Anti-Inflammatory Effects of Chinese Herbal Medicine on COPD: A Systematic Review

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Abstract

Background: Airway inflammation and inflammatory mediators play an imperative role in the pathogenesis of COPD. Currently, understanding of the anti-inflammatory effect of Chinese herbal medicine (CHM) on COPD is limited, and CHM’s mechanism of actions is unclear. This systematic review (SR) evaluates anti-inflammatory effects of CHM on the concentration of various inflammatory mediators, such as Tumor Necrosis Factor-alpha (TNF-α) and interleukin-8 (IL-8), in the sputum and serum of COPD patients.

Methods: The studies chosen for this SR were obtained from Chinese and English databases. The study selection criteria were based on randomized, controlled trials of stable COPD patients on adjunct oral CHM; and the changes in concentration of inflammatory mediators post-treatment were analyzed via meta-analysis.

Results: 2,268 patients in 29 studies were evaluated. 2 studies were assessed to be of low-risk in all domains. The results showed significant reduction in the serum level of IL-8 (mean: -1.27 and 95% confidence interval [CI] [-1.86, -0.68]) and TNF-α (Mean: -0.72 and 95% CI [-1.01, -0.43]) in patients treated with CHM plus bronchodilators, compared to bronchodilators alone.

Conclusion: This SR explains CHM’s mechanism of action, and demonstrates CHM’s anti-inflammatory effects on patients with stable COPD.

Keywords: Chinese herbal medicine; Chronic obstructive pulmonary disease; Tumor necrosis factor-α; Interleukin-8; Systematic review

Abbreviations AE: Adverse Events; BALF: Bronchial Alveolar Lavage Fluid; CENTRA: Cochrane Central Register of Controlled Trials; CHM: Chinese herbal medicine; CI: Confidential Interval; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNKI: China National Knowledge Infrastructure; COPD: Chronic obstructive pulmonary disease; CONSORT: Consolidated Standards of Reporting Trials; CQVIP: Chongqing VIP; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IL-6: Interleukin-6; IL-8: Interleukin-8; MD: Mean Difference; MMP-9: Matrix Metalloproteinase-9; MOA: Mechanism Of Action; QoL: Quality of Life; PRISMA: Systematic Reviews and Meta-Analyses; RCTs: Randomized Controlled Trials; SR: Systematic Review; Std: MD: Standardized Mean Difference; TGF-β1: Transforming Growth Factor-β1; TNF-α: Tumor Necrosis Factor-alpha

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease with multiple pathogeneses [1]. Airway inflammation plays an imperative role in the pathogenesis of COPD. A wide range of inflammatory mediators are associated with COPD; interleukin-8 (IL-8), IL-6, Tumor Necrosis Factor-alpha (TNF-α), and matrix metalloproteinase (MMP-9) have been shown to induce neutrophil production, alveolar macrophages release, emphysema formation, and lung remodeling [2]. Compared to healthy subjects, patients with stable COPD had an increased expression of inflammatory mediators, particularly in sputum and serum [3,4]. In addition, these inflammatory mediators correlated with clinical outcomes of lung function, BODE index, frequency of COPD exacerbation, and severity and mortality of COPD [5-7].

The use of Chinese herbal medicine (CHM) as an adjunct therapy for COPD has been documented in more than one hundred clinical trials over the past decade. Previous systematic reviews (SR) have shown that oral CHM provided symptom relief, improved Quality of life (QoL) and lung function, and reduced frequency of COPD exacerbation [8,9]. However, understanding of CHM’s anti-inflammatory effects is limited and CHM’s mechanism of action (MOA) is not clear. This study aims to investigate the effects of CHM on inflammatory mediators in induced sputum and serum in patients with stable COPD, as well as its MOA.

Materials and Method

This SR was conducted by Standard for Systematic Review [10] and guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [11].

Search strategy included identifying search databases and search terms. Relevant studies were selected from both English and Chinese databases. English databases included PubMed, CINAHL, and CENTRAL (Cochrane Central Register of Controlled Trials); Chinese databases included CNKI, CQVIP and Wan fang. Appropriate search terms (per guideline of Cochrane Airways Group) were used to identify appropriate studies. Potential studies were chosen from their respective inceptions until August 2014, without language restrictions.

Search terms were identified through PubMed using medical subject headings (MeSH) relevant to COPD and from the Cochrane Airways Group Specialized Register of COPD trials. These terms were separated into those relevant to COPD, such as ‘Pulmonary disease,
chronic obstructive’ etc.; relevant to randomized clinical trials such as ‘Clinical trials’, ‘Randomized controlled trials’, etc.; relevant to Chinese medicine such as ‘Traditional Chinese Medicine’ and ‘Herbal Medicine’.

Study selection criteria

The criteria for study inclusion were based on study type, patient population, treatment method, and resulting outcomes. Studies that qualified for all previously stated criteria included: randomized controlled trials (RCTs) with a parallel group design; patients with stable COPD without complication of asthma, bronchiectasis, cor-pulmonale, or pulmonary hypertension; interventions that used oral administration of CHM; outcomes that focused on testing biomarkers of IL-8, TNF-α, in serum and sputum, transforming growth factor-β1 (TGF-β1), and IL-6 in serum.

Assessment of methodological quality

The methodological quality of each study’s risk-of-bias was assessed by Cochrane Collaboration, which consists of six domains: Sequence Generation, Allocation Concealment, Blinding Method and Outcomes Assessment, Incomplete Data, Selective Reporting and Other Bias [12]. The risk-of-bias of each study was evaluated as high, low or unclear. Selective Reporting was assessed by each study’s reporting protocol. Other Bias was assessed by comparing baseline data and method of statistical analysis in each respective study.

The quality of grading of recommendation

Grading of Recommendations Assessment, Development and Evaluation (GRADE) and GRADEpro [13] were used; the quality rating of each study was evaluated as high, moderate, low, or very low. Assessment of quality-of-evidence was based on Risk-of-Bias, Inconsistency, Indirectness, Imprecision, and Publication Bias. The Large Effect, Plausible Confounding Variables, and Dose-Response Gradient were evaluated as strongly supportive, weakly supportive, strongly oppose, or weakly oppose.

Outcome measure

The outcomes were mainly focused on the level of IL-8 examined and TNF-α in serum and sputum, and also involved the level of transforming growth factor-β1 (TGF-β1), and IL-6 in serum.

Data extraction and collection

The relevance of title, abstract, and citations were assessed by two reviewers. Full articles were assessed by two reviewers. The Methodological Quality was assessed by two reviewers, audited by a third reviewer. The decision making process to include potential studies was based on CONSORT (CONsolidated Standards of Reporting Trials) [14]. Details of each study’s treatment regimen were reported as RCTs using Consolidated Standards of Reporting Trials (CONSORT) [14].

Data synthesis and analysis

Datasets were analyzed with RevMan 5.3. The continuous data was expressed as Mean Difference (MD), standardized MD (Std. MD), and 95% Confidential Interval (CI). The model of Random Effects was applied for heterogeneity. All data sets were imported from RevMan and assessed by GRADEpro.

Results

3,886 potential studies were initially identified. 3,143 remained after duplicates were eliminated. Further screening resulted in the exclusion of 2,921 studies for various reasons: 323 were not RCTs (case reports, surveys, retrospective studies, etc.), 333 did not relate to COPD or had additional complications of respiratory failure, heart failure, pulmonary hypertension or cor-pulmonale, 94 had inappropriate treatment regimen, 965 did not include biomarkers in its outcomes, 212 were non-human trials, 807 were review articles, and 187 used non-CHM adjunct therapy. Of the 222 remaining studies, 81 did not administer oral CHM, 66 did not include desired outcomes, and 3 had patients with non-stable COPD (such as COPD exacerbation or unidentified COPD courses) as well as 3 others. 29 studies met all required criteria, and were retrieved and analyzed in this SR (Figure 1).

Demographic information

Of the twenty nine studies, 27 were conducted in China and 2 in Japan. All of them were designed as parallel RCTs. Participants in each study were diagnosed with stable COPD, in accordance with the GOLD guideline modified by the CSRD [15]. Six studies [16-21] were done in out-patient settings only; one study [22] was in in-patient setting only, and five studies included participants in both out-patient and in-patient settings. Average age of participates ranged from 54.3 ± 4.7 to 72 in all studies except three, which did not specify age range [23-25]. 2,268 subjects were randomly selected and 2,193 subjects completed the entirety of their respective assessments, 75 subjects withdrew. 1,359 male subjects and 709 female subjects were identified, with the exception of two studies that did not include the gender of the participants [24,26]. Five studies identified the severity of COPD of their subjects as mild, moderate, or severe based on the GOLD guideline [19,27-30]. Seventeen studies defined COPD’s Differentiation of Syndrome in Chinese Medicine (CM) to be: lung and spleen qi deficiency [19,20,31-33], lung and kidney qi deficiency [21,22,27-29,34,35], or qi deficiency and blood stasis [17,23,30,36,37]; while other studies did not clearly define its differentiation of syndromes. Duration of treatment varied from: six months in seven studies [18,24,26,29,33-35], three months in nine studies [17,19-21,23,27,28,30,37], two months in six studies [16,19,22,31,38,39], six weeks in one study [40], one month in five studies [25,36,41-43], and two weeks in one study [44] (Table 1).

Intervention

Medication regimens were based on GOLD guideline for management of patient with stable COPD [45]. Bronchodilators such as inhaled beta-2-agonists (salbutamol and salmeterol), anticholinergics (Tiotropium bromide), or theophylline tablets with salmeterol/fluticasone propionate were used as mainstay treatments. Experimental groups consisted of CHM formulae or extraction of a single Chinese herb plus one drug of any category of bronchodilators. Control groups consisted of one drug of any category of bronchodilators alone or with placebo.

Oral forms of CHM formulae include oral liquid, capsules, granules, powder, or decoctions; their respective dosages are shown in Table 2. In seven studies [19,27,29,33,35,41,43], the CHM formula was produced as granule or capsule by pharmaceutical companies certified with Good Manufacturing Practice with strict quality control. Each CHM formula is comprised of 1 to 16 herbs, from a total of 77 different kinds of herbs. The most commonly used herbs in all studies were Huang Qi (Astragalus membranaceus), Gan Cao (Glycyrrhiza uralensis), Chen Pi (Citrus reticulate), Dang Shen (Codonopsis pilosula), Di Huang (Rehmannia glutinosa) and Fu Ling (Poria cocos) (Table 2).

Assessment of methodological quality

Sequence Generation in thirteen studies [16-18,21,27,29,31-33,35-37,42] were low risk. Allocation Concealment in three studies [27,31,40]
| First author, Reference No. | Location          | Out/in patients | No. subjects (R/A) | No. M/F | Age Mean SD (years) | *Severity of COPD/ No. subjects | *CMSD | COPD history (years) |
|----------------------------|-------------------|-----------------|-------------------|---------|----------------------|---------------------------------|-------|----------------------|
| Guo et al. [17]            | Tianjin           | Out             | T: 70/69 C: 70/61 | T: 41/28 C: 39/22 | T:60.8 ± 1.18 C:60.91 ± 11.03 | NS                               | Deficiency of Lung and Spleen Qi | T: 14.56 ± 6.32 C:14.52 ± 5.96 |
| Su et al. [23]             | Beijing           |                 | T: 35/35 C: 37/37 | T:16/19 C:18/19   | T:60.6 ± 8.9 C:56.6 ± 8.8     | NS                               | Deficiency of Qi and sputum blood stasis | T: 12.36 ± 6.2 C:12.74 ± 6.5 |
| Wang et al. [29]           | Shanghai          |                 | T1:109/82 T2:109/89 C:113/91 | T:64.7 ± 7.5 C:63.2 ± 5.4 | NS | Yln deficiency of Lung and Kidney | NS |
| Wang et al. [28]           | Luiyang, Huangan  |                 | T:30/30 C:30/30 | T:16/14 C:18/12   | T:65.22 ± 2.45 C:62.75 ± 3.66 | NS | Deficiency of Lung and Kidney | T:12.57 ± 8.39 T2:12.75 ± 8.95 |
| Xiao et al. [27]           | Guangzhou, Guangdong |               | T:34/34 C:31/31 | T:26/8 C:25/6     | T:62.3 ± 7.11 C:64.6 ± 8.62 | NS | Deficiency of Lung and Kidney | NS |
| Xiong et al. [34]          | Shenzhen          |                 | T:30/30 C:30/30 | T:20/10 C:21/9    | T:72 ± 11 C:71 ± 8 | NS | Deficiency of Lung and Kidney | NS |
**Table 1:** The characteristics of each study.

| Study                | Location               | Syndrome | Treatment | Control | TNS Mean ± SD | P-value | Diagnosis          |
|----------------------|------------------------|----------|-----------|---------|---------------|---------|--------------------|
| Zhang et al. [33]    | Zhengzhou, Henan       | NS       | T: 35/34  | C: 35/34| 76.7 ± 7.8    | NS      | Deficiency of Lung and Spleen Qi |
| Zheng et al. [35]    | Xining, Henan          | NS       | T: 30/30  | C: 30/30| 75.5 ± 5.6    | NS      | Deficiency of Lung and Kidney Qi |
| Zheng [43]           | Tangshan, Hebei        | Both     | T: 45/45  | C: 45/45| 75.2 ± 5.1    | NS      | Deficiency of Lung and Kidney Qi |
| Zhong et al. [21]    | Shenzhen, Zhejiang     | Out      | T: 35/35  | C: 35/35| 75.0 ± 5.0    | NS      | Deficiency of Lung and Kidney Qi |

R: Randomized; A: Analyzed; T: Treatment; C: Control; *Severity of COPD: I-Mild; II-Moderate; III-Severe; CMSD: Chinese Medicine Syndrome Differentiation

**Figure 1:** The process of selection of studies.
| First author, date | Intervention | Formula name (form) | Dosage regimen | Qualitative testing | Plus bronchodilators | *TD | outcomes |
|-------------------|-------------|---------------------|----------------|--------------------|----------------------|-----|----------|
| Cao [38]          | Xiaoangling Decoction | Baisha10 g, Banxia10 g, Gancao10 g, Ganjiang10 g, Guizh10 g, Mahuang10 g, Wuwei20 g, Xuxin10 g | 1 Dose, BID | Hospital | Salmeterol/ fluticasone | 2 mths | Lung function, *MMP-9 |
| Che et al. [40]   | ZhikeQingfei Oral liquid (10 ml oral liquid contains) | Banlangen1.67 g, Gancao1.67 g, Huangqi1.67 g, Jiujinhua1.67 g, Jiegen0.83 g, Kuandonghua0.67 g, Liangqiao0.83 g, Mahuang0.5 g, Pipaiy 0.83 g, Yuxingcao 0.83 g, Zizan 0.67 g | 20 ml, TID | Hospital | Bronchodilators | 6 wks | Lung function |
| Du et al. [16]    | Yinxiangy extract tablet: Ginkgo biloba extract | 2 Tablets, TID | Hospital | No | 2 mths | Lung function |
| Huang [18]        | BufeiYianghuatanggranules: Bajitai, Chuanbei, Dangshen, Duzhong, Gouji, Huanghuadouchuan, Huangqi, Juj, Maimeng, Pipaiye, Sangbai, Wuwei, Yipichou, Yuxingcao .Zizan | 20 g, BID | Hospital | Bronchodilators | 6 mths | NS |
| Lu et al. [20]    | Lijunzi Decoction contains (150 ml): Baizhu 9 g, Banxia 9 g, Chenpi 6 g, Dangshen 15 g, Huangqi 15 g, Kuandonghua 10 g, Sangbaipi 10 g, Tusizi 10 g, Xuanshen 10 g, Zizune 9 g | 150 ml, BID | Hospital | Bronchodilators | 3 mths | Sputum *HDACs activity |
| Wang et al. [31]  | YifeiJianpi Fang: Decoction (1 dose contains): Baizhu 15 g, Banxia 15 g, Chenpi 10 g, Dangshen15 g, Dilong 8 g, Fangfeng 10 g, Fuling 10 g, Gancao 10 g, Kuandonghua 10 g | 1 Dose, BID | Hospital | Bronchodilators | 2 mths | Lung function |
| Xiao et al. [39]  | ManzhiKechuanling: Oral liquid: Baizhu, Banxia, Buguzhi, Chuanbei, Ejiqao, Fuling, Gancao, Gejie, Hetaorou, Huangqi, Jupi, Maimendong, Pipaye, Bajitian, Chuanbeimu, Ejiao, Fuling, Gancao, Gejie, Zizun | 10 ml, BID | Hospital | Bronchodilators | 2 mths | MMP-9 |
| Zhou et al. [25]  | FeisaitongHeji: Oral liquid (100 ml contains): Chantai 9 g, Danshen 30 g, Dilong 12 g, Gancao 6 g, Huangqi 30 g, Jiegen9 g, Jinyinhua 18 g, Laifuzi 12 g, Shashen 18 g, Yiyiren 30 g, Zizun 9 g | 100 ml, TID | Hospital | Bronchodilators | 1 mth | Lung function, Syndromes |

**Studies with sputum test**

| First author, date | Intervention | Formula name (form) | Dosage regimen | Qualitative testing | Plus bronchodilators | *TD | outcomes |
|-------------------|-------------|---------------------|----------------|--------------------|----------------------|-----|----------|
| Chen et al. [37]  | BufeiHuxue Decoction (dose contains): Banxia 10 g, Chuanxiong 15 g, Danggui 10 g, Dihuang 20 g, Dilong 10 g, Fuling 15 g, Gancao 6 g, Honghua 6 g, Huanghui 15 g, Huangjing 20 g, Huangqi 30 g, Kuandonghua 10 g, Sangbaipi 10 g, Tusizi 9 g, Xuanshen 10 g | 1 Dose, QD | Hospital | No | 3 mths | Lung function, *6 MWD, *CAT, *SGRQ |
| Cheng et al. [41] | SuhuanguZhike Capsule: Dilong, Mahuang, Niubangzi, Qianhu, Wuwei, Zisu | 3 Capsules, TID | Yangzhe River Pharmaceutical Group | No | 1 mth | Lung function |
| Feng et al. [30]  | Qi-replenishing Blood-activating and Phlegm-removing Decoction: Huangqi, Shuizhi, Banxia, Dilong | 1 Dose, BID | Hospital | Bronchodilators | 3 mths | Quality of life, |
| Fu et al. [42]    | Bufei granules: Chenp, Dangshen, Dihuang, Mahuang, Shanzhuyu, Zizun | 16 g, BID | Hospital | No | 1 mth | *TCM syndromes |
| Guo et al. [17]   | Bufei granules: Banxia, Chenpi, Chishao, Danggui, Dangshen, Dihuang, Gancao, Huangqin, Mahuang, Shanzhuyu, Zizun | 16 g, BID | Hospital | No | 3 mths | NS |
| Hu [22]           | Jiajianbufei Decoction: Baibu10 g, Baijilan15 g, Buguzhi15 g, Chenpi 12 g, Dangshen 15 g, Danshen, Huangqi 20 g, Jiejeng 10 g, Maimeng10 g, Sangbai10 g, Tusi10 g, Xuanshen10 g | 1 Dose, QD | Hospital | Inhaled albuterol & Aminophylline Sustained release tablets | 2 mths | Lung function |
| Jiang et al. [44] | BufenNashen Decoction: Every dose contains: Chenhuiyang 10 g, Songshen20 g, Dihuang20 g, Fuling15 g, Gancao 6 g, Gejei 1 pair, Huangqi 20 g, Sangbai 15 g, Wuwei 15 g, Zizun15 g | 2 Doses, QD | Hospital | Salmeterol/ fluticasone | 2 wks | Lung function |
| Li et al. [36]    | SanyiYanggui Decoction &Shengqingxi Decoction: Baijie 20 g, Baisha15 g, Chuanxiong15 g, Danggui10 g, Dihuang10 g, Honghui10 g, Laifuzi10 g, Taoren15 g, Zizun15 g | 150 ml, QD | Hospital | Aminophylline Sustained release tablets | 1 mth | Lung function |
| Li et al. [19]    | YiQiJianghuatangDecoction: Baizhu, Banxia, Chenpi, Dangshen, Huangqi, Xingren | 1 Dose, BID | Jiangyi Tianshan Pharmaceutical Co | Bronchodilators | 3 mths | SGRQ |
| Ou et al. [32]    | Jiajianbufei Decoction: Huangqi 20 g, Huangshen 15 g, Ganprog 15 g, Banxia 10 g, Sangbai 10 g | 300 ml, QD | Hospital | Bronchodilators | 3 mths | Lung function, TCM syndromes |
| Shinozuka et al. [26] | Hochuukito extract (BuzhongYiqi Tang): 7.5 g extract | 2.5 g, TID | Hospital | No | 6 mths | Lung function |
| Su et al. [23]    | Feixiang Granules: Huangqi, Haiqingqiao | 10 g, TID | Hospital | No | 3 mths | Lung function |

*TD: Therapeutic drug; MMP-9: Matrix metalloproteinase-9; HDACs: Histone deacetylases; +*: p < 0.05, ***: p < 0.01, ***: p < 0.001, NS: Not significant.
Table 1: Intervention of included studies.

| First author, date | Intervention | Formula name (form) | Dosage regimen | Qualitative testing | Plus bronchodilators | *TD | outcomes |
|------------------|--------------|---------------------|----------------|-------------------|---------------------|-----|----------|
| Tatsmi et al. [24] | Hochuekkito extract(BuzhongYiqi Tang): 7.5 g extract | 2.5 g, TID | NS | Bronchodilators | 6 mths | Lung function, SGRQ |
| Wang et al. [29] | BushenFangchuan tablet, BushenYiqi granule | 5 tablets, TID & 1 Bag, BID | The 2nd TCM manufactury of Taji Group &Tianjiang Pharmacy company Ltd | Inhaled albuterol | 6 mths | 6 MWD, lung function, AEF, BODE SGRQ |
| Wang et al. [28] | FufangYishenDuji Capsule (0.7 g); Dangshen15 g , Wuweizhi10 g , Maidong 10 g , Baihu10 g , Xingren10 g, Duthong10 g , Ma huang 8 g , Yi yiren 20 g, Kuandonghua10 g, Zisu10 g , Chenxiang 3 g, Baijei10 g, Bais hao10 g, Baihe,10 g Hupo10 g, Shanzhuyu 15 g | 0.7 g, TID | Hospital | Tirotropium Brome Powder | 3 mths | SGRQ, TCM syndromes |
| Xiao et al. [27] | ZhengqiFuzheng granules: Huangqi, Nvzhenzi | 15 g, BID | Xiu zheng Pharmaceutical Group | Bronchodilators | 3 mths | Lung function, TCM syndromes |
| Xiong et al. [34] | Shenjie powder: Gejie, Ren shen | 5 g, BID | Hospital | Salmeterol/ fluticasone propionate | 6 mths | Lung function |
| Zhang et al. [33] | Fixed prescription of TCM therapy: Granules: | 3 Bags, TID | Jiangyin Tianjiang Pharmaceutical Co. | No | 6 mths | T-cell subset numbers |
| Zhao et al. [35] | Bailing Capsule: Fermentation of cordycepsinensis powder | 1.0 g, TID | East China Pharmaceutical Group Limited Co | Inhaled albuterol | 6 mths | 6 MWD, lung function |
| Li et al. [43] | Jinsihuo Bao capsule: Fermentation of cordycepsinensis powder | 3 capsules (0.99 g), TID | Jiangxi Jinmeixin Group Co | Bronchodilators | 1 mths | NS |
| Zhong et al. [21] | JiweiniushuiJiunian Decoction: Dangshen15 g, Huang qi 20 g, Banxia 10 g, Dang gui 10 g, Dihuang 20 g, Fuling 10 g, Shen jiang 5 g, Gan cao 5 g, Wuweizi 5 g | 100 ml, BID | Hospital | Aminophylline Sustained release tablets | 3 mths | Syndromes, Amount of sputum |

Due to the usage of both Enzyme-Linked Immunosorbent Assay and Radioimmunoassay, the different units were converted and consolidated based on the Wang study before the meta-analysis [29].

**Results of serum level of IL-8, TNF-α, IL-6 and TGF-β1**

The serum level of IL-8 was analyzed in ten studies with 1,020 participants. Wang 2014 [29] was a three-arm clinical trial that compared the control group with two CHM groups. The data from Wang 2014 was used twice. Figure 3 showed that the serum level of IL-8 was significantly reduced in eleven studies with 1,111 patients [17,21,28,29,32-37,41] (MD=1.26, CI [-1.24, -0.38]) (p<0.0001). In eight studies with 648 participants, the serum level of TNF-α was found to be significantly reduced [17,21,22,27,32,33,36,43] (MD=0.72, CI [-0.79, -0.65]) (p<0.0001) (Figure 4).

In five studies with 602 participants, the serum level of IL-6 was found to be significantly reduced [17,21,22,27,32,33,36,43] (MD=0.72, CI [-0.79, -0.65]) (p<0.0001) (Figure 4).

In four studies with 552 participants, the serum level of TGF-β1 was found to be significant reduced [17,19,29,43]. Figure 3 shows six studies with 643 patients. The data was used from Wang [29] twice (MD=0.72, CI [-0.79, -0.65]) (p<0.0001) (Figure 6).

**Assessment of the quality of grading of recommendation**

The quality of Grading of Recommendation for the serum concentration of IL-8, TNF-α, TGF-β1, IL-6, and the sputum concentration of IL-8 was assessed as moderate level. The sputum concentration of TNF-α was assessed as low level due to its sample size (Table 3).

**Outcomes**

In twenty two studies with 1,755 participants, the serum level of IL-8, TNF-α, TGF-β1, and IL-6 were analyzed. Sputum levels of IL-8 and TNF-α were tested and reported in eight studies with 498 participants. Sputum level of IL-10 and MMP-9 was tested in one study [38]. The original data of IL-8, IL-6, TNF-α, and TGF-β1 were not included in four studies, and therefore not analyzed in the meta-analysis [23,24,26,30].
Figure 2: The assessment of risk of bias of 29 studies.

| Study or Subgroup | Mean SD Total | Mean SD Total | Weight IV Random, 95% CI | Mean Difference IV Random, 95% CI |
|-------------------|--------------|--------------|--------------------------|----------------------------------|
| CHM plus bronchodilators VS bronchodilators (Serum IL-8) |
| Chen 2014         | 1.93 0.74    | 36 2.84 0.72 | 38 8.9%                   | -0.71 [-1.05, -0.37]             |
| Cheng 2013        | 4.98 1.8     | 40 5.96 2    | 40 7.7%                   | -1.97 [-2.82, -1.12]             |
| Guo 2014          | 2.01 0.45    | 69 5.43 1.89 | 61 8.6%                   | -0.42 [-1.10, 0.26]              |
| Li 2013 (1)       | 2.64 1.59    | 49 3.71 1.78 | 48 9.2%                   | -1.07 [-1.74, -0.40]             |
| Ou 2013           | 7.34 1.02    | 30 9.84 0.84 | 30 8.6%                   | -2.50 [-3.29, -1.70]             |
| Wang 2011         | 5.68 0.95    | 30 5.32 0.64 | 30 8.7%                   | -0.76 [-1.17, -0.36]             |
| Wang 2014         | 4.66 1.83    | 89 4.87 1.92 | 91 8.5%                   | 0.29 [0.26, 0.32]                |
| Wang 2014         | 5 2.03      | 82 4.87 1.92 | 91 8.4%                   | 0.33 [0.26, 0.40]                |
| Xiong 2008        | 1.98 0.23    | 30 3.02 0.63 | 30 9.0%                   | -1.04 [-1.29, -0.79]             |
| Zhang 2013        | 3.55 0.84    | 36 3.63 0.53 | 38 8.9%                   | -0.46 [0.07, -0.86]              |
| Zhao 2012         | 7.09 2.68    | 30 9.94 2.65 | 30 6.2%                   | -1.73 [-3.10, -0.36]             |
| Zhen 2012         | 9.64 1.04    | 35 12.02 1.08 | 35 8.6%                   | -2.36 [-2.87, -1.85]             |
| Subtotal (95% CI) | 554          | 557 100.0%   | -1.27 [-1.86, -0.68]      |

Heterogeneity: Tau² = 1.00; Ch² = 214.02, df = 11 (P < 0.00001); P = 95%
Test for overall effect: Z = 4.21 (P < 0.0001)

Figure 3: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum IL-8 at the end of treatment as the outcome.

| Study or Subgroup | Mean SD Total | Mean SD Total | Weight IV Random, 95% CI | Mean Difference IV Random, 95% CI |
|-------------------|--------------|--------------|--------------------------|----------------------------------|
| CHM plus bronchodilators VS bronchodilators (Serum TNF-α) |
| Guo 2014          | 1.21 0.13    | 69 2.89 0.78 | 61 12.5%                  | -1.14 [-1.68, -0.60]             |
| Hu 2009           | 2.54 0.32    | 35 2.79 0.36 | 32 13.0%                  | -0.45 [-0.65, -0.24]             |
| Li 2013 (1)       | 1.74 1.14    | 43 2.59 1.45 | 48 6.8%                   | -0.86 [-1.17, -0.55]             |
| Ou 2013           | 5.74 1.68    | 30 7.05 0.48 | 30 11.4%                  | -1.31 [-1.70, -0.92]             |
| Xiao 2014         | 4.06 0.65    | 34 4.32 0.72 | 31 12.0%                  | -0.25 [0.00, 0.50]               |
| Zhang 2013        | 1.11 0.36    | 34 1.6 0.69  | 35 11.8%                  | -0.41 [0.08, -0.74]              |
| Zhong 2010        | 1.99 0.36    | 45 2.59 0.62 | 45 13.1%                  | -0.60 [0.04, -0.18]              |
| Zhong 2012        | 2.53 0.04    | 35 2.89 0.05 | 35 14.5%                  | -0.46 [0.05, -0.91]              |
| Subtotal (95% CI) | 331          | 317 100.0%   | -0.72 [-1.01, -0.43]      |

Heterogeneity: Tau² = 0.15; Ch² = 121.94, df = 7 (P < 0.00001); P = 94%
Test for overall effect: Z = 4.90 (P < 0.0001)

Figure 4: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum TNF-α at the end of treatment as the outcome.
Quality assessment

| Quality assessment | No of patients | Effect | Quality |
|--------------------|----------------|--------|---------|
| Serum IL-8 (Better indicated by lower values) | 11 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 1.27 lower | MD 0.27 lower | MODERATE |
| Control 0.68 lower | MD 0.68 lower | MODERATE |
| Absolute | 554 | 557 | |
| Serum TNF-α (Better indicated by lower values) | 8 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 0.72 lower | MD 0.72 lower | MODERATE |
| Control 0.43 lower | MD 0.43 lower | MODERATE |
| Absolute | 331 | 317 | |
| Serum IL-6 (Better indicated by lower values) | 5 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 1 lower | MD 1 lower | MODERATE |
| Control 0.1 lower | MD 0.1 lower | MODERATE |
| Absolute | 349 | 344 | |
| Serum TGF-β1 (Better indicated by lower values) | 4 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 278.66 lower | MD 278.66 lower | MODERATE |
| Control 96.75 lower | MD 96.75 lower | MODERATE |
| Absolute | 320 | 323 | |
| Sputum IL-8 (Better indicated by lower values) | 7 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 0.88 lower | MD 0.88 lower | MODERATE |
| Control 0.31 lower | MD 0.31 lower | MODERATE |
| Absolute | 221 | 217 | |
| Sputum TNF-α (Better indicated by lower values) | 4 | Serious | Serious |
| Inconsistency | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Indirectness | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Imprecision | No serious | No serious | Reduced effect for RR>>1 or RR<<1 |
| Other considerations | CHM 1.05 lower | MD 1.05 lower | LOW |
| Control 0.13 lower | MD 0.13 lower | LOW |
| Absolute | 103 | 103 | |

*Allocation concealment in majority of studies was unclear; ITT was not applied in some incomplete data analysis

*Heterogeneity was high

*Severity of COPD and duration of treatment

*The sample size was small

Table 3: The quality of grading of recommendation assessment by GRADE pro.

Figure 5: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum IL-6 at the end of treatment as the outcome.

Figure 6: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum TGF-β1 at the end of treatment as the outcome.
Results of sputum level of IL-8 and TNF-α

In seven studies with 438 participants, the sputum level of IL-8 was found to be significantly reduced [16,18,20,31,38-40] (MD -0.88, 95% CI [-1.45, -0.31]) (p=0.002) (Figure 7).

In four studies with 206 participants, the sputum level of TNF-α was found to be significantly reduced [20,25,31,40]. Due to the wide range of values of TNF-α among these studies, Std.MD was used in the analysis (Std.MD -1.05, 95% CI [-1.97, -0.13]) (p=0.02) (Figure 8).

Adverse events

Minor adverse events (AEs), such as abdominal distension, were found in five patients in one study [40]; two studies reported no AEs [16,24]; Wang [29] reported similar percentage ratio of subjects that experienced AEs. The remaining studies did not mention occurrence of AEs.

Discussion

This SR included 29 RCTs, and focused on the change in concentration levels of inflammatory mediators in both serum and sputum in patients with stable COPD. The experimental group received oral CHM (in the form of pill, tablet, granule, capsule, or decoction) plus bronchodilators (per GOLD guideline). The control group received bronchodilators, either alone or with placebo. Six studies were found in English databases and twenty three in Chinese databases. Twenty seven studies were conducted in China and two in Japan.

The methodological quality was of low risk-of-bias for all domains in two studies. The quality of evidence was assessed as low by GRADEpro for the meta-analysis of TNF-α in induced sputum, and moderate for other inflammatory mediators.

The study findings indicated that certain CHM formulae appear to reduce systemic inflammatory response in patients with stable COPD. A significant reduction in the concentration of IL-8, IL-6, and TNF-α, and TGF-β1 in serum, and IL-8 and TNF-α in induced sputum were found in the experimental groups compared to control groups. In addition, a statistically significant higher heterogeneity rate was also found through meta-analysis, which maybe correlated to the duration of intervention, severity of COPD, various differentiation syndromes, usage of various bronchodilators, and subject population in each trial. Further sub-analysis was not conducted in this SR due to limitation of high amount of studies.

Three RCTs reported a change in the concentration level of IL-8, IL-6, MMP-9, and TNF-α in induced sputum for stable COPD patients treated with salmeterol/fluticasone, roflumilast, and nutritional supplementation [46-48]; improvement to lung function and quality of life were also observed in the same studies. Therefore, the reduced level of inflammatory mediators in either induced sputum or serum may have caused a decrease in airway inflammation, which presumably explains the MOA.
TGF-α, IL-8 in serum, and lung function were assessed in twelve studies [22-24,26,27,29,32,34-37,41]. The QoL was assessed by the St. George Respiratory Questionnaire in five studies [19,24,29,30,37]. TNF-α in sputum and lung function was assessed in three studies [25,31,40]. All results demonstrated that usage of adjunctive CHM had similar anti-inflammatory effect as salmeterol/fluticasone, roflumilast and nutritional supplementation, which further indicates CHM’s potential MOA.

The theory of Chinese Medicine (CM) defines COPD as lung distension, and its differentiation of syndromes (differential diagnosis) include phlegm retention and deficiency of organs, which mainly correlates to deficiencies in lung, spleen, and kidney function. The goal of CM is to replenish the lung, invigorate the spleen, and tonify the kidney. In the 29 studies, the two most commonly used formulae 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), Dan Shen (Codonopsis pilosula), and Wu Wei Zi (Schisandra chinensis).

Previous studies (on animal models) have shown that Bu Fei Tang affected the expression of MMP-9 on airway remodeling, and significantly reduced the level of TNF-α and IL-8 in a COPD rat model in Bronchial Alveolar Lavage Fluid with lung Qi deficiency [49,50]. Bu Zhong Yi Qi Tang has been shown to increase the rat T-lymphocytes division and the amount of IL-2 produced in mice with spleen deficiency [51].

Ginseng is consisted of ginsenosides and ginseng polysaccharides. Its pharmacological actions have been investigated worldwide. In mice, the extract was found to decrease airway inflammation [52].

Astragalus was found to modify responses of lipopolysaccharide-stimulated macrophages and reduce the production of TNF-α, IL-6 and IL-10 [53]. Dan Shen extract (Codonopsis pilosula) was found to suppress the release of TNF-α, also indicating anti-inflammatory effects [54].

One of the components of Wu Wei Zi (Schisandra chinensis) is Schisandrin B, which down-regulated the production of pro-inflammatory mediators, such as TNF-α and IL-6. Bai Zhu (Atractylodes macrocephala) extracts were found to have anti-inflammatory effects on TNF-α and nitric oxide production from peritoneal macrophages in mice [55] and in a rat lung cell membrane chromatography model [56].

Based on clinical studies and experiments, the MOA of CHM on COPD includes: 1. Decrease in cytokine levels and suppression of airway inflammation; 2. Improvement of overall immune functions; 3. Maintenance of oxidant-antioxidant balance; and 4. Regulation of proteases and anti-proteases levels [57].

However, due to inconsistent methods used to measure inflammatory mediators, the small number of studies, the small sample size, and poor quality of methodology of certain studies, the effect of CHMs on inflammatory mediators could not be completely confirmed. Moreover, AEs related to liver and kidney function should be investigated in future clinical trials. Further, RCTs on CHM therapy should be reported through CONSORT 2010 [14,58].

Conclusion
This SR explains CHM’s mechanism of action, demonstrates CHM’s anti-inflammatory effects, and shows that CHM is well tolerated by patients with stable COPD. Furthermore, using CHM adjunctively has shown to be beneficial in treating and slowing the progression of COPD.

Author’s Contribution
Dr. Xuedong An and Dr Qing Miao are the guarantor, and will take responsibility for the manuscript, including the data and analysis of data. They contributed to the concept and design of this systematic review. XC, CQ, and BW contributed to data research and extraction. Dr. Yifei Du, Xiaodong Cong and Carole Yujia Qiao had full access to all the data in the study and take responsibility for the integrity of the data, accuracy of data analysis, and interpretation of data. Xuedong An and Carole Yujia Qiao contributed to writing the first draft of this manuscript. Xiaodong Cong, Bing Wang, and Qing Miao contributed by reviewing the manuscript. Xiaodong and Yifei Du contributed to the final revision of the manuscript.

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