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Acupoint Herbal Patching with or without Conventional Treatment for Stable Chronic Obstructive Pulmonary Disease: a Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: Acupoint herbal patching (AHP) alone or as an adjuvant therapy with conventional treatment (CT) has been widely used for prevention and treatment of chronic obstructive pulmonary disease (COPD). However, current clinical evidence from a systematic review of RCTs is lacking.

Objective: To evaluate the effectiveness and safety of AHP with or without CT for people with COPD at stable stage.

Methods: We searched randomized controlled trials comparing AHP (with or without CT) with no intervention, placebo, or CT from six databases. Two authors selected studies, extracted data and evaluated risk of bias of included trials. RevMan 5.2 software was used to analysis data.

Results: Twenty one RCTs (2327 participants) were included. AHP of non *sanfu* applied on no fixed dates with CT significantly decreased the mean frequency of acute exacerbation of COPD (times per year) (MD: −1.24; 95% CI: −2.02 to −0.46; 2 trials), and improved lung function parameters and quality of life. The AHP with CT showed no better effect in 6-minute walking distance (6MWD) that CT alone. AHP applied at *sanfu* (specific dates based on lunar calendar) with CT had significant effect for 6MWD (MD: 11.20; 95% CI: 0.83 to 21.56; I^2 = 0%; 3 trials). One trial reported skin irritation from AHP. Another trial reported two patients had eye discomfort, which was inferred as the adverse effects of seretide.

Conclusion: AHP used as an adjunct to CT, appears to be more effective than CT alone in patients with stable COPD. However, further large, rigorously designed trials are warranted to confirm these potential effects.

Key words: Traditional chinese medicine, Acupoint herbal patching, Chronic obstructive pulmonary disease, Treatment, Systematic review, Randomized controlled trials

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a progressive disease which presents with dyspnea, cough, sputum production, wheezing and chest tightness[1]. It is one of the leading causes of morbidity, disability, and mortality globally. According to the World Health Organization, it was the fifth most common cause of death in 2002 and will be up to the third most common cause of death in 2030[2]. If an acute exacerbation of COPD occurs there is usually an acceleration of the rate of lung function decline, substantial socioeconomic costs, and a significant first of mortality and diminished quality of life[3–5].

The 2011's Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines summarized the major pharmacologic treatments for stable COPD and preventative interventions to avoid acute exacerbations of COPD; this includes administering bronchodilators and corticosteroids alone or in combination, mainly in the form of inhalers. These pharmacologic treatments do not halt the deterioration of lung function and are associated with adverse effects[1]. Forty to 60% of patients with COPD do not adhere to their prescribed medications and between 4% and 94% of patients fail to use their inhalers correctly[6] mainly because of the variety of medicines[7] and complication of the inhaler devices[8].

In China, acupoint herbal patching (AHP, sticking herbal medicine patches on acupuncture points) is first described in the *Wu Shi Er Bing Fang*[9] to help wheezing and cough[10]. It is one of the external therapies used to prevent or treat conditions through combined transcutaneous absorption of herbal extracts and stimulation of acupuncture points[11]. AHP for COPD can be given in 2 ways: applied only on *sanfu* days or on *non-sanfu* days. *Sanfu* (literally hibernating days) usually last from around the Lesser Heat, the 11th Solar Term and through the Autumn, the 13th Solar Term. The duration of the 13th Solar Term varies from 30 days to 40 days depending on the lunar calendar for each year. This period of time is of special significance in TCM in treating certain diseases and is characterized by high temperatures and muggy weather when *yang* is strongest in human body. If

AHP is applied on *non-sanfu* days it is with the aim of both of prevention and treatment.

There have been five systematic reviews published for COPD using Chinese herbal medicines administered by oral or intravenous route[12–16]. Most suggest a promising benefit for herbal medicine. Another systematic review[17] covers a similar area to this one but the search retrieval is limited to Chinese databases. It evaluated a composite outcome (clinical efficacy) and ignored other patient centered outcomes such as quality of life and it did not classified the AHP as *sanfu* or *non-sanfu*. Our review adopted a more comprehensive search strategy and focused on clinical end-point outcomes incorporating of Traditional Chinese Medicine (TCM) theory by comparing *sanfu* and *non-sanfu* AHP application.

MATERIALS AND METHODS

Standard protocol registrations

This systematic review protocol was registered in an international prospective register of systematic reviews, PROSPERO. The registration No is CRD42014008999[18].

Inclusion and exclusion criteria

Randomized controlled trials (RCTs) were included for data analysis in participants with stable COPD using AHP with or without conventional treatment (CT, which means therapy referred by GOLD[1]) compared with no intervention, placebo, and conventional therapy. Combination of AHP and conventional therapy compared with the same conventional therapy was also included.

Participants with stable COPD regardless of gender, age, etiology, ethnic group, severity, diagnosed with specific criteria (i.e. mention any one of criteria for diagnosis of COPD) are eligible for inclusion. Participants of COPD complicated with asthma were excluded.

Primary outcome measure was acute exacerbation of COPD. Secondary outcome measures included clinical symptom improvement, quality of life, lung function parameters, 6-minute walking distance and adverse events.

Data Source and Searches

Two authors (YWS and FZ) searched the following electronic databases from their inception to April 2014: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP Database, Sino-med and Wanfang Database.

In order to acquire comprehensive search, FZ also searched for ongoing trials from mainstream registries including Current Controlled Trials, the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov trials registry, The Australian New Zealand Clinical Trials Registry, and CentreWatch.

Unpublished postgraduate theses in China Doctoral Dissertations Full-text Database (CDFD), China Master's Theses Full-text Database (CMFD) and China Master's Theses Full-text Database supplement-2013 (CMFD supplement-2013) were also searched.

Search terms used for Pubmed were as follows: (COPD OR chronic obstructive pulmonary disease OR emphysema, pulmonary disease) for COPD search, (acupoint OR acupoint application OR local application OR acupuncture point OR acupoint sticking OR acupoint herbal patching OR sanfutie OR sanjiutie) for acupoint herbal patching search were combined. For other databases, these terms were slightly modified. No language limitation was applied. Searches were limited to randomized controlled trials and a filter applied to limit by humans.

Reference lists of all full text papers were hand-searched in order to find additional relevant reports.

Details of the search strategy are available from the author (FZ) on request.

Study Selection

YWS and FZ identified studies for eligibility and checked against the inclusion criteria.

Methodological quality

Risk of bias for included studies was assessed by two authors (YWS and FZ) according to the Cochrane Handbook (Version 5.2) for Systematic Reviews of Intervention[19]. Six items were evaluated: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); (6) other bias (namely as baseline comparability and sample-size calculation). All these bias were categorized as low (met all items), high (met none of the item) and unclear risk (without sufficient information to judge). If there are any disagreements happened between the aforementioned two authors, a third author (JPL) was involved.

Data collection and Synthesis

YWS and FZ independently extracted data on patient characteristics, details of the intervention and control, outcome measures, main results, and consensus was reached by discussion with a third party (JPL) in case of discrepancy.

Statistical analyses were performed using RevMan 5.2 software (The Cochrane Collaboration). Dichotomous data were presented as risk ratio (RR) with 95% confidence interval (CI); while the continuous data were presented as mean difference (MD) with 95% CI. If different measurement scales were used, standardized mean difference (SMD) was performed to analyze continuous data. Heterogeneity was assessed using the I-square statistic, and we considered an I-square value greater than 50% indicating substantial heterogeneity. For $I^2 \leq 50\%$, a random-effect model was applied.

RESULTS

Study Characteristics

Figure 1 shows the flow chart for search process and study selection. We included twenty one RCTs[20–40] in this review. All of them were conducted in China and published in Chinese. Among the included studies, six trials were reported as dissertations[20,21,24,25,33,34]. One trial was a conference

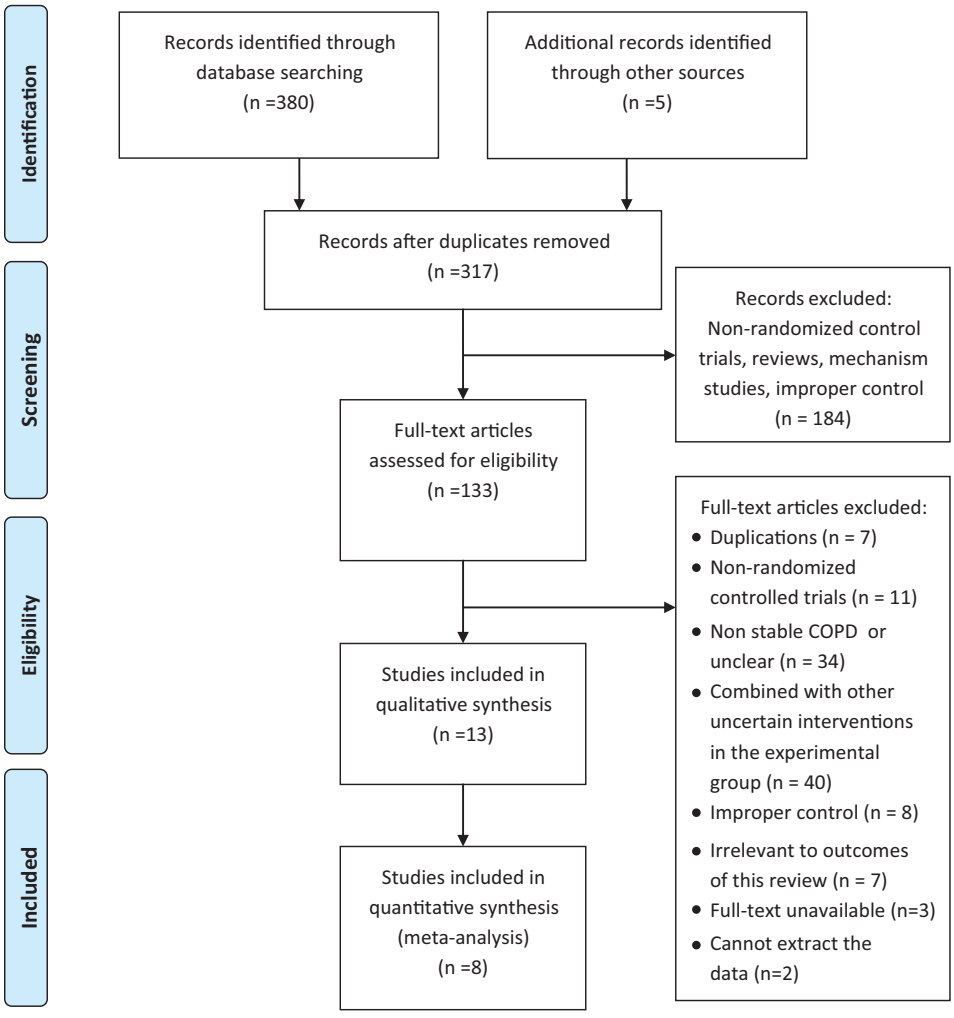

Figure 1. Flow diagram of study searches and selection.

paper[32]. The remaining fourteen trials[22,23,26–31,35–40] were published in scientific journals.

The total number of participants with stable COPD in twenty one trials was 2327, aged between 55 to 85 years old, and the duration of disease varied from 3 to 56 years. All the participants came from hospitals. Eight trials reported from outpatients and inpatients[22,24,25,30,33,34,36,40]; seven trials were from outpatients alone[20,21,26,28,32,35,39]; one trial was from inpatients[37]; the other five trials were unclear[23,27,29,31,38]. Although there were several different diagnostic criteria applied in the included trials, they had similar criteria showing the presence of a post-bronchodilator $FEV_1/FVC<0.70$. Other detailed characteristics of included trials are listed in Table 1.

There were no trials using AHP as a single intervention on stable COPD. All the four comparisons were in combination with CT: Four trials were *sanfu* AHP plus CT versus placebo plus CT[20–22]; Eleven trials were *sanfu* AHP plus CT versus CT[23–33]; Two trials were *non-sanfu* AHP plus CT versus placebo plus CT[34,35]; Five trials were *non-sanfu* AHP plus CT versus CT[36–40]. The treatment sessions varied from 9 times to 60 times per one treatment duration. The detailed characteristics of interventions of included trials are listed in Table 2.

Five trials[23,27,33,35,38] mentioned the sources of financial support. Among them, three trials were sponsored by different government funds[27,33,35], the other two trials were sponsored by industry[23,38].

Methodological Quality

According to the predefined quality assessment criteria, all included trials had a high risk of bias (Fig. 2). The general methodological quality of the majority of trials was poor.

1. Random Sequence Generation

Four of the twenty one trials[23,26,37,38] used a random number table, while only one trial[21] used central randomization, and 16 trials did not provide the specific random sequence generation method and only reported as "randomization used".

2. Allocation Concealment

Two trials[21,34] used an opaque sealed envelope while the rest nineteen trials did not provide any information.

Table 1. Characteristics of included trials

First author, year [Ref.]	Sample(R/A)	Age Mean±SD (Years)	Sex(M/F) no. Subjects	Severity of COPD: no. Subjects	History Mean ±SD (Years)	CM Syndrome Differentiation	Comparsion Type	Outcome measures
Tian 2011[20]	T:unclear/30 C:unclear/20	T:64.97 ± 7.38 C:65.55 ± 8.46	T:19/11 C:12/8	T:I(8)II(10) III(12) C:I (5)II(8) III(7)	T:16.44 ± 17.04 C:13.02 ± 10.26	NR	*Sanfu* AHP+CT vs Placebo+CT	mMRC QoL-SGRQ
Wu 2011[21]	T:71/63 C:71/63	T:62.75 ± 8.02 C:65.56 ± 9.39	T:41/22 C:39/24	T: II(31) III(25)IV(7) C: II () 32 III(25)IV(6)	T:15.98 ± 13.10 C: 15.25 ± 14.49	NR	*Sanfu* AHP+CT vs Placebo+CT	FEV_1 FEV_1/PR% FEV_1/FVC FAECOPD QoL-SGRQ
Wang 2009[22]	T:43/43 C:42/42	NR	NR	NR	3~45(range)	NR	*Sanfu* AHP+CT vs Placebo+CT	ER FAECOPD
Guan 2009[23]	T:unclear/42 C: unclear/40	T:61.30 ± 9.86 C:62.75 ± 12.98	T:25/17 C:28/22	NR	T: 10.3 ± 2.2 C:11.3 ± 2.4	Lung Qi and Kindey Qi deficiency	*Sanfu* AHP+CT vs CT	FEV_1/FVC QoL-SGRQ
Gong 2010[24]	T:40/40 C:40/40	T:65.80 ± 11.37 C:63.00 ± 9.66	T:26/14 C:26/14	T:II(18) III(22) C:II(18) III(22)	NR	NR	*Sanfu* AHP+CT vs CT	mMRC FEV_1PR% QoL-Cai's
Kan 2010[25]	T:30/30 C:30/30	T:55.33 ± 8.25 C:56.28 ± 7.14	T:18/12 C:19/11	NR	T: 3~18 C:4~17 (range)	Lung Qi and Kindey Qi deficiency	*Sanfu* AHP+CT vs CT	ER FCOPDE Adverse events
Li 2012[26]	T:44/44 C:44/44	T:63.95 ± 10.75 C:62.78 ± 11.02	T:24/20 C:23/21	T:I(5)II(20) III(15)IV(4) C:I(6)II(19) III(16) IV(3)	T:17.28 ± 2.98 C:18.20 ± 2.18	NR	*Sanfu* AHP+CT vs CT	ER
Liu 2010[27]	T:150/150 C:150/150	T:58.21 C:57.16	T:86/64 C:83/67	NR	NR	Lung Qi and Kindey Qi deficiency	*Sanfu* AHP+CT vs CT	ER
Tan 2011[28]	T:32/32 C:31/31	T:60.91 ± 6.27 C:57.51 ± 7.82	T:21/11 C:22/9	T:I(8)II(24) C:I(9)II(22)	NR	Lung Qi Spleen and Kidney Qi deficiency phlegm stasis	*Sanfu* AHP+CT vs CT	FEV_1 FEV_1/FVC FAECOPD QoL-SGRQ
Wu 2012[29]	T:40/40 C:40/40	T:65 C:64	T:30/10 C:32/8	NR	T: 5~15 C:5~15 (range)	NR	*Sanfu* AHP+CT vs CT	ER FAECOPD
Xia 2010[30]	T:37/37 C:37/37	T:66.23c6.72 C:63.63 ± 5.69	T:29/8 C:31/6	NR	T:11.38 ± 3.26 C:12.41 ± 4.52	NR	*Sanfu* AHP+CT vs CT	FEV_1/FVC ER
Yang 2011[31]	T:62/62 C:63/63	T:65.27 ± 12.35 C:67.38 ± 11.67	T:32/30 C:30/33	NR	T: 10.1 ± 3.4 C:11.8 ± 3.3	NR	*Sanfu* AHP+CT vs CT	FEV_1/PR% FEV_1/FVC ER FAECOPD QoL-Cai's
Zhou 2010[32]	T:90/90 C:90/90	T:65 C:64	T:63/27 C:65/25	NR	T:9~39 C:10~32 (range)	NR	*Sanfu* AHP+CT vs CT	ER

Table 1. (Continued)

First author, year [Ref.]	Sample(R/A)	Age Mean±SD (Years)	Sex(M/F) no. Subjects	Severity of COPD: no. Subjects	History Mean ±SD (Years)	CM Syndrome Differentiation	Comparsion Type	Outcome measures
Zhu 2010[33]	T:65/60 C:65/60	T:60.37 ± 5.65 C:59.92 ± 6.22	T:32/28 C:33/27	T:II(33) III(27) C:II(29) III(31)	T:13.57 ± 2.11 C:13.50 ± 1.94	Lung Qi and Kindey Qi deficiency	*Sanfu* AHP+CT vs CT	FEV_1/PR% FEV_1/FVC ER FAECOPD
Ayoufu 2013[34]	Total:120/110	64.62 ± 11.902	NR	NR	NR	NR	Non *sanfu* AHP +CT vs Placebo+CT	FEV_1/PR%
Li 2009[35]	T:71/71 C:71/71	T:63.66 ± 4.75 C:62.63 ± 6.96	T:55/16 C:55/16	NR	T:18.38 ± 1.05 C:19.41 ± 6.61	Lung Qi and Kindey Qi deficiency	Non *sanfu* AHP +CT vs Placebo+CT	ER
Chen 2009[36]	T:33/33 C:33/33	T:60.5 C:61	T:22/11 C:20/13	NR	T: 16 C:17	NR	Non *sanfu* AHP +CT vs CT	FEV_1 FEV_1/PR% FEV_1/FVC ER
Deng 2012[37]	T:45/45 C:45/45	T:56.2 ± 7.1 C:57.1 ± 6.7	T:28/27 C:26/19	NR	T: 8~25 C:8~25 (range)	NR	Non *sanfu* AHP +CT vs CT	FEV_1 FEV_1/PR% FEV_1/FVC ER
Du 2013[38]	T:80/79 C:80/78	T:64.12 ± 9.13 C:62.13 ± 7.34	T:54/25 C:51/27	T:I(24) II(35) C:I(21) II(57)	T: 14.76 ± 9.57 C:15.34 ± 10.76	NR	Non *sanfu* AHP +CT vs CT	ER FCOPDE
Shi 2009[39]	T:60/60 C:60/60	T:72.07 ± 5.54 C:70.32 ± 7.04	T:32/28 C:34/26	NR	T:45~55.5 C:30~52 (range)	Lung Qi Spleen and Kidney Qi deficiency phlegm stasis	Non *sanfu* AHP +CT vs CT	FEV_1/PR% FEV_1/FVC ER FAECOPD
Xu 2008[40]	T:103/103 C:81/81	T:61.49 ± 4.87 C:60.32 ± 4.69	T:62/41 C:51/30	NR	T:16.72 ± 0.38 C:17.22 ± 0.40	Lung Qi Spleen and Kidney Qi deficiency phlegm stasis	Non *sanfu* AHP +CT vs CT	FEV_1 FEV_1/FVC ER QoL-SGRQ

R: number subjects randomized; A: number subjects analyzed; M: male; F: Female; SD: standard deviation; T: treatment group; C: control group; NR: not reported.
ER, effective rate; QoL, quality of life; SGRQ, St. George's Respiratory Questionnaire; FCOPDE, frequency of AECOPD; NR, not reported; FEV_1, forced expiratory volume in 1 second ; FEV_1/PR%: FEV1% predicted; FVC,forced vital capacity.

Table 2. Characteristics of interventions and outcomes measures of included trials

First author, year [Ref.]	Acupoints selected	Ingredients	Pasting Time	Frequency and Duration of AHP	Follow up
Tian 2011[20]	BL13, BL15, BL17	Fructus Piperis Longi, Herba Ephedrae, Rhizoma Acori Tatarinowii	*Sanfu*, once in first *fu*,then once every 10 days	Once per fu, keep patching 6 hours,1 *sanfu*	12 months
Wu 2011[21]	BL13, BL15, BL17	Semen Sinapis, Radix et Rhizoma Asari, Herba Ephedrae, Rhizoma Acori Tatarinowii, Rhizoma Zingiberis Recens	*Sanfu*, once ten days	Once per *fu*, keep patching 6 hours, 3 *sanfu*s	12 months
Wang 2009[22]	RN17, BL13, BL20, BL23, BL43	Unclear	*Sanfu*, first day of each *fu*	Once per *fu*, keep patching 1~2 hours, 3 years	Unclear
Guan 2009[23]	Unclear	Radix Astragali, Rhizoma Pinelliae, Pheretima, Hirudo	*Sanfu*, first day of each *fu*	Once per *fu*, keep patching 4~6 hours,1 *sanfu*	12 months
Gong 2010[24]	EX-B1, BL13, BL23	Semen Sinapis, Radix Astragali, Flos Carthami, Rhizoma Pinelliae	*Sanfu*, first day of each *fu*	Once per fu, keep patching 2~4 hours, 1 *sanfu*	Unclear
Kan 2010[25]	DU14, BL13, BL14, BL23	Semen Sinapis, Radix et Rhizoma Asari, Radix Kansui, Radix Scrophulariae, Rhizoma Cyperi, Cortex Cinnamomi	*Sanfu*, first day of each *fu*	Once per *fu*, keep patching 2~4 hours, 2 *sanfu*s	12 months
Li 2012[26]	BL13, BL17, BL23	Semen Sinapis, Rhizoma Corydalis, Radix Kansui, Radix et Rhizoma Asari	*Sanfu*	Once every 5~7days(or first day of each fu), 5 times, keep patching 2~3 hours, 3 *sanfu*s	Unclear
Liu 2010[27]	DU14, BL13,BL12, BL14, BL15	Semen Sinapis, Herba Ephedrae, Semen Armeniacae Amarum	*Sanfu*, first day of each *fu,sanjiu*,first day of each *jiu*	Once per *fu*, once every 10 days, keep patching 3 hours, 4 *sanfu*s	Unclear
Tan 2011[28]	BL13, BL20, BL23, RN12, LU7, DU14, BL17, EX-HN15, ST36, RN22, RN17	Semen Sinapis, Radix et Rhizoma Asari, Rhizoma Pinelliae, Fructus Piperis, Flos Caryophylli, Realgar, Cortex Cinnamomi, Herba Ephedrae, Olibanum, Myrrha, Succus Rhizomatis Zingiberis	*Sanfu*, once every 5days	Keep patching 8 hours, 3 *sanfu*s	Unclear
Wu 2012[29]	BL13, BL12, BL20, BL23, RN4, RN22, ST36	Semen Sinapis, Rhizoma Corydalis, Radix et Rhizoma Asari, Radix Kansui, Radix Paeoniae Alba, Rhizoma Pinelliae,Flos Caryophylli, Cortex Cinnamomi, Succus Rhizomatis Zingiberis	*Sanfu*, first day of each *fu*	Once per *fu*, keep patching 4~6 hours, 3 *sanfu*s	Unclear
*Xia 2010[30]	BL13,BL43, EX-B1, BL20, BL23, ST36, RN22, RN17	Semen Sinapis, Rhizoma Corydalis, Radix Kansui, Radix et Rhizoma Asari, Cortex Cinnamomi, Succus Rhizomatis Zingiberis	*Sanfu*, first day of each *fu*	Once per *fu,1 sanfu*	11~12 months
Yang 2011[31]	DU14, BL13, BL43, DU9	Semen Sinapis, Radix Kansui, Succus Rhizomatis Zingiberis	*Sanfu*, first day of each *fu*	Once per *fu* (first day of *fu*), keep patching 2~8 hours, *1 sanfu*	6 months
Zhou 2010[32]	DU14, BL13, BL23, EX-B1, BL43, BL20, EX-HN15, BL17, BL15	Semen Sinapis, Radix et Rhizoma Asari, Radix Kansui, Rhizoma Corydalis, Succus Rhizomatis Zingiberis	*Sanfu*, first day of each *fu*	Once per *fu* (first day of *fu*), keep patching 3~8 hours, *2 sanfu*s	2 years
Zhu 2010[33]	BL13, BL20, BL23, RN17, RN4, RN6, ST36, BL43	Semen Sinapis, Radix Kansui, Radix et Rhizoma Asari, Herba Ephedrae, Borneolum Syntheticum, Succus Rhizomatis Zingiberis	*Sanfu*, first day of each *fu*	Once per *fu*, keep patching 2~4 hours, 1 *sanfu*	2~9 months
Ayoufu 2013[34]	BL13, BL20	Herba Ephedrae, Semen Armeniacae Amarum, Radix Astragali	non *sanfu*, 11 o'lock (in Beijing)	Twice per week, keep patching 6 hours, 12 times	6 weeks
Li 2009[35]	RN22, RN17, BL23, BL43, LU1	Semen Sinapis, Semen Zanthoxyli, Flos Genkwa, Rhizoma Corydalis, Rhizoma Zingiberis, Radix et Rhizoma Asari, Cortex Cinnamomi	non *sanfu*	twice per week, keep patching 5~6 hours,18 times	Unclear
Chen 2009[36]	RN22, RN17, BL13, EX-B1, DU14, BL17, BL43, BL20, BL23	Semen Sinapis, Radix Astragali, Radix Platycodonis, Ramulus Cinnamomi, Fructus Schisandrae Chinensis, Rhizoma Corydalis, Radix et Rhizoma Asari	Non *sanfu*	Once every 2 days, keep patching 10 hours, 30 times	Unclear

Table 2. (Continued)

First author, year [Ref.]	Acupoints selected	Ingredients	Pasting Time	Frequency and Duration of AHP	Follow up
Deng 2012[37]	BL13,BL23,BL20, BL12, RN4, RN22	Semen Sinapis, Radix Kansui, Radix et Rhizoma Asari, Rhizoma Corydalis, Succus Rhizomatis Zingiberis,	Non *sanfu*	once per day, keep patching 8 hours, 7 times	Unclear
Du 2013[38]	BL13, BL20, BL12, RN17, EX-B1	Herba Ephedrae, Semen Armeniacae Amarum, Radix Astragali	Non *sanfu*,12 AM per day	Once per day, 28 times	12 months
Shi 2009[39]	RN22, DU14, BL13, BL43	Semen Sinapis, Radix Kansui, Radix et Rhizoma Asari, Radix Angelicae Dahuricae, Radix Scutellariae, Cortex Cinnamomi, Succus Rhizomatis Zingiberis	Non *sanfu*, twice per week	Keep patching 4 hours, 12 times	12 months
Xu 2008[40]	KI1	Moschus, Radix et Rhizoma Asari, Cortex Eucommiae	Non *Sanfu*, once per night	Once per night, keep patching one night	Unclear

*:only report the data of experimental group.

Figure 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.

3. Blinding

Two trials[21,34] applied double-blinding (for participants and personnel), three trials[20,22,35] didn't provide information about blinding, but they used placebo, so we considered them as single-blinding method (only for participants).

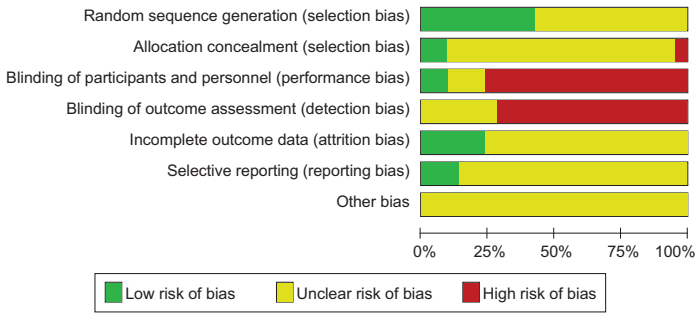

Figure 3. Risk of bias graph. Presentation of the risk of bias graph of the review author's judgments about each risk of bias item presented as percentages across all included trials.

4. Incomplete Outcome Data

Five trials[20,21,25,34,39] provided the number of withdrawals, but no information about the reasons for withdrawal. Only one trial[34] did an intention-to-treat analysis.

5. Selective Outcome Reporting

Since no trials gave clinical trial registration information, we could not compare the trial reported with the corresponding protocol, so could not identify whether there was selective outcome reporting.

For other bias, all the trials reported that there was a comparable baseline between two groups and none of them reported sample-size calculations in their methodology.

Effects of interventions

For the two comparisons, we divided the included trials into different subgroups according to the treatment time, treatment sessions and follow up period (only for quality of life). Although some of the ingredients of AHP are different among the included trials, the formulae of the herbal patches had the same purpose to warm *yang* for dispelling cold, benefit *qi* for relieving wheezing, making expectoration easier and freeing the flow of Qi in the meridians. Due to variations in study quality, intervention types and limited information about the participants' age or disease severity, most outcome data could not be pooled quantitatively.

The overall effect estimates of AHP were shown in the Table 3, and all the units used for the continuous data are also listed in Table 3.

1. Acute exacerbation of COPD

Eight trials reported outcomes for acute exacerbations of stable COPD (AECOPD).

Sanfu *AHP plus CT versus placebo plus CT*

Two trials[21,22] reported the mean frequency of AECOPD, each of them had three years' data. But no differences were seen at three sessions respectively (1.first year: MD: 0.19; 95% CI: −0.03 to 0.40; I^2 = 4%; 2.second year: MD: −1.34; 95%CI: −3.18 to 0.50; random effects model; I^2 = 92%; 3.third year: MD: −1.68; 95%CI: −4.17 to 0.80; random effects model; I^2 = 97%; 2 trials). We attributed the significant heterogeneity to low methodological quality.

Sanfu *AHP plus CT versus CT alone*

Four trials compared *sanfu* AHP plus CT with CT alone, which showed a significant difference (MD: −0.92; 95%CI: −1.58 to −0.27; random effects model; I^2 = 87%; 4 trials). When we excluded two trials[29,33] with outliers the data showed *sanfu* AHP plus CT had a better effect on reducing frequency of AECOPD (MD: −0.50; 95%CI: −0.66 to −0.33; I^2 = 0%; 2 trials).

Non sanfu *AHP plus CT with CT alone*

Two trials[38,39] belonged to this comparison type and found a significant difference between non *sanfu* AHP plus CT and CT alone in reducing the frequency of AECOPD (MD: −1.24; 95%CI: −2.02 to −0.46; random effects model; I^2 = 84%; 2 trials). The heterogeneity in this meta-analysis may due to disease severity differences after comparing the baseline of the included two trials.

2. Symptom improvement

Seventeen trials[20,22,25–27,29–33,35–40] reported the symptom improvement. Among them, fifteen trials[22,25–27,29–33,35–40] used an unvalidtated composite outcome index which combined symptoms, signs and laboratory tests together. There were three to four levels of improvement: cure, markedly effective, effective (only for some trials), and ineffective. The classification for each level were unclear and some of them overlapped so we did not extract these data. The two trials[20,24] used modified medical research council questionnaires for assessing the severity of breathlessness (mMRC) so we only extracted the data from them.

Sanfu *AHP plus CT versus CT alone*

Gong's trial[24] reported the data's difference of pre and post treatment, which showed that the *sanfu* AHP plus CT improved patients' breathless symptom (MD: 0.90; 95% CI: 0.63 to 1.17).

Sanfu *AHP plus CT versus placebo plus CT*

Tian's[20] trials reported the severity of breathlessness at three different follow up times, and no differences were found (MD: 0.00; 95%CI: −0.44 to 0.44 at three months; MD: 0.03; 95%CI: −0.41 to 0.47 at six months; MD: 0.18; 95% CI: −0.63 to 0.27 at 12 months).

Table 3. Estimate effect of AHP combine with CT for improving clinical outcomes of patients with COPD

Study ID	Total No. of participants	Mean Difference (IV, Fixed, 95% CI)	*P* value
1. Frequency of AECOPD (times per year**)**		Mean Difference (IV, Random, 95% CI)	
1.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wang 2009[22]	85	−0.32[−1.32, 0.68]	
Wu 2011[21]	126	0.21[−0.01, 0.43]	
Pooling analysis 1.1(I^2 =4%)		0.19[−0.03, 0.40]Fixed	0.08
1.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wang 2009[22]	85	−2.35[−3.36, −1.34]	
Wu 2011[21]	126	−0.47[−0.52, −0.42]	
Pooling analysis 1.2(I^2 =92%)		−1.34[−3.18, 0.50]	0.15
Li 2011[19]	125	−0.60[−0.93, −0.27]	0.003
1.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wang 2009[22]	85	−2.99[−3.82, −2.16]	
Wu 2011[21]	126	−0.45[−0.50, −0.40]	
Pooling analysis 1.3(I^2 =97%)		−1.68[−4.17, 0.80]	0.18
1.4 sanfu AHP plus CT vs CT			
Yang 2011[31]	125	−0.49[−0.66, −0.32]	
Kan 2010[35]	60	−0.55[−1.12, 0.02]	
Pooling analysis 1.4(I^2 =0%)		−0.50[−0.66, −0.33]Fixed	<0.0001
Zhu 2010[33]	120	−1.82[−2.35, −1.29]	<0.0001
Wu 2012[29]	80	−0.90[−1.79, −0.01]	0.05
1.5 non sanfu AHP plus CT vs CT, treatment duration 2 months			
Du 2013[38]	157	−1.69[−2.28, −1.10]	
Shi 2009[39]	120	−0.89[−1.09, −0.69]	
Pooling analysis 1.5(I^2=84%)		−1.24[−2.02, −0.46]	0.002
2. Symptom improvement (scores)			
2.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Gong 2010 (pre-after difference)[24]	80	0.90[0.63, 1.17]	<0.00001
2.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 3 months			
Tian 2011[20]	50	0.00[−0.44, 0.44]	1
2.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 6 months			
Tian 2011[20]	50	0.03[−0.41, 0.47]	0.89
2.4 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 12 months			
Tian 2011[20]	50	0.18[−0.63, 0.27]	0.43
3. Spirometric parameter- FEV_1(liters)			
3.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wu 2011[21]	126	−0.10[−0.28, 0.08]	0.29
3.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wu 2011[21]	126	−0.10[−0.31, 0.11]	0.35
Li 2011[19]	125	−0.11[−0.34, 0.12]	0.36
3.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wu 2011[21]	126	0.01[−0.19, 0.21]	0.92
3.4 sanfu AHP plus CT vs CT, treatment session = 9			
Tan 2011[28]	63	0.38[0.00, 0.76]	0.05
3.5 non sanfu AHP plus CT vs CT, treatment duration = 3 months			
Chen 2009[36]	66	0.31[0.01, 0.61]	
Deng 2012[37]	90	0.50[0.38, 0.62]	
Xu 2008[40]	184	0.65[0.46, 0.84]	
Pooling analysis 1.4(I^2 =48%)		0.52[0.42, 0.62]Fixed	<0.00001
4. FEV_1/PR% (percentage)			
4.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wu 2011[21]	126	−8.91[−14.65, −3.17]	0.002
4.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wu 2011[21]	126	−4.98[−11.18, 1.22]	0.12
Li 2011[19]	125	1.04[−2.75, 4.83]	0.59
4.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wu 2011[21]	126	−1.04[−7.14, 5.06]	0.74
4.4 sanfu AHP plus CT vs CT, treatment session = 3			
Zhu 2010[33]	120	0.81[−0.98, 2.60]	

Table 3. (Continued)

Study ID	Total No. of participants	Mean Difference (IV, Fixed, 95% CI)	*P* value
Yang 2011[31]	125	4.67[−1.30, 10.64]	
Pooling analysis 4.4(I^2 = 32%)		1.13[−0.58, 2.84]Fixed	0.20
4.5 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Gong 2010 (pre-after difference)[24]	40	1.47[−3.86, 6.81]	0.59
4.6 nonsanfu AHP plus CT vs Placebo plus CT, treatment session = 6 weeks			
Ayoufu 2013[34]	52	−5.90[−18.34, 6.54]	0.35
4.7 nonsanfu AHP plus CT vs CT, treatment duration< = 3 months			
Chen 2009[36]	66	5.14[0.34, 9.94]	
Deng 2012[37]	90	5.39[3.20, 7.58]	
Shi 2009[39]	82	11.55[5.31, 17.79]	
Pooling analysis 4.6(I^2 = 42%)		5.92[4.02, 7.82]Fixed	<0.0001
5. FEV_1/FVC (propotions)			
5.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wu 2011[21]	126	−1.03[−4.74, 2.68]	0.59
5.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wu 2011[21]	126	−0.79[−4.92, 3.34]	0.71
5.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wu 2011[21]	126	1.53[−2.98, 6.04]	0.51
5.4 sanfu AHP plus CT vs CT, treatment session = 3			
Guan 2009[23]	82	2.46[−4.87, 9.79]	
Yang 2011[31]	125	4.42[0.53, 8.31]	
Zhu 2010[33]	120	0.96[0.00, 1.92]	
Pooling analysis 5.4(I^2 = 33%)		1.18[0.26, 2.10]Fixed	0.10
5.5 nonsanfu AHP plus CT vs Placebo plus CT, treatment duration = 6 weeks			
Ayoufu 2013[34]	52	−2.88[−13.28, 7.52]	0.59
5.6 nonsanfu AHP plus CT vs CT, treatment duration< = 3 months			
Chen 2009[36]	66	5.46[1.15, 9.77]	
Deng 2012[37]	90	14.23[11.17, 17.29]	
Shi 2009[39]	82	1.32[−3.87, 6.51]	
Xu 2008[40]	184	8.71[6.15, 11.27]	
Pooling analysis 5.6(I^2 =87%)		7.76[2.88, 12.63]	0.002
6. QoL (scores)			
6.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 3 months			
Tian 2011[20]	50	−8.36[−14.10, −2.62]	0.004
6.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 6 months			
Tian 2011[20]	50	−14.02[−21.04, −7.00]	<0.0001
6.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3, follow up = 12 months			
Tian 2011[20]	50	−10.61[−16.87, −4.35]	0.0009
Wu 2011[21]	126	−0.71[−7.22, 5.80]	0.83
6.4 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6, follow up = 12 months			
Wu 2011[21]	126	−0.19[−6.89, 6.51]	0.96
6.5 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9, follow up = 12 months			
Wu 2011[21]	126	−6.84[−13.29, −0.39]	0.04
6.6 sanfu AHP plus CT vs CT, treatment session =3			
Guan 2009[23]	82	1.64 [−6.79, 10.07]	0.70
Yang 2011[31]	125	−0.27 [−0.46, −0.08]	0.005
Gong 2010 (pre-after difference)[24]	80	6.75 [3.24, 10.26]	0.0002
6.7 sanfu AHP plus CT vs CT, treatment session = 9			
Tan 2011[28]	63	−4.77 [−9.37, −0.17]	0.04
6.8 nonsanfu AHP plus CT vs CT, treatment duration< = 3 months			
Xu 2008[40]	184	−16.23 [−18.93, −13.53]	<0.0001
7. 6 WMD (meters)			
7.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wu 2011[21]	126	6.06[0.88, 11.24]	0.02
7.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wu 2011[21]	126	2.51[−2.03, 7.05]	0.28
7.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wu 2011[21]	126	28.14[23.90, 32.38]	<0.00001

Table 3. (Continued)

Study ID	Total No. of participants	Mean Difference (IV, Fixed, 95% CI)	*P* value
7.4 sanfu AHP plus CT vs CT			
Kan 2010[25]	104	18.00[−21.00, 57.00]	
Tan 2011[28]	126	32.00[−15.91, 79.91]	
Zhu 2010[33]	120	9.55[−1.48, 20.58]	
Pooling analysis 57.4(I^2 = 0%)		11.20[0.83, 21.56]Fixed	0.03
7.5 nonsanfu AHP plus CT vs Placebo plus CT			
Ayoufu 2013[34]	49	24.97[−26.98, 76, 92]	0.35
8. Hospitalization (times per year)			
8.1 sanfu AHP plus CT vs Placebo plus CT, treatment session = 3			
Wu 2011[21]	126	0.05[−0.25, 0.35]	0.74
8.2 sanfu AHP plus CT vs Placebo plus CT, treatment session = 6			
Wu 2011[21]	126	−0.13[−0.36, 0.10]	0.27
8.3 sanfu AHP plus CT vs Placebo plus CT, treatment session = 9			
Wu 2011[21]	98	−0.16[−0.33, 0.01]	0.07
9. Hospital stays (days)			
9.1 sanfu AHP plus CT vs CT			
Zhu 2010[33]	120	−1.45[−1.91, −0.99]	<0.00001

3. Lung function parameters

Eleven trials evaluated the lung function parameters. FEV_1 was reported in five trials[20,21,36,37,40]. Wu's trial[21] reported three years' data. Eight trials reported the FEV_1/PR%[21,24,31,33,34,36,37,39]. Nine trials[21,23,31,33,34,36,37,39,40] reported the FEV_1/FVC.

Sanfu *AHP plus CT versus placebo plus CT*

Only Wu's trial[21] belonged to this category which did not find significant difference in all the three spirometric parameters in any of the three years respectively.

Sanfu *AHP plus CT versus CT alone*

Marginal but significant differences were found in absolute FEV_1 in this comparison in Tan's trial[28] (MD: 0.38; 95% CI: 0.00 to 0.76; 1 trial). Such changes were not observed in FEV_1% predicted (MD: 1.13; 95% CI: −0.58 to 2.84; I^2 = 32%; 2 trials), and in FEV_1/FVC (MD: 1.18; 95% CI: 0.26 to 2.10; I^2 = 33%; 3 trials). Besides, Gong's trial[24] reported the data's difference of pre and post treatment, which demonstrated no significant difference in this comparison (MD: 1.47; 95% CI: −3.86 to 6.81; 1 trial).

Non sanfu *AHP plus CT with placebo plus CT*

Trial by Ayoufu et al[34] reported no significant increases in FEV_1/PR% (MD: −5.90; 95% CI: −18.34 to 6.54; 1 trial) and FEV_1/FVC (MD: −2.88; 95% CI: −13.28 to 7.52; 1 trial) as well.

Non- sanfu *AHP plus CT with CT alone*

There were significant differences between *non- sanfu* AHP plus CT and CT alone on FEV_1 (MD: 0.52; 95% CI: 0.42 to 0.62;3 trials), on FEV_1/PR% (MD: 5.92; 95% CI: 4.02 to 7.82; 3 trials), and on FEV_1/FVC (MD: 7.76; 95% CI: 2.88 to 12.63; random effects model; I^2 = 87%; 4 trials) as well.

4. Quality of life (QoL)

Seven trials[20,21,24,28,23,31,40] evaluated quality of life. Among them, most trials were measured by SGRQ (St. George's Respiratory Questionnaire), only Yang's trial[31] used the self-modified questionnaire by Cai et al.

Sanfu *AHP plus CT versus placebo plus CT*

Tian's[20] trial reported three follow up periods for quality of life's data and all of these data showed positive QoL improvement (third month: MD: −8.36; 95% CI: −14.10 to −2.62; sixth month: MD: −14.02; 95% CI: −21.04 to −7.00; 12 month: MD: −10.61; 95% CI: −16.87, −4.35; 1 trial). Wu's trial[21] found no significant difference after two sessions (first session: MD: −5.70; 95% CI: −15.40 to 4.00; second session: MD: −0.19; 95% CI: −6.89 to 6.51; 1 trial), but improvement was observed after the third session (MD: −6.84; 95% CI: −13.29 to −0.39; 1 trial).

Sanfu *AHP plus CT versus CT alone*

Yang's[31] trial used Cai et al's questionnaire to evaluate QoL, which demonstrated significant difference in this comparison (MD: −0.27; 95%CI: −0.46 to −0.08; 1 trial). Such changes were not observed in Guan's and Tan's pooled data in the score of QoL based on SGRQ (SGRQ) (MD: −2.58; 95% CI: −8.54 to 3.38; I^2 = 42%; 2 trials).

Furthermore, Gong's trial[24] reported pre and a post treatment data, which showed significant differences (MD: 6.75; 95% CI: 3.24 to 10.26; 1 trial).

Non-sanfu *AHP plus CT with CT alone*

Xu's[40] trial reported quality of life in this comparison and reported significant difference (MD: −16.23; 95% CI: −18.93 to −13.53; 1 trial).

5. 6 minutes walking distance (6-MWD)

Five trials[21,25,28,33,34] assessed the effects of AHP plus CT on 6-MWD. Wu's trial[21] reported three years' data. Zhu, Kan and Tan's trials[25,28,33] compared *sanfu* AHP plus CT with CT alone after one year, two years and three years respectively. Ayoufu's trial compared non *sanfu* AHP plus CT with CT alone.

Sanfu *AHP plus CT versus placebo plus CT*

Wu's[21] trial showed significant increase the 6-MWD after first session(MD: 6.06; 95% CI: 0.88 to 11.24; 1 trial) and third session (MD: 28.14; 95% CI: 23.90 to 32.38; 1 trial), and no significance after the second session (MD: 2.51; 95% CI: −2.03 to 7.05; 1 trial).

Sanfu *AHP plus CT versus CT alone*

Significant difference was found in this comparison in pooled data (MD: 11.20; 95% CI: 0.83 to 21.56; I^2 = 0%; 3 trials).

Non-sanfu *AHP plus CT with placebo plus CT*

Ayoufu's[34] trial showed no significant difference in this index (MD: 24.94; 95% CI: −26.98 to 76.92;1 trial).

Adverse events

Wu's[21] trial stated that the number of skin irritation according to different severity level. And there were no significant difference between two groups in three sessions. Kan's trial[25] reported that two patients had eyes discomfort, but which was inferred as the adverse effects of seretide by the original author. The remaining trials did not report adverse events.

DISCUSSION

Statement of Main Findings

Twenty one RCTs conducted in China were included in this systematic review, which used AHP plus CT in at least one arm. *Non-sanfu* AHP used in combination with CT appears to be more effective than CT alone in managing patients' with stable COPD. *Non-sanfu* AHP was given more frequently and at closer intervals than *sanfu* AHP suggesting this might be a dose effect. *Sanfu* AHP plus CT compared CT alone showed improvement in reducing frequency of AECOPD, increasing quality of life and 6-MWD compared with placebo plus CT, the efficacy of *sanfu* AHP or *non-sanfu* AHP plus CT seemed to be unclear for most outcomes (except for QoL and 6-MWD) but there were only two trials (*sanfu* AHP plus CT vs CT) and one trial (*non-sanfu* AHP plus CT vs CT) in the comparisons. Only one trial reported the skin irritation which happened in both groups, indicating that AHP therapy might be well tolerated.

Limitations of this systematic review

The methodological quality of the included trials is poor indicating a high risk of bias consequently our findings need to be interpreted cautiously. The inadequacy of randomization, prior sample size calculations, allocation concealment and a near absence of blinding were found in the majority of the 22 included trials. None of the included trials reported protocol registration information. The trials included in the meta-analyses showed a relatively high degree of heterogeneity. The reasons for this heterogeneity may partly be related to the differences of the severity of participants' condition, the acupoints selected, the AHP formula selected, and the different conventional treatments used.

We did not contact the authors to clarify information. Fifteen trials didn't report the severity of participants' condition[22,24,27,29,30–32,34,36,37,39,40]; while for most trials' the follow up periods were unclear.

Differences with the similar reviews' findings

In 2012, Li et al published a systematic review which was similar with our review[17]. Li's review only searched Chinese databases and included RCTs as long as they contained any AHP intervention. Li's review concuded that AHP plus western medicine showed significant improvement for FEV_1 and predicted FEV_1% predict compared with western medicine. Unlike Li's review, our review focused on AHP alone or combination with CT (whose effect were confirmed) compared with same CT in the control group. Although none of the included trials were published outside of China, nine new trials were included in our current review[20,21,25,26,29,34,36–38]. The beneficial results on the pulmonary function parameters of *non- sanfu* AHP plus CT were congruent with Li's reports. But the result of comparing of *sanfu* AHP plus CT with CT alone did not show any significant. The reason may be the increased frequency of *non-sanfu* AHP application.

Implications for Future Research

Our suggestions for future research are:

1 Trials Registration. Completing registration before the first patient is entered and including this in the publication should reduce selective reporting and encourage prior sample size calculations.
2 Improving Methodology. Secure randomization and strict allocation concealment are needed. Although using double (both health professionals and participants) or single blinding (only for participants) is still a challenge for AHP, blinding for outcome can be applied to most trials. An intention-to-treat analyses, especially for evaluating long term AHP intervention, is essential.
3 Standardized Reporting. Using a CONSORT to report the trail outcome is essential[41].
4 Selecting Patients' Centered Outcomes. Most trials did not report symptom improvement such as dyspnea, cough, and sputum production. We suggest that the future trials should focus the COPD patient centered outcomes.

CONCLUSIONS

AHP used in combination with conventional medication, especially when it is applied over a long time and more frequently may be more effective than conventional medication alone in managing patients' with stable COPD. However, further large, rigorously designed trials are warranted to confirm these effects.

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AUTHOR CONTRIBUTIONS

Designers: FZ and JPL; Trials searchers: FZ and YWS; Trials appraisers: FZ, YWS and JPL; Data extractors: FZ and YWS; Analyzer: FZ and JPL; Writers: FZ and JPL.

DISCLOSURE STATEMENT

No competing financial interests to claim.

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