.81</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>I^2 = 85%</td>
<td>P = 0.22, 3 RCTs)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>SMD: 11.54</td>
<td>95% CI: -6.73 to 29.81</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>I^2 = 85%</td>
<td>P = 0.22, 3 RCTs)</td>
<td>16</td>
</tr>
</tbody>
</table>

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**Figure 8** FVCs of SAHP plus CT vs CT or CT plus placebo

FVC: forced vital capacity; SAHP: Sanfu acupoint herbal patching; CT: conventional therapy.

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**Figure 9** Heterogeneity among the studies of FEV1/FVC

FEV1/FVC: forced vital capacity rate of one second/ forced vital capacity.
Figure 10 FEV1/FVC of SAHP plus CT vs CT or CT plus placebo.
FEV1/FVC: forced vital capacity rate of one second/forced vital capacity; SAHP: Sanfu acupoint herbal patching; CT: conventional therapy.

Figure 11 Heterogeneity among the studies of SGRQ.
SGRQ: St. George Respiratory Questionnaire.
In 28 trials, only 7 trials reported on adverse events: 2 trials reported that no adverse events occurred, while 3 trials demonstrated that adverse events found skin irritation, redness, and one trial only referred to anaphylaxis, but gave no exact details. Only one trial reported that some patients who felt unwell or had larger blisters were treated properly.

Sensitivity analysis
Sensitivity analysis was performed for the results of each Meta-analysis. The single item study was eliminated one by one to observe the difference between the combined effect volume and the total effect quantity of the residual study, and it showed that the results were stable.

Results Publication bias analysis
The inverted funnel plot analysis was performed on 16 trials with clinical efficiency as the outcome. The results showed that the symmetry of inverted funnel plot was general, and the estimation of effect was mostly located in the middle position. The distribution range was narrow and gradually concentrated to the center of the merging effect quantity, and the large sample data with high precision was less. It indicated the possibility of publication bias, the possible reasons for inclusion in the test method research of low quality and small sample size led to low quality literature; negative results might not be published; the application and course of intervention in the test group and the control group were not identical (Figure 16).

DISCUSSION
Effectiveness and safety
Totally 25 RCTs were included in this review. Descriptive analysis shows that SAHP with CT seems to improve clinical effective rate. The results of Meta-analysis showed that SAHP with CT applied in the treatment of COPD seems to be better than CT, in second sessions’ data of FEV₁, in third sessions’ data of FEV₁/FVC, in three sessions’ data of SGRQ, in third session’s data of mMRC and 6MWT. The difference was statistically significant. The results of descriptive analysis showed that SAHP with CT had a certain preven-
tive effect on acute exacerbation of COPD, and the curative effect seemed to be better with the increase of treatment course. However, we could not draw conclusion due to the included studies with high or unclear risk of bias. We may not conclude that SAHP with CT could improve clinical effective rate because most of RCTs have different criteria for determining clinical effective rate and we did not make a merger analysis.

The effect of lowering mMRC and increasing 6MWT should be considered carefully, because the number of RCTs was less. At the same time, we could not conclude that SAHP with CT had a preventive effect on COPD, because some of the literature provided incomplete data, and we did not perform a quantitative analysis. Thus, SAHP with CT for improve lung function, improve the quality of life seems to be more effective than CT. Some results extended with follow-up time shows better effect than CT, but the follow-up time is limited, we cannot determine the clinical effect of SAHP treatment of COPD.

Figure 14 Heterogeneity among the studies of 6MWT
6MWT: six-minute walk test.

Figure 15 6MWT of SAHP plus CT vs CT or CT plus placebo
6MWT: six-minute walk test; SAHP: Sanfu acupoint herbal patching; CT: conventional therapy.
The diverse duration of treatment (2-34 h every time, every Fu), the vary course of treatment (ranging from 30-40 d every course), the different length of follow-up time (ranging from 1, 3, 6, 9, 12 months or 2, 3 years) may exist bias. The end point index of relevant reports is different, we cannot determine whether or not there any differences between the trial group and the control group in reducing the mortality of patients and other endpoint event. Adverse reactions are a small amount of partial skin redness or allergies, and large blisters. In general, the symptoms of SAHP’s adverse reactions were mild and the incidence is low. It indicates that SAHP treat COPD have short-term high security, good tolerance. However, the included trials are short term studies (less than three years), the long-term safety is not clear, so we cannot make an exact conclusion. The evaluation of the safety needs more high-quality clinical research observation and more non randomized research evidence.

**Internal and external validity**

Only one of the retrieved articles was from the China clinical trial registration center, and the completion of the trial was unclear. Publication bias may exist. And one trial published in different journals, which resulted in repeated publication bias. We found that the content was slightly changed, but the data were the same, so we merge the two trials. Although bias was reduced, the bias still existed. All 28 RCTs conducted in China in this systematic review may cause language bias. In the study, only 2 trials use allocation concealment and double blinded methods, which avoided selection bias. Incomplete reports of 6 trials failed to provide sufficient information about the data, which could lead to potential attrition bias. Therefore, the potential bias limited the interpretability of the results.

All the patients included in this study were Chinese, mainly middle-aged and elderly, with a relatively balanced sex ratio. Grades 1 to 4 of stable COPD patients were all present. So SAHP been seen at least applicable to the stable COPD elderly patients in China, and has a higher acceptance rate and good effect in the preven-

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**Table 3 Descriptive analysis of the frequency of acute exacerbation**

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete data</th>
<th>Course of treatment</th>
<th>Compare with before treatment/the previous year</th>
<th>Comparison with the control group in the same period</th>
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<td>U</td>
<td>D</td>
</tr>
<tr>
<td>Wu RH et al 2011</td>
<td>Y</td>
<td>1 year</td>
<td>R</td>
<td>D</td>
</tr>
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<td>Wang HF et al 2009</td>
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<td>R</td>
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<td>Ding RM et al 2016</td>
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<td>U</td>
</tr>
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<td>Li J et al 2014</td>
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<td>U</td>
</tr>
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<td>1 year</td>
<td>R</td>
<td>D</td>
</tr>
<tr>
<td>Yang YZ et al 2011</td>
<td>N</td>
<td>1 year</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Zhu XL et al 2010</td>
<td>Y</td>
<td>1 year</td>
<td>R</td>
<td>D</td>
</tr>
</tbody>
</table>

Notes: Y: Yes; N: No; U: unstatistics; R: significantly reduced; D: not significant and difference.

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![Figure 16 Funnel plot analysis](image_url)

The diverse duration of treatment (2-34 h every time, every Fu), the vary course of treatment (ranging from 30-40 d every course), the different length of follow-up time (ranging from 1, 3, 6, 9, 12 months or 2, 3 years) may exist bias. The end point index of relevant reports is different, we cannot determine whether or not there any differences between the trial group and the control group in reducing the mortality of patients and other endpoint event. Adverse reactions are a small amount of partial skin redness or allergies, and large blisters. In general, the symptoms of SAHP’s adverse reactions were mild and the incidence is low. It indicates that SAHP treat COPD have short-term high security, good tolerance. However, the included trials are short term studies (less than three years), the long-term safety is not clear, so we cannot make an exact conclusion. The evaluation of the safety needs more high-quality clinical research observation and more non randomized research evidence.

**Internal and external validity**

Only one of the retrieved articles was from the China clinical trial registration center, and the completion of the trial was unclear. Publication bias may exist. And one trial published in different journals, which resulted in repeated publication bias. We found that the content was slightly changed, but the data were the same, so we merge the two trials. Although bias was reduced, the bias still existed. All 28 RCTs conducted in China in this systematic review may cause language bias. In the study, only 2 trials use allocation concealment and double blinded methods, which avoided selection bias. Incomplete reports of 6 trials failed to provide sufficient information about the data, which could lead to potential attrition bias. Therefore, the potential bias limited the interpretability of the results.

All the patients included in this study were Chinese, mainly middle-aged and elderly, with a relatively balanced sex ratio. Grades 1 to 4 of stable COPD patients were all present. So SAHP been seen at least applicable to the stable COPD elderly patients in China, and has a higher acceptance rate and good effect in the preven-
tion and treatment of COPD in China. But due to the limitations of the race in the study, the prevention and treatment effect of SAHP of other races are still unknown. Only 3 trials documented the history of smoking or smoking index of patients. Smoking as a risk factor for COPD may affect the test results, we suggest that the history of smoking will be recorded in future RCTs in order to further clinical research.

**Implication for clinical practice**

SAHP’s herbs are mainly composed of Semen Sinapis, Asarum, Ephedra and other divergent herbs. It has been reported that Semen Sinapis can enter into lung meridian, and has the effect of antitussive expectorant, antiasthmatic, promoting transdermal absorption, activating blood stasis, detumescence and relieve pain. But it has some stimulation to make the skin redness, warm, and even foaming. This is the main cause why the application time should not be too long. Asarum has antipyretic, analgesic and anti-inflammatory effects. The volatile oil of Asarum can significantly reduce the barrier of skin, and this effect is beneficial to promote the transdermal penetration of Sinapine’s active principle, and has the effect of promoting permeability. Ephedra has the effect of relieving asthma and sweating, and ephedra alkaloids as its main effective component can stimulate the beta receptor directly, relax bronchial smooth muscle, and prevent the release of allergic mediators. Acupoints as the reaction points of organs, Qi and blood transfusion in meridian can make drugs directly come into the organs and play a role. The sticking points check acupoints of lung meridian such as Zhongfu (LU 1), Dingchuan (EX-B 1), and the acupoints of relating and adjacent organs such as Feishu (BL 13), Geshu (BL 17), Xinshu (BL 15). After herbs sticking to the corresponding points, they are absorbed through the skin penetration, and then through the blood circulation reached where are Qi and viscera disorder diseases, playing herbs’ meridian function and effect, resulting in the treatment of disease. These herbs and acupoints have good curative effect in the treatment of stable COPD, and can be used as reference in the clinical diagnosis and treatment process. However, considering the high risk of bias all the conclusions should be interpreted with caution.

**Strengths and weaknesses**

Compared with the recent Meta-analysis, our study is not only better than Lin’s study in searching RCT’s range. Lin’s study only proved that the clinical efficiency, FEV1/FVC, SGRQ and BODE of CT and SAHP were significantly improved. The advantages of this study included comprehensive literature retrieval, no language restrictions, and inclusion of completely randomized controlled trials, group analysis and evaluation according to follow-up phase. The negative results were also reported, which could be used as a clue for future research.

The results of high heterogeneity Meta-analysis may be related to SAHP’s components and different selection of sticking points. Although it is one of the characteristics of TCM therapy, it has become one of the difficulties in quantitative research. In order to make the same color and viscosity, the components of placebo in the trials also contained herbs. It is difficult to judge whether the herbs affect the treatment of COPD. The difference of odors between SAHP and placebo also become a challenge to make a placebo. Its solution needs to be further explored. The deficiency of study included a limited quantity of RCTs, the small sample, the varied experimental method, the possible limitations bias in evaluation, and so on. As a secondary study, more exact effect still needs more high-quality and large-scale clinical RCTs to provide more powerful evidence.

**Implications for further research**

Compared with CT, SAHP plus CT seems to be effective for preventing 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. Our study found that the lack of unified standards for research methods, unclear random method, the lack of strict allocation concealment and blinding method, the small sample are the keys to affect the quality of systematic review and Meta-analysis in the future. So how to unified RCT standard will be the most imperative problems to be solved. In conclusion, SAHP with CT appears to be more effective than CT in second and third sessions’ data of FEV1/FVC and frequency of acute, in three sessions’ data of SGRQ, in third session’s data of mMRC and 6MWT. SAHP with CT can be used in any grade to safely treat stable COPD patients. In clinical, it has been applied widely and obtained satisfied results in China, which has a certain value of promotion. However, our findings still need to be further confirmed with better-designed RCTs.

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