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SYSTEMATIC REVIEW AND META-ANALYSIS

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Chinese Herbal Medicine and Salmeterol and Fluticasone Propionate for Chronic Obstructive Pulmonary Disease

Systematic Review and Network Meta-Analysis

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Abstract: Among Chinese populations worldwide, Chinese herbal medicines (CHMs) are often used as an adjunct to pharmacotherapy in managing chronic obstructive pulmonary disease (COPD). However, the relative performance among different CHM is unknown.

The aim of this study was to evaluate comparative effectiveness of different CHM when used with salmeterol and fluticasone propionate (SFP), compared with SFP alone.

This study is a systematic review of randomized controlled trials (RCTs) with network meta-analyses (NMAs).

Eight electronic databases were searched. Data from RCTs were extracted for random effect pairwise meta-analyses. Pooled relative risk (RR) with 95% confidence interval (CI) was used to quantify the impact of CHM and SFP on forced expiratory volume in 1 second (FEV_1), St George's Respiratory Questionnaire (SGRQ) scoring, and 6-Minute Walk Test (6MWT). NMA was used to explore the most effective CHM when used with SFP.

Eleven RCTs (n = 925) assessing 11 different CHM were included. Result from pairwise meta-analyses indicated favorable, clinically relevant benefit of CHM and SFP on FEV_1 [7 studies, pooled weighted mean difference (WMD) = 0.20 L, 95% CI: 0.06–0.34 L], SGRQ scoring (5 studies, pooled WMD = −4.99, 95% CI: −7.73 to −2.24), and 6MWT (3 studies, pooled WMD = 32.84 m, 95% CI: 18.26–47.42). Results from NMA showed no differences on the comparative effectiveness among CHM formulations for improving FEV_1. For SGRQ, NMA suggested that Runfeijianpibushen decoction and Renshenbufei pills performed best. Use of CHM on top of SFP can provide clinically relevant benefit for COPD patients on FEV_1 and SGRQ. Additional use of Runfeijianpibushen decoction and Renshenbufei pills showed better effect on improving SGRQ.

Use of CHM and SFP may provide clinically relevant benefit for COPD patients on FEV_1, SGRQ, and 6MWT. Use of different CHM formulae included in this NMA showed similar effect for increasing FEV_1, while the additional use of Runfeijianpibushen formula and Renshenbufei Pills showed better effect on improving SGRQ. Well conducted, adequately powered trials are needed to confirm their effectiveness in the future.

(*Medicine* 95(20):e3702)

Abbreviations: 6MWT = 6-Minute Walk Test, APS = Astragalus polysaccharide, CHM = Chinese herbal medicines, CI = confidence interval, CONSORT = Consolidated Standards of Reporting Trials, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, HPLC = High-Performance Liquid Chromatography, MID = minimally important difference, NMA = network meta-analyses, RCTs = randomized controlled trials, RR = relative risk, SFP = salmeterol and fluticasone propionate, SGRQ = St George's Respiratory Questionnaire, SUCRA = surface under the cumulative ranking curve, TCM = traditional Chinese medicine, WMD = weighted mean differences.

INTRODUCTION

Characterized by progressive persistent airflow limitation, chronic obstructive pulmonary disease (COPD) is a major mortality and morbidity burden. Globally, it is the fourth leading cause of death, accounting for 27.2/100,000 age-adjusted deaths among US populations. The mortality figure is even higher among Chinese population, of which it reached 130.5/100,000.[1] As disease burden caused by COPD continues to grow, it has been estimated that by 2020, COPD will be the fifth leading cause of disability.[2] In face of such burden, the management of COPD has significant public health and health care implications.[3]

Long-acting beta agonist salmeterol is commonly prescribed in combination with inhaled corticosteroid fluticasone propionate in the treatment of COPD.[4] Evidence has suggested the beneficial effects of salmeterol and fluticasone propionate (SFP) in reducing the annual rate of exacerbations and improving health status when compared with placebo.[5] However, these drugs comprise certain side effects such as dry mouth, constipation, urinary retention, tremor, and dysphagia.[6]

Chinese herbal medicines (CHMs) are widely used in the Chinese health care system daily clinical practice in China.[7] Around 75% community health centers provide not only western medicine services but also traditional Chinese medicine (TCM) treatments. At in-patient level, TCM hospitals comprised 13.8% of all hospitals. Furthermore, 90% of the western medicine hospitals have TCM departments.[8] Under this integrative health care environment, it is very common for clinicians to prescribe CHM as an adjunct to western drugs for treating chronic conditions such as COPD.[9]

Editor: Jian Liu.
Received: December 15, 2015; revised: March 16, 2016; accepted: April 2, 2016.
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The authors declare no conflicts of interest with regard to this manuscript.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003702

Despite the popular use of CHM among COPD patients, clinical evidence on its add-on benefit when used with SFP is yet to be synthesized. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) on the effectiveness of CHM for COPD as an add-on to SFP, with a focus on a critical endpoint such as the forced expiratory volume in 1 second (FEV_1). The 6-Minute Walk Test (6MWT) and the St George's Respiratory Questionnaire (SGRQ) were adopted as secondary outcomes. In addition, we performed a network meta-analysis (NMA) to evaluate the comparative effectiveness of different CHM formulae.

METHODS

This systematic review and NMA is reported in accordance to the PRISMA recommendation. As all the analyses were performed by using data extracted from published trials, it is not necessary to obtain ethical approval for this study.

Inclusion Criteria

Literature screening and selection was performed by 2 reviewers, with disagreements resolved by discussion and consensus adjudication. We included RCTs comparing the effectiveness of oral CHM and SFP versus SFP alone. The primary outcome of this systematic review was a change in FEV_1. To be included, the RCTs must report FEV_1 results with treatment duration of at least 12 weeks. SGRQ scoring and 6MWT were the secondary outcomes of this review. We selected our outcomes according to recommendations from the European Medicines Agency and the United States Food and Drug Administration.[10]

Data Sources and Search Strategy

We searched 8 electronic databases, including Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the Allied and Complementary Medicine Database, Chinese Biomedical Database, Chinese Medical Current Contents, China Journal Net, and Wanfang database. Search key words included 3 elements, which were COPD, salmeterol, and CHM-related terms. Search results on these 3 elements were combined with "AND." Search filters for randomized trials were used while searching MEDLINE[11] and EMBASE.[12] Besides, we searched for existing systematic reviews on the topic that might include eligible trials up to July 2015. We applied no language restrictions.

Data Extraction and Risk of Bias Assessment

Data of included RCTs were extracted with a piloted data extraction form. Risks of bias were appraised with the Cochrane risk of bias tool,[13] which includes 6 evaluation domains (sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting). Each domain was graded as having low, unclear, or high risk of bias based on information reported by each included RCT.[13] Data extraction and risk of bias assessment were completed by 2 authors independently, with discrepancies resolved by discussion and consensus making.

Data Analysis

Pairwise meta-analyses were conducted with the Meta-analyst software.[14] Estimation on treatment effects about continuous outcomes were measured with weighted mean differences (WMDs) and 95% confidence intervals (CIs). Random effect model was used in all the meta-analyses. Chi-squared test was used for the heterogeneity test. A P value <0.1 was considered as existing of significant heterogeneity. I^2 statistic was to measure the level of heterogeneity, with I^2 <25% regarded as low level of heterogeneity, 25% to 50% as moderate level, and $I^2 > 50\%$ as high level.[15] We explored heterogeneity in subgroup and sensitivity analysis with reference to difference in COPD severity and length of follow-up.

Minimally important difference (MID) values were applied to aid interpretation. Results from meta-analyses were compared against established MID values for each outcome: 0.10 L for FEV_1,[16] 4 points for SGRQ scoring,[17] and 26 m for 6MWT.[18]

NMA is a recently developed method that allows the simultaneous comparison of more than 2 herbal treatments.[19] Indirect evidence for the comparison that lacks head-to-head comparison (e.g., A versus B) can be provided if studies that compare A versus C and B versus C are analyzed jointly. Using SFP as a common comparator, indirect comparison between different CHM formulae through the consistency model was implemented with the *mvmeta* command in STATA.[20] Results from NMA were reported as WMD for each possible pair of comparison. We also calculated the probability of each CHM formula being the most effective regimen, the second best regimen, the third best regimen, and so on by calculating the WMD for each CHM formula and SFP compared with SFP-alone group. Ranking probabilities of each CHM formula being at each possible rank were summarized in a graph. The surface under the cumulative ranking curve (SUCRA)[21] and mean ranks were used to obtain a formula's hierarchy. SUCRA is a useful method to display the cumulative therapeutic ranking of each treatment within an NMA graphically.[21] For example, if an intervention is likely to be the best within the NMA, the SUCRA ranking for being the best would be approaching 1, while the intervention with the lowest probability to be the best would have a SUCRA ranking approaching 0.

RESULTS

Literature Search

We identified a total of 745 citations from all searches, including 374 trials incorporated in 22 existing systematic reviews on the topic. After screening of titles and abstracts, we retrieved 35 full texts for further assessment. Of these, 24 were excluded for the following reasons: head-to-head comparison of CHM and western medicine (n = 11), did not report prespecified outcomes (n = 5), did not satisfy inclusion criteria (n = 7), and failure to meet the prespecified length of duration (n = 1). Finally, 11 studies were considered eligible for inclusion (Figure 1).

CHARACTERISTICS OF INCLUDED STUDIES

Participants

Characteristics of included trials are summarized in Table 1.[22–33] Patients' characteristics were similar among included studies. A total of 925 participants with COPD were included in the 11 trials. The average age of the participants was 65.5 ± 5.7 years. The average size of the trials was 84 participants (ranging from 60 to 120 participants per trial). Five trials included outpatients only, and 5 trials included both inpatients and outpatients. One trial did not specify the study settings.

Diagnostic Criteria

For diagnostic criteria, 9 (81.8%) studies applied the Chinese guidelines for diagnosis and management of COPD (2007 revised edition),[34] which is equivalent to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [postbronchodilator FEV_1 <80% of the predicted value,

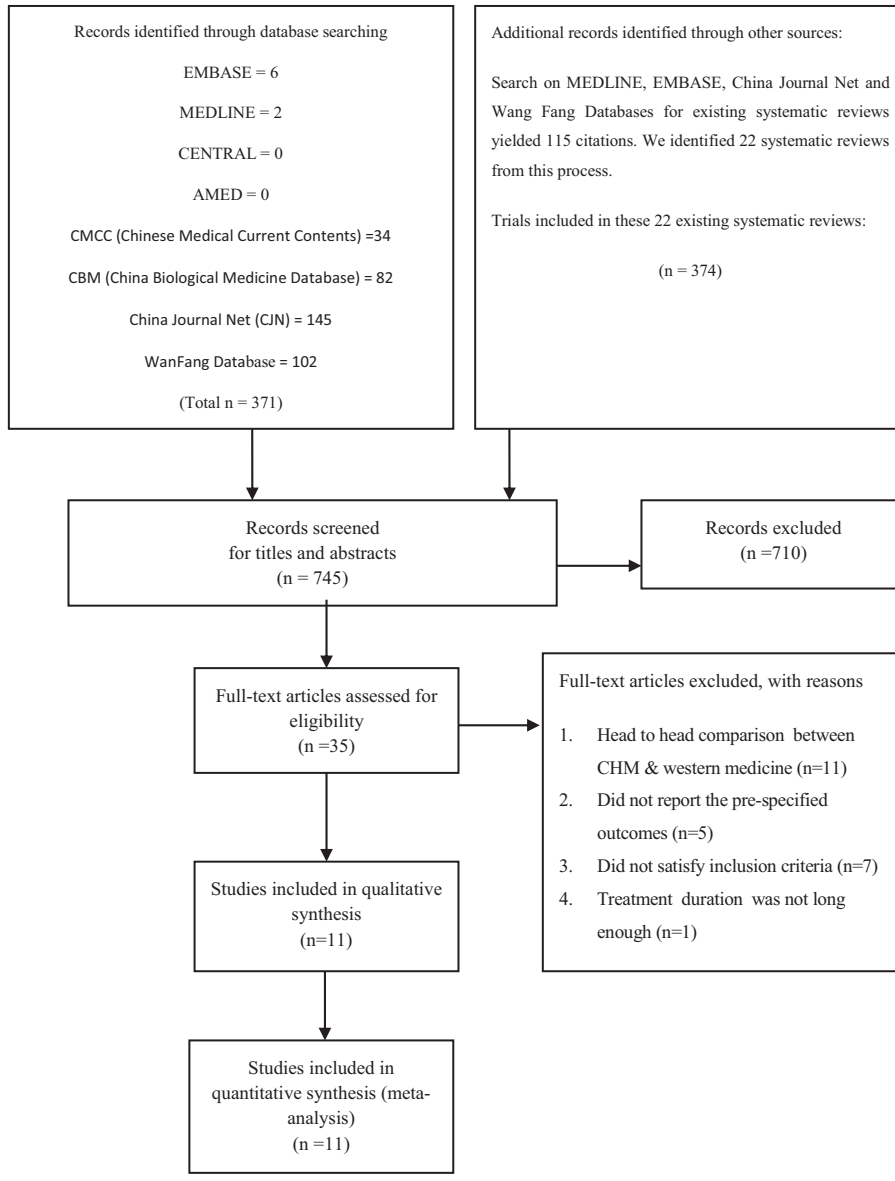

FIGURE 1. Flow of literature search and selection.

with a ratio of FEV_1 to forced vital capacity (FVC) <70%].[35] The remaining 2 trials did not report the diagnostic criteria used.

Intervention

The formulations of CHM were different for each trial. Among the 11 types of CHM interventions, 7 were herbal decoctions,[22–28] 1 was prescribed as pills,[29] and the remaining 3 were capsules.[30–32] The length of follow-up varied from 12 weeks to 1 year.

Risk of Bias Among Included studies

Risk of bias among included studies was mediocre overall, with poor reporting on methodological details (Table 2). Amongst these 11 RCTs, only 2 were at a low risk for bias for allocation sequence generation,[23,30] while the remaining 9 RCTs did not report their sequence generation procedure clearly.[22,24–29,31,32] None of the included studies described the implementation of allocation concealment and the use of blinding. However, we regarded the risks of bias associated with lack of blinding to be minimal, as the majority of selected outcomes (FEV_1, 6MWT) were of objective nature.[16,17,35] Nine of the included studies had a low risk of bias for incomplete data,[24–32] and 6 of them achieved 100% follow-up rate.[24,25,29–32] The drop-out rates ranges from 0% to 12%, with a mean (SD) of 2.18% (4.30%) and a median of 0%. Two of the studies did not describe the drop-out rate.[22,23]

POOLED RESULTS ON CHM AND SFP VERSUS SFP ALONE

Changes in FEV_1

A total of 7 RCTs (n = 532) reported FEV_1 change from 12 weeks to 1 year (Table 3).[22–24,26,27,30,31] Pooled findings favored combined treatment (WMD = 0.20 L, 95% CI: 0.06–

TABLE 1. Main Characteristics of Included Studies

Ref	Source of Patients	No. of Participants R/A	Age: Mean ±SD (yrs)	Time Since COPD Diagnosis (yrs)	Diagnostic Criteria	Disease Severity	Intervention	Control	Length of Follow-Up
Chen et al[22]	Outpatient	I: 30/30 C: 30/30	I & C: mean: 70.1 (range: 56–78)	Not reported	2007 Chinese COPD guideline	Severe and very severe stage (III, IV); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.) + jiaweiqiweiduqi decoction (250 mL, b.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	12 wks
Lu et al[23]	Outpatient	I: 40/not reported C: 40/not reported	I: 67.11 ± 6.54 C: 65.94 ± 9.63	I:13.43 ± 6.32 C:15.32 ± 6.93	2007 Chinese COPD guideline	Severe and very severe stage (III, IV); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.) + yiqihuoxue decoction (150 mL, b.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	12 wks
Jia and Huang[29]	Outpatient and hospital discharge	I: 60/60 C: 60/60	I: mean: 65.73 C: mean: 67.69	I: mean: 15.32 C: mean: 18.05	2007 Chinese COPD guideline	Moderate, severe and very severe stage (II–IV); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.) + renshenbufei pills (1 pill, b.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	12 wks
Liu and Zhou[24]	Not specified	I: 60/60 C: 60/60	I: 60.5 ± 6.5 (range: 42–81) C: 61.2 ± 6.7 (range: 40–80)	Not reported	2007 Chinese COPD guideline	Severity not specified. COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.) + jiaweisanao decoction (100 mL, t.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	12 wks
Liang et al[25]	Outpatient	I: 30/30 C: 30/30	I:65.23 ± 6.09 C:66.33 ± 6.29 (range: 50–80)	Not reported	2007 Chinese COPD guideline	Very severe stage (IV); COPD patients in stable or nonacute phase	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.) +runfeijianpibushen decoction (100 mL, b.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	3 mo
Mo et al[26]	Outpatient and inpatient	I: 31/31 C: 31/31	I: mean: 72 (range: 62–78) C: mean: 73 (range: 58–75)	I: mean: 20 (range: 6–33) C: mean: 22 (range: 7–34)	2007 Chinese COPD guideline	Mild and moderate stages (I, IIA); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/250 μg) (b.i.d.) + jiajianbufei decoction (Dosage: not reported, b.i.d.)	Salmeterol and fluticasone propionate powder (50/250 μg) (b.i.d.)	12 wks
Tang et al[27]	Outpatient	I: 32/30 C: 32/30	Not reported	Not reported	Not specified	Moderate stage (II); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/250 μ g) (b.i.d.) + baoyuan decoction (Dosage: not reported, t.i.d.)	Salmeterol and fluticasone propionate powder (50/250 μg) (b.i.d.)	3 mo
Zhang et al[28]	Not specified	I: 50/43 C: 50/45	I: 56.20 ± 7.12 C: 55.21 ± 7.01 (range: 45–65)	I: 16.02 ± 8.96 C: 15.26 ± 9.10	Not specified	Moderate stage (II); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/500 μ g) (b.i.d.)+ yupingfengsan hejinshuiliujun decoction (dosage: not reported)	Salmeterol and fluticasone propionate powder (50/500ug) (b.i.d.)	24 wks
Jin et al[30]	Outpatient and hospital discharge	I: 45/45 C: 45/45	I: 57 ± 6.2 (range: 40–78) C: 61 ± 8.1 (range: 45–80)	Not reported	2007 Chinese COPD guideline	COPD patients at remission stage, severity not specified.	Salmeterol and fluticasone propionate powder (50/500 μ g) (b.i.d.) + baining capsule (5 pills, t.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	24 weeks
Pu[31]	Outpatient	I: 30/30 C: 30/30	I: 64.5 ± 8.5 C: 63.5 ± 9.0	I: 9.8 ± 4.2 C: 10 ± 3.5	2007 Chinese COPD guideline	Moderate and severe stages (II, III); COPD patients in stable phase	Salmeterol and fluticasone propionate powder (50/250 μ g) (b.i.d.) + shenha capsule (4 pills, t.i.d.)	Salmeterol and fluticasone propionate powder (50/250 μg) (b.i.d.)	6 mo
Huang[32]	Inpatient and outpatient	I: 55/55 C: 54/54	I: 59.1 ± 7.2 C: 60.6 ± 6.9	I: 22.3 ± 12.4 C: 23.2 ± 12.7	2007 Chinese COPD guideline	COPD patients in stable phase, severity not specified.	Salmeterol and fluticasone propionate powder (50/500 μ g) (b.i.d.) + yishenfangchuan capsule (5 pills, t.i.d.)	Salmeterol and fluticasone propionate powder (50/500 μg) (b.i.d.)	1 yr

1997 Chinese COPD guideline: Chinese guidelines for the diagnosis and treatment of COPD (1997 draft).
2007 Chinese COPD guideline: Chinese guidelines for the diagnosis and treatment of COPD (2007 revised edition).
A = Number of patients analyzed, b.i.d. = twice a day, C = Control group, COPD = chronic obstructive pulmonary disease, I = Intervention group, q.d. = once a day, R = Number of patients randomized, SD = standard deviation, t.i.d. = three times a day.

TABLE 2. Risk of Bias Among Included Studies

Source	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment*	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Chen et al[22]	Unclear risk Quote: ''All 60 patients were randomly divided into two groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned but its impact maybe low, as FEV_1 is an objective outcome measure.	Unclear risk: 60 patients were randomized, while the author did not mention the follow-up rate.	Unclear risk: Protocol is not available.
Lu et al[23]	Low risk: Random sequence was generated from a table of random numbers.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers.	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Unclear risk: 80 patients were randomized, while the author did not mention the follow-up rate.	Unclear risk: Protocol is not available.
Jia and Huang[29]	Unclear risk Quote: ''120 cases of COPD patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk Details not stated.	Unclear risk The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Low risk: All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.
Liu and Zhou[24]	Unclear risk Quote: ''60 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV1 is an objective outcome measure.	Low risk: All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.
Liang et al[25]	Unclear risk Quote: ''60 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers.	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure	Low risk: All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.
Mo et al[26]	Unclear risk Quote: ''62 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk Details not stated.	Unclear risk The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure	Low risk All participants completed the study. Drop-out rate: 0%	Unclear risk Protocol is not available.
Tang et al[27]	Unclear risk Quote: ''60 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Low risk: Proportion of drop out among study groups differs by $\leq$ 10%. Four of 64 patients dropped out, 2 in intervention group, and 2 in control group. Drop-out rate: 6.3%	Unclear risk: Protocol is not available.
Zhang et al[28]	Unclear risk Quote: ''100 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Low risk: Proportion of drop out among study groups differ by $\leq$10%. Twelve of 100 patients dropped out, 7 in intervention group and 5 in control group. Drop-out rate: 12%	Unclear risk: Protocol is not available.
Jin et al[30]	Low risk: Random sequence was generated from a table of random numbers.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers.	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Low risk: All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.

Source	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment*	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Pu[31]	Unclear risk Quote: ''60 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers.	Low risk: Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome, measure	Low risk: All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.
Huang[32]	Unclear risk Quote: ''109 patients were randomly divided into 2 groups.'' Random sequence generation method not stated.	Unclear risk: Details not stated.	Unclear risk: The study did not mention blinding of participants and researchers.	Low risk Blinding of assessors not mentioned, but its impact maybe low, as FEV_1 is an objective outcome measure.	Low risk All participants completed the study. Drop-out rate: 0%	Unclear risk: Protocol is not available.

We assumed that the impact of assessor blinding on FEV_1 measurement is minimal.
FEV_1 = forced expiratory volume in 1 second.
*Assessed on the basis of the outcome of FEV_1 measurement.

0.34), but a high level of heterogeneity existed (heterogeneity $\chi^2 = 40.90$, $P < 0.01$, $I^2 = 85\%$). After examining the forest plot, we found that the study by only Liu and Zhou[24] did not overlap with the summary estimate. However, we could not identify possible factors that had contributed to the heterogeneity after examining the patients' characteristics in Table 1. In order to test the effect of the study by Liu and Zhou,[24], we performed sensitivity analysis. We found that omission of study by Liu and Zhou[24] had led to a reduction of overall effect estimate (WMD = 0.13 L, 95% CI: 0.05–0.21), although the pooled finding still favored combined treatment with a magnitude larger than the MID of 0.1 L. Heterogeneity was also significantly reduced (heterogeneity $\chi^2 = 8.29$, $P = 0.14$, $I^2 = 40\%$).

In a subgroup analysis limiting to 4 trials with follow-up at 3 months (n = 262)[22,23,26,27] and 2 trials at 6 months (n = 150),[30,31] both of the pooled results showed superiority of combined treatment over SFP alone (Table 3). At 3 months, the WMD was 0.11 L (95% CI: 0.00–0.22, $I^2 = 50\%$) and WMD for 6 months was 0.19 L (95% CI: 0.07–0.32, $I^2 = 0\%$).

These 7 trials, evaluating 7 different CHM formulae, contributed to a star-shaped trial network on FEV_1 change with SFP alone as a common comparator. Table 4 summarizes the NMA results on the 7 CHM formulae regarding change in FEV_1.[22–24,26,27,30,31] No statistically significant difference was found between the 7 CHM formulae.

The SUCRA of seven CHM and SFP and SFP alone are shown in Figure 2. The results indicated that SFP and jiaweisanao decoction had a slightly higher probability of being the best choice, while the SFP and jiaweiqiweiduqi decoction had a slightly lower probability of being the best choice than the remaining choices.

The seven formulae share similar herbal compositions. Shenha capsule and baining capsule are similar in that they both contain *Cordyceps sinensis* (冬蟲夏草). In 4 formulae (baoyuan decoction,[28] jiajianbufei decoction,[27] jiaweiqiweiduqi decoction,[20] and yiqihuoxue decoction[21]), all of them contain *Astragalus membranaceus* (黃芪), 3 of them contain *Rehmanniae radix preparata* (熟地黃), 2 of them contain *Fructus schisandrae* (熟地黃), *Radix codonopsis* (五味子), *Gecko* (黨參), *Root bark of paeonia suffruticosa andr* (蛤蚧), and *Radix et rhizoma ginseng* (人參).

Changes in SGRQ

Five studies (n = 429) comparing combined treatment with SFP alone had reported SGRQ score change (Table 3).[22,23,25,29,32] Pooled findings favored combined treatment (WMD = −4.99, 95% CI: −7.73 to −2.24), but a high level of heterogeneity exists (heterogeneity $\chi^2 = 127.01$, $P < 0.01$, $I^2 = 97\%$). Two studies are clinically heterogeneous from the remaining trials: Liang et al[25] included COPD patients at spirometric stage IV exclusively, while patients in other studies were at stages II to IV. Huang[32] had a follow-up duration of 1 year, while other studies lasted for 3 months.

We performed a sensitivity analysis by removing these 2 studies and found that the heterogeneity was significantly reduced (heterogeneity $\chi^2 = 1.98$, $P = 0.37$, $I^2 = 0\%$), and pooled results of the 3 remaining trials demonstrated superiority of combined CHM and SFP treatment above the MID value of -4, with a WMD of −5.11 (95% CI: −5.53 to − 4.69).

The four trials with 3 months follow-up evaluating 4 distinct CHM formulae formed a star-shaped trial network on SGRQ change with SFP as a common comparator. NMA

TABLE 3. Chinese Herbal Medicine and Salmeterol and Fluticasone Propionate Versus Salmeterol and Fluticasone Propionate Alone for Treating COPD: Random Effect Meta-Analysis

		No. of Participants		Combined Effect		Test for Heterogeneity		
Outcome Measurement	**No. of Studies**	**CHM + SFP Group**	**SFP-Only Group**	**WMD (95% CI)**	***P****	**χ^2 statistic**	***P**†*	**I^2 value**
FEV_1 (L)								
All studies	7	266	266	0.20 (0.06–0.34)	<0.05	40.90	<0.01	85%
All studies without Liu and Zhou[24]	6	206	206	0.13 (0.05–0.21)	<0.05	8.29	0.14	40%
3 months follow-up only	4	131	131	0.11 (0.00–0.22)	<0.05	6.04	0.11	50%
6 months follow-up only	2	75	75	0.19 (0.07–0.32)	<0.05	0.20	0.66	0%
SGRQ								
All study	5	215	214	−4.99 (−7.73 to −2.24)	<0.05	127.01	0.00	97%
3 months follow-up only	3	130	130	−5.11 (−5.53 to −4.69)	<0.05	1.98	0.37	0%
6MWT (m)								
All study (3–6 mo follow-up)	3	118	120	32.84 (18.26–47.42)	<0.05	1.25	0.54	0%

6MWT = 6-minute walk test, 95% CI = 95% confidence interval, CHM = Chinese herbal medicine treatment, FEV_1 = forced expiratory volume in 1 second, SFP = salmeterol and fluticasone propionate, SGRQ = St George's Respiratory Questionnaire, WMD = Weighted mean difference.
*Test for overall effect.
†Chi-square test for heterogeneity.

indicated that SFP along with runfeijianpibushen decoction and SFP along with renshenbufei pills were significantly more effective than the remaining 3 choices in SGRQ score improvement (Table 5). SFP and runfeijianpibushen decoction appeared to be slightly more effective than SFP and renshenbufei pills, but there was no statistically significant difference. Results from SUCRA suggested that SFP and runfeijianpibushen decoction and SFP and renshenbufei pills had similar probability of being the best treatment, while SFP alone had the lowest probability (Figure 3).

The 4 included formulae share similar compositions. All of them contain *Astragalus membranaceus* (黄芪), two of them contain *Atractylodis macrocephalae* rhizome (白术), *Rehmanniae radix* preparata (熟地黄), *Radix codonopsis* (黨參), and Root bark of paeonia suffruticosa (牡丹皮).

Changes in 6MWT

Pooled results from 3 RCTs[22,28,30] (n = 238) reporting 6MWT change also favored combined treatment (WMD = 32.8 m,

TABLE 4. Mean Differences in FEV_1 and 95% Credibility Intervals Between 7 CHM Formulae: Indirect Comparison

SFP and Shenha Capsule						
−0.12 (−8.00, 7.77)	SFP and Baining capsule					
−0.03 (−6.80, 6.73)	0.08 (−7.65, 7.82)	SFP and Baoyuan decoction				
0.12 (−7.43, 7.66)	0.23 (−8.20, 8.66)	0.15 (−7.25, 7.54)	SFP and Jiajianbufei decoction			
1.04 (−5.13, 7.21)	1.16 (−6.07, 8.38)	1.07 (−3.57, 5.71)	0.92 (−5.93, 7.78)	SFP and Jiaweisanao decoction		
−0.32 (−7.29, 6.66)	−0.20 (−8.12, 7.72)	−0.28 (−5.52, 4.96)	−0.43 (−8.02, 7.15)	−1.35 (−7.05, 4.34)	SFP and Yiqihuoxue decoction	
−0.49 (−8.49, 7.52)	−0.37 (−9.21, 8.47)	−0.46 (−6.60, 5.68)	−0.61 (−9.15, 7.94)	−1.53 (−8.33, 5.27)	−0.17 (−7.53, 7.19)	SFP and Jiaweiqiweiduqi decoction
−0.56 (−5.46, 4.34)	−0.44 (−6.62, 5.73)	−0.53 (−5.19, 4.14)	−0.68 (−6.42, 5.07)	−1.60 (−5.35, 2.15)	−0.24 (−5.20, 4.71)	−0.07 (−6.40, 6.26) SFP only

Results are the mean difference and related 95% credibility intervals of mean FEV_1 values in the row-defining treatments, compared with mean FEV_1 values in the column-defining treatment. Mean difference higher than 0 favors the column-defining treatment, and vice versa.
CHM = Chinese herbal medicine, FEV_1 = forced expiratory volume in 1 second, SFP = salmeterol and fluticasone propionate.

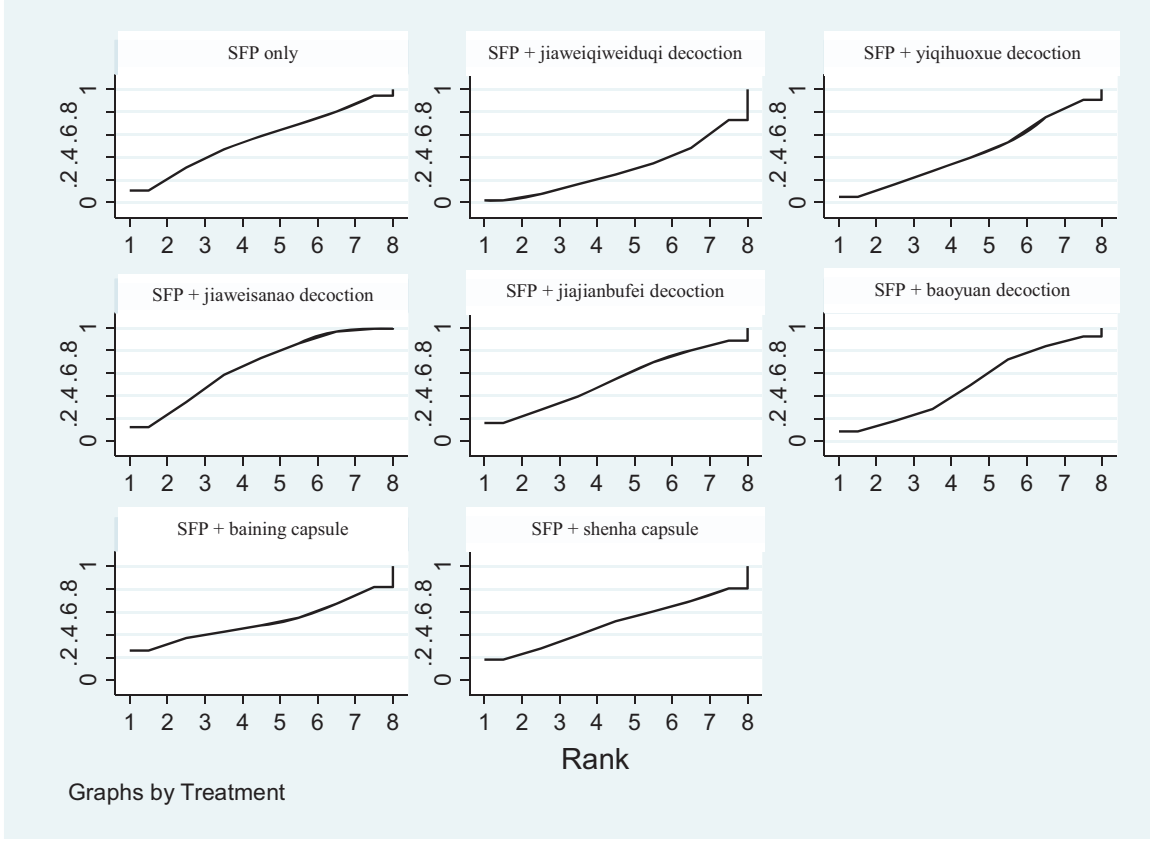

FIGURE 2. Comparative effectiveness of the 7 CHM formulae: surface under the cumulative ranking curve (SUCRA) for FEV_1. Note: The x-axis represents the possible rank of each treatment (from the first best rank to the worst according to FEV_1 change). The y-axis indicates the cumulative probability for each treatment to be the best treatment, the second best treatment, the third best treatment, and so on. SFP = salmeterol and fluticasone propionate.

95% CI: 18.3–47.4, $I^2 = 0\%$, Table 3), which was above the MID value of 26 meters.[18]

DISCUSSION

CHM is widely used as an adjuvant treatment for COPD in China. This systematic review quantitatively summarized evidence on the add-on effect of CHM on top of SFP. Results from meta-analyses indicated favorable effects of the combination of CHM and SFP on changes in FEV_1 (pooled WMD = 0.13 L), changes in SGRQ (pooled WMD = -5.11), and changes in 6MWT (pooled WMD = 32.8 m) when compared with SFP alone. The adjuvant effect of CHM on the all the 3 outcomes reached their respective MID values, suggesting the potential clinical usefulness of adding CHM on top of SFP. The 11 trials covered mild to very severe COPD patients, with 4 trials only

TABLE 5. Mean Differences in SGRQ and 95% Credibility Intervals Between 4 CHM Formulae: Indirect Comparison

SFP and Runfeijianpibushen Decoction				
−0.07 (−2.13, 1.98)	SFP and Renshenbufei pills			
−3.01 (−5.71, −0.30)	**−2.94 (−4.70, −1.18)**	SFP and Yiqihuoxue decoction		
−3.93 (−6.13, −1.74)	**−3.86 (−4.63, −3.09)**	−0.93 (−2.45, 0.60)	SFP and Jiaweiqiweiduqi decoction	
−4.31 (−6.36, −2.26)	**−4.24 (−4.24, −4.24)**	−1.31 (−3.06, 0.46)	−0.37 (−1.14, 0.39)	SFP only

Results are mean difference and related 95% credibility intervals of mean SGRQ values at the row-defining treatments, compared with mean SGRQ value in the column-defining treatment. Mean difference higher than 0 favor the column-defining treatment, and vice versa. Significant results are in bold and are underlined.

CHM = Chinese herbal medicine, SFP = salmeterol and fluticasone propionate, SGRQ = St George's Respiratory Questionnaire.

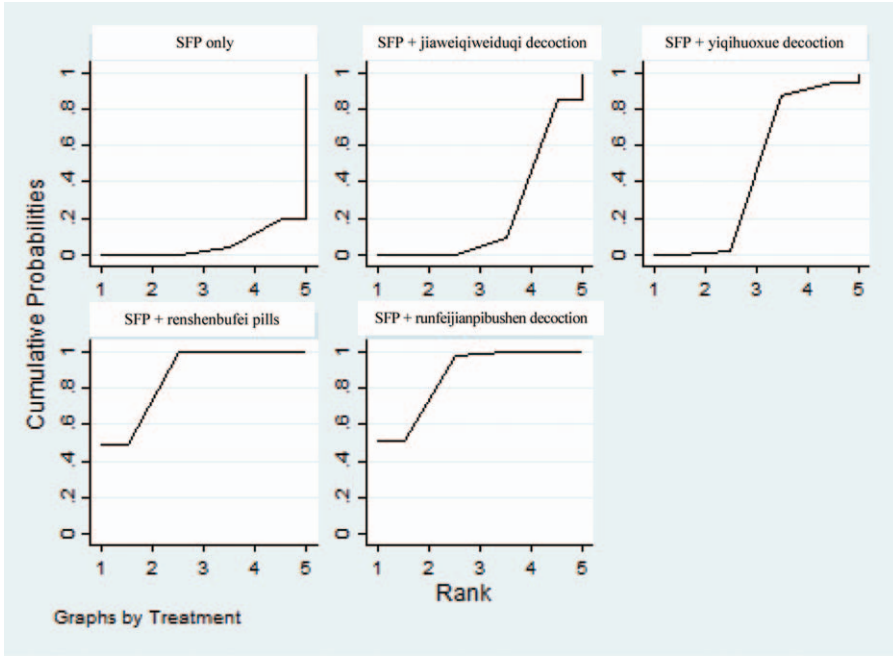

FIGURE 3. Comparative effectiveness of the 4 CHM formulae: Surface under the cumulative ranking curve (SUCRA) for SGRQ. Note: The x-axis represents the possible rank of each treatment (from the first best rank to the worst according to SGRQ change). The y-axis indicates the cumulative probability for each treatment to be the best treatment, the second best treatment, the third best treatment, and so on. SFP = salmeterol and fluticasone propionate.

including stage IV and/or stage III patients, and the data suggest that CHM could be effective even in patients with more severe COPD. However, disease severity, as reflected by spirometric staging, might have contributed to heterogeneity in the pooling of SGRQ, and the association between baseline severity and SGRQ needs to be further evaluated in future trials and meta-regression. Duration of follow-up might be another source of heterogeneity in the pooling of SGRQ, as FEV_1 results at 6 months seemed to be better than that at 3 months. Future trials should consider a longer follow-up time for capturing outcome. Despite heterogeneity of included studies, for both FEV_1 and SGRQ pooling, the direction of effect did not change in sensitivity and subgroup analyses, and the effect size stayed above the MID threshold. Finally, it should be highlighted that all the included trials were conducted in the Chinese population, which limited the generalizability of the evidence to patients of other ethnicity.

Our assessment suggested that the risk of bias among included trials is often unclear due to poor reporting, and some others had a moderate risk of bias. As all studies are prospective controlled studies, quality of evidence from these publications may not be considered low or very low, as their design cannot be poorer than case–control studies or case series.[36] In addition, a recent meta-epidemiological study suggested that lack of allocation concealment and blinding tend to have a less impact on the measurement of objective outcomes.[37,38] Accordingly, we may be less concerned about the bias caused by high or unclear risk of bias by focusing on objective outcome such as FEV_1. Nevertheless, results on subjective outcome (SGRQ) could be biased due to methodological limitations. Finally, although we have conducted a comprehensive literature search to identify potential trials and existing systematic reviews, we were unable to evaluate the existence of publication bias, as less than 10 trials were included for each outcome.[38]

We also conducted NMA to evaluate the comparative effectiveness of different CHM formulations. For FEV_1, no statistical differences among different CHM formulations were observed. For SGRQ scoring, results from NMA suggested that runfeijianpibushen decoction[25] and renshenbufei pills[29] could be considered as the first choices, as they have the highest probability being the best add-on to SFP. Relatively small overall sample size within the NMA could be a reason for not detecting any significant differences between CHM formulations for FEV_1, but another plausible explanation could be the similarity of herbal composition among included CHM formulae.

For instance, *A. membranaceus* is the most commonly used herb among the trials. Its active compound, *Astragalus polysaccharide* (APS), is known to facilitate the decrement of hydroxyproline lung content as well as matrix metalloproteinase-9 expression in rats with COPD.[39] *Astragalus* injection also shows therapeutic effect in rats with COPD, by reducing the levels of interleukin (IL)-8 and tumor necrosis factor-alpha (TNF-α) in Bronchoalveolar lavage fluid and serum, and inflammatory cells level.[40] Five classical prescriptions of TCM that contained herbs used by the included trials has demonstrated an effect on reducing inflammatory cell infiltration and the secretion of emphraxis in vessel cavity of bronchiole and terminal bronchiole, recovering cilium adhesion, lodging, and abscission, and lowering airway hyperreactivity and promoting airway reconstruction.[41] The included CHM formulae may share these common mechanisms when achieving therapeutic effects. However, COPD patients may have different diagnoses according to Chinese medicine perspective.[42] Clinicians can make reference to Chinese medicine diagnosis when considering the use of *A. membranaceus*, as it may not be an appropriate herb to use for all COPD patients.

Satisfying the assumptions of trial similarity and consistency is essential for ensuring reliability of NMA results.[43] To

maintain trial similarity, we have imposed strict inclusion criteria on participants, interventions, controls, and outcome measures. The evaluation of consistency requires data on both direct and indirect comparisons.[43] In this systematic review, we did not include head-to-head trials between CHM formulae, and thus, direct comparison data were unavailable. Statistical evaluation of consistency is therefore not conducted, but existing meta-epidemiological study has suggested that indirect evidence is often consistent with the corresponding direct evidence, and the chance of disagreements between these 2 types of evidence is not high.[44] Further rigorous trials are needed to confirm the superiority of runfeijianpibushen decoction[25] and renshenbufei pills. Before such trials, quality of the herbal products should be guaranteed. Chemoprofiles of these herbal preparations should be determined and compared [e.g., by high-performance liquid chromatography (HPLC)], and variations in the composition of chemical ingredients from batch to batch should be avoided. Contaminations and adulterations should be prevented as well.

In conclusion, the use of CHM on top of SFP may provide clinically relevant benefit for COPD patients on FEV_1, SGRQ, and 6WMT. Use of different CHM formulae included in this systematic review showed similar effect for increasing FEV_1, while the additional use of runfeijianpibushen decoction and renshenbufei pills showed better effect on improving SGRQ. Included formulae had a high overlap of herb choice and a core combination can be devised and evaluated in the future. Baseline severity and duration of follow-up may influence effect sizes, and their impact should be assessed formally in future trials and meta-regression. Finally, future trials should adhere to the CONSORT reporting statement,[45] so as to improve the usefulness of study results and transparency on methodological standards.

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