Miao et al., Lung Dis Treat 2016, 2:2
DOI: 10.4172/2472-1018.1000107

Journal of Lung Diseases & Treatment

Review Article Open Access

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,

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Received February 25, 2016; **Accepted** May 10, 2016; **Published** May 16, 2016

Citation: Miao Q, Cong X, Du Y, Wang B, Qiao CY, et al. (2016) Anti-Inflammatory Effects of Chinese Herbal Medicine on COPD: A Systematic Review. Lung Dis Treat 2: 107. doi:10.4172/2472-1018.1000107

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 low, high 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 is outlined as a flow diagram based on the template provided by PRISMA [11]. 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 RewMan 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 RewMan 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 were 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)
Studies with sputum test								
Cao [38]	Xingtai, Hebei	NS	T: 40/40 C: 40/40	T: 23/17 C: 24/16	T: 56 ± 13 C: 55 ± 14	NS	NS	NS
Che et al. [40]	Shenyang, Liaoning	NS	T: 25/23 C: 25/23	T: 18/7 C: 16/9	T: 65.6 ± NS C: 64.5 ± NS	T: IIA: 11, IIB: 10, III: 4 C: IIA: 10, IIB: 12, III: 3	NS	T: 14 ± 8 C:15 ± 7.6
Du et al. [16]	Shiyan, Hubei	Out	T: 18/18 C: 18/18	T: 16/2 C: 15/3	T:58.61 ± 10.69 C: 58.44 ± 9.54	T: IIA: 7, IIB: 6, III: 2 C: IIA:6, IIB: 7, III: 1	NS	NS
Huang [18]	Fangcheng gang, Guangxi	Out	T: 30/30 C: 30/30	T: 16/14 C: 17/13	T:67.38 ± 5.66 C:65.25 ± 6.13	T: IIA: 12, IIB: 14, III: 4 C: IIA:10, IIB: 14, III: 6	NS	NS
Lu et al. [20]	Fuzhou, Fujian	Out	T: 30/30 C: 30/30	T: 25/5 C: 23/7	T:64.6 ± NS C:63.8 ± NS	T: II 30 C: II 30	Deficiency of Spleen Qi	T: 11.2 ± NS C:10.6 ± NS
Wang et al. [31]	Hefei, Anhui	NS	T: 20/20 C: 20/20	T: 18/2 C: 19/1	T:59.4 ± 7.5 C:60.9 ± 7.9	T: IIA: 8, IIB: 9, III: 3 C: IIA:9, IIB: 9, III: 2	Deficiency of Lung and Spleen Qi	T: 11.2 ± 4.1 C:11.8 ± 4.5
Xiao et al. [39]	Zhanjiang, Guangdong	NS	T: 60/60 C: 56/56	T: 38/22 C: 35/21	T:66.4 ± 8.8 C:61.2 ± 6.3	T: IIA: 23, IIB: 25, III: 12 C: IIA:21, IIB: 22, III: 13	NS	T:17.3 ± 10.2 C:18.5 ± 9.3
Zhou et al. [25]	Taiwu, Shandong	Both	T: 30/30 C: 30/30	T: 22/8 C: 21/9	T:NS C:NS	T: IIA: 30 C: IIA:30	NS	NS
Studies with serum test								
Chen et al. [37]	Wuhan, Hubei	NS	T: 36/36 C: 36/36	T: 24/12 C: 26/10	T:62.9 ± 7.3 C:62.2 ± 7.8	T:III:25, IV:11 C:III:26, IV:10	Deficiency of Lung and Kidney Qi and blood stasis	T:5.9 ± 1.7 C:6.2 ± 1.8
Cheng et al. [41]	Chongqing	Both	T: 40/40 C: 40/40	T:35/5 C: 33/7	T: 83.2 ± 7.8 C: 82.7 ± 5.6	NS	NS	NS
Feng et al. [30]	Beijing	NS	T: 46/46 C: 30/30	T:25/21 C:14/16	T:63.37 ± 8.99 C:62.26 ± 8.72	T: IIA:24, IIB:22 C: IIA:16, IIB:14	Deficiency of Qi and sputum blood stasis	NS
Fu et al. [42]	Tianjin	NS	T: 39/39 C: 31/31	T:31/31 C:31/31	T:60.56 ± 8.60 C:60.21 ± 10.01	NS	NS	NS
Guo et al. [17]	Tianjin	Out	T: 70/69 C: 70/61	T:41/28 C:39/22	T:60.81 ± 8.18 C:60.51 ± 11.03	NS	Deficiency of Lung Spleen Kidney Qi and sputum blood stasis	T: 14.56 ± 6.32 C:14.52 ± 5.96
Hu [22]	Lanzhou, Gansu	In	T: 35/35 C: 32/32	T:20/15 C:14/18	T:64.7 ± 7.5 C:63.2 ± 5.4	NS	Yin deficiency of Lung and Kidney	NS
Jiang et al. [44]	Hezhou, Guangxi	NS	T: 30/30 C: 30/30	T:20/10 C:20/10	T:52.3 ± 10.9 C:51.8 ± 11.1	NS	NS	T: 12.36 ± 6.2 C:12.74 ± 6.5
Li et al. [36]	Guangzhou, Guangdong	Both	T: 50/49 C: 50/48	T:27/22 C:28/20	T:66.3 ± 10.1 C:65.9 ± 9.8	NS	Sputum blood stasis in Lung	T: 8.9 ± 5.0 C:9.1 ± 4.8
Li et al. [19]	Haerbin, Heilongjiang	Out	T: 35/35 C: 35/35	T:23/12 C:24/11	T:63.7 ± 5.3 C:60.1 ± 5.3	T:I:6, IIA:19, IIB:10 C:I:5, IIA:20, IIB:10	Deficiency of Lung and Spleen Qi	T: 15.4 ± 3.1 C:13.1 ± 4.1
Ou et al. [32]	Guiyang, Guizhou	Both	T: 36/30 C: 34/30	T:23/13 C:22/12	NS	NS	Deficiency of Lung and Spleen Qi	NS
Shinozuka et al. [26]	Chiba, Japan	NS	T: 17/17 C: 18/18	NS	NS	NS	NS	NS
Su et al. [23]	Beijing	NS	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	NS
Tatsumi et al. [24]	Chiba, Japan	NS	T: 34/34 C: 37/37	NS	NS	NS	NS	NS
Wang et al. [29]	Shanghai	NS	T1:109/82 T2:109/89 C:113/91	T1:64/18 T2:62/27 C:69/22	T1:62.43 ± 9.04 T2:61.51 ± 8.79 C:62.68 ± 8.10	T1:I:1, II:34, III:45, IV:2 T2:I:0, II:42, III:44, IV:3 C:I:2, II:34, III:50, IV:5	1.Deficiency of Qi 2.Deficiency of Kidney Qi 3.Deficiency of Kidney Yang	T1:12.57 ± 8.39 T2:12.75 ± 8.95 C:12.43 ± 9.46
Wang et al. [28]	Liuyang, Hunan	Both	T: 30/30 C: 30/30	T:16/14 C:18/12	T:65.22 ± 2.45 C:62.75 ± 3.66	T:I:5,T:II:19, T:III:6 C:I:5,C:II:20, C:III:5	Deficiency of Lung and Kidney	NS
Xiao et al. [27]	Guangzhou, Guangdong	NS	T: 34/34 C: 31/31	T:26/8 C:25/6	T:62.3 ± 7.11 C:64.6 ± 8.62	T:I:6, II:25, III:3 C:I:7, II:21, III:3	Yin deficiency of Lung and Kidney	NS
Xiong et al. [34]	Shenzhen	Both	T: 30/30 C: 30/30	T:20/10 C:21/9	T:72 ± NS C:71 ± NS	NS	Deficiency of Lung and Kidney	NS

Zhang et al. [33]	Zhengzhou, Henan	NS	T: 35/34 C: 35/34	T:NS C:27/8	T:NS C:61.77 ± 10.18	NS	1.Deficiency of Lung and Spleen Qi 2.Deficiency of Lung and Kidney Qi 3.Deficiency of Qi and Yin	NS
Zhao et al. [35]	Xinxiang, Henan	NS	T: 30/30 C: 30/30	T:16/14 C:18/12	T:72.68 ± 7.18 C:72.18 ± 7.36	NS	Deficiency of Lung and Kidney Qi	NS
Zheng [43]	Tangshan, Hebei	Both	T: 45/45 C: 45/45	T:30/15 C:28/17	T:54.3 ± 4.7 C:55.2 ± 4.1	NS	NS	T:11.3 ± 4.3 C:10.9 ± 4.8
Zhong et al. [21]	Shenzhen	Out	T: 35/35 C: 35/35	T:20/15 C:21/14	T:68.3 ± 9.8 C:68.2 ± 9.5	NS	Deficiency of Lung and Kidney	NS

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

Table 1: The characteristics of each study.

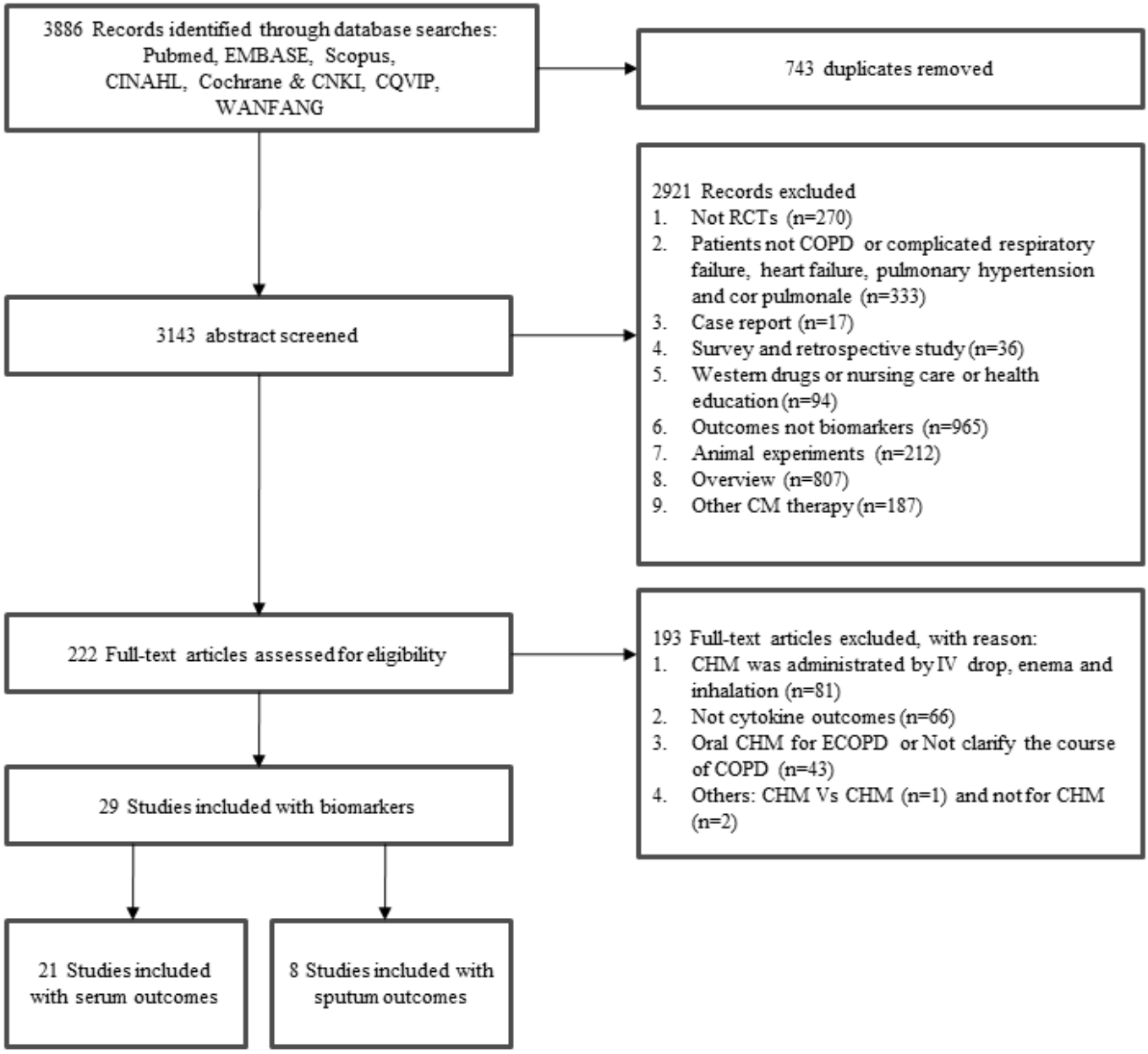

Figure 1: The process of selection of studies.

First author, date	Intervention				*TD	outcomes
	Formula name (form) /Ingredients/quantitative	Dosage regimen	Qualitative testing	Plus bronchodilators		
Studies with sputum test						
Cao [38]	Xiaoqinglong Decoction Baishao10 g, Banxia10 g, Gancao10 g, Ganjiang10 g, Guizhi10 g, Mahuang10 g, Wuweizi10 g, Xixin10 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, Huangqin1.67 g, Jinyinhua1.67 g, Jiegeng0.83 g, Kuandonghua0.67 g, Lianqiao0.83 g, Mahuang0.5 g, Pipaye 0.83 g, Yuxingcao 0.83 g, Ziwan 0.67 g	20 ml, TID	Hospital	Bronchodilators	6 wks	Lung function
Du et al. [16]	Yinxingye extract tablet: Ginkgo biloba extract	2 Tablets, TID	Hospital	No	2 mths	Lung function
Huang [18]	BufeiYiyangHuatangranules: Bajitian, Chuanbeimu, Dangshen, Duzhong, Gouqizi, Huanghuadaoshuilian, Huangqi, Jupi, Maimendong, Pipaye, Sangbaipi, Wuweizi, Yipichou, Yuxingcao ,Ziwan	20 g, BID	Hospital	Bronchodilators	6 mths	NS
Lu et al. [20]	Liu Junzi Decoction contains (150 ml): Baizhu 9 g, Banxia 9 g, Chenpi 6 g, Dangshen 20 g, Fuling 15 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,Dangshen 15 g, Dilong 8 g, Fangfeng 10 g, Fuling 15 g, Gancao 10 g, Huangqi 30 g, Kuandonghua 10 g	1 Dose, BID	Hospital	Bronchodilators	2 mths	Lung function
Xiao et al. [39]	ManzhiKechuanling: Oral liquid: Baizhu, Banxia, Buguzhi, Chuanbeimu, Ejiao, Fuling, Gancao, Gejie, Hetaorou, Huangqi, Lujiaojia, Renshen, Shanyao, Taoren, Yimucao, Ziheche, Zisuzi	10 ml, BID	Hospital	Bronchodilators	2 mths	MMP-9
Zhou et al. [25]	FeisaitongHeji: Oral liquid (100 ml contains): Chantui 9 g, Danshen 30 g, Dilong 12 g, Gancao 6 g, Huangqi 30 g, Jiegeng 9 g, Jinyinhua 18 g, Laifuzi 12 g, Shashen 18 g, Yiyiren 30 g, Zisuye 9 g	100 ml, TID	Hospital	Bronchodilators	1 mth	Lung function, Syndromes
Studies with serum test						
Chen et al. [37]	BufeiHuoxue 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, Huajuhong 15 g, Huangjing 20 g, Huangqi 30 g, Laifuzi 15 g, Taoren 10 g, Wuweiz 6 g, Xiyangshen 10 g, Yinyanghuo 10 g	1 Dose, QD	Hospital	No	3 mths	Lung function *6 MWD, *CAT,
Cheng et al. [41]	SuhuangZhike Capsule: Dilong, Mahuang, Niubangzi, Qianhu, Wuweizi, Zisuye	3 Capsules, TID	Yangtze 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, QD	Hospital	Bronchodilators	3 mths	Quality of life,
Fu et al. [42]	Bufei granules: Chenpi, Dangshen, Dihuang, Mahuang, Shanzhuyu, Ziwan	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, Ziwan	16 g, BID	Hospital	No	3 mths	NS
Hu [22]	Jiajianbufei Decoction: Baibu10 g, Bajitian15 g, Buguzhi15 g, Chenpi 12 g, Dangshen 15 g, Danshen, Huangqi 20 g, Jiegeng 10 g, Maidong10 g, Sangbaipi10 g, Tusizi10 g, Xuanshen10 g	1 Dose, QD	Hospital	Inhaled albuterol & Aminophylline Sustained release tablets	2 mths	Lung function
Jiang et al. [44]	BufeiNashen Decoction: Every dose contains: Chenxiang10 g, Dangshen20 g, Dihuang20 g, Fuling15 g , Gancao 6 g, Gejie1 pair, Huangqi 20 g, Sangbaipi 15 g, Wuweizi 15 g, Ziwan15 g	2 Doses, QD	Hospital	Salmeterol/ fluticasone	2 wks	Lung function
Li et al. [36]	SanziYangqin Decoction &TaohongSiwu Decoction: Baijiezi10 g, Baishao15 g, Chuanxiong15 g, Danggui10 g, Dihuang10 g, Honghua10 g, Laifuzi10 g, Taoren15 g, Zisuzi15 g	150 ml, QD	Hospital	Aminophylline Sustained release tablets	1 mth	Lung function
Li et al. [19]	YiqiJianpiHuatanFangDecoction: Baizhu, Banxia, Chenpi, Dangshen, Huangqi, Xingren	1 Dose, QD	Jiangyin Tianjiang Pharmaceutical Co	Bronchodilators	3 mths	SGRQ
Ou et al. [32]	JiajianBufei Decoction: Huangqi 20 g, Danshen15 g, Dangshen10 g, Buguzhi15 g, Baibu 10 g, Sangbaipi10 g	300 ml, QD	Hospital	Bronchodilators	3 mths	Lung function, TCM syndromes
Shinozuka et al. [26]	Hochuekkito extract (BuzhongYiqi Tang): 7.5 g extract	2.5 g, TID	NS	Bronchodilators	6 mths	Lung function
Su et al. [23]	Feikang Granules: Huangqi, Haigeqiao	10 g, TID	Hospital	No	3 mths	Lung function

First author, date	Intervention				*TD	outcomes
	Formula name (form) /Ingredients/quantitative	Dosage regimen	Qualitative testing	Plus bronchodilators		
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 manufactory of Taiji Group &Tianjiang Pharmacy company Ltd	Inhaled albuterol	6 mths	6 MWD, lung function, *AEF, *BODE SGRQ
Wang et al. [28]	FufangYishenDuqi Capsule (0.7 g): Dangshen15 g , Wuweizi10 g , Maidong 10 g , Baibu10 g , Xingren10 g, Duzhong10 g , Mahuang 6 g, Yiyiren 20 g, Kuandonghua10 g, Zisuzi 10 g, Chenxiang 3 g, Baijiezi 15 g, Baishao10 g, Baihe,10 g Houpo10 g, Shanzhuyu 15 g	0.7g, TID	Hospital	Tiotropium Bromide Powder	3 mths	SGRQ , TCM syndromes
Xiao et al. [27]	ZhenqiFuzheng granules: Huangqi, Nvzhenzi	15 g, BID	Xiuzheng Pharmaceutical Group	Bronchodilators	3 mths	Lung function, TCM syndromes
Xiong et al. [34]	Shenge powder: Gejie, Renshen	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 cordycepssinensis powder	1.0 g, TID	East China Pharmaceutical Group Limited Co	Inhaled albuterol	6 mths	6 MWD, lung function
Zheng [43]	Jinshuibao Capsule: Fermentation of cordycepssinensis powder	3 capsules (0.99 g), TID	Jiangxi Jiminkexin Group Co	Bronchodilators	1 mths	NS
Zhong et al. [21]	JiaweiJinshuiLiujunJian Decoction: Dangshen15 g, Huangqi 20 g, Banxia 10 g, Danggui 10 g, Dihuang 20 g, Fuling 10 g, Chenpi 10 g, Shengjiang 5 g, Gancao 5 g, Wuweizi 5 g	100 ml, BID	Hospital	Aminophylline Sustained release tablets	3 mths	Syndromes, Amount of sputum

TD: Treatment Duration; **MMP-9:** MatrixMetalloprotein-9; **HDACs:** Histone Deacetylases; **6 MWD:** 6-Minute Walk Distance; **CAT:** COPD Assessment Test; **TCM:** Traditional Chinese Medicine; **AEF:** Acute Exacerbation Frequency; **BODE index:** The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index.

Table 2: Intervention of included studies.

were low risk. The Blinding Method in three studies [17,29,42] were low risk; one study [20] had high risk due to its inadequate description of its Blinding Method. The remaining twenty five studies did not clearly describe its methods. Outcome Assessments were low risk in every study. Incomplete Data was either high risk in three studies without using of intention to treat analysis [17,33,36] or unclear in three studies [21,24,26]. Two studies were unclear of their Selective Reporting method [24,26]. Other Bias was assessed as low risk in all studies based on baseline data comparison (Figure 2).

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 small 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 included in the meta-analysis [23,24,26,30].

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-1.27, 95% CI [-1.86, -0.68]) (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, 95% CI [-1.01, -0.43]) (p<0.00001) (Figure 4).

In five studies with 602 participants, the serum level of IL-6 was found to be significantly reduced [17,29,41,42,44]. Figure 5 shows six studies with 693 patients. The data was used from Wang [29] twice (MD-0.75, 95% CI [-0.90, -0.60]) (p=0.02) (Figure 5).

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 -123.62, 95% CI [-134.33, -122.91]) (p=0.003) (Figure 6).

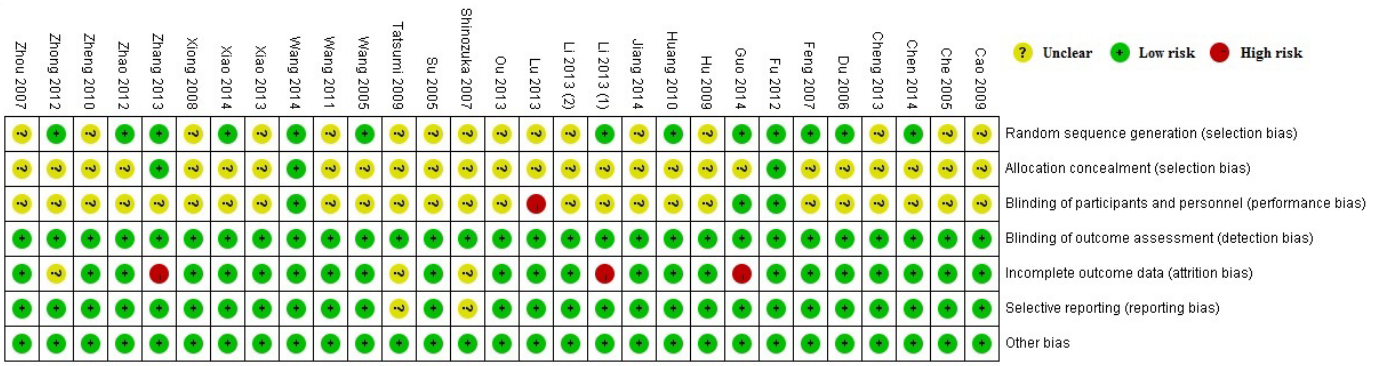

Figure 2: The assessment of risk of bias of 29 studies.

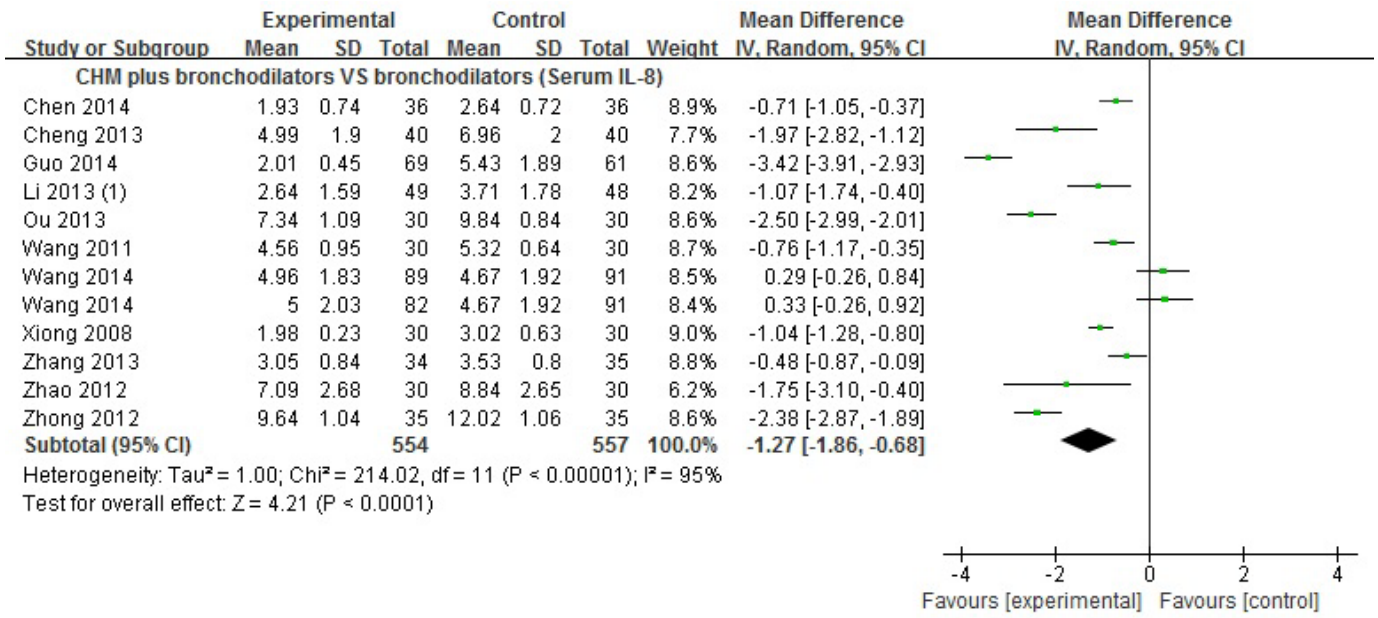

Figure 3: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum IL-8 at the end of treatment as the outcome.

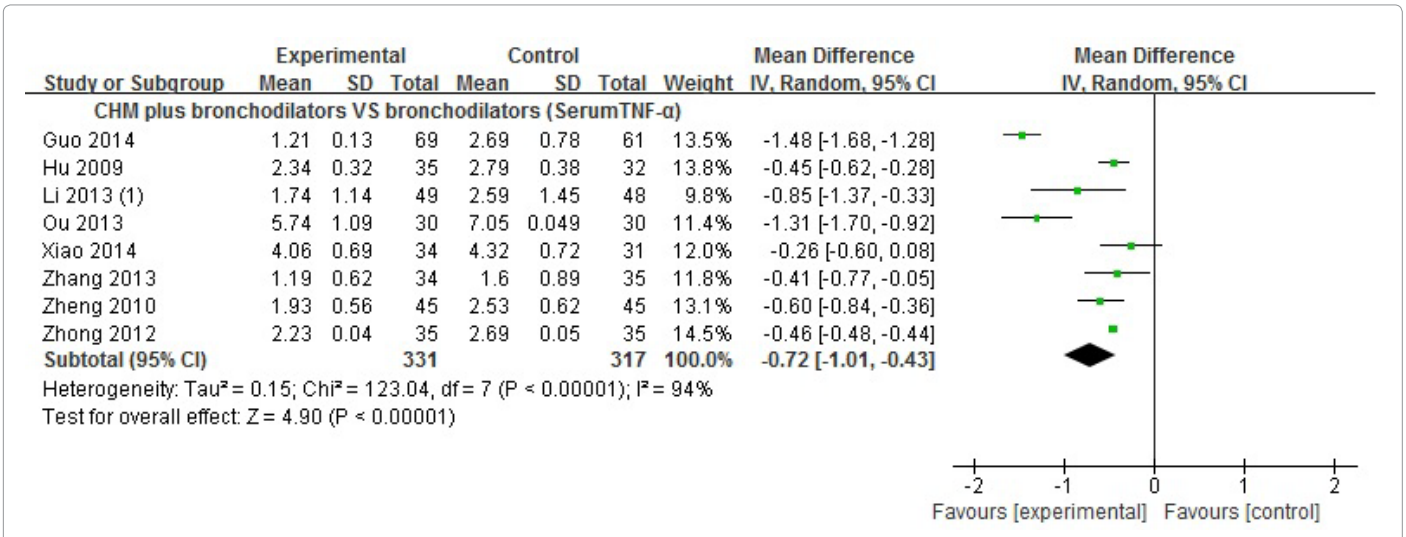

Figure 4: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum TNF-α at the end of treatment as the outcome.

Quality assessment						No of patients		Effect	Quality
No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHM	Control	Absolute	
Serum IL-8 (Better indicated by lower values)									
11	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1[3]	554	557	MD 1.27 lower (1.86 to 0.68 lower)	MODERATE
Serum TNF-α (Better indicated by lower values)									
8	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1[3]	331	317	MD 0.72 lower (1.01 to 0.43 lower)	MODERATE
Serum IL-6 (Better indicated by lower values)									
5	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1[3]	349	344	MD 1 lower (1.87 to 0.14 lower)	MODERATE
Serum TGF-β1 (Better indicated by lower values)									
4	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1[3]	320	323	MD 278.66 lower (460.57 to 96.75 lower)	MODERATE
Sputum IL-8 (Better indicated by lower values)									
7	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1[3]	221	217	MD 0.88 lower (1.45 to 0.31 lower)	MODERATE
Sputum TNF- α (Better indicated by lower values)									
4	Serious[1]	Serious[2]	No serious indirectness	Serious[4]	Reduced effect for RR>>1 or RR<<1[3]	103	103	SMD 1.05 lower (1.97 to 0.13 lower)	LOW

[1]Allocation concealment in majority of studies was unclear; ITT was not applied in some incomplete data analysis
[2]Heterogeneity was high
[3]Severity of COPD and duration of treatment
[4]The sample size was small

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

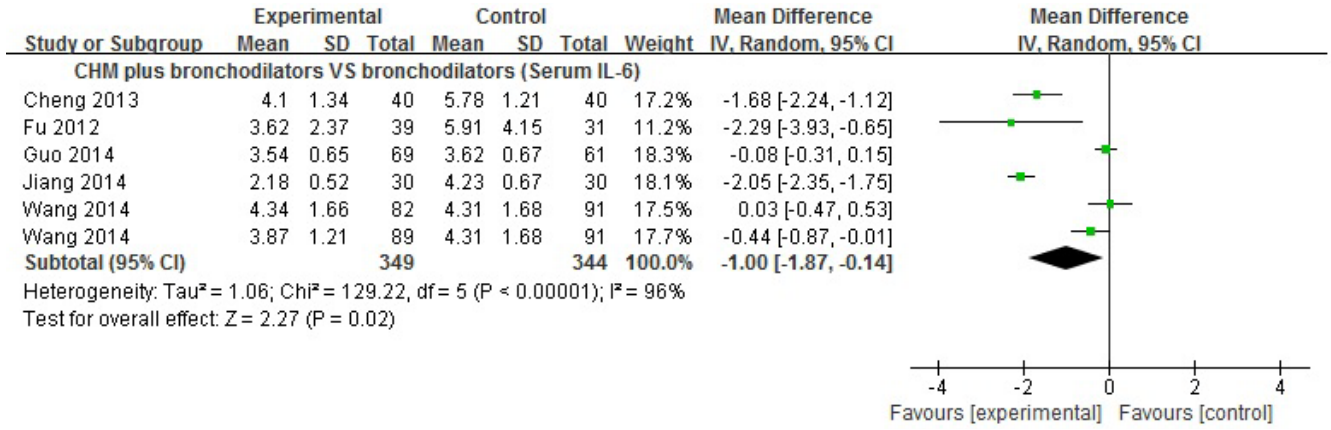

Figure 5: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum IL-6 at the end of treatment as the outcome.

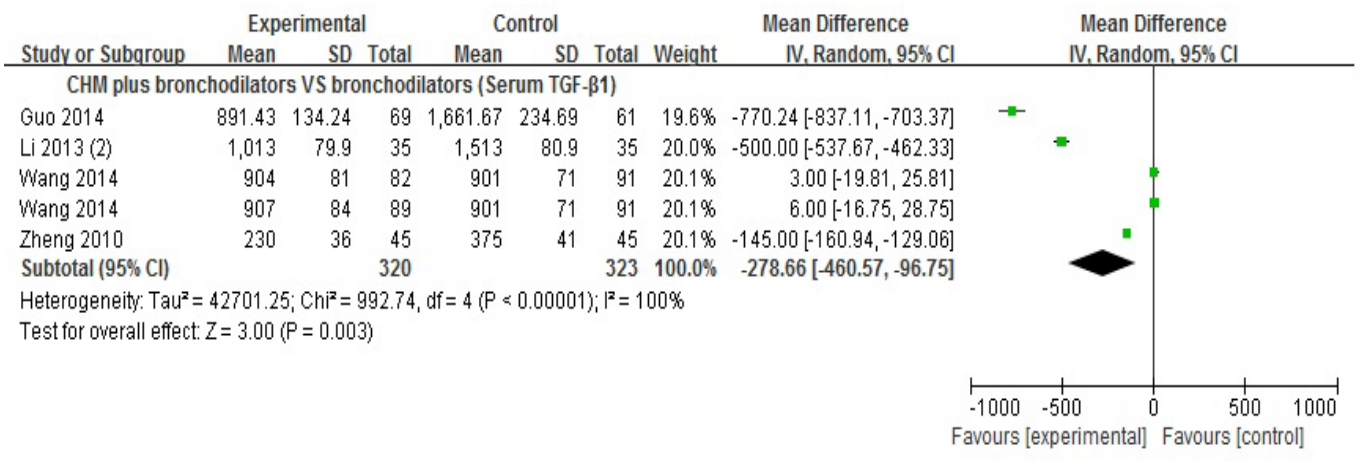

Figure 6: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of serum TGF-β1 at the end of treatment as the outcome.

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.

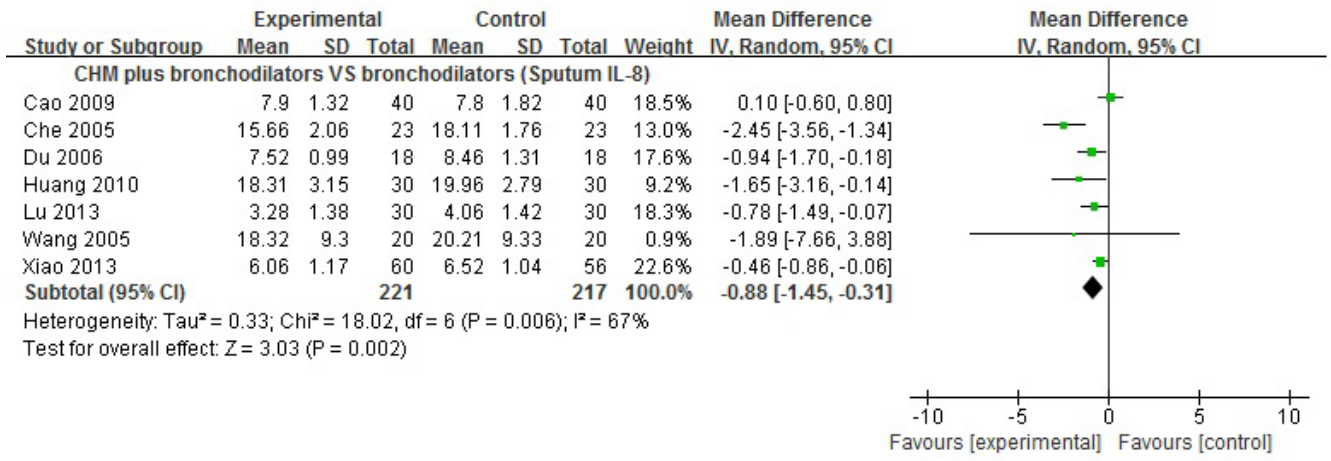

Figure 7: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of sputum IL-8 at the end of treatment as the outcome.

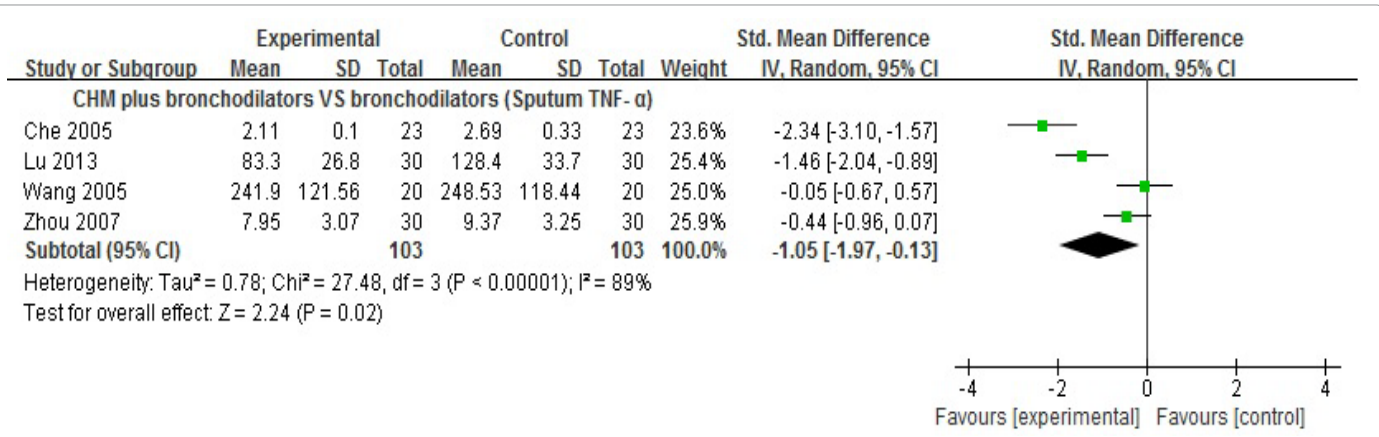

Figure 8: Meta-analysis of CHM plus bronchodilators versus bronchodilators with reduction of sputum TNF-α at the end of treatment as the outcome.

TNF-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*), Dang 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]. Dang 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. Xuedong and Yifei Du contributed to the final revision of the manuscript.

Funding

This study was funded by Beijing Municipal Science and Technology Commission of China (NO.Z131107002213053). The sponsors were not involved in this manuscript.

Acknowledgement

We thank the Beijing Municipal Science and Technology Commission of China for supporting this study.

References

1. Hogg JC, Timens W (2009) The pathology of chronic obstructive pulmonary disease. Annu Rev Pathol 4: 435-459.
2. Chung KF (2001) Cytokines in chronic obstructive pulmonary disease. Eur Respir J Suppl 34: 50s-59s.
3. Hacievliyagil SS, Mutlu LC, Temel I (2013) Airway inflammatory markers in chronic obstructive pulmonary disease patients and healthy smokers. Niger J Clin Pract 16: 76-81.
4. Petrescu F, Voican SC, Silosi I (2010) Tumor necrosis factor-alpha serum levels in healthy smokers and nonsmokers. Int J Chron Obstruct Pulmon Dis 5: 217-222.
5. Hacievliyagil SS, Gunen H, Mutlu LC, Karabulut AB, Temel I (2006) Association between cytokines in induced sputum and severity of chronic obstructive pulmonary disease. Respir Med 100: 846-854.
6. Gaki E, Kontogianni K, Papaioannou AI, Bakakos P, Gourgoulianis KI, et al. (2011) Associations between BODE index and systemic inflammatory biomarkers in COPD. COPD 8: 408-413.
7. Gan WQ, Man SF, Senthilselvan A, Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59: 574-580.
8. An X, Zhang AL, May BH, Lin L, Xu Y, et al. (2012) Oral Chinese herbal medicine for improvement of quality of life in patients with stable chronic obstructive pulmonary disease: a systematic review. J Altern Complement Med 18: 731-743.
9. Guo R, Pittler MH, Ernst E (2006) Herbal medicines for the treatment of COPD: a systematic review. Eur Respir J 28: 330-338.
10. Eden J, Levit L, Berg A, Morton S (2011) Finding What Works in Health Care: Standards for Initiating a Systematic Review, Chapter 2, P74. Washington (DC) National Academies Press (US).
11. Moher D, Liberati A, Tetzlaff J, Altman DG (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8: 336-341.
12. Hand book (2016) Cochrane Handbook for Systematic Reviews of Interventions, Part I, Chapter 8 (Version 5.0.2).
13. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, et al. (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64: 383-394.
14. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, et al. (2006) Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med 144: 364-367.
15. CSRD (2007) Chinese Society of Respiratory Disease (CSRD): Guideline for diagnosis and management of chronic obstructive pulmonary disease. ChinJ Inrern Med 46: 254-261.
16. Du C, Tu M, Liu W, Liu Y, Liu X (2006) Effects of Ginkgo Biloba extact (GBE) on the inflammatory cell and the level of interlukin-8 in induced sputum from patients with chronic obstructive pulmonary disease. The Journal of Practical Medicine 22: 1246-1248.
17. Guo S, Sun Z, Liu E, Feng J, Fu M, et al. (2014) Effect of bufei granule on stable chronic obstructive pulmonary disease: a randomized, double blinded, placebo-controlled, and multicenter clinical study. J Tradit Chin Med 34: 437-444.
18. Huang B (2010) Effect of Chinese herbal medicine of Bufei Yiyang Huatan on cytokine cells IL-10□IL-8 in stable chronic obstructive pulmonary disease patients. Chinese Medicine Modern Distance Education of China 8: 144-145.

19. Li Z, Tian C, Liu W (2013) Clinical study of Yiqijianpi recipe for treating stable chronic obstructive pulmonary disease. Acta Chinese Medicine and Pharmacology 41: 119-120.

20. Lu F, Wang S (2013) Influence of Liujunzi Decoction on Endogenous Anti-inflammatory Mechanisms in Patients with Chronic Obstructive Pulmonary Disease. Journal of Liaoning University of TCM 7: 161-163.

21. Zhong M, Ye X, Li D (2012) Effect of Jiawei Jinshuiliujunjian on cytokine in patients with stable chronic obstructive pulmonary disease. Chinese Journal of Geriatric Care 10: 11-12.

22. Hu C (2009) Integrated Bu Fei Tang and western medicine in treatment 35 cases with stable chronic obstructive pulmonary disease. Journal of Traditional Chinese Medicinal Research 22: 24-26.

23. Su H, Wu W, Feng C, Zhou S, Tian X, et al. (2005) Effects of the therapy for nourishing qi, activating circulation and dispersing phlegm on expressions of serum TGF-β1 and IL-8 in the patients with chronic obstructive pulmonary disease. Journal of Beijing University of Traditional Chinese Medicine 28: 48-51.

24. Tatsumi K, Shinozuka N, Nakayama K, Sekiya N, Kuriyama T, et al. (2009) Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. J Am Geriatr Soc 57: 169-170.

25. Zhou Y, Wei G, Qi S, Qi Y, Shi Y, et al. (2007) Clinical study on the effects of treating stable chronic obstructive pulmonary disease with Fei Sai Tong He Ji. Journal of Taishan medical college 28: 515-517.

26. Shinozuka N, Tatsumi K, Nakamura A, Terada J, Kuriyama T (2007) The traditional herbal medicine Hochuekkito improves systemic inflammation in patients with chronic obstructive pulmonary disease. J Am Geriatr Soc 55: 313-314.

27. Xiao H, Chen R, Zou M, Xiong C, Zhang J (2014) Regulatory Effect of Zhenqi Fuzheng Granule on Th1/Th2 in Lung-kidney-yin Deficiency Type of Stable COPD Patients. Chinese and foreign medical research 12: 8-10.

28. Wang Q, Wang L, Xu L, Huang S, Wu Z (2011) Curative effects of compund Yifei Duqi capsules on stable chronic obstructive pulmonary disease and effect of it on serum interleukin-8. Journal of TCM Univ of Hunan 31: 58-60.

29. Wang G, Liu B, Cao Y, Du Y, Zhang H, et al. (2014) Effects of two Chinese herbal formulae for the treatment of moderate to severe stable chronic obstructive pulmonary disease: a multicenter, double-blind, randomized controlled trial. PLoS One 9: e103168.

30. Feng C, Wu W, Wu H, Su H, Zhou G, et al. (2007) Analysis on clinical materials from 76 cases of COPD treated with qi-replenishing, blood-activating and phlegm-removing therapy. Journal of Beijing University of Traditional Chinese Medicine 30: 419-422.

31. Wang S, Ji H, Zhang N, Zhuo X, Zhao L, et al. (2005) Effect of Yifei Jianpi Recipe on Inflammatory Cells, Levels of Interleukin-8 and Tumor Necrosis Factor-α in Sputum from Patients with Chronic Obstructive Pulmonary Disease. CJITWM 25: 111-113.

32. OU J, Liu L (2013) Chronic Obstructive Pulmonary Disease in Stable Stage Treated with Jiajian Bufei Decoction. Chinese Journal of Experimental Traditional Medical Formulae 19: 303-306.

33. Zhang H, Cao F, Wang M, Li S, Ma L, et al. (2013) Influence of systemic inflammatory response and human T-cell subset numbers in stable chronic obstructive pulmonary disease by differentiation treatment with traditional Chinese medicine. Chinese Journal of Gerontology 33: 5225-5228.

34. Xiong G, Chen S, Xie W, Ye X, Lin J (2008) Clinical observation of Shenge granule on effect of lung function and serum IL-8, TNF-α for stable chronic obstructive pulmonary disease. Chinese Journal of Geriatric Care 6: 37-39.

35. Zhao T, Xu H (2012) Effect of Bailing Capsule on Lung function and serum IL-8 in patients with stable chronic obstructive pulmoary disease. Chinese Journal of Clinical Research 25: 665-666.

36. Li S, Fan L, Guo S, He Q (2013) A study of the mechanism of Jianpi Huoxue therapy in treatment of stable chronic obstructive pulmonary disease by improving airway inflammation. Modern Journal of Integrated Traditional Chinese and Western Medicine 22: 2398-2400.

37. Chen X, Ke J, Liu Q, Sheng L (2014) Discussion About Bufei Huoxue Decoction Combined Salmeterol Fluticasone Treatment on Chronic Obstructive Pulmonary Disease in Curative Effect and Action Mechanism. Chinese Journal of Experimental Traditional Medical Formulae 20: 220-223.

38. Cao D (2009) Effects of Xiaoqilongtang decoction on airway inflammation and airway remodeling in patients with COPD. Med J West China 21: 575-577.

39. Xiao B, Liu H, Zeng Y, Lao J, Chen K (2013) Effect of Manzhi Kechuanling on Inflammatory Cells and MMP-9-IL-8-CRP levels in Sputum of Chronic Obstructive Pulmonary Disease Patients. Journal of new Chinese medicine 45: 34-36.

40. Che H, Pang J, Changjian L, Wang Y (2005) Effects of Zhike Qingfei Oral Liquid on Inflammatory Cell Interleulin-8 and Tumor Necrosis Factor-α in the Sputum in 25 Cases of Chronic Obstructive Pulmonary Disease. Journal of Traditional Chinese Medicine 16: 759-761.

41. Cheng L, Liu X (2013) Influence of Suhuang Zhike Capsule Combined with Seretide on Pulmonary function and Proinflammatory Factors in Elderly Chronic Obstructive Pulmonary Disease. China Pharmaceuticals 22: 16-17.

42. Fu M, Sun Z, Liu E, Feng J, Wang Q (2012) Impacts of Bufei Granules on Serum IL-6 level for COPD Patients at the Stable Stage. Would Journal of Integrated Traditional and Western Medicine 7: 529-531.

43. Zheng Y (2010) Influence of traditional Chinese medicine Jinshuibao capsule on levels of serum cytokines in patients with chronic obstructive pulmonary disease. China Journal of Modern Medicine 20: 1096-1098.

44. Jiang J, Li F (2014) The influence on Lung Function and Inflammatory Mediators of Bufeinashen Decoction in Patients with Stable Chronic Obstructive Pulmonary Disease. Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine 14: 1-3.

45. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, et al. (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187: 347-365.

46. Sugawara K, Takahashi H, Kashiwagura T, Yamada K, Yanagida S, et al. (2012) Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD. Respir Med 106: 1526-1534.

47. Perng DW, Tao CW, Su KC, Tsai CC, Liu LY, et al. (2009) Anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone or tiotropium in COPD. Eur Respir J 33: 778-784.

48. Grootendorst DC, Gauw SA, Verhoosel RM, Sterk PJ, Hospers JJ, et al. (2007) Bredenbroker D, Bethke TD, Hiemstra PS, Rabe KF: Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. Thorax 62: 1081-1087.

49. Zhang K, Liu LL, OU JQ, Zhan HJ, Liu HR (2008) Effect of Jia Jian Bu Fei decoction on TNF-alpha and IL-8 of bronchoalveolar lavage fluid in COPD rats with deficiency of lung-qi. Tianjin Journal of Traditional Chinese Medicine 25: 491-493.

50. Zhang K, Zhang Y, Cheng YJ, Lu L (2008) Effects of Shenqi Bufei Tang on expessions of NF-kappaB, MMP-9 and TIMP-1 in airway remodeling of COPD rat model with lung-Qi deficiency syndrome. Zhongguo Zhong Yao Za Zhi 33: 2129-2132.

51. Hu B, An HM, Shen KP (2008) Pharmaceutical study on Bu Zhong Yi Qi Tang for anti-infection, anti-tumor and immuno function. Central south pharmacy 6: 731-734.

52. Kim DY, Yang WM (2011) Panax ginseng ameliorates airway inflammation in an ovalbumin-sensitized mouse allergic asthma model. J Ethnopharmacol 136: 230-235.

53. Clement-Kruzel S, Hwang SA, Kruzel MC, Dasgupta A, Actor JK (2008) Immune modulation of macrophage pro-inflammatory response by goldenseal and Astragalus extracts. J Med Food 11: 493-498.

54. Byeon SE, Choi WS, Hong EK, Lee J, Rhee MH, et al. (2009) Inhibitory effect of saponin fraction from Codonopsis lanceolata on immune cell-mediated inflammatory responses. Arch Pharm Res 32: 813-822.

55. Li CQ, He LC, Jin JQ (2007) Atractylenolide I and atractylenolide III inhibit Lipopolysaccharide-induced TNF-alpha and NO production in macrophages. Phytother Res 21: 347-353.

56. Dong H, He L, Huang M, Dong Y (2008) Anti-inflammatory components isolated from Atractylodes macrocephala Koidz. Nat Prod Res 22: 1418-1427.

57. Le Y, Sun Y (2013) The progress of Chinese medicine for prevention and treatment of chronic obstructive pulmonary disease mechanism. Global Traditional Chinese Medicine 6: 226-229.

58. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152: 726-732.