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Herbal medicines for the treatment of COPD: a systematic review

R. Guo, M.H. Pittler and E. Ernst

ABSTRACT: The aim of the current study was to systematically assess the effectiveness of herbal medicines in treating chronic obstructive pulmonary disease (COPD).

Randomised clinical trials (RCTs) testing herbal medicines against any type of control intervention in patients with COPD and assessing clinically relevant outcomes were included. The selection of studies, data extraction and validation were performed independently by at least two reviewers. Methodological quality was evaluated using the Jadad score. Effect sizes and their 95% confidence intervals were calculated.

Fourteen eligible RCTs, testing 14 different herbal medicines, were located. Herbal medicines were compared against placebo or no treatment in six trials. Significant intergroup differences for one or more outcome were reported for several herbal medicines including *Panax ginseng* and *Salvia miltiorrhiza*. In seven RCTs, which compared herbal medicines with other herbal medicines, the results were mixed. A single trial compared a herbal medicine (*Hedera helix* leaf extract) with a conventional treatment (ambroxol tablet) and reported no significant difference between groups. Due to the heterogeneity of the data, statistical pooling was not performed. The median methodological quality score was 2 out of a possible maximum 5.

The effectiveness of herbal medicines for treating chronic obstructive pulmonary disease is not established beyond reasonable doubt. Currently, the evidence from randomised clinical trials is scarce and often methodologically weak. Considering the popularity of herbal medicine among chronic obstructive pulmonary disease patients, rigorously designed studies seem warranted.

KEYWORDS: Chronic bronchitis, chronic obstructive pulmonary disease, complementary therapy, herbal medicine

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Chronic obstructive pulmonary disease (COPD) is a group of conditions characterised by airflow obstruction [1]. Chronic bronchitis (CB) and emphysema are two major conditions within this group. COPD is a public health concern worldwide, and the prevalence of this disease is increasing. According to the World Health Organization report in 1998, COPD was the sixth leading cause of death and the twelfth most common cause of morbidity worldwide. Both the direct and indirect economic costs of COPD to the society are substantial. In the USA, 16 million people have symptomatic COPD incurring estimated total economic costs for COPD-related morbidity and mortality of US$23.9 billion [2]. In the UK, about 1.5 million patients suffer from COPD with a total annual cost to the National Health Service of ~£491 million for direct costs only and £982 million including indirect costs [1].

There is no cure for COPD [3]. Current conventional treatment is aimed at relieving symptoms, preventing recurrent exacerbations, preserving optimal lung function and enhancing the quality of life [4]. Smoking cessation is the only therapeutic intervention shown to reduce disease progression [5]. Although the conventional management of COPD has been improved since the 1990s, the progress is slow [6]. Unsatisfactory treatment outcomes from conventional drugs, and adverse effects associated with several classes of drugs, such as steroids and theophylline, contribute substantially to the increasing popularity of complementary and alternative medicine (CAM) and, in particular, herbal medicine [7].

There is a long history of using herbal remedies to treat COPD, particularly in China, India and other Asian countries. Herbal expectorants, based on extracts from *Hedera helix* (ivy) or *Thymus vulgaris* (thyme) also enjoy considerable popularity in many European countries [8]. Despite the popularity of herbal medicine, there has been no comprehensive systematic review of herbal medicines for treating COPD. The objective of the current review, therefore, was to systematically

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review the existing evidence on the effectiveness of herbal medicines for the treatment of COPD.

METHODS

All methods detailed below were according to a pre-defined, unpublished protocol.

Search strategy

Five electronic databases (AMED, MEDLINE, EMBASE, CINAHL and the Cochrane Library) were searched, from their respective inception to August 2005, without language restriction. Search terms were as follows: bronchitis, chronic obstructive pulmonary disease, COPD, acute exacerbation of chronic bronchitis (*i.e.* AECB), AECB, emphysema, herb*, botanic*, phyto*, Chinese medicine, plant extract*, plant preparation*, and individual common plant names and botanical names. Hand searches were performed in files and journals of the authors' own library. Three manufacturers of relevant herbal remedies were contacted and asked to contribute further information, particularly unpublished data. The bibliographies of all included trials and other relevant reviews were searched to identify further potential trials.

Study selection

The clinical trials included in this review had to be of herbal preparations administered systemically for CB, emphysema or COPD, in which patients of either sex and of any age were randomly assigned to receive either herbal medicines or control treatments (*i.e.* placebo, no treatment, conventional therapy or other herbal medicines). Only trials assessing clinical outcomes (*e.g.* forced expiratory volume in one second (FEV_1), global clinical assessment of effectiveness, symptom scores, health-related quality of life, exacerbation severity and frequency) were included. Trials including asthma patients were excluded.

Data extraction and methodological quality assessment

Titles and abstracts of identified articles were screened and full-text articles of potentially relevant trials were obtained. Articles in English and Chinese were read by R. Guo and articles in German by M.H. Pittler. These authors then discussed the articles and made decisions whether to include or exclude and, if needed, the third co-author (E. Ernst) was consulted. Data concerning the details of study design, participants, interventions, outcomes and adverse events were extracted from all included articles (R. Guo and M.H. Pittler). Missing data from one trial [9] were requested by contacting the author of the report. To date, a response has not been received.

The methodological quality of the included trials was assessed using the five-point scale developed by JADAD *et al.* [10]. This was done either independently by two authors (R. Guo and M.H. Pittler) for randomised clinical trails (RCTs) published in English or by discussion of the same two authors for RCTs published in German or Chinese.

Data analysis

The included RCTs were categorised according to the type of control intervention and the following comparisons were made. 1) Herbal medicine *versus* placebo or no treatment; 2) herbal medicine *versus* conventional therapy; and 3) herbal medicine *versus* herbal medicine.

Due to the inadequate reporting, the overall results were unclear in some trials. The effect sizes and the 95% confidence intervals (CI) of primary outcomes of each of the studies were therefore calculated (R. Guo). Most trials reported FEV_1 (in absolute volume or percentage of predicted value) as primary outcomes. Symptom scores and exacerbation frequency were also reported in some trials. Several Chinese trials reported the results of global assessment of effectiveness as the primary outcome measure. This was based on the ''Chinese National criteria for the clinical diagnosis and treatment evaluation of chronic bronchitis'' [11], where responses are categorised into four levels (excellent, good, moderate and no effect). The responder rates for the levels ''good'' and ''excellent'' were assessed. This was defined as the proportion of patients who met the following criteria: at least two of four symptoms (cough, sputum, dyspnoea and rale) disappeared and the other symptoms significantly improved, or at least three of the four symptoms significantly improved and the other symptom improved. Results for continuous data (FEV_1, vital capacity (VC), symptom score, and exacerbation frequency and severity) were calculated as weighted mean differences and results for dichotomous data (responder rate) were calculated as risk ratio (the proportion of the responders in the test group divided by the proportion of responders in the control group). These results are presented in table 1 and are summarised descriptively. Pooled results were not calculated because only single trials were located for each herbal intervention.

RESULTS

The current authors located a total of 529 potentially relevant titles and abstracts. Of these, 48 articles were obtained for detailed evaluation and 19 RCTs [9, 12–30] were subsequently identified for further analysis. No unpublished RCTs were located. Of the 19 RCTs identified for further analysis, five were excluded because they did not report clinically relevant outcomes [26, 27], did not test a herbal remedy [29], did not use a systemic route of administration [28], or included asthmatic patients [30]. Figure 1 provides a flowchart of all included and excluded trials.

Fourteen RCTs [9, 12–24] met all inclusion criteria and were assessed. The main characteristics of these studies are summarised in table 2. They originate from four countries (China, n=10; Germany, n=2; Switzerland, n=1; and Italy, n=1) and were published between 1991 and 2004 in three languages (Chinese, n=8; English, n=4; and German, n=2). A total of 1,359 subjects were randomised and 1,314 were analysed by the original investigators. Most of the trials studied herbal mixtures whereas four trials tested herbal monopreparations. Eleven studies included only adult subjects (three trials specified their subjects as senile), two included both children and adults, and one included children only. Patients were diagnosed as having COPD in five RCTs and CB in nine RCTs. In one RCT, patients were specified as being in remission whereas three other RCTs included patients in acute exacerbation.

The methodological quality of the trials was generally low with a median Jadad score of 2, ranging from 1 to 5 (tables 2 and 3).

TABLE 1 Summary of the results of all included randomised clinical trials

First author [ref.]	Intervention[#]		Outcomes and results: effect size[+]	Adverse events (cases)
	Test[¶]	Control		
Herbal medicine *versus* placebo or no treatment				
Wei [12]	Danshen injection	No treatment	Responder rate: RR 1.43 (0.93–2.21); FEV_1: WMD 0.53 (0.36–0.70)	Not reported
Zhao [13]	Jinshui Liujin decoction	No treatment	Responder rate: RR 1.42 (0.96–2.11); FEV_1(%): WMD 3.70 (-2.43–9.83); VC (%): WMD 2.5 (-8.18–13.18)	Not reported
Fang [14]	Shen Mai injection	No treatment	Responder rate: RR 3.90 (1.32–11.51); FEV_1: WMD 0.58 (0.19–0.97); VC: WMD 1.64 (0.98–2.30); symptom score (Borg): WMD -1.20 (-2.02– -0.30)	Dry mouth and constipation (individual)
Gross [9]	*Panax ginseng* extract capsule Ginsana®	Placebo	FEV_1, FVC, FEV_1/FVC. Insufficient data to estimate an effect size and 95% CI	None
Hauke [15]	Esberitox® N	Placebo	FEV_1(%): WMD 5.76 (-6.01–17.53)	Mild to moderate (test, n=8; control, n=11)
Huang [16]	Jiawei Yupingfeng	No treatment	Responder rate: RR 1.44 (0.80–2.58)	Not reported
Herbal medicine *versus* conventional medicine				
Meyer-Wegener [17]	Ivy leaf extract	Ambroxol tablets	VC: WMD 0.24 (-0.22–0.7)	13 events (test, n=7; control, n=6)
Herbal medicine *versus* herbal medicine				
Cheng [18]	Ke Chuan Ping decoction	Qing Jin Hua Tan decoction	Responder rate: RR 1.62 (1.00–2.61); FEV_1(%): WMD 1.92 (-2.86–6.7)	Not reported
Chen [19]	13-Herb anti-cough–dyspnoea decoction	Ephedra-almond decoction	Responder rate: RR 2.77 (1.96–3.93)	Not reported
Xu [20]	Yiqi Mianyi granule	Zhenqi Fuzheng granule	Responder rate: RR 1.96 (1.15–3.34); symptom score: WMD -2.70 (-5.57– -0.17)	Not reported
Gulyas [21]	Prospan® cough syrup	Prospan® herbal drops	FEV_1: WMD 0.01 (-0.03–0.05); VC: WMD 0.01 (-0.02–0.04)	Not reported
Mao [22]	Kesuning granule and placebo	Jinbei Tankeqing granule	Responder rate: RR 1.13 (0.82–1.56)	None
Liu [23]	Bufei Keli granule	Yupingfeng Keli granule	Responder rate: RR 1.71 (1.11–2.64); exacerbation severity: (symptom score): WMD -1.03 (-2.03– -0.03; days of exacerbation): WMD -7.20 (-11.50– -2.90);	Not reported
Wu [24]	Gubenhuatanquyu decoction	Buyiguben decoction	Symptom score: WMD -2.00 (-3.88– -0.12)	None

RR: risk ratio; FEV_1: forced expiratory volume in one second; WMD: weighted mean difference; FEV_1 (%): FEV_1 as percentage of predicted value; VC: vital capacity; FVC: forced vital capacity; FEV_1/FVC: FEV_1 as a percentage of FVC; 95% CI: 95% confidence interval. [#]: table 2 contains details of daily doses and any concomitant medications; [¶]: details of all named herbal medicines are given in the Appendix; [+]: 95% CI are given in parentheses.

Of the 14 included RCTs, only three [9, 16, 24] described the methods for randomisation and five [9, 15, 17, 21, 22] mentioned double blinding, of which only one [9] described the method of blinding appropriately. Details of dropouts and withdrawals were described in only five trials [9, 15, 17, 21, 24]. Only two trials [9, 15] were placebo controlled.

The 14 RCTs were categorised into three groups according to the type of control interventions. Detailed results are summarised in table 1 and described below. Information on the preparations, such as manufactures and compositions, can be found in the Appendix.

Herbal medicines versus *placebo or no treatment*

The current authors located a total of six RCTs that compared herbal medicines with placebo or no treatment. Two RCTs [9, 15] compared herbal medicines with placebo and the other four [12–14, 16] compared herbal medicines with no treatment.

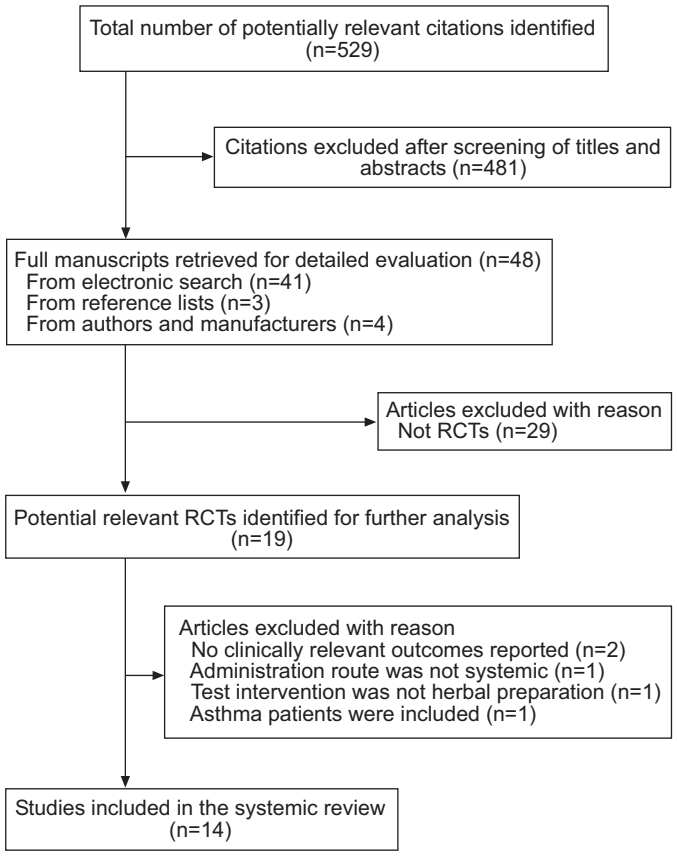

FIGURE 1. Flow chart of the study selection process. RCT: randomised clinical trial.

In all of these RCTs, both the experimental and the control groups received the same adjunctive treatment regimen with conventional therapies (table 2). Significant differences for pulmonary function, symptom score and/or responder rate were seen in several herbal remedies.

Panax ginseng

In one double-blind, placebo-controlled RCT [9], *Panax ginseng* (Ginsana®; Pharmaton SA, Basel, Switzerland) was found to be significantly superior to placebo in improving pulmonary functions, including FEV1. However, the available data were insufficient for effect size calculations. Another RCT [14] tested Shen Mai injection (Affiliated Pharmaceuticals of West China University, Chengdu, Sichuan, People's Republic of China), which is a combination preparation containing three herbs including *P. ginseng* as the main ingredient (see Appendix), against no treatment. Significant improvements were found in all outcomes, including pulmonary function tests (FEV1, VC), global clinical assessment of effectiveness (responder rate) [11] and the Borg scale symptom score.

Salvia miltiorrhiza

One RCT [12] tested *Salvia miltiorrhiza* injection (Danshen injection; Sichuan Ya-an Pharmaceuticals, Ya-an, Sichuan, People's Republic of China) against no treatment and found a significant improvement in FEV1. No significant difference in responder rate was found between treatment regiments.

Traditional Chinese herbal medicine

Two RCTs [13, 16] tested two traditional Chinese herbal medicine (TCHM) decoctions, Jinshui Liujin and Jiawei Yupingfeng (Appendix), against no treatment. In the Jiawei Yupingfeng trial [16], the responder rate in the TCHM group was found to be significantly higher compared with the no treatment group. In the Jinshui Liujin trial [13], the author reported significant improvement of all outcomes in both groups from baseline ($p<0.05$). Calculations of effect size and 95% CI showed no significant difference in any of the outcomes, including responder rate, FEV1 and VC, between groups.

Echinacea

One double-blind, placebo-controlled RCT [15] studied the effectiveness of Esberitox® N (Schaper and Brümmer GmbH & Co., Salzgitter, Germany), a liquid extract made from three herbs (Appendix), including Echinacea, as a supportive medication. Significant improvements in FEV1 were reported.

Herbal medicine versus *conventional therapy*

Only one RCT [17] was located that compared a herbal remedy with a conventional therapy. VC was assessed as the primary outcome. No statistically significant difference was seen between *H. helix* leaf extract (Prospan®) and ambroxol tablets (table 1).

Herbal medicine versus *herbal medicine*

Seven RCTs [18–24] compared one herbal medicine with another (table 1). One RCT [21] compared two forms of *H. helix* extract (Prospan® cough syrup and Prospan® herbal drops). No significant differences were found between groups in either FEV1 or VC. The other six RCTs tested one TCHM remedy against another. Five of these RCTs reported the results for the responder rate. Four trials [18, 19, 20, 23] showed positive results favouring test groups and one [22] showed no significant difference between groups. Only one trial [18] reported data for the pulmonary function test (FEV1), which showed no significant difference between groups. Two trials [24, 20] reported the results of symptom scores and both showed positive results favouring the test group. One trial [23] reported the assessment of exacerbation severity and frequency. The results suggested that both severity and frequency of exacerbation were significantly reduced in the test group compared with the control group.

Adverse events

Only five out of 14 trials included information on adverse events (AE). Two of these RCTs reported no AE in either group. The other studies reported mild-to-moderate AE with no further details (table 1).

DISCUSSION

The present study has identified several herbal remedies with the potential to improve pulmonary function, to relieve symptoms or to reduce exacerbation severity and frequency in the treatment of COPD. Studies on herbal products containing *P. ginseng*, *H. helix*, *S. miltiorrhiza* and some TCHM decoctions generated encouraging results. However, interpretation and extrapolation of these results are difficult for a number of reasons.

TABLE 2 Characteristics of all included randomised clinical trials

First author [ref.]	Design and quality[#]	Participants			Intervention and daily dose		Treatment duration/follow-up period days
		R/A[¶]	Diagnosis	Age range yrs	Experimental group[+]	Control group	
Cheng [**18**]	Single-blind parallel (1)	62/62 (31, 31)	CB	37–63	Ke Chuan Ping decoction, 170 g[§], *p.o.*	Qing Jin Hua Tan decoction, 118 g[§], *p.o.*	12/12
Chen [**19**]	Open parallel (1)	400/400 (300, 100)	CB	1–60	13-Herb anti-cough–dyspnoea decoction, 118 g[§], *p.o.*	Ephedra-almond decoction, 111 g[§], *p.o.*	10/10
Meyer-Wegener [**17**]	Double-blind parallel (3)	99/94 (49, 48)	CB	25–70	Prospan® drops, 60–100 drops, *p.o.*, and placebo tablets, three tablets (dosage not specified), *p.o.*	Ambroxol tablets, three tablets (dosage not specified) *p.o.*; and placebo solution, 60–100 drops, *p.o.*	28/28
Wei [**12**]	Open parallel (1)	53/53 (33, 20)	CB	52–71	Danshen injection, 20 mL in 250 mL 5% glucose, *i.v.* and ciprofloxacin, 0.4 g in 200 mL, *i.v.*; dexamethasone, 10 mg in 2 mL, *i.v.* for 3 days only; aminophylline, 0.8g, *p.o.*	Ciprofloxacin, 0.4 g in 200 mL *i.v.*; dexamethasone, 10 mg in 2 mL *i.v.* for 3 days only; aminophylline, 0.8 g, *p.o.*	10/10
Xu [**20**]	Open parallel (1)	102/102 (72, 30)	COPD	34–73	Yiqi Mianyi granule, 60 g, *p.o.*	Zhenqi fuzheng granule, 30 g, *p.o.*	30/30
Gulyas [**21**]	Double-blind cross-over (3)	27/25 (25, 25)	COPD	10–16	Prospan® syrup 15 mL (105 mg dried extract), and placebo drops	Prospan® drops, 60 drops (42 mg dried extract) and placebo syrup	10/10
Zhao [**13**]	Open parallel (1)	82/82 (41, 41)	CB	42–80	Jinshui Liujin patent decoction, 15 mL, *p.o.* and penicillin 28–32 million units *i.v.* for 7 days in severe cases (n=12)	Penicillin ~28–32 million units *i.v.* for 7 days; compound ammonium chloride decoction, 15 mL, *p.o.*	12/12
Fang [**14**]	Open parallel (1)	38/38 (20, 18)	COPD	66.4±6.2	Shen Mai injection (100 mL in 500 mL 5% glucose, *i.v.*) and conventional treatment: antitussive, bronchodilator, antibiotics and expectorant (daily dosage not specified)	Conventional treatment: antitussive, bronchodilator, antibiotics and expectorant (daily dosage not specified)	14/14
Gross [**9**]	Double-blind parallel (5)	100/92 (51, 41)	COPD	23–80	Ginseng extract capsules (Ginsana®; 200 mg) and "current medical treatment continued", *p.o.*	Placebo capsules and "current medical treatment continued" *p.o.*	90/90
Hauke [**15**]	Double-blind parallel (3)	53/52 (25, 27)	AECB	<75	Esberitox® N, 8.8 mL (3.8 mL alcoholic–aqueous extract) and macrolide antibiotic (mainly azithromycin), 500 mg for the first day, and then 250 mg for further 4 days *p.o.*	Placebo solution and macrolide antibiotic (mainly azithromycin), 500 mg for the first day and then 250 mg for further 4 days *p.o.*	28/90
Mao [**22**]	Double-blind parallel (2)	120/116 (60, 60)	AECB	18–70	Kesuning granule, 24 g, *p.o.* and placebo A, 21 g, *p.o.*	Jinbei Tankeqing granule, 21 g, *p.o.* and placebo B, 24 g, *p.o.*	6/6
Liu [**23**]	Open parallel (1)	62/62 (31, 31)	CB remission	23–74	Bufei Keli granule, 12 g, *p.o.*	Yupingfeng Keli granule, 15 g, *p.o.*	30/365
Wu [**24**]	Open parallel (3)	65/52 (34, 31)	COPD	46–74	Gubenhuatanquyu decoction, 180 g[§], *p.o.*	Simple Buyiguben decoction, 144 g[§], *p.o.*	90/90
Huang [**16**]	Open parallel (2)	84/84 (44, 40)	AECB	46–69	Jiawei Yupingfeng decoction 82 g[§] and cephradine 6 g, *i.v.*; kfloxacin 0.2 g *i.v.*; aminophylline, 0.6 g, *p.o.*; bromhexine, 48 mg, *p.o.*	Cephradine, 6 g *i.v.*; kfloxacin, 0.2 g *i.v.*; aminophylline, 0.6 g, *p.o.*; bromhexine, 48 mg, *p.o.*	14/14

Data are presented as range or mean±SD unless otherwise stated. R: number of patients randomised; A: number of patients analysed; CB: chronic bronchitis; COPD: chronic obstructive pulmonary disease; AECB: acute exacerbation of chronic bronchitis. [#]: The Jadad score (maximum of five points) is given in parentheses; [¶]: test, control is given in parentheses; [+]: details of all named herbal medicines are given in the Appendix; [§]: weight of dried raw herbal mixture.

TABLE 3 Details of quality assessment of included randomised clinical trials (RCTs)

First author [ref.]	Double blinded	Appropriate method for blinding	Appropriate method for randomisation	Details of dropouts and withdrawals described	Placebo controlled
Cheng [18]	N	NA	NR	NR	N
Chen [19]	N	NA	NR	NR	N
Meyer-Wegener [17]	Y	NR	NR	Y	N
Wei [12]	N	NA	NR	NR	N
Xu [20]	N	NA	NR	NR	N
Gulyas [21]	Y	NR	NR	Y	N
Zhao [13]	N	NA	NR	NR	N
Fang [14]	N	NA	NR	NR	N
Gross [9]	Y	Y	Y	Y	Y
Hauke [15]	Y	NR	NR	Y	Y
Mao [22]	Y	NR	NR	NR	N
Liu [23]	N	NA	NR	NR	N
Wu [24]	N	NA	Y	Y	N
Huang [17]	N	NA	Y	NR	N
RCTs with each design feature n	5	1	3	5	2

N: no; NA: not applicable; NR: not reported; Y: yes.

First, insufficient data are currently available for any specific herbal remedy. Only one trial was identified for each of the tested herbal interventions and most of these trials were of small sample size and none reported formal sample size or power calculations.

Secondly, the overall methodological quality of the studies is low (table 3). Blinding and randomisation are two essential features for minimising bias [31]. However, in this review, only five out of 14 RCTs were double blinded. Part of the reason for the lack of blinding may be the difficulty in finding a credible placebo that is indistinguishable in colour, taste and smell, and also pharmacologically inert in the conditions under investigation. This may be particularly problematic for herbal decoctions. Similarly, four trials compared herbal medicines against ''no treatment'', which does not account for placebo effects and is a source of bias. The method for randomisation was rarely described. In two RCTs [19, 20], there was a substantial difference between the numbers of patients in test and control groups. This could suggest that inappropriate methods of randomisation were used. These weaknesses, and the lack of descriptions of dropouts and withdrawals, contribute to the often low scores on the Jadad scale. The validity of some RCTs was further limited by failings to report the concealment of treatment allocation and details of statistical analysis, or inappropriate analyses.

Thirdly, seven RCTs compared a herbal medicine with another herbal medicine. Despite some positive results shown in these trials, interpretation is difficult due to the unknown effect of the control intervention.

Furthermore, quality control of the herbal extracts is important to ensure the reproducibility of the study. Of the 12 herbal preparations (excluding herbal decoctions) listed in the Appendix, data on extract standardisation are only available for one preparation. Details on the extract solvent were also only reported for one preparation.

Finally, the European Agency for the Evaluation of Medicinal Products recommended using both FEV_1 and a measure of symptomatic benefit as a combined primary outcome, and states that the end-point for symptomatic benefit should be justified by referencing published data that support its validity [32]. However, only one trial [14] used a referenced symptomatic benefit measure, in spite of the availability of a number of validated, well accepted and widely applied instruments, such as the St George's Respiratory Questionnaire [33] and Chronic Respiratory Questionnaire [34].

The increasing popularity and, particularly, the easy access to herbal remedies raises safety issues. The common assumption among consumers that herbal medicines are safe is dangerous. Herbal medicines might be linked to serious AE and herb–drug interaction may have serious clinical consequences [35]. Several relevant herbs, such as *Salvia milhiorrhiza*, *Glycyrrhiza uralensis*, *P. ginseng* and *Angelica sinensis* were reported to interact with a range of conventional medicines [36–38]. Unfortunately, in most of the included RCTs, AE were not monitored and herb–drug interactions were considered in none of the reports. The included studies involved a large number of individual herbs in various combinations (see Appendix). The AE and herb–drug interactions of most of these herbs and preparations are not well documented. Therefore, further studies on the safety of these remedies are required.

Limitations of the current review and, indeed, systematic reviews in general pertain to the potential incompleteness of the reviewed evidence. The distorting effects arising from publication bias and location bias are well documented [39–43]. In the current review, 10 out of 14 included RCTs were

published in China, a country which has been previously shown to produce large numbers of positive CAM studies [44]. For the current study, databases were searched with a focus on the American and European literature and those which specialise in complementary medicine, and included hand-searches. There were no restrictions in terms of publication language. The current authors are, therefore, confident that their search strategy has located most of the published trials on the subject. However, whether all unpublished trials were identified remains uncertain. A further limitation of this review is (as pointed out previously) the paucity and limited quality of the primary data.

Conclusion

The effectiveness of herbal medicines for treating chronic obstructive disease is not established beyond reasonable doubt. Currently, the evidence from randomised clinical trials is scarce and often methodologically weak. Considering the popularity of herbal medicine among chronic obstructive pulmonary disease patients, rigorously designed studies seems to be warranted.

REFERENCES

1 Chronic obstructive pulmonary disease – national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary NICE, secondary care, *Thorax* 2004; 59: Suppl. 1, 1–232.
2 Petty TL. Scope of the COPD problem in North America. *Chest* 2000; 117: Suppl. 2, 326S–331S.
3 Johannsen J. Chronic obstructive pulmonary disease: current comprehensive care for emphysema and bronchitis. *Nurse Pract* 1994; 19: 59–67.
4 Siafakas N, Vermeire P, Pride P, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8: 1398–1320.
5 Barnes PJ. Chronic obstructive pulmonary disease * 12: new treatments for COPD. *Thorax* 2003; 58: 803–808.
6 Gross NJ. The GOLD standard for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1047–1048.
7 George J, Ioannides DLL, Santamaria NM, Kong DC, Stewart K. Use of complementary and alternative medicines by patients with chronic obstructive pulmonary disease. *Med J Aust* 2004; 181: 248–251.
8 Ziment I. Complementary and alternative medicine therapies for chronic obstructive pulmonary disease. *Focus Alternat Complement Therap* 2003; 8: 385–391.
9 Gross D, Shenkman Z, Bleiberg B, Dayan M, Gittelson M, Efrat R. Ginseng improves pulmonary functions and exercise capacity in patients with COPD. *Monaldi Arch Chest Dis* 2002; 57: 242–246.
10 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
11 Criteria for the clinical diagnosis and treatment evaluation of chronic bronchitis – revised on the national conference of chronic bronchitis, *Zhong Hua Jie He He Hu Xi Za Zhi* 1980; 3: 61–62.
12 Wei ZM. Effects of injection *Salviae miltiorrhizae* on senile chronic asthmatic bronchitis patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1996; 16: 402–404.
13 Zhao CY, Shen YS, Meng H. Clinical and experimental study on Jinshui Liujun decoction in treating chronic bronchitis. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1997; 17: 264–266.
14 Fang Z, Jiang H, Wang L. Therapeutic effect of Shengmai injection on respiratory function in chronic obstructive pulmonary disease. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1998; 18: 520–522.
15 Hauke W, Köhler G, Henneicke Von Zepelin HH, Freudenstein J. Esberitox N as supportive therapy when providing standard antibiotic treatment in subjects with a severe bacterial infection acute exacerbation of chronic bronchitis: a multicentric, prospective, double-blind, placebo-controlled study. *Chemotherapy* 2002; 48: 259–266.
16 Huang HQ, Lu F, Lu SY. Effect of Jiawei Yupingfeng powder on T-lymphocyte subsets in patients with senile chronic bronchitis in acute onset stage. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2004; 24: 109–111.
17 Meyer-Wegener J, Liebscher K, Hettich M, Kastner HG. Ivy *versus* ambroxol in the treatment of chronic bronchitis: a double-blind comparative study of clinical efficacy and tolerance of ivy dried leaf extract and ambroxol. *Z Allg Med (Ind Med Gaz)* 1993; 69: 61–66.
18 Cheng CL. Clinical and experimental research on chronic bronchitis treated with Ke Chuan Ping decoction. *Zhong Xi Yi Jie He Za Zhi* 1991; 11: 203–205.
19 Chen YQ, Zhang YP. Analysis of clinical effect and experimental study of 13 herbs anti-cough–dyspnea decoction in the treatment of chronic bronchitis. *Zhongguo Zhong Xi YI Jie He Za Zhi* 1993; 13: 27–29.
20 Xu XY, Liu QR, Chen J. Clinical observation of Qi deficiency syndrome in 72 patients with chronic obstructive pulmonary disease treated with Yiqi Mianyi granule. *Zhongguo Zhong Xi YI Jie He Za Zhi* 1996; 16: 81–83.
21 Gulyas A, Repges R, Dethlefsen U. Therapy of chronic obstructive pulmonary diseases in children. *Atemwegs Lungenkr* 1997; 23: 291–294.
22 Mao B, Zhang RM, Li TQ. Clinical observation on effect of Kesuning granule in treating acute onset of chronic bronchitis. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2002; 22: 597–598.
23 Liu Y, Wang N, Wang N, Liu G, Yan H. Clinical observation in 31 cases of chronic bronchitis at remission stage treated with Bufei Keli. *J Tradit Chin Med* 2003; 23: 246–250.
24 Wu GZ, Liu HJ, Gao SF. Effect of Gubenhuataquyufa on plasma levels of nitric oxide and endothelin in chronic obstructive pulmonary disease patients during emission period: a randomized controlled study. *Chin J Clin Rehab* 2003; 7: 3352–3353.
25 Zhang JY. Clinical and experimental observations on chronic bronchitis treated with Pukeling. *Zhonghua Jie He He Hu Xi Xi Ji Bing Za Zhi* 1983; 6: 169–170.
26 Scaglione F. Immunomodulatory effects of Panax ginseng C.A. Meyer (G115) on alveolar macrophages from patients suffering with chronic bronchitis. *Int J Immunother* 1994; X: 21–24.

27 Scaglione F, Weiser K, Alessandria M. Effects of the standardised ginseng extract G115® in patients with chronic bronchitis: a nonblinded, randomised, comparative pilot study. *Clin Drug Invest* 2001; 21: 41–45.

28 Huo GR, Ma LQ, Huang CH. Clinical study on treatment of chronic bronchitis by tracheitis plaster. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001; 21: 816–818.

29 Habermann W, Zimmermann K, Skarabis H, Kunze R, Rusch V. The effect of a bacterial immunostimulant (human *Enterococcus faecalis* bacteria) on the occurrence of relapse in patients with chronic bronchitis. *Arzneimittelforschung* 2001; 51: 931–937.

30 Mansfeld H-J, , Hohre H, Repges R, Dethlefsen U. Klinische Studie: behandlung von Kindern mit chronisch obstrucktiven Atemwegserkrankungen mit Efeublättertrockenextrakt. [Clinical study: treatment for children with COPD using ivy extract.] *TW Pädiatrie* 1997; 10: 155–157.

31 Resch K-L, Ernst E. : Research methodologies in complementary medicine: making sure it works. *In*: Ernst E, ed. Complementary Medicine: An Objective Appraisal. Oxford, Butterworth, 1996.

32 EMEA. Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD). CPMP/EWP/562/98. London, EMEA, 1999.

33 Jones PW, Quirk FH, Baveystock CM, *et al*. A self complete measure for chronic airflow limitation: the St. Georges Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.

34 Guyatt GH, Berman LB, Townsend M, *et al*. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773–778.

35 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001; 61: 2163–2175.

36 Fugh-Berman A. Herb–drug interactions. *Lancet* 2000; 355: 134–138.

37 Izzo AA. Herb–drug interactions: an overview of the clinical evidence. *Fundam Clin Pharmacol* 2004; 19: 1–16.

38 Ioannides C. Pharmacokinetic interactions between herbal remedies and medicinal drugs. *Xenobiotica* 2002; 32: 451–478.

39 Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990; 263: 1385–1389.

40 Egger M, Davey Smith G. Bias in location and selection of studies. *BMJ* 1998; 316: 61–66.

41 Ernst E, Pittler M. Alternative therapy bias. *Nature* 1997; 385: 480.

42 Pittler M, Abbot N, Harkness E, Ernst E. Location bias in controlled clinical trials of complementary/alternative therapies. *J Clin Epidemiol* 2000; 53: 485–489.

43 Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997; 350: 326–329.

44 Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. *Control Clin Trials* 1998; 19: 159–166.

APPENDIX: COMPOSITION AND CHARACTERISTICS OF MEDICINAL HERBAL PREPARATIONS USED IN THE INCLUDED RANDOMISED CLINICAL TRIALS

Preparation name (formulation)	Manufacturer	Herbal concentration# or standardisation data	Extract solvent	Herbal composition
13-Herb anti-cough–dyspnoea (decoction)	NA	NA	NA	*Ephedra sinica*, *Poria cocos*, *Pinellia ternate*, *Prunus armeniaca*, *Citrus reticulata*, *Sinapis alba*, *Glycyrrhiza uralensis*, *Perilla frutescens*, *Baphicacanthus cusia*, *Trichosanthes kirilowii*, *Raphanus sativus*, *Zingiber officinale*, *Radix Glehniae*
Bufei Keli (granule)	Chengdu Ninth People's Hospital, Chengdu, Sechuan, People's Republic of China	Unclear	Unclear	*Astragalus membranaceus*, *Acanthopanax senticosus*, *Salvia miltiorrhiza*, *Cornus officinalis*
Danshen (injection)	Sichuan Ya-an Pharmaceuticals, Ya'an, Sichuan, People's Republic of China	1 mL/1.5 g	Not reported	*S. miltiorrhiza*
Prospan® (syrup)	Engelhard Arzneimittel GmbH & Co., Niederdorfelden, Germany	Unclear	Unclear	*Hedera helix*
Prospan® (liquid extract)	Engelhard Arzneimittel GmbH & Co.	Unclear	Unclear	*H. helix*
Ephedra-almond (decoction)	NA	NA	NA	*E. sinica*, *P. armeniaca*, *Calcium sulphate*, *G. uralensis*, *P. cocos*, *P. ternate*, *C. reticulata*, *Citrus aurantium*, *Bambusa breviflora*
Esberitox® N (liquid extract)	Schaper and Brümmer GmbH & Co., Salzgitter, Germany	1 mL/39 mg	Alcoholic-aqueous	*Herba Thujae occidentalis*, *Radix Echinaceae*, *Baptisiae tinctoriae*
Ginsana® (capsule)	Pharmaton SA, Lugano, Switzerland	1 mg G115® extract/4% total ginsenosides	Unclear	*Panax ginseng*

APPENDIX (continued)

Preparation name (formulation)	Manufacturer	Herbal concentration[#] or standardisation data	Extract solvent	Herbal composition
Gubenhuatanquyu (decoction)	NA	NA	NA	*Cordyceps sinensis*, *A. membranaceus*, *Codonopsis tangshen*, *P. cocos*, *Atractylodes macrocephala*, *Cuscuta chinensis*, *Eucommia ulmoides*, *P. armeniaca*, *S. miltiorrhiza*, *Angelica sinensis*
Jiawei Yupingfeng (decoction)	NA	NA	NA	*A. membranaceus*, *A. macrocephala*, *Radix Glehniae*, *Saposhnikovia divaricata*
Jinbei Tankeqing (granule)	Haerbin Shiyitang Pharmaceuticals, Haerbin, Heilonghiang, People's Republic of China	Unclear	Unclear	*P. armeniaca*, *Fritillaria verticillata*, *Lonicera hypoglauca*, *Houttuynia cordata*, *Bupleurum Chinese*
Jinshui Liujin (decoction)	NA	NA	NA	*Rehmannia glutinosa*, *P. ternate*, *A. sinensis*, *C. reticulata*, *P. cocos*, *G. uralensis*
Ke Chuan Ping (decoction)	NA	NA	NA	*Paris polyphlla*, *Scutellaria baicalensis*, *T. kirilowii*, *Aristolochia debilis*, *Pyrrosia drakeana*, *Dioscorea nipponica*, *Stemona sessilifolia*, *Pinellia ternate*, *Cyclinae sinensis*, *Polygonum tinctorium*, *E. sinica*, *C. reticulata pericarpium rubrum*
Kesuning (granule)	Hunan Wuma Pharmaceuticals, Changsha, Hunan, People's Republic of China	One sachet (8 g out of 30.7 g)	Unclear	*E. sinica*, *P. armeniaca*, *F. verticillata*, *Lonicera hypoglauca*, *Houttuynia cordata*
Qing Jin Hua Tan (decoction)	NA	NA	NA	*Gardenia jasminoides*, *Scutellaria baicalensis*, *T. kirilowii*, *Morus alba*, *C. reticulata pericarpium rubrum*, *Ophiopogon japonicus*, *Platycodon grandiflorum*, *F. verticillata*
Shen Mai (injection)	Affiliated Pharmaceuticals of West China University, Chengdu, Sichuan, People's Republic of China	1 mL/568 mg	Unclear	*Ophiopogon japonicus*, *P. ginseng*, *Schisandra chinensis*
Simple Buyiguben (decoction)	NA	NA	NA	*Cordyceps sinensis*, *A. membranaceus*, *Codonopsis tangshen*, *P. cocos*, *Atractylodes macrocephala*, *Cuscuta chinensis*, *Eucommia ulmoides*
Yiqi Mianyi (granule)	Affiliated Pharmaceuticals to Luzhou Medical School, Luzhou, Sichuan, People's Republic of China	1 g/1.17 g	Unclear	*Atractylodes macrocephala*, *P. cocos*, *C. officinalis*, *A. senticosus*, *P. ginseng*
Yupingfeng Keli (granule)	Guangdong Global Pharmaceuticals, Rongqi Town, Shunde, Guangdong, People's Republic of China	Unclear	Unclear	*A. membranaceus*, *Radix Glehniae*, *Saposhnikovia divaricata*
Zhenqi Fuzheng (granule)	Gansu Dingxi Pharmaceuticals, DingXi, Gansu, People's Republic of China	Unclear	Unclear	*A. membranaceus*, *Ligustrum lucidum*

NA: not available. [#]: Herbal concentration refers to the corresponding quantity of dried raw herbs in one unit (*e.g.* mL or mg) of the final product.