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RESEARCH ARTICLE

EFFICACY OF SHENLING BAIZHU SAN FOR THE TREATMENT OF STABLE COPD: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To assess the efficacy and safety of Shenling Baizhu San (SLBZS) for the treatment of stable chronic obstructive pulmonary disease (COPD) through systematic review.

Methods: Biomedical databases, including PubMed, EMbase, The Cochrane Central Register of Controlled Trials (CENTRAL), CBM-disk, CNKI, VMIS and WFMO were searched from their inceptions until 31th October 2015. Randomized controlled trials of oral SLBZS involving the outcome measures of symptom improvement, quality of life assessment, forced expiratory volume in one second (FEV_1), arterial blood gas analysis and/or frequency of dyspnea or diaphragmatic fatigue. Twelve studies were identified and extracted by two reviewers. The Cochrane Risk of Bias tool was conducted for the assessment of Methodological quality. Data were analyzed using the RevMan 5.3.0 software.

Results: Twelve studies involving 814 participants were included and all of them were carried out in china. The results of meta-analysis indicated patients receiving SLBZS plus conventional therapy showed a significantly relieving in clinical manifestation than those receiving conventional therapy alone (RR:5.00, 95% CI: 2.98 to 8.39), SLBZS plus conventional therapy also had greater improvement in the quality of life no matter using CAT (RR:-4.52, 95% CI: -5.72 to -3.32) or SGRQ (RR:-13.33, 95% CI: -15.97 to -10.68) for assessment. SLBZS may have a potential benefit in increasing dyspnea remission rate and decreasing the incidence of respiratory failure (RR:0.95, 95% CI: 0.62 to 1.47), as well as improving ventilation in patients (RR:-1.41, 95% CI:-2.49 to -0.33). It seems all trails had showed beneficial tendency. Nevertheless, the interpretation of research results still need to be cautious, because none of the trails described the method of allocation concealment, blind and follow-up.

Conclusions: SLBZS seems to be an acceptable, additional treatment measures for stable stage COPD patients. The further evaluation of SLBZS in efficacy and safety needs more high quality randomized controlled clinical trial evidence.

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INTRODUCTION

It still remains a major public health problem as COPD has became the fourth leading cause of chronic morbidity and mortality in the United States. The increasing burden of COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population (Global Initiative for Chronic Obstructive Lung Disease, 2015). Yet, COPD remains relatively unknown or ignored by the public as well as public health and government officials. Recent epidemiological survey shows that the prevalence rate with COPD is 8.2% among Chinese adult over 40 years old, which means the total number of patients has reached more than thirty-eight million (Fang, 2011). It has surely became the largest city's fatal disease and the fourth lethal in rural area. Disappointed, there is no permanent cure for COPD patients. There is no evidence shows that Drug therapy could reversing the progression of the disease. According to the guideline, the goals were to improve prevention and management of COPD through all facets of health care and health care policy, as the drug therapies may lead to problems such as the abuse of large doses of drug, side effects. Undoubtedly, Chinese medicine treating COPD shows better application prospect in the prevention of COPD. Stable COPD patients treated with integrative method of traditional Chinese medicine can effectively improve lung function, relieve clinical signs and symptoms, improve the quality of life. It can be used as a good method of treatment in clinical application (Wang, 2015). There is no doubt that the traditional

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Chinese medicine becomes increasingly the focus of international attention. Shenling Baizhu San (SLBZS, from the world's first official medical manual named "Prescriptions People's Welfare Pharmacy", written in the Song Dynasty of ancient China, is a representative prescription of the method of "reinforcing earth to strengthen metal"). More and more clinical trials show reliable therapeutic effect and safety in treating stable COPD with this prescription (Xue, 2012 and Zhang, 2013). Due to the low methodological quality of trials, evidences of the effectiveness and safety of the SLBZS are still needed.The purpose of this system evaluation is to assess the efficacy and safety of the SLBZS in treating patients with COPD in stable period.

MATERIALS AND METHODS

Search Strategy

Databases included PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP medicine information system (VMIS), and Wanfang Medicine Online (WFMO) were searched from their inceptions of the databases to October 2015, without language restriction. Search terms were divided into three groups: condition (COPD, chronic bronchitis, emphysema, and their synonyms); intervention (Shenling Baizhu, reinforcing earth to strengthen metal, and their synonyms) and study type (controlled clinical trial, and their synonyms). All the search results were downloaded and combined, and duplicates were removed. The article was screened based on title, abstract, and full text as needed.

Inclusion criteria

Studies included in this review must meet the following criteria: (1) Type of study: randomized controlled trials (RCTs) published in English or Chinese, with or without blinding were considered. (2) Participants: patients diagnosed with COPD in the stable stage (There were no evidence of recent infection, exacerbation or hospitalization), Without considering the lung function grading. (3) Type of intervention: interventions were orally administered SLBZS in any form (i.e. decoction, pill, powder, liquid, or capsule) alone or combination of pulmonary rehabilitation, conventional therapy, compared with placebo, pulmonary rehabilitation or conventional therapy as controls. Definition of SLBZS: SLBZS as the original prescription or modified in the foundation, but the meaning unchanged. Conventional therapy includes bronchodilators (anticholinergics, beta2-agonists, methylxanthine), corticosteroids, smoking cessation, et al. (4) Type of Outcome measurement: symptom improvement, quality of life assessment, frequency of exacerbations, spirometric parameters (FEV_1), six minute walk distance and dyspnea or diaphragmatic fatigue were considered.

Exclusion criteria

The following types of studies were excluded: (1) Studies that included participants with asthma, bronchiectasis or combined with other system severe primary disease; (2) Conventional therapy using antibiotic resistance to infection for stable COPD; (3)Test interventions that were combined with other TCM therapies such as moxibustion, acupuncture or other oral Chinese herbs.

Data extraction and quality assessment

Two researchers (Qigang Zeng and Chenxia Duan) independently extracted data from each study using a predefined extraction form which included details of study design, author, source of participants, lung function grading, interventions, control medicine, treatment duration, outcome measures, numbers of dropouts, and adverse events reported. If opinions different from each other, the third reviewer (Yong Dai) was consulted to make the final decision. Email, letter or phone were made to contact the original investigators regarding any missing data or to obtain data clarification.

Base on the recommendations in the Cochrane System Evaluation Handbook (5.2.0 version), two searchers (Qigang Zeng and Chenxia Duan) independently assessed methodological quality of the included studies using the Cochrane risk of bias assessment tool. Any study need to be assessed the following domains: (1) Random sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data; (6) Selective outcome reporting; (7) Other bias. Low risk , high risk or unknown risk were used to assess the above domains.

Data analysis

All data were analyzed using RevMan 5.3.0 which developed by the Cochrane Collaboration. Risk ratio (RR) was used for dichotomous data and Mean difference (MD) was calculated for continuous data with 95% confidence intervals (95% CI). Statistical heterogeneity was calculated by the Cochrane's Q test and I^2. If the I^2 statistic was less than 50% and the value of P was more than 0.1, it meant the analysis showed low heterogeneity, thus data were pooled using a fixed effect model. Otherwise, a random effect model was applied. Sensitivity analysis was used to explore if the analysis appears obvious heterogeneity. Publication bias was calculated using funnel plots when five or more studies reported the same outcome measure. When it was difficult to determine whether the funnel plot symmetry, egger's test was conducted using Stata 12.0 software (StataCorp LP, USA).

RESULTS

Description of studies

258 records related to the research by screening, 208 records were excluded because of duplications, 38 studies were excluded after reading the articles and/or contacting the authors, and 12 studies (including 814 participants) met all criteria were included in the review (Chen, 2010; Du, 2013; Du, 2013; Du, 2012; Jiang, 2013; Jiang, 2013; Luo, 2007; Song, 2004; Wang, 2010; Wang, 2012; Wang, 2013 and Xi, 2011) The selection process is outlined in Figure 1. Of these 12 studies, all studies were indexed in Chinese databases. 8 studies were published and one was conference paper (Du, 2013), three was dissertations (Chen, 2010; Luo, 2007; Song, 2004). All the trials were conducted in China from 2004 to 2013. Treatment duration ranged from 4 weeks to 6 months. Four researches mentioned participants' pulmonary function grading. Ten studies described the Chinese medicine differentiation of syndrome (Chen, 2010; Du, 2013; Huang, 2012; Jiang, 2013; Lin, 2013; Luo, 2007; Song, 2004; Wang, 2010; Wang, 2012 and Wang, 2013).

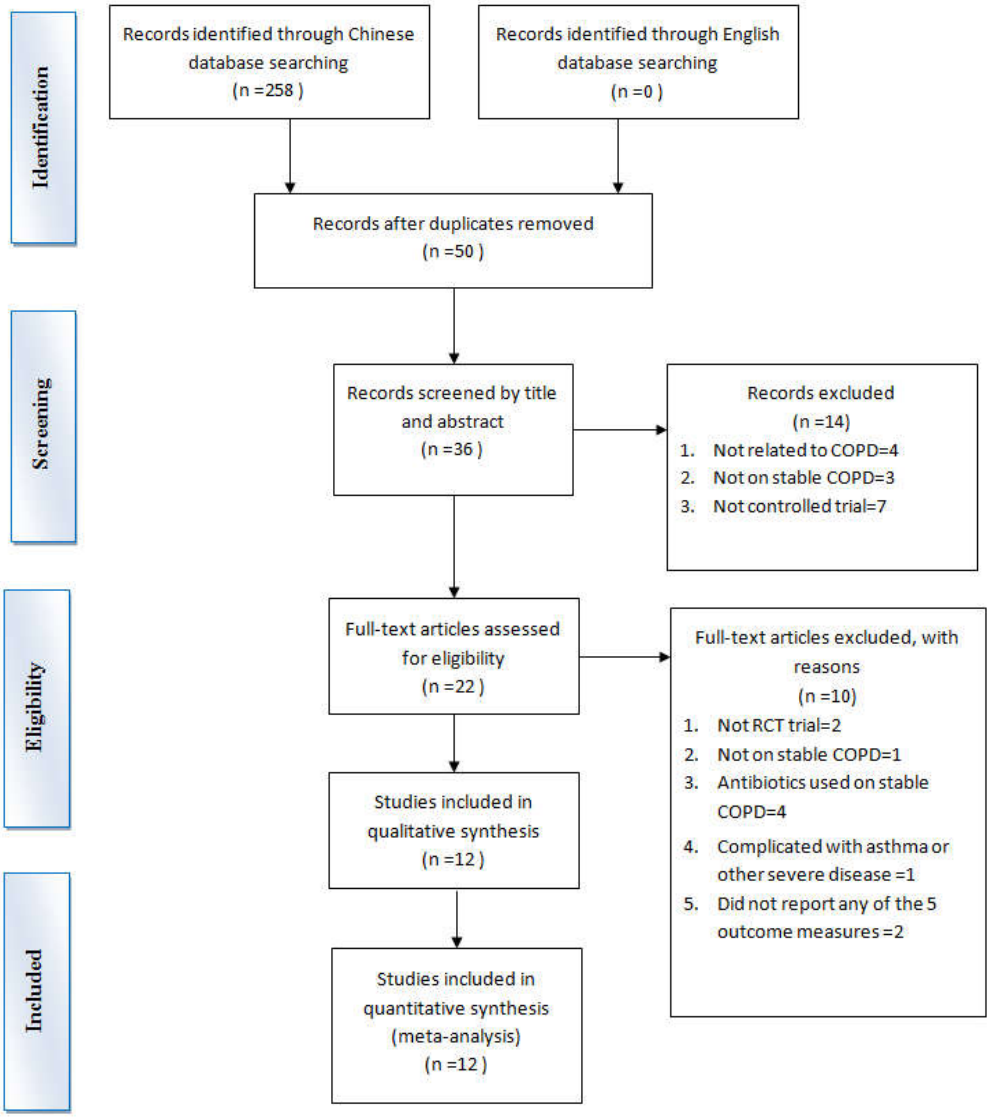

Figure 1. Flow diagram showing the trial selection process for the systematic review

Tables 1. Characteristics of included studies

First author, Year (Ref)	Location	No of Participants (R/A)	Age Mean±SD (years)	Severity of COPD	COPD History Mean±SD (years)
Chen DJ 2010[6]	China	T:30/30 C:30/30	T:63.97±6.95 C:64.10±6.49	NR	T:4.09±3.51 C:4.05±3.46
Du LJ 2013[7]	China	T:30/28 C:30/30	T:63.43±6.14 C:62.79±6.23	NR	NR
Du YM 2013[8]	China	T:24/24 C:24/24	62.50±7.8	NR	15.3±6.0
Huang SX 2012[9]	China	T:39/39 C:39/39	T:74.0±4.3 C:71.7±3.8	NR	NR
Jiang RM 2013[10]	China	T:30/30 C:30/30	T:64.0±2.1 C:61.7±3.2	T:II 20; III 10 C:II 22; III 8	NR
Lin ZY 2013[11]	China	T:60/60 C:60/60	55.52±8.56	I:38 II:46 III:14 IV:22	NR
Luo S 2007[12]	China	T:30/28 C:30/29	T:62.21±7.96 C:61.75±7.70	I to III	T:10.82±3.37 C:10.51±2.84
Song WC 2004[13]	China	T:40/40 C:38/38	T:54.9 C:55.1	I to III	NR
Wang HY 2010[14]	China	T:30/30 C:30/30	56.14±4.58	NR	NR
Wang L 2012[15]	China	T:30/28 C:30/29	T:65.21±7.68 C:63.52±7.76	NR	NR
Wang XX 2013[16]	China	T:30/30 C:30/30	50-75	NR	T:4.09±3.51 C:4.05±3.46
Xi C 2011[17]	China	T:40/40 C:38/38	T:64.36±7.52 C:63.64±8.16	NR	T:6.90±2.70 C:6.40±3.80

T: treatment; C: control; NR: not reported; R: number subjects randomized; A: number subjects analysed; SD: standard deviation.

Seven studies used FEV_1 as part of the outcome measures of lung function (Du, 2013; Jiang, 2013; Lin, 2013; Song, 2004; Wang, 2010; Wang, 2012; Xi, 2011). One study used the BMI as an index of prognosis indicator (Huang, 2012). Two studies used arterial blood gas index as the outcome measures of respiratory muscle strength [13,17]. Ten studies used Symptom improvement (Chen, 2010; Du, 2013; Jiang, 2013; Lin, 2013; Song, 2004; Wang, 2010; Wang, 2012; Xi, 2011). Five studies used quality of life assessment (Du, 2013; Jiang, 2013; Luo, 2007; Wang, 2010; Wang, 2012), as the index. One studies used BODE index (Wang, 2012) as the outcome measures. All studies compared SLBZS plus conventional therapy with conventional therapy. Three studies indicated that SLBZS was used as the original prescription (without modification) (Du, 2013; Huang, 2012; Jiang, 2013). The rest of the studies were SLBZS for basic addition and subtraction (Chen, 2010; Du, 2013; Lin, 2013; Song, 2004; Wang, 2010; Wang, 2012; Xi, 2011). The characteristics of the included studies are summarized in Table 1 and Table 2.

Figure 2. Summary of assessment of risk of bias for 12 studies

Risk of bias of the included studies

ALL studies directly indicated that the random sequence was generated by a random number table. All twelve studies did not mention the allocation concealment method and blind. Three studies reported drop-outs (Du, 2013; Luo, 2007; Wang, 2012), the reason was complicated with other diseases and exit, but it didn't mention whether they had used intention-to-treat analysis. Selective outcome reporting was judged as low risk of bias in all trials. Risk of bias assessment details are provided in Figure 2.

Publication Bias

Three studies reporting only symptom improvement, the other measure outcomes were less than five, so a funnel plot was applicable. For symptom improvement studies, the funnel plot was relative symmetric, it indicated that the risk of publication bias was not high. Risk of publication Bias are showed in Figure 3.

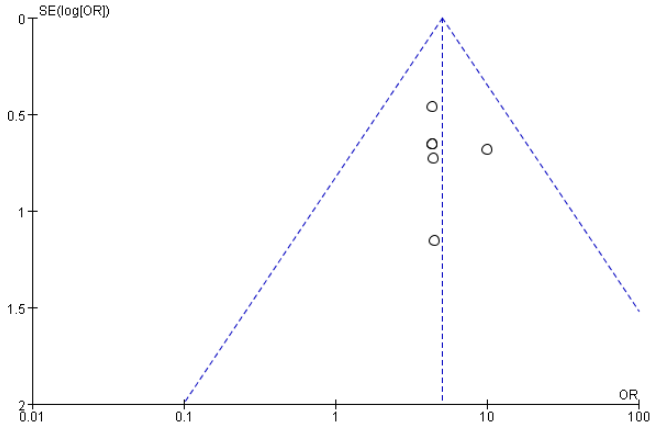

Figure 3. Funnel plot of publication bias using symptom improvement

Outcome measures

Effective rate of symptom improvement

Patients receiving SLBZS plus conventional therapy showed a significantly relieving in clinical manifestation than those receiving conventional therapy alone (RR:5.00, 95% CI: 2.98 to 8.39), based on six trials (Chen, 2010; Lin, 2013; Luo, 2007; Song, 2004; Wang, 2010; Wang, 2012 and Wang, 2013). From the Analysis of the causes, the conventional treatment in control group is oral Theophylline sustained-release tablets or Ipratropium Bromide Solution for inhalation and Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation. These drugs are on the first-line treatment list in recommended guidelines. Results indicate that oral SLBZS is an important adjuvant treatment for improving the effective rate than conventional therapy alone (Figure 4).

Quality of life assessment

Five studies had compared SLBZS plus Western medicine treatment with Western medicine treatment alone of the impact on the quality of life (Du, 2013; Jiang, 2013; Luo, 2007; Wang, 2010; Wang, 2012). Two studies compared the impact on the quality of life based on the CAT scale (Du, 2013 and Jiang, 2013). Results show a significantly greater improvement in total score (RR:-4.52, 95% CI: -5.72 to -3.32) and without heterogeneity. Three studies (Luo, 2007; Wang, 2010; Wang, 2012) indicated that SLBZS plus conventional therapy had greater improvement in the quality of life based on the SGRQ scale (RR:-13.33, 95% CI: -15.97 to -10.68), with middle heterogeneity were identified (Figure 6). Although all of the above results is conducive to SLBZS instead of conventional western medicine treatment measures, none of studies included in statistic data ever mentioned of grading of COPD of the patients. We can hardly known the certain quality of life before they had treated with SLBZS. With these limitations, the conventional western medicine treatment measures may lead to different results of the main reasons for the differences.

Table 2. Characteristics of included studies

First author, Year(Ref)	Intervention (ingredients of fomula)	Control	Duration /Follow-up	Adverse event	Outcome measures				
					FEV_1(L)	PESI	QLA	FCOPDE	DF
Chen DJ 2010[6]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) +Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	12 weeks/NR	No	No	Yes	No	No	No
Du LJ 2013[7]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen Lablab Album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza, Angelica sinensis, Ligusticum wallichia) + Bronchodilators	Bronchodilators	6 mths/NR	No	No	No	Yes	No	No
Du YM 2013[8]	SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza)+Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	3 mths/NR	NR	Yes	No	No	No	No
Huang SX 2012[9]	SLBZ Granule (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) + Theophylline Sustained-release Tablets	Theophylline Sustained-release Tablets	6 mths/NR	NR	No	No	No	No	No
Jiang RM 2013[10]	SLBZ Granule (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) + Theophylline Sustained-release Tablets	Theophylline Sustained-release Tablets	6 mths/NR	NR	Yes	No	Yes	No	No
Lin ZY 2013[11]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) + Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	1 mths/NR	NR	Yes	Yes	No	No	No
Luo S 2007[12]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) + Theophylline Sustained-release Tablets, Ipratropium Bromide Solution for Inhalation, Salmeterol Fluticasone	Theophylline Sustained-release Tablets, Ipratropium Bromide Solution for Inhalation, Salmeterol Fluticasone	3 mths/NR	No	No	Yes	Yes	No	No
Song WC 2004[13]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Glycyrrhiza) + Bronchodilators	Bronchodilators	3 mths/NR	NR	Yes	Yes	No	No	Yes
Wang HY 2010[14]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Pinellia ternata, Glycyrrhiza)+ Theophylline Sustained-release Tablets, Ipratropium Bromide Solution for Inhalation	Theophylline Sustained-release Tablets, Ipratropium Bromide Solution for Inhalation	2 mths/NR	NR	Yes	Yes	Yes	No	No
Wang L 2012[15]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza, Angelica sinensis, Ligusticum wallichii) + Bronchodilators	Bronchodilators	3 mths/NR	NR	Yes	No	Yes	No	No
Wang XX 2013[16]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza) + Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation	12 weeks/NR	NR	No	Yes	No	No	No
Xi C 2011[17]	Jiawei SLBZS (Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Glycyrrhiza) + Inhaled bronchodilators, inhaled corticosteroids, or both	Inhaled bronchodilators, ICS, or both	3 mths/NR	NR	Yes	No	No	No	Yes

PESI: Percentage of effectiveness of symptom improvement; QLA:Quality of life assessment; FCOPDE: Frequency of COPD exacerbation; DF: Dyspnea or diaphragmatic fatigue; NR: not reported.

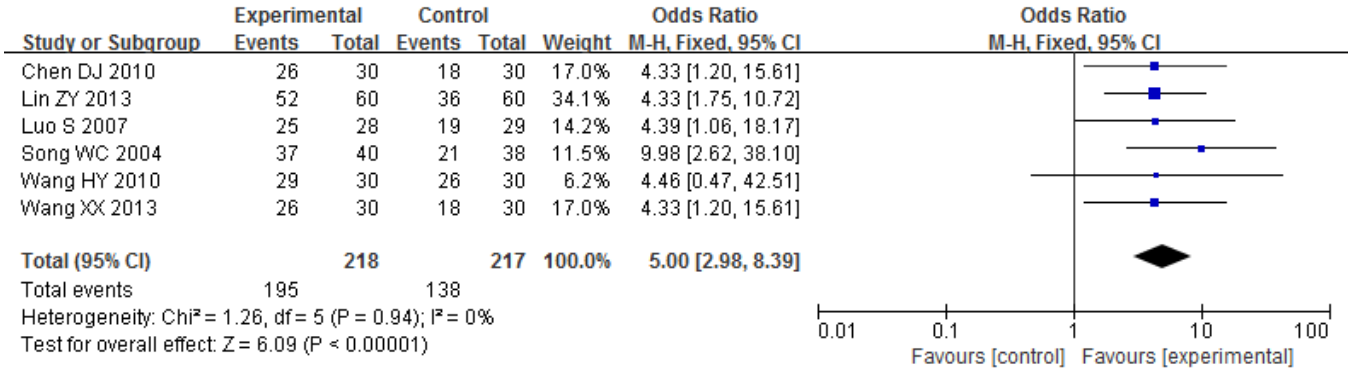

Figure 4. Comparison of SLBZS plus conventional therapy versus conventional therapy alone for stable COPD: effective rate of symptom improvement

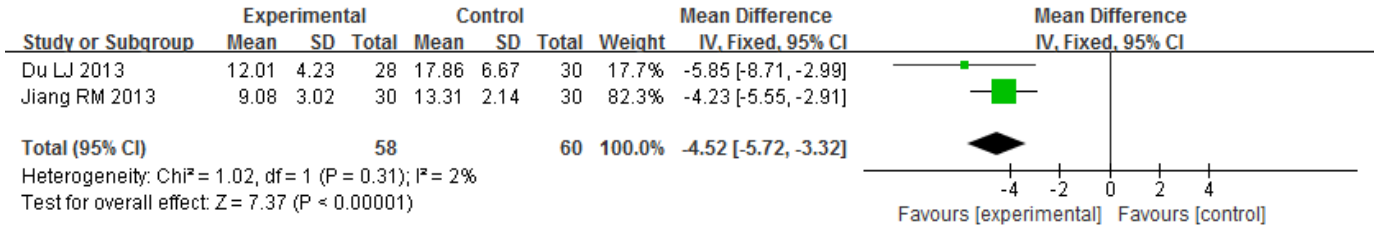

Figure 5. Comparison of SLBZS plus conventional therapy versus conventional therapy alone for stable COPD: CAT scale

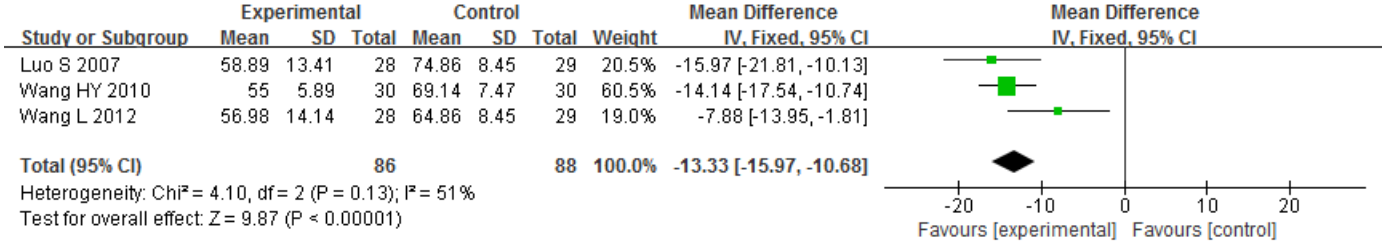

Figure 6. Comparison of SLBZS plus conventional therapy versus conventional therapy alone for stable COPD: SGRQ scale

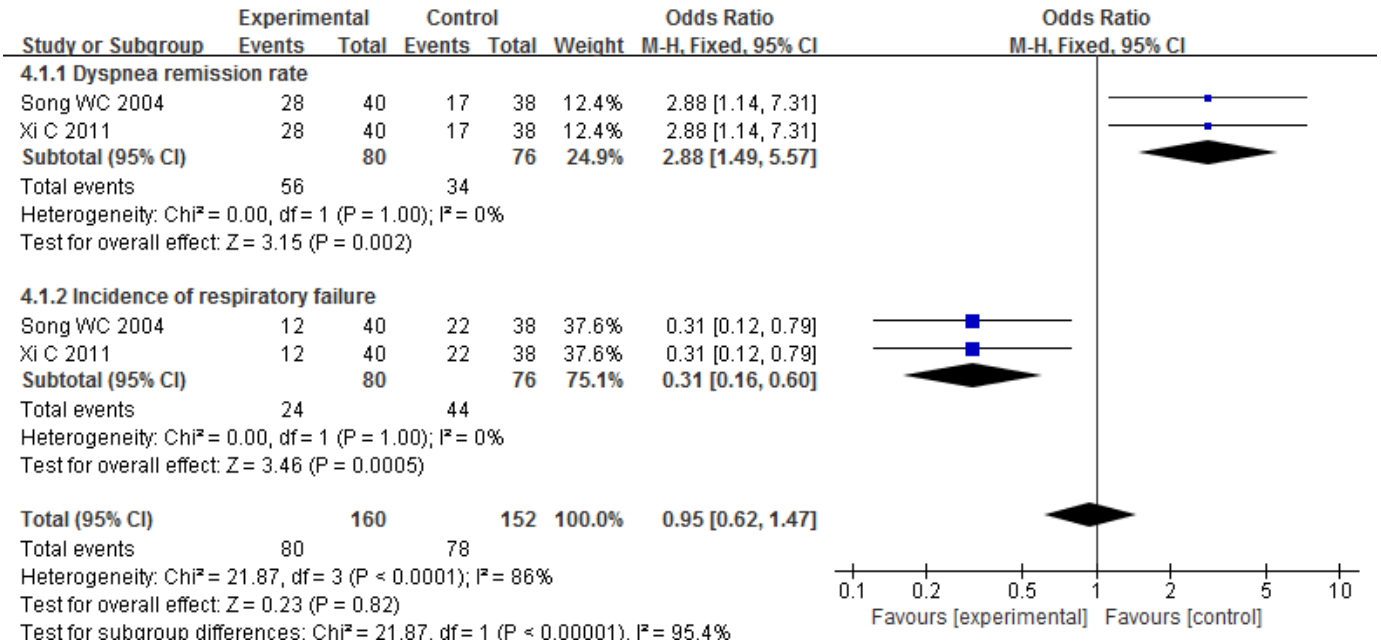

Figure 7. Comparison of SLBZS plus Western medicine treatment versus Western medicine treatment alone for stable COPD: change in dyspnea or diaphragmatic fatigue

In general, the results of these studies already indicated that SLBZS may potentially improving the quality of life.

Dyspnea or diaphragmatic fatigue

Two studies (Song, 2004 and Xi, 2011), reported showed that there was difference in the incidence of respiratory failure and dyspnea remission rate.

Anyway, SLBZS was tend to improve the pulmonary function measured as FEV_1 in short term, based on three studies (Du, 2013; Jiang, 2013 and Lin, 2013) (Figure 9)

Adverse events

Three studies reported that no adverse events occurred (Chen, 2010; Du, 2013 and Luo, 2007).

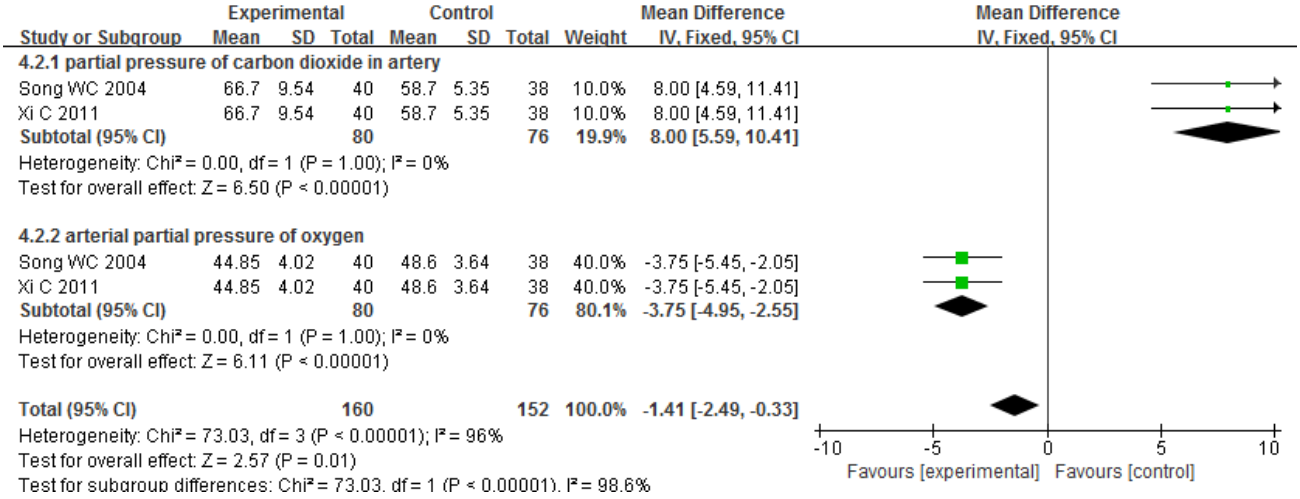

Figure 8. Comparison of SLBZS plus Western medicine treatment versus Western medicine treatment alone for stable COPD: change in arterial blood gas analysis

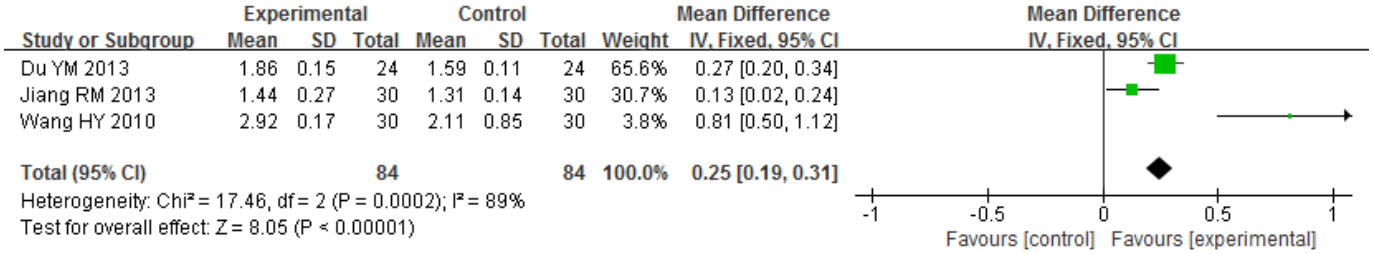

Figure 9. Comparison of SLBZS plus conventional therapy versus conventional therapy alone for stable COPD: change in FEV_1 (L)

It seemed that SLBZS plus conventional therapy had greater improvement in improving dyspnea remission rate and decreasing the incidence of respiratory failure (RR:0.95, 95% CI: 0.62 to 1.47), but there was heterogeneity (Figure 7). Also, results in the arterial blood gas analysis showed there was a relative benefit in increasing the blood oxygen pressure and depressing blood carbon dioxide pressure in SLBZS plus conventional therapy than using conventional therapy alone(RR:-1.41, 95% CI:-2.49 to -0.33), but there was high heterogeneity. This appeared due to the same results with the two trials. Overall, SLBZS may have a positive effects on improving dyspnea remission rate and decreasing the incidence of respiratory failure, as well as improving ventilation in patients (Figure 8).

Spirometric parameters

Three studies showed that there was a significant difference in improving FEV_1 in the trials when using SLBZS plus conventional therapy than using conventional therapy alone (RR:0.25, 95% CI:0.19 to 0.31), but there was heterogeneity. One study was excluded from statistic data for the authenticity of the data is suspect. This result appeared due to the difference in interventions and treatment period, especially the treatment period, explained a lot on the result of FEV_1.

It suggests that SLBZS seems to be a well tolerated formulae, even in combination with conventional drug treatment. The information on adverse events was not provided in other nine studies. Obviously, there was not sufficient data to assess the safely of SLBZS.

DISCUSSION

SLBZS, from the world's first official medical manual named "Prescriptions People's Welfare Pharmacy", written in the Song Dynasty of ancient China, is a representative prescription of the traditional Chinese method of "reinforcing earth to strengthen metal". This prescription is mainly used for the treatment of spleen and lung Qi deficiency, syndrome of Qi sinking and Qi deficiency syndrome of disease in respiratory system. With the great significant effect of SLBZS, the decoction is widely used in clinical treatment through repeated practice and exploration. Nowadays, SLBZS was developed into different formulations such as granule, pill, capsule and oral liquid. These improvements have provided us with more convenient and better extensive of clinical application. In Japan, South Korea and other Asian countries, SLBZS has found an increasingly wide utilization in many fields, and new developments in the research of this decoction are still coming forward. COPD is described as "lung distension" or "dyspnea"

in traditional chinese medicine, according to its clinical manifestations. As to the Five Elements Theory, spleen to earth, lungs to metal, so as to explain the relations among the physiological and pathological changes of the viscera. Thus there is a close relationship between the occurrence and development of disease with the function of lung and spleen. Disease first attacks the lung, then the impact spread to spleen, especially to those with stable COPD. The theory of "reinforcing earth to strengthen metal" is used during treatment throughout all stage of COPD, especially patient in stability, are often based on invigorating spleen for benefiting lung. SLBZS is exactly the representative prescription mainly used to invigorating spleen and replenishing qi of the lung. The results of this systematic review indicate that the use of SLBZS plus conventional therapy could significantly relieve clinical manifestation and improve the quality of life when compared with conventional therapy alone. Besides, the decoction plays an active role in improving lung function and dyspnea remission rate, decreasing the incidence of respiratory failure, as well as improving ventilation in patients.

FEV_1 is an important index to evaluate the severity of airflow limitation and can effectively evaluate the patient's condition and prognosis. So far, drugs can only be proved to slow down the rate of decline in lung function and there is no evidence shows that any kind of drugs (including Chinese medicine and Western medicine) can be proved to preventing lung function decline confirmed by FEV_1. In this research, most studies were from four weeks to six months and none of them had studied the follow-up assessment, which may lead to an incomprehensive evaluation of change in pulmonary function. Sometimes the lung function could improve to a certain extent after treatment, but decline after a period of time. So more rigorous clinical trials, especially those with a year or above study period are still required to estimate whether SLBZS can improve FEV_1 and slow the rate of decline in lung function or not.

The COPD assessment test, known as CAT, is an assessment tool recommended by GOLD guideline. SGRQ, designed by Professor Paul Jones, is to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis and has been used successfully in patients. It is not suitable for cysticfibrosis. It is in two parts. Part I produces the Symptoms score, and Part 2 is the Activity and Impacts scores. A total score is also produced in the conditions of China project. Through the two validity and reliability test, the scale is widely used in clinical and research work over years[1]. SLBZS plus conventional medications showed a potential advantage in improving the quality of patients' daily life. Results also indicated that SLBZS appeared to be well tolerated, since three studies have reported that no adverse events were noted while the rest of the studies were failed to provide enough information on adverse events and the security of data is incomplete. The safety evaluation results from the systematic review of oral SLBZS still need to be treated with caution. The characteristic of COPD is chronic airway inflammation involving a number of pro-inflammatory mediators and cytokines. One study has found that SLBZS could significantly reduce inflammatory infiltration and inhibit the inflammatory response in the gastrointestinal tract through down-regulating the expression of TNF-alpha, IL-6, IL-1 and other inflammatory factors (You Yu, 2012), Another research showed that the efficacy of SLBZS on tumor-bearing mice is due to the improving in IFN-γ, IL-10, and the increasing level of $CD4^+$ cells and NK cell (Li zhong, 2013). The results were also confirmed by another study (Feng Zhe, 2013), which showed that SLBZS could significantly improved growth inhibition of COX-2、VEGF、MVD on tumor-bearing mice. One experimental study also support the conclusion that SLBZS can augment the activation of IgA and sIgA, thus increasing the immune organ and plays an important role in immune regulation (Bai Jing-lin, 2015). The above pharmacological properties of SLBZS may at least partially explain the clinical benefits reported by the studies included in this review. The systematic review from Guo (Guo, 2006), indicates that Chinese medicine is an effective treating measures in stable COPD with better tolerance, and the use of Chinese medicine treatment in these patients may achieve additional benefits. This systematic review narrowed the focus to a specific formulae and further more clearly verifies the validity of the TCM treatment of COPD. SLBZS is formed with Codonopsis pilosula, Atractylodes, Poria coco, Dried tangerine peel, Semen lablab album, Lotus seed, Chinese yam, Platycodon grandiflorum, Coix seed, Amomun villosum, Salviae miltiorrhizae, Glycyrrhiza. Of all these herbs, half of them is regarded as the sovereign drug which belongs to the spleen and lung meridian. The main efficacy of these drugs is invigorating qi of lung and consolidation of superficies. The minister drug of the decoction is Codonopsis pilosula and it can greatly tonifying Qi of the whole body when compatibly combined with the sovereign drug. Codonopsis pilosula is similar to Ginseng in pharmacological effects. Many studies (Shergis, 2013; An, 2011) of oral ginseng and ginseng-containing formulae indicated that it could relieve clinical symptoms, improve lung function measured as FEV_1 and also decrease SGRQ scores. Along with a study (Miao, 2016) has showed that the two most commonly used formulae using in treating COPD were Bu Fei Tang (replenish lung) and Bu Zhong Yi Qi Tang (invigorate spleen). The most commonly used herbs consisted of Huang Qi (Astragalus membranaceus), Bai Zhu (Atractylodes macrocephala) and Dang Shen (Codonopsis pilosula), wihic are exactly the three main herb components in SLBZS. Dang Shen extract (Codonopsis pilosula) was found to suppress the release of TNF-α, also indicating anti-inflammatory effects (Byeon, 2009) Bai Zhu (Atractylodes macrocephala) extracts were found to have anti-inflammatory effects on TNF-α and nitric oxide production from peritoneal macrophages in mice (Li, 2007) and in a rat lung cell membrane chromatography model (Dong, 2008). Based on clinical studies and experiments, the mechanism of SLBZS on COPD includes: 1. Decrease in cytokine levels and suppression of airway inflammation and enhance the immune function of organism; 2. Maintenance both of oxidant-antioxidant balance and proteases and anti-proteases levels. However, due to inconsistent methods used to measure all mediators, the small number of studies, the small sample size, and poor quality of methodology of certain studies, the effect of SLBZS on treating COPD could not be completely confirmed. Further, RCTs related to spleen and lung Qi deficiency should be investigated in future clinical trials. Meanwhile, the observations of this research should be interpreted with caution for several reasons. A range of methodological issues were identified. Although all of the twelve studies had provided specific descriptions of the random sequence generation process. Blind assessment and allocation concealment were lacking in all studies. Overall, whether randomization and allocation concealment were effectively conducted in all the included studies remains unclear. The meta-analysis results indicate that the use of

SLBZS to routine pharmacotherapies may produce additional benefits in terms of improving quality of life and lung function, reducing respiratory muscle fatigue, relieving clinical manifestation and decreasing ventilation disorder. These potential benefits could be also plagued by methodological problems theoretical ambiguities. The overemphasizing of positive effects arising from publication bias and language bias may be a limitation in this review. It includes only studies written in English or Chinese and all the included studies were conducted in China. Although the funnel plot of symptom improvement is symmetrical, suggesting that publication bias is not high, but other measurement results are not supposed to be concluded in the funnel plot analysis because of the lacking of shortage in studies and there still exists the risk of bias.

Therefore these potential benefits of SLBZS as a supportive intervention still require further appraisal through more and higher quality trials that strictly adhere to methodological principles and procedures in order to provide better evidence-based medicine proof. Large sample, multi center study of RCT are required as well. In order for outcomes to be fully interpretable, participants should have similar COPD severity at baseline, Blind assessment and allocation concealment also need to be Strictly implemented. Further evaluated through trials that address the identified methodological deficiencies, have published protocols, provide quality-control data for both the CHM and control interventions and are of sufficient duration to assess any change. Trials should focus more on detailed specification of the adverse reaction reports and address the identified methodological deficiencies, have published protocols, provide quality-control data for both the CHM and control interventions and are of sufficient duration to assess any change. Safety evaluations included monitoring for adverse events and laboratory tests are still needed to provide detailed evidence and information for clinical practice.

Conclusions

For the stable stage COPD patients, in addition to conventional treatment of Western medicine, SLBZS seems to be an acceptable, additional treatment measures. Because the meta-analysis results indicate that SLBZS has the advantages in reducing the clinical symptoms of patients , improving the quality of life, and may have the potential impact in improving dyspnea remission rate and decreasing the incidence of respiratory failure. On the other hand, SLBZS might have well-tolerance. These potential benefits of SLBZS as a supportive intervention need to be further evaluated through trials with high quality, rigorous scientific evaluation of RCTs.

Author Contributions

Yong Dai initiated and supervised the project. Qigang Zeng and Chenxia Duan retrieved the English and Chinese databases, Screened and extracted the selected studies. Ziyi Fu and Qigang Zeng analyzed the data. Qigang Zeng wrote the paper. Qigang Zeng, Ziyi Fu, Chenxia Duan, Yong Dai were all involved in the data interpretation, revision, and final approval of the paper.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix 1. Search strategies

English databases

#1 Shenling Baizhu San OR Shen-Ling-Bai-Zhu-San OR Shenling Baizhu OR Reinforce the Spleen to benefit the Lung OR Strengthening the Spleen and replenishing the Qi OR Invigorating Spleen and replenishing Qi

#2 Chronic obstructive pulmonary disease OR COPD OR emphysema OR Chronic obstructive lung disease OR Chronic obstructive airway disease OR emphysema, pulmonary disease OR Airflow obstruction, Chronic OR Chronic Airflow Obstruction OR Pulmonary Emphysema

#3 Clinical Trial OR clinical study OR random control Trial OR random control study OR Controlled Trial OR Controlled study OR placebo control OR Multicenter Study OR random allocation OR double-blind OR single-blind OR blinding OR comparative study OR evaluation study OR follow-up study OR prospective study OR control group OR clinical research OR medical trial OR case control study OR intervention study

#4 #1 AND #2 AND #3

Chinese databases: Search by using simplified Chinese character

#1 Man Xing Zu Sai Xing Fei Bing (Chronic obstructive pulmonary disease) OR Man Xing Zu Sai Xing Fei Ji Bing (Chronic obstructive pulmonary disease) OR Man Zu Fei (Chronic obstructive pulmonary disease) OR Man Xing Zu Sai Xing Fei Bu Ji Bing (Chronic obstructive lung disease) OR COPD OR Zu Sai Xing Fei Ji Bing (Obstructive pulmonary disease) OR Zu Sai Xing Fei Bing (Obstructive pulmonary disease) OR Man Xing Zu Sai Xing Fei Qi Zhong (Chronic obstructive pulmonary emphysema) OR Zu Sai Xing Fei Qi Zhong (Obstructive pulmonary emphysema)

#2 Shen Ling Bai Zhu OR Pei Tu Sheng Jin (reinforcing earth to strengthen metal) OR Jian Pi Bu Fei (Reinforce the Spleen to benefit the Lung)

#3 #1 AND #2

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