Chinese herbal medicine for chronic obstructive pulmonary disease (COPD): systematic analyses of modern and classical approaches

A thesis submitted in fulfilment of the requirements for Degree of Doctor of Philosophy

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Declaration

I declare that all works in this thesis carried out during my Degree of Philosophy in Science in the Discipline of Chinese Medicine, School of Health Sciences, RMIT University were of my own. No part of this thesis has been submitted to this or any other university or institutions for any other award. To the best of my knowledge, this thesis contains no part that has been published previously by others except where due references are made.

Xue Dong An

Date 12/01/2013
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Published manuscripts

1. *Chinese herbal medicine improvement of quality of life for stable chronic obstructive pulmonary disease: A systematic review*
   An X, Zhang AL, May BH, Lin L, Xu Y, Xue CC.

2. *Oral ginseng formulae for stable chronic obstructive pulmonary disease: A systematic review*
   An XD, Zhang AL, Yang AW, Lin L, Wu D, Guo X, Shergis JL, Thien FC, Worsnop CJ, Xue CC
   Respir Med. 2011 Feb; 105 (2):165-76

Conferences

1. *Oral Chinese Herbal medicine for patients with stable COPD: a systematic review of randomized controlled trials*
   Xuedong An, Anthony Lin Zhang, Brian H May¹, Lin Lin, Yinji Xu, Charlie Changli Xue
   By poster on 10th meeting of Consortium for Globalization of Chinese Medicine (CGCM) (Shanghai, 26-28 August 2011)

2. *The Effect of oral Chinese herbal medicine on quality of life for stable chronic obstructive pulmonary disease (COPD): A systematic review*
   Xuedong An MD, Tony Zhang PhD, Brian May PhD, Yinji Xu PhD, Charlie Xue PhD
   By oral presentation at The 6th Asian-Pacific Conference on Evidence Based Medicine organised by the Chinese Evidence-based Medicine Centre, in Anhui, China (25-09-2010) (supported by RMIT Postgraduate Research Student International Conference Fund).

3. *Chinese herbal medicine (ginseng) formulae for stable chronic obstructive pulmonary disease: a systematic review*
   Xuedong An, Tony Zhang, Angela Yang, Lin Lin, Charlie Xue
   The 6th World Congress of Chinese Medicine 2009 (05-12-2009)

4. *Ginseng for treating patients with moderate chronic obstructive pulmonary disease (COPD): a protocol*
   Xuedong An, Tony Zhang, Angela Yang, Frank Thien, David Story, Charlie Xue
   Conference of College of Sciences, Engineering and Health (23-10-2009)
Abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>Albumin</td>
</tr>
<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BALF</td>
<td>Bronchoalveolar lavage fluid</td>
</tr>
<tr>
<td>BODE</td>
<td>‘B’ is body mass index; ‘O’ is the degree of airflow obstruction, as determined by post-bronchodilator FEV1; ‘D’ is dyspnoea assessed by the MMRC dyspnoea scale; and ‘E’ is exercise capacity as assessed by the 6-minute walk test</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and alternative medicine</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>cGMP</td>
<td>Cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CHM</td>
<td>Chinese herbal medicine</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CSRD</td>
<td>Chinese Society of Respiratory Diseases</td>
</tr>
<tr>
<td>CXCL</td>
<td>CXC chemokine ligand</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECOPD</td>
<td>Exacerbation of COPD</td>
</tr>
<tr>
<td>ET</td>
<td>Endothelin</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte–macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>Hct</td>
<td>Haematocrit</td>
</tr>
<tr>
<td>HRCT</td>
<td>High-resolution CT</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>LPD</td>
<td>Lipid peroxide</td>
</tr>
<tr>
<td>LTB4</td>
<td>Leukotriene B4</td>
</tr>
<tr>
<td>MD</td>
<td>Mean differences</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximum inspiratory pressure</td>
</tr>
<tr>
<td>MMEF</td>
<td>Maximum mid-expiratory flow</td>
</tr>
<tr>
<td>MMPs</td>
<td>Matrix metalloproteinases</td>
</tr>
<tr>
<td>MMRC</td>
<td>Modified Medical Research Council</td>
</tr>
<tr>
<td>MPO</td>
<td>Myeloperoxidase</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MVC</td>
<td>Maximum voluntary ventilation</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Arterial blood at partial pressure</td>
</tr>
<tr>
<td>PAI</td>
<td>PA inhibitor</td>
</tr>
<tr>
<td>PALB</td>
<td>Prealbumin</td>
</tr>
<tr>
<td>PaO2</td>
<td>Arterial blood at partial pressure</td>
</tr>
<tr>
<td>PDE4</td>
<td>Phosphodiesterase type 4</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PG</td>
<td>Prostaglandin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>PH</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>PVR</td>
<td>Pulmonary vascular resistance</td>
</tr>
<tr>
<td>Raw</td>
<td>Airway resistance</td>
</tr>
<tr>
<td>RCTs</td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td>RNS</td>
<td>Reactive nitrogen species</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>RP</td>
<td>Routine pharmacotherapy</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratios</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndromes</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>SOD</td>
<td>Superoxidase dismutase</td>
</tr>
<tr>
<td>SRs</td>
<td>Systematic reviews</td>
</tr>
<tr>
<td>SR3</td>
<td>The third systematic review</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Tc1</td>
<td>Type 1 cytotoxic</td>
</tr>
<tr>
<td>TCM</td>
<td>traditional Chinese medicine</td>
</tr>
<tr>
<td>TGF</td>
<td>Transform growth factor</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor-alpha</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue-type plasminogen activator</td>
</tr>
<tr>
<td>TX</td>
<td>Thromboxane</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>VA/Q</td>
<td>Ventilation–perfusion ratio</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>ZHYD</td>
<td>Zhong Hua Yi Dian</td>
</tr>
<tr>
<td>6MWD</td>
<td>Six-minute walk distance</td>
</tr>
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</table>
Summary

Chronic obstructive pulmonary disease (COPD) is a common lung disorder that encompasses chronic bronchitis and emphysema. It is characterised by irreversible airflow limitation with progressive worsening and has complications of respiratory failure and cor pulmonale. It is a major cause of morbidity. In Australia, 10.2% of individuals aged 40 years or older suffer from Stage 2 or higher of COPD. Globally, COPD is an increasing public health problem. It was the fifth leading cause of death worldwide in 2002 and is projected to be the third leading cause of death by 2030.

The main causes of COPD are cigarette smoking and inhalation of noxious particles or gases. The pathogenesis of COPD is not fully understood but it involves chronic inflammation, oxidative stress, protease/anti-protease imbalance, abnormal apoptosis and immune responses.

Clinically, COPD symptoms include chronic cough, sputum production, shortness of breath or dyspnea and chest tightness. It can be divided into remission/stable phase and exacerbation phase. Exacerbations of COPD involve episodes of deterioration of symptoms, which are mainly triggered by respiratory viruses and bacteria. Exacerbations are major causes of morbidity, hospitalization and mortality and strongly affect health-related quality of life (HRQoL), and thus represent a significant proportion of costs associated with COPD.

The pharmacotherapy for stable COPD, as recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD), includes bronchodilators (β2-agonists, anti-cholinergics and methylxanthines) and inhalation of corticosteroids. However, these are associated with a range of unwanted side effects and do not provide long-term relief for COPD. During the exacerbation phase, pharmacotherapies and other support are commonly effective in managing the symptoms.

Internationally, the increasing use of complementary and alternative therapies including Chinese herbal medicine (CHM) has generated broad interest from the World Health Organisation (WHO), academia, governments, healthcare professionals and the community. Recent advancements in the understanding of the pharmacological actions of Chinese herbs and formulae, such as their anti-inflammation actions and effects on immune function, may contribute to clinical decision making in increasing the use of CHM for the management of COPD.
A number of randomised controlled trials (RCTs) have evaluated the benefits of oral CHM formulae and herbal extracts for stable COPD over the last two decades. Furthermore, a number of reviews of clinical studies on herbal medicines for COPD have been conducted but these only included small numbers of studies and did not adequately represent non-English studies such as those conducted in China.

CHMs have a long history of use for chronic lung disorders, including conditions similar to chronic bronchitis and emphysema. In China, CHMs are frequently used in the management of COPD and are used in conjunction with conventional pharmacotherapy. Clinical studies suggest CHMs appear to have benefits for treating COPD. Moreover, experimental studies indicate certain CHMs have pharmacological actions relevant to COPD. Therefore, at least some of the CHMs appear to have potential to assist in the management of COPD.

The main objectives of this study were to: 1) evaluate the efficacy and safety of using oral CHM in treating patients with COPD based on systematic reviews (SRs) and meta-analysis of the results of RCTs and experimental studies; and 2) to determine which herbs and formulae show the greatest promise for further clinical research based on their history of use in the classical literature, analysis of results from RCTs and the findings of experimental studies.

This thesis consists of the following main components: 1. Reviews of the current conceptions and the current treatment of COPD in Conventional medicine and Chinese medicine; 2. Analysis of the traditional classification of COPD-like disorders in Classical Chinese medicine books (i.e. written up until 1911); 3. Identification of the main formulae and individual herbs used for COPD-like disorders over the span of the Classical Chinese medicine literature; 4. Systematic searches of RCTs on CHM for COPD; meta-analyses of results from RCTs for each main outcome measure; and analyses of the usage of herbal formulae and individual herbs in the RCTs; and 5. Identification of the likely mechanisms of action of the shortlisted herbs.

To address objective 1, SRs were conducted guided by the *Cochrane Handbook for Systematic Reviews of Interventions*. English and Chinese databases were searched, 101 RCTs for CHM in stable COPD were selected and three SRs were conducted. Overall, the findings of these three SRs supported the use of oral CHM in:

- the improvement and prevention of decline of FEV$_1$% predicted of stable COPD patients for CHM plus routine pharmacotherapy (RP) compared with RP (MD 5.12;
95% CI 3.56 to 6.68) in 20 studies; for CHM alone versus RP (MD 8.79; 95% CI 4.66 to 12.92) in 8 studies; and for CHM versus placebo (MD 7.46; 95% CI 3.72 to 11.20);

- improving QoL when CHM plus RP was compared with RP using St. George Respiratory Questionnaire (SGRQ) (MD -5.15; 95% CI -7.26, -3.05) or using Cai’s QoLQ (MD -0.25; 95% CI -0.37, -0.13);
- reduction of COPD exacerbation frequency when CHM plus RP was compared with RP (MD -1.40; 95% CI -2.34, -0.46);
- improving exercise tolerance capacity as tested by 6-minute walk distance (6MWD) when CHM plus RP was compared with RP (MD 41.39; 95% CI 28.69, 54.10); and
- relief of a range of symptoms in favour of the CHMs versus the control groups.

CHM as an adjunct therapy for COPD patients appeared to be well tolerated. However, there were insufficient data for meta-analyses to determine the effectiveness of CHM when compared with placebo.

In addition, certain CHMs appear to have had the effects of lowering the levels of TNF-α and IL-8 in sputum and serum, and regulating the levels of T lymphocyte subsets as well as immunoglobulins such as IgA and IgG. Experimental studies provided supporting evidence for the actions of a number of the formulae and herbs used in the RCTs.

To address Objective 2, based on results from the RCTs and the classical Chinese medicine literature, a number of formulae were identified as promising: Liu Jun Zi Tang ‘Six Gentleman Decoction’, Bu Fei Tang ‘Tonify the Lungs Decoction’ and Shen Ge San ‘Ginseng and Gecko Powder’ etc. The following herbs were found to be frequently used for COPD: Ren shen (Panax ginseng), Dang shen (Codonopsis pilosula), Huang qi (Astragalus membranaceus), Bai zhu (Atractylodes macrocephala), Fu ling (Poria cocos), Mai dong (Ophiopogon japonicus), Wu wei zi (Schisandra chinensis), Dan shen (Salvia miltiorrhiza) and Tao ren (Prunus persica). Moreover, experimental studies found that certain of these herbs and formulae have anti-inflammatory actions and may improve immune functions through the regulation of the levels of cytokines and T lymphocyte subsets.

In conclusion, this study comprehensively and systematically analysed modern RCTs and classical Chinese medicine interventions for COPD. Employing a range of methods of analysis, this study demonstrates that certain CHMs are potentially effective for the symptomatic management of COPD and appear to be safe adjunct therapies for adult patients.
with stable COPD. Nevertheless, further studies are needed to determine the therapeutic benefits. Such studies should address methodological weaknesses identified in the relevant reviews such as randomisation, allocation concealment, blinding and sample sizes, and would preferably be conducted in a multi-centre setting. Once efficacy of specific individual herbs or formulae is confirmed, further studies to elucidate the mechanisms of action of these herbs or formulae such as anti-inflammatory effect need to be undertaken to facilitate more informed clinical decision making for effective use of CHMs for COPD.
Chapter One: General Introduction

1.1. Background

Chronic obstructive pulmonary disease (COPD) is a common lung disorder characterised by progressive worsening and irreversible airflow limitation, and is a major cause of morbidity and mortality worldwide (1, 2). Because of the increasing prevalence of COPD and its substantial economic and social burden, greater awareness initiatives and worldwide research studies have been conducted in an attempt to improve the management and prevention of this global health problem.

1.1.1 Definition of COPD

1.1.1.1 Development of COPD

The concept of COPD has evolved over a 200-year history. Its primary components include chronic bronchitis and emphysema (3).

The clinical understanding of chronic bronchitis, first referred to as a disabling disease characterised by chronic cough and mucus hypersecretion, was traced to Badham in 1814 (4). The earliest description of emphysema was termed ‘voluminous’ by Bonet in 1679 (5) and ‘turgid’ by Morgagni in 1769 (6). In 1821, the term emphysema was used by Laënnec to describe a hyperinflated lung (7). The spirometer was invented by Hutchinson in 1846 (8). After 100 years, in 1962, the American Thoracic Society (ATS) defined chronic bronchitis as chronic cough lasting at least three months per year for more than two years and described emphysema anatomically as enlarged alveolar spaces and loss of alveolar walls. The term ‘COPD’ was used by Briscoe in a discussion at the 9th Aspen Emphysema Conference in 1965 (3). These established concepts of COPD and its components alongside 50 years of research form the foundation of the definitions of COPD in the 21st century.

1.1.1.2 Modern definition of COPD

COPD is defined as a chronic lung disease characterised by irreversible airflow limitation, according to the GOLD (9), the ATS and European Respiratory Society (ERS) guidelines (10). The airflow limitation in COPD is progressive and also associated with an abnormal inflammatory response of the lungs which is in response to noxious particles and/or gases
with the primary cause being cigarette smoking (11). COPD also produces significant systemic consequences which can contribute to the increased severity of the condition. The components of COPD include chronic bronchitis and emphysema. The former is defined by the presence of chronic or recurrent cough and sputum production that persists on most days for a minimum of three months per year for at least two consecutive years, which is not attributed to other pulmonary or cardiac causes. Emphysema is defined anatomically by permanent, destructive enlargement of airspaces distal to the terminal bronchioles in the absence of obvious fibrosis (12).

1.1.2 International variations of COPD prevalence

The prevalence of COPD is increasing in association with the ageing population (13). Studies estimating the prevalence of COPD are variable worldwide, based on the severity of COPD by GOLD and ATS/ERS criteria that categorise patients into four stages by Spirometric assessment (tested after administration of an adequate dose of inhalation of a short-acting bronchodilator, on the premise of that the ratio of forced expiratory volume in one second (FEV₁)/ forced vital capacity (FVC) is less than 70%): Stage 1 (FEV₁ ≥80% predicted); Stage 2 (FEV₁ 50 ≤ to <80% predicted); Stage 3 (FEV₁ 30 ≤ to < 50% predicted); Stage 4 (FEV₁ <30% predicted) (9, 10).

The prevalence of COPD at Stage 1 or higher was 13.9% in the general population in individuals aged 18 years and older as reported by the Third National Health and Nutrition Examination Survey in 2007 (14). In individuals aged 40 years and older, the prevalence of COPD at Stage 2 or higher was 10.2% in Australia (15), 8.2% in China (16), 5.8% in Germany (17), 10% in The Netherlands (18), 10.7% in Austria (19), 8.2% in Canada (20), 7.7% in Korea (21) and >8.4% in New Zealand (22).

1.1.2.1 Geographic and racial factors

According to an international survey, there were differences in the prevalence of COPD among different geographic regions. Compared to the Americas, Europe and the Pacific, the prevalence of COPD was higher in Southeast Asia and Latin America (13, 23). In addition, the prevalence of COPD also varies among different regions of the same country, as reported by the 2008 National Health Survey (Figure 1.1) in Australia (24) and as reported by Zhong et al. in 2007 in China (Figure 1.2) (16).
Figure 1. 1 The prevalence of COPD among the different states in Australia

Figure 1. 2 The prevalence of COPD among the different provinces in China
A study conducted by Chamberlain et al. suggested that COPD was not associated with racial factors, as whites and blacks had the same trend of increasing COPD-related mortality in the US (25).

1.1.2.2 Age and gender factors

COPD is typically diagnosed in middle-aged or elderly people, although it may occur early in life, with a family history of asthma and respiratory infections in childhood being the other important determinants of COPD (26). In some healthy young adults, lung function performance may predict airflow obstruction 20 years later (9).

COPD was more common in men; however, because of increased tobacco use in high-income countries and increased exposure to indoor air pollution (such as biomass fuels used for cooking and heating) in low-income countries in women, this disease now affects men and women almost equally (27). In Australia, since women aged 20–29 years have higher smoking rates than any other sub-group of the population, the prevalence of COPD in women is likely to increase in the coming decades (28).

1.1.3 Risk factors for COPD

The risk factors for COPD are related to the interaction between genetic factors and various environmental factors. The main contributory risk factors are genetic factors, cigarette smoke, occupational exposure and indoor and outdoor air pollutants.

1.1.3.1 Tobacco smoking (active and passive smoking)

Tobacco smoking, including cigarette, pipe, cigar and other types of tobacco use, as well as environmental tobacco smoke is a major cause and the most important risk factor for COPD worldwide, as approximately 10–15% of all smokers have been reported to develop COPD (29). According to estimates of the World Health Organization (WHO), 73% and 40% of mortality due to COPD is associated with smoking in high-income countries and low and middle-income countries, respectively (30). The risk of developing COPD was also significantly increased in current and former smokers in the United Kingdom (UK) (31). Therefore, smoking prevention initiatives should be given the highest priority to reduce the incidence of COPD.
1.1.3.2 Genetic factors

Although smoking is closely related to COPD incidence, not all smokers develop COPD in their lifetime, and approximately 10% of COPD sufferers (32) have never smoked. These findings imply that genetic factors may be involved in the development of COPD (33). Stoller and Aboussouan found that alpha1-antitrypsin deficiency is a genetic disorder that confers susceptibility to COPD (34).

1.1.3.3 Occupational exposure

Approximately 15% of COPD cases may be attributable to workplace exposure according to a systematic epidemiological review (35), which found a strong association between increased COPD risk and exposure to dusts and chemicals (vapours, irritants and fumes) (36). The latest study suggested that increased occupational diesel exhaust exposure was also associated with increased COPD risk (37).

1.1.3.4 Indoor air pollution

Exposure to indoor air pollutants is also associated with COPD development. For example, cooking or heating using biomass fuels, performing domestic work using cleaner fuels in badly ventilated buildings in rural areas and inhalation of smoke in homes are important risk factors for COPD (38, 39).

1.1.3.5 Outdoor air pollution

Exposure to outdoor air pollution has been demonstrated to confer the highest relative risk associated with mortality following chronic respiratory disease (40). A large multi-city study of elderly subjects hospitalised for COPD (41) also found that exposure to outdoor air pollution had a significant long-term effect on mortality rates.

1.1.4 Co-morbidity in COPD patients

Th pulmonary inflammation in COPD is often associated with systemic inflammation. Consequently, COPD may be linked or co-exist with some other disorders. It is estimated that approximately two-thirds of patients with COPD have one or two co-morbidities (13). The main co-morbidities include cardiovascular (myocardial infarction, stroke, high blood pressure, pulmonary hypertension (PH), cor pulmonale, tachyarrhythmia) (42-45), other respiratory (pulmonary embolism)(46), endocrine (obesity, type 2 diabetes mellitus) (47-49),
gastroenterological (gastric ulcer and gastro-oesophageal reflux disease) (50), osteoarticular (Osteoporosis) and psychiatric disorders (depression, anxiety) (51, 52), malignant tumours (lung cancer) (53) and anemia (approximately 29%, and presents as low levels of haemoglobin (<11 g/dL)) (54).

In addition, co-morbid conditions may result in impaired functional capacity, worsening dyspnoea, reduced HRQoL and increased mortality (55). Therefore, it is important to also consider the frequent association of co-morbidities when treating COPD.

1.1.5 Impact of COPD

1.1.5.1 Morbidity and mortality of COPD

According to the Global Burden of Disease Project conducted by the WHO, COPD was the fifth leading cause of death worldwide in 2002 and is projected to be the third leading cause of death by 2030 (27). Based on WHO estimates, 80 million people worldwide have moderate to severe COPD, and more than 3 million people died from COPD in 2005, which accounted for 5% of all deaths globally. Therefore, COPD is becoming a growing health and economic burden throughout the world.

1.1.5.2 Burden of COPD

The total burden of COPD involves both the economic and social aspects. The economic burden is estimated by the overall costs of COPD, including both direct and indirect costs. Direct costs are those related to the detection, treatment, prevention and rehabilitation for COPD, while indirect costs refer to those related to the morbidity and mortality caused by COPD. The annual combination of direct and indirect costs of COPD has been estimated to $8.9 billion in Australia (15), $23.9 billion in the US (50) and nearly £1.5 billion in the UK (56).

From a patient’s perspective, COPD has a profound effect on quality of life (57).

1.1.6 Management of COPD

COPD is a preventable and treatable disease. Treatment strategies mainly include managing stable COPD and its exacerbations, as no cure has been found to date (9). It is generally understood that current pharmacotherapy approaches do not prevent the progression of COPD or improve lung function (9). Furthermore, pharmacotherapeutic drugs have been associated
with significant adverse events such as potential cardiac rhythm disturbances, oropharyngeal candidiasis, dryness of the mouth, nausea and heartburn, headache and insomnia, skin bruising, and precipitate the risk of pneumonia and cardiovascular diseases (58). Since there is no cure for COPD, symptom management, quality of life improvement and reducing exacerbations have become the primary treatment objectives, particularly in stable COPD (58).

1.1.7 Complementary and alternative medicine (Chinese medicine)

Complementary and alternative medicine (CAM) approaches have been used increasingly in patients with chronic disease (59). Chinese herbal medicin (CHM) has been used for over 3,000 in China and has been gaining acceptance in developed countries (60, 61). CHM, as the main component of traditional Chinese medicine (TCM), is used by 14% of adults with chronic pulmonary conditions; specifically, ginseng is used by 23% of herbal medicine consumers in the US (62). CHM has been shown to be effective for chronic diseases such as irritable bowel syndrome, type 2 diabetes mellitus and COPD (63-65).

Numerous studies regarding CHM for COPD have been conducted in China and other countries since 1990. Some studies demonstrated that CHM formulae were effective for relieving symptoms, improving lung ventilation function and quality of life in patients with COPD (66, 67). It has also been suggested that CHM could be potentially effective for COPD treatment in terms of immunomodulation, anti-inflammation, oxidant–antioxidant balance, promotion of hemorheology and prevention of hypoxia-induced PH (68-73). However, conclusive evidence of the effectiveness and safety of CHM for COPD is lacking.

1.2. Study rationale

1.2.1 COPD is a significant global health problem

The prevalence of COPD is expected to increase because of increased smoking in both high-income and low-income countries worldwide. COPD is predicted to become the third leading cause of death worldwide by 2030 because of its high rates of morbidity and mortality (74, 75). COPD is an important economic burden associated with globally increasing direct and indirect costs (30). In Australia, COPD is the third leading cause of disease burden (76) and an important public health problem.
1.2.2  Limitations of pharmacotherapy and associated side effects

Current medical approaches include the long- or short-acting, inhaled or oral bronchodilators (beta$_2$-agonists and anticholinergics) and inhaled corticosteroids used independently or in combination. They are recommended as the first-line treatment of patients with COPD. Methylxanthines (theophylline, etc.) have been used as the third-line therapy. These medical approaches can prevent symptoms or reduce their severity, although they not inhibit the decline of lung function. Thus, the effectiveness of the recommended medical approaches are limited and are associated with side effects such as easy bruising, dry mouth and minor cardiovascular events (77). In addition, if the consideration of cost is also included, high expense is a barrier to the use of inhaled bronchodilators (9).

1.2.3  Promising results from CHM studies

CHMs have a long history of use for chronic lung disorders, including conditions similar to chronic bronchitis and emphysema. In China, CHMs are frequently used in the management of COPD and are used in conjunction with pharmaceutical management (78). There is increasing scientific evidence of the efficacy of CHM for the treatment of stable COPD. A preliminary study suggested that a single herb, ginseng extract, was effective in improving lifelong function of patients with moderate COPD (79), while other investigators have reported effectiveness using other herbal formulae (69, 80). Nevertheless, these data have yet to be critically reviewed, and many clinical trials to date suffer from poor methodological design quality. Thus, a critical review and more stringently designed randomised, controlled clinical trials are needed to delineate which single herbs or formulae may produce the best efficacy for the treatment of stable COPD.

1.2.4  Potential benefit for COPD

More than 10% of adults aged ≥40 years have COPD, and the prevalence of this disease is increasing worldwide. With growing causes of morbidity, mortality and hospitalisation in both developing and developed countries, COPD is a global burden and a major public health concern. COPD has no cure; therefore, it is critical to consider new approaches for preventing disease progression, particularly in earlier stages of COPD. This study will create a profile of the efficacy and safety of CHM for the treatment of COPD based on a systematic analysis of the contemporary literature and the results of clinical trials, and an analysis of the classical literature to provide scientific assessment of the available evidence for herbs and herbal
formulae best suited for COPD treatment.

1.3. Aims and objectives

This study aims to evaluate the efficacy and safety of oral CHM formulae for the treatment of patients with stable COPD through systematic reviews (SRs) of the modern literature, analysis of the results of RCTs and the finding of experimental studies. In addition, this study will identify which herbs and formulae are most frequently used to treat patients with stable COPD in clinical trials and which have histories of use for disorders analogous to COPD in the classical Chinese herbal literature. Another major objective of this study is to determine the specific types of herbs and formulae most likely to be beneficial in the treatment of COPD by analysis of both the modern and classical literature in order to provide directions for future clinical and experimental research.

1.4. Research questions

The research questions targeted by this study are as follows:

1. In COPD patients, based on RCT evidence, do CHMs:
   – improve Lung function?
   – improve of Quality of life?
   – reduce of COPD exacerbation frequency?
   – alleviate symptoms?
   – provide good clinical tolerance?

2. Which CHMs appear the most effective for the management of stable COPD based on the RCT evidence?

3. Which CHMs (formulae and individual herbs) have the most consistent histories of use in the classical Chinese medical literature for disorders analogous to COPD?

4. Based on all sources of evidence, which are the most promising herbs or formulae for ongoing research into the clinical management of COPD?

1.5. Thesis outline

This thesis consists of the following main components:

1. Reviews of the current conceptions, and the current treatment of COPD in Conventional medicine and CM; and
2. Analysis of the traditional classification of COPD-like disorders in Classical Chinese medicine books (i.e. written up until 1911); and

3. Identification of the main formulae and individual herbs used for COPD-like disorders over the span of the Classical Chinese medicine literature; and

4. Systematic searches of randomised controlled trails (RCTs) on CHM for COPD; meta-analyses of results from RCTs for each main outcome measure; and analyses of the usage of herbal formulae and individual herbs in the RCTs; and

5. Identification of the likely mechanisms of action of the shortlisted herbs.

The following flow diagram illustrates the overall study design (Figure 1.3).
Chinese herbal medicine for patients with stable COPD

Systematic reviews & analyses of modern RCTs

- Lung function
- Quality of life
- Relief of symptoms
- Reduction of exacerbation rate

Analysis of classical literature

Formulae and herbs used

Comparison of results of formulae and herbs between analyses of modern and classical sources

Identification of most promising formulae & herbs for treating COPD

Figure 1.3 Overview of the study design
1.5.1 *Analysis of Chinese classical literature relevant to COPD*

This analysis will be completed through a search of terms relating to COPD through ‘Zhong Hua Yi Dian’ (Encyclopaedia of TCM). It will determine which herbs and formulae were frequently used in treating combinations of symptoms which are likely to have been associated with COPD.

1.5.2 *Analyses of the modern literature and clinical trial results*

The analyses of the results of the modern randomised clinical trials (RCTs) will be conducted according to an evidence-based medicine approach as defined by Resenberg (81). According to its potential for bias, evidence can be classified into five levels, as shown in Appendix 1. Level 1 includes SRs of RCTs, which can include a meta-analysis and a more precise estimate of treatment effect (82). A large number of clinical trials have investigated the use of CHM for COPD over the past few decades. Therefore, three SRs were conducted in this study according to the methods or the Cochrane airway group (83). The three SRs are ‘oral ginseng formulae for stable COPD’ (84), SR2 ‘oral CHM for the improvement quality of life in stable COPD’ (85) both in Chapter 6 and SR3 ‘oral CHM for treatment of stable COPD’ in Chapter 7.
Chapter Two: Review of western medicine-based literature concerning chronic obstructive pulmonary disease

2.1 Introduction

This chapter focuses on the advanced knowledge accumulated by a review of western medicine-based literature concerning chronic obstructive pulmonary disease (COPD), including diagnosis, classification, differential diagnosis, pathogenesis and management of stable COPD.

2.2 Diagnosis of COPD

COPD includes the co-existence of two conditions: chronic bronchitis and emphysema. Therefore, diagnosis should include both of these conditions.

2.2.1 Symptoms of COPD

Individuals that meet the following criteria should be considered for a diagnosis of COPD:

- Age over 35 years;
- History of exposure to risk factors such as cigarette smoking; and
- Presence of persistent, progressive symptoms involving chronic cough (the cough may initially be intermittent and present only early in the morning, and it may later progress to daily occurrence, often throughout the day. It may or may not be unproductive), chronic sputum production, shortness of breath and dyspnoea (hallmark); these symptoms may be accompanied by wheezing and chest tightness.

2.2.2 Physical signs of COPD

The physical signs of COPD include the following:

- Tachypnoea (rapid breathing rate);
- Wheezing sounds or crackles in the lungs as heard by a stethoscope;
- Duration of exhalation longer than that of inhalation; enlargement of the chest, particularly the anteroposterior diameter (hyperaeration);
• Active use of the neck muscles to aid in breathing (three depressions sign); breathing through pursed lips;
• Increased anteroposterior to lateral diameter ratio of the chest (barrel chest);
• Bluish colour of the skin and lips (cyanosis, referred to as blue bloaters), most commonly seen in patients with advanced COPD with chronic primary bronchitis rather than emphysema;
• Pink colour of the face, most commonly seen in patients suffering from emphysema in whom exhalation is particularly laborious (referred to as pink puffers).

2.2.3 Spirometry in COPD

The diagnosis of COPD is confirmed by spirometry breathing tests. Spirometry measures the FEV$_1$, which is the greatest volume of air that can be exhaled in the first second of a large breath. Spirometry also measures the FVC, which is the greatest volume of air that can be completely exhaled after a large breath. Normally, at least 70% FVC is exhaled in the first second (FEV$_1$/FVC >70%). A below-normal FEV$_1$/FVC ratio is necessary for COPD diagnosis. More specifically, the GOLD criteria for COPD diagnosis also requires that values should be measured after the intake of a bronchodilator (9). The FEV$_1$ (measured after bronchodilator intake) is expressed as a percentage of a predicted normal value based on an individual’s age, gender, height and weight. Furthermore, spirometry can aid in determining the severity of COPD (9).

2.2.4 Diagnostic imaging and other tests for COPD

Diagnostic imaging for COPD includes radiological imaging, computed tomography (CT) and magnetic resonance imaging (MRI).

2.2.4.1 Chest X-ray

Chest X-ray examination displays a black and white image of the lungs and heart for assessment of the airways, parenchyma and vasculature. Although COPD cannot be diagnosed by chest X-ray alone, it may be useful for diagnosing advanced emphysema or for identifying and ruling out alternative diagnoses of diseases with symptoms mimicking those of COPD exacerbations, such as lung cancer, heart failure, pneumonia or tuberculosis (TB). Abnormal findings on chest X-rays of COPD patients may show the following:

• Flattening of the diaphragm;
• Increased anteroposterior diameter of the chest;
• A long narrow heart; and/or
• Abnormal air collection within the lung (focal bullae) (86).

2.2.4.2 Computed tomography

In contrast to the chest X-ray, CT has been used in this field for fewer years. Emphasis is on structural imaging of the lung parenchyma and airways and differential diagnosis of lung disease. In particular, high-resolution CT (HRCT) has been shown to correlate well with pathology and is currently the best method for sensitive, non-invasive assessment of pathological changes in the lung (87). Using modern multi-slice CT (MSCT) technology, the entire lung can be displayed in a high-resolution mode, creating thin slices ≤1 mm during a single breath hold (3D-HRCT). Therefore, MSCT enables a more straightforward assessment of the distribution of emphysema (88).

2.2.4.3 Magnetic resonance imaging

MRI of the lung involves a unique combination of structural and functional assessment (such as perfusion, ventilation and respiratory dynamics) within a single imaging study. It is routinely used in clinical practice for diagnosing pulmonary hypertension, airway diseases, cystic fibrosis, lung cancer and other disease states. Although the role of MRI in phenotyping COPD has yet to be determined, it is highly useful in assessing COPD (89).

2.2.5 Arterial blood gas measurement

Arterial blood gas analysis is the gold standard method for obtaining information regarding oxygenation, ventilation and acid base status of the body (90). Blood is drawn from an artery, usually one in the wrist and blood gases are measured to determine the amount of oxygen dissolved in the arterial blood at partial pressure (PaO₂), the percentage of haemoglobin saturated with oxygen (PO₂ sat), the amount of carbon dioxide dissolved in arterial blood at partial pressure (PaCO₂) and the amount of acid in the blood (normal pH, 7.35–7.45).

With regard to advanced COPD, arterial blood gases should be measured in stable patients with FEV1 <50% predicted. The results of blood gas measurement in COPD patients often show a normal or decreased PaO₂, increased PaCO₂, respiratory acidosis or clinical signs that suggest respiratory failure or right heart failure (58).
2.2.6 Alpha1-antitrypsin deficiency screening

Patients who develop COPD at a young age (<45 years) or have a family history of COPD may have co-existing alpha1-antitrypsin deficiency (i.e. <15%–20% of the normal value) (34).

2.3 Classification of COPD severity

The severity of COPD is classified into four stages as per spirometry performed after bronchodilator intake. This classification scheme of the severity of COPD differs according to the current COPD guidelines of different countries, which are summarized in Table 2.1.

Table 2.1 Severity of COPD by spirometry results

<table>
<thead>
<tr>
<th>Classification of COPD</th>
<th>Severity</th>
<th>FEV1 value (FEV1/FVC ratio &lt;70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GOLD</td>
</tr>
<tr>
<td>Stage I</td>
<td>Mild</td>
<td>FEV1 ≥80% Predicted</td>
</tr>
<tr>
<td>Stage II</td>
<td>Moderate</td>
<td>50%–80% Predicted</td>
</tr>
<tr>
<td>Stage III</td>
<td>Severe</td>
<td>30%–50% Predicted</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Very severe</td>
<td>&lt;30% Predicted or &lt;50% Predicted plus CRF</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; CRF, chronic respiratory failure; GOLD: Global initiative for Chronic obstructive Lung Disease (9); COPD-X, Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease (58); NICE, National Institute for Health and Clinical Excellence-COPD guideline updated in 2010, CSRD, Chinese Society of Respiratory Disease (91, 92).
### 2.4 Stable COPD and COPD exacerbations

COPD can be divided into two stages: stable disease and disease exacerbation. Exacerbations of COPD involve episodes of worsening of symptoms, which are mainly triggered by respiratory viruses and bacteria (93). They are a major cause of morbidity, hospitalization and mortality and strongly affect HRQoL (94). Exacerbations of COPD were categorized into three types by Anthonissen et al. in 1987: type 1 refers to COPD characterized by the major symptoms of worsened dyspnoea, increased sputum volume and sputum purulence; type 2 refers to COPD characterized by only the latter two of the abovementioned symptoms; and type 3 refers to COPD characterized by only one of the abovementioned symptoms combined with coughing, wheezing or symptoms of an upper respiratory tract infection (95). Diagnosis of major exacerbation requires the occurrence of two new symptoms that persist for minimum of two days, one of which must be a major symptom such as increased dyspnoea, sputum volume or sputum purulence. Minor exacerbation symptoms include coughing, wheezing, sore throat, nasal discharge and/or fever (96).

### 2.5 Differential diagnosis

Other lung diseases such as asthma (in particular), bronchiectasis, TB, obliterative bronchiolitis, diffuse panbronchiolitis (DPB) and congestive heart failure (CHF) need to be distinguished from COPD. These differential diagnoses are discussed below and summarized in Appendix 2.

#### 2.5.1 Asthma

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness leading to reversible airway obstruction, whereas airflow limitation is irreversible in COPD. Approximately 300 million people throughout the world are affected (97). The condition affects girls more than boys during early childhood, and this gender preponderance extends to adolescence. Asthma is the most common childhood disease and is the leading cause of childhood morbidity according to figures from school absences, hospital emergency departments and hospitalizations (98).

The development of asthma is related to sensitization to aeroallergens (house dust mites, pet allergens, cockroaches and fungi), maternal diet during pregnancy and/or abnormal lactation, pollutants (especially tobacco smoke), microbes and their products and psychosocial factors.
Typical symptoms include recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early in the morning. Asthma is classified into four types: intermittent, persistent-mild, persistent-moderate and persistent-severe. Some of the diagnostic tests for asthma include chest radiography or HRCT scanning. The most essential diagnostic component is spirometry, which is used to demonstrate the extent of obstruction and assess reversibility; however, this test is not suitable for elderly patients. The key parameter for the diagnosis of asthma is $\text{FEV}_1$ of at least 12% after inhalation of a short-acting $\beta$-adrenergic agonist bronchodilator.

The pathogenic mechanism of asthma differs according to the age of the patient. Asthma with onset during childhood and adulthood (<40 years of age) is usually immunoglobulin IgE-mediated, and exacerbations are typically caused by exposure to allergens or by acute respiratory tract viral infections. Asthma that develops at middle age or later is generally not mediated by IgE. In the elderly, it often develops with a component of irreversible airway obstruction (99). Therefore, asthma and COPD are not easily distinguishable because these conditions tend to overlap and converge in elderly individuals, thus making diagnosis difficult in these patients.

### 2.5.2 Bronchiectasis

Bronchiectasis is a common condition that is a major cause of respiratory morbidity. It is characterized by abnormal dilatation of the bronchi and bronchioles caused by *Haemophilus influenzae* and *Pseudomonas aeruginosa* (100), resulting in airway restriction; in this respect, this condition is similar to COPD. Bronchiectasis is associated with many factors, but most patients have idiopathic disease or rhinosinusitis and occurs more frequently in adults than in children (101). Patients present with chronic cough with productive mucopurulent sputum and other symptoms such as dyspnoea and haemoptysis, rhinosinusitis, fatigue and bi-basal crackles. These symptoms persist for many years and are associated with respiratory function decline despite treatment. HRCT is the gold standard for diagnosis and severity assessment (102). Spirometry results typically show moderate airflow obstruction with a high prevalence of bronchial hyper-reactivity.

There may be considerable overlap between bronchiectasis and COPD. Treatment regimens are still not well defined. Anti-inflammatory therapy and macrolides have been suggested for the treatment of bronchiectasis (103).
2.5.3 *Tuberculosis*

Tuberculosis (TB) is characterized by blood-stained sputum, is caused by specific bacteria (usually *Mycobacterium tuberculosis*) and is infectious, whereas COPD does not have any of these features. The classic symptoms of TB include chronic cough with blood-stained sputum or haemoptysis, fever, night sweats and weight loss. TB is diagnosed by tests that include sputum mycobacterial load assessed by time to positivity in liquid culture, tuberculin skin testing and chest X-ray or scan showing radiological cavitation. Treatment for TB involves the use of antibiotics to eradicate bacteria, particularly in cases of *Mycobacterium tuberculosis* infection.

2.5.4 *Obliterative bronchiolitis*

Obliterative bronchiolitis (also called constrictive bronchiolitis or bronchiolitis obliterans) is an irreversible fibrotic respiratory disease of the small airway. Its characteristic features include fibrotic and destructive lesions in the bronchiolar submucosal layer, which develop external to the airway lumen but do not extend into the alveoli (104). The most common symptom is shortness of breath with or without cough, which occurs early in the disease course. Chest physical examination may be normal or show early inspiratory crackles or squeaks. The expiratory HRCT scan typically shows a mosaic pattern, which is a patchwork of high- and low-density regions resulting from air trapping. Similar to COPD, this condition displays irreversible airflow obstruction as indicated by decreased FEV₁ or FEV₁/FVC ratio according to pulmonary function test results (105). COPD is also an irreversible respiratory disease presenting with shortness of breath; however, unlike obliterative bronchiolitis, COPD-mediated destruction extends deep into the alveoli and terminal bronchioles.

2.5.5 *Diffuse panbronchiolitis*

Diffuse panbronchiolitis (DPB) is an idiopathic inflammatory disease characterized by progressive, suppurative and obstructive airway disease (106). Prominent pathological changes seen in the respiratory bronchioles are unique to DPB (107). The inflammatory infiltrate destroys the bronchiolar epithelium and extends to the peribronchiolar spaces, although most of the alveoli are unaffected. Neutrophils and T lymphocytes, particularly CD8+ T cells, together with the cytokines IL-8 and macrophage inflammatory protein-1 are recognized to play important roles in the development of DPB (108). Symptoms (cough and sputum) typically occur between the second and fifth decades of life. Exertional dyspnoea usually follows. Physical examination reveals crackles, wheezes or both. The majority (80%)
of patients with DPB have a history of chronic paranasal sinusitis or suffer from persistent disease. In half of the untreated patients, sputum volume exceeds 50 mL per day, followed by progression to bronchiectasis, respiratory failure and eventually death (109).

2.5.6 Congestive heart failure (CHF)

Congestive heart failure (CHF) is a common condition with a higher prevalence in the elderly. CHF symptoms include dyspnoea, ankle or pulmonary oedema, fatigue and heart palpitations. It is associated with an average life expectancy of approximately three years after diagnosis, which is significantly less than that associated with many other serious illnesses such as cancer of the breast or colon (110). Although CHF shares a common symptom of dyspnoea with COPD, it is not difficult to distinguish between these diseases because of the obvious cardiac involvement of CHF.

2.6 Pathological changes in COPD

COPD is a mixture of disease manifestations such as bronchitis, small airway disease and emphysema. The presence of airway inflammation and remodelling are the most important features of COPD. These changes typically occur in the proximal airways (trachea and bronchi >2 mm internal diameter), peripheral airways (internal diameter <2 mm), lung parenchyma (respiratory bronchioles and alveoli) and pulmonary vasculature.

The aetiology of COPD is attributed to exposure to cigarette smoke and other occupational or environmental noxious particles, which induce the inflammatory response in the small airways (peripheral airways) and lungs. This response results in increased numbers of inflammatory cells [macrophages, CD8+ (cytotoxic) T lymphocytes, neutrophils or eosinophils], leading to excessive mucus production in the airway lumen, goblet cell hyperplasia and sub-mucosal gland hypertrophy. The primary consequence of mucus hypersecretion is airway obstruction. Concurrently, inflammatory cell infiltration results in a cycle of airway wall injury, scarring and remodelling, leading to abnormal tissue alterations such as squamous metaplasia. Chronic inflammation is followed by scarring and remodelling that thickens the airway walls and results in narrowing of the airways (e.g. fibrosis). Consequently, these changes lead to airflow limitation. On the other hand, inflammation and damage to the lung parenchyma (respiratory bronchioles and alveoli) result in emphysema development. Inflammation associated with substantially increased numbers of macrophages, CD8+, T lymphocytes and other inflammatory cells ultimately cause destruction of the alveolar walls.
Furthermore, increased inflammatory cell infiltration in emphysema destroys the air space walls (e.g. fibrosis), causes apoptosis of epithelial and endothelial cells, decreases the surface area available for gaseous exchange of oxygen and carbon dioxide during breathing and reduces the elasticity of the lungs, which results in enlargement of the alveolar space and a loss of support for the airways in the lungs.

Conventionally, there are three types of emphysema, namely centriacinar, panacinar and distal acinar. Distal acinar emphysema, however, is not associated with airflow limitations (111) and will not be discussed here. Centriacinar emphysema is most commonly observed in smokers, and it is characterized by regions of dilatation and destruction of respiratory bronchioles in the central area of the acinus. In contrast, panacinar emphysema involves the dilatation and destruction of the entire acinus, including the alveolar sacs as well as respiratory bronchioles, with the lower lobe dilated to a larger degree than the upper lobe. Deficiency of alpha1-antitrypsin and an early onset are commonly associated with panacinar emphysema. Both centriacinar and panacinar emphysema are characterized by alveolar destruction with loss of the capillary bed that is likely to collapse, causing further airflow limitation. Moreover, inflammatory cell immigration to the small airways, together with fibrosis and smooth muscle cell proliferation, result in a decreased diameter and increased airway resistance, leading to airflow limitation (112).

Increased numbers of inflammatory cells also cause structural changes to the pulmonary vasculature, including intimal thickening, endothelial dysfunction in the pulmonary vessels, smooth muscle hypertrophy and inflammatory infiltration. These alterations inevitably lead to the development of PH (112).

### 2.7 Pathogenesis of COPD

Several extensively investigated physiological mechanisms contribute to the pathogenesis of COPD. These pathogenic mechanisms are described below, and they include specific mediators of chronic inflammation, oxidative stress, protease–anti-protease imbalance, apoptosis, autoimmune responses and neurogenic mechanisms (113). Deficiencies in repair and replacement of destroyed alveolar walls and tissue have also been proposed to be responsible for COPD.
2.7.1 Roles of chronic inflammation and inflammatory cells in the pathogenesis of COPD

The hallmark of COPD is chronic immune inflammation, which involves a wide variety of inflammatory cells that release proteolytic enzymes and pro-inflammatory mediators into the lung. It has been demonstrated that the development of COPD is linked to an increased infiltration of inflammatory cells such as neutrophils, macrophages, T lymphocytes (CD4+ and CD8+ cells), B lymphocytes, eosinophils and epithelial cells into the lung and peripheral airways (114). This inflammatory response involves innate and adaptive immune responses of the lung and plays a key role in the pathogenesis of COPD. Important inflammatory mediators of COPD include chemokines such as interleukin-8 (IL-8) and pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), IL-1β and IL-6. The function and activity of each inflammatory mediator is described individually in the following sections. COPD may worsen with the occurrence of exacerbations in patients infected with viruses or bacteria, resulting in severe decline of lung function (115, 116). Normally, innate immune responses are critical mediators of the host response in COPD patients and involve complex molecular and cellular systems. This innate immunity may progressively be compromised in COPD patients, leading to susceptibility to frequent exacerbations of the disease. Therefore, innate immune responses are partially responsible for maintaining inflammation and tissue destruction in COPD patients (117).

2.7.1.1 Neutrophils

Neutrophils are the predominant inflammatory cells in the conducting airway and are related to mucus hyper-secretion. The severity of COPD is correlated to increased numbers of neutrophils in the airway lumen, parenchyma, bronchial glands and sputum (118). Testing of sputum and bronchiolar and bronchoalveolar lavage samples from COPD patients revealed a direct correlation between neutrophil count and COPD severity, with neutrophils rising from 30% to 70%. Of these, 15% neutrophils were present in the bronchoalveolar lavage fluid (BALF). Neutrophils can be destructive to the lung because they contain high levels of proteolytic enzymes such as serine proteinases, neutrophil elastase, proteinase-3 and cathepsin G. In addition, neutrophil elastase and cathepsin G are secretagogues that probably contribute to mucus hyper-secretion in both large and small airways in COPD patients (119).

Myeloperoxidase (MPO) is stored in the primary granule and is the only enzyme in the body that produces hypochlorous acid, which effectively chlorinates tyrosine protein residues into...
3-chlorotyrosine. Patients with stable COPD have been shown to have 3-chlorotyrosine in sputum, which is related to MPO activity. Therefore, MPO may play a role in the inflammatory process of COPD (120). Elevated human neutrophil lipocalin in the sputum of patients strongly correlated to decreased FEV1 and the degree of airway obstruction and emphysema. Neutrophil elastase is also increased in sputum and is directly related to the severity of emphysema and decreased lung function (121, 122). Neutrophil elastase can also degrade connective tissue components, activate serum proteins, inhibit ciliary activity and stimulate pro-inflammatory CXC chemokine ligand (CXCL)-8 and transform growth factor (TGF)-β synthesis, inactivate tissue inhibitors of MMPs and cleave cytokines (123). This proteolytic enzyme in combination with MMPs and cathepsins may also lead to emphysema and mucus hyper-secretion.

2.7.1.2 Macrophages

Macrophages are substantially increased throughout the respiratory airway, lumen, epithelium, lung parenchyma and pulmonary vasculature in COPD patients, and they are directly related to the severity of disease, obstruction of airway and degree of alveolar wall damage in emphysema (119). They also contribute to the adaptive immune response (124). Macrophages can produce an array of mediators to accomplish phagocytosis of inhaled particles and bacteria as well as clearance via the mucociliary escalator to keep the lungs healthy and free of infection (119). Cytokines are released by macrophages in the early immune response, including and IL-1β during the recurrence of COPD. Macrophages can also produce a variety of chemokines and other chemotactic mediators such as leukotriene B4 (LTB4), and they may be the source of elevated CXCL8, CXCL1 and LTB4 in the secretions of COPD patients.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) is also released by macrophages and is increased in sputum obtained from patients with COPD exacerbations; this may enhance survival of neutrophils. Macrophages provide antioxidants and antioxidant enzymes such as glutathione catalase and superoxide dismutase, both of which dampen oxidative stress from exogenous (e.g. cigarette smoke) and endogenous (e.g. phagocytosis of bacteria) sources. Proteolytic enzymes produced by pulmonary macrophages include MMP1, MMP2, MMP9, MMP12 and MMP14, all of which are involved in emphysema (125).

Cyclic adenosine monophosphate (cAMP) is a second messenger that is essential for relaying hormonal responses in many biological processes (126). Signalling of this molecule also directly controls inflammation by regulation of the immune response of leukocytes. Most
leukocytes express the exchange protein activated by cAMP-1 which links cAMP signalling to the inflammatory response (127).

2.7.1.3 T lymphocytes

T lymphocytes play a key role in the regulation of airway inflammation in COPD patients. T lymphocytes can damage the lung by directly or indirectly releasing inflammatory mediators such as interferon-gamma (IFN-γ) from activated CD4+ cells and TNF-α from CD8+ cells (128). Therefore, a hallmark of COPD is the infiltration of T cells that can cause further inflammation and emphysema (129). The T lymphocyte and its subsets play an important role in the pathogenesis of COPD (130). The relationship between the severity of COPD and the degree of lymphocytic infiltration into the lung has been demonstrated by Zhu et al (131).

2.7.1.4 B Lymphocytes

B lymphocytes (B cells) play a critical role in the humoral immune response and are an essential component of the adaptive immune system. B cells have been found in the lungs of COPD patients and are associated with inflammatory reaction-mediated development of COPD (132).

2.7.1.5 Epithelial cells

The role of epithelial cells and their interaction with the underlying cell layers in COPD is not well understood (133). Epithelial cells initiate and augment airway host defence mechanisms (134). They also participate in innate and adaptive immune responses and in mucosal inflammation. Epithelial cells produce antimicrobial host defence molecules, pro-inflammatory cytokines and chemokines in response to activation via pathogen recognition receptors. They are also responsible for mucus production in both protective immune responses and allergic airway inflammatory diseases (134).

2.7.2 Inflammatory mediators

Inflammatory mediators are critical to the pathophysiology of COPD. Numerous inflammatory mediators, including chemokines, lipid mediators, cytokines, reactive oxygen species (ROS), reactive nitrogen species (RNS), inflammatory peptides and growth factors, are involved in the complex inflammatory process driving COPD pathogenesis (135). This review primarily discusses chemokines, cytokines, ROS and RNS.
2.7.2.1 Chemotactic factors: lipid mediators and LTB4

Smokers susceptible to the development of COPD exhibit up-regulated LTB4 in their peripheral lungs (136). LTB4 is a pro-inflammatory mediator derived from membrane phospholipids by the sequential actions of cytosolic phospholipase A2, 5-lipoxygenase and leukotriene A4 hydrolase (137). It is produced from a variety of inflammatory cells, predominantly from macrophages and neutrophils. LTB4 is the most potent pro-inflammatory chemo-attractant (138). It promotes the recruitment of CD8+ T cells to the sites of inflammation (139). The activation of LTB4 is mediated by the BLT1 receptor, which is a high-affinity G protein-coupled cell surface receptor of LTB4 and is expressed predominantly in leukocytes (137). The inactivation of LTB4 is promoted by peroxisome proliferator-activated receptor-α cells, a group of transcription factors that regulate the gene expression of enzymes associated with lipid homeostasis and control various types of inflammatory responses (140).

2.7.2.2 Chemokines

Chemokines regulate the movement of inflammatory and immune cells to the target organs (141). Among the chemokines, a CXC chemokine, is a potent chemotactic and paracrine regulator of neutrophils. The infiltration of activated neutrophils plays a central role in inflammation and oxidative injury of the lungs.

Interleukin-8 (IL-8)

IL-8 plays a critical role in the pathogenesis of COPD. It is secreted by various cells, including macrophages, neutrophils and airway epithelial cells (142). Other chemokines involved in the recruitment of inflammatory cells are growth-related oncogene-alpha cells, epithelial cell-derived neutrophil-activating peptide-78, monocyte chemo-attractant protein-1 and macrophage inflammatory protein-1α (135).

2.7.2.3 Cytokines

Cytokines are extracellular signalling proteins produced by different cell types and are involved in cell–cell interactions (143). Cytokines associated with COPD include TNF-α, IFN-γ, IL-1β, IL-6, GM-CSF and IL-32. These cytokines play important roles in the pathogenesis of COPD and have recently attracted more interest in research investigations. Some of these cytokines are increased or activated in COPD and are associated with COPD
severity (144). Therefore, cytokine inhibitors may have beneficial effects against COPD (145).

**Tumour necrosis factor-α (TNF-α)**

TNF-α has a wide range of pro-inflammatory activities and plays an important role in mediating inflammation in COPD patients (146). It is produced from several cells, including monocytes/macrophages, T lymphocytes, mast cells and cells of the airway epithelium (143). TNF-α has multiple pro-inflammatory actions, including neutrophil degranulation accompanied by release of proteolytic enzymes, enhancement of intercellular adhesion molecule-1 expression and control of cellular migration and permeability. It also stimulates the secretion of GM-CSF, IL-6 and IL-8 and activates the nuclear transcription factor-κB (NF-κB), which activates the IL-8 gene in epithelial cells and macrophages. Therefore, TNF-α has a major role in the induction and maintenance of airway inflammation, so TNF-α inhibitors may be effective for treating COPD (147).

**IL-6**

IL-6 is a pleiotropic, pro-inflammatory and immunomodulatory cytokine secreted by monocytes, macrophages, T cells, B cells, fibroblasts, airway epithelial cells and endothelial cells. IL-6 is secreted from airway smooth muscle and is involved in the activation, proliferation and differentiation of T cells. It serves as a terminal differentiating factor for B cells and induces production of IgG, IgA and IgM (148). It appears to have an important role in COPD pathogenesis. Some studies report that high levels of IL-6 in serum or sputum samples are associated with impaired lung function or a more rapid decline in lung function. Furthermore, IL-6 is an important mediator of the acute phase response and can up-regulate C-reactive protein (CRP) at the transcriptional level. CRP has been associated with lung function in healthy individuals and/or lung function decline in smokers with COPD. In addition, IL-6 has recently been shown to contribute to the development of PH, a well-known complication of COPD that is associated with pulmonary artery remodelling triggered by alveolar hypoxia (149).

**IL-2**

The role of IL-2 in the inflammatory process is complex and involves both the pro-inflammatory and regulatory components of the immune response (150). IL-2 is associated with signal transducer and activator of transcription 5, TGF-β, CD4 and CD25 (150, 151).
Other relevant cytokine markers include IL-32 (152), (153) which is related to progression of COPD and airflow obstruction (154) and IL-1β which is increased in airway secretions and is directly correlated with COPD severity (155).

2.7.3 Oxidative stress

Oxidative stress is an imbalance between oxidants and antioxidants, which can cause damage to the cellular structures of the lung. Therefore, it is critical in the pathogenesis of COPD (156). Oxidative stress is caused by increased exposure to oxidants contained in inhaled particles and cigarette smoke and those released from Reactive oxygen species (ROS) generated by inflammatory cells such as macrophages, neutrophils and eosinophils (157) as well as immune and epithelial cells of the airways. Oxidative stress also aggravates COPD by altering nuclear histone acetylation and deacetylation, resulting in increased gene expression of pro-inflammatory mediators in the lung (158).

2.7.4 Protease–anti-protease imbalance

Imbalances between proteases and anti-proteases also contribute to the development of emphysema. This balance may be disrupted by cigarette smoke or genetically related conditions such as alpha-1 antitrypsin deficiency, which increase the activity of inflammatory cells and cause imbalance between the two enzymes (159). For example, an increase in proteinases such as MMPs has been implicated in the development of emphysema (132, 133), in the degradation of collagen in the skin of smokers (134) and in age-related remodelling of vascular walls (135).

2.7.5 Apoptosis in COPD

The term apoptosis was first proposed by Kerr et al. in 1972 to describe the process of cell turnover in healthy adult tissues (160). It is a protective mechanism of cell death against the expression of heritable genotypic changes in cells associated with mutagenesis and carcinogenesis, which are commonly seen in embryonic development (161). Recent evidence suggests that apoptosis may be an important mechanism of COPD pathogenesis. The study by Segura–Valdez in 2000 demonstrated increased alveolar cell death in the endothelium and epithelium by employing the technique of in situ end labelling of fragmented deoxyribonucleic acid (DNA) in BALF from patients with COPD (162). In addition to endothelial and epithelial cell death, this process was also demonstrated in the alveolar parenchymal cells, thereby contributing to chronic lung damage. It was later found by
Yokohori in 2004 that there was an increase in cell proliferation in emphysematous lung tissue following apoptosis of the abovementioned cells (163). Therefore, it appears that in COPD patients, emphysema may be a dynamic repeated process of cell death and proliferation.

2.7.6 Autoimmune responses

Autoimmune responses, including innate and adaptive immune processes, have been implicated in the pathogenesis of COPD (164). COPD represents a pattern of overlapping diseases (165) such as asthma. Both COPD and asthma are obstructive airway diseases involving chronic inflammation of the respiratory tract, although the patterns of inflammatory cells and mediators between the two diseases are markedly different. These different inflammatory cell profiles result in distinct patterns of structural damages in the respective diseases (166). The unique inflammatory cell types and mediators are in turn determined by the involvement of different immune cells, which recruit and activate specific inflammatory cells and result in respiratory tract cell damage (166), thus implicating immune involvement in COPD pathogenesis.

2.7.7 Reactive oxygen species (ROS) and Reactive nitrogen species (RNS)

ROS include a variety of free oxygen radicals and derivatives of oxygen that contain paired electrons (167). They can be produced by enzymatic reactions or obtained from inhalation. When ROS react with nitric oxide, RNS can be formed. Both ROS and RNS cause oxidative damage to DNA, lipids, proteins and carbohydrates, leading to impaired cellular function and enhanced inflammatory reactions. Therefore, ROS and RNS may contribute to the pathogenesis of several lung diseases, including COPD (168).

2.7.8 Neurogenic mechanisms in COPD pathogenesis

Neurogenic mechanisms may also be important in COPD pathogenesis because neuropeptide substance P, vasoactive intestinal peptide and neuropeptide Y levels are elevated in the airways of COPD patients and smokers with normal lung function (169).

The process of COPD pathogenesis, including the involvement of key inflammatory and immune cells, is shown in Figure 2.1.
Figure 2.1 The pathogenesis of chronic obstructive pulmonary disease involves key inflammatory and immune cells.

MMP: metalloproteinase; Tc1: type 1 cytotoxic T; TGF-beta: transforming growth factor-beta
2.8 Pathophysiology

Several factors cause gaseous exchange abnormalities, airflow limitation, mucus hypersecretion and pulmonary hypertension PH (170). Therefore, these components contribute to the pathophysiology of COPD, including mucociliary dysfunction, airway inflammation and structural changes.

2.8.1 Airflow limitation and air trapping

The pathophysiology of COPD is mainly characterized by inflammation throughout the central and peripheral airways, lung parenchyma and pulmonary vasculature (171). Narrowing of the lumen in the peripheral airways and parenchymal destruction contributes to the loss of alveolar attachments around the peripheral airways and the lung parenchyma because of repeated cycles of inflammation and repair (172). Concomitantly, lesions in the peripheral airways and lung parenchyma result in chronic airflow limitation (111). This impediment of airflow causes progressive trapping of air during expiration with subsequent hyperinflation, which diminishes elastic recoil and decreases the inspiratory capacity. The end result is dyspnoea and decreased exercise tolerance (172).

2.8.2 Gaseous exchange abnormalities

Breathing involves the mouth or nose, the oropharynx, nasopharynx, larynx, bronchi, bronchioles and the alveoli in which gaseous exchange of oxygen and carbon dioxide takes place. Gaseous exchange is increasingly affected as COPD worsens, resulting in an imbalance in the ventilation-perfusion ratio (VA/Q) and ultimately causing arterial hypoxemia with or without hypercapnia (173). These biochemical parameters directly correlate to the severity of emphysema. As the disease progresses in severity, the ventilatory muscles are impaired, leading to decreased ventilation and carbon dioxide retention. The abnormalities in alveolar ventilation and a decreased pulmonary vascular bed further worsen the abnormalities in VA/Q (174).

2.8.3 Mucus hyper-secretion

One of the pathophysiological features of COPD is hypersecretion of mucus in the airway. This feature is related to the increase in the number of surface epithelial goblet cell hyperplasia and to the size of the submucosal glands (175). During central airway
inflammation caused by inhaled irritants, mucus production is increased and mucociliary clearance is impaired. In the end mucus glands are enlarged and the number of goblet cells increases leading to mucus hypersecretion. The impaired clearance will provide suitable viral and bacterial growth conditions and subsequent infections in the respiratory tract, which will damage the airway further. Ciliary cells will also be lost leading to further loss of mucus clearance and increase of exacerbation risk (170). A recent study showed that MUC5AC, is found to be the predominant mucin secreted by mucosal glands in the central airways in stable COPD patients (176).

2.8.4 Pulmonary hypertension (PH)

Another pathophysiological feature of COPD is the development of PH as a result of changes in the structure and function of pulmonary vessels. The pathogenic mechanism of PH involves pulmonary vascular remodelling and endothelial dysfunction (177). The process of pulmonary vascular remodelling involves the thickening of arterial walls and small and pre-capillary arteries. This thickening is associated with the proliferation of hyperplastic intima of the pulmonary muscular arteries (178). Endothelial cells function to decrease vascular tone, regulate vessel adaptation to increased blood flow and modulate hypoxic vasoconstriction (177). Therefore, endothelial cell dysfunction may result in vasoconstriction due to endothelin-1 or angiotensin or vasodilatation due to nitric oxide (NO) or prostacyclin (179). Therefore, the development of PH can be attributed to the combination of pulmonary vascular remodelling, endothelial dysfunction and inflammatory cell infiltration, which impairs the ventilation-perfusion balance and ultimately leads to hypoxia (177).

2.9 Management of stable COPD

COPD is a chronic condition without a cure, and it can be divided into two stages: stable disease and exacerbation. Management during the stable stage focuses on improving lung function, health status and exercise tolerance, relieving symptoms and complications and decreasing the frequency and intensity of exacerbations to avoid disease progression and mortality.

2.9.1 Routine pharmacotherapy for the treatment of stable COPD

Routine pharmacotherapeutic approaches for the treatment of stable COPD include the use of bronchodilators and corticosteroids.
2.9.1.1 Bronchodilators

Bronchodilators include β2-agonists, anti-cholinergics and methylxanthines.

β2-agonists

β2-agonists are commonly used for the treatment of stable COPD because they can relax the smooth muscles of the airway, dilate the trachea and relieve airway limitation by increasing the quantity of cAMP via their agonistic effects on β2-adrenergic receptors (180, 181). β2-adrenoceptors are one of the three subgroups of β-adrenoreceptors, namely β1, β2 and β3, which are present in cardiac muscle, airway smooth muscle and adipose tissue, respectively. β2-adrenergic receptors are found not only in airway smooth muscle cells (around 30,000–40,000 per cell) but also in several other types of cells, including lung epithelial and endothelial cells and mast cells. However, they are most abundant in the small airways, particularly the alveoli. Because the smaller airways of the alveoli are most affected in COPD patients, β2-agonists are commonly used for the management of stable COPD. There are two types of β2-agonists that differ with regard to their onset and duration of effects: short-acting β2-agonists (SABAs) and long-acting β2-agonists (LABAs). SABAs have rapid onset of effects within a few minutes, and their effects last for 4–6 hours, whereas LABAs have longer-lasting effects that last for at least 12 hours. Since the 1990s, LABAs such as formoterol and salmeterol have shown an acceptable safety index and are used for the treatment of COPD (182). However, like all agonists, they have side effects due to their inotropic and chronotropic properties, including increased incidence of arrhythmias and cardiomyopathy and worsening or induction of myocardial ischemia. Tremor is also a common adverse effect of β-agonists. Long-term use of β-agonists may lead to tolerance, poor disease control, sudden life-threatening exacerbations and asthma-related death (183).

Anti-cholinergics

The parasympathetic motor system regulates the bronchomotor tone through the mediation of muscarinic (M) and nicotinic receptors to cause constriction of bronchial muscles and release of mucus into the airway lumen. This parasympathetic bronchoconstrictive effect is mediated by the M1 and M3 receptors in the lung tissue (184), and this cholinergic effect is harmful for COPD patients. On the other hand, M2 receptors present in the postganglionic parasympathetic nerves in the lung tissue inhibit acetylcholine release from these nerve terminals (185). This anti-cholinergic effect is beneficial for COPD patients because it can inhibit M1 and M3 receptors and spare M2 receptors. Therefore, anti-cholinergics are used as
the first-line maintenance treatment for COPD. Two types of anticholinergic bronchodilators given primarily in the form of aerosol are used for COPD: short-acting drugs such as ipratopium bromide and oxtropium bromide and long-acting drugs such as tiotropium bromide (Spiriva).

Tiotropium bromide is a long-acting anticholinergic bronchodilator that maintains bronchodilation for at least 24 hours, allowing once-daily administration. It reportedly improves lung function (particularly FEV₁) and decreases the occurrence of exacerbation in COPD patients (186-188). Bateman et al. suggested that this drug may also have positive effects on inflammatory cells, airway remodelling, cough and mucus production (189). As a first-line treatment, it plays an important role in maintenance treatment for COPD. Potential adverse effects of anti-cholinergics include dry mouth and supraventricular tachycardia according to the results of a randomized, controlled trial (183).

In addition to the use of long-acting β-agonists and anti-cholinergics, combinations of these two groups of medications, such as albuterol/ipratropium, have also been used for COPD treatment. However, the preliminary observed side effects of combined pharmacotherapy are similar to those of an individual drug alone. The potential of harmful synergistic effects warrants further investigation (190).

**Methylxanthines**

Methylxanthines such as aminophylline and theophylline are commonly used for the treatment of stable COPD (191) because of their properties of bronchoprotection, bronchodilation and immune modulation (192). Pharmacologically, methylxanthines are weak bronchodilators that relax the bronchial muscles, and they may also have anti-inflammatory properties. The proposed anti-inflammatory mechanism involves competitive antagonism of G-coupled adenosine A(1) and A(2) receptors and inhibition of phosphodiesterases (193). Theophylline improves lung function, PO₂ and walking distance in COPD patients. However, because of its adverse effects, particularly nausea, its use for treatment of COPD is controversial (194).

**2.9.1.2 Glucocorticosteroids**

Inhaled glucocorticosteroids such as beclomethasone, budesonide, fluticasone and triamcinolone are also used for the treatment of COPD. Some glucocorticosteroid inhaler medications are combined with long-acting β₂-agonists such as formoterol/budesonide and salmeterol/fluticasone. However, regular use of inhaled glucocorticosteroids does not modify
the long-term decline in FEV$_1$ (195). On the other hand, oral glucocorticosteroids have been shown in two retrospective studies to have clinical effects on short-term changes in FEV$_1$ (196). However, severe side effects are associated with long-term systemic administration of glucocorticosteroids in addition to an increased risk of pneumonia; therefore, their benefit as oral medications is limited (197, 198).

Glucocorticosteroids are the most effective anti-inflammatory therapy for numerous chronic inflammatory and immune diseases via the activation of anti-inflammatory genes and post-transcriptional effects (199). This activation involves a complex mechanism in which glucocorticoids bind to glucocorticoid receptors in the cytoplasm, translocate to the nucleus and bind to glucocorticoid response elements and co-activator molecules. In COPD patients who smoke, histone deacetylase 2 activity is markedly impaired as a result of oxidative/nitrative stress; therefore, inflammation is resistant to the anti-inflammatory effects of corticosteroids (200). This may explain the lack of long-term effects of corticosteroid medications in COPD patients.

2.9.1.3 Mucoactive medicines

One of the pathological symptoms of COPD is hyper-secretion of mucus in the airway. Therefore, mucoactive medications are used to improve sputum expectoration and/or decrease mucus hyper-secretion. These medications include expectorants, mucoregulators, mucolytics and mucokinetics (201). Expectorants induce the removal of sputum through coughing. Mucolytics thin the mucus and decrease its viscosity. Mucokinetics mobilize cough and increase sputum expectoration while mucoregulators suppress chronic hyper-secretion of mucus (202).

2.9.1.4 Phosphodiesterase type 4 inhibitors

cAMP has a wide range of anti-inflammatory effects on numerous key effectors involved in COPD. Phosphodiesterase type 4 (PDE4) inhibitors increase the intracellular concentrations of cAMP by inhibiting the enzymatic breakdown of cyclic nucleotides cAMP and cyclic guanosine monophosphate (cGMP) to their respective 5-nucleotide monophosphates by phosphodiesterases (203). There are 11 categories of phosphodiesterases (203), of which PDE4 inhibitors are relevant to COPD. PDE4 is a group of pharmacologically distinct enzymes encoded by at least four distinct genes (PDEA, PDEB, PDEC, PDED) that are specific for cAMP (204). PDE4 inhibitors are used for the treatment of COPD; of these, inhibitors of p38 MAPK, NF-κB kinase and phosphoinositide 3 kinase (PI3K) -gamma and -
delta have side effects, particularly nausea and other gastrointestinal effects. Therefore, delivery of this particular type of inhibitors via inhalation may be necessary (205). Other oral PDE4 inhibitors such as roflumilast represent a new class of drugs that have shown efficacy and acceptable tolerability in pre-clinical and short-term clinical studies involving COPD patients. Oral roflumilast for treatment of COPD has been demonstrated to improve lung function and decrease exacerbations in four studies that were published in the *Lancet* (206, 207). The side effects of roflumilast were found to include intractable diarrhoea, acute pancreatitis, weight loss and psychiatric symptoms such as anxiety, depression and insomnia, as well as increasing risk of incidence of cancer (208).

### 2.9.2 New therapeutic approaches for COPD

Till date, COPD has been preventable and treatable but not curable. Current therapies cannot prevent disease progression or mortality, despite recent advances in the development of longer-acting inhaled β2-agonists and M antagonists (and combinations). These new drugs still fail to suppress chronic lung inflammation in COPD patients. Indacaterol, a new LABA, has been shown to be efficacious for the treatment of COPD and asthma (209-211). It is considered to be a potentially useful drug for combination therapy in the future (212, 213). However, some studies have shown that it has an adverse effect profile similar to that of other β2-agonists (214, 215).

A different (and perhaps more promising) approach involves inhibition of the inflammatory and destructive process involved in the pathogenesis of COPD. Several mediator antagonists have proved disappointing. Thus far, the more promising drugs include CXCR2 antagonists that block the pulmonary recruitment of neutrophils and monocytes. Broad-spectrum anti-inflammatory drugs may be more effective, and further investigations to clarify their mechanism of action are warranted.

The most promising therapeutic strategy may still lie in the potent anti-inflammatory effects of corticosteroids. As mentioned above, in COPD patients who smoke, inflammation is resistant to the anti-inflammatory effects of corticosteroids because histone deacetylase 2 activity is markedly impaired as a result of oxidative/nitrative stress. Therefore, the better approach may be to increase histone deacetylase 2 activity using theophylline-like drugs and PI3K-delta inhibitors and decrease oxidative/nitrative stress using more effective antioxidants and non-antibiotic macrolides (216). A recent clinical trial showed that oral isomapimod, an
inhibitor of the signalling mediator p38 MAPK, significantly decreased plasma fibrinogen in COPD patients (217).

It is evident that there have been little therapeutic advances in the treatment of COPD over the past few decades. The pathophysiology of COPD is multi-factorial, and successful treatment can be difficult to define. At present, the most quantitative endpoint is FEV$_1$ using spirometry. Perhaps, the most suitable strategy for COPD treatment is the development of a biomarker that can be used as an endpoint measure for new pharmacotherapies (218).
Chapter Three: Chinese medicine for chronic obstructive pulmonary disease (COPD)

3.1. Introduction

This chapter will introduce the history of Chinese herbal medicine (CHM) and modern research related to COPD. It will also discuss Traditional Chinese medicine (TCM) theories and modern Chinese medicine (CM) research regarding the pathogenesis, treatment and CHM therapeutic mechanism for the treatment of COPD. Finally, evidence derived from clinical trials and animal experiments using CHM will be reviewed.

3.2. Background of complementary and alternative medicine

3.2.1. Definition of complementary and alternative medicine

Complementary and Alternative Medicine (CAM) is defined by National Centre for CAM as ‘a group of diverse medical and health care systems, practices and products that are not generally considered to be a part of conventional medicine’ (219). CAM consists of natural products including herbal medicines and dietary supplements, mind-body medicine (meditation, yoga etc) and manipulative and body-based practices (spinal manipulation and massage).

When CAM is used together with conventional medicine it is termed ‘complementary medicine’, whereas the use of CAM in place of conventional medicine is referred to as ‘alternative medicine’. The combination of CAM and conventional medicine for uses in which evidence of effectiveness and safety exists is referred to as ‘integrative medicine’, e.g. the integration of CM and western medicine.

3.2.2. Prevalence of complementary and alternative medicine practice

The use of CAM is developing rapidly within western countries and the connection with conventional health care services is expanding (220). The trend in the use of CAM has markedly increased over the last decade. For example, the use of CAM increased from 34% in 1990 to 62% in 2002 in the US (221), from 20% in 1998 to 27% in 2002 in the UK (222) and from 20.3% in 1993 to 23.3% in 2000 in Australia (223). The prevalence of CAM practice in the general population was high in some countries: 60% in Australia in 2007 (224), 73% in
Germany in 2002 (225) and 76% in Japan in 2002 (226). Approximately 38% of adults used CHM in the US in 2007 (227). The prevalence of CAM practice in England was 28.3% in 2008 (228). The overall prevalence of use of CAM in Ireland was 27% in 2002 (222). In Canada, the use of CAM was lower than other countries (12%) (229). CAM approaches are increasingly utilised by patients with chronic disease (59, 230), such as diabetes (231) and cancer (232, 233).

3.3. Chinese herbal medicine

Chinese herbal medicine (CHM) is derived from ancient China before the Christian era. It was developed and boomed during the 12th and 18th centuries, and was accepted and applied worldwide by 1970s. CHM has been modernised and industrialised over the past few decades.

3.3.1. History of Chinese Herbal Medicine

CM, also referred to as traditional CM (TCM), is a major health care system that has been used for more than 4,000 years in China before the introduction of western medicine. The theory of CM is derived from the ancient fundamental philosophy of Yin and Yang as well as the Five Phase Theory and developed gradually into a holistic system, which includes physiology, pathology, aetiology, a diagnostic system, treatment principles and treatment methods as well as disease prevention (234).

Various CM therapies are used in an effort to promote health and treat disease. The most commonly used approaches are CHM and acupuncture. CHM is a crucial modality in TCM, which includes Chinese Materia Medica, herbal formulae and the applications of formulae as internal and external medicines. These formulations are a unique feature of CHM.

CHM was invented by Emperor Shennong prior to the 17th century (BC) after risking his life by tasting numerous herbs. Initially, CHM began with the treatment of a symptom with single herb. The physical descriptions, properties and growing regions of the herbs were first described in the classical book of Shan Hai Jing-Xi Shan Jing (山海经西山经), published before the Xianqin (221 BC 先秦), while the CHM formulae were recorded in the oldest medical book, Prescriptions for Fifty-Two Diseases.

Further progress of syndrome differentiation, treatment principles, principles of herbal formulation and examples of prescription preparation were summarised in The Yellow Emperor’s Classic of Internal Medicine (黄帝内经) published during the Spring and Autumn
period (770–746 BC 春秋时代). This book provided the foundation for the development CM theories as well as TCM formulae. The first Chinese pharmacological book was entitled Shen Nong Ben Cao Jing and included 365 herbs categorised into three types (上,中,下三品) and was written by several physicians during the period of Qin-Han dynasty (221–220 BC). The first clinical medicine treatise, entitled Treatise on Cold-Attack and Miscellaneous Diseases 伤寒论 ), containing 314 formulae was written by an outstanding physician, Zhang Zhongjing in the Donghan (Eastern Han) dynasty (25 BC–220 AD 东汉).

After a few hundred years, formulae were further developed during the Tang and Song dynasties (618–1279). Typical works included the Bei Ji Qian Jin Yao Fang 备急千金要方) with 5,300 formulae written by Sun Simiao during the Tang dynasty (652), Tai Ping Sheng Hui Fang 太平圣惠方) with 16,834 formulae compiled by Wang Haiyin and issued in 992 and Shen Ji Zong Lu 圣济总录) with 20,000 formulae organised by the government and compiled from 1111–1117. Corrections were made to Tai Ping Hui Min He Ji Ju Fang 太平惠民和剂局方) by Chen Shiwen et al. in 1151, which comprised the first formula dictionary. The TCM formulae were improved during the Ming and Qing dynasty (1368–1911). For example, the well-known works such as Pu Ji Fang 普济方) with 61,739 formulae was written by Zhu Li and published in 1406, and Gu Jin Tu Shu Ji Cheng-Yi Bu Quan Lu 古今图书集成-医部全录) was compiled by Jiang Tingxi et al. and published in 1726, which was the largest book of CM (235).

### 3.3.2. Development of Chinese Herbal Medicine and modern research

During the early 19th century, western medicine was introduced to China. Initially, western medicine was regarded as ‘witchcraft’ and not accepted by the Chinese. In 1859, the first hospital was established by John Glasgow Kerr who came to China from the United States and recruited students to learn western medicine (236). Gradually, the knowledge of western medicine spread across China and impacted CM. In 1918, a medical book, Yi Xue Zhong Zhong Can Xi Lu 医学衷中参西录) written by Zhang Xichun was published. This was the first book to integrate CM and western medicine.

After 1950, several TCM tertiary colleges, CM academic institutes and hospitals specialising in CM were established in numerous capital cities in China. Over the past six decades under the auspices of the new government, these CM institutions undertook extensive research into the pharmacological and chemical properties of CM herbs and their active components by
employing modern scientific techniques and methodologies. These studies formalised the knowledge of CHM into a tertiary education system while evaluating and describing classical and modern CM formulae. As a result, CHM combined with western medicine have become the mainstream health care system for the Chinese population.

CHM was introduced to the UK, Germany and France in the early 18th century. Some classical CHM books were translated to foreign languages. In 1970, CHM was approved by the WHO, and since then CHM has become accepted worldwide. Over the past decade, CHM has become more impactful with regard to global health, particularly playing a prominent role in the treatment of severe acute respiratory syndromes (SARS) (237). To date, industries in countries such as China, India, the US and Nigeria as well as WHO have heavily invested in research on CHM in an attempt to identify promising medicinal herbs and novel chemical compounds (238). It is anticipated that CHM will play an important role in global health in future.

3.3.3. Chinese Herbal Medicine in treatment of diseases

CHM is an important aspect of CAM practice (239). CHM is used not only in the treatment of acute diseases such as SARS (237), H1N1 influenza (240) and acute ischemic stroke (241), but also of chronic diseases such as diabetes (242), endometriosis (243), chronic kidney disease (244) and disordered breathing during sleep (245). Herbal medicines are used by 14% of adults with chronic pulmonary conditions; specifically, ginseng is used by 23% of herbal medicine consumers in the US (62) and 6% of the Victorian herb users (246).

3.4. COPD in Chinese Medicine

There is no specific mention of COPD in traditional CM. However, based on its clinical manifestations, there are some symptoms or diseases of pulmonary systems (Fei xi bing Zheng-肺系病症) in CM, which are thought to be similar to COPD according to the Practice of Chinese Internal Medicine textbook (247). Categories of symptoms or diseases of pulmonary systems such as ‘cough’, ‘long-term cough’ (Jiu ke sou, 久咳嗽), ‘dyspnea’ (Chuan zheng, 喘证), ‘asthma with wheezing’ (哮证), ‘lung distension’ (Fei zhang, 肺胀), ‘phlegm-fluid retention’ (Tan yin, 痰饮), ‘cough and dyspnea’ (Ke chuan 咳喘) and ‘lung obstruction’ (Fei bi, 喘痹) were first described in The Yellow Emperor’s Classic of Internal Medicine, published during the Spring and Autumn period (770–746 BC). These descriptions were next published in Jin Gui Yao Lue (金匮要略), which was written by Zhang Zhongjing
in Donghan (25–220 BC). Additional information regarding the pathogenesis of these symptoms was recorded in *Zhu Bing Yuan Hou Lun* (诸病源候论) by Chao Yuanfang in the period of the Sui Dynasty (581-618 AD). During the past three decades, ‘cough’ (Ke sou), ‘dyspnea’ (Chuan zheng), ‘asthma with wheezing’, ‘lung distension’ (Fei zhang) and ‘phlegm-fluid retention’ (Tan yin) are commonly regarded as COPD because of their symptomatic similarity to the disease. However, ‘cough and dyspnoea’ (Ke chuan) and Fei bi are also associated with COPD but are not listed in *Practice of Chinese Internal Medicine* (248).

### 3.4.1 Definitions of COPD-related terms in CM

#### 3.4.1.1 Jiu ke sou (Long-term cough)

Cough is a symptom and condition of pulmonary disease. In CM, it is called Ke sou, which includes two words. Ke (咳) means audible cough without sputum, while Sou (嗽) is an inaudible cough with sputum. These conditions are difficult to distinguish and are generally regarded as a single condition. Based on the duration of cough, it is divided into acute cough and chronic cough. Chronic cough is referred to as Jiu ke sou (long-term cough) or Ji nian ke sou (cough for many years, 积年咳嗽) and is relevant to COPD. Therefore, the COPD-related condition involves a long-term cough in addition to impairment of the internal organs. The aetiology of cough can be classified into exopathic factors and internal impairment. Stable COPD is associated with internal impairment whereas exacerbation of COPD is because of exopathic factors (249).

#### 3.4.1.2 Chuan zheng (Dyspnea)

Dyspnoea is referred to as Chuan zheng in CM, which is a feature of dyspnoeic respiration. The patient presents with an open mouth, flaring nostrils, lifted shoulders and failure to remain horizontal because of difficult breathing. It is the chief manifestation of pulmonary disease or a result of pathologic changes of other organs that affect the lung and may be present in a variety of disorders including COPD (248).

#### 3.4.1.3 Fei zhang (Lung distension)

The TCM condition of lung distension (i.e. Fei zhang) may be regarded as a condition related to COPD. It is caused by prolonged unresolved cough or asthma with wheezing leading to impairment and deficiency of the lung, spleen and kidney with resultant impediment of qi flows. The condition is characterised by manifestations that include fullness and distension of
the chest, excessive phlegm and saliva production, coughing and wheezing. These symptoms are aggravated by physical activities. In serious cases, the complexion may be lack-lustre, lips and tongue cyanotic and face and limbs dropsy (248). The condition is typically chronic and difficult to cure.

3.4.1.4 Tan yin (Phlegm-fluid retention)

Tan yin is a pathological condition that results from retention of body fluids in different regions of the body because of abnormal circulation and transportation. The concept of Tanyin is defined in both a broad sense and a narrow sense. According to the chapter on ‘Treatment of Cough and Tan yin’ in the Essentials from the Golden Cabinet (Jin Gui Yao Lue, 金匮要略), the narrow sense of Tan yin refers to the common condition of phlegm-fluid retention, while the broad sense of Tan yin consists of four conditions depending on where the fluid accumulates in the body. One of them is caused by fluid retention in chest and lung, and is termed Zhi yin (thoracic fluid retention, 支饮). This condition is due to a deficiency of lung qi manifesting as difficulty in breathing, cough with wheezing, shortness of breath, the need to sit up to breathe more easily and the inability to lie flat while sleeping (248). Based on its clinical description, this condition is also relevant to the western concept of COPD (248).

3.4.2 Differentiation of COPD-related diseases from other similar respiratory conditions in TCM

Based on the symptoms and key manifestations of COPD, it can be diagnosed as Jiu ke sou, Chuan zheng, Fei zhang and Tan yin in CM, as described above. However, there are several other TCM respiratory conditions that share common clinical manifestations with the above COPD conditions, and it is important to recognise their characteristic features and be able to differentiate them from similar COPD-related diseases. The following sections discuss the clinical features of respiratory diseases and their distinctions from similar but COPD-related diseases.

3.4.2.1 Xiao zheng (Asthma with wheezing)

Xiao zheng (哮证) is an acute cough condition characterised by laboured breathing with a whistling sound, cough with sputum and stuffiness in the chest. It is always accompanied with dyspnoea. It generally begins in childhood, and can be triggered by external wind-cold or wind-heat attacks, changes in weather or inappropriate lifestyle. The condition may last years or decades. It is clinically similar to the COPD-related condition of Chuan zheng. The hallmark feature of Chuan zheng is dyspnoeic respiration, which presents during the
developing stages of certain acute or chronic diseases. Chuan zheng is not an independent
disease, while Xiao zheng is an independent disease. Apart from the commonly shared feature
of dyspnoeic respiration, the patient exhibits a characteristic water gurgling sound in the
throat during attacks. Therefore, the differentiation between the two conditions is that the
COPD-related Chuan zheng involves rapidity and difficulty in breathing, whereas Xiao zheng
is related to the respiratory gurgling sound (248).

3.4.2.2 Fei yong (Bronchiectasis)

In TCM, Fei yong (lung abscess, 肺痈) is described as a disease of the lung characterised by
putrid accumulation due to internal heat attack on the lung; the heat remains unresolved and
blocks the lung meridian, leading to formation and accumulation of pus in the lung. The
characteristic clinical manifestations include fever, cough, pain in the chest, profuse sputum
production with marked foul smell or coughing with blood. It is easy to misdiagnose this
condition as the COPD-related phlegm-fluid retention condition of the Tan yin group since
they share the common symptoms of cough, inability to lie flat and profuse sputum
production. However, the development of cough in phlegm-fluid retention is slow compared
to the rapid and acute cough development in Fei yong. Furthermore, in profuse sputum
observed in phlegm-fluid retention is not thick or putrid, and there is no blood in the sputum.
Also, heat involvement is substantially more severe in Fei Yong than in cough due to phlegm-
fluid retention (248).

3.4.2.3 Fei wei (Lung atrophy)

Fei wei (肺痿) is a condition of weakness of the lobes of the lung caused by long-term
unresolved coughing and wheezing, which damages the lung qi and excessively consumes the
body fluids. The key features include shortness of breath, coughing or spitting turbid saliva
and repeated occurrences. Its pathogenesis is primarily caused by excessive dryness and heat
in the lung, coldness and deficiency of lung qi. In lung yin deficiency, Fei wei presents with
expectoration of white and turbid sputum or thick bloody sputum, similar to Fei yong.
Therefore, it is necessary to distinguish this condition from Fei yong (bronchiectasis), and
subsequently from the COPD-related condition of cough due to phlegm-fluid retention. The
major differences between the two conditions are that Fei yong are caused by stagnant lung qi
causing flow impediment, whereas Fei wei is due to deficiency of lung qi causing weakness in
flow. Fei yong is an excess yang condition of rapid onset, with thick, putrid and foul sputum,
while Fei wei is a deficiency of yin condition of slow onset, with turbid sputum that is not
foul. Furthermore, patients suffering from Fei yong generally have a normal body weight whereas those with Fei wei are emaciated because of the prolonged nature of the disease. In modern CM, Fei wei may refer to Idiopathic pulmonary fibrosis (248).

### 3.4.2.4 Fei lao (Tuberculosis)

Fei lao (lung consumption, 肺痨) is caused by *Mycobacterium tuberculosis* infection in the lung, and is an infectious and chronic degenerative disease. In TCM, Fei lao has a root deficiency of yin, and during its course of disease progression often results in damage of the five zang organs. The common presentations include cough, coughing up blood, tidal fever, night sweat, pain in the chest and emaciation. Fei lao can mimic other respiratory diseases, particularly Fei yong and the COPD-related Fei zhang and critical discrimination is necessary to differentiate Fei lao from them.

Fei yong usually involves presentations of high fever, aversion to cold, cough and pain in the chest, as well as coughing or throwing up profuse amounts of yellowish-green, thick sputum that may be laden with blood. Its pathogenesis is attributed to heat toxins, and can be easily distinguished from the chronically progressive nature of the yin deficiency disease of Fei lao (248).

Fei zhang is regarded as a COPD-related condition and is characterised by four key features, namely, cough, expectoration of sputum, wheezing and oedema. When wheezing is presented with dyspnoea, it typically is the consequence of the worsening of prolonged cough, or Xiao zheng. This is different from the yin deficiency of Fei lao.

### 3.4.3 Aetiology of COPD-related conditions

Since COPD is a long-term condition related to a group of diseases including cough, asthma-related wheezing, dyspnoea, lung distension and phlegm-fluid retention; therefore, the aetiology and pathogenesis of COPD in CM is a complex process. In CM, an acute attack of COPD (i.e. exacerbation COPD) is related to the invasion of external pathogens, while stable COPD is thought to be associated with internal pathogens. The causes of COPD depend on which particular disease it is related to. Nevertheless, the causes can be generalised into two types, namely, the exopathic causes and internal impairment.
3.4.3.1 Exopathic causes

The exopathic causes of COPD are also called predisposing causes. They mainly include invasion by exopathogens, improper diet, emotional disturbances and stress.

- Invasion by exopathogenic wind involves cold, heat and dryness when the organism fails to adapt to sudden climatic changes, or inhalation of pollen, smoke and dust and irritating smells, which may induce cough, asthma with wheezing, dyspnoea, lung distension or excessive fluid retention in the chest and hypochondrium.
- Improper diet consisting of partiality for a particular kind of food, excessive intake of greasy, sweet, or pungent food, mutton or fish or excessive alcohol consumption may induce asthma-related wheezing, dyspnoea and excessive fluid retention in the chest and hypochondrium.
- Emotional disturbances or drastic variation of the seven emotions may obstruct the ascent and descent of qi, and the stagnation of lung qi may further enliven the endopathic induction of asthma with wheezing and dyspnoea.
- Stress may consume and injure the qi of the spleen, kidney and lung, which enlivens internally latent pathogens and leads to asthma with wheezing and dyspnoea and excessive fluid retention in the chest and hypochondrium.

However, invasion by an exopathogen results in an acute condition or acute attack during the chronic illness process. Thus, it will not be considered relevant to the chronic illness during the remission period (248).

3.4.3.2 Internal impairment

Internal impairment as the cause of COPD is related to impairment of the lung, spleen and kidney, which includes spontaneous pulmonary diseases such as the phlegm retention in the lung, stagnation of lung qi because of phlegm produced by spleen dampness or by failure of the impaired kidney to receive qi. These processes induce cough, asthma with wheezing, dyspnoea, lung distension and excessive fluid retention in the chest and hypochondrium. Therefore, internal impairment of the viscera and bowel (Zang-fu) function is a key cause of COPD during the remission period (248).

3.4.4 Physiology and pathology of COPD-related conditions

In CM, COPD involves the lung, spleen and kidney; functional failure in any of these organs
will affect the others. The physiological relationship between the lung, spleen and kidney determines the interrelation of their shared pathology.

### 3.4.4.1 Physiology and pathology of the lung

In CM, the lung (Fei, 肺) is responsible for performing respiration, dominating dispersion, depuration and descending of qi, as well as regulating both qi activity and the metabolism of body fluids. When the lung is impaired by a pathogen, it will lead to the conversion of body fluid into phlegm stored in the lung, and further dysfunction of lung will damage its normal function of dispersing and descending of qi. This process results in adverse flow of qi and presents as symptoms such as cough, sputum production, difficulty in breathing and chest tightness (234).

### 3.4.4.2 Physiology and pathology of the spleen

The spleen (Pi, 脾) is the central organ involved in the secretion of saliva and production of qi, and is called the ‘foundation of postnatal existence’. It is responsible for the transportation and transformation of food and fluids to the lung and heart, where qi and blood are formed, respectively, with assistance of Yuan qi from the kidney. In addition, it controls the flow of blood to the muscles and limbs and raises qi. The spleen is impaired by improper diet, which includes indulgence in greasy, cold, uncooked/raw or pungent food, or excessive alcohol consumption; these dietary factors result in deficiency of spleen qi and dysfunction of the spleen with respect to transportation and transformation. Consequently, fluid may be accumulated to form dampness and phlegm or the spleen may fail to govern the blood (234).

### 3.4.4.3 Physiology and pathology of the kidney

The kidney (Shen, 肾) functions to store the essence that is the foundation of life activities and all physiological activities of the human body, dominates the reception of qi and regulates body fluids to maintain normal metabolism. If the kidney is deficient in qi, it is unlikely to maintain normal inspiration and to grasp qi, leading to shortness of breath and dyspnoea (234).

### 3.4.4.4 The relationship between the lung, spleen and kidney

Based on Five Phase Theory, the relationship between the lung (metal), spleen (earth) and kidney (water) is such that the lung is generated by the spleen and the kidney is generated by the lung. On the other hand, the interaction between the spleen and kidney is one in which
spleen overpowers the kidney. The main function of these relationships manifests by way of the formation of qi and water metabolism. The lung controls the qi and respiration, the kidney controls inspiration and the grasping of qi, while the spleen is the source of formation of qi and controls the raising of qi (234).

3.4.5 Pathogenesis of COPD-related conditions

COPD is closely related to ‘cough’, ‘dyspnoea’, ‘asthma with wheezing’, ‘fluid retention’ and ‘lung distension’. The causative factors of these symptoms or diseases are numerous and are briefly explained as follows.

The pathogeneses of cough and chronic cough are invasion by exopathogens and internal impairment due to disorders of the viscera and bowel (Zang-fu) function. This disease is associated with the lung and other organs, particularly in the chronic cough condition. This was described in the classical work of *Za Bing Yuan Liu Xi Chu* (杂病源流犀烛) written by Shen Jinao which states ‘If lung is not impaired, it would not present cough, if spleen is not impaired, it would not present prolonged cough, if kidney is not impaired and fire is not in excess, the cough is not serious’. Chronic cough in the remissive stage is regarded as mainly relevant to internal impairment, which is due to deficiency of lung qi or lung yin as a result of spontaneous pulmonary disease, phlegm produced from spleen dampness, transformed fire from stagnated liver qi or failure of the kidney to receive qi.

Asthma with wheezing is a paroxysmal disease. Its pathogenesis is due to internal impairment of the spleen and kidney resulting in retention of phlegm in lung. The leading endopathic cause of asthma with wheezing is complicated by a syndrome interwoven with deficiency and excess. At the acute attack stage, it is regarded as a syndrome of excess in superficiality with either cold-phlegm or heat-phlegm, whereas during remission it is a deficiency syndrome of the lung, spleen and kidney. Deficient lung qi with lowered resistance leads to failure of the dispersing function of the superficies and accumulation of phlegm in the lung. Deficiency of spleen qi leads to failure of transportation and further deficiency of the middle qi and accumulation of phlegm and dampness in the body. Deficiency of kidney yang or yin leads to failure of respiration and controlling reception of qi.

The pathogenesis of dyspnoea is similar to asthma with wheezing. In general, dyspnoea is derived from the disorder of qi in its normal function of ascending and descending, ingoing and outgoing. The occurrence of dyspnoea is largely governed by the lung and kidney, with
the lung controlling qi movement and the kidney being the root of qi. Dyspnoea is also classified into two types: excess and deficiency. The former originates from the lung and the latter from the kidney.

The pathogenesis of excessive fluid retention in the chest and hypochondrium is due to cold-fluid retention in the lung and deficiency of yang in the spleen and kidney. Chronic fluid retention occurs in the spleen and kidney, causing them to fail in their warming and transforming functions, resulting in suffusion of water.

Lung distension results from chronic cough and dyspnoea with recurrent episodes, which are primarily due to deficiencies of the lung, spleen and kidney. These deficiencies result in abnormal water metabolism and cause fluid retention, qi deficiency, qi stagnation and phlegm and stasis intertexture (247).

3.4.6 Syndromes and treatment of COPD-related conditions

The above COPD-related conditions and their respective syndromes and treatments are summarised according to references (247, 250) in Appendix 3.

3.5. Advanced research progress for COPD in TCM

For past two decades, along with increasing incidences of COPD in China, TCM has also made significant advances in its understanding of COPD in the areas of disease definition, syndrome differentiation, pathogenesis, treatment, experimental research and clinical trials.

3.5.1 Disease definition

In 2009, lung distension (Fei zhang) was matched along with COPD by the ‘definition of Chinese medicine dominant entities’ addressed by the State of Administration of TCM of the People’s Republic of China (251).

3.5.2 Syndrome differentiation

COPD diagnosis is complex, involving syndrome differentiation based on the concepts of exterior impairment, interior impairment, deficiency syndrome and excessive syndrome, regardless of whether it is diagnosed as cough, dyspnoea, lung distension or fluid retention. To date, there is no standardised syndrome differentiation method for COPD alone. According to a review of the current research of CM approaches for COPD treatment during the non-
attack period, deficiency syndrome is regarded as the principal condition. Deficiency syndrome primarily involves qi deficiencies of the lung, spleen and kidney, deficiency of yang of the kidney and yin deficiency of the lung and kidney. However, yin deficiency is only a minor presentation. At different phases of COPD development, the presenting symptoms may be either deficiency in the functions of the lung, the lung and spleen, the lung and kidney, or all of these. Otherwise, the excess syndromes of phlegm and/or blood stasis should be considered. The presentation of prolonged sputum production in the morning is due to phlegm produced by the spleen that is stored in lung. The manifestation of blood stasis always manifests as chest tightness, shortness of breath and purplish lips and nails. Symptoms of each syndrome are as follows:

- Deficiency of lung qi: cough with shortness of breath, clear sputum, fatigue and aversion to talking, weak and low voice, intolerance of wind, spontaneous perspiration, pale tongue with thin and whitish fur, and weak and feeble pulse.
- Deficiency of qi of the lung and spleen with phlegm and dampness: cough with profuse thin sputum production, easy expectoration, sensation of stuffiness and fullness in the chest or dyspnoea with rumbling of sputum in the throat, pale tongue with white and greasy fur, and slippery pulse.
- Deficiency of qi of the lung and kidney: shortness of breath or dyspnoea, exhaling more than inhaling, interrupted respiration that becomes more serious with movement, spontaneous perspiration, listlessness, low voice, lassitude in the loins and knees, pale tongue with white fur, and deep and feeble pulse.
- Deficiency of yin of the lung and kidney: cough with dyspnoea, low volume of sticky sputum (sometimes blood streaked), dry mouth and throat, dysphoria with feverish sensation in the chest, palms and soles, lassitude in the loins and knees, emaciation, red tongue with little fur, and rapid pulse (252).

3.5.3 Pathogenesis of COPD in Chinese Medicine

Pathogenesis of COPD is characterised by deficiency, phlegm production and blood stasis. Deficiency refers to vital qi deficiency and impairment that primarily involves the lung, spleen and kidney, and is an important internal factor responsible for COPD occurrence, phlegm production and blood stasis (253). Sputum production is one of the primary symptoms of COPD. Therefore, phlegm not only results from pathological conditions but is also a pathogenic factor resulting in COPD. Blood stasis is caused by qi stagnancy or qi deficiency (254).
3.5.3.1 Deficiencies of the lung, spleen and kidney

COPD is a long-term condition with recurrent attacks and a protracted disease course that leads to the consumption of the vital qi inside the body. First, COPD is caused by a prolonged illness consisting of cough and dyspnoea leading to impairment of lung qi. Thus, deficiency of lung qi essentially causes the development of COPD. In addition, according to the CM Five Phase Theory, the spleen is the mother of the lung, i.e. the lung (metal) is generated by the spleen (earth). Prolonged deficiency of lung qi eventually leads to impairment of the spleen and stomach and further causes deficiency of spleen qi, i.e. ‘Child’s illness involving the Mother’. Deficiency of spleen qi plays a key role in the progress of COPD. On the other hand, kidney (water) is generated by the lung (metal); thus, prolonged deficiency of lung qi eventually affects the kidney by depletion of kidney qi and failure to breathe qi into the kidney. Therefore, deficiency of kidney qi is the consequence of gradual aggravation of COPD. The lung, spleen and kidney affect and interact with each other during the development of COPD (255).

3.5.3.2 Phlegm-fluid retention

Phlegm is the accumulation product of pathological change of the internal organs as a result of an internal pathogenic factor. Deficiencies of the lung, spleen and kidney lead to failure of fluid metabolism. Deficiency of lung qi results in the loss of the capability of the lung to distribute body fluids, with subsequent accumulation of phlegm-dampness in the lung and the presentation of sputum production. Deficiency of spleen qi inhibits it from performing its function of transportation and transformation, which leads to abnormal stagnancy and fluid retention in the lung. Thus, it is said in the classic that the ‘lung is a utensil for storage of phlegm and the spleen is a source of forming phlegm’. Deficiency of the kidney (particularly kidney yang) leads to its inability to control body fluids, maintain normal metabolism and maintain warmth. The loss of the function of transforming fluid will result in the abnormal conversion of fluid to sputum and cough.

On the other hand, abnormal distribution of body fluids due to dysfunction of the lung, spleen and kidney produces phlegm and dampness, which are regarded as an internal injury that further leads to stagnation of phlegm in lung and obstruction of lung qi, causing failure of the descending function of the lung and presenting as cough, sputum and dyspnoea. In addition, phlegm is an interior pathogenic factor, which may also be evoked by exterior pathogenic factors with accompanying heat, dampness or cold syndrome. Stagnation of phlegm as fluid
retention is a perennial condition in the progression of COPD. It is distributed through qi, spreading throughout the body, thereby swelling the body or filling the upper orifices and resulting in severe conditions such as disturbance of consciousness. Therefore, phlegm is regarded as an important factor for exacerbation of COPD in CM. However, the onus lies mainly with the spleen, because if the spleen is proficient at transportation, transformation is ensured. Then, Tan yin can be moved and stagnation can be avoided.

The lung is the utensil for storage of phlegm, while the spleen is the source of phlegm production. Consequently, lung deficiency indicates that phlegm cannot be transformed easily, while spleen deficiency suggests that dampness is not transported. Thus, phlegm ascends leading to cough with wheezing, and dampness descends and accumulates resulting in oedema of the lower limbs. Therefore, both oedema and wheezing are the consequence of the failure of normal movement of ascending and descending qi and loss of qi’s ability to move freely. If both the spleen and lung are treated simultaneously, normal transportation and transformation of phlegm and dampness will be assured (253).

3.5.3.3 Blood stasis

Blood stasis is also a consequence of pathological changes in COPD. The blood vessels converge in the lung, and the lung is responsible for the coordination of functional activities. Since circulation of blood depends on qi’s function of promoting and warming, abnormal flow of the lung qi will cause abnormal blood flow to the heart. Deficiency of lung qi or deficiency of the spleen and kidney (particularly involving heart yang) weakens the function of qi’s promoting and warming the blood circulation and results in poor circulation or further formation of blood stasis. In addition, stagnation of phlegm in the lung affects the lung’s function of ascending and descending and qi movement, thus inhibiting the movement of qi and causing blood stasis. If altered circulation or stagnation of blood occurs in the blood vessels of the lung, lung qi will be inhibited or impaired, leading to the dysfunction of qi dispersal; this process results in failure of the lung to distribute fluid throughout the body and subsequently dampness turns into phlegm. Therefore, blood and phlegm can affect each other during the development of COPD (256).

In summary, deficiency syndromes are the primary cause of the development of COPD whereas phlegm and blood stasis are involved in excessive syndromes that are the secondary cause. Therefore, the combination of the primary cause of deficiency and the secondary cause of excess is the fundamental cause of the development of COPD. The presence of these
factors and their interactions can lead to a cycle of repeated onset and protracted course of COPD.

3.5.4 Treatment of COPD

Based on the differentiation of the syndromes of chronic cough, asthma with wheezing, dyspnoea, lung distension and excessive fluid retention in the chest and hypochondrium, the prescription of herbal medicine targets the symptom pattern (i.e. syndrome). Thus, the establishment of the treatment principles of COPD is based on the following differentiation of syndromes common in COPD, which include replenishing and restoring the lung qi, replenishing the lung and invigorating the spleen, replenishing the lung and tonifying the kidney, replenishing the lung, invigorating the spleen and tonifying the kidney and moisturizing the lung and nourishing the kidney. Formulae and herbal preparations:

- Replenishing and restoring the lung qi: Bu Fei Tang includes Ren shen, Huang qi, Shu di huang, Wu wei zi, Zi wan, Sang bai pi;
- Replenishing the lung and invigorating the spleen: Liu Jun Zi Tang includes Ren shen, Fu ling, Bai zhu, Chen pi, Ban xia (Zhi), Gan cao (Zhi);
- Replenishing the lung and tonifying the kidney: Shen Ge San includes Ren shen, Ge jie;
- Replenishing the lung, invigorating the spleen and tonifying the kidney: Bu Fei Fang & Liu Jun Zi Fang & Shen Ge San;
- Moisturizing the lung and nourishing kidney: Bai He Gu Jin Tang includes Sheng di huang, Shu di huang, Mai dong, Bei mu, Bai he, Dang gui, Shao yao, Gan cao, Xuan shen, Jie geng (248).

3.5.5 Clinical trial research

Early research studies of COPD were conducted in the 1960s and were largely based on clinical observations of CHM in the treatment for COPD. Randomised clinical trials (RCTs) were applied only in the 1990s (257, 258). Until then, COPD patients were identified as having chronic bronchitis, emphysema or chronic asthmatic bronchitis; it was not until the late 1990s that the concept of COPD was introduced and patients were identified according to the Guideline of Diagnosis and Management for COPD which was issued by the Chinese Society of Respiratory Diseases (CSRD) in 1997 (259). The RCTs evaluated the effectiveness of CHM in treatment of stable COPD patients (260-262) and those in the acute stage of exacerbation (263-265). These trials involved various treatment interventions that included
CHM by oral, inhalation and injection administrations, fumigation-washing therapy, acupuncture and acupressure, Qigong, Taiji as well as co-intervention strategies such as oral administration of CHM combined with acupuncture or acupressure. Results from numerous trials for stable COPD patients indicated that CHM not only relieved symptoms but also improved HRQoL status, decelerated the decline of lung function, reduced the incidence of acute exacerbations and hospitalisations and improved nutrition status (266). In Chapters 6 and 7, we will focus on the assessment of the trials that evaluated the effectiveness and safety of oral CHM in the treatment of patients with stable COPD, through SRs and meta-analyses. These trials and animal experiments have revealed certain biochemical and immunological mechanisms of CHM in the treatment COPD and this knowledge is described in the following sections.

3.5.6 *Research in animal models*

In past decade, approximately 90 reports have been published regarding animal models of COPD. Studies using CHM formulae in a rat COPD model focused on establishing different syndromes and determining the mechanism of action of CHM in the treatment of COPD. Common syndromes in a murine COPD model involved cold-fluid retention in the lung, phlegm-heat retention in the lung, lung qi deficiency with stable COPD and deficiency of the lung, spleen and kidney (267). Studies of the mechanism of action of CHM focused on the effects of CHM formulae or extracts of single herb on airway structure remodelling, inflammatory cells and mediators, genetic factors, vasculature endothelial function and effects on lung function (268).

3.5.7 *Research on the therapeutic mechanism of CHM for COPD*

Based on results of this literature review of clinical trials and animal experimental research, the therapeutic mechanism of CHM for treating COPD is summarised according to the following aspects:

- Immunoregulation,
- Balance of oxidants and antioxidants,
- Improvement of blood rheology,
- Prevention of pulmonary hypertension,
- Improvement of respiratory muscle function, anti-inflammatory, antibacterial and bronchodilator action as well as mucous clearance.
3.5.7.1 Immunoregulation

The ability of CHM to improve immunoregulatory functions of cellular and humoral immunity has been demonstrated by the effects of inflammatory mediators, the level of immunoglobulins (Ig) and regulation of T lymphocyte subsets (269).

Reduced levels of released inflammatory mediators

COPD is characterised by chronic inflammation of the airway, pulmonary parenchyma and pulmonary vasculature, with impairment of pulmonary structure by inflammatory mediators such as leukotrienes, tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-8. Significantly reduced serum levels of TNF-α and IL-8 have been found in clinical trials (270-272) and experimental research studies (273, 274). Therefore, CHM may have effects on cytokine activities and prevent the inflammatory response in COPD patients.

Enhanced Ig levels

The serum levels of IgA, IgM and IgG were decreased in patients with COPD relative to healthy subjects (275). CHM has been demonstrated to significantly enhance the levels of IgA, IgG and IgM in patients with COPD compared to controls after Sheng Mai Injection (276). Therefore, CHM may potentially improve immune-related defences in patients suffering from COPD.

Regulation of T lymphocytes

COPD patients have reduced levels of T lymphocytes including CD3+, CD4+ and CD4+/CD8+ subsets, B cells and natural killer cells compared to healthy subjects, thus implying impairment of cellular immunity function in COPD (277). It was reported that CHM regulated the level of CD3+, CD4+, CD4+/CD8+ and CD8+ T cells in a study that used a formula containing Ren shen, Fu ling, Bai zhu and Ci wu jia and Shan zhu yu etc. and a separate study that used a formula containing Ren shen, Huang qi, Shan yao, Fang feng, Mai dong, Wei jin, Dan shen, Tao ren, Guo lou and Bei mu (275, 278). Therefore, CHM may improve the immunodeficiency of patients with COPD.

3.5.7.2 Regulation of oxidant-antioxidant balance

Because of excessive secretion of TNF-α and IL-8 in patients with COPD leading to neutrophil aggregation in the small airway and accumulation of oxygen radicals, these oxygen
radicals may attack the endothelial cell membrane and mitochondrial membrane in the airway; this process causes lipid peroxidation leading to impairment and apoptosis of cells. Dang shen \((Salvia miltiorrhiza)\) injection was found to increase the plasma level of human glutathione peroxidase (GSH-Px) and catalase and decrease lipid peroxidation, which indicated that \(Salvia miltiorrhiza\) could markedly attenuate lipid peroxide (LPO) reactions and adjust the antioxidant imbalance in patients with chronic cor pulmonale (279).

### 3.5.7.3 Improvement of blood rheology

In patients with COPD or cor pulmonale, recurrent infection, hypoxemia and carbon dioxide retention lead to increased haematocrit (Hct) blood and plasma viscosity and fibrinogen, thereby resulting in hyperviscosity syndrome and forming micro-thrombi in the lung. In COPD patients treated with CHM formulae by either oral or inhaled administration, including Zao jiao and Da zao in one study and Ma huang (Zhi), Xing ren, Gan cao, Huang qi and Chi shao in another (280, 281), CHM treatment decreased Hct, fibrinogen, blood viscosity and shear rate.

### 3.5.7.4 Prevention of pulmonary hypertension

As a result of long-term hypoxemia leading to increased aggregative index of red blood cell and blood viscosity that further cause blood stasis and dysfunction of lung tissue microcirculation, complications of pulmonary hypertension and cor pulmonale are common. Although the prevalence of pulmonary hypertension in patients with mild and moderate COPD is not known, studies have reported a high prevalence of pulmonary hypertension, which ranges from 30–70% in patients with advanced COPD and hypoxemia. Patients with COPD and hypoxemia had severely elevated pulmonary pressure and pulmonary vascular resistance (PVR) that lead to right heart ventricle dysfunction.

Vasodilator therapy may be effective in decreasing both pulmonary hypertension and systemic blood pressure, although this may also worsen hypoxemia. Studies have demonstrated that CHM may be potentially effective in selectively reducing pulmonary hypertension while not affecting the systemic blood pressure or worsening hypoxemia. In addition, pulmonary hypertension by hypoxemia is recognised to correlate with disturbances of blood coagulation and humoral factors. Therefore, maintaining balance of the ratio of tissue-type plasminogen activator (tPA)/PA inhibitor (PAI) and prostaglandin I\(_2\) (PGI\(_2\))/thromboxane A (TXA\(_2\)) as well as that of endothelin and Nitric oxide (NO) is critical for relief of pulmonary hypertension. CHM formulae or single extracts have been
demonstrated to have possible effects on pulmonary hypertension through different mechanisms described in the following sections.

**Decreased mean pulmonary arterial pressure and pulmonary vascular resistance**

Decreased mean pulmonary arterial pressure and PVR were found in studies using injection of extracts of single herbs such as Dang gui, Dan shen and Huang qi in the treatment of patients with stable COPD and pulmonary hypertension (PH) (282, 283). In addition, decreased mPAP was also found in studies using oral administration of CHM formulae by comparing pre- and post-treatment data. For example, Zhang (2001) used CHM formulae that included Ren shen, Huang qi, Lu jiao jiao, Ge jie powder, Fa ban xia, Mu li, Ting li zi, Fu ling, Gu zhi, Chuan xiong and Shui zhi for the treatment of patients with stable COPD and pulmonary hypertension (284), while Sun Zikai (2001) used CHM formulae that included Xie bai, Ting li zi, Huang qin, Gua lou pi, Sang bai pi, Zhi ma huang, Fang feng, Dan shen, She gan, Xing ren and Gan cao in the treatment of patients with COPD exacerbations and PH (285).

**Enhancement of type plasminogen activator (tPA) / PA inhibitor (PAI) ratio**

The tPA protein is involved in the breakdown of blood clots and is found in endothelial cells. PAI is the inhibitor of activators of plasminogen and fibrinolysis. PAI1 is a serine protease inhibitor protein and is a main inhibitor of the PA. It was reported that a CHM formula Qing Ning Oral Liquid including Huang qi, Bai zhu, Fang feng, Dan shen and Chuan xiong may increase tPA activity and decrease PAI activity in senile COPD patients treated for PH. Meanwhile, it has been implied that PH is potentially correlated with tPA activity and PAI activity (286).

**Prostaglandin I₂/Thromboxane A₂ balance**

Humoral factors play an important role in pulmonary vasoconstriction. Pulmonary vasoconstriction or vasodilatation depends on the ratio of vasoconstrictors/vasodilators. PGI₂ is a vasodilator, and causes increases in cAMP in blood platelet cells and suppresses their aggregation, whereas TXA₂ is a vasoconstrictor that stimulates activation of new platelets and increases platelet aggregation. Imbalances in the ratio of PGI₂/TXA₂ lead to hypertension. Extracts of Mao dong qing leaf administered as a Dihydroxyacetophenone injection were found to reduce the level of plasma atrial natriuretic peptide (ANP), cGMP and blood viscosity, enhance the level of cAMP/cGMP and regulate the balance of the PGI₂/TXA₂ ratio in patients with stable COPD (287). A Xie Bai capsule consisting of Xie bai, Gua lou, Ban xia
and Huang lian etc. was found to have similar functions in the treatment of patients with COPD and PH (288).

**Nitric oxide (NO) and Endothelin balance**

Endothelin (ET) is a protein that constricts blood vessels and raises blood pressure. NO is recognised as an important endothelium-derived vasodilator that plays a major role in maintaining vascular tone in normal pulmonary vasculature (289). Increased ET and decreased NO lead to strongly constricted pulmonary vasculature and PH. Wu found that a CHM formula containing Di huang (Shu), Dang shen, Huang qi, Fu ling, Bai zhu, Ling zhi, Tu si zi, Du zhong, Xing ren (Bei), Su zi, Dan shen and Dang gui decreased the level of serum ET and increased serum NO levels in patients with stable COPD (290), while ET1 was decreased in a study using Dang gui injection in patients with COPD and PH (283).

**3.5.7.5 Improvement of respiratory muscle function**

In COPD patients, because of increased lung volume, malnutrition, increased airway resistance, hypoxaemia, hypercapnia and respiratory acidosis that cause structural changes of the respiratory muscle and reduction of respiratory function, there is increased energy demand of the respiratory muscle. Conversely, respiratory muscle fatigue is one of causes of leading worsening hypercapnia and respiratory failure that finally form a vicious cycle, thereby accelerating the reduction of exercise tolerance and quality of life. Studies on the effect of Shen Mai Injection have indicated that it may improve diaphragmatic function in COPD patients with respiratory failure and diaphragm fatigue (291); it may also improve respiratory muscle strength and respiratory muscle endurance in COPD patients (292). Shen Mai Injection has been demonstrated to improve adaptability of the diaphragm muscles and further improve the relaxation and contractility function of fatigued diaphragm muscles in a rat experimental model (293).

The results found in randomised clinical trials for the effects of CHMs in stable COPD will be analysed and discussed in chapters six and seven and the results of experimental studies of specific CHM will be discussed in Chapter 8.
Chapter Four: Methods for analysing the classical literature and modern clinical trials

This chapter is divided into two parts: 1) methods used for analysing the classical literature (4.1) and 2) methods used for systematically reviewing and analysing contemporary clinical trials (4.2).

All books relevant to CM written up to 1911 belong to classical literature, whereas books written after 1911 belong to modern literature (294). The classical literature was analysed based on searches of the Encyclopaedia of Traditional Chinese Medicine, which comprises about 1,000 classical books, while the modern literature analysis focused on the contemporary clinical trial literature published during the 1970s and later.

The methods used for the classical literature included the following: search strategies; selection of search terms; establishing selection criteria (both inclusion and exclusion criteria); developing coding and rating systems based on the selection criteria; procedures for data extraction and data entry for both formulae and herbs; and procedures for data analysis using SPSS.

The analyses of the modern literature included SRs and meta-analyses based on evidence-based medicine. The methods for the SRs included the following: search strategies, including identifying search terms and databases for searching; establishing criteria for considering these studies, including identifying the types of patients, studies, interventions and outcome measures; assessments of risk of bias and methodological quality of included studies; data collection and data analysis using Review Manager (5.1.0); and data interpretation. In addition, analyses are conducted of the frequency of usage of herbal formulae and individual herbs.

4.1 Methodology for searching the classical literature

In general, searches of the classical literature tend to be more productive for diseases for which clearly identifiable classical terms exist or for conditions that can be identified based on the kinds of signs and symptoms that are frequently recorded in the classical literature. In these cases, the classical terms for each of the signs and symptoms can be identified and used as primary search terms. In the case of COPD, because it is a modern disease category, it
modern designation, Fei zhang, and the major clinical symptoms of COPD formed the basis of the search terms.

The search procedure used an electronic database: Zhong Hua Yi Dian (ZHYD: Encyclopaedia of Traditional Chinese Medicine) (295). The ZHYD is a large series of electronic books on compact disk. It is a comprehensive collection of classical Chinese medical books that was issued by the Hunan electronic and audio-visual publishing house. The latest version of ZHYD contains 1,000 ancient and pre-modern Chinese medical books in more than 10,000 volumes and 0.4 billion words. It is the most ambitious collection of Chinese electronic books that has been accumulated to date and includes the major Chinese ancient works, many of which are from rare manuscripts and are the only existing copies. These books cover the period from ancient times up to the period of the Republic of China (1911-1948). Relevant results from searches were entered into Excel spreadsheets. Inclusion and exclusion criteria were applied to the extracted data. Finally, the data were rated for their relevance to COPD and analyzed by SPSS (version 19).

4.1.1 Search terms and search strategy

The search strategies included the following:

- Search for and identify suitable search terms;
- Establish inclusion and exclusion criteria for selecting suitable data; and
- Develop criteria for classifying, coding and rating data.

4.1.1.1 Search methods for identifying search terms

As discussed in Chapter 3, there are no disease names that correspond exactly to COPD within traditional Chinese medicine, either in modern texts or in the classical literature. However, disorders similar to the contemporary concept of COPD may have been classified under other disease names in the classical literature.

Discussions of terms used for disorders analogous to COPD appear in books on Chinese internal medicine and in modern literature reviews of the classical literature. Thus, it was necessary search these sources to identify suitable search terms. The approach used was to locate the sections on disorders similar to COPD in the following sources: TCM books issued in past decades; classical books; journal articles; and CM dictionaries. Terms relevant to COPD were defined based on the symptoms and signs that are typical of COPD; for example,
chronic cough, dyspnoea and sputum.

The methods used to identify search terms involved the following steps. The results for each of these steps are discussed in detail below.

Step 1: Search books on Chinese medicine, including general books and specialist books on respiratory diseases, to identify disease names used in the traditional literature that are relevant to COPD and to ensure that a wide range of possible terms are considered.

Step 2: Use CM dictionaries to identify terms related to COPD.

Step 3: Search the journal databases CNKI and CQVIP for any articles on the origin of COPD, its names during the classical period or how it was treated in pre-modern China.

Step 4: Categorize the classical terms into the following: those that appear to be good matches with the modern terms for COPD and could be considered as search terms; classical terms that are not clear or do not match with COPD; terms whose scopes of meaning are too broad to be considered as useful search terms.

Step 5: Conduct ZHYD searches to determine the number of results for each term and examine example references to determine if they are good matches to the disease.

4.1.1.2 Method for identifying and selecting search terms for the classical literature

Searches were conducted of relevant books in the Library at Guangdong Provincial Hospital of Chinese Medicine or Beijing University of TCM, books in Xin Hua Book store in Beijing, China and books and dictionaries held at RMIT University in Melbourne.

Step 1: Book Searches

A workshop was held at Guangdong Provincial Chinese Medicine Hospital from October 7-14, 2010 that focused on methods used for analysis of the classical CM literature. More than ten books were located in the library at Guangdong Provincial Chinese Medicine Hospital. These included books on Chinese internal medicine, clinical Chinese internal medicine and specialty books on respiratory diseases, which contained chapters on COPD and/or pulmonary diseases associated with COPD and listed in Appendix 4.

The TCM disease names commonly related to COPD in these chapters were Ke sou (咳嗽), Chuan zheng (喘证) and Fei zhang (肺胀). Ke sou was further divided into Bao ke (暴咳) and
Jiu ke (久咳) in two books written by Wu and Zhu (296, 297). The former term refers to a suddenly occurring violent cough of short duration and the latter term refers to a long-term cough. In addition, syndrome names like Tan ke (痰咳) and Tan sou (痰嗽) were described in the book written by Wang in 2009 (248). The term Zhi yin (支饮) was also found in the book by Wu (296), but it was not classified under pulmonary diseases. Fei zhang was mentioned in all of the books (Appendix 4).

**Step 2: Dictionary Searches**

The words pertaining to major symptoms, syndromes and disease names for COPD and related disorders were looked up in dictionaries, including Zhong Yi Da Ci Dian (中医大辞典), Jian Ming Zhong Yi Ci Dian (简明中医辞典) and Xin Pian Jian Ming Zhong Yi Ci Dian (新编简明中医辞). These terms are listed in (Table 4.1). The TCM disease names associated with COPD found in these dictionaries included the following: Ke sou; Chuan zheng; and Chuan sou (喘嗽). The syndrome names included the following: Ke ni (咳逆) Chuan man (喘满); Chuan tan (喘痰); Fei zhang; Tan ke (痰咳); Tan sou (痰嗽); Tan chuan (痰喘); Tan yin ke sou (痰饮咳嗽); Tan yin chuan ji (痰饮喘急); and Tan yu sou (痰瘀嗽) (Table 4.1).

<table>
<thead>
<tr>
<th>First Author, date</th>
<th>Dictionary name (in English)</th>
<th>Dictionary name (in Chinese)</th>
<th>Disease names relevant to COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, 2004</td>
<td>Concise Chinese Medicine Dictionary</td>
<td>简明中医辞典 (修订本)</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Li, 2005</td>
<td>Great Dictionary of Chinese Medicine</td>
<td>中医大辞典</td>
<td>Ke sou, Chuan zheng, Fei zhang, Tan yin</td>
</tr>
<tr>
<td>Yan, 2007</td>
<td>New Concise Dictionary of Chinese Medicine</td>
<td>新编简明中医辞典</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
</tbody>
</table>

**Step 3: Journal Database Searches**

As discussed in Chapter 4, 102 articles were included in the systematic review based on searches of several journal databases, including CNKI, CQVIP and Wanfang. COPD was considered to belong to the Chinese medicine category of Chuan zheng (including Jiu chuan 久喘 and Xu chuan 虚喘) in 57 articles, to the category of Fei zhang in 57 articles, to the category of Ke sou (including Jiu ke and Ke sou by internal impairment, 内伤咳嗽) in 35 articles, to the category of Tan yin in 15 articles and to Xiao zheng (哮证) in 12 articles.
In addition, the terms Ke chuan (咳喘), Duan qi (短气) and Xu lao (虚劳) were reported in one article each. Chuan zheng and Fei zhang were simultaneously mentioned in 52 articles, while the three terms Ke sou, Chuan zheng and Fei zhang were all mentioned in 28 articles.

Step 4 Categorization of the classical terms

Cough is one of the most common symptoms not only for COPD, but also for other lung and non-lung diseases. Thus, it is not a symptom unique to COPD. Cough in and of itself does not lead to a diagnosis of COPD, even if it is chronic. A positive diagnosis of COPD is made when cough also presents with terminal bronchiectasis (i.e. emphysema as a result of partial blockage of terminal bronchioles).

Similarly, wheezing is a syndrome that can be observed in many different diseases, such as cardiac or renal insufficiency, both of which may present with breathing difficulties. Tan Yin, a by-product of a disturbance in water metabolism, can stagnate in any Zang fu (viscera and bowels) organs causing various types of disease. In Chinese medicine, the condition of Tan yin is not classified within the category of pulmonary diseases. Also, the three presentations of Cough, Wheezing and Tan yin described above actually encompass a wide range of medical conditions.

The important issue was how to differentially identify the circumstances when these terms were relevant to the diagnosis of COPD. Identifying conditions that were likely to have been COPD was based on the age of the patient, descriptions of the symptoms and their onset (whether the condition was acute or chronic) and other aspects (see details below).

Step 5 Search procedures for ZHYD

When the ZHYD is opened, two separate window panes are displayed to the left and right of the interface. These interact with each other as the user navigates through the different sections of the CD-ROM. The pane on the left-hand side shows the outline of the dictionary and a catalogue of books. The pane on the right-hand side shows the contents of relevant works. There are five functions on the top of the right pane that include the search field and buttons for book search, headings search, content search and results exchange.

The following figures show the procedure for searching the ZHYD using a particular search term. In Figure 4.1, Ke sou was entered into the search field, the categories/headings (Mu lu) search was selected and 839 hits were found for this term in the categories/headings in the
books (shown in red text).

Figure 4. I Search procedure for the ZHYD using Ke sou as the search term and showing the initial results
After this, the ‘show results’ button is selected to display all of the book headings in which results were found in the left-hand pane (see Figure 4.2).

Figure 4.2 Search procedure for the ZHYD using Ke sou as the search term, showing the book headings that contain results (left pane)
By selecting the arrow key at the right bottom corner, one can scroll down to see all of the contents in the book that are shown under each heading displayed in the right-hand pane (see Figure 4.3).

**Figure 4. 3 Search procedure for the ZHYD using Ke sou as the search term, showing the book contents in the right pane for each heading in results left pane.**
Results of trial searches of the ZHYD for search term selection

Trial searches of the ZHYD were conducted for each candidate search term to determine its utility and specificity (see Table 4.2). For example, the terms Tan yin (phlegm, sputum) and Ke sou (cough) were entered into the ZHYD. Both search terms were found to be too broad. There were 297 results found in a headings search for Tan yin. These included a wide variety of conditions that involved Tan yin as a symptom or as part of the aetiology. Similarly, there were 839 results found when searching the term Ke sou, which involved many kinds of Ke sou (cough) with numerous instances of children with Ke sou. Some of these results referred to long-term or many years cough that were described as Jiu ke sou, Jinian kesou (积年咳嗽), Yuannian kesou (远年咳嗽) or Tanyin kesou. Thus, these more specific terms were considered to be more suitable as search terms for COPD.

Table 4.2 Results from heading searches and content searches for candidate search terms

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Heading search</th>
<th>Content search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ke sou (cough)</td>
<td>839</td>
<td>10,830</td>
</tr>
<tr>
<td>Jiu ke sou (long-term cough)</td>
<td>11</td>
<td>94</td>
</tr>
<tr>
<td>Jiu ke (chronic cough)</td>
<td>21</td>
<td>609</td>
</tr>
<tr>
<td>Jiu sou (chronic sputum)</td>
<td>39</td>
<td>1083</td>
</tr>
<tr>
<td>Chuan zheng (dyspnoea)</td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td>Chuan sou (dyspnoea and sputum)</td>
<td>46</td>
<td>1845</td>
</tr>
<tr>
<td>Ke chuan (cough and dyspnoea)</td>
<td>13</td>
<td>629</td>
</tr>
<tr>
<td>Fei zhang (lung distension)</td>
<td>13</td>
<td>656</td>
</tr>
<tr>
<td>Zhi yin (Thoracic fluid retention)</td>
<td>8</td>
<td>520</td>
</tr>
<tr>
<td>Tan yin (phlegm-fluid retention)</td>
<td>297</td>
<td>4318</td>
</tr>
<tr>
<td>Tanyin kesou (phlegm-fluid retention causing cough)</td>
<td>25</td>
<td>84</td>
</tr>
</tbody>
</table>

4.1.1.3 Finalisation of search terms

Based on the steps discussed above, the following list of search terms was identified: Jiu ke; Jiu sou; Ke chuan; Chuan sou; Chuan zheng; Fei zhang; Zhi yin; and Tan yin ke sou. The majority of these search terms are disease names in Chinese medicine, in addition to some syndrome names that are related to cough and dyspnoea. Zhi yin also belongs to the category of Tan yin with a presentation of either cough, dyspnoea, sputum or chest tightness. According to respiratory experts’ opinions on the correlation between terms used in CM and COPD, the term Zhi yin was suggested by Guangdong Provincial Hospital as a suitable search term.
4.1.1.4 Establishing selection criteria based on clinical features

Based on the results of the trial searches, it was evident that each search term could find many references that were irrelevant to COPD because all examples of the term were included in the ZHYD search results. Therefore, it was important to establish criteria for identifying irrelevant references. Also, the remaining references could include examples that were more or less clear examples of COPD; thus, a method for distinguishing these was also needed.

Based on the diagnostic features of COPD, inclusion and exclusion criteria were established to assist in identifying relevant references resulting from the searches.

Inclusion criteria

The key clinical features for a positive diagnosis of COPD are as follows: 1) patients older than 18 years of age of either gender; 2) long-time or perennial cough accompanied by sputum production or shortness of breath or dyspnoea; and 3) chronic condition. Therefore, classical references that included these three features were considered as the mostly likely to refer to COPD. In addition, treatments were limited to 4) oral preparations, such as an herbal decoction or a pill.

Exclusion criteria

References that mentioned the following features were considered as exclusion criteria: 1) exacerbation or acute condition; 2) hard breathing diagnosed as Xiao zheng (asthma) or Hou chuan (齁喘) in Chinese medicine; 3) haemoptysis or purulent sputum with abnormal smell that was diagnosed as Fei yong (肺痈), Fei lao (肺痨), Fei wei or a similar symptom in Chinese medicine; 3) children or pregnant or postpartum women; 4) intervention with acupuncture or moxibustion, acupressure, steaming and inhaling; 5) dietary interventions or use of special foods, such as animal organs. Also, instances of references duplicated in the same book were excluded.

4.1.1.5 Scoring the inclusion and exclusion criteria for COPD

Based on the trial searches using candidate search terms it was evident that there was no disease name that always directly corresponded to COPD in the classical works of Chinese medicine. Therefore, to select references from the classical literature that more or less closely corresponded to COPD, a scoring procedure for the above COPD diagnostic features was established.
The key symptoms of cough, sputum, dyspnoea and chest tightness are not only associated with COPD, but are also present in other respiratory diseases. In addition, disorders involving children, women or haemoptysis needed to be identified and scored.

Scoring of the key symptoms included the following:

- Dyspnoea was scored from 0 to 4: ‘0’ was no mention of dyspnoea and ‘4’ was severe dyspnoea;
- Cough was scored from 0 to 3: ‘0’ was no mention of cough and ‘3’ was chronic or long term cough;
- Sputum was scored the same way as Cough;
- Chest tightness was scored from 0 to 2: ‘0’ was no mention of chest tightness and ‘2’ was chest tightness.

The details of the scoring system are shown in Table 4.3.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>No mention</td>
<td>No</td>
<td>Yes</td>
<td>Worse with exercise</td>
<td>Severe dyspnoea</td>
</tr>
<tr>
<td>Cough</td>
<td>No mention</td>
<td>No</td>
<td>Yes</td>
<td>Chronic or long time cough</td>
<td>NS</td>
</tr>
<tr>
<td>Sputum</td>
<td>No mention</td>
<td>No</td>
<td>Yes</td>
<td>Chronic sputum</td>
<td>NS</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>No mention</td>
<td>No</td>
<td>Yes</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

In addition, children and women (pregnant and post partum) needed to be identified and excluded. The scoring for children and women was from 0 to 2, with ‘0’ as no mention, ‘1’ for children and ‘2’ for women (pregnant and post partum).

Normally, haemoptysis is not relevant to COPD, so this condition should be excluded. This was scored the same way as chest tightness. Also, acute injury or acute lung diseases should be excluded. Acute conditions were scored from 0 to 2. The scoring systems for these exclusions are listed in Table 4.4.

<table>
<thead>
<tr>
<th>Exclusions</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children/women</td>
<td>No mention</td>
<td>Yes children</td>
<td>Yes women</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>No mention</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute condition</td>
<td>No mention</td>
<td>No, chronic disorders</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 4. 3 Key symptoms of COPD: Numerical scores and meanings

Table 4. 4 Exclusions: Numerical scores and meanings
To integrate all of the factors described above, plus any other information that was consistent with a diagnosis of COPD, a global score was also used. The global score was from 0 to 4: ‘0’ indicated that no relevant information was provided, ‘1’ was not COPD, and ‘4’ was likely COPD (see Table 4.5).

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meaning of score</td>
<td>No information</td>
<td>Not COPD</td>
<td>Possible COPD</td>
<td>Possible complication of COPD</td>
<td>Likely COPD</td>
</tr>
</tbody>
</table>

4.1.1.6 Search procedure for identifying references in the ZHYD CD

Each search term (i.e., Jiu ke, Jiu sou, Chuan zheng, Tanyin kesou, Ke chuan, Chuan sou, Fei zhang and Zhi yin) was searched for separately in the ZHYD using the headings search. For each search, one term was entered into the search field, ‘headings search’ was chosen, the number of hits was recorded and the ‘show results’ button was used to show a catalogue of the results in the left-side pane. When each item from the left pane was chosen, the catalogued content of the book section appeared in the right pane. When the reference included an herbal formula, all of the content in the right-hand pane for each item along with the formulae was copied into an Excel spreadsheet. Results that were simply a title, had content that was not related to formulae or were duplicated items were not copied. A content search was not used because the results found in trial content searches were too broad and consisted of a great deal of content that was irrelevant to the use of herbal formulae. For example, Ke sou located 839 items through ‘headings search’ and more than 10,000 items using ‘content search’. Thus, it was impractical to use ‘content search’ for each of the search terms.

4.1.2 Data entry into Excel spreadsheets

The content of each item that was relevant to the oral administration of herbal formulae was copied to a single line in an Excel spreadsheet that had been set up for data extraction. Each spreadsheet included the following columns: search term; book; symptoms described; formula name; and formula ingredients and preparation. When the reference included more than one herbal formula, each was listed on a separate line in the spreadsheet so that each line contained one herbal formula associated with the search term.
Columns for the inclusion and exclusion criteria and global scores were also established as follows: key symptoms - dyspnoea in column 1 (C1), cough in C2, sputum in C3, chest tightness in C4 and haemoptysis in C7. Each of these was assessed using the COPD rating scales discussed above and these scores were entered in the spreadsheet. In addition, children and pregnant or post partum women were identified in C5 and acute conditions were identified in C6. The ‘global scores’ were coded in Excel in C8. Each formula and each herb was assigned a code number in Excel.

4.1.3 Data entry into SPSS

The Excel data were entered into SPSS (Version 19) as numerical values with each column in Excel becoming a variable in SPSS. Each herb in each formula comprised a single line of data, which was referred to as an ‘herb entry’ (HE). Each herb entry included the identity of the herb as a numerical code based on its Chinese name, the name of the formula and book from which it was derived, the search term used to locate the entry and the categorization scores (i.e. inclusion/exclusion criteria scores and global score). The HE formed the main unit of analysis because the ultimate aim was to locate individual herbs for further research.

4.1.4 Data analysis with SPSS

Any duplication due to repetition of the same formula for the same indications within the same book or repetition of the book under a different name or section in the ZHYD was identified. These were excluded from further analysis. Baseline data for the key variables were calculated after excluding duplicated citations.

At the next stage, based on the exclusion criteria, formulae identified as unlikely to be COPD were excluded (e.g. disorders of children, acute conditions). Total frequencies of formulae and individual herbs were calculated. Frequencies were also calculated according to the four principal COPD symptoms. To conduct this analysis, these variables were recoded as dichotomous outcomes. The aim was to determine whether there were variations in the herbs used according to each symptom.

Subsequently, the entries were grouped based on combinations of the four principal COPD symptoms; first in pairs, then in groups of three, and finally the citations that combined all four symptoms were identified. These were considered the groups most likely to have referred to conditions consistent with the modern concept of COPD. For these citations, formula and herb frequencies were calculated and individual citations were examined.
Independent of the hierarchical analysis and after excluding duplications, the citations were grouped based on the global rating scores. The aim here was to identify citations that were more or less likely to have referred to COPD based on the rater reading the item and allocating a value, rather than the step-wise procedure outlined above.

Frequencies were calculated for herbs identified according to the sub-groups identified by the global rating procedure. The results were compared with those obtained using the hierarchical procedure.

### 4.2 Methodology used for the systematic reviews (SRs) and analyses of clinical trials

SRs were performed to identify randomized clinical trials (RCTs) that had used oral CHM formulae or extracts of single herbs to treat patients with stable COPD. The review methods included identifying studies for consideration, search methods, establishing criteria for the inclusion and exclusion of studies, assessments of risk of bias and methodological quality of the included studies, and data extraction and analyses of the outcomes and herbal treatments used.

#### 4.2.1 Criteria for considering studies

The following selection criteria were established to identify the types of studies, patients’ characteristics, interventions and outcome measures (shown in Table 4.6).

<table>
<thead>
<tr>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parallel RCT</strong></td>
<td>Oral administration of CHM formulae or single herbs in any form</td>
<td>Inhalation, intravenous, injection, plaster or steaming</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>CHM used in combination with acupuncture or acupressure</td>
<td>Not RCTs or Quasi-randomized trials</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Older than 18 years of age</td>
<td>Younger than 18 years of age</td>
</tr>
<tr>
<td></td>
<td>Either gender and any ethnic origin</td>
<td>COPD exacerbations</td>
</tr>
<tr>
<td></td>
<td>Diagnosed with COPD in the stable stage</td>
<td>Other lung disease</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td>At least one outcome measure for COPD</td>
<td>None of the defined outcome measures reported</td>
</tr>
</tbody>
</table>

Table 4.6 Summary of the study selection criteria
4.2.1.1 Types of studies

Randomized, parallel, controlled clinical trials were included regardless of whether or not they were blinded. Quasi-randomized trials and controlled clinical trials without randomization were excluded.

4.2.1.2 Study subject characteristics

Male and female patients, older than 18 years of age, of any ethnic origin, and who had a diagnosis of stable COPD were included. Stable COPD fulfilled any of the following diagnostic criteria: 1. Guidelines of the global strategy for the diagnosis, management and prevention of COPD by the Global initiative for COPD (GOLD) (9); 2. ATS and the European Respiratory Society (298); 3. COPD-X Plan issued by the Australian Lung Foundation and the Australian and New Zealand Thoracic Society (58); or 4. Guidelines for the diagnosis and management of COPD issued by the CSRD (91, 92).

Patients were diagnosed as having stable COPD. Stable COPD was defined as no current infection, no disease exacerbation and no use of antibiotics prior to study entry. Patients in the severe stage of COPD, but without respiratory failure, pulmonary hypertension or cor pulmonale were also included. Patients with significant lung diseases other than COPD, such as a diagnosis of asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, or respiratory failure, pulmonary hypertension and cor pulmonale were excluded.

4.2.1.3 Types of interventions

The interventions reviewed were all oral administrations of herbal medicines, including single herbs (or extracts of single herbs), multi-herb formulations, Chinese proprietary medicines or preparations involving decoctions, oral liquids, tablets, capsules, pills, granules or syrups. Any CHM administrations through inhalation, intravenous injection, plaster or steam-inhalation were excluded.

CHM intervention plus routine pharmacotherapy (RP) versus RP alone were included. In addition, CHM interventions alone compared to a control intervention involving placebo, no treatment, or other CHM were also included. Studies that included co-interventions such as CHM formulae plus acupressure, acupuncture or Qigong compared to CHM formulae or acupressure or acupuncture or Qigong alone were excluded.
4.2.1.4 Types of outcome measures

In these systematic reviews, studies that reported data for at least one of the outcome measures listed below at baseline and at the end of the treatment and/or follow-up period were included: Pulmonary function, Health-related quality of life, Frequencies of COPD exacerbations and hospitalizations, Symptom relief, BODE index, 6MWD, Body mass index, biomarkers and others as well as adverse events recorded.

1. Pulmonary function

Pulmonary function testing uses a spirometer that measures the volume and flow velocity of air that can be breathed into and out of the lung. A spirometer can be used to generate pneumotachographs that can be useful in the diagnosis of respiratory diseases such as asthma, COPD and pulmonary fibrosis. Spirometric parameters include the following:

- FEV\(_1\), usually given as FEV\(_1\)% predicted or Volume of FEV\(_1\) (L) (FEV\(_1\)% predicted is the percentage of the ratio of FEV\(_1\)/predicted FEV\(_1\) that is calculated based on a subject’s age, sex, weight and height);
- FVC, usually given as FVC% predicted or Volume of FVC (L);
- Peak expiratory flow (PEF);
- Maximum mid-expiratory flow (MMEF);
- Maximum voluntary ventilation (MVV);
- Maximum inspiratory pressure (MIP); and
- Airway resistance (Raw).

Respiratory muscle weakness is an important clinical problem among COPD sufferers and contributes to their developing mobility disability (299). Measurements of respiratory muscle strength are useful for examining the degree of respiratory muscle weakness and for evaluating the severity of mobility disability (300). Maximal inspiratory mouth pressure is one of the commonly used measurements of inspiratory and respiratory muscle strength (301). This measure reflects the pressure developed by the respiratory muscles plus the passive elastic recoil pressure of both the lung and chest wall, which is tested using a mouthpiece connected to a device as described by the ATS/ERS (American Thorax Society/ European Respiratory Society) statement on Respiratory muscle testing (302).

2. Health-related quality of life
For those with COPD, there is a close relationship between FEV\textsubscript{1} and their health HRQoL. Patients with lower FEV\textsubscript{1} values have been shown to have worse HRQoL (303). Therefore, health status has been regarded to be a predictor of COPD severity and mortality (304).

The SGRQ (see Appendix 5) is a standardized, self-administered questionnaire used to assess impaired health and perceived HRQoL among those with airways diseases including COPD (305, 306). It consists of 76 items that are categorized into the three domains of ‘symptoms’, ‘activity’ and ‘impact’ and a ‘total score’. The ‘symptoms’ score assesses the patient’s perception of his/her most recent (within 4 weeks) respiratory problems. The ‘activity’ score assesses the patient’s current disturbances in performing daily physical activities. The ‘impact’ score evaluates the whole range of disturbances that the patient currently experiences in daily life due to respiratory problems. Finally, the ‘total’ score sums and weighs all of the other components. Scores can range from 0 (no impairment) to 100 (very severe impairment) for each component; higher scores indicate greater distress and, thus, a worse HRQoL.

The QolQ is a modified SGRQ that was developed by Cai et al. based on specific conditions in China (307). It consists of 35 items that are divided into the following four domains: ‘activities of daily living’; ‘social activities’; ‘depression’; and ‘anxiety’, as well as a total score. Each item is graded from 1 (high Qol) to 4 (low Qol). The calculation of the total score for the QolQ is different from that used for the SGRQ. The total score is the sum of each item score divided by the number of items.

3. Reductions in exacerbations of COPD

Exacerbation of COPD (ECOPD) is recognized as an important cause of COPD morbidity and mortality and hospital admissions. It has a strong effect on HRQoL(96). Therefore, preventing acute exacerbations is one of the management goals for stable COPD. Assessing reductions in ECOPD is determined using two methods: 1) the rate of ECOPD (ratio of the number of subjects with ECOPD attacks/number of subjects in the group during the episode); and 2) frequency of ECOPD (mean number of ECOPDs that occurred in each group).

4. Symptom relief

Assessments of the relief of symptoms were guided by the *Guiding Principle of Clinical Research on New Drugs of Chinese Medicine* (中药新药临床研究指导原则) published in 2002 (308). Symptom relief was determined either as 1. the average of the total scores of symptoms including cough, sputum production, dyspnœa, etc., 2. the averages of the sub-
scores for each symptom, or 3. the effectiveness rate (ratio of post-test total symptom scores minus the pre-test total symptom scores divided by the pre-test total symptom scores).

Dyspnoea (shortness of breath) is the most common and disabling symptom for patients with COPD (309) and is regarded as a clinical indicator of COPD severity and survival (310). Dyspnoea was assessed by the Modified Medical Research Council (MMRC) Scale that consists of five levels of dyspnoea as in Appendix 6.

The MRC Scale to assess dyspnoea ranges from 0 to 3: ‘0’ indicates not breathless and is equivalent to grades 0-1 on the MMRC; ‘1’ is MMRC grade 2; ‘2’ is MMRC grade 3; and ‘3’ is the worst condition and is equivalent to MMRC grade 4 (311).

5. BODE index

The BODE index is a grading system that includes four variables: ‘B’ is body mass index; ‘O’ is the degree of airflow obstruction, as determined by post-bronchodilator FEV1; ‘D’ is dyspnoea assessed by the MMRC dyspnoea scale; and ‘E’ is exercise capacity as assessed by the 6-minute walk test. BODE index scores range from 0 to 10, with a higher score indicating higher mortality. Thus, the BODE index is a tool for assessing disease severity and can predict COPD patients’ survival (312).

6. 6MWD

6MWD test measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes, which is a better reflection of the level of functional exercise for daily physical activities (313). The 6MWD is also an important tool for assessing the respiratory function of patients with COPD (314) and is an even better predictor of COPD mortality and survival than is FEV1 (315).

7. Body-mass index

Nutritional status, weight loss and cachexia have important prognostic implications for COPD patients. The body mass index (BMI) has been used to assess COPD risk, particularly that associated with mortality during acute exacerbations of COPD (316).

8. Arterial blood gas measurements

Assessing blood gas status is important for both the diagnosis and management of patients
with chronic pulmonary diseases, particularly those with severe conditions (317); for example, COPD-related respiratory failure. Blood gas analysis includes a number of aspects, such as oxygenation and acid-base status within the body. These are discussed in more detail in section 4.5.12. The SR focused on analyses of partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCO2).

9. Biomarkers

Systemic inflammation has been shown to be involved in the pathogenesis of COPD. Increased levels of systemic inflammatory markers are associated with declines in lung function, which may have important pathophysiological and therapeutic implications for subjects with stable COPD (318). T lymphocyte subgroups including CD3 T cells, CD4 T cells, CD8 T cells and CD4/CD8 ratios have been shown to be related to COPD disease activity. The numbers of CD4 T cells, CD3 T cells and the CD4/CD8 ratio in peripheral blood may decrease, whereas the numbers of CD8 T cells increase in patients with stable COPD (319, 320). Variations in the following biomarkers have been used in COPD research: inflammatory cytokines, lymphocyte subsets and immunoglobulin levels. In this review, inflammatory cytokines, such as IL-8, TNF-α and IL-2 were measured in sputum or serum, and lymphocyte subsets and immunoglobulins (Ig) (levels of serum of IgA, IgM and IgG) were measured in peripheral blood samples.

10. Blood rheology index

In patients with COPD, significant alterations in the peripheral circulation and a relationship between the magnitude of peripheral circulation alterations and the severity of COPD were found by Boussuges at el (321). A blood rheology index is a key measure of blood circulation within the human body. Its parameters include the Hct, haemoglobin concentration and the status of red blood cells (322).

11. Outcome measures for nutrition

Nutritional deficits are common in COPD patients. COPD patients also have increased energy and protein needs, so adequate energy and protein intake is essential for improving pulmonary function, maintaining the immune system, preventing weight loss and maintaining muscle mass and strength (323). In clinical trials, nutritional outcome measures include measures of albumin (ALB), prealbumin (PALB) and leptin.
Lung function, symptoms relief, exacerbations and QoLQ were reported in SR 1 (chapter 6.1); QoLQ was reported in SR 2 (chapter 6.2); and all of these outcomes are reported in SR 3 (chapter 7).

4.2.2 Search methods for identifying studies

Search methods included identifying search terms and electronic database searches.

4.2.2.1 Identifying search terms

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. The terms were divided into the following three groups:

1. Terms relevant to COPD, including ‘Pulmonary disease, chronic obstructive’, ‘Bronchitis, chronic’, ‘Emphysema’;
2. Terms relevant to randomized clinical trials, such as ‘Clinical trials’, ‘Randomized controlled trials’, ‘Random allocation’, ‘Double-blind method’, ‘Single-blind method’, ‘Placebo’; and;

4.2.2.2 Electronic database searches

These searches followed the methods developed by the Cochrane Airways Group for use in reviews (324). The electronic databases that were searched included PubMed, CINAHL, CENTRAL (Cochrane Central Register of Controlled Trials) and the Chinese e-databases CNKI, CQVIP and Wanfang from their respective inceptions to April 2011, without language restrictions. The search terms used in PubMed and the search procedures are shown in Appendix 7.

4.2.3 Assessments of risk of bias in included studies

Assessments of risk of bias used the Cochrane risk of bias that consists of six domains: adequate sequence generation; allocation concealment; blinding of study-involved personnel; incomplete outcome data addressed; free of selective outcome reporting; and free of other bias
(Table 4.7).

**Table 4. 7 Cochrane Collaboration’s tool for assessing risk of bias**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>Describe the method used to generate the allocation sequence in sufficient detail.</td>
<td>Was the allocation sequence adequately generated?</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Describe all means used to conceal the allocation sequence in sufficient detail</td>
<td>Was allocation adequately concealed?</td>
</tr>
<tr>
<td>Blinding of participants, personnel and outcome assessors</td>
<td>Describe all means used, if any, to blind participating personnel from knowledge of which intervention a subject received.</td>
<td>Was knowledge of the allocated intervention adequately prevented during the study?</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from analysis.</td>
<td>Were incomplete outcome data adequately addressed?</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>State how the possibility of selective outcome reporting was examined by review authors and what was found.</td>
<td>Are reports of the study free of any suggestion of selective outcome reporting?</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>State any important concerns regarding bias not addressed in the other domains in this tool.</td>
<td>Was the study apparently free of other problems that could put it at a high risk of bias?</td>
</tr>
</tbody>
</table>

Ref: *Cochrane Handbook for Systematic Reviews of Interventions* published in 2008 (325)

A new version of the Cochrane handbook for SRs of interventions (5.1.0) was issued in March 2011. Some of the domain names in part of C changed and the question mark was removed for each domain. The changes in the Cochrane risk of bias tool were the following (326):

1) ‘Adequate sequence generation?’ was changed to ‘random sequence generation’;
2) ‘Allocation concealment?’ was changed to ‘allocation concealment’;
3) ‘Blinding?’ was changed to ‘Blinding of participants and personnel’ and ‘Blinding of outcome assessment’;
4) ‘Incomplete outcome data addressed?’ was changed to ‘Incomplete outcome data’;
5) ‘Free of selective outcome reporting?’ was changed to ‘Selective reporting’
6) ‘Free of other bias?’ was changed to ‘Other bias’

Bias categories were as follows: 1) selection bias involving random sequence generation and allocation concealment; 2) performance bias (blinding of participants and personnel); 3) detection bias (blinding of outcome assessment); 4) attrition bias (incomplete outcome data); 5) reporting bias (selective reporting); and 6) other bias (focusing on baseline data comparability).

Judgments were denoted simply as either ‘yes’, which meant adequate (i.e., low risk of bias), ‘no’, which meant inadequate (i.e., high risk of bias) or ‘unclear’, which meant unclear or information was not provided (i.e., uncertain risk of bias) based on the *Cochrane Handbook*
Judgment of the risk of bias was guided by this handbook in the earlier two SRs (i.e., *Oral Ginseng Formulae for Stable COPD* and *Oral CHM for Improving QoL with Stable COPD*). Subsequently, for the 101 studies, the judgment for risk of bias of the included studies was guided by the updated version of the *Cochrane Handbook for Systematic Reviews of Interventions* published in 2011, which used the terms ‘low risk’ of bias, ‘high risk’ of bias or ‘unclear risk’ of bias (326).

### 4.2.4 Assessments of methodological quality of included studies

The methodological quality of each study was assessed on a standardized 0-5 point scale that was developed and validated by Jadad *et al* (327). The scale includes the following questions. One point was given for a ‘Yes’ and 0 points was given for a ‘No’:

1) Is the study randomized?
2) Is the study double blinded?
3) Is there a description of withdrawals?
4) Is the method of randomization adequately described and appropriate?
5) Is the blinding adequately carried out and appropriate?
6) One point is deducted if the methods of randomization or blinding were inappropriate.

When there was no description of withdrawals in a study, but the results indicated that the number of patients was the same at the beginning and the end of the study, the study was considered to have no withdrawals and was given one point. Any disagreement was resolved by discussion with one of the other two reviewers.

### 4.2.5 Data collection and extraction

#### 4.2.5.1 Data collection

Titles, abstracts and citations were reviewed by one reviewer to assess their potential relevance for full review. If there was any unclear information in the title or abstract, the full article was retrieved for further clarification. Full text articles were assessed by two reviewers for study selection. The procedure for determining studies for inclusion was presented as a flow diagram based on the template provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (328).
4.2.5.2 Data extraction

Data were extracted from published, identified studies. Details of each study were extracted, including trial design, sample size, methodological quality, participants, severity of COPD, syndrome differentiation, intervention, outcome measures and adverse events, as well components of each herbal formula as recommended in elaborated CONSORT statement (329).

4.2.5.3 Issues of missing data

When data extracted from text, tables or figures were missing or not clear, the reviewer attempted to contact the authors to request additional information or clarification.

4.2.5.4 Issues of duplicated trials

When different outcome measures for the same RCT were reported in different articles and/or published in different journals, these were considered duplicated articles for the purpose of calculating the number of studies, although the data were combined as one study for the purpose of analysis. When different articles reported results at different stages of the same trial, for example preliminary results followed by final results, the articles were considered as duplicates and only the final results were used in the analysis. When there were articles that were considered duplicates by the review authors, for the purpose of referencing the RCT, the article that was published earliest was chosen. However, when there was an article in an English database plus an article in a Chinese database that reported on the same trial, the article in the English database was chosen as the reference.

4.2.6 Data analysis

4.2.6.1 Data analysis software and general methods

Data analysis used RevMan 5.1 (83). Results for dichotomous variables were expressed as risk ratios (RR) with their corresponding 95% confidence intervals (CI). Results for continuous variables were expressed as mean differences (MD) with 95% CI. Heterogeneity was measured using the Z score and a Chi square statistic with significance set at P<0.01. Overall results were calculated by a fixed effects model or a random effects model based on the I² value. If p>0.05 or I²<50%, this was taken as an indication that the same scale was being used for the outcome and a meta-analysis was undertaken using a fixed-effects model. If p≤0.05 or I²>50%, this was taken as an indication of different scales being used in the
outcomes and a random effects model was selected for meta-analysis.

4.2.6.2 Subgroup analysis, sensitivity analyses and investigating heterogeneity

Analyses were pooled across studies and subgroup analyses were performed for different comparisons, CHM versus placebo and CHM versus RP.

When heterogeneity was substantially large ($I^2 > 50\%$), this indicated that there was a substantial level of inconsistency among the studies included in the comparison; thus, it was necessary to consider what factors influenced the heterogeneity in the meta-analysis (325). Therefore, a sensitivity analysis was performed.

Specific data sensitivity analysis for the spirometric parameters was based on the length of the treatment period. This was stratified into < 3 months and > 3 months.

4.2.6.3 Assessments of reporting bias

There are some types of reporting bias in meta-analyses, including publication bias, time lag bias, multiple publication bias, location bias, citation bias, language bias and outcome reporting bias (326). Funnel plots can be used to inspect for possible publication bias in a meta-analysis (330).

Results of these SRs are separately reported in two chapters: Chapter 6, SR 1: Oral Ginseng Formulae for Stable COPD and SR2: Oral CHM Formulae for Improving QoL with stable COPD; and Chapter 7, SR3: Oral CHM Formulae for Specific Outcome Measures.
5 Chapter Five: Results of systematic analysis of the classical literature on Chinese herbal medicines for disorders analogous to COPD

This part reports the results for each term searched in Zhong Hua Yi Dian using 'headings search' (Mu lu) and also reports the higher frequency herbs and formulae for each term and for combinations of symptoms consistent with the modern conception of COPD.

5.1 Results for each search term

5.1.1 Jiu Kesou (Long-term Cough)

Jiu ke or Jiu sou (久嗽) means Long-term cough in Chinese medicine. For Jiu ke, 21 results were found in seven books as listed in Table 5.1. Five items that did not mention a formula, one item that was duplicated and one that referred to moxibustion (灸) were excluded. There were also three items with 17 formulae for hemoptysis, and twelve items with 68 formulae for long-term cough.

The results for Jiu sou were as follows. A total of 39 items were found in twenty seven books (see Table 5.1). Three items that did not mention a formula, 6 items that were duplicated and one that was for an intervention with plaster applied to Acupoints were excluded. One reference involved hemoptysis for one formula, and two references were for children and included ten formulae.

In total, Jiu ke appeared in seven books the earliest being the diagnostic manual Zhu Bing Yuan Hou Lun completed in 610 and the most recent being the Qing dynasty work Qi Xiao Jian Bian Liang Fang (1880). Jiu sou was found in books ranging from the Tang dynasty work Hua Tuo Shen Fang (c. 682) to Ling Lin Ling Fang (1893). Of the two terms, Jiu ke appears to be the earlier whereas Jiu sou became more commonly used from the Song dynasty onwards.
Table 5.1 Search terms Jiu ke and Ke sou by the books in which entries were found

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<td>610</td>
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<td>寿山笔记</td>
<td>1814</td>
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</tbody>
</table>

Freq: frequency

5.1.2 Ke chuan (Cough and dyspnea)

For Ke chuan (cough and dyspnea) (咳喘), 13 items were found in eleven books ranging from Ji Yan Fang (1170) to Liu Xuan Si Jia Yi An (1900) as listed in Table 5.2. Ke chuan was commonly used in the Qing dynasty. Three items were excluded including one without a formula and one involving acupuncture treatment, and one being duplicated. Four items were for children and included twenty-six formulae.

83
Table 5. 2 Search term Ke chuan by the books in which entries were found

<table>
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<tr>
<th>Search Term</th>
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<td>Ji Zhi Tang Yi An (Liu Xuan Si Jia Yi An)</td>
<td>继志堂医案 (柳选四家医案)</td>
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<td>Huai Xi Cao Tang Yi An (Liu Xuan Si Jia Yi An)</td>
<td>怀溪草堂医案 (柳选四家医案)</td>
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<td>Yi De Ji</td>
<td>一得集</td>
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5.1.3 Chuan zheng (Dyspnea)

For Chuan zheng (喘证), 20 items were found in sixteen books as shown in Table 5.3, and most were from the Qing Dynasty. Six items did not mention a formula or the term was only used in a title, one item was for children with asthma involving fourteen formulae, and one was for post partum with one formula.

Table 5. 3 Search term Chuanzheng by the books in which entries were found

<table>
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<tr>
<th>Search Term</th>
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<td>Ming Yi Zhi Zhang</td>
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5.1.4 Chuan sou (Dyspnea and sputum)

For Chuan sou (喘嗽), dyspnea with sputum, 46 items were found in thirty-four books, with the earliest being the treatment manual *Hua Tuo Shen Fang* (华佗神方) of the Tang dynasty (c. 682) and the latest being written at the end of the Qing dynasty *Yi Xue Zhong Zhong Can Xi Lu* (医学衷中参西录) (published 1918) as listed in Table 5.4. Chuan sou was frequently used in the Qing dynasty. In this case, 14 items did not mention a formula, two were for other interventions (one for acupuncture and one for an inhalation), two were for lung TB (Fei lao), one was for food, one was a duplicated item, five items involved children with 20 formulae, four were for acute conditions with four formulae, one was for pregnancy (3 formulae) and one was for post partum (2 formulae).
Table 5. Search term Chuan sou by the books in which entries were found

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5.1.5  Zhi yin (Thoracic fluid retention)

For Zhi yin (支饮), eight items were found in eight books ranging from the late Tang dynasty to the Qing dynasty as shown in Table 5.5. One item had no hits on a formula and was excluded.

Table 5.5 Search term Zhi yin by the books in which entries were found

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</tr>
<tr>
<td></td>
<td>Sheng Ji Zong Lu</td>
<td>圣济总录</td>
<td>c. 1117</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Shi Yi De Xiao Fang</td>
<td>世医得效方</td>
<td>c. 1345</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pu Ji Fang</td>
<td>普济方</td>
<td>c. 1406</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zhu Bing Yuan Hou Lun</td>
<td>诸病源侯论</td>
<td>610</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zheng Yin Mai Zhi</td>
<td>症因脉治</td>
<td>1641</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yi Chun Sheng Yi</td>
<td>医醇剩义</td>
<td>1863</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Wai Tai Mi Yao</td>
<td>外台秘要</td>
<td>752</td>
<td>1</td>
</tr>
</tbody>
</table>

5.1.6  Fei zhang (lung distension)

For Fei zhang (肺胀), lung distension, 13 items were found in twelve books as shown in Table 5.6. Of these three appeared in the Tang or Song dynasties, and the remaining citations appeared in the Qing dynasty. In this case, two items did not mention a formula or were only found in a title, and one was for children with 2 formulae. Fourteen actually referred to Fei wei (肺痿) which was a type of chronic lung disease caused by heat deficiency, so these were consequently excluded.
Table 5. 6 Search term Fei zhang by the books in which entries were found

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Book name</th>
<th>Chinese name</th>
<th>Year</th>
<th>Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fei zhang</td>
<td>Hua Tuo Shen Fang</td>
<td>华佗神方</td>
<td>c. 682</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sheng Ji Zong Lu</td>
<td>圣济总录</td>
<td>c. 1117</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pu Ji Fang</td>
<td>普济方</td>
<td>c. 1406</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zheng Yin Mai Zhi</td>
<td>症因脉治</td>
<td>1641</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zhang Shi Yi Tong</td>
<td>张氏医通</td>
<td>1695</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Za Bing Yuan Liu Xi Zhu</td>
<td>杂病源流犀烛</td>
<td>1773</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Yi Zong Shuo Yue</td>
<td>医宗说约</td>
<td>1663</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Lan Tai Gui Fan</td>
<td>兰台轨范</td>
<td>1764</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chi Shui Xuan Zhu</td>
<td>赤水玄珠</td>
<td>1584</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Wai Tai Mi Yao</td>
<td>外台秘要</td>
<td>752</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zheng Zhi Zhun Sheng</td>
<td>证治准绳</td>
<td>1602</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ji Yang Gang Mu</td>
<td>济阳纲目</td>
<td>1626</td>
<td>1</td>
</tr>
</tbody>
</table>

5.1.7 Tanyin kesou (phlegm-fluid with cough)

For Tanyin kesou (痰饮咳嗽), phlegm-fluid with cough, 25 items were found in fourteen books, see Table 5.7. All of the books appeared in the Qing dynasty except for three that were from the Song dynasty. Nine items that were duplicated and two items that had no hits on formulae were excluded. The final formulae were mainly from three books Tai Ping Hui Min He Ji Ju Fang (太平惠民和剂局), Ye Shi Lu Yan Fang (叶氏录验方) and Zheng Zhi Zhai Yao (证治摘要).

Table 5. 7 Search term Tanyin kesou by the books in which entries were found

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Book name</th>
<th>Chinese name</th>
<th>Year</th>
<th>Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanyin kesou</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>太平惠民和剂局方</td>
<td>1078</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Fang Ge Kuo</td>
<td>金匮方歌括</td>
<td>1811</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ye Shi Lu Yan Fang</td>
<td>叶氏录验方</td>
<td>1186</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Gao Zhu Jin Gui Yao Lue</td>
<td>高注金匮要略</td>
<td>1872</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yu Han Yao Lue Ji Yi</td>
<td>金匮玉涵要略辑义</td>
<td>1806</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yu Han Jing Er Zhu</td>
<td>金匮玉涵经二注</td>
<td>1687</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yu Han Yao Lue Shu Yi</td>
<td>金匮玉涵要略述义</td>
<td>1810</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ding Zheng Zhong Jing Quan Shu</td>
<td>订正仲景全书</td>
<td>1743</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yao Lue Xin Dian</td>
<td>金匮要略心典</td>
<td>1729</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yao Lue Qian Zhu</td>
<td>金匮要略浅注</td>
<td>1803</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yao Lue Guang Zhu</td>
<td>金匮要略广注</td>
<td>1682</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Xuan Jie</td>
<td>金匮悬解</td>
<td>1756</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Jin Gui Yao Lue Fang Lun</td>
<td>金匮要略方论</td>
<td>1065</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zheng Zhi Zhai Yao</td>
<td>证治摘要</td>
<td>1862</td>
<td>1</td>
</tr>
</tbody>
</table>
5.1.8 Overall numbers of hits from each search term

The overall numbers of hits found when searching each term in ZHYD and the details of the excluded hits by sub-type are summarized in Table 5.8.

Table 5. 8 Summary results for each search term with exclusions

<table>
<thead>
<tr>
<th>Terms</th>
<th>Number of hits</th>
<th>Non formulae</th>
<th>Duplications</th>
<th>Other intervention</th>
<th>Other condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiu ke (久咳)</td>
<td>21</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>Hemoptysis (n=3)</td>
</tr>
<tr>
<td>Jiu sou (久嗽)</td>
<td>39</td>
<td>3</td>
<td>6</td>
<td>Acupoint plaster (膏贴) (n=1) Steam (n=2)</td>
<td>Hemoptysis (n=1) Children (n=3)</td>
</tr>
<tr>
<td>Chuan zheng (喘证)</td>
<td>20</td>
<td>6</td>
<td>NS</td>
<td>NS</td>
<td>Children (n=3) Asthma (n=1) Post partum (n=1)</td>
</tr>
<tr>
<td>Feizhang (肺胀)</td>
<td>13</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
<td>Children (n=2) Fei wei (n=14)</td>
</tr>
<tr>
<td>Chuan sou (喘嗽)</td>
<td>46</td>
<td>14</td>
<td>1</td>
<td>Acupuncture (n=1) Inhalation (n=1)</td>
<td>Food (n=1) Children (n=5) Acute (n=1) Pregnant (n=1) Post partum (n=1) Asthma (n=1) Insomnia (n=1)</td>
</tr>
<tr>
<td>Ke chuan (咳喘)</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>acupuncture (n=1)</td>
<td>Children (n=4)</td>
</tr>
<tr>
<td>Tanyin kesou (痰饮咳嗽)</td>
<td>25</td>
<td>2</td>
<td>9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Zhi yin (支饮)</td>
<td>8</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

5.2 Database characteristics

The full data set contained 1,052 formulae comprised of 6,916 herbs. Two books appeared twice in ZHYD. These were Ling Lin Ling Fang (凌临灵方) which appeared in both sections 4 and 11, the other was You Ke Zheng Zhi Zhuo Sheng (幼科证治准) which is the same book as Zheng Zhi Zhuo Sheng (证治准绳): You ke, which are both in section 9. These resulted in 53 duplicated herb entries which were subsequently excluded. Also a further 283 herb entries were excluded since they were components of formulae that appeared more than once in the same book. Therefore, a total of 335 herb entries were excluded leaving 6,581 herb entries derived from 1,006 formulae in the data set.

The most productive search term was Jiu sou which located 221 formulae resulting in 1,325 herb entries which comprised 20.1% of the data set. This was closely followed by Chuan sou which located 19.8% of the HEs in the set of included data (see Table 5.9).
Table 5.9 Frequencies of formulae and herb entries by search term

<table>
<thead>
<tr>
<th>Term</th>
<th>Frequency of formulae</th>
<th>Frequency of HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fei zhang</td>
<td>57</td>
<td>389</td>
<td>5.9</td>
</tr>
<tr>
<td>2. Jiu ke</td>
<td>74</td>
<td>448</td>
<td>6.8</td>
</tr>
<tr>
<td>3. Jiu sou</td>
<td>221</td>
<td>1325</td>
<td>20.1</td>
</tr>
<tr>
<td>4. Ke chuan</td>
<td>115</td>
<td>959</td>
<td>14.6</td>
</tr>
<tr>
<td>5. Chuan sou</td>
<td>196</td>
<td>1300</td>
<td>19.8</td>
</tr>
<tr>
<td>6. Zhi yin</td>
<td>69</td>
<td>315</td>
<td>4.8</td>
</tr>
<tr>
<td>7. Tanyin kesou</td>
<td>132</td>
<td>806</td>
<td>12.2</td>
</tr>
<tr>
<td>8. Chuan zheng</td>
<td>142</td>
<td>1039</td>
<td>15.8</td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The search term Fei zhang did not co-occur with any of the other 7 search terms, nor was there any overlap between the other search terms. Therefore each formula entry was intended to treat only one of the search terms although it may also have been intended for other disorders or symptoms not included in the list of 8 terms.

The 6,581 herbal entries were derived from 69 different books written between c. 583 and c. 1934. The most frequently cited books were the multi-volume formulary *Pu Ji Fang* (c. 1406) which provided 21.4% of the herbal entries, followed by *Liu Xuan Si Jia Yi An* with 10.2% of entries. The ten most frequently cited books are listed in Table 5.10.
<table>
<thead>
<tr>
<th>Book code &amp; name</th>
<th>Year</th>
<th>Frequency of formulae</th>
<th>Frequency of HEs</th>
<th>Percent of HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>267 Pu Ji Fang 普济方</td>
<td>c.1406</td>
<td>230</td>
<td>1406</td>
<td>21.4</td>
</tr>
<tr>
<td>859 Liu Xuan Si Jia Yi An 柳选四家医案</td>
<td>c.1900</td>
<td>73</td>
<td>673</td>
<td>10.2</td>
</tr>
<tr>
<td>170 Tai Ping Hui Min He Ji Ju Fang 太平惠民和剂局方</td>
<td>1078</td>
<td>51</td>
<td>365</td>
<td>5.5</td>
</tr>
<tr>
<td>506 Ji Yang Gang Mu 济阳纲目</td>
<td>1626</td>
<td>47</td>
<td>274</td>
<td>4.2</td>
</tr>
<tr>
<td>560 Wai Tai Mi Yao 外台秘要</td>
<td>752</td>
<td>51</td>
<td>261</td>
<td>4.0</td>
</tr>
<tr>
<td>166 Tai Ping Sheng Hui Fang 太平圣惠方</td>
<td>772</td>
<td>34</td>
<td>245</td>
<td>3.7</td>
</tr>
<tr>
<td>543 Jing Yue Quan Shu 景岳全书</td>
<td>1624</td>
<td>40</td>
<td>239</td>
<td>3.6</td>
</tr>
<tr>
<td>171 Sheng ji zong lu 圣济总录</td>
<td>1117</td>
<td>39</td>
<td>236</td>
<td>3.6</td>
</tr>
<tr>
<td>473 Zhang Shi Yi Tong 张氏医通</td>
<td>1695</td>
<td>24</td>
<td>194</td>
<td>2.9</td>
</tr>
<tr>
<td>507 Zheng Zhi Zhai Yao 证治摘要</td>
<td>1862</td>
<td>33</td>
<td>191</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

c.: circa; HE: individual herb entry

Of the 1,006 formulae, 206 were not named. The two most common named formulae were *Xiao Qing Long Tang* which appeared 10 times followed by *Xiao Ban Xia Tang* which appeared 9 times. *Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang* and *Yue Bi Jia Ban Xia Tang Fang* both appeared 7 times. The most frequently cited formulae are listed in Table 5.11. There was a considerable diversity of formulae with 464 of the named formulae only being cited once and the unnamed formulae also varied in their ingredients. On average, the formulae contained 6.5 herbs but some only included one or two herbs, whereas others contained ten or more.
Table 5.5 Most frequent formulae in total data set

<table>
<thead>
<tr>
<th>Formula code &amp; name</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unnamed</td>
<td>205</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>10</td>
</tr>
<tr>
<td>59 Xiao Ban Xia Tang</td>
<td>9</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang</td>
<td>7</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>7</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi Gao Tang</td>
<td>6</td>
</tr>
<tr>
<td>57 Xiao Ban Xia Jia Fu Ling Tang</td>
<td>6</td>
</tr>
<tr>
<td>54 Mu Fang Ji Tang</td>
<td>5</td>
</tr>
<tr>
<td>63 Wu Ling San</td>
<td>5</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>5</td>
</tr>
<tr>
<td>319 Wu Hu Tang</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1006</strong></td>
</tr>
</tbody>
</table>

5.3 Results for symptoms typical of COPD

5.3.1 Cough

Each of the formula entries was scored according to the symptoms of relevance to a diagnosis of COPD as follows: cough, dyspnoea, sputum production and chest tightness.

The most commonly mentioned of the four symptoms was cough (in 70.0% of herbal entries). This was not surprising since five of the search terms contained a word for cough. In 398 formulae, the nature of the cough was not specified but in 303 formulae (27.2% of herbal entries) there was the more specific mention of chronic or long-term cough (see Table 5.12).

Table 5.6 Frequency of mention of cough in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>305</td>
<td>1977</td>
<td>30.0</td>
</tr>
<tr>
<td>Mention of cough</td>
<td>398</td>
<td>2817</td>
<td>42.8</td>
</tr>
<tr>
<td>Chronic/long term cough</td>
<td>303</td>
<td>1787</td>
<td>27.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1006</strong></td>
<td><strong>6581</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

HE: individual herb entry

Cough was mentioned frequently across all eight search terms but did not always occur in entries located using search terms that contained a term for ‘cough’ (see Table 5.13). For example, 49.1% of the herbal entries located using the term tanyin kesou have no score for cough. This is because, not all formulae indexed in the books under this term were individually specified for cough. Tan yin is a disease name whereas tanyin kesou is one of the syndromes of tanyin. In addition, tanyin is also the pathogenesis of many kinds of diseases. Therefore, under this search term some of the symptoms caused by Tan yin, other than cough, were included. Cough was most infrequent in citations located by the search term Chuan
zheng with 85% of herbal entries having no mention. Chuan zheng is an independent syndrome characterised by dyspnea and caused by dysfunction of lung or spleen or kidney. Cough and Chuanzheng may present together or separately.

Table 5. 7 Frequency of mention of cough by search term

<table>
<thead>
<tr>
<th>Description</th>
<th>Feizhang</th>
<th>Jiuke</th>
<th>Jiusou</th>
<th>Kechuan</th>
<th>Chiansou</th>
<th>Zhiyin</th>
<th>Tanyinkesou</th>
<th>Chuanzheng</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>97 (24.9%)</td>
<td>0</td>
<td>20 (1.5%)</td>
<td>250 (26.1%)</td>
<td>210 (16.2%)</td>
<td>121 (38.4%)</td>
<td>396 (49.1%)</td>
<td>883 (85.0%)</td>
</tr>
<tr>
<td>Mention of cough</td>
<td>274 (70.4%)</td>
<td>26 (5.8%)</td>
<td>202 (15.2%)</td>
<td>636 (66.3%)</td>
<td>971 (74.7%)</td>
<td>194 (61.6%)</td>
<td>360 (44.7%)</td>
<td>154 (14.8%)</td>
</tr>
<tr>
<td>Chronic/long term cough</td>
<td>18 (4.6%)</td>
<td>422 (94.2%)</td>
<td>1103 (83.2%)</td>
<td>73 (7.6%)</td>
<td>119 (9.2%)</td>
<td>0 (0.0%)</td>
<td>50 (6.2%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>389</td>
<td>448</td>
<td>1325</td>
<td>959</td>
<td>1300</td>
<td>315</td>
<td>806</td>
<td>1039</td>
</tr>
</tbody>
</table>

These results demonstrate the importance of scoring the entries in terms of the symptoms mentioned, rather than only on the basis of the search term that located the entry in ZHYD.

5.3.2 Dyspnoea

Dyspnoea was a component of three search terms and was the second most frequently mentioned symptom, appearing in 559 formulae and 59.1% of herbal entries. The more specific descriptions of ‘dyspnoea that is worse with exercise’ and ‘severe dyspnoea’ were infrequent at 2.1% and 3.3% of herbal entries respectively (see Table 5.14).

Table 5. 8 Frequency of mention of dyspnoea in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>447</td>
<td>2694</td>
<td>40.9</td>
</tr>
<tr>
<td>Mention of dyspnoea</td>
<td>502</td>
<td>3531</td>
<td>53.7</td>
</tr>
<tr>
<td>Dyspnoea that is worse with exercise</td>
<td>27</td>
<td>138</td>
<td>2.1</td>
</tr>
<tr>
<td>Severe dyspnoea</td>
<td>30</td>
<td>218</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HE: individual herb entry

Dyspnoea was a frequent symptom in citations located by all eight search terms but was least common under Jiusou (no mention in 73.8% of herbal entries) and Tanyin kesou (no mention in 64.9%). As could be expected, there were few no mentions under Chuan zheng but the 51.8% of no mentions under Ke chuan was unexpected (see Table 5.15).

Both cough and dyspnoea are independent diseases so they were not expected to frequently co-occur. Under the term Jiusou, dyspnoea can be an associated symptom. In the case of Ke
chuan, it belongs in the category of Ke sou, so the focus is on Ke sou and this term is not specific for dyspnoea. Tanyin chuanji was also found under the term Tan yin but only in a few cases, so it was not included as a search term. The few mentions of dyspnoea under the term Tanyin kesou were not surprising.

### Table 5. 9 Frequency of mention of dyspnoea by search term

<table>
<thead>
<tr>
<th>Description</th>
<th>Fei zhang</th>
<th>Jiu ke</th>
<th>Jiu sou</th>
<th>Ke chuan</th>
<th>Chuan sou</th>
<th>Chuan zheng</th>
<th>Zhi yin</th>
<th>Tan yin ke sou</th>
<th>Chuan zheng</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>109 (28.0%)</td>
<td>225 (50.2%)</td>
<td>978 (73.8%)</td>
<td>497 (51.8%)</td>
<td>202 (15.5%)</td>
<td>93 (29.5%)</td>
<td>515 (63.9%)</td>
<td>75 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>Mention of dyspnoea</td>
<td>218 (56.0%)</td>
<td>198 (44.2%)</td>
<td>294 (22.2%)</td>
<td>436 (45.5%)</td>
<td>1028 (79.1%)</td>
<td>201 (63.8%)</td>
<td>271 (33.6%)</td>
<td>885 (85.2%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea that is worse with exercise</td>
<td>0 (0.8%)</td>
<td>0 (0.8%)</td>
<td>10 (1.6%)</td>
<td>15 (1.6%)</td>
<td>54 (4.2%)</td>
<td>21 (6.7%)</td>
<td>20 (2.5%)</td>
<td>18 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Severe dyspnoea</td>
<td>62 (15.9%)</td>
<td>25 (5.6%)</td>
<td>43 (3.2%)</td>
<td>11 (1.1%)</td>
<td>16 (1.2%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>61 (5.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>389</td>
<td>448</td>
<td>1325</td>
<td>959</td>
<td>1300</td>
<td>315</td>
<td>806</td>
<td>1039</td>
<td></td>
</tr>
</tbody>
</table>

#### 5.3.3 Sputum production

Sputum production was a component of two search terms and was mentioned in 155 formulae and 18% of Herbal entries, but in only 8 formulae and 1% of Herbal entries was chronic sputum production mentioned (see Table 5.16).

### Table 5. 10 Frequency of mention of sputum production in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>854</td>
<td>5400</td>
<td>82.1</td>
</tr>
<tr>
<td>Mention of sputum production</td>
<td>147</td>
<td>1116</td>
<td>17.0</td>
</tr>
<tr>
<td>Chronic sputum production</td>
<td>8</td>
<td>65</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HE: individual herb entry

Although it was expected that sputum production would have been most commonly a feature of citations located by the search term Tanyin kesou, only 24.5% of Herbal entries received a score (see Table 5.17). This was still the second most productive search term in terms of this symptom, but it was less frequent than Fei zhang with 29.8% of Herbal entries receiving a score.
Table 5.11 Frequency of mention of sputum production by search term

<table>
<thead>
<tr>
<th>Description</th>
<th>Fei zhang</th>
<th>Jiu ke</th>
<th>Jiu sou</th>
<th>Ke chuan</th>
<th>Chuan sou</th>
<th>Zhi yin</th>
<th>Tanyin kesou</th>
<th>Chuan zheng</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>273 (70.2%)</td>
<td>390 (87.1%)</td>
<td>1090 (82.3%)</td>
<td>767 (80.0%)</td>
<td>1055 (81.2%)</td>
<td>310 (98.4%)</td>
<td>608 (75.4%)</td>
<td>907 (87.3%)</td>
</tr>
<tr>
<td>Mention of sputum production</td>
<td>98 (25.2%)</td>
<td>58 (12.9%)</td>
<td>193 (14.6%)</td>
<td>192 (20.0%)</td>
<td>245 (18.8%)</td>
<td>5 (1.6%)</td>
<td>193 (23.9%)</td>
<td>132 (12.7%)</td>
</tr>
<tr>
<td>Chronic sputum production</td>
<td>18 (4.6%)</td>
<td>0 (0.0%)</td>
<td>42 (3.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>5 (0.6%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>389</td>
<td>448</td>
<td>1325</td>
<td>959</td>
<td>1300</td>
<td>315</td>
<td>806</td>
<td>1039</td>
</tr>
</tbody>
</table>

As mentioned above, Tanyin kesou is under the category Tan yin. Tan yin can refer to a pathogenesis involving Tan yin which does not necessarily involve sputum as a symptom.

5.3.4 Chest tightness

The least frequent of the four symptoms was chest tightness which occurred in only 129 formulae and 13.3% of Herbal entries (see Table 5.18).

Table 5.12 Frequency of mention of chest tightness in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>877</td>
<td>5707</td>
<td>86.7</td>
</tr>
<tr>
<td>Mention of chest tightness</td>
<td>129</td>
<td>874</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HE: individual herb entry

Chest tightness was most frequently mentioned in citations located under Zhi yin (58.4% of Herbal entries) and Fei zhang (55.0% of Herbal entries). It was relatively infrequent under the other search terms but some citations located by each term did receive scores (see Table 5.19).

Table 5.13 Frequency of mention chest tightness by search term

<table>
<thead>
<tr>
<th>Description</th>
<th>Fei zhang</th>
<th>Jiu ke</th>
<th>Jiu sou</th>
<th>Ke chuan</th>
<th>Chuan sou</th>
<th>Zhi yin</th>
<th>Tanyin Kesou</th>
<th>Chuan zheng</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>175 (45.0%)</td>
<td>390 (87.1%)</td>
<td>1276 (96.3%)</td>
<td>918 (95.7%)</td>
<td>1180 (90.8%)</td>
<td>131 (41.6%)</td>
<td>636 (78.9%)</td>
<td>1001 (96.3%)</td>
</tr>
<tr>
<td>Mention of chest tightness</td>
<td>214 (55.0%)</td>
<td>58 (12.9%)</td>
<td>49 (3.7%)</td>
<td>41 (4.3%)</td>
<td>120 (9.2%)</td>
<td>184 (58.4%)</td>
<td>170 (21.1%)</td>
<td>38 (3.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>389</td>
<td>448</td>
<td>1325</td>
<td>959</td>
<td>1300</td>
<td>315</td>
<td>806</td>
<td>1039</td>
</tr>
</tbody>
</table>

Overall, each of the eight search terms was productive in terms of locating formula citations
which were used to treat each of the primary symptoms of COPD. However, the co-occurrence of symptoms was somewhat less common than had been expected based on the the disease and syndrome names used as search terms.

5.4 Symptoms, signs and disorders not typical of COPD

Citations were scored based on three criteria that were atypical of COPD in order to facilitate the elimination of formulae unlikely to have been used for COPD.

5.4.1 Children & specific disorders of women

For 89 of the formulae located by the 8 search terms, the application was for children, so these were not possible cases of COPD. Similarly, 14 formulae were specifically indicated for disorders of women in pregnancy or post partum (see Table 5.20).

Table 5.20 Frequency of mention of disorders specifically of children or women in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>903</td>
<td>5887</td>
<td>89.5</td>
</tr>
<tr>
<td>Children</td>
<td>89</td>
<td>598</td>
<td>9.1</td>
</tr>
<tr>
<td>Women (pregnacy, post-partum)</td>
<td>14</td>
<td>96</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>1,006</td>
<td>6,581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HE: individual herb entry

5.4.2 Acute disorders

Since COPD is a chronic disorder, formulae intended for acute disorders needed to be excluded. In 935 (93.1%) citations there was no information specifying that the disorder was acute or chronic but 14 citations (1.5% of Herbal entries) were specifically for acute disorders and were therefore excluded (see Table 5.21).

Table 5.21 Frequency of mention of acute disorders or other disorders unlike COPD in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>935</td>
<td>6130</td>
<td>93.1</td>
</tr>
<tr>
<td>No, chronic disorder</td>
<td>57</td>
<td>351</td>
<td>5.3</td>
</tr>
<tr>
<td>Yes, acute disorder</td>
<td>14</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>1,006</td>
<td>6,581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HE: individual herb entry

5.4.3 Haemoptysis

Haemoptysis is a complication of cough that is uncommon in COPD, so formula citations
intended for treating haemoptysis were identified and excluded in the latter stages of the analysis. There were 40 such citations which accounted for 5.3% of Herbal entries (see Table 5.22).

Table 5.15 Frequency of mention of haemoptysis in total data set

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention</td>
<td>966</td>
<td>6232</td>
<td>94.7</td>
</tr>
<tr>
<td>yes</td>
<td>40</td>
<td>349</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,006</strong></td>
<td><strong>6,581</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

5.5 Results for formulae and herbs

5.5.1 Formulae

After the exclusion of disorders specific to children and women, acute disorders and disorders that were unlike COPD, the frequency of unnamed formulae declined from 205 to 187. However, the exclusions had little effect on the identity of the higher frequency formulae with *Xiao Qing Long Tang* remaining the most common named formula with its frequency unchanged at 10, followed by *Xiao Ban Xia Tang* (see Table 5.23).

Table 5.16 Ten most frequent formulae in total data set following general exclusions*

<table>
<thead>
<tr>
<th>Formula code &amp; name</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unnamed</td>
<td>187</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>10</td>
</tr>
<tr>
<td>59 Xiao Ban Xia Tang</td>
<td>9</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>7</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi Gao Tang</td>
<td>6</td>
</tr>
<tr>
<td>57 Xiao Ban Xia Jia Fu Ling Tang</td>
<td>6</td>
</tr>
<tr>
<td>54 Mu Fang Ji Tang</td>
<td>5</td>
</tr>
<tr>
<td>63 Wu Ling San</td>
<td>5</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>5</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>898</strong></td>
</tr>
</tbody>
</table>

*disorders specifically of children or women, acute disorders and other disorders unlike COPD

5.5.2 Herbs

The most frequent of the 5,858 herbs remaining after the exclusions was Gan cao with a total frequency of occurrence of 372 in the 898 formulae. However, Gan cao is present in many formulae due to its functional role of harmonizing the combined actions of the herbs, so its
presence may have little to do with any specific benefit in COPD (see Table 5.24).

Table 5.17 Twenty most frequently occurring herbs in the 898 formulae in the data set following general exclusions*

<table>
<thead>
<tr>
<th>Rank</th>
<th>Herb name</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gan cao</td>
<td>372</td>
<td>6.4</td>
</tr>
<tr>
<td>2</td>
<td>Ban xia</td>
<td>266</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>Xing ren</td>
<td>249</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>Ren shen</td>
<td>217</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>Fu ling</td>
<td>209</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>Wu wei zi</td>
<td>181</td>
<td>3.1</td>
</tr>
<tr>
<td>7</td>
<td>Chen pi</td>
<td>170</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>Sang gen bai pi</td>
<td>142</td>
<td>2.4</td>
</tr>
<tr>
<td>9</td>
<td>Sheng jiang</td>
<td>127</td>
<td>2.2</td>
</tr>
<tr>
<td>10</td>
<td>Kuan dong hua</td>
<td>124</td>
<td>2.1</td>
</tr>
<tr>
<td>11</td>
<td>Ma huang</td>
<td>117</td>
<td>2.0</td>
</tr>
<tr>
<td>12</td>
<td>Zi wan</td>
<td>114</td>
<td>1.9</td>
</tr>
<tr>
<td>13</td>
<td>Rou gui</td>
<td>113</td>
<td>1.9</td>
</tr>
<tr>
<td>14</td>
<td>Bei mu</td>
<td>102</td>
<td>1.7</td>
</tr>
<tr>
<td>15</td>
<td>Jie geng</td>
<td>99</td>
<td>1.7</td>
</tr>
<tr>
<td>16</td>
<td>Gan jiang</td>
<td>92</td>
<td>1.6</td>
</tr>
<tr>
<td>17</td>
<td>Mai men dong</td>
<td>87</td>
<td>1.5</td>
</tr>
<tr>
<td>18</td>
<td>Zhi shi</td>
<td>87</td>
<td>1.5</td>
</tr>
<tr>
<td>19</td>
<td>Bai zhu</td>
<td>82</td>
<td>1.4</td>
</tr>
<tr>
<td>20</td>
<td>Da zao</td>
<td>78</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>5,858</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*disorders specifically of children or women, acute disorders and other disorders unlike COPD

The frequency of occurrence of individual herbs was calculated according to the four main symptoms (see Table 5.25).
Table 5. 18 Most frequently occurring herbs in the 898 formulae in the data set following general exclusions* by principal symptom

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td>372</td>
<td>Gan cao</td>
<td>222</td>
<td>Gan cao</td>
<td>253</td>
<td>Gan cao</td>
<td>72</td>
<td>Ban xia</td>
<td>54</td>
</tr>
<tr>
<td>Ban xia</td>
<td>266</td>
<td>Ban xia</td>
<td>169</td>
<td>Xing ren</td>
<td>203</td>
<td>Ren shen</td>
<td>50</td>
<td>Gan cao</td>
<td>52</td>
</tr>
<tr>
<td>Xing ren</td>
<td>249</td>
<td>Xing ren</td>
<td>150</td>
<td>Ban xia</td>
<td>172</td>
<td>Ban xia</td>
<td>49</td>
<td>Fu ling</td>
<td>33</td>
</tr>
<tr>
<td>Ren shen</td>
<td>217</td>
<td>Ren shen</td>
<td>129</td>
<td>Ren shen</td>
<td>155</td>
<td>Xing ren</td>
<td>43</td>
<td>Ren shen</td>
<td>32</td>
</tr>
<tr>
<td>Fu ling</td>
<td>209</td>
<td>Fu ling</td>
<td>116</td>
<td>Wu wei zi</td>
<td>139</td>
<td>Wu wei zi</td>
<td>41</td>
<td>Rou gui</td>
<td>30</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td>181</td>
<td>Wu wei zi</td>
<td>110</td>
<td>Fu ling</td>
<td>126</td>
<td>Fu ling</td>
<td>35</td>
<td>Chen pi</td>
<td>26</td>
</tr>
<tr>
<td>Chen pi</td>
<td>170</td>
<td>Chen pi</td>
<td>108</td>
<td>Kuan dong hua</td>
<td>120</td>
<td>Chen pi</td>
<td>32</td>
<td>Xing ren</td>
<td>25</td>
</tr>
<tr>
<td>Sang gen bai pi</td>
<td>142</td>
<td>Sang gen bai pi</td>
<td>88</td>
<td>Sang gen bai pi</td>
<td>117</td>
<td>Sang gen bai pi</td>
<td>32</td>
<td>Sang gen bai pi</td>
<td>25</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td>127</td>
<td>Ma huang</td>
<td>87</td>
<td>Zi wan</td>
<td>108</td>
<td>Bei mu</td>
<td>27</td>
<td>Shi gao</td>
<td>24</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td>124</td>
<td>Rou gui</td>
<td>74</td>
<td>Chen pi</td>
<td>102</td>
<td>Kuan dong hua</td>
<td>25</td>
<td>Ma huang</td>
<td>24</td>
</tr>
<tr>
<td>Ma huang</td>
<td>117</td>
<td>Kuan dong hua</td>
<td>65</td>
<td>Ma huang</td>
<td>94</td>
<td>Mai men dong</td>
<td>22</td>
<td>Wu wei zi</td>
<td>23</td>
</tr>
<tr>
<td>Zi wan</td>
<td>114</td>
<td>Sheng jiang</td>
<td>63</td>
<td>Bei mu</td>
<td>93</td>
<td>Jie geng</td>
<td>21</td>
<td>Sheng jiang</td>
<td>20</td>
</tr>
<tr>
<td>Rou gui</td>
<td>113</td>
<td>Zi wan</td>
<td>59</td>
<td>Sheng jiang</td>
<td>81</td>
<td>Sheng jiang</td>
<td>19</td>
<td>Zhi shi</td>
<td>18</td>
</tr>
<tr>
<td>Bei mu</td>
<td>102</td>
<td>Mai men dong</td>
<td>53</td>
<td>Rou gui</td>
<td>76</td>
<td>E jiao</td>
<td>17</td>
<td>Gan jiang</td>
<td>17</td>
</tr>
<tr>
<td>Jie geng</td>
<td>99</td>
<td>Jie geng</td>
<td>50</td>
<td>Jie geng</td>
<td>69</td>
<td>Zi wan</td>
<td>17</td>
<td>Kuan dong hua</td>
<td>17</td>
</tr>
<tr>
<td>Gan jiang</td>
<td>92</td>
<td>Gan jiang</td>
<td>50</td>
<td>Gan jiang</td>
<td>64</td>
<td>Ma huang</td>
<td>16</td>
<td>Fang ji</td>
<td>16</td>
</tr>
<tr>
<td>Mai men dong</td>
<td>87</td>
<td>Xi xin</td>
<td>47</td>
<td>Mai men dong</td>
<td>61</td>
<td>Zhi mu</td>
<td>14</td>
<td>Bing lang</td>
<td>16</td>
</tr>
<tr>
<td>Zhi shi</td>
<td>87</td>
<td>Zhi shi</td>
<td>46</td>
<td>E jiao</td>
<td>61</td>
<td>Rou gui</td>
<td>13</td>
<td>Zi wan</td>
<td>15</td>
</tr>
<tr>
<td>Bai zhu</td>
<td>82</td>
<td>Bei mu</td>
<td>44</td>
<td>Xi xin</td>
<td>60</td>
<td>Da zao</td>
<td>13</td>
<td>Da zao</td>
<td>14</td>
</tr>
<tr>
<td>Da zao</td>
<td>78</td>
<td>Shi gao</td>
<td>42</td>
<td>Da zao</td>
<td>55</td>
<td>Huang qin</td>
<td>13</td>
<td>Xi xin</td>
<td>13</td>
</tr>
<tr>
<td>Xi xin</td>
<td>75</td>
<td>Da zao</td>
<td>41</td>
<td>Zhi mu</td>
<td>49</td>
<td>Bai zhu</td>
<td>12</td>
<td>Bai zhu</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>5858</td>
<td>total</td>
<td>3416</td>
<td>total</td>
<td>4206</td>
<td>total</td>
<td>1047</td>
<td>total</td>
<td>861</td>
</tr>
</tbody>
</table>

*disorders specifically of children or women, acute disorders and other disorders unlike COPD

Overall, there are only minor variations in the main herbs used according to principal COPD symptom. The herbs Gan cao, Ban xia, Xing ren, Ren shen, and Fu ling are always near the top of the frequency lists. Some other herbs vary according to their principal uses, for example Bei mu is considerably higher on the list of herbs in formulae for sputum compared with formulae for chest tightness or dyspnoea. In other cases there was no variation, with Sang gen bai pi (also called Sang bai pi) ranking 8th in total for all four main symptoms.

5.5.3 Hierarchical combination of four principal COPD symptoms

Firstly, any entries with scores for hemoptysis or any of the general exclusions were removed from the analysis. Then, the four principal COPD symptoms were combined into clusters of two, three and four respectively using dyspnoea as the leading symptom since it is always present in COPD, so that at step 7 all the remaining citations were used for all four symptoms
(see Table 5.26).

Table 5.19: Step-wise hierarchical combinations of four principal COPD symptoms: summary data

<table>
<thead>
<tr>
<th>Step</th>
<th>Formulae</th>
<th>HE</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General exclusions* &amp; hemoptysis</td>
<td>859</td>
<td>5524</td>
</tr>
<tr>
<td>2.1</td>
<td>dyspnoea + cough</td>
<td>329</td>
<td>2251</td>
</tr>
<tr>
<td>2.2</td>
<td>dyspnoea + sputum</td>
<td>71</td>
<td>539</td>
</tr>
<tr>
<td>2.3</td>
<td>dyspnoea + chest tightness</td>
<td>96</td>
<td>684</td>
</tr>
<tr>
<td>3.1</td>
<td>cough + sputum</td>
<td>108</td>
<td>816</td>
</tr>
<tr>
<td>3.2</td>
<td>cough + chest tightness</td>
<td>88</td>
<td>631</td>
</tr>
<tr>
<td>4</td>
<td>sputum + chest tightness</td>
<td>24</td>
<td>183</td>
</tr>
<tr>
<td>5.1</td>
<td>dyspnoea + cough + sputum</td>
<td>64</td>
<td>79</td>
</tr>
<tr>
<td>5.2</td>
<td>dyspnoea + cough + chest tightness</td>
<td>80</td>
<td>579</td>
</tr>
<tr>
<td>5.3</td>
<td>dyspnoea + sputum + chest tightness</td>
<td>21</td>
<td>158</td>
</tr>
<tr>
<td>6</td>
<td>cough + sputum + chest tightness</td>
<td>24</td>
<td>183</td>
</tr>
<tr>
<td>7</td>
<td>dyspnoea + cough + sputum + chest tightness</td>
<td>21</td>
<td>158</td>
</tr>
</tbody>
</table>

*disorders specifically of children or women, acute disorders and other disorders unlike COPD

Of the combinations of two symptoms, dyspnoea plus cough (step 2.1) was the most common combination with 329 citations which referred to 231 different named formulae and 43 unnamed formulae. The most frequent formulae were Xiao Qing Long Tang (n=7) and Yue Bi Jia Ban Xia Tang Fang (n=7) (see Table 5.27).

Table 5.20: Most frequent formulae in total data set at step 2.1 (dyspnoea plus cough)

<table>
<thead>
<tr>
<th>Formula code &amp; name</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 no name</td>
<td>43</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>7</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>7</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi gao Tang</td>
<td>5</td>
</tr>
<tr>
<td>4 Ma Huang Tang</td>
<td>4</td>
</tr>
<tr>
<td>8 Zi Wan Tang</td>
<td>4</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>4</td>
</tr>
<tr>
<td>58 Ze Xie Tang</td>
<td>3</td>
</tr>
<tr>
<td>60 Ting Li Da Zao Tang</td>
<td>3</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>329</strong></td>
</tr>
</tbody>
</table>

At step 2.1 there were 2,251 herb entries for 238 different herbs. Gan cao remained the most common, followed by Ban xia, Xing ren and Ren shen (see Table 5.28). Most of the 21 herbs are same as in the top 20 in the total data set (Table 5.24) except that Zhi shi, Bai zhu and Da zao are not frequent at step 2.1 and Xi xin, Zhi mu, Zao Jia and Ying su ke appear at Step 2.
Table 5. 21 Most frequently occurring herbs in the 229 formulae at step 2.1 (dyspnoea plus cough)

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td>146</td>
<td>6.5</td>
</tr>
<tr>
<td>Ban xia (zhi)</td>
<td>117</td>
<td>5.2</td>
</tr>
<tr>
<td>Xing ren</td>
<td>103</td>
<td>4.6</td>
</tr>
<tr>
<td>Ren shen</td>
<td>82</td>
<td>3.6</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td>74</td>
<td>3.3</td>
</tr>
<tr>
<td>Fu ling</td>
<td>70</td>
<td>3.1</td>
</tr>
<tr>
<td>Ma huang</td>
<td>67</td>
<td>3.0</td>
</tr>
<tr>
<td>Chen pi</td>
<td>64</td>
<td>2.8</td>
</tr>
<tr>
<td>Sang gen bai pi</td>
<td>59</td>
<td>2.6</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td>52</td>
<td>2.3</td>
</tr>
<tr>
<td>Zi wan</td>
<td>49</td>
<td>2.2</td>
</tr>
<tr>
<td>Rou gui</td>
<td>46</td>
<td>2.0</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td>40</td>
<td>1.8</td>
</tr>
<tr>
<td>Xi xin</td>
<td>38</td>
<td>1.7</td>
</tr>
<tr>
<td>Bei mu</td>
<td>37</td>
<td>1.6</td>
</tr>
<tr>
<td>Jie geng</td>
<td>33</td>
<td>1.5</td>
</tr>
<tr>
<td>Gan jiang</td>
<td>33</td>
<td>1.5</td>
</tr>
<tr>
<td>Mai men dong</td>
<td>30</td>
<td>1.3</td>
</tr>
<tr>
<td>Zhi mu</td>
<td>29</td>
<td>1.3</td>
</tr>
<tr>
<td>Zao jia</td>
<td>27</td>
<td>1.2</td>
</tr>
<tr>
<td>Ying su ke</td>
<td>27</td>
<td>1.2</td>
</tr>
<tr>
<td>Total</td>
<td>2251</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

When three symptoms were combined, dyspnoea plus cough plus chest tightness was the most common (step 5.2, 80 citations) but the combination of dyspnoea plus cough plus sputum (step 5.1, 64 citations) more closely matches the current conception of COPD, so lists of formulae and herbs were generated at this step. The 64 formula citations comprised 54 different named and 7 unnamed formulae. The most frequent named formula was Zao Jiao Jian Wan (n=3), followed by Ma huang san (n=2) with all the remaining formulae appearing once only.

The most frequent herb was again Gan cao (n=35) followed by Ban xia and Ren shen (see Table 5.29). Compared to step 2.1 two new herbs appear on the list, Shan yao and E jiao, whereas both Sheng jinag and Gan jiang disappear, as does Zao jiao.
Table 5.22 Most frequently occurring herbs in the 64 formulae at step 5.1 (dyspnoea plus cough plus sputum)

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td>35</td>
<td>7.3</td>
</tr>
<tr>
<td>Ban xia (zhi)</td>
<td>27</td>
<td>5.6</td>
</tr>
<tr>
<td>Ren shen</td>
<td>25</td>
<td>5.2</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td>19</td>
<td>4.0</td>
</tr>
<tr>
<td>Xing ren</td>
<td>19</td>
<td>4.0</td>
</tr>
<tr>
<td>Fu ling</td>
<td>16</td>
<td>3.3</td>
</tr>
<tr>
<td>Chen pi</td>
<td>15</td>
<td>3.1</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td>14</td>
<td>2.9</td>
</tr>
<tr>
<td>Sang gen bai pi</td>
<td>13</td>
<td>2.7</td>
</tr>
<tr>
<td>Bei mu</td>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td>Rou gui</td>
<td>9</td>
<td>1.9</td>
</tr>
<tr>
<td>Zhi mu</td>
<td>9</td>
<td>1.9</td>
</tr>
<tr>
<td>Ma huang</td>
<td>9</td>
<td>1.9</td>
</tr>
<tr>
<td>Mai men dong</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>E jiao</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>Xi xin</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>Ying su ke</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>Zi wan</td>
<td>7</td>
<td>1.5</td>
</tr>
<tr>
<td>Shan yao</td>
<td>6</td>
<td>1.3</td>
</tr>
<tr>
<td>Total</td>
<td>479</td>
<td>100.0</td>
</tr>
</tbody>
</table>

At step 7 all four symptoms were present leaving 21 citations that satisfied all principal criteria. All the 21 formulae at step 7 were different, one was unnamed and the names of the others are listed in Table 5.30. All the formulae were derived from 6 books. The most frequent source book was Pu Ji Fang (普济方) with 9 formulae followed by Tai Ping Hui Min He Ji Ju Fang (太平惠民和剂局方) with 7 formulae.

In the 21 formulae, 68 different herbs were used but the list of top herbs by total frequency varied little from the total set. The main differences are that Ying su ke appears in the top 10 and Ma huang (n=2) has dropped lower down and off the list (see Table 5.31). This list is very similar to step 2.1 with the addition of E jiao and Bai fan and the loss of Gan jiang.
Table 5. 30 Frequency of formulae occurring in the data set at step 7 (dyspnea, cough, sputum & chest tightness)

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Frequency</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>no name</td>
<td>1</td>
<td>Ji Yang Gang Mu</td>
<td>1626</td>
</tr>
<tr>
<td>Ban Xia Yin Fang</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Zi Wan Tang</td>
<td>1</td>
<td>Pu Ji fang</td>
<td>1406</td>
</tr>
<tr>
<td>Zi Wan San Jia Jian</td>
<td>1</td>
<td>Zhang Shi Yi Tong</td>
<td>1695</td>
</tr>
<tr>
<td>Jian Wei Si Wu Tang</td>
<td>1</td>
<td>Ji Yang Gang Mu</td>
<td>1626</td>
</tr>
<tr>
<td>Ban Xia Wan</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Run Fei Wan</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Kuan Dong Hua San</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Xi Xin Wu Wei Zi Tang</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Yang Zhong Tang</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Ren Shen Yang Wei Han</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Wen Fei Wan</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Fu Fang</td>
<td>1078</td>
</tr>
<tr>
<td>Zao Jiao Jian Wan</td>
<td>1</td>
<td>Wai Tai Mi Yao</td>
<td>756</td>
</tr>
<tr>
<td>Shen Su Ban Xia Tang</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Shen Ying Dan</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Ren Shen Ding Chuan Tang</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Chen Sha Li Ge Wan</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Dao Tan Wan</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Ting Li San</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Jin Bu Huan San</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>Qing Jin Tang</td>
<td>1</td>
<td>Chi Shui Xuan Zhu</td>
<td>1584</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21</td>
<td></td>
<td>6 different books</td>
</tr>
</tbody>
</table>

Table 5. 23 Nineteen most frequently occurring herbs (n=3 and above) in the 21 formulae in the data set at step 7

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Frequency</th>
<th>HE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td>13</td>
<td>8.2</td>
</tr>
<tr>
<td>Ban xia</td>
<td>12</td>
<td>7.6</td>
</tr>
<tr>
<td>Ren shen</td>
<td>8</td>
<td>5.1</td>
</tr>
<tr>
<td>Xing ren</td>
<td>8</td>
<td>5.1</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td>6</td>
<td>3.8</td>
</tr>
<tr>
<td>Fu ling</td>
<td>6</td>
<td>3.8</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td>5</td>
<td>3.2</td>
</tr>
<tr>
<td>Sang gen bai pi</td>
<td>5</td>
<td>3.2</td>
</tr>
<tr>
<td>Ying su ke</td>
<td>5</td>
<td>3.2</td>
</tr>
<tr>
<td>Chen pi</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>E jiao</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Rou gui</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Jie geng</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Zi wan</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Bei mu</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Xi xin</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Zao jiao</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Bai fan</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>158</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Overall, the list of herbs remained fairly stable through steps 2.1, 5.1 and 7 with most changes being in the less frequent items.
5.5.4 Global scores

The Global scores were based on a subjective assessment that was undertaken through reading each full citation. This identified 309 citations that appeared to be a disease other than COPD (32.0% of Herbal entries) and 39 citations (3.5% of Herbal entries) that did not provide enough information for a judgment to be made (see Table 5.32).

Table 5.24 Frequency of global assessments of likelihood of COPD in total data set before general exclusions

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not enough information to decide</td>
<td>39</td>
<td>230</td>
<td>3.5</td>
</tr>
<tr>
<td>Other disease unlike COPD</td>
<td>309</td>
<td>2105</td>
<td>32.0</td>
</tr>
<tr>
<td>Possible COPD</td>
<td>282</td>
<td>1969</td>
<td>29.9</td>
</tr>
<tr>
<td>Possible complication of COPD</td>
<td>294</td>
<td>1681</td>
<td>25.5</td>
</tr>
<tr>
<td>Most likely COPD</td>
<td>82</td>
<td>596</td>
<td>9.1</td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>6581</td>
<td>100.0</td>
</tr>
</tbody>
</table>

When the two variables for disorders specific of children or women and for acute disorders or other disorders unlike COPD were combined and applied as exclusion criteria, 898 formula citations and 5,858 Herbal entries remained in the data set. These exclusions reduced the number classified as ‘disease unlike COPD’ to 217 but did not affect the numbers classified as ‘Possible complication of COPD’ or ‘Most likely COPD’, so the exclusion criteria appear to have been consistent with the global score criteria (see Table 5.33).

Table 5.25 Frequency of global assessments of likelihood of COPD in total data set after exclusion of disorders specifically of children or women, acute disorders and other disorders unlike COPD

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency of formulae</th>
<th>Frequency HEs</th>
<th>Percent HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not enough information to decide</td>
<td>27</td>
<td>132</td>
<td>2.3</td>
</tr>
<tr>
<td>Other disease unlike COPD</td>
<td>217</td>
<td>1497</td>
<td>25.6</td>
</tr>
<tr>
<td>Possible COPD</td>
<td>278</td>
<td>1952</td>
<td>33.3</td>
</tr>
<tr>
<td>Possible complication of COPD</td>
<td>294</td>
<td>1681</td>
<td>28.7</td>
</tr>
<tr>
<td>Most likely COPD</td>
<td>82</td>
<td>596</td>
<td>10.2</td>
</tr>
<tr>
<td>Total</td>
<td>898</td>
<td>5,858</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The top 20 formulae based on the total of the three categories are listed in Table 5.34. Of the 82 formulae in the category ‘most likely COPD’, 16 were unnamed and of the named formulae only Ban Xia Yin Fang appeared twice, with the others all only appearing once. However, Ban Xia Yin Fang does not appear in Table 5.34, since its overall frequency in the three categories was only 2. However, this is one of the formulae included at step 7 (see Table 5.30).
The most frequent of the named formulae was Yue Bi Jia Ban Xia Tang Fang with 7 citations but only one of these was for a condition classified as ‘most likely COPD’, with the remaining six being for ‘Possible complication of COPD’. Of the top ten named formulae, only two received scores in the ‘most likely COPD’ category. Also, only one of the formulae in the top 20 in Table 5.34, i.e. Zi Wan San Jia Jian, appeared at step 7. So, in terms of formula name, the two lists show little overlap.

Table 5.26 Twenty most frequent formulae by global score: full data set (after duplicates removed)

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Possible COPD</th>
<th>Possible complication of COPD</th>
<th>Most likely COPD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 no name</td>
<td>45</td>
<td>77</td>
<td>16</td>
<td>138</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi Gao Tang</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>59 Xiao Ban Xia Tang</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>54 Mu Fang Ji Tang</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>4 Ma Huang Tang</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>8 Zi Wan Tang</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>60 Ting Li Da Zao Tang</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>337 Su Zi Jiang Qi Tang</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>21 Zi Wan San Jia Jian</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>55 Shi Zao Tang</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>57 Xiao Ban Xia Jia Fu ling Tang</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>58 Ze Xie Tang</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>66 Mu Fang Ji Tang Qu Shi Gao Jia Fu Ling Mang Xiao Tang</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>127 Jiu Xian San</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>226 Ren Shen Kuan Dong Hua San</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>477 Jiu Sou Wan Zi</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>282</strong></td>
<td><strong>294</strong></td>
<td><strong>82</strong></td>
<td><strong>658</strong></td>
</tr>
</tbody>
</table>

Conversely, when the much shorter list of 21 formulae included at step 7 is considered as the basis for comparison (see Table 5.35), 14 were included in the 82 formulae classified as ‘most likely COPD’ and the remaining 7 were classified as ‘possible complication of COPD’. Therefore the step-wise process identified a sub-set of the formulae that were also identified by the broader global scoring procedure.
Table 5. 27 Frequency of formulae occurring in the data set at step 7: most consistent with COPD, showing Global scores

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Frequency</th>
<th>Global score 4*</th>
<th>Global score 3*</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 no name</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Ji Yang Gang Mu</td>
<td>1626</td>
</tr>
<tr>
<td>6 Ban xia yin fang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>8 Zi Wan Tang</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>21 Zi Wan San Jia Jian</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Zhang Shi Yi Tong</td>
<td>1695</td>
</tr>
<tr>
<td>33 Jian Wei Si Wu Tang</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Ji yang gang mu</td>
<td>1626</td>
</tr>
<tr>
<td>83 Ban Xia Wan</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>92 Run Fei Wan</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>96 Kuan Dong Hua San</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>97 Xi Xin Wu Wei Zi Tang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>98 Yang Zhong Tang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>108 Ren Shen Yang Fei Wan</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>112 Wen Fei Wan</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Wai Tai Mi Yao</td>
<td>756</td>
</tr>
<tr>
<td>213 Shen Su Ban Xia Tang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>220 Shen Ying Dan</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>258 Ren Shen Ding Chuan Tang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>259 Chen Sha Li Ge Wan</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>273 Dao Tan Wan</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>278 Ting Li San</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>454 Jin Bu Huan San</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>484 Qing Jin Tang</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Chi Shui Xuan Zhu</td>
<td>1584</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21</strong></td>
<td><strong>14</strong></td>
<td><strong>7</strong></td>
<td><strong>6 different books</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Global score 4: ‘most likely COPD’; Global score 3 ‘possible complication of COPD’

The 20 most frequent herbs are listed in Table 5.36 according to the three main global score categories: ‘most likely COPD’, ‘possible complication of COPD’ and ‘possible COPD’. As with previous lists of herbs, Gan cao is the most frequent in each category and there is considerable similarity between lists. The only notable differences are the inclusion of Ying suke and Zhi mu in the list for ‘most likely COPD’.
Table 5. 28 Twenty most frequent HEs by global score: full data set (after duplicates removed)

<table>
<thead>
<tr>
<th>Most likely COPD</th>
<th>HEs</th>
<th>Total HEs</th>
<th>possible complication of COPD</th>
<th>HEs</th>
<th>possible COPD</th>
<th>HEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td>35</td>
<td>436</td>
<td>Gan cao</td>
<td>91</td>
<td>Gan cao</td>
<td>141</td>
</tr>
<tr>
<td>Ren shen</td>
<td>31</td>
<td>245</td>
<td>Xing ren</td>
<td>82</td>
<td>Ban xia</td>
<td>103</td>
</tr>
<tr>
<td>Ban xia</td>
<td>29</td>
<td>286</td>
<td>Ren shen</td>
<td>70</td>
<td>Xing ren</td>
<td>88</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td>25</td>
<td>193</td>
<td>Ban xia</td>
<td>57</td>
<td>Fu ling</td>
<td>76</td>
</tr>
<tr>
<td>Xing ren</td>
<td>25</td>
<td>292</td>
<td>Zi wan</td>
<td>55</td>
<td>Ren shen</td>
<td>74</td>
</tr>
<tr>
<td>Chen pi</td>
<td>23</td>
<td>185</td>
<td>Ma huang</td>
<td>54</td>
<td>Chen pi</td>
<td>69</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td>21</td>
<td>137</td>
<td>Wu wei zi</td>
<td>51</td>
<td>Wu wei zi</td>
<td>61</td>
</tr>
<tr>
<td>Fu ling</td>
<td>20</td>
<td>235</td>
<td>Kuan dong hua</td>
<td>48</td>
<td>Sheng jiang</td>
<td>49</td>
</tr>
<tr>
<td>Sang gen bai pi</td>
<td>18</td>
<td>172</td>
<td>Sang gen bai pi</td>
<td>47</td>
<td>Sang gen bai pi</td>
<td>46</td>
</tr>
<tr>
<td>Bei mu</td>
<td>15</td>
<td>124</td>
<td>Rou gui</td>
<td>45</td>
<td>Mai men dong</td>
<td>37</td>
</tr>
<tr>
<td>Ying su ke</td>
<td>14</td>
<td>40</td>
<td>Fu ling</td>
<td>34</td>
<td>Bei mu</td>
<td>36</td>
</tr>
<tr>
<td>Zi wan</td>
<td>12</td>
<td>124</td>
<td>Sheng jiang</td>
<td>33</td>
<td>Jie geng</td>
<td>36</td>
</tr>
<tr>
<td>Mai men dong</td>
<td>11</td>
<td>101</td>
<td>Chen pi</td>
<td>31</td>
<td>Kuan dong hua</td>
<td>33</td>
</tr>
<tr>
<td>Rou gui</td>
<td>10</td>
<td>119</td>
<td>Bei mu</td>
<td>29</td>
<td>Zi wan</td>
<td>32</td>
</tr>
<tr>
<td>Zhi mu</td>
<td>10</td>
<td>66</td>
<td>Xi xin</td>
<td>28</td>
<td>Zhi shi</td>
<td>32</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td>9</td>
<td>143</td>
<td>Shi gao</td>
<td>28</td>
<td>Ma huang</td>
<td>29</td>
</tr>
<tr>
<td>Jie geng</td>
<td>9</td>
<td>113</td>
<td>Gan jiang</td>
<td>26</td>
<td>Da zao</td>
<td>27</td>
</tr>
<tr>
<td>E jiao</td>
<td>8</td>
<td>75</td>
<td>Jie geng</td>
<td>25</td>
<td>Bai zhu</td>
<td>27</td>
</tr>
<tr>
<td>Xi xin</td>
<td>8</td>
<td>77</td>
<td>Da zao</td>
<td>24</td>
<td>Gan jiang</td>
<td>25</td>
</tr>
<tr>
<td>Ma huang</td>
<td>8</td>
<td>139</td>
<td>Fang ji</td>
<td>22</td>
<td>E jiao</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>596</strong></td>
<td><strong>6581</strong></td>
<td></td>
<td><strong>1681</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At step 7, of the 158 Herbal entries, 118 were scored as ‘most likely COPD’ and 40 were considered ‘possible complications of COPD’. All herbs of a frequency of 2 or more for ‘most likely COPD’ are presented in Table 5.37.

Within the list of 23 different herbs included under ‘most likely COPD’ are all of the 20 herbs listed in Table 5.36 under ‘most likely COPD’ based on the global scores alone. Consequently, the same list of high frequency herbs was identified using either procedure.
Table 5. 29 Most frequent Herbal entries by global score following exclusions: Step 7

<table>
<thead>
<tr>
<th>Most likely COPD</th>
<th>Frequency</th>
<th>Possible complication of COPD</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao*</td>
<td>11</td>
<td>Xing ren</td>
<td>3</td>
</tr>
<tr>
<td>Ban xia*</td>
<td>10</td>
<td>Fu ling</td>
<td>3</td>
</tr>
<tr>
<td>Ren shen*</td>
<td>6</td>
<td>Gan cao</td>
<td>2</td>
</tr>
<tr>
<td>Wu wei zi*</td>
<td>5</td>
<td>Ban xia</td>
<td>2</td>
</tr>
<tr>
<td>Xing ren*</td>
<td>5</td>
<td>Ren shen</td>
<td>2</td>
</tr>
<tr>
<td>Ying su ke*</td>
<td>5</td>
<td>Zao jia</td>
<td>2</td>
</tr>
<tr>
<td>Chen pi*</td>
<td>4</td>
<td>He zi</td>
<td>2</td>
</tr>
<tr>
<td>Sheng jiang*</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>E jiao*</td>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Kuan dong hua*</td>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Sang gen bai pi*</td>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fu ling*</td>
<td>3</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Rou gui*</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bei mu*</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Xi xin*</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Mai men dong*</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Zhi mu*</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Jie geng*</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Zi wan*</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Tian nan xing</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ma huang*</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bai fan</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Zi su ye</td>
<td>2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>118</strong></td>
<td></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

*also included in table 5.36 under ‘most likely COPD

5.5.5 **Comparison between the step-wise and the global score approach**

When only the duplicates were excluded, 82 formulae were scored as ‘most likely COPD’, 294 were ‘possible complications of COPD’ and 282 were classified as ‘possible COPD’ using the subjective global scoring approach (see Table 5.32). However, most of the 82 formulae scored as ‘most likely COPD’ only had a frequency of one so this presented difficulties with short-listing them. Similarly, at step 7, the 21 formulae that remained after the step-wise exclusions all had frequencies of one. Although the number is considerably smaller using the step-wise approach, no hierarchical ranking was possible. However, when both approached were combined, 14 formulae were scored as ‘most likely COPD’ and 7 were considered ‘possible complications of COPD’. None were considered unlikely instances (see Table 5.35). So both approaches appear to have had consistent results and the combination of approaches had allowed additional refinement.

Although step 7, which combined four main symptoms, located a set of herbs and formulae that satisfied the main criteria for COPD, and the list of herbs found at this step was consistent with those found by the global scoring procedure for ‘most likely COPD’, the total number of citations remaining in the data set was relatively small. Therefore, all the 21 formulae only
appeared with a frequency of one and the highest frequency for any of the herbs was only 13 (for Gan cao). With these low frequencies it is not possible to rank the formulae and it is difficult to be confident about the meaningfulness of the relative ranking of the herbs. At step 5.1 the three main COPD symptoms of dyspnoea plus cough plus sputum are all targeted by the 64 included formulae, but the diversity of formula names meant that only two formulae had frequencies greater than one. Step 2.1 (dyspnoea plus cough) is less specific but its much larger number of citations (329 formulae) allows the ranking of formulae in terms of frequency of appearance for these two combined symptoms in the data set. Consequently each of these three steps is considered in the following discussion.

5.6 Discussion of Search terms

5.6.1 Discussion of search terms

The main clinically observable symptoms of COPD are related to the progression of COPD. Chronic cough tends to occur in the earlier stages with sputum and shortness of breath becoming more prominent as the condition deteriorates. Severe dyspnoea and chest tightness are characteristic of the later stages and of exacerbations. However, the clinical presentation of COPD can vary considerably from person to person and according to stage. Also, the above combinations of symptoms can appear in a number of other chronic lung disorders.

Cough and dyspnoea was found to be the most common combination of any two symptoms in the step-wise hierarchical combination of four symptoms of COPD. This is consistent with the clinical presentation of COPD in western medicine.

Of the search terms, chronic cough was most frequently associated with Jiu ke and Jiu sou, which was expected since both are terms for ‘cough’. However, descriptions of chronic cough appeared for the other terms at less than 10 percent. In particular, for Zhi yin there was no mention of chronic cough although 61.6% of citations simply mentioned ‘cough’. For the term Chuan zheng mention of ‘cough’ was less than 15% with only 0.2% for ‘chronic cough’. Therefore, amongst the eight terms, Zhi yin and Chuan zheng appear the least likely to refer to conditions consistent with COPD.

Mention of dyspnea was predictably high for Chuan zheng and Chuan sou, and lowest for Jiu sou (26.2%) and Tanyin kesou (35.1%) compared with almost 72% for Fei zhang. ‘Dyspnœa that is worse with exercise’, was not mentioned for Fei zhang or Jiu ke but the the overall percentages were low (0.8%-6.7%) for the other terms. ‘Severe dyspnoea’, was not described
for Zhi yin or Tanyin kesou, but again there were only low percentages for the other terms (1.5%-15.9%). ‘Severe dyspnoea’ appeared highest for Fei zhang. Therefore, based on the symptoms, Ke chuan, Zhi yin, Chuan zheng and Jiu sou appear to be the terms least likely to correspond with COPD.

Sputum production is also one of the characteristic symptoms of COPD. However, more than 70 percent of no mentions were found for all terms. Furthermore, chronic sputum production was not described for the terms Jiu ke, Ke chuan, Chuan sou, Zhi yin or Chuan zheng, whereas there was mention for the terms Fei zhang, Jiu sou and Tanyin kesou at 4.6%, 3.2% and 0.6% respectively. Overall, sputum production was most commonly mentioned for Fei zhang but it was not a common mention for any of the terms, so it cannot be used to identify any further terms as being less likely to refer to COPD.

Chest tightness as a symptom of COPD appeared most frequently in Fei zhang and Zhi yin followed by Tanyin kesou, Jiu ke and Chuan sou, and was lower for the terms Jiu sou, Ke chuan and Chuan zheng.

In the step-wise combinations of main symptoms, distinction was not made between levels of severity of dyspnea or features of cough. When symptoms were combined at steps 2.1, 5.1 and 7 the numbers of formulae remaining in the data set were dramatically reduced and some search terms ceased to be represented. Notably, Zhi yin was eliminated at step 5.1 while Jiu ke, Ke chuan and Chuan zheng were greatly reduced when compared to the total data set. At step 7, Ke chuan and Chuan zheng were eliminated leaving Fei zhang, Chuan sou and Tanyin kesou as the main terms (see Table 5.38).
Table 5. 30 Frequency of formulae by search term at the main stages of the step-wise combinations of symptoms (n, %)

<table>
<thead>
<tr>
<th>Term</th>
<th>Frequency of formulae total</th>
<th>Frequency of formulae 2.1 dyspnea + cough</th>
<th>Frequency of formulae 5.1 dyspnea + cough+sputum</th>
<th>Frequency of formulae 7 dyspnea + cough+sputum+chest tightness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fei zhang</td>
<td>57 (5.7)</td>
<td>33 (10.0)</td>
<td>6 (9.4)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>2. Jiu ke</td>
<td>74 (7.4)</td>
<td>14 (4.3)</td>
<td>2 (3.1)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>3. Jiu sou</td>
<td>221 (22.0)</td>
<td>44 (13.4)</td>
<td>11 (17.2)</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>4. Ke chuan</td>
<td>115 (11.4)</td>
<td>25 (7.6)</td>
<td>3 (4.7)</td>
<td>0</td>
</tr>
<tr>
<td>5. Chuan sou</td>
<td>196 (19.5)</td>
<td>130 (39.5)</td>
<td>23 (35.9)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>6. Zhi yin</td>
<td>69 (6.9)</td>
<td>37 (11.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Tanyin kesou</td>
<td>132 (13.1)</td>
<td>30 (9.1)</td>
<td>16 (25.0)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>8. Chuan zheng</td>
<td>142 (14.1)</td>
<td>16 (4.9)</td>
<td>3 (4.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1006 (100%)</strong></td>
<td><strong>329 (100%)</strong></td>
<td><strong>64 (100%)</strong></td>
<td><strong>21 (100%)</strong></td>
</tr>
</tbody>
</table>

Chuan zheng and Fei zhang are regarded as the classical terms most closely related to COPD (331-333). However, chronic cough and sputum production were infrequently described for Chuan zheng and this term was infrequent at step 5.1 and eliminated at step 7. Fei zhang tended to be consistent in relation to the main symptoms and their combinations. Despite having the lowest frequency in the total data set, Fei zhang was one of the three main terms at step 7. Cough with dyspnoea was also commonly mentioned for the term Chuan sou which also remained a main term at steps 5.1 and 7. However, the term Ke chuan was infrequent at step 5.1 and was eliminated at step 7.

Jiu kesou is regard as a disease name in two modern books ((296, 297)) but it was not mentioned as an historical term for COPD in the published papers related to the 101 clinical trials. The terms Jiu ke and Jiu kesou appear in many classical books and both are included under Jiu ke in these data. Chronic cough with dyspnoea was fairly common for Jiu ke (approx. 50%) but lower for Jiu sou (approx. 26%) but Jiu sou was the most frequent term in the total data set. Both terms remained at steps 5.1 and 7 but as relatively low frequency terms.

In the case of Tanyin kesou, both cough and dyspnea were relatively common symptoms and this term increased its relative frequency at step 5.1 and was one of the three main terms at step 7. It is also described in two modern books (248, 334).

Overall the three terms that were most likely to be associated with conditions that combined the four main symptoms of COPD were Fei zhang, Chuan sou and Tanyin kesou, while the least likely term was Zhi yin. Chuan zheng and Ke chuan both located a few references that combined the three main COPD symptoms. Chuan zheng and Ke chuan tended to be closer to
Xiao zheng (asthma) than COPD in the located references. Zhi yin in the located references was more relevant to a ‘possible complication of COPD’ associated with heart disorders such as cor pulmonale. It is mentioned as belonging to COPD in one modern book (296). However, it was generally excluded by the global scores. Jiu ke is a very common symptom of chronic bronchitis which is regarded as one component of COPD. However, if cough is the only symptom present or it is combined with sputum production, it is considered to be cough-variant asthma (CVA) (335).

5.6.2 Discussion of the most frequent formulae

In the the next sections, the formulae identified at the various levels of selection are discussed.

5.6.2.1 Formulae in total data set following exclusions

The top ten formulae in the total data set following exclusions are presented in Appendix 8. These were found in 5 books and were located under the terms Fei zhang, Zhi yin and Tanyin kesou.

In modern CHM, Xiao Qing Long Tang, Xiao Qing Long Jia Shi Gao Tang and Yue Bi Jian Ban Xia Tang are still commonly used for wheezing at the acute stage due to attack caused by exopathogenic factors. Xiao Qing Long Tang is for treating aversion to wind-cold, cold phlegm accumulated in the lung and obstructing lung qi, while for conditions complicated with interior heat, Xiao Qing Long plus Shi Gao Tang is used. Yue Bi Jian Ban Xia Tang is used for wheezing caused by aversion to wind-heat and phlegm heat accumulated in the lung. Xiao Qing Long Tang is also used in treating both thoracic fluid retention and subcutaneous fluid retention.

Mu Fang Ji Tang and Wu Ling San are applied for different syndromes of thoracic fluid retention; Mu Fang Ji Tang’s action is similar to Xiao Qing Long Tang for cold fluid retention in lung while Wu ling San is for deficiency of spleen and kidney yang. Zao Jiao Jian Wan was for dyspnea in the original books which gave its actions as tonify qi and resolve phlegm to calm dyspnea but it is no longer in common use.

Ma Huang Gan Cao plus Xing Ren Sheng Jiang Tang is used for cough with a lot of sputum caused by wind-cold and its actions are to warm lung to dispel cold, and resolve phlegm to suppress cough. Xiao Ban Xia Tang and Xiao Ban Xia Jia Fu Ling Tang are mostly used for nausea caused by phlegm-fluid retention in the spleen and stomach.

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These formulae are mostly used for acute disorders or for removing fluid. Such formulae can be used for a wide range of lung disorders. However, these kinds of conditions are not good examples of COPD, although some may be related to exacerbations of COPD. Therefore, formula selection based on the symptoms alone did not provide formulae directly relevant to the treatment of stable COPD, only to COPD exacerbations.

5.6.2.2 Formulae selected by Global score as possible, likely or possible complication of COPD

The 20 most frequent formulae in the data set defined by the global scores as ‘possible’, ‘likely’ or ‘possible complication’ of COPD are presented in Appendix 9. These were found in 10 books under the terms of Fei zhang, Zhi yin, Tan yin ke sou, Chuan zheng, Chuan sou and Jiu ke sou.

Eight of the nine named high frequency formulae found in the total data set following general exclusions (see Appendix 8) also appeared in Appendix 9. So there is a broad consistency between the formulae remaining after the general exclusions and those considered to be associated with conditions that were at least possible instances of COPD. The exception is Wu Ling San which is mainly used for fluid retention rather than for cough or dyspnea and did not get selected under any of the three global scores.

Some of newly appearing formulae in Appendix 9 are for removing fluid – in fact all the following are for thoracic fluid retention with cold fluid retention in lung: Shi Zao Tang, Ting Li Da Zao Tang, Ze Xie Tang and Mu Fang Ji Tang Jia Jian. Other formulae are for acute conditions that may be exacerbations, including Ma Huang Tang, Zi Wan Tang, Jiu Sou Wan Zi and Su Zi Jiang Qi Tang, which are for cough, dyspnea and wheezing with excess patterns but Su Zi Jiang Qi Tang is also used when there is fullness above and deficiency below. Those that appear most relevant to stable COPD are Zi Wan San Jian Jian, Jiu Xian San and Ren Shen Kuan Dong Hua San which are all for long-term cough with dyspnea. However, none of these formulae appear in the top ten based on these selection criteria. Therefore, these general criteria tended to include many formulae that may be relevant to the treatment of COPD exacerbations but only a few relevant to stable COPD (336).

5.6.2.3 Formulae located in the step-wise combinations of four principal COPD symptoms

Of the nine most frequently named formulae at step 2.1 (dyspnea + cough), five were also in
the top 10 formulae found in the total data set (after general exclusions) and the remaining four were included in the top 20 formulae identified by the global scoring procedure.

All of these formulae are used for acute conditions which may include exacerbations of COPD characterised by wheezing or dyspnea with excess patterns or for thoracic fluid retention with cold fluid retention in lung. Therefore, combining the symptoms of dyspnea plus cough still mainly located formulae for exacerbations. Acute condition was one of the general exclusions, but entries were excluded as ‘acute condition’ when the entry explicitly stated this, whereas this aspect frequently was not mentioned.

At step 5.1 (dyspnoea plus cough plus sputum) there were 54 different formulae identified but only two of the named formulae had frequencies greater than one. One of these, Zao Jiao Jian Wan, was included at step 2.1 as well as in the top 10 formulae overall and in the top 10 formulae identified by the global scoring system (see Table 5.23 & 5.34). The other is Ma Huang San (麻黄散) (Gan cao, Rou gui, Xing ren, Ma huang, Ke zi, Kuan dong hua) which did not appear amongst the higher frequency items in the earlier lists but is actually a variant on the more common and frequently occurring formula Ma Huang Tang. Ma Huang San was used for treating chronic cough caused by phlegm accumulated in the lung. Both of these higher frequency formulae were for the acute stages of a lung disorder. Two of the three formulae identified by the global scores (Appendix 8) as relevant to stable COPD, Zi Wan San Jia Jian and Ren Shen Kuan Dong Hua San, remained in the list of 54 formulae at step 5.1 but due to the excessive number of formulae remaining at this stage, the individual actions of all the various formulae are not discussed.

At step 7, there remained 21 formulae that all appeared once but when the global scores were also applied, 14 were scored as ‘most likely COPD’ while the other 7 were all considered ‘possible complications of COPD’. The main reason for this division is those considered ‘possible complication’ tended to have more acute symptoms.

For ‘most likely COPD’, the 14 formulae are presented in Appendix 10. They were found in 5 different books under the search terms of Fei zhang, Tanyin kesou, Chuan sou and Jiu kesou.

All of the 14 formulae in the data set at step 7 and also ranked as ‘most likely COPD’ (see Appendix 10) are not commonly used in modern CHM but most of their constituent herbs remain in use. Six of the 14 formulae are ginseng formulae. Ginseng is considered one of the most suitable herbs for stable COPD in modern TCM. However, with the exception of Ren shen, Wu wei zi and Fu ling which are used for tonifying qi, most of the herbs in these
formulae are for diffusing the lung to resolve phlegm, suppressing cough or for calming dyspnea. Overall, about half of these formulae were focused on the symptoms and the remainder included herbs for tonifying qi and/or yin. For example, Qing Jin Tang also included herbs for strengthening spleen and resolving damp along with herbs for cough and phlegm. The remaining formulae were mainly focused on cough with dyspnea which may be an exacerbation of a chronic condition, for example Shen Ying Dan, Ban Xia Yin Fang, Kuan Dong Hua San, Xi Xin Wu Wei Zi Tang, and Jin Bu Huan San (336).

For ‘possible complications of COPD’, seven formulae were located under Fei zhang, Tanyin kesou or Chuan sou in four books issued from the Song to Qing dynasties (see Appendix 11). None were associated with the search terms Jiu ke, Jiu sou, Ke chuan, Chuan zheng or Zhi yin. Four of the seven formulae were focused on the symptoms while the others also included herbs for tonifying qi such as Ren shen, Ge jie, Huang qi, Fu ling, Shan yao.

Zao Jiao Jian shown in Appendix 8 and Zi Wan Tang in Appendix 9 were discussed earlier (sections 5.3.8.1 and 5.3.8.2). Ban Xia Wan is Xiao Ban Xia Tang plus Bai fan and the action is similar to Xiao Ban Xia Tang. These three formulae are used for phlegm-fluid retention with an excess pattern in modern TCM. This is more characteristic of the aggravation stage of a chronic condition.

The formula Jia Wei Si Wu Tang uses the therapeutic principle of regulating qi and resolving phlegm and blood stasis without using herbs for tonifying qi. This is similar to one of the concepts for treating COPD in modern TCM but it focuses on contribution of the phlegm and blood stasis rather than on qi deficiency.

Ting Li San is a modification of Shen Ge Tang which is used for cough with dyspnea with a pattern of upper excess and lower deficiency, which may be applied in the acute or remission stages of cough with dyspnea. Ren Shen Yang Fei Wan is the only formula which includes Ren shen and Huang qi for tonifying the lung and fortifying the spleen to resolve phlegm. This is consistent with principles for treating stable COPD in modern TCM.

Overall, from the viewpoint of modern TCM, most of the formulae remaining at step 7 would be considered applicable for exacerbations of COPD involving cough, phlegm-fluid retention and/or dyspnea rather than for stable COPD. This was irrespective of the two categories of global score applied at this stage. The probable reason is the difficulty in making a global decision that distinguishes an ‘exacerbation’ from ‘likely COPD’. Since the scoring procedure focused on symptoms and had eliminated recently occurring symptoms due to external
pathogenic factors, the remaining formulae all address these symptoms. At step 7 most of the formulae that focused on fluid retention, which is more likely to be associated with heart failure than COPD alone, had been removed. Of the included formulae, about half addressed both the presenting symptoms and the underlying syndromes (qi and/or yin deficiency, blood stais etc) and a few formulae such as Jia Wei Si Wu Tang, Ren Shen Yang Fei Wan and Qing Jin Tang showed similarities to formulae used in the modern CHM management of COPD.

Also, this step which combines four symptoms, may have been overly restrictive since a number of candidate formulae identified using the global scores were eliminated, such as Zi Wan San Jian Jian, Jiu Xian San and Ren Shen Kuan Dong Hua San. It is not necessarily the case that all four symptoms would be present in COPD or these symptoms would be sufficiently remarkable to be recorded in a particular case, even when there was an exacerbation.

5.6.3 Discussion of the most frequent herbs

5.6.3.1 Herbs in total data set following general exclusions

The top of twenty-one frequent herbs after general exclusions (see Table 5.24) are Gan cao, Ban xia, Xing ren, Ren shen, Fu ling, Wu wei zi, Chen pi, Sang bai pi, Sheng jiang, Kuan dong hua, Ma huang, Zi wan, Rou gui, Bei mu, Jie geng, Gan jiang, Mai men dong, Zhi shi, Bai zhu, Da zao and Xi xin.

For each of the terms dyspnoea, cough, sputum and chest tightness, there are few differences among the top twenty-one frequent herbs. E jiao and Zhi mu are more frequent for cough and replaced Bai zhu and Zhi shi; Rou gui replaced Wu wei zi in chest tightness. E jiao, Zhi mu and Huang qin are more frequent for phlegm and replaced Gan jiang, Zhi shi and Xi xin; Shi gao is more frequent and replaced Bai zhu; Shi gao, Fang ji and Bing lang are more frequent for chest tightness and replaced Bei Mu, Jie geng and Mai men dong. These differences reflect the uses of these herbs for these specific symptoms.

The top herbs at this step were not necessarily the same as the herbs included in the top ten formulae at this step, for example, some of the herbs included in these formulae, such as Ze xie, Shi gao, Zhu ling, Shao yao and Gui zhi did not appear in 20 most frequent herbs in the total data set following exclusions (see Table 5.25).
5.6.3.2 Herbs selected by Global score as used for possible, likely or possible complication of COPD

According to the global score analysis (see Table 5.39), for ‘most likely COPD’, there was no change in the top ten herbs except that Bei mu replaced Sheng jiang which dropped to number 16. This was likely due to the exclusion of formulae for conditions related to exterior wind-cold pathogens. Other notable changes were that Ying su ke appeared in 11th place along with the following other new herbs in the top 20: Zhi mu and E jiao while Ma huang dropped to number 20 and Bai zhu, Gan jiang, Zhi shi, and Da zao were not in the top 20. These changes appear due to a greater focus on treating cough.

For ‘possible complications of COPD’, Fu ling, Sheng jiang and Chen pi were replaced by Zi wan, Ma huang and Rou gui in the top ten. The new herbs Fang ji and Shi gao entered the top 20 while Bai zhu, Zhi shi and Mai men dong dropped off the list. This reflects the greater focus on the symptoms of cough, dyspnea and chest tightness. Rou gui was included for its actions, along with herbs such as Fang ji as well as the more frequent Fu ling and Ban xia, in removing the fluid build up associated with dyspnea and chest tightness.
Table 5. 31 Comparison of high frequency herbs: Total data set after general exclusions versus subsets defined by step-wise exclusion and global scores

<table>
<thead>
<tr>
<th>Rank</th>
<th>Total data set</th>
<th>Step 2.1</th>
<th>Step 5.1</th>
<th>Step 7</th>
<th>Global score 3</th>
<th>Global score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
</tr>
<tr>
<td>2</td>
<td>Ban xia</td>
<td>Ban xia (zhi)</td>
<td>Ban xia (zhi)</td>
<td>Ban xia</td>
<td>Ren shen</td>
<td>Xing ren</td>
</tr>
<tr>
<td>3</td>
<td>Xing ren</td>
<td>Xing ren</td>
<td>Ren shen</td>
<td>Ren shen</td>
<td>Ban xia</td>
<td>Ren shen</td>
</tr>
<tr>
<td>4</td>
<td>Ren shen</td>
<td>Ren shen</td>
<td>Wu wei zi</td>
<td>Xing ren</td>
<td>Wu wei zi</td>
<td>Ban xia</td>
</tr>
<tr>
<td>5</td>
<td>Fu ling</td>
<td>Wu wei zi</td>
<td>Xing ren</td>
<td>Wu wei zi</td>
<td>Xing ren</td>
<td>#Zi wan</td>
</tr>
<tr>
<td>6</td>
<td>Wu wei zi</td>
<td>Fu ling</td>
<td>Fu ling</td>
<td>Fu ling</td>
<td>#Ma huang</td>
<td>Wu wei zi</td>
</tr>
<tr>
<td>7</td>
<td>Chen pi</td>
<td>#Ma huang</td>
<td>Chen pi</td>
<td>Sheng jiang</td>
<td>Kuan dong hua</td>
<td>Wu wei zi</td>
</tr>
<tr>
<td>8</td>
<td>Sang gen bai pi</td>
<td>Chen pi</td>
<td>Kuan dong hua</td>
<td>Sang gen bai pi</td>
<td>Fu ling</td>
<td>Kuan dong hua</td>
</tr>
<tr>
<td>9</td>
<td>Sheng jiang</td>
<td>Sang gen bai pi</td>
<td>Sang gen bai pi</td>
<td>Yingsu ke</td>
<td>Sang gen bai pi</td>
<td>Sang gen bai pi</td>
</tr>
<tr>
<td>10</td>
<td>Kuan dong hua</td>
<td>Kuan dong hua</td>
<td>#Bei mu</td>
<td>Chen pi</td>
<td>#Bei mu</td>
<td>Rou gui</td>
</tr>
<tr>
<td>11</td>
<td>Ma huang</td>
<td>Zi wan</td>
<td>Rou gui</td>
<td>E jiao</td>
<td>Yingsu ke</td>
<td>*Fu ling</td>
</tr>
<tr>
<td>12</td>
<td>Zi wan</td>
<td>Rou gui</td>
<td>Zhi mu</td>
<td>Kuan dong hua</td>
<td>Zi wan</td>
<td>Sheng jiang</td>
</tr>
<tr>
<td>13</td>
<td>Rou gui</td>
<td>*Sheng jiang</td>
<td>Ma huang</td>
<td>Rou gui</td>
<td>Mai men dong</td>
<td>*Chen pi</td>
</tr>
<tr>
<td>14</td>
<td>Bei mu</td>
<td>#Xi xin</td>
<td>Mai men dong</td>
<td>Jie geng</td>
<td>Rou gui</td>
<td>Bei mu</td>
</tr>
<tr>
<td>15</td>
<td>Jie geng</td>
<td>Bei mu</td>
<td>E jiao</td>
<td>Zi wan</td>
<td>Zhi mu</td>
<td>Xi xin</td>
</tr>
<tr>
<td>16</td>
<td>Gan jiang</td>
<td>Jie geng</td>
<td>Xi xin</td>
<td>Bei mu</td>
<td>Sheng jiang</td>
<td>Shi gao</td>
</tr>
<tr>
<td>17</td>
<td>Mai men dong</td>
<td>Gan jiang</td>
<td>Yingsu ke</td>
<td>Xi xin</td>
<td>Jie geng</td>
<td>Gan jiang</td>
</tr>
<tr>
<td>18</td>
<td>Zhi shi</td>
<td>Mai men dong</td>
<td>*Zi wan</td>
<td>Zao jiao</td>
<td>E jiao</td>
<td>Jie geng</td>
</tr>
<tr>
<td>19</td>
<td>Bai zhu</td>
<td>Zhishi</td>
<td>Shan yao</td>
<td>Bai fan</td>
<td>Xi xin</td>
<td>Da zao</td>
</tr>
<tr>
<td>20</td>
<td>Da zao</td>
<td>Zao jia</td>
<td>Bai fan</td>
<td>Xi xin</td>
<td>Da zao</td>
<td>Da zao</td>
</tr>
<tr>
<td>21</td>
<td>Xi xin</td>
<td>Yingsu ke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Herbs appearing at each step but not in column 1 (total data set) are in bold. Herbs that have markedly increased in relative frequency compared to column 1 are marked with a hash #, whereas those that have decreased are marked with an asterisk*. The total data set: Total classical data set (after general exclusions); Step 2.1: dyspnea + cough; Step 5.1: dyspnea + cough + sputum; Step 7: dyspnea + cough + sputum + chest tightness; Global score 4: ‘likely COPD’; Global score 3: ‘complication of COPD’

Some of the herbs in the top formulae based on global score, such as Shi gao, Shan yao, Zhao jiao, Bing lang, Ting li zi, Shao yao and Gui zhi did not appear in the 20 most frequent herbs in the total data set following exclusions listed in Table 5.25. Overall, the number of different herbs was high, so only herbs that appeared in many different formulae also appeared high up the frequency list for individual herbs.
5.6.3.3 Herbs located in the step-wise hierarchical combinations of four principal COPD symptoms

Based on the analysis of the hierarchical combinations of the four principal COPD symptoms, the most common combination of any two symptom terms was for dyspnoea plus cough with 346 formulae (step 2.1). At this step the top ten herbs remained similar to the full list following general exclusions, except that Ma huang had moved up the list replacing Sheng jiang which dropped to number 13, while Xi xin moved up to 14th place (see Table 5.39). Three new herbs appeared on the list: Zhi mu, Zao jia and Ying su ke replacing Bai zhu, Zhi shi and Da zao. These changes appear to reflect a greater focus on dyspnea (Ma huang, Xi xin), chronic cough (Zhi mu & Ying su ke).

When the three symptoms of dyspnoea plus cough and sputum were combined (step 5.1), out of 479 herb citations (see Table 5.22) the top ten herbs remained similar, with Bei mu entering the list replacing Sheng jiang which dropped off the list together with Bai zhu, Gan jiăng, Zhi shi and Da zao. The herbs that entered the list were Zhi mu, E jiao and Ying su ke for cough and sputum plus the tonic herb Shan yao.

In the 21 formulae that remained after the combination of four symptoms (step 7), the only differences in the top ten herbs were that Ying su ke appeared in 9th place while Kuan dong hua dropped to number 12. Other new herbs on the list were E jiao, Zao jia and Bai fan while Bai zhu, Gan jiăng, Zhi shi, Da zao, and Ma huang had all dropped out of the top 20. These changes mostly reflect a greater focus on chronic cough and phlegm.

A number of the herbs that composed the formulae at step 7, such as Qian hu, Su zi, Bing lang, Dang gui, Zhu ye, Di huang, Da huang, Dan pi, Sang ye, Yi yi ren, Ting li zi, Gua lou, Bo he and others did not appear in the list of most frequent herbs or the list of high frequency herbs at step 7. This is because the overall number of different herbs used was high, so the frequency of many of the herbs was relatively low.

5.6.3.4 General characteristics of the most frequent herbs

All of the 20 herbs included in the full list after general exclusions (see Table 5.25) were recorded in earliest and most famous book belonging to the Ben Cao genre, which is Shen Nong Ben Cao Jing (神农本草经) and was issued in or soon after the Han dynasty. In this book, herbs were divided into a hierarchy of three groups. Herbs in the top grade were regarded as Chief or King Medicines without toxicity that could be taken for long time and
benefit long life. Herbs in the medium grade were recognized as Deputy or Minister Medicines without or with little toxicity that can treat disease and strengthen a weak person. Herbs in the inferior grade were referred as Assistant or Adjutant medicines with greater toxicity, which are for dispelling heat and cold evil, breaking up abdominal masses and treating diseases but which should not be taken long term.

Among the top herbs at step 7 (see Table 5.31), Gan cao, Ren shen, Mai men dong, E jiao, Xi xin, Fu ling, Wu wei zi, Rou gui (Mu gui or Jun gui) and Chen pi (Juyou or Jupi) belong to the top grade in *Shen Nong Ben Cao Jing*. Bei mu, Zhi mu, Ma huang, Zi wan, Kuan dong hua, Sang gen bai pi are in the medium grade, and Bai fan, Ban xia, Jie geng, Xing ren, and Zao jia occupy the inferior grade. In addition, Sheng jiang belongs to medium grade in the *Ben Cao Tu Jing* (本草图经) issued in the Song dynasty.

Ying su ke (called Yu mi ke) was found in *Ben Cao Fa Hui* (本草发挥) but this did not indicate to which grade it belonged. Ying su ke has the actions of astringing the lung and nourishing the kidney, so it is mostly used with Wu wei zi for treating Jiu kesou and the deficiency syndrome of Chuan zheng.

Zhi mu which appeared at steps 2.1 and 5.1 and for the global score ‘most likely COPD’ is a medium grade herb that belongs to the category of purging fire drugs with a bitter flavor and cold property and has the effect of nourishing yin. It is commonly used with Bei mu for treating cough.

Since COPD is a long-term disorder, herbs that can be used over a long time are necessary, and these kinds of herbs appear frequently in the formulae. COPD also can present in the exacerbation stage, so herbs that address the main symptoms also appear, such as Ma huang for dyspnea, Zi wan for cough and Bei mu for phlegm. Conditions that were considered ‘most likely COPD’ appeared to include those presenting with coexisting syndromes of deficiency and excess, which are more complex than single syndromes or symptoms. So a varity of herbs with different functions would be expected to appear on the lists of herbs.

The actions of the main herbs and the associated research in relation to COPD are discussed in detail in chapter 8.
Chapter Six: Results of systematic reviews of oral ginseng formulae for stable COPD and oral CHM for improvement of QoL with stable COPD

This section reports the systematic reviews (SRs) on studies in which oral CHM formulae containing ginseng were used for treating suffers with stable COPD (84) and in which oral formulae affect on quality of life of patients with stable COPD.

6.1 A systematic reviews for Oral Ginseng formulae for stable COPD

6.1.1 Introduction

In herbal medicine practice, stable COPD is considered as a pattern of Qi deficiency involving lung and/or spleen. Qi is refined nutritive substance involved with functional activities (337). Ginseng, the root of a perennial plant, is a potent tonic herb used to restore and replenish the Qi of the Lung and Spleen to improve their functions. It has been used for treating a wide range of chronic respiratory conditions, can be used as a single herb, and is included in many formulae for respiratory disorders (338).

There is an increasing number of CHM clinical trials for the management of stable COPD including the use of Ginseng and Ginseng formulae (i.e. a combination of ginseng with several herbal ingredients) (339). This review aimed to evaluate of effects of oral ginseng formulae for stable COPD through four outcome measures including spirometric parameters, symptom improvement, HRQoL and ECOPD.

Study selection focused on studies using Ginseng formulae. The included studies needed to report at least one of the following four outcome measures: spirometric parameters, symptom improvement, HRQoL or ECOPD.

6.1.2 Search results

The initial searches identified 938 entries from English databases and Chinese databases, as described in the search method above, from their respective inceptions to June 2009, without language restriction. Further screening of abstracts and full texts identified 477 citations requiring detailed evaluation. Of these 465 were excluded for various reasons, including 165 studies that were not solely orally administered CHM and 251 studies that were not for stable COPD and/or included non-COPD patients. Finally, twelve studies met all the selection
criteria and were included in this SR (Figure 6.1).

Figure 6.1 Flowchart of the study selection process for the review of Ginseng formulae for stable COPD
6.1.3 Description of included studies

Of the 12 studies that met the selection criteria, 11 were conducted in China and one in Israel. The characteristics of the included studies are summarized in Table 4.3. There were no disagreements in data extraction between the two reviewers. The 12 studies involved a total of 1,560 stable COPD patients, ranging from 36 to 600 with four studies having more than 100 subjects (340-343). Eight subjects dropped out and they were excluded in one study (79), and 1,552 subjects (1,050 males and 502 females, mean age 63.73) were included in the data analysis.

As shown in Table 6.1, the severity of COPD of participants in five studies (69, 341, 342, 344, 345) were classified as mild, moderate or severe. Three studies (340, 346, 347) employed the classification system developed by the Chinese Medical Association of Respiratory Diseases (91), which stratified the severity of participants’ COPD as stages I to III. One study (79) adapted the American Thoracic Society’s Standardization of Spirometry (348) and moderate severity of COPD was defined as FEV₁ 50-65% of predicted. Three studies (80, 343, 349) did not specify the stage of COPD of the participants, and none of the papers referenced quality standards of spirometry performance (350).
<table>
<thead>
<tr>
<th>First author, year [ref. no.]</th>
<th>Location of Hospital</th>
<th>Source of patients</th>
<th>Number of Participants (R/A)</th>
<th>Number of Male/Female</th>
<th>Age Mean ± SD (years)</th>
<th>Severity of COPD</th>
<th>Syndrome Differentiation of CM</th>
<th>COPD History Mean ± SD (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2007[34]</td>
<td>Chendu, China</td>
<td>Outpatients</td>
<td>T: 59/59</td>
<td>T: 45/14</td>
<td>T: 59.03±6.70</td>
<td>T: I: 13, IIA: 20, IIB: 18, III: 8</td>
<td>Lung &amp; Kidney deficiency</td>
<td>NS</td>
</tr>
<tr>
<td>Chen, 2004[34]</td>
<td>Nanping, China</td>
<td>Inpatients</td>
<td>T: 30/30</td>
<td>35/25</td>
<td>65.00±NA</td>
<td>Mild 15, Moderate 26, Severe 19</td>
<td>NS</td>
<td>60.21±NS</td>
</tr>
<tr>
<td>Gross, 2002[79]</td>
<td>Tel Aviv, Israel</td>
<td>NS</td>
<td>T&amp;C: 100/91</td>
<td>T: 30/21</td>
<td>T: 59.0±12.6</td>
<td>FEV₁: 50-65% of predicted</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Guo, 2008[34]</td>
<td>Tangshan, China</td>
<td>Outpatients</td>
<td>T: 50/50</td>
<td>T: 36/14</td>
<td>T: 56.00±NA</td>
<td>T: mild 8, moderate 33, severe 9</td>
<td>NS</td>
<td>T: 16.00±NS</td>
</tr>
<tr>
<td>Hong, 2005[34]</td>
<td>Zhangzhou, China</td>
<td>Inpatients &amp; outpatients</td>
<td>T: 18/18</td>
<td>T: 16/2</td>
<td>T: 67.56±5.19</td>
<td>T: II: 3, III: 5; C: II: 3, III: 15</td>
<td>Lung &amp; Spleen &amp; Kidney deficiency</td>
<td>C: 14.00±NS</td>
</tr>
<tr>
<td>Huang, 2002[34]</td>
<td>Xuzhou, China</td>
<td>Inpatients &amp; outpatients</td>
<td>T: 300/300</td>
<td>T: 185/115</td>
<td>T: 52.50±4.40</td>
<td>Mild to moderate</td>
<td>Lung &amp; Kidney deficiency</td>
<td>C: 8.30±3.50</td>
</tr>
<tr>
<td>Li, 2006[69]</td>
<td>Zhengzhou, China</td>
<td>NS</td>
<td>T: 31/31</td>
<td>T: 22/9</td>
<td>T: 72.00±5.00</td>
<td>T: mild 5, moderate 21, severe 6</td>
<td>Lung &amp; Kidney deficiency</td>
<td>C: 18.40±1.10</td>
</tr>
<tr>
<td>First author, date</td>
<td>Location of Hospital</td>
<td>Source of patients</td>
<td>Number of Participants (R/A)</td>
<td>Number of Male /Female</td>
<td>Age Mean ± SD (years)</td>
<td>Severity of COPD</td>
<td>Syndrome Differentiation of CM</td>
<td>COPD History Mean ± SD (years)</td>
</tr>
<tr>
<td>-------------------</td>
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<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Lin, 2003[34]</td>
<td>Guangzhou, China</td>
<td>inpatients &amp; outpatients</td>
<td>T: 30/30; C: 30/30</td>
<td>T: 20/10; C: 22/8</td>
<td>T: 62.00±NS; C: 60.50±NS</td>
<td>NS</td>
<td>Spleen deficiency</td>
<td>T: 16.00±NS; C: 15.40±NS</td>
</tr>
<tr>
<td>Wu, 2006[342]</td>
<td>Xinxiang, China</td>
<td>Inpatients &amp; outpatients</td>
<td>T: 100/100; C: 100/100</td>
<td>T: 68 /32; C: 72/28</td>
<td>T: 71.87±4.37; C: 69.33±5.71</td>
<td>T: mild 21, moderate 48, severe 31 C: mild 23, moderate 51, severe 26</td>
<td>Lung &amp; Kidney deficiency</td>
<td>T: 18.70±3.72; C: 17.81±4.57</td>
</tr>
<tr>
<td>Xiong, 2008[380]</td>
<td>Shenzhen, China</td>
<td>Inpatients &amp; outpatients</td>
<td>T: 30/30; C: 30/30</td>
<td>T&amp;C: 20/10; C: 21/9</td>
<td>Average of FEV1: 52.3%</td>
<td>NS</td>
<td>Lung &amp; Kidney deficiency</td>
<td>NS</td>
</tr>
<tr>
<td>Xu, 1996[343]</td>
<td>Luzhou, China</td>
<td>Inpatients &amp; outpatients</td>
<td>T: 72/72; C: 30/30</td>
<td>T: 52/20; C: 21/9</td>
<td>T: 63.50±NS; C: 60.80±NS</td>
<td>NS</td>
<td>Qi deficiency</td>
<td>T: 9.50±NS; C: 9.00±NS</td>
</tr>
</tbody>
</table>

T: treatment; C: control; NS: not specified; COPD: chronic obstructive pulmonary disease; SD: standard deviation; CM: Chinese medicine; [1]reference’s number.
Guided by Chinese medicine syndrome differentiation guidelines such as the Chinese Medicine Clinical Research Guidelines for New Drugs (351), eight studies reported stable COPD patients as Lung deficiency with Kidney and/or Spleen deficiency (69, 80, 340-342, 346, 349) or Qi deficiency (343). Six of the 12 studies compared oral Ginseng formulae with placebo or no treatment (69, 79, 341, 342, 346, 349). Two studies compared Ginseng formulae with other oral CHM formulae without Ginseng (340, 343). Four studies compared the Ginseng formulae plus RP or Ginseng formulae alone with RP (inhaled β₂ agonist and anti-cholinergic or oral theophylline alone) (80, 344, 345, 347) (Table 6.2). Duration of treatment ranged from one month in three studies (341, 343, 345), two months in three studies (69, 342, 349), three months in three studies (340, 344, 347), to six months in three studies (79, 80, 346). Three studies mentioned a 6-month follow-up period (340, 346, 347). None of the included studies mentioned a run-in period (Table 6.2).
Table 6. 2 Characteristics of interventions and outcome measures of included studies for the review of Ginseng formulae for stable COPD

<table>
<thead>
<tr>
<th>First author, year [ref. no.]</th>
<th>Intervention (ingredients of Ginseng formulae)</th>
<th>Controlled Interventions</th>
<th>Jadad's scale</th>
<th>Duration/ Follow up</th>
<th>Adverse event</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2007[340]</td>
<td>Feikongning capsule (Panax Ginseng, Cordyceps, Radix Salviae Miltiorrhizae, Semen Armeniacae Amarum), 3 capsules, 3 times daily</td>
<td>Jinshuibao capsules (Fermented Cordyceps powder), 3 capsules, 3 times daily</td>
<td>2</td>
<td>3 mths / 6 mths</td>
<td>No</td>
<td>Yes, Yes, NS, Yes</td>
</tr>
<tr>
<td>Chen, 2004[341]</td>
<td>Yifei pill (Panax Ginseng, Gecko, Fructus Psoraleae) 2 pills, 3 times daily</td>
<td>Pharmacotherapy (NS)</td>
<td>1</td>
<td>3 mths / NS</td>
<td>NS</td>
<td>Yes, NS, NS, NS</td>
</tr>
<tr>
<td>Gross, 2002[79]</td>
<td>Panax Ginseng extract 100mg, twice daily</td>
<td>Placebo control</td>
<td>5</td>
<td>6 mths / NS</td>
<td>No</td>
<td>Yes, NS, NS, NS</td>
</tr>
<tr>
<td>Guo, 2008[341]</td>
<td>Jianfei capsule (Panax Ginseng, Gecko, Rhizoma Fagopyri Dibotryis, Bulbus Fritillariae Cirrhosae, Lumbricus, Semen Armeniacae Amarum) 2-3 pills, 3 times daily</td>
<td>Pharmacotherapy (Long acting β2 agonists &amp; Theophylline)</td>
<td>1</td>
<td>1 month / NS</td>
<td>NS</td>
<td>NS, Yes, NS, NS</td>
</tr>
<tr>
<td>Hong, 2005[346]</td>
<td>Yufeining pill (Panax Ginseng, Radix Astragali, Rhizoma Atractylodis Macrocephalae, Radix Saposhnikoviae, Placenta Hominis, Semen Armeniacae Amarum, Semen Cuscutae, Fructus Corni, Fructus Schisandrae, Semen Juglandis, Fructus Trichosanthis, Semen Persicae)</td>
<td>No treatment</td>
<td>2</td>
<td>6 mths / 6 mths</td>
<td>No</td>
<td>Yes, NS, NS, NS</td>
</tr>
<tr>
<td>First author, year [ref. no.]</td>
<td>Intervention (ingredients of Ginseng formulae)</td>
<td>Controlled Interventions</td>
<td>Jadad's scale</td>
<td>Duration/ Follow up</td>
<td>Adverse event</td>
<td>Outcome measures</td>
</tr>
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</tr>
<tr>
<td><strong>Huang, 2005</strong>&lt;sup&gt;[347]&lt;/sup&gt;</td>
<td>Jianpiyifei granule (Panax Ginseng, Rhizoma Atractylodis Macrocephalae, Poria, Radix Ophiopogonis, Cortex Mori, Radix Astragali) 10g, 3 times daily</td>
<td>Pharmacotherapy (NS)</td>
<td>1</td>
<td>3 mths / 6 mths</td>
<td>Mild</td>
<td>NS Yes Yes Yes</td>
</tr>
<tr>
<td><strong>Huang, 2002</strong>&lt;sup&gt;[341]&lt;/sup&gt;</td>
<td>Bufeiguben granule (Panax Ginseng, Gecko, Herba Epimedii, Semen Juglandis, Fructus Psoraleae, Fructus Schisandrae), 10g, 3 times daily</td>
<td>Placebo (Hawthorn)</td>
<td>1</td>
<td>1 month / NS</td>
<td>NS</td>
<td>NS Yes NS NS</td>
</tr>
<tr>
<td><strong>Li, 2006</strong>&lt;sup&gt;[69]&lt;/sup&gt;</td>
<td>Bufeiyishen granule (Panax Ginseng, Radix Astragali, Radix Saposhnikoviae, Fructus Psoraleae, Fructus Schisandrae, Rhizoma Ligusticum, Semen Armeniaca Amurum, etc.) 10g, 3 times daily</td>
<td>Placebo control (Hawthorn fruit and Malt)</td>
<td>2</td>
<td>2 mths / NS</td>
<td>NS</td>
<td>Yes NS NS NS</td>
</tr>
<tr>
<td><strong>Lin, 2003</strong>&lt;sup&gt;[140]&lt;/sup&gt;</td>
<td>Jianpiyifei granule (Radix Ginseng, Rhizoma Atractylodis Macrocephalae, Poria, Radix Ophiopogonis, Cortex Mori, Radix Astragali), 10g, 3 times daily</td>
<td>Placebo control (Stroma granule)</td>
<td>1</td>
<td>2 mths / NS</td>
<td>NS</td>
<td>Yes Yes NS NS</td>
</tr>
<tr>
<td><strong>Wu, 2006</strong>&lt;sup&gt;[142]&lt;/sup&gt;</td>
<td>Jiaweishenge granule (Panax Ginseng, Gecko, Semen Armeniaca Amurum, Bulbus Fritillariae) Placebo control (Hawthorn, Fructus Hordei Germinatus,</td>
<td>Placebo control (Hawthorn, Fructus Hordei Germinatus,</td>
<td>1</td>
<td>2 mths / NS</td>
<td>No</td>
<td>Yes NS NS NS</td>
</tr>
<tr>
<td>First author, year [ref. no.]</td>
<td>Intervention (ingredients of Ginseng formulae)</td>
<td>Controlled Interventions</td>
<td>Jadad’s scale</td>
<td>Duration/ Follow up</td>
<td>Adverse event</td>
<td>Outcome measures</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------</td>
<td>--------------------------</td>
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<td>---------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Xiong, 2008[80]</td>
<td>Shenge granule (Panax Ginseng, Gecko), 5g, twice daily</td>
<td>Pharmacotherapy (Inhaled Salmeterol &amp; fluticasone, 50/250 ug, one puff, twice daily)</td>
<td>1</td>
<td>6 mths / NS</td>
<td>NS</td>
<td>PESI NS QoL NS FCOPDE NS</td>
</tr>
<tr>
<td>Xu, 1996[34]</td>
<td>Yiqimianyi granule (Panax Ginseng, Rhizoma Atractylodis Macrocephalae, Poria) 20g, 3 times daily</td>
<td>Zhenqi Fuzheng granule (Fructus Ligustri Lucidi, Radix Astragali) 15g, twice daily</td>
<td>1</td>
<td>30 days / NS</td>
<td>NS</td>
<td>PESI NS QoL NS FCOPDE NS</td>
</tr>
</tbody>
</table>

NS: Not specified; PESI: Percentage of effectiveness of symptoms improvement; QoL: Quality of life; FCOPDE: Frequency of COPD exacerbation; [ref. no.]: Reference number.
6.1.4 Risk of bias assessment

This SR was conducted in 2010, so risk of bias assessment was based on Cochrane handbook for SRs of interventions (version 5.0.1) 2008 (352), consisting of six domains of potential bias which were answered by denoting ‘yes’ (low risk of bias), or ‘no’ (high risk of bias) or ‘unclear’ (uncertain risk).

Information on sequence generation was adequate for three studies at low risk of bias (yes) (79, 340, 346) and inadequate for nine studies with unclear risk of bias (unclear) (69, 80, 341-345, 347, 349). The methods of allocation concealment were judged as ‘unclear’ in all studies. Blinding was reported in two studies with one being described as double blind (79) and another as single blind (347). However blinding of participants, personnel and outcome assessors in all studies was ‘unclear’. Low risk of bias from incomplete outcome data was noted in 11 studies (69, 79, 80, 340, 342-347, 349), and one was ‘unclear’ (341). Intention-to-treat analysis was not conducted in any of these studies. Selective outcome reporting was judged as low risk of bias in six studies (69, 340, 341, 343, 347, 349) and as high risk of bias in six studies (79, 80, 342, 344-346). Assessments of other sources of bias involved baseline data imbalance. All 12 studies indicated no significant difference of baseline data between the two groups; none of the studies reported the sample size calculation method, therefore information on early stopping was insufficient. Overall, other sources of bias were ‘unclear’. Detailed information is provided in Figure 6.2.
Figure 6.2 Summary of assessment of risk of bias for the review of Ginseng formulae for stable COPD
6.1.5 Methodological quality assessment by Jadad’s scale

One study was rated with a score of 5 (highest quality) (79); three studies with a score of 2 (69, 340, 346) and eight studies with a score of 1 (80, 341-345, 347, 349) (see Table 6.2).

6.1.6 Outcomes

Spirometric parameters was performed in ten studies, symptom improvement was assessed five by studies, HRQoL using SGRQ or Cai’s QoLQ was reported in two studies and COPD exacerbations was mentioned in two studies.

6.1.7 Results of all outcomes for ginseng formulae

6.1.7.1 Spirometric parameters

Pre and post-treatment mean FEV₁ (69, 80, 340-342, 346, 347) (Fig 6.3) and FEV₁ % predicted (69, 340, 344, 346) (80, 342, 349) (Fig 6.4) were reported in seven studies respectively. Another study did not report post-treatment FEV₁ (79) and it was not included in this analysis.

Marginal but significant differences in absolute FEV₁ (MD 0.30, 95%CI 0.02 to 0.58) (69, 341, 342) and FEV₁ % predicted (MD 9.43, 95%CI 3.64 to 15.21) (69, 342, 349) were found between Ginseng formulae and placebo. Similar changes were shown in studies comparing Ginseng formulae with non-Ginseng formulae, absolute FEV₁ (MD 0.25, 95%CI 0.06 to 0.44), and FEV₁ % predicted (MD 4.76, 95%CI 0.36 to 9.16) (340). Such changes were not observed using Ginseng formulae alone versus no treatment (FEV₁ [MD 0.10, 95%CI -0.11 to 0.31] and FEV₁ % predicted [MD 2.32, 95%CI -6.84 to 11.48]) (346) or versus RP alone (FEV₁ [MD 0.25, 95%CI -1.84 to 2.34] and FEV₁ % predicted [MD 2.03, 95%CI -2.63 to 6.69]) (80) (Figures 6.3 & 6.4).
### 6.3.1 Ginseng Formulae vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang 2002</td>
<td>1.49 (0.7)</td>
<td>1.37 (0.51)</td>
<td>300 1.37 (0.51)</td>
<td>300 21.1% 0.11 (0.03, 0.19)</td>
</tr>
<tr>
<td>Li 2005</td>
<td>1.87 (0.5)</td>
<td>1.38 (0.44)</td>
<td>31 1.38 (0.44)</td>
<td>31 14.5% 0.29 (0.08, 0.51)</td>
</tr>
<tr>
<td>Yú 2006</td>
<td>1.46 (0.7)</td>
<td>1.36 (0.5)</td>
<td>100 1.36 (0.5)</td>
<td>100 15.2% 0.61 (0.38, 0.94)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>431</td>
<td>431</td>
<td>55.2% 0.30 (0.02, 0.58)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.05, Chi² = 26.11, df = 2 (P < 0.00001), I² = 92%  
Test for overall effect: Z = 2.87 (P = 0.04)

### 6.3.2 Ginseng Formulae vs No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong 2005</td>
<td>1.07 (0.32)</td>
<td>1.07 (0.32)</td>
<td>18 1.07 (0.32)</td>
<td>18 15.6% 0.10 (0.11, 0.31)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>18</td>
<td>18</td>
<td>15.6% 0.10 (0.11, 0.31)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: Z = 0.34 (P = 0.35)

### 6.3.3 Ginseng Formulae vs Non-Ginseng Formulae

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2007</td>
<td>1.31 (0.49)</td>
<td>1.31 (0.49)</td>
<td>59 1.31 (0.49)</td>
<td>59 18.7% 0.25 (0.08, 0.44)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>59</td>
<td>59</td>
<td>18.7% 0.25 (0.08, 0.44)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: Z = 2.54 (P = 0.01)

### 6.3.4 Ginseng Formulae alone vs Pharmacotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiong 2008</td>
<td>1.32 (3.8)</td>
<td>1.32 (3.8)</td>
<td>30 1.32 (3.8)</td>
<td>30 0.6% 0.25 (-1.84, 2.34)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>30</td>
<td>30</td>
<td>0.6% 0.25 (-1.84, 2.34)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: Z = 0.23 (P = 0.81)

### 6.3.5 Ginseng Formulae Plus Pharmacotherapy vs Pharmacotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Total Mean (SD)</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang 2005</td>
<td>1.73 (0.63)</td>
<td>1.73 (0.63)</td>
<td>32 1.73 (0.63)</td>
<td>32 11.5% 0.25 (-0.07, 0.57)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>32</td>
<td>32</td>
<td>11.5% 0.25 (-0.07, 0.57)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: Z = 1.51 (P = 0.13)

Total (95% CI) 570 568 100.0% 0.25 (0.09, 0.41)  
Heterogeneity: Tau² = 0.05, Chi² = 27.45, df = 6 (P = 0.0001), I² = 78%  
Test for overall effect: Z = 2.13 (P = 0.032)  
Test for subgroup differences: Chi² = 1.68, df = 4 (P = 0.79), I² = 0%

---

Figure 6.3 Ginseng formulae versus placebo, no treatment, non-Ginseng formulae, or pharmacotherapy as well as Ginseng formulae plus pharmacotherapy versus pharmacotherapy for pre-post changes of FEV<sub>1</sub> (L) of patients with stable COPD
Table 6.4.1 Ginseng Formulae versus Placebo, no treatment, non-Ginseng formulae, or pharmacotherapy as well as Ginseng formulae plus pharmacotherapy versus pharmacotherapy for pre-post changes of FEV₁ (% of patients with stable COPD)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2009</td>
<td>61.93</td>
<td>12.89</td>
<td>31</td>
<td>50.74</td>
<td>14.28</td>
<td>31</td>
<td>19.6%</td>
<td>10.96 [4.16, 17.76]</td>
<td></td>
</tr>
<tr>
<td>Lin 2003</td>
<td>67.80</td>
<td>10.81</td>
<td>30</td>
<td>54.31</td>
<td>12.77</td>
<td>30</td>
<td>12.6%</td>
<td>3.82 [-2.20, 9.64]</td>
<td></td>
</tr>
<tr>
<td>Yu 2006</td>
<td>62.84</td>
<td>18.99</td>
<td>100</td>
<td>48.84</td>
<td>13.10</td>
<td>100</td>
<td>17.1%</td>
<td>13.90 [6.27, 19.73]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>161</td>
<td>161</td>
<td>161</td>
<td>161</td>
<td>161</td>
<td>39.6%</td>
<td>9.43 [3.64, 15.21]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 18.38; Chi² = 8.03, df = 2 (P = 0.03); P = 71%
Test for overall effect: Z = 3.20 (P = 0.001)

6.4.2 Ginseng Formulae vs No Treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong 2005</td>
<td>42.17</td>
<td>11.08</td>
<td>18</td>
<td>38.85</td>
<td>16.45</td>
<td>18</td>
<td>7.2%</td>
<td>2.32 [1.84, 11.48]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>7.2%</td>
<td>2.32 [1.84, 11.48]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

6.4.2 Ginseng Formulae vs Non-Ginseng Formulae

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2007</td>
<td>69.53</td>
<td>11.84</td>
<td>50</td>
<td>64.77</td>
<td>12.61</td>
<td>50</td>
<td>15.4%</td>
<td>4.76 [0.38, 9.16]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>15.4%</td>
<td>4.76 [0.36, 9.16]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)

6.4.4 Ginseng Formulae alone vs Pharmacotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiong 2009</td>
<td>71.56</td>
<td>6.8</td>
<td>30</td>
<td>69.53</td>
<td>11.23</td>
<td>30</td>
<td>14.8%</td>
<td>2.03 [-2.63, 6.69]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>14.8%</td>
<td>2.03 [-2.63, 6.69]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.39)

6.4.5 Ginseng Formulae Plus Pharmacotherapy vs Pharmacotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2004</td>
<td>74</td>
<td>1.5</td>
<td>30</td>
<td>65.85</td>
<td>1.8</td>
<td>30</td>
<td>23.6%</td>
<td>9.09 [8.18, 9.94]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>23.6%</td>
<td>9.09 [8.16, 9.84]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 21.04 (P = 0.00001)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total N</th>
<th>Mean Difference</th>
<th>Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
</table>
| 298               | 297 | 100.0% | 7.07 [4.13, 10.01] | Others Intervention | Ginseng Formulae

Figure 6.4 Ginseng formulae versus placebo, no treatment, non-Ginseng formulae, or pharmacotherapy as well as Ginseng formulae plus pharmacotherapy versus pharmacotherapy for pre-post changes of FEV₁ (% of patients with stable COPD)
6.1.7.2  Symptom improvement

The Ginseng formulae group showed a higher percentage of symptom improvement when compared with placebo (RR 1.53, 95%CI 1.09 to 2.16) (349), or non-Ginseng formula group (RR 1.11, 95%CI 1.00 to 1.24) (340, 343), or Ginseng formulae plus pharmacotherapy versus pharmacotherapy (RR 1.14, 95%CI 1.00 to 1.31) (345). However such a change was not observed using Ginseng formulae alone versus pharmacotherapy alone (RR 1.17, 95%CI 0.93 to 1.48) (80) (Figure 6.5).

Figure 6.5  Ginseng formulae versus placebo, no treatment, non-Ginseng formulae, or pharmacotherapy as well as Ginseng formulae plus pharmacotherapy versus pharmacotherapy for pre-post changes of symptoms improvement of patients with stable COPD
6.1.7.3 Quality of life

In the study in which QoL was measured by using a validated instrument (SGRQ), there was an improvement in the SGRQ when comparing Ginseng formulae plus pharmacotherapy to pharmacotherapy alone (MD -10.32, 95%CI -14.99 to -5.65) (347). Furthermore, a positive QoL improvement was also reported by another study (346) using a self-modified questionnaire developed by Cai et al.

6.1.7.4 Exacerbation of COPD

Two studies (340, 347) reported on ECOPD during the follow-up period. Significant reduction in the number of patients developing ECOPD was reported in the study using a Ginseng formula compared to a non-Ginseng formula (RR 0.40, 95%CI 0.18 to 0.90) (340), but no additional benefit of a Ginseng formula to pharmacotherapy was shown (RR 0.68, 95%CI 0.42 to 1.09) (347). In addition, one study compared Ginseng formula with no treatment and reported that the number of COPD exacerbations per annum was significantly less in the treatment group (MD -1.52 95%CI-2.32 to -0.72) (346).

6.1.7.5 Adverse events

One study involving 63 subjects stated that dry mouth, mild stomach bloating and reduced appetite were observed in three subjects (two from the treatment group and one in the control group). These symptoms disappeared within one week without medical interventions (347). Four studies reported that there were no adverse events in the trials (79, 340, 342, 346). The remaining seven studies did not report adverse events (69, 341, 344, 345) (80, 343, 349).

6.1.8 Discussion of results for ginseng formulae

This review shows that the Ginseng formulae were more effective in improving FEV1 when compared with placebo (69, 341, 342, 349) or non-Ginseng formulae (340) for subjects with stable COPD at various stages. Ginseng formulae were also associated with higher percentages of symptom improvement versus placebo or pharmacotherapy. A Ginseng formula was beneficial for QoL based on SGRQ (347) and two Ginseng formulae reduced the frequency of exacerbations (340, 347). Overall, Ginseng formulae were well tolerated by subjects.
The majority of the 12 included studies suffered from methodological weaknesses based on assessment of the Cochrane risk of bias and the Jadad’s scale. The inadequacy of blinding and placebo control (353), allocation concealment and sequence generation (354) were the major sources of potential bias as well as treatment durations ranging from one month (341, 343, 345) to six months (79, 80, 346) and using Ginseng formulae as an add-on treatment to RP for COPD (80, 344, 345, 347). Therefore, the findings from this review need to be interpreted with caution.

Despite the methodological weakness and potential risk of bias, the findings of the present review are promising. Particularly for the improvement of the lung functions based on pre and post FEV$_1$ and FEV$_1$ % predicted between Ginseng formulae and placebo or no treatment or non-Ginseng formulae groups. These findings are consistent with recent RCTs on the effect of a phosphodiesterase-4 (PDE4) inhibitor (roflumilast) (206) on lung function in patients with moderate to severe COPD who were on salmeterol and tiotropium treatment. The two trials, involving 1,676 COPD subjects, concluded that, compared with placebo, 24 weeks of roflumilast treatment significantly and consistently improved mean pre and post-bronchodilator FEV$_1$ (p < 0.0001).

A large study involving almost 6,000 subjects conducted in 37 countries demonstrated that prolonged intervention (4 years) of a long acting bronchodilator, tiotropium, on moderate COPD patients (GOLD Stage II) was effective in reducing the rate of decline of post-bronchodilator FEV$_1$. However, such changes were not shown in pre-bronchodilator FEV$_1$ between the treatment groups (188). Tiotropium also improved the general health status, QoL based on SGRQ as well as reducing the frequencies of exacerbations and subsequent hospitalizations (355). It was therefore concluded earlier and long-term intervention is critical to the treatment of COPD.

When Ginseng formulae were compared with placebo or non-Ginseng formulae, the observed benefits were clearly demonstrated (69, 80, 340-342, 344, 349). Such findings showed the potentially important role that Ginseng might have played in these studies, particularly in the study in which a standardized Ginseng extract was used alone (79).

Ginseng as the key herb possesses a broad range of pharmacological activities which may offer plausible explanations to the observed clinical benefits found in this review. For example, Ginseng raw extract or purified ginsenosides have been shown to enhance markedly the action of the diterpene forskolin in elevating intracellular cAMP levels in rat cultured
glioma cell (356). Two ginsenosides, panaxadiol (PD) and panaxatriol (PT) have been shown to have potent inhibitory effects on the expression of matrix metalloproteinase-9 (MMP-9) (357). Compound K of ginseng showed similar effects in an experiment with human astroglialoma cells (358). Ginseng taken daily for 4 weeks has been found to linearly increase plasma concentrations of certain antioxidants in smokers.

These findings are significant since oxidative damage caused by free radicals associated with smoking is thought to contribute to the development of COPD (359). Protopanaxadiol ginsenosides (PPDGs) such as Rb1 and Rb2 have been demonstrated to have significant potency as inhibitors of lipopolysaccharide-induced production of tumor necrosis factor-alpha (TNF-α) in murine (RAW264.7) cells and human (U937) macrophages (360). This effect was significantly enhanced by various TNF-α antagonists (360).

It is also important to note that due to the heterogeneity of the studies included in this review, the observed benefits could be a combined outcome of inclusion of unspecified proportions of patients at various stages of COPD, the use of a range of herbal formulations, the uncertain quality of spirometric measurements; and the potential of real benefit of Ginseng in treating COPD.

Generally speaking adverse event reporting in the included studies was inadequate. However, the safety profile of Ginseng has been demonstrated in a systematic review, which concluded that Panax ginseng mono-preparations are rarely associated with adverse events or drug interactions (361).

**6.1.9 Conclusions for ginseng formulae**

Despite the quality concerns of the included studies, the observed benefits of Ginseng formulae are encouraging. Further trials are warranted to determine the true benefits of Ginseng. These trials must address the methodological problems identified in this review.
6.2 Effectiveness of CHM for improving health-related quality of life

6.2.1 Introduction

COPD causes impairment in HRQoL of these patients. Even with optimal medical treatment, the HRQol status inevitably worsens (362). Therefore new interventions that slow the decline in HRQoL are needed. A second SR on CHM for improving HRQoL was conducted in June 2010, and the search data was updated in April 2011. The updated version was accepted by Journal of Alternative Complementary Medicine in September 2011.

In this SR the search strategy including the search terms and databases searched was the same as in the above section on methods for SRs (Section 4.2).

Study selection inclusion criteria were: 1. RCTs of CHM for stable COPD; and 2. using a QoL questionnaire (QoLQ) as a primary outcome measure; 3. the comparison was with placebo, no treatment or RP and 4. the CHM was orally administered

6.2.2 Search results

A total of 1,713 potential articles were initially identified. Further screening of abstracts and full texts identified 348 requiring detailed evaluation. Of these 321 were excluded for various reasons, including six studies that administered the CHM via IV drip and 3 studies that used QoLQ as an outcome. Finally, twenty-seven studies met all the selection criteria and were included in this SR (Figure 6.6).
Figure 6.6 Flow diagram for study selection process for review of Chinese herbal medicine for Quality of Life improvement in stable COPD

1713 Records identified through database searches: Pubmed, EMBASE, Scopus, CINAHL, Cochrane & CNKI, CQVIP, WANFANG

1597 Records after duplicates removed

1597 Records screened

1249 Records excluded

321 Full-text articles excluded, with reason:
1. CHM was administrated by IV drop (n=6)
2. Not RCTs (n=30)
3. Patients with asthma & cor pulmonale (n=26)
4. Oral CHM for not stable COPD (n=157)
5. Duplicated trials (n=20)
6. QoLQ not used as outcome measure (n=74)
7. CHM as control groups (QoLQ used) (n=3)
8. Other (n=5)

348 Full-text articles assessed for eligibility

27 Studies included in qualitative synthesis

24 Studies included in quantitative synthesis (Meta-analysis)
6.2.3 Characteristics of included studies

The main characteristics of the individual studies: study location, study design, sample size, gender, average age of patients, and the severity of COPD, Chinese medicine syndrome differentiation, and average years of COPD are summarized in Table 6.3.

6.2.3.1 Participants

The twenty-seven included studies were all conducted in China. They involved 1,966 participants. The average ages ranged from 59.4 to 72.0 across the studies. All participants were in the stable stage and diagnosis was based on the GOLD guideline modified by the CSRD (91). There were drop-outs during the treatment period in five studies totaling 52 participants but intention-to-treat (ITT) analysis was not applied (363-367). In twenty studies the severity of COPD in individual patients was described as four stages: I - mild, II - moderate, III - severe, IV - very severe (235, 312, 346, 347, 363-365, 368-378), which was in accord with the guidelines by CSRD (91). Severity of COPD was not described in seven studies (367, 379-384). CM differentiation of syndromes was described in ten studies (235, 346, 368, 369, 371, 376, 379, 381, 383, 384). Sixteen studies reported the average number of years patients had suffered from COPD (235, 346, 347, 366, 369, 372-374, 376, 377, 379, 381-384).

6.2.3.2 Duration of treatment and follow up

Duration of treatment was up to two months in six studies (366, 373, 375, 381, 383, 384), two to four months in six studies (312, 347, 365, 368, 369, 376), and six months in fifteen studies (235, 346, 363, 364, 367, 370-372, 374, 377-380, 382, 385). A follow up period was mentioned in four studies (346, 364, 366, 380) (see Table 6.3).
<table>
<thead>
<tr>
<th>First author, year [ref. no.]</th>
<th>Location, Design [duration / follow up]</th>
<th>Out /in patients</th>
<th>No. subjects (R/A)</th>
<th>M/F</th>
<th>Age Mean SD (years)</th>
<th>Severity of COPD: No. subjects</th>
<th>CM Syndrome Differentiation</th>
<th>COPD history (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2009[312]</td>
<td>Fujian, China RCT [3 mths/NS]</td>
<td>Out patients</td>
<td>T: 30/30</td>
<td>29/31</td>
<td>70.1</td>
<td>III &amp; IV: NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fang, 2008[363]</td>
<td>Guangdong, China RCT [6 mths /NS]</td>
<td>NS</td>
<td>T: 35/30</td>
<td>26/4</td>
<td>68.0 ± 5.70</td>
<td>T: I 8, II 22</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Feng, 2005[308]</td>
<td>Beijing, China RCT [3 mths/NS]</td>
<td>Out patients</td>
<td>T: 35/35</td>
<td>16/19</td>
<td>60.59±8.99</td>
<td>T: 0 8, I 9, II 9, III 9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Feng, 2008[309]</td>
<td>Hebei, China RCT [6 mths/NS]</td>
<td>NS</td>
<td>T: 60/60</td>
<td>63.0 ± 5.0</td>
<td></td>
<td>Lung &amp; Spleen &amp; Kidney deficiency</td>
<td>14.0±5.0</td>
<td></td>
</tr>
<tr>
<td>Hong, 2005[386]</td>
<td>Fujian, China RCT [6 mths/6 mths]</td>
<td>NS</td>
<td>T: 20/20</td>
<td>17/3</td>
<td>67.7±5.68</td>
<td>T: II 5, III 15</td>
<td>Lung &amp; Spleen &amp; Kidney deficiency</td>
<td>15.05±5.54</td>
</tr>
<tr>
<td>Huang, 2005[347]</td>
<td>Guangdong, China RCT [3 mths/NS]</td>
<td>Out patients</td>
<td>T: 32/32</td>
<td>21/11</td>
<td>69.5±11.8</td>
<td>T: II 17, III 15</td>
<td>NS</td>
<td>T: 8.5±3.2</td>
</tr>
<tr>
<td>Jia, 2007[370]</td>
<td>Jiangsu, China RCT [6 mths/NS]</td>
<td>NS</td>
<td>T: 30/30</td>
<td>23/7</td>
<td>61.6±6.1</td>
<td>T: I 5, II 18, III 7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lang, 2010[380]</td>
<td>Shanghai, China RCT [6 mths/6 mths]</td>
<td>NS</td>
<td>T: 30/30</td>
<td>20/12</td>
<td>69.73±NS</td>
<td>T: IIA13, III 12, IV 7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Liang, 2009[322]</td>
<td>Guangxi, China</td>
<td>Out patients</td>
<td>T: 32/32</td>
<td>20/12</td>
<td>T: 69.73±NS</td>
<td>T: IIA13, III 12, IV 7</td>
<td>NS</td>
<td>T: 17.32±NS</td>
</tr>
<tr>
<td>First author, year [ref. no.]</td>
<td>Location, Design [duration / follow up]</td>
<td>Out /in patients</td>
<td>No. subjects (R/A)</td>
<td>M/F</td>
<td>Age Mean SD (years)</td>
<td>Severity of COPD: No. subjects</td>
<td>CM Syndrome Differentiation</td>
<td>COPD history (years)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------</td>
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<td>---------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>Guangdong, China RCT [6 mths/6 mths]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Out/</td>
<td>T: 30/26</td>
<td></td>
<td>T: 68.0 ± 5.70</td>
<td>T: I 4, II 22</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In patients</td>
<td>C: 30/25</td>
<td></td>
<td>C: 68.0±4.96</td>
<td>C: I 5, II 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guangdong, China RCT [6 mths/NS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Out/</td>
<td>T: 30/30</td>
<td></td>
<td>T: 67.37±6.03</td>
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<td>C: 67.27±5.75</td>
<td>C: I 5, II 25</td>
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<td>T: I 15, II 29, III 19</td>
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<td>Location, Design [duration / follow up]</td>
<td>Out /in patients</td>
<td>No. subjects (R/A)</td>
<td>M/F</td>
<td>Age Mean SD (years)</td>
<td>Severity of COPD: No. subjects</td>
<td>CM Syndrome Differentiation</td>
<td>COPD history (years)</td>
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<td>Zhang, 2009[368]</td>
<td>Guangdong, China RCT [6 mths/NS]</td>
<td>Out patients</td>
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<td>C: 60/48</td>
<td>T: 68.4±NS</td>
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</table>

NS: not specified; R: number subjects randomized; A: number subjects analysed; RCT: randomized controlled trial; CM: Chinese medicine; [1] reference’s number.
6.2.3.3 Intervention and control groups

CHM was compared with placebo alone in one study (375), with no treatment control in seven studies (346, 347, 363-365, 367, 373), and with RP in one study (378). In one study CHM plus RP was compared with placebo plus RP (381). The remaining studies compared CHM plus RP with RP alone.

6.2.3.4 Routine pharmacotherapy used in the studies

The RP used was variable. It mainly involved bronchodilators such as the beta 2 agonists salbutamol and salmeterol, anticholinergics (e.g. ipratropium bromide) or theophylline. These were used alone or in combination (366, 368, 372-374, 381, 384, 385). Five studies used inhalation of a β2 agonist or an anticholinergic alone or a combination of β2 agonist and anticholinergic (235, 312, 370, 371, 378). Inhalation of a β2 agonist with oral theophylline was used in three studies (372, 381, 384). One study used inhalation of a β2 agonist plus a glucocorticosteriod (Becotide) (366). Oral theophylline was used alone in two studies (374, 385). CHM alone versus inhalation of ipratropium bromide aerosol was used in one study (378). One study mentioned that the RP included antibiotics, expectorants and bronchodilators but provided no further detail (381). Seven studies did not provide information on the RP used(347, 369, 373, 376, 379, 380, 382) (see Table 6.4).

CHM formulae were in the form of pills, capsules, granules, syrup or decoctions (see table 2). The individual formulae comprised from 1 to 17 different herbs. Two studies used syndrome differentiation according to CHM principles to select the most appropriate of four CHM treatment interventions. Both these studies used very similar designs and formula selection (379, 382). Another two studies investigated almost identical formulae (368, 369). Two studies investigated modified versions of formulae of the same name (Zhou Fei Tang) (363, 364).

6.2.3.5 Herbs used in the studies

Eighty three different herbs were used in the studies (see Table 6.4). The five most commonly used herbs were:

1) Huang qi Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao (root) in fourteen studies (235, 312, 346, 347, 363-365, 367-370, 372, 373) (376, 377, 379, 382);
2) Bai zhu *Atractylodes macrocephala* Koidz (rhizome) in thirteen studies (235, 312, 346, 347, 365, 366, 372, 374, 376, 377, 379, 382, 384);

3) Dang shen *Codonopsis pilosula* (Franch.) Nannf. (root) in twelve studies (312, 363-365) (235, 373-377, 379, 382);

4) Fu ling *Poria cocos* (Schw.) Wolf (sclerotium) in twelve studies (312, 347, 365-367, 374, 377, 379, 382, 384-386); and

5) Wu wei zi *Schisandra chinensis* (Turcz.) Baill (fruit) in ten studies (312, 346, 363, 364, 373, 374, 378, 379, 381, 382) (Table 6.4).

Quality control data on the herbal ingredients was not provided in any of the studies.
Table 6. 4 Interventions, controls and adverse events for review of Chinese herbal medicine for Quality of Life improvement in stable COPD

<table>
<thead>
<tr>
<th>First author, year [ref. no.]</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse events</th>
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</thead>
<tbody>
<tr>
<td><strong>Formula name (form): Dose, ingredients</strong></td>
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<tr>
<td><strong>Qiweiduqitang</strong> (decoction): 250 ml Bid</td>
<td>Salmeterol 50μg &amp; fluticasone 500μg inhaled Bid</td>
<td>Salmeterol 50μg &amp; fluticasone 500μg inhaled Bid</td>
<td>No</td>
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<tr>
<td>Shanzhuyu, Shanyao, Shudihuang, Mudanpi, Zexie, Fuling, Wuweizi, Huangpi, Danshen, Baizhu</td>
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<tr>
<td><strong>Zoufei Granule:</strong> 10g Tid</td>
<td>No</td>
<td>No treatment</td>
<td>NS</td>
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<tr>
<td>Dangshen, Guizhi, Ziyuan, Kuandonghua, Wuweizi, Xingren, Taoren, Chenxiang, Zishiyi</td>
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<tr>
<td><strong>Yiqihuxuehuatan Formula</strong> (decoction): 1 packet per day Huangqi, Shuizhi, Beimu, Guangdilong etc.</td>
<td>Stage 0: No treatment</td>
<td>Stage 0: No treatment</td>
<td>NS</td>
</tr>
<tr>
<td>OR <strong>Feikang Granule:</strong> 10g daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc.</td>
<td>Stage 1: Bronchodilators (short-acting as needed)</td>
<td>Stage 1: Bronchodilators (short-acting as needed)</td>
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<tr>
<td>+ <strong>Bailing Capsule:</strong> 0.8g Tid, extract of Dongchongxiacao</td>
<td>Stage 2: Bronchodilators OR glucocorticoids (inhaler)</td>
<td>Stage 2: Bronchodilators OR glucocorticoids (inhaler)</td>
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<tr>
<td><strong>Yiqihuxuehuatan Formula</strong> (decoction): 1 packet per day Huangqi, Shuizhi, Banxia, Guangdilong etc.</td>
<td>Routine medication</td>
<td>Routine medication</td>
<td>NS</td>
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<tr>
<td>OR <strong>Feikang Granule:</strong> 3g daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc.</td>
<td>Routine medication</td>
<td>Routine medication</td>
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<tr>
<td>+ <strong>Bailing Capsule:</strong> 4 caps Tid, extract of Dongchongxiacao</td>
<td>Routine medication</td>
<td>Routine medication</td>
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<tr>
<td><strong>Buifeitang</strong> (decoction): 1 packet per day, in 2 doses (morning &amp; night) Dangshen, Huangqi, Baizhu, Shanyao, Wuweizi, Maidong, Yuzhu, Zhimu, Jiegen, Chenpi, Baibu, Zhigancao</td>
<td>Routine medication</td>
<td>Routine medication</td>
<td>NS</td>
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<tr>
<td>OR <strong>Qiweiduqiwian</strong> + <strong>Shengmaisan</strong> (decoction): as above Shudi, Shanzhuyu, Shengshanyao, Fuling, Danpi, Gouji, Wuweizi, Taizishen, Maidong, Nvzhenzi, Hanliancao</td>
<td>OR <strong>Jingushenqian</strong> (decoction): as above Shudi, Shanzhuyu, Chaoshanyao, Fuling, Shufuzi, Rougui, Lujiaoqiao, Tusizi, Dangshen, Baizhu, Danshen, Huainiuxi, Yiyiren</td>
<td>OR <strong>Suzijiangqitang</strong> (decoction): as above Zisuzi, Banxia, Qianhu, Houpo, Danshen, Baizhu, Danshen, Taoren.</td>
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<tr>
<td>OR <strong>Zisuzi</strong> + <strong>Shengmaisan</strong> (decoction): as above Shudi, Shanzhuyu, Chaoshanyao, Fuling, Shufuzi, Rougui, Lujiaoqiao, Tusizi, Dangshen, Baizhu, Danshen, Huainiuxi, Yiyiren</td>
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<td><strong>Yuefeining Pill:</strong> 6g Bid</td>
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<td>No</td>
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<td>Renshen, Huangqi, Baizhu, Fangfeng, Zhehe, Hetaorou, Tusizi, Shanzhuyu, Wuweizi, Xingren, Gualou, Danshen, Taoren.</td>
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</table>
| Huangqi, Fangfeng, Baizhu  
+ Jianpiyifei Granule: 10g Tid  
Renshen, Baizhu, Fuling, Maidong, Sangbaipi, Huangqi.  
+ Bailing Capsule: 1g Tid, extract of Dongchongxiacao | Anticholinergics (ipratropium bromide inhaler) | Anticholinergics (ipratropium bromide inhaler) | NS |
| Jia, 2007[370] | Yiqluhoxue Formula (decoction): 1 packet per day  
Huangqi, Dilong, Xuanshen, Danshen, Taizishen, Danggui, etc | | |
| | Ipratropium inhaler, 2 puffs, Bid | Ipratropium inhaler, 2 puffs, Bid | NS |
| Huangqi, Dilong, Xuanshen, Danshen, Taizishen, Danggui, etc | Routine medication | Routine medication | No |
| Jia, 2007[370] | Yiqluhoxue Formula (decoction): 1 packet per day  
Huangqi, Dilong, Xuanshen, Danshen, Taizishen, Danggui, etc | Anticholinergics (ipratropium bromide inhaler) | Anticholinergics (ipratropium bromide inhaler) | NS |
| | Ipratropium inhaler, 2 puffs, Bid | Ipratropium inhaler, 2 puffs, Bid | NS |
| | Routine medication | Routine medication | No |
| Liu, 2005[384] | Zoufeitang (decoction): 200ml Bid  
Dangshen, Gejie, Taoren, Wuweizi, Guizhi, Ziyuan, Kuandonghua, Hutaoren, Wuweizi, Kuxingren, Chenxiang, Yangfei. | No | No treatment | NS |
| | Huatanghuoxue Formula (decoction): 1 packet per day  
Chenpi, Fabanxia, Laifuizi, Zisuzu, Zhebeimu, Xingren, Taoren, Fuling, Maodongqing, Baijiezi, Gancao. | Theophylline 0.2g Bid | Theophylline 0.2g Bid | NS |
| Liu, 2006[385] | Yiqihuoxuehuatantongluo Formula (decoction): 1 packet per day  
Huangqi, Dangshen, Fuling, Baizhu, Chuanbeimu, Dilong, Danshen, Xixin, Baijiezi, Zishiying, Hongjingtian | Salbutamol inhaler 1 or 2 puffs daily OR salbutamol tablet 10g daily | Salbutamol inhaler 1 or 2 puffs daily OR salbutamol tablet 10g daily | NS |
<table>
<thead>
<tr>
<th>First author, year [ref. no.]</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula name (form): Dose, ingredients</strong></td>
<td><strong>Plus RP</strong></td>
<td><strong>Routine medication</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Mai, 2009[373]</td>
<td><em>Bufeitang + Renshejingjietang</em> (decoction): 200ml per day</td>
<td>Routine medication (antibiotics, expectorants, bronchodilators)</td>
<td>Routine medication (antibiotics, expectorants, bronchodilators)</td>
</tr>
<tr>
<td></td>
<td><strong>Dangshen, Huangqi, Shudihuang, Wuweizi, Ziyuan, Sangbaipi, Gejie etc.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Bushennaqi Granule: 10g Tid</strong></td>
<td>Salbutamol inhaler, Theophylline, Prednisone</td>
<td>Placebo (Shanzha granule) + Salbutamol inhaler, Theophylline, Prednisone</td>
</tr>
<tr>
<td></td>
<td><strong>Buguzhi, Yinyanghuo, Fupenzi, Wuweizi</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shan, 2007[373]</td>
<td><em>Peitushengjintang</em> (decoction): 1 packet per day</td>
<td>Theophylline tablets 0.2g Bid</td>
<td>Theophylline tablets 0.2g Bid</td>
</tr>
<tr>
<td></td>
<td><strong>Dangshen, Wuzhualong, Fuling, Baizhu, Shanyao, Wuweizi, Kuanqionghua, Xingren, Taoren, Suzi, Jineijin.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shi, 2009[32]</td>
<td><em>Bufeitang</em> (decoction): 1 packet per day, in 2 doses (morning &amp; night)</td>
<td>Routine medication</td>
<td>Routine medication</td>
</tr>
<tr>
<td></td>
<td><strong>Huangqi, Dangshen, Baizhu, Jiegeng, Chenpi, Zhihancao, Chaoshanyao, Zhihu, Wuweizi, Maidong, Yuzhu, Zhibaiwu</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em><em>OR Qiweiduqiwon + Shengmaisan</em> (decoction): as above</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Shudi, Shanyourou, Shenshanyao, Gouji, Maidong, Nvzhhenzi, Hanliancao, Fuling, Danpi, Wuweizi, Taizishen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>OR Jinguishenqiwon (decoction): as above</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Shudi, Danshen, Yiiren, Shanyourou, Chaoshanyao, Fuling, Danshen, Baizhu, Huainuxi, Shufuzi, Tuzi, Rougui, Lujiaojiao</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em><em>OR Suzijiangqitang</em> (decoction): as above</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Zisuzi, Banxia, Qianhu, Houpo, Chenpi, Danggui, Rougui, Gancao.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun, 2009[373]</td>
<td><em>Bufei Granule: 16g Bid</em></td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td><strong>Dangshen, Shudihuang, Danggui, Shanzhuyu, Mahuang, Sangbaipi, Chenpi, Ziyuan.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang, 2009[383]</td>
<td><em>Bailing Capsule: 3 capsules Tid</em></td>
<td>No routine medication but medical support provided as required</td>
<td>No routine medication but medical support provided as required</td>
</tr>
<tr>
<td></td>
<td><strong>extract of Dongchongxiacao.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang, 2010[376]</td>
<td><em>Jianpiyishen Formula</em> (decoction): 1 packet per day</td>
<td>Smoking cessation + Routine medication</td>
<td>Smoking cessation + Routine medication</td>
</tr>
<tr>
<td></td>
<td><strong>Huangqi, Dangshen, Baizhu, Shashen (Nan), Shashen (Bei), Buguzhi, Bajitian, Danggui etc.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang, 2009[384]</td>
<td><em>Sanshenjianfeitang</em> (decoction): 1 packet per day</td>
<td>Salbutamol inhaler: 200 μg OR theophylline tablets if dyspnoea more severe: theophylline 0.25g + 0.9%</td>
<td>Salbutamol inhaler: 200 μg OR theophylline tablets</td>
</tr>
<tr>
<td>First author, year [ref. no.]</td>
<td>Intervention</td>
<td>Plus RP</td>
<td>Control</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| **Wu, 2007[365]**           | *Liujunzitang* (decoction): 100ml Bid  
Dangshen, Baizhu, Fuling, Chenpi, Zhibanxia, Gancao.  
Erythromycin 100g Bid  
(to relieve airway inflammation)  
No treatment | Saline OR 5% GS (250-500ml) IV drip 15 drip/min  
0.9% NS OR 5% GS (250-500ml) IV drip 15 drip/min | NS |
| **You, 2008[366]**          | *Yifei Mixture* (decoction): 100ml Bid  
Yinyanghuo, Xianmao, Renshen, Fuling, Baizhu, Danshen, Fabanxia,  
Zhuru, Gualoupi, Houpo, Zhiqiao.  
Salbutamol or Becotide inhaler & theophylline tablets | No treatment | NS |
| **Zhang, 2006[377]**        | *Jiaqiufeiibushen Formula* (decoction): 1 packet per day  
Huangqi, Dangshen, Baizhu, Fuling, Maidong, Shashen, Buguzhi, Tusizi,  
Nvzhenzi, Gejie, Xingren, Gualou, Beimu, Danshen, Chuanxiong  
No | No treatment | NS |
| **Zhang, 2009[368]**        | *Yifeiyangyintang* (decoction): 300ml Bid  
Baihe, Shengdihuang, Shudihuang, Chuanbei, Jiegeng, Zhiqiao, Maidong,  
Baishao, Danshen, Shashen, Huangqi, Shenggancao.  
No routine medication but medical support as required  
+ Smoking cessation | No routine medication but medical support as required  
+ Smoking cessation | NS |
| **Zhu, 2007[378]**          | *Tianlongkechuanling Capsule*: 4 capsules, Tid  
Qingtiankui, Kuandonghua, Fabanxia, Shufuzi, Wuweizi etc.  
No | Salbutamol + Becotide inhaler  
2 puffs, Qid | NS |

* Use of syndrome differentiation in selection of Chinese medicine formula; RP: routine pharmacotherapy; NS: not stated; GS: Glucose solution; [ ] reference’s number.
6.2.4 Assessment of risk of bias

Assessment of the Cochrane risk of bias revealed that there was adequate sequence generation in nine studies (346, 368, 369, 371, 376, 378, 383-385) and only one study provided information on allocation concealment (383). Seven studies were not blinded since they compared CHM with no treatment (346, 363-365, 367, 377, 383). Blinding was not described adequately in the two single blind studies (347, 381) and blinding was not mentioned in the remaining nineteen studies. Incomplete outcome data was addressed in seventeen studies (235, 346, 347, 369, 371-379, 382, 383, 385); and seventeen studies were judged as free of selective reporting (235, 312, 346, 347, 363, 365, 367, 368, 370, 373-377, 379, 381, 383, 385). All but one of the studies was free of bias of baseline data incomparability (Figure 6.7) (235, 346, 347, 363-385).
Figure 6. 7 Methodological quality summary: review authors' judgments about each methodological quality item for each study in review of Chinese herbal medicine for Quality of Life improvement in stable COPD
6.2.5 Outcome measure—quality of life questionnaire

SGRQ was used in ten studies (312, 347, 365-367, 370, 375, 376, 378, 380) and a modified SGRQ was used in three studies (235, 368, 369). The remaining fourteen studies used Cai’s QoLQ (346, 363, 364, 371-374, 377, 379, 381-385). The twenty seven included studies were grouped into six types according to the study design. Three studies did not report data suitable for meta-analysis (235, 368, 369).

6.2.6 Results of QoLQs

6.2.6.1 CHM compared to placebo (n=2)

One study compared CHM with placebo and used SGRQ as an outcome (n = 60) (375). CHM was significantly better than placebo in improving QoL: [MD]: -8.60, 95% CI [-14.54, -2.66] (see Figure 6.8). Further analysis was conducted of the individual domains of SGRQ: symptoms [MD]: -3.20, 95% CI [-6.13, -0.27]); activity [MD]: -1.23, 95% CI [-2.78, -0.32]); and impact [MD]: -4.47, 95% CI [-7.02, -1.92]), all of which showed significant improvement. Cai’ QoLQ was used in other one with sixty eight participants (381). It was found to have a significant improvement QoL when CHM plus RP was compared to placebo plus RP, but the data were not suitable entry RevMan.

6.2.6.2 CHM compared to no treatment (n=7)

Pooling of data for the two studies using SGRQ (n = 226) found a significant improvement in total scores in the CHM group compared with no treatment (MD -6.07, 95% CI [-9.21, -2.93]) with low heterogeneity (Chi² = 1.32, df = 1 (P =0.25); I² = 24 %) (365, 367) (Figure 6.8). Five studies using Cai’s QoLQ (n = 251) were pooled and a significant improvement in total scores again was found (MD: -0.20 95% CI [-0.32, -0.07]) with severe heterogeneity (Chi² = 37.43, df = 4 (P =0.00001); I² = 89 %) (346, 363, 364, 377, 383) (Figure 6.9). The two studies using SGRQ did not report information on the scores for individual domains. Further analysis of individual domains of Cai’s QoLQ showed significant improvement of: activities of daily living (MD: -0.16 95% CI [-0.30, -0.01]); depression (MD -0.28 95% CI [-0.51, -0.06]); and anxiety (MD -0.28 95% CI [-0.47, -0.09]) but not in social activities (MD: -0.11 95% CI [-0.36, 0.13]) (363, 364, 383).
6.2.6.3  CHM compared to RP (n=1)

One study with 67 participants compared CHM alone versus RP using SGRQ. Analysis revealed a significant improvement in total score (MD: -7.05 95% CI [-13.55, -0.55]) (378) (Figure 6.8) and in the individual domains of symptoms (MD: -12.76 95% CI [-18.02, -7.50]) and activity (MD: -7.18 95% CI [-12.70, -1.66]) but not for impact (MD: 0.77 95% CI [-4.29, 5.83]).

6.2.6.4  CHM plus RP compared to RP (n=17)

Sixteen of the eighteen studies that compared CHM plus RP with RP alone reported data suitable for analysis. Seven studies used SGRQ (n = 427). Significant improvements were found for total score in seven studies with 471 participants (MD: -5.15 95% CI [-7.26, -3.05]) (235, 312, 347, 366, 370, 376, 380) (Figure 6.8). Four studies also reported data on the individual domains of: symptoms (MD: -5.15 95% CI [-7.26, -3.05]) with moderate heterogeneity ($\chi^2 = 22.70$, df = 6 (P =0.0009); $I^2 = 74\%$); and four studies reported in terms of activity (MD: -5.21 95% CI [-5.86, -4.57]) and impact (MD: -5.73 95% CI [-6.35, -5.12]) individually (366, 370, 376, 380). Eight studies used Cai’s QoLQ (n = 664). For Cai’s QoLQ, only six studies reported total scores (n = 364) (371-374, 384, 385). A significant change in the total score was found (MD: -0.25 95% CI [-0.37, -0.13]) with severe heterogeneity ($\chi^2 = 66.83$, df = 5 (P =0.00001); $I^2 = 93\%$) (Figure 6.9). In the eight studies (n = 664) that reported data for individual domains there were significant changes in: activities of daily living (MD: -0.30 95% CI [-0.42, -0.19]); social activities (MD: -0.36 95% CI [-0.57, -0.15]); depression (MD: -0.38 95% CI [-0.55, -0.21]); and anxiety (MD: -0.39 95% CI [-0.56, -0.23]) (371-374, 384, 385).

Two studies used a modified SGRQ (368, 369) and reported significant differences for CHM plus RP versus RP alone for total scores as well as the individual scores for symptoms, activity and impact. The actual scores were not available for these studies, even after contacting the authors. Therefore, data for these studies were not included in the meta-analyses.
Figure 6.8 Comparison of CHM versus placebo, no treatment or routine pharmacotherapy in patients with stable COPD: Total SGRQ score at the end of treatment in review of Chinese herbal medicine for Quality of Life improvement in stable COPD
Figure 6.9 Comparison of CHM versus no treatment or routine pharmacotherapy in patients with stable COPD: Total Cal’s QoLQ score at the end of treatment in review of Chinese herbal medicine for Quality of Life improvement in stable COPD
6.2.7 Results for adverse events

Adverse events were reported in five studies. In four of these, no adverse events were observed (312, 346, 375, 380). In one study (63 participants), two subjects in the CHM treatment group reported dry mouth, mild stomach bloating and one subject in the control group reported reduced appetite (347). There was no mention of adverse events in the remaining studies (363-367) (235, 368-374, 376-379, 381-385).

6.2.8 Discussion

This systematic review includes all RCTs of CHM for stable COPD available at the time of searching that included outcome measures of the quality of life of participants. All of the included studies were conducted and published in China from 2000 to 2010. Two of these were also indexed in MEDLINE (346, 368).

Meta-analysis indicated most studies showed oral CHM improved the health status of patients with stable COPD when compared with no treatment, placebo. CHM combined with RP was also found to be better than RP. Considerable heterogeneity was evident in comparisons (see 6.8.4 in Figure 6.8 and 6.9.1, 6.9.2 in Figure 6.9). The variation in COPD severity in patients is a likely source of the wide range in HRQoL scores. Overall, methodological quality was problematic. Only two studies used a placebo in the control and no study satisfied all of the methodological criteria included in the Cochrane risk of bias, so the findings of the meta-analyses should be considered with caution. The absence of severe adverse events suggests the CHMs were well tolerated.

Meta-analyses (Figs 6.8 & 6.9) suggest that the combination of CHM and RP is better at promoting HRQoL in patients with stable COPD compared to RP alone. However, the effects of the RPs used in the included studies may not have been optimal. According to the GOLD guidelines, theophylline in the management of stable COPD is controversial (9). Also, a recent review suggested that newer long-acting β₂ agonists and long-acting anticholinergic medications are better than the combination of salbutamol and ipratropium bromide for moderate and severe COPD (190). In future studies the RP should be standardized to international best practice.

COPD is a chronic disease with progressive development that requires long-term therapy so the 15 studies that lasted six months are the most relevant. Of these, the largest were Shi 2009
(n=180), Feng 2008 (n=120) and Zhang 2009 (n=120). Feng 2008 and Shi 2009 included the five most commonly used herbs whereas Zhang 2009 included two of them (huangqi & fuling). For each of the five most commonly used herbs there is additional evidence for bioactivity related to the respiratory system. Experimental studies on extracts of Huangqi in mice found that airway hyperresponsiveness was inhibited by astragaloside IV (387) and an aqueous extract decreased inflammatory infiltration and mucus secretion in lung tissues (388). There is human experimental evidence to suggest Dangshen can improve respiratory symptoms in acute altitude sickness (389). Extracts of Baizhu were found to have anti-inflammatory effects in acute and chronic animal models (390) and on rat lung cells (391). Fuling has been shown to have anti-inflammatory effects (392-394). Wuweizi is considered an ‘adaptogen’ with stress protective effects (395) and its constituent schisandrin demonstrated anti-inflammatory activity in mice (396). These herbs appear to warrant further investigation.

6.2.9 Conclusions

CHM appears to be a well-tolerated addition to pharmacotherapy for stable COPD and may confer an additional benefit in terms of improving HRQoL of these patients. Such potential benefits need to be further evaluated through trials that address the identified methodological deficiencies and provide quality control data for the CHM interventions. Trials should employ randomized double-blind method using standard outcome instruments. Comparisons should be with placebo or a RP which reflects current best practice.
7 Chapter Seven: Results of systematic review and data analyses of oral CHM for stable COPD with physiological and symptomatic outcome measures

This chapter includes the search results and descriptions of each study, the risk of bias and methodological quality assessments, the meta-analyses of outcome data and the analyses of herbal usage for all included studies.

The methods used in this SR are in accordance with the method for SRs that has been described in section 4.2.2. Therefore, the search results are reported directly without repeating the method.

7.1 Search results

Search data were updated in April 2011 which was the same time as for SR2 of oral CHM for improvement in HRQoL in patients with stable COPD. A total of 1,715 records were identified through the initial searches of the databases.

After removing duplicates, 1,599 records were screened by reading the abstracts. Finally 349 full-text articles were assessed for eligibility. Eventually, 101 articles matched the selection criteria and were included. The study selection process is shown in Figure 7.1.
1715 Records identified through database searches: Pubmed, EMBASE, Scopus, CINAHL, Cochrane & CNKI, CQVIP, WANFANG and hand search

1599 Records after duplicates removed

1599 Records screened

1250 Records excluded

349 Full-text articles assessed for eligibility

248 Full-text articles excluded, with reason:
1. CHM was administrated by IV drop (n=6)
2. Not RCTs (n=30)
3. Patients included asthma, chronic bronchitis & cor pulmonale (n=27)
4. Oral CHM for not stable COPD (n=157)
5. Duplicated trials (n=21)
6. Other (n=4)
7. Study included children (n=1)
8. Study used antibiotics (n=1)
9. Same ingredient of capsules in two

101 Studies included in qualitative synthesis

Lung function: 70 Studies
ECOPD: 27 Studies
Relief of symptoms: 55 Studies
Blood gas analysis: 10 Studies
Biomarkers: 23 Studies
Other outcomes: 16 Studies

Figure 7. 1 Flow diagram for selection study process in review of Chinese herbal medicine for stable COPD physiological and symptomatic outcome measures
7.2 Description of the included studies

The characteristics of the individual studies including study design, study location, patients’ source, age and gender of participants, diagnosis and severity of COPD, syndromes of Chinese medicine, COPD history, smoking history as well as duration of treatment and follow-up are provided in Appendix 12. These details are summarised below.

7.2.1 Characteristics of included studies

Of the 101 included studies, 98 studies were conducted in China, three studies were conducted in Japan and one in Israel. Most articles were retrieved from Chinese language databases or from English databases and published in Chinese language journals. A few articles located from English language databases were published in English language journals.

7.2.2 Characteristics of excluded studies

Based on screening from reading the abstracts, 1,250 articles were eliminated and a further 248 were excluded after reading the full text and applying the exclusion criteria. One study included patients aged less than 18 years and 27 studies included patients with pulmonary diseases such as asthma, chronic bronchitis, cor pulmonale or chronic respiratory failure. In 157 studies the condition was acute COPD, or both acute and stable COPD, or the COPD status could not be verified, so these were excluded. In 21 articles there were duplicated publications of the same study which were combined when different papers reported on different outcome measures. In one study the comparison was between two varieties of Cordyceps, which was considered an inappropriate comparison, therefore this study was excluded (397).

7.2.3 Participants

There were 8,014 participants in total in the included studies. Of these 4,165 participants were randomized into the CHM treatment groups and 3,798 participants were randomized into the control groups. All participants were inpatients or outpatients of hospitals in different regions and were diagnosed as COPD at the stable stage. The age of participants ranged from 24 to 88 years old, but two studies did not mention the age of participants (380, 398). Most studies reported mean ages ranging from 50 to 70 years old, but mean age was not reported in six studies (399-404). The numbers of males were 5,022 and females were 2,648.
Withdrawals were described in 11 studies with 98 participants dropping out during the treatment period. Eight participants who were randomized did not enter into treatment (79). There were 28 withdrawals from the CHM treatment groups in seven studies (363, 366, 367, 405-408), while there were 37 withdrawals from the control groups in seven studies (363, 366, 367, 384, 405, 406, 408). For 25 withdrawals in four studies it was not indicated which group these drop-outs were from (364, 365, 404, 409). The numbers of male and female withdrawals were not mentioned in any studies.

7.2.4 Diagnosis and severity of COPD

‘Guideline for diagnosis and management of chronic obstructive pulmonary disease’ is based on the GOLD guideline. It was modified by the CSRD and issued in 1997, with a revision in 2002 (91). The latest version issued by CSRD in 2007 is in accordance with the GOLD guideline (92).

Participants in eleven studies were diagnosed as stable COPD according to the diagnostic criteria specified by CSRD in 1997, fifty one studies used the CSRD criteria published in 2002, and sixteen studies used the 2007 CSRD criteria. Diagnosis of COPD was based on the GOLD guideline in one study (410). Participants in seven studies were diagnosed according to the guideline issued by the National Heart Lung and Blood Institute (NHLBI) and World Health Organization (WHO) in 2001 (69, 368, 369, 383, 398, 411, 412).

Inclusion criteria for participants in one study were defined by FEV\textsubscript{1}% predicted that was based on ‘Standardization of Spirometry’ issued by the ATS (79). In a few studies, participants’ diagnosis of COPD was based on medical books such as ‘The standardization of diagnosis and management of diseases’ (疾病诊疗标准) written by Wang Zhenhai in 1983 in one study (413), or the textbook of Chinese Internal Medicine (中医内科学) by Tian Delu (414) in one study (415), or The Practice of Internal Medicine (实用内科学) written by Lin et al. (416) in one study (343). Eleven studies did not mention how to diagnose patients (65, 341, 342, 366, 382, 399, 417-421).

According to the GOLD guideline, the severity of COPD was classified into five stages based on spirometric classification, that is, post bronchodilator the ratio of FEV\textsubscript{1} / FVC <0.70 or the value of FEV\textsubscript{1} % predicted. The severity of COPD was described as: stage 0 ‘at risk’; stage I: ‘mild’ (FEV\textsubscript{1}≥80% predicted); stage II: ‘moderate’ (50 %≤FEV\textsubscript{1}<80% predicted); stage III:
‘severe’ (30%≤FEV$_1$<50% predicted); and stage IV: ‘very severe’ (FEV$_1$<30% predicted or FEV$_1$<50% predicted plus chronic respiratory failure).

There is no difference in classification between GOLD and the new version of CSRD published in 2007. However, the version of CSRD published in 2002 was modified from GOLD, and the severity of COPD was classified as: IIA ‘moderate’; IIB ‘severe’; and III ‘very severe’. When available, COPD severity is reported in Appendix 12.

In the 101 studies, patients were diagnosed as COPD and further classified by severity in 57 studies. There was no study that only included patients diagnosed as COPD at the mild stage; only patients with moderate COPD were included in two studies (73, 422), and only participants defined as FEV$_1$ 50-65% of predicted at moderate stage were included in one study (79). Patients with mild to moderate COPD were included in seven studies (69, 341, 378, 423-426); patients with moderate to severe COPD were included in six studies (369, 375, 398, 404, 427, 428); patients at the stages mild, moderate or severe COPD were included in twenty two studies (69, 342-345, 363, 364, 366, 368, 371, 374, 385, 386, 406, 412, 419, 429-434); patients with moderate to very severe were included in eight studies (346, 347, 372, 373, 377, 405, 435, 436); patients at all stages of COPD were included in ten studies (340, 365, 370, 376, 408, 420, 437-440); patients with severe and very severe COPD were included in one study (312). Forty three studies did not mention the severity of COPD of the participants.

**7.2.5 Chinese medicine syndrome differentiation**

According to CM theories on COPD at the stable stage, the CM syndrome differentiation can be classified as: Lung qi deficiency, Lung and spleen Qi deficiency, or Lung, spleen and kidney Qi deficiency, with or without phlegm stasis or blood stasis. However, of the 101 studies, forty three studies (see Appendix 12) mentioned syndrome differentiation involving seventeen different syndromes as follows. Lung and Kidney Qi deficiency was reported in 11 studies (69, 80, 340-342, 371, 383, 415, 422, 429, 441); Lung and Spleen Qi deficiency in 6 studies (73, 417, 426, 436, 442, 443); Lung, Spleen and Kidney Qi deficiency in 4 studies (346, 347, 433, 434), Lung Qi deficiency in three studies (423, 432, 444), Qi deficiency with blood stasis was mentioned in three studies (368, 369, 411); Spleen and Kidney Qi deficiency with phlegm in one study (445), and Lung and Spleen deficiency with phlegm in one study (425).

Other syndromes were mentioned in one study each: Qi deficiency (343); Spleen deficiency
Kidney deficiency (381); Kidney deficiency with phlegm (446); Yin deficiency of Lung and Kidney (447); Yin deficiency of Kidney (407); Qi deficiency and phlegm stasis (386); Sanyin Xuhan, Xinfei luobi (Emptiness and Cold of the hand three Yin, heart and lung channel blocked) (439); Liver Qi stasis (448); or Spleen and stomach deficiency (440). Multiple syndromes were included in 4 studies (379, 382, 401, 404). The remaining 58 studies did not differentiate syndromes.

7.2.6 The COPD history and smoking history

The COPD history of subjects ranged from 3 to 30 years. The mean or average was between 5 and 22 years in sixty eight studies. However the COPD history was not described in thirty three studies. In addition, the smoking history of subjects was mentioned in three studies (420, 438, 449).

7.2.7 Duration of treatment and follow up and run in

The lengths of duration of treatment were variable in the included studies, and ranged from 10 days to one year.

The lengths of duration of treatment were less than three months in forty five studies, involving only 10 days in one study (418), three weeks in two studies (450, 451), one month (four weeks) in fourteen studies (341, 343, 345, 375, 400, 419, 425, 428, 440, 444, 449, 452-454), 6 weeks in two studies (405, 421), and two months (eight weeks) in twenty six studies (69, 344, 349, 366, 373, 381, 383, 384, 401, 404, 406, 407, 410, 417, 423, 424, 432, 433, 435, 436, 440, 442, 447, 455, 456).

The lengths of duration of treatment were more than three months in fifty six studies including three months or 90 days in twenty five studies (73, 312, 340, 347, 368, 369, 376, 399, 408, 409, 411-413, 429-431, 434, 437, 438, 446, 448, 457-460), four months in one study (365); six months or twenty four weeks in twenty seven studies (65, 79, 80, 346, 363, 364, 367, 370-372, 374, 377-380, 382, 385, 386, 398, 402, 415, 422, 426, 427, 439, 441, 445); and one year of treatment duration in three studies (403, 420, 460).

The lengths of the follow up period were mentioned in thirteen studies. Two months of follow up period was performed in one study (421), four months in one study(381), six months in four studies (340, 346, 380, 382), nine months in two studies (399, 412), ten months in one
study (442), and one year in four studies (366, 415, 439, 446).

None of the included studies mentioned a run-in period in their study design.

7.2.8 Sample size

There were seventeen studies with more than one hundred participants (79, 340-343, 345, 365, 367, 379, 382, 400, 406, 407, 415, 419, 429, 455). Huang 2002 was the largest study with 300 participants in the CHM treatment group and 300 participants in the control group (341). Sample size calculation was not mentioned in any studies.

7.3 Assessment of risk of bias in included studies

The risk of bias of included studies was assessed using Cochrane Risk of Bias with six domains as below. The results from the judgments of the review authors for each item of risk of bias for each included study and the overview of the findings are summarized in Fig 7.2 below.

7.3.1 Random sequence generation

Of the 101 studies, 28 specified the method of randomization including a random number table, computer generated numbers, stratified blocked randomization, or randomized block design (69, 73, 79, 340, 346, 364, 366, 368, 369, 371, 374, 378, 383, 385, 403, 407, 410, 412, 423, 425, 426, 432, 435, 436, 444, 452, 460, 461), all of which were judged as low risk of bias. The remaining studies did not provide details of the randomization process and were judged as unclear risk of bias.

7.3.2 Allocation concealment

Allocation concealment using opaque envelopes was described in one study which was judged as low risk of bias (383). The remaining studies did not mention information on allocation concealment and were judged as unclear risk of bias.

7.3.3 Blinding

Double blinding was performed in three studies (79, 404, 461). Although limited information about the blinding procedure was provided, they were judged as low risk of bias. Single
blinding, which is not a suitable method of blinding, was performed in three studies with no further details available. They were judged as high risk of bias (347, 376, 411). The remaining studies did not provide information on blinding and were considered as unclear risk of bias.

7.3.4 **Incomplete outcome data**

Twelve studies had incomplete outcome data due to dropouts during the treatment period with or without the reasons being provided. Since the data analysis excluded the withdrawals in eleven studies, these studies were judged as high risk of bias (79, 363, 364, 366, 404, 406, 409). In contrast, intention to treat (ITT) was applied in one study which was considered low risk of bias (408).

In seven studies the number of participants at completion of treatment was not specified in the data table, these were judged as unclear risk of bias. Complete data were provided in the remaining studies which were judged as low risk of bias.

7.3.5 **Selective reporting**

Bias due to selective reporting was considered low risk of bias in seventy nine studies because the complete results of each outcome were reported in the studies. Some results were incomplete for the stated outcome measures in twenty two studies and these were judged as high risk of bias (65, 73, 340, 343, 345, 399, 400, 403, 417, 419, 421, 428, 432, 439, 442, 445, 448, 450, 451, 454, 458, 462).

7.3.6 **Other bias**

In this review, other bias focussed on baseline data comparability involving demographic and outcome data. Baseline data comparability was adequately addressed in 99 studies which were considered as low risk of bias. However, there was no mention of information on baseline data comparability in two studies. They were judged as unclear risk of bias (65, 402) (Figure 7.2).
Figure 7.2 Summary of review authors’ judgements about risk of bias for studies included in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures
7.4 Methodological quality assessment of all included trials by Jadad’s scale

The results of the methodological quality of each study as assessed by Jadad’s scale are shown in Appendix 13.

7.4.1 Description of randomization

All the included studies were described as ‘randomized’. Randomization using a random digit table was reported in 22 studies (69, 79, 340, 346, 366, 368, 369, 371, 378, 385, 403, 407, 410, 423, 426, 432, 435, 436, 444, 452, 460, 461); stratified blocked randomization was applied in one study (376); randomized block design was applied in one study (412); and randomization was described as simple randomization in four studies (73, 364, 374, 425). Randomization generated by clinic order was described in one study but this was not considered a suitable method of randomization (434).

7.4.2 Withdrawals

The reasons for withdrawals included patients dropping out due to onset of exacerbation of their condition or death were reported in six studies and these received one point (366, 384, 404, 405, 407, 408). However, there was no description of the reason for withdrawals in six studies so these did not receive one point (79, 363-365, 406, 409). In addition, neither the number of withdrawals nor the number of participants completing the study was reported in fifteen studies, so these did not receive a point (65, 69, 73, 312, 341, 343, 398, 419, 422, 427, 433, 438, 440, 451, 454). The remaining studies reported complete outcome data so each received one point. In all of the included studies, no participant dropped out due to an adverse event of CHM.

7.4.3 Description of double blinding

Double blinding was described in three studies which received one point. However, there was no further information on how the blinding was performed and who were blinded.

7.4.4 Jadad’s scale for each study

Of the 101 studies, a final score of ‘4’ was achieved in one study (461), ‘3’ was achieved in 25

7.5 Intervention and control groups

In this review, a number of different types of control groups were used. The types of comparisons between treatment and control groups are summarised below:

7.5.1 Comparison of CHM with placebo control

Oral administration of CHM formulae or extracts of single herbs was compared with placebo in twelve studies (73, 79, 341, 342, 349, 375, 381, 411, 426, 435, 449, 454).

Three studies involved CHM plus RP compared to placebo plus RP (79, 381, 426). The RP used in the two studies that provided details was Theophylline Sustained-release Tablets (Shu Fu Mei Pian) in one study and theophylline plus Salbutamol inhaler (Chuan Le Ning Qi Wu Ji) in the other study.

The use of bronchodilators in both groups was mentioned in one study but no details were provided (79) (Appendix 14).

7.5.2 Comparison of CHM alone with RP

CHM alone was compared to RP in fifteen studies (80, 378, 402, 403, 407, 421, 423, 428, 432, 439, 440, 444, 445, 455, 459).

The RP involved using theophylline tablets or Theophylline Controlled Release Capsules (Cha Jian Kong Shi Jiao Nang) alone in three studies (423, 444, 459); compound aminophylline tablets with salmeterol xinafoate/ fluticasone propionate (Shu Li Die) or theophylline with Ipratropium Bromide Aerosol (Yi Bing Tuo Xi An Qi Wu Ji) Pulmicort Aerosol (Budesonode) (Pu Mi Ke Qi Wu Ji) or theophylline with Salbutamol and Ipratropium Bromide in three studies (402, 439, 445); Theophylline Sustained-release Tablets (Cha Jian Huan Shi Pian) with ambroxol hydrochloride (Yan Suan An Xi Suo) in one study (428); and
Theophylline Controlled Release Tablets (*Cha Jian Kong Shi Pian*) plus Ultrasonic atomizing inhalation in one study (455) (see details in Appendix 15).

In addition, three studies used salbutamol or Compound Ipratropium Bromide Aerosor (*Ke Bi Te Qi Wu Ji*) (consists of Ipratropium Bromide and Salbutamol sulfate) or salmeterol xinafoate/fluticasone propionate (*Shu Li Die*) alone was used in two studies (80, 378).

Non RPs such as the immune enhancing medication nucleotide and Casein Oral Solution and Mannatide tablets were used in two studies (407, 432); Diastase Pancreatin and Pepsin Tablet as an aid to digestion medications were used in two studies (421, 440). One study mentioned bronchodilators being used in the control group but no specific details were provided (403) (Appendix 15).

### 7.5.3 Comparison of CHM plus RP with RP

CHM plus RP was compared with RP alone in forty six studies. Oral methylxanthines including Theophylline, Doxofylline, Theophylline Sustained-release were used in both groups in seven studies (374, 385, 401, 430, 431, 448, 453); theophylline plus Ipratropine was used in one study (417); theophylline plus terbutaline sulfate was used in one study (458) and theophylline plus Bromhexine Hydrochloride was used in one study (460); Theophylline plus Salbutamol or Becotide inhaler was used in one study (366); theophylline controlled release plus Carbocisteine was used in one study (457).

Theophylline was combined with two kinds of drug, such as β2-agonists and/or anticholinergics and/or inhalation of glucocorticosteriods and/or expectorants in five studies (345, 372, 419, 438, 447).

Salbutamol inhaler was used in both groups in one study (378); Salbutamol (or Albuterol) inhaler or Theophylline were used in both groups in three studies (366, 384, 456); and Salbutamol inhaler plus Ambroxol Hydrochloride in one study (436).

Adavir (Salmeterol plus Fluticasone propionate) was used in three studies (312, 404, 427); and Adavir plus Singulair (Montelukast Sodium) was used in one study (386). Ipratropium bromide was used in both groups in four studies (370, 371, 412, 415); and an expectorant alone was used in one study (446).

Bronchodilators were used in both groups in two studies (398, 463) but no details on the RPs
were provided. Bronchodilators and inhalation of glucocorticoids were used in both groups, without further information being available, in two studies (368, 376).

The use of RP was mentioned in eleven studies (344, 347, 369, 373, 379, 380, 382, 405, 410, 450, 451) but details of the medications used were not supplied (Appendix 16).

**7.5.4 Comparison of CHM with no treatment**

CHM was compared to a no treatment control group in sixteen studies (346, 363-365, 367, 377, 383, 400, 406, 408, 409, 411, 413, 420, 424, 462). No treatment means no use of RP or other medications (Appendix 17).

**7.5.5 Comparison of test CHM with other CHM**

A test CHM was compared with another CHM in twelve studies (340, 343, 399, 422, 429, 433, 434, 437, 441, 442, 452, 461). In these studies the control CHMs were all medicines with a history of use for COPD and/or other respiratory disorders.

*Gubenkechuan* tablets were used in the control groups in four studies (433, 434, 441, 461).

*Jinshuibao* capsule which contains an extract of *Dongcongxiacao (Cordyceps sinensis)* was used in the control group in four studies (340, 422, 429, 437).

*Zhen Qi Fu Zheng* capsule which consists of Nv zhen zi (*Ligustrum lucidum*) and Huang qi (*Astragalus membranaceus*), was administered to the control group in two studies (343, 399).

Other formulae with unspecified ingredients were used in the control groups in two studies (442, 452) (Appendix 18).

**7.6 Outcome measures**

**7.6.1 Pulmonary function**

Pulmonary function measurements were performed in 70 studies with 5,574 participants. FEV$_1$ $\%$ predicted was reported in 52 studies with 3,332 participants; volume of FEV$_1$ (L) was reported in 37 studies with 3,475 participants. FVC $\%$ predicted was reported in 12 studies with 730 participants and volume of FVC (L) was measured in 30 studies with 2,283 participants.
FEV$_1$/RVC% was reported in 37 studies with 2,635 participants, PEF% or PEF (L/s) was reported in 4 studies with 257 participants, MMEF in 8 studies with 575 participants, MVV in 11 studies with 455 participants, MIP in one study with 60 participants, and Raw was reported in one study of 54 participants.

7.6.2 Reduction of COPD exacerbations

Exacerbations of COPD including exacerbation rate and frequency of exacerbation were reported in 21 studies with 1,619 participants. In addition, days of hospitalization was reported in 3 studies with 245 participants.

7.6.3 Symptom relief

Relief of symptoms was assessed in 55 studies with 3,885 participants. Two approaches were used:

1. The percentage of effectiveness based on the number of patients who reported symptom improvement in each group;

2. Reduction in total scores of symptoms and the subscores for chronic cough, sputum production and dyspnea.

In addition, the MMRC dyspnea scale was reported in 3 studies with 180 participants.

7.6.4 BODE index, the six-minute-walk distance test and body-mass index

The BODE index was reported by two studies with 133 participants. The six-minute-walk distance (6MWD) test was performed in ten studies with 366 participants. Body-mass index (BMI) was measured in four studies with 232 participants.

7.6.5 Arterial blood gas measurement

Arterial blood gas measurement involving PaO$_2$ and PaCO$_2$ was reported in ten studies with 713 participants.

7.6.6 Biomarkers

Biomarkers involving inflammatory cytokines, lymphocyte subsets and immunoglobulins
were measured in 23 studies in SR3 with 1,431 participants. Inflammatory cytokines such as IL-8, TNF-α and IL-2 were measured in ten studies with 531 participants and lymphocyte subsets were measured in 8 studies with 605 participants. Immunoglobulins (Ig) consisting of the level of serum Ig A, Ig M and Ig G were measured in nine studies with 600 participants.

Blood rheology index was tested in three studies with 239 participants.

Outcome measures of nutrition involving ALB, prealbumin and leptin were performed in four studies with 234 participants.

The levels of superoxidase and LPO were tested in one study with 60 participants.
7.7 Results of physiological and symptomatic outcome measures

7.7.1 Results of spirometric parameters

In this review, a spirometry test was performed in 70 studies that included 5,574 participants suffering from COPD at a stable stage. In these studies 89 participants dropped out from 11 studies during the treatment period, eight participants were randomized but did not enter into treatment (79).

The CHM was compared with placebo control in 10 studies; with no treatment control in 14 studies; with other CHM in 8 studies and with RP in 7 studies. CHM plus RP was compared with RP in 31 studies.

Duration of treatment ranged from 10 days to one year. For the purpose of conducting sensitivity analyses, the studies were divided into two groups based on duration: Group 1 ‘short term’ of less than three months, or Group 2 ‘long term’ of three months and longer.

The twenty eight studies forming group 1 had durations of treatment less than three months. It was only 10 days in 1 study (418), one month (four weeks or 28 days or 30 days) in 9 studies (341, 375, 401, 425, 440, 449, 451-453), six weeks in 1 study (405), and two months (eight weeks or 60 days) in 17 studies (69, 342, 349, 366, 373, 381, 404, 406, 410, 423, 424, 433, 435, 436, 447, 455, 456).

There were 38 studies in group 2 with durations of treatment for 3 months or longer including three months (12 weeks) in 20 studies (312, 340, 344, 347, 364, 385, 386, 409, 413, 429-431, 434, 437, 438, 446, 448, 457, 459, 461), four months in 1 study (365), and six months (24 weeks) in 17 studies (79, 80, 346, 367, 370, 372, 377, 379, 383, 402, 408, 412, 415, 422, 426, 427, 441).

Duration of the follow up period was six months in one study (408), nine months in one study (412), and one year in 4 studies (366, 413, 415, 446). The remaining 64 studies did not report follow up.

The spirometric parameters performed included: FEV\textsubscript{1}, FVC, PEF and MMEF, MVV and MIP, as well as Raw. These methods have been described as above (section 4.2.1.5).

According to the GOLD guideline for COPD, the diagnosis and severity of COPD depend on
the level of FEV1 and FEV1/FVC, therefore, this section focuses on analyzing FEV1 and
FEV1/FVC between the intervention and control groups. In addition, some measurements
have two forms of expression, such as FEV1 expressed as FEV1 % predicted or volume (L),
FVC expressed as FVC % predicted or volume (L) and PEF expressed as percentage or
velocity of flow (L/s). The results for each measurement are reported separately below.

7.7.1.1 FEV1% predicted

FEV1% predicted was measured and reported in 52 studies with 1,698 participants in the
treatment groups and 1,634 participants in the control groups (Figure 7.3).

Late response of FEV1% was reported in 32 studies with 2,075 participants in the long term
treatment group (3 months and longer), while the early response of FEV1% was reported in 20
studies with 1,324 participants in the short term treatment group (less than 3 months).

Sensitivity analysis was performed for the long term and short term therapy groups (Figures
7.4 & 7.5).

CHM Vs Placebo

FEV1% predicted was measured and reported in nine studies on 716 participants. Among
these studies, CHMs were compared with placebo alone in six studies with 458 participants
(69, 342, 349, 375, 435, 449), while CHM plus RP versus placebo plus RP was the
comparison in three studies with 258 participants (79, 381, 426).

Meta-analysis manifested significant improvement of FEV1% predicted between CHM and
placebo groups (MD 7.46 95% CI [3.72, 11.20]) with moderate heterogeneity (Chi² = 13.15,
df = 5 (P = 0.02); I² = 62%).

However, the meta-analysis of the He (2010) and Ni (2008) studies (CHM plus RP versus
placebo plus RP) showed no significant change in FEV1% predicted (MD 5.78, 95%CI [-
27.60, 39.16]) due to the fact that one study demonstrated significant change in FEV1% predicted while the other study found no significant change (381, 426).

One study did not provide a value for FEV1% post treatment, so it could not be included in
the meta-analysis. However, the authors reported that no significant change of FEV1% predicted after treatment was found in this study (79).
**CHM Vs RP**

FEV$_1$% predicted was measured in seven studies with 451 participants (80, 402, 403, 423, 440, 455, 459), which showed a significant change between CHM and RP at completion of treatment (MD 8.52, 95%CI [2.51, 14.54]) with high heterogeneity (Chi$^2$ = 101.26, df = 6 (P < 0.00001); I$^2$ = 94%).

**CHM plus RP Vs RP**

Comparison of CHM plus RP with RP was performed for 21 studies with 1,263 participants (312, 344, 366, 370, 372, 373, 385, 386, 401, 404, 410, 412, 425, 427, 436, 438, 447, 451, 453, 457, 460).

Meta-analysis indicates that there was a significant improvement of FEV$_1$% predicted between the two groups post treatment (MD 5.74, 95%CI [4.49, 6.98]) with moderate heterogeneity (Chi$^2$ = 60.64, df = 20 (P = 0.00001); I$^2$ = 67%).

**CHM Vs Other CHM**

Lung function was tested in nine studies that compared CHM with other CHM. The FEV$_1$% predicted was measured in eight studies with 550 participants (340, 422, 429, 433, 434, 437, 441, 461).

There was significant improvement of FEV$_1$% predicted after treatment (MD 3.22, 95%CI [1.09, 5.35]) with low heterogeneity (Chi$^2$ = 7.76, df = 7 (P =0.35); I$^2$ = 10 %). However, the FEV$_1$% result was not reported in one study (452).

**CHM Vs No Treatment Control**

The FEV$_1$% predicted was conducted in eight studies with 444 participants that compared CHM with no treatment (346, 363, 364, 377, 383, 408, 413, 424).

There was significant improvement of the FEV$_1$% predicted after treatment between the two groups (MD 4.19, 95%CI [2.13, 6.26]) with no heterogeneity (Chi$^2$ = 4.23, df = 7 (P =0.75); I$^2$ = 0 %).
Figure 7.3 Meta-analysis of CHM versus control with FEV1 % at end of treatment as outcome
Sensitivity Analysis of FEV₁% predicted

1) Long term therapy (study duration of three months or more)

For the long term therapy group, meta-analysis found a significant improvement in FEV₁% of participants treated with CHM compared to RP in 4 studies on 228 participants (MD 7.94, 95%CI [4.18, 11.69]) with high heterogeneity (Chi² = 24.41, df = 3 (P < 0.0001); I² = 88%) (80, 402, 403, 459). Heterogeneity was reduced but remained high.

For CHM plus RP compared to RP, there was a significant improvement in 12 studies on 731 participants (MD 5.89, 95%CI [3.40, 8.37]) with moderate heterogeneity (Chi² = 35.84, df = 11 (P = 0.002); I² = 69%) (312, 344, 370, 372, 385, 386, 412, 427, 438, 447, 457, 460).

For CHM compared to other CHM, there was a significant improvement in 7 studies on 512 participants (MD 2.86, 95%CI [0.42, 5.29]) with low heterogeneity (Chi² = 7.05, df = 6 (P = 0.32); I² = 15%) (340, 422, 429, 434, 437, 441, 461).

For CHM compared to no treatment, there was a significant improvement in eight studies on 444 participants (MD 4.19, 95%CI [2.13, 6.26]) without heterogeneity (Chi² = 4.23, df = 7 (P = 0.75); I² = 0%) (346, 363, 364, 377, 383, 408, 413, 424).

In addition, the duration of treatment was more than three months in two studies of 160 participants which compared CHM to placebo with RP in both studies (69, 426).

A significant improvement in FEV₁% of participants treated with CHM compared to placebo was found in 1 study on 62 participants (MD 10.88, 95%CI [4.16, 17.61]) (69), and for CHM plus RP compared to placebo plus RP in 1 study on 98 participants (MD 22.35, 95%CI [20.66, 24.04]) (426) (see Figure 7.4).
Figure 7.4 Meta-analysis of CHM group versus control with FEV1 % at the end of treatment as the outcome (treatment period ≥ 3 months)
2) Short-term therapy - less than three months

For the short term therapy group, meta-analyses found a significant improvement in FEV\(_1\)% of participants treated with CHM compared to placebo in 5 studies on 396 participants (MD 7.75, 95%CI [5.47, 10.03]) with moderate heterogeneity (Chi\(^2\) = 12.40, df = 4 (P = 0.01); I\(^2\) = 68%) (342, 349, 375, 435, 449).

For CHM compared to RP a significant improvement was found for 3 studies on 223 participants (MD 16.19, 95%CI [14.61, 17.76]) with high heterogeneity (Chi\(^2\) = 26.20, df = 2 (P < 0.00001); I\(^2\) = 92%) (423, 440, 455).

For CHM plus RP compared to RP there was significant improvement based on 10 studies with 599 participants (MD 7.35, 95%CI [7.12, 7.58]) with moderate heterogeneity (Chi\(^2\) = 21.34, df = 9 (P = 0.01); I\(^2\) = 58%) (366, 373, 401, 404, 410, 425, 436, 447, 451, 453).

In addition, a significant improvement in FEV\(_1\)% of participants treated with CHM compared to other CHM was found in 1 study on 38 participants (MD 5.06, 95%CI [0.29, 9.83]) (p<0.04) (433), whereas no difference in FEV\(_1\)% between CHM plus RP and placebo plus RP was found for one study on 68 participants (MD -11.72, 95%CI [-22.87, -0.57]) (381) (see Figure 7.5).
Figure 7.5 Meta-analysis of CHM group versus control with FEV\(_1\) % at the end of treatment as the outcome (treatment period < 3 months)
7.7.1.2 Volume of FEV$_1$ (L)

FEV$_1$ (L) was measured and reported in 37 studies with 1,819 participants in the treatment groups and 1,656 participants in the control groups (Figure 7.6).

**CHM Vs Placebo**

The volume of FEV$_1$ (L) was reported in three studies with 862 participants. There was a marginally significant change after treatment (MD 0.30, 95%CI [0.02, 0.58]) but heterogeneity was high (Chi$^2 = 26.12$, df = 2 (P < 0.00001); I$^2 = 92\%$) (69, 341, 342).

**CHM Vs RP**

In contrast, there is no significant change of the volume of FEV$_1$ (L) in three studies comparing CHM to RP with 188 participants (MD 0.16, 95%CI [-0.01, 0.33]) (80, 423, 459).

**CHM plus RP Vs RP**

The volume of FEV$_1$ (L) was measured in eighteen studies with 1,378 participants (347, 373, 379, 385, 386, 404, 405, 415, 418, 427, 430, 431, 446, 447, 453, 456, 457, 460). A meta-analysis showed a significant improvement of the volume of FEV$_1$ (L) after treatment (MD 0.22, 95%CI [0.12, 0.33]). Heterogeneity was high (Chi$^2 = 153.70$, df = 17 (P < 0.00001); I$^2 = 89\%$).

**CHM Vs Other CHM**

The volume of FEV$_1$ (L) was measured in four studies with 337 participants (340, 429, 437, 461). There was no significant change in the volume of FEV$_1$ (L) after treatment between the experimental CHM and the other CHM (MD 0.20, 95%CI [-0.01, 0.42]).

**CHM Vs No treatment control**

The volume of FEV$_1$ (L) was reported in 9 studies that included 710 participants (346, 363-365, 367, 406, 409, 420, 424). A meta-analysis indicated a significant improvement in the volume of FEV$_1$ (L) at completion of treatment (MD 0.20, 95%CI [0.06, 0.35]). Heterogeneity was high (Chi$^2 = 59.48$, df = 8 (P < 0.00001); I$^2 = 87\%$).
### Figure 7.6 Meta-analysis of CHM group versus control with FEV\(_1\) (L) at the end of treatment as the outcome

<table>
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<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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<th>IV, Random, 95% CI</th>
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<td>[0.05, 0.53]</td>
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<td>Wu 2003</td>
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<td>0.46</td>
<td>100</td>
<td>1.36</td>
<td>0.5</td>
<td>100</td>
<td>34.3%</td>
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<td><strong>Total (95% CI)</strong></td>
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Test for overall effect: Z = 2.08 (P = 0.04)

### 7.6.2 CHM vs Pharmacotherapy

<table>
<thead>
<tr>
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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2008</td>
<td>1.37</td>
<td>0.22</td>
<td>35</td>
<td>1.28</td>
<td>0.57</td>
<td>35</td>
<td>34.3%</td>
<td>0.29</td>
<td>[0.05, 0.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2003</td>
<td>1.37</td>
<td>0.33</td>
<td>30</td>
<td>1.51</td>
<td>0.52</td>
<td>30</td>
<td>39.1%</td>
<td>0.29</td>
<td>[0.05, 0.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhao 2003</td>
<td>1.63</td>
<td>0.36</td>
<td>30</td>
<td>1.57</td>
<td>0.48</td>
<td>30</td>
<td>26.6%</td>
<td>0.26</td>
<td>[0.04, 0.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>90</td>
<td></td>
<td>100%</td>
<td>90</td>
<td></td>
<td>100%</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Test for overall effect: Z = 1.58 (P = 0.06)

### 7.6.3 CHM vs Other CHM

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao 2008</td>
<td>1.37</td>
<td>0.22</td>
<td>35</td>
<td>1.15</td>
<td>0.55</td>
<td>35</td>
<td>34.3%</td>
<td>0.30</td>
<td>[0.06, 0.54]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2003</td>
<td>1.37</td>
<td>0.33</td>
<td>30</td>
<td>1.51</td>
<td>0.52</td>
<td>30</td>
<td>39.1%</td>
<td>0.29</td>
<td>[0.05, 0.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhao 2003</td>
<td>1.63</td>
<td>0.36</td>
<td>30</td>
<td>1.57</td>
<td>0.48</td>
<td>30</td>
<td>26.6%</td>
<td>0.26</td>
<td>[0.04, 0.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>90</td>
<td></td>
<td>100%</td>
<td>90</td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.58 (P = 0.06)

### 7.6.4 CHM vs No treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang 2009</td>
<td>1.26</td>
<td>0.28</td>
<td>30</td>
<td>1.43</td>
<td>0.32</td>
<td>30</td>
<td>39.1%</td>
<td>0.07</td>
<td>[0.03, 0.11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2005</td>
<td>1.37</td>
<td>0.33</td>
<td>30</td>
<td>1.51</td>
<td>0.52</td>
<td>30</td>
<td>39.1%</td>
<td>0.29</td>
<td>[0.05, 0.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li (1) 2006</td>
<td>1.63</td>
<td>0.36</td>
<td>30</td>
<td>1.57</td>
<td>0.48</td>
<td>30</td>
<td>26.6%</td>
<td>0.26</td>
<td>[0.04, 0.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>90</td>
<td></td>
<td>100%</td>
<td>90</td>
<td></td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.58 (P = 0.06)
Sensitivity analysis of volume of FEV$_1$ (L)

1) Long-term therapy - three or more months

Long-term therapy was conducted in 24 studies with 1,759 participants. Meta-analysis indicated a significant improvement of FEV$_1$ (L) when CHM plus RP was compared to RP in 11 studies with 823 participants (MD 0.27, 95%CI [0.11, 0.42]), but heterogeneity was high ($\chi^2 = 84.45$, df = 10 ($P < 0.00001$); $I^2 = 88\%$) (P=0.0006) (347, 379, 385, 386, 415, 427, 430, 431, 446, 457, 460).

For CHM compared to no treatment there was a significant improvement in 7 studies with 481 participants (MD 0.18, 95%CI [0.01, 0.34]), but heterogeneity was high ($\chi^2 = 49.29$, df = 6 ($P < 0.00001$); $I^2 = 88\%$) (p=0.04) (346, 363-365, 367, 409, 420).

There was no significant change of FEV$_1$ (L) when CHM was compared to RP in two studies with 118 participants (MD 0.06, 95%CI [-0.16, 0.29]), but heterogeneity was high ($\chi^2 = 0.03$ df = 1 ($P=0.86$); $I^2 = 0\%$) (80, 459).

There was no significant change of FEV$_1$ (L) when the experimental CHM was compared to other CHM in four studies with 337 participants (MD 0.20, 95%CI [-0.01, 0.42]), but heterogeneity was again high ($\chi^2 = 7.92$, df = 3 ($P =0.05$); $I^2 = 62\%$) (340, 429, 437, 461) (Figure 7.7).
### Figure 7.7 Meta-analysis of CHM group versus control with FEV₁ (L) at the end of treatment as the outcome (treatment period ≥ 3 months)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD Total</th>
<th>Control Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference IV Random, 95% CI</th>
<th>Mean Difference IV Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2003</td>
<td>1.57</td>
<td>0.22</td>
<td>0.90</td>
<td>0.23</td>
<td>29</td>
<td>0.67 [-0.18, 0.26]</td>
<td></td>
</tr>
<tr>
<td>Xue 2006</td>
<td>1.92</td>
<td>3.6</td>
<td>0.50</td>
<td>48</td>
<td>6</td>
<td>0.22 [-0.16, 2.34]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59</td>
<td>100.0% (0.9, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>τ² = 0.09, Chi² = 0.03, df = 1 (P = 0.89), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.59 (P = 0.61)</td>
<td></td>
<td></td>
<td></td>
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#### 7.7.2 CHM plus Pharmacotherapy Vs Pharmacotherapy

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD Total</th>
<th>Control Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference IV Random, 95% CI</th>
<th>Mean Difference IV Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Fang 2006</td>
<td>1.71</td>
<td>0.52</td>
<td>0.90</td>
<td>0.23</td>
<td>29</td>
<td>0.13 [-0.15, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Hao 2006</td>
<td>2.41</td>
<td>0.108</td>
<td>0.87</td>
<td>0.16</td>
<td>11</td>
<td>0.52 [0.4, 0.66]</td>
<td></td>
</tr>
<tr>
<td>Hsu 2005</td>
<td>1.73</td>
<td>0.08</td>
<td>0.79</td>
<td>0.16</td>
<td>9</td>
<td>0.16 [0.07, 0.35]</td>
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<tr>
<td>Ji 2010</td>
<td>2.44</td>
<td>0.112</td>
<td>0.89</td>
<td>0.23</td>
<td>22</td>
<td>0.47 [0.36, 0.58]</td>
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<tr>
<td>Li 2005</td>
<td>1.78</td>
<td>0.11</td>
<td>0.67</td>
<td>0.18</td>
<td>20</td>
<td>0.18 [0.05, 0.31]</td>
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<tr>
<td>Liu 2006</td>
<td>1.3</td>
<td>0.43</td>
<td>0.87</td>
<td>0.15</td>
<td>9</td>
<td>-0.02 [-0.22, 0.18]</td>
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<tr>
<td>Liu 2010</td>
<td>1.02</td>
<td>0.75</td>
<td>0.87</td>
<td>0.29</td>
<td>39</td>
<td>0.72 [0.44, 0.92]</td>
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<tr>
<td>Liu 2002</td>
<td>0.2</td>
<td>0.67</td>
<td>0.72</td>
<td>0.25</td>
<td>29</td>
<td>0.22 [0.02, 0.42]</td>
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<td>Pu 2006</td>
<td>0.96</td>
<td>0.25</td>
<td>0.89</td>
<td>0.25</td>
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<td>0.21 [0.03, 0.39]</td>
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</tr>
<tr>
<td>Zhang 2010</td>
<td>1.22</td>
<td>0.24</td>
<td>0.94</td>
<td>0.24</td>
<td>69</td>
<td>0.29 [0.03, 0.55]</td>
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<tr>
<td>Zhang 2009</td>
<td>0.245</td>
<td>1.12</td>
<td>0.66</td>
<td>0.26</td>
<td>69</td>
<td>0.46 [0.37, 0.56]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td>428</td>
<td>100.0% (0.57, 0.67)</td>
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<tr>
<td>Heterogeneity</td>
<td>τ² = 0.05, Chi² = 0.45, df = 16 (P = 0.0001), I² = 87%</td>
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<tr>
<td>Test for overall effect Z = 0.41 (P = 0.68)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
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#### 7.7.3 CHM Vs Other CHM

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD Total</th>
<th>Control Mean</th>
<th>SD Total</th>
<th>Weight</th>
<th>Mean Difference IV Random, 95% CI</th>
<th>Mean Difference IV Random, 95% CI</th>
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<tbody>
<tr>
<td>Chen 2007</td>
<td>1.91</td>
<td>0.46</td>
<td>0.94</td>
<td>0.45</td>
<td>59</td>
<td>0.97 [0.6, 1.34]</td>
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</tr>
<tr>
<td>Gao 2006</td>
<td>1.57</td>
<td>0.41</td>
<td>0.94</td>
<td>0.45</td>
<td>16</td>
<td>1.54 [0.86, 2.22]</td>
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</tr>
<tr>
<td>Hsu 2009</td>
<td>1.56</td>
<td>0.34</td>
<td>0.84</td>
<td>0.37</td>
<td>30</td>
<td>0.56 [0.4, 0.73]</td>
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</tr>
<tr>
<td>Zhang 2006</td>
<td>1.59</td>
<td>0.38</td>
<td>0.90</td>
<td>0.51</td>
<td>30</td>
<td>0.25 [0.07, 0.44]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td>164</td>
<td>100.0% (0.49, 0.71)</td>
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<tr>
<td>Heterogeneity</td>
<td>τ² = 0.03, Chi² = 7.32, df = 3 (P = 0.05), I² = 79%</td>
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<tr>
<td>Test for overall effect Z = 1.92 (P = 0.06)</td>
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#### 7.7.4 CHM Vs No treatment

<table>
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<th>SD Total</th>
<th>Control Mean</th>
<th>SD Total</th>
<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Fang 2006</td>
<td>1.28</td>
<td>0.26</td>
<td>0.94</td>
<td>0.24</td>
<td>29</td>
<td>0.14 [0.02, 0.26]</td>
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</tr>
<tr>
<td>Hong 2005</td>
<td>1.67</td>
<td>0.32</td>
<td>1.07</td>
<td>0.32</td>
<td>18</td>
<td>0.13 [0.01, 0.25]</td>
<td></td>
</tr>
<tr>
<td>Liu 2007</td>
<td>2.25</td>
<td>0.87</td>
<td>1.93</td>
<td>0.73</td>
<td>18</td>
<td>0.32 [0.15, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Liu 2005</td>
<td>1.28</td>
<td>0.29</td>
<td>1.02</td>
<td>0.27</td>
<td>25</td>
<td>0.26 [0.03, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Shao 2005</td>
<td>1.11</td>
<td>0.34</td>
<td>0.77</td>
<td>0.34</td>
<td>18</td>
<td>0.34 [0.12, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Wu 2007</td>
<td>1.88</td>
<td>0.39</td>
<td>1.38</td>
<td>0.64</td>
<td>59</td>
<td>0.55 [0.31, 0.84]</td>
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</tr>
<tr>
<td>Zhang (1) 2009</td>
<td>1.88</td>
<td>0.39</td>
<td>1.38</td>
<td>0.64</td>
<td>49</td>
<td>0.51 [0.3, 0.7]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td></td>
<td>249</td>
<td>100.0% (0.38, 0.41)</td>
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</tr>
<tr>
<td>Heterogeneity</td>
<td>τ² = 0.04, Chi² = 6.29, df = 6 (P = 0.0001), I² = 79%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 2.09 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Test for subgroup differences: Chi² = 2.24, df = 3 (P = 0.93), I² = 0%
2) Short-term therapy - Less than three months

A meta-analysis for short term therapy was conducted for thirteen studies with 1,716 participants. This found a significant improvement of FEV\(_1\) (L) for CHM compared to placebo in three studies with 862 participants (MD 0.22, 95%CI [0.15, 0.28]), but heterogeneity was high (Chi\(^2\) = 26.12, df = 2 (P < 0.00001); I\(^2\) = 92%) (P<0.00001) Li, 2006 #82\{341, 342\}.

For CHM plus RP versus RP there was a significant improvement in 7 studies with 555 participants (MD 0.13, 95%CI [0.08, 0.17]), and heterogeneity was moderate (Chi\(^2\) = 13.70, df = 6 (P =0.03); I\(^2\) = 56%) (P<0.00001) (404, 405, 418, 432, 447, 453, 456).

For CHM compared to no treatment in two studies with 229 participants, there was a significant improvement (MD 0.28, 95%CI [0.13, 0.42]) but heterogeneity was high (Chi\(^2\) = 5.86, df = 1 (P =0.02); I\(^2\) = 83%) (P=0.0002) (406, 424).

In addition, for the comparison of CHM with RP in one study on 70 participants there was significant improvement of FEV\(_1\) (L) (MD 0.29, 95%CI [0.03, 0.55]) (423) (Figure 7.8).
Figure 7. 8 Meta-analysis of CHM group versus control with FEV1 (L) at the end of treatment as the outcome (treatment period < 3 months)
7.7.1.3 FEV₁/FVC%

FEV₁/FVC% was measured and reported in 37 studies with 1,376 participants in the treatment groups and 1,259 participants in the control groups.

A meta-analysis (Figure 7.9) showed that there was a significant improvement of FEV₁/FVC% for:

- CHM compared with placebo based on two studies with 96 participants (MD 3.88, 95%CI [0.78, 6.97]), with no heterogeneity (Chi² = 0.06, df = 1 (P =0.81); I² = 0%) (P=0.01) (375, 435);
- CHM compared with RP in four studies with 215 participants (MD 4.77, 95%CI [1.36, 8.18]) with high heterogeneity (Chi² = 9.56, df = 3 (P = 0.02); I² = 69%) (P=0.007) (80, 402, 403, 440);
- CHM plus RP compared with RP in 20 studies with 1,389 participants (MD 4.05, 95%CI [2.10, 5.99]) with high heterogeneity (Chi² = 149.59, df = 19 (P < 0.00001); I² = 87%) (P<0.0001) (347, 366, 370, 372, 373, 379, 401, 404, 405, 410, 412, 415, 418, 425, 427, 430, 431, 436, 438, 451); and
- CHM compared with other CHM in five studies with 390 participants (MD 5.08, 95%CI [2.55, 7.62]) with no heterogeneity (Chi² = 2.22, df = 4 (P=0.70); I² = 0%) (P<0.0001) (340, 422, 429, 434, 452) and
- CHM compared with no treatment in five studies with 477 participants (MD 5.05, 95%CI [3.37, 6.73]) with low heterogeneity (Chi² = 8.00, df = 4 (P=0.09); I² =50%) (P<0.00001) (365, 367, 377, 406, 409).

In contrast, there was no significant improvement for FEV₁/FVC% when CHM plus RP was compared with placebo plus RP in one study with 68 participants (MD -7.47, 95%CI [-14.54, -0.43]) (381).
Figure 7.9 Meta-analysis of CHM group versus control with FEV1/FVC (%) at the end of treatment as the outcome
7.7.1.4 FVC% predicted

FVC% predicted was reported in 12 studies with 378 participants in the treatment groups and 352 in the control groups.

A meta-analysis (Figure 7.10) showed a significant improvement of FVC% predicted for:

- CHM compared with RP in two studies with 162 participants (MD 7.95, 95%CI [1.70, 14.20]) with moderate heterogeneity ($I^2 = 63\%$) ($p=0.01$) (455, 459); and
- CHM compared with other CHM in three studies with 178 participants (MD 5.97, 95%CI [1.95, 9.99]) with no heterogeneity ($I^2 = 0\%$) ($p=0.004$) (434, 441, 452) and
- CHM compared with no treatment in two studies with 122 participants (MD 7.02, 95%CI [1.10, 12.94]) with no heterogeneity ($I^2 = 0\%$) ($p=0.02$) (346, 424).

There was a non-significant change in FVC % predicted in favour of the experimental groups when CHM plus RP was compared to RP in four studies on 232 participants (MD 2.50, 95%CI [-0.05, 5.06]), with no heterogeneity ($I^2 = 0\%$) ($p=0.05$) (312, 410, 412, 457).

In addition, there was no change of FVC % predicted in one study of 60 participants that compared CHM with a placebo group (MD 3.77, 95%CI [-6.22, 13.76]) (375).
Figure 7.10 Meta-analysis of CHM group versus control with FVC (%) at the end of treatment as the outcome
7.7.1.5 The volume of FVC (L)

FVC (L) was measured and reported in 30 studies with 1,215 participants in the treatment groups and 1,068 participants in the control groups. A meta-analysis indicated a significant improvement in the volume of FVC (L) treated for:

- CHM compared to RP in three studies on 184 participants (MD 0.25, 95%CI [0.07, 0.43]) with no heterogeneity ($I^2 = 0\%$) (p=0.007) (80, 423, 459);
- CHM plus RP compared to RP in 14 studies on 1,119 participants (MD 0.21, 95%CI [0.13, 0.29]) with high heterogeneity ($I^2 = 70\%$), (p<0.0001) (344, 347, 370, 379, 386, 415, 418, 430, 431, 447, 453, 456, 457, 460); and
- CHM compared with no treatment in 7 studies on 545 participants (MD 0.28, 95%CI [0.15, 0.42]), with moderate heterogeneity ($I^2 = 66\%$) (p<0.0001) (346, 365, 383, 406, 409, 413, 424).

In addition, a significant improvement of the volume of FVC (L) was found for CHM versus placebo in one study with 60 participants (MD 0.42, 95%CI [0.16, 0.67]) (349).

However, there was no significant change in the volume of FVC (L) after treatment for CHM versus other CHM in 5 studies with 375 participants (MD 0.17, 95%CI [-0.03, 0.38]) with high heterogeneity ($I^2 = 85\%$), (p<0.0001) (340, 429, 433, 437, 461) (Figure 7.11).
Figure 7.11 Meta-analysis of CHM group versus control with FVC (L) at the end of treatment as the outcome
7.7.1.6 The maximum mid-expiratory flow

The MMEF was reported in 8 studies with 575 participants in the treatment groups and 555 participants in the control groups.

A significant improvement of MMEF was found for the comparison of CHM versus other CHM in one study with 38 participants (MD 0.74, 95%CI [0.08, 1.40]) (433). There was an apparent change of MMEF which did not achieve significance for CHM versus placebo group in two studies with 800 participant (MD 0.43, 95%CI [-0.01, 0.86]) (341, 342). A similar result was found for CHM plus RP compared with RP in three studies with 176 participants (MD 1.30, 95%CI [-0.59, 3.19]) (344, 453, 457).

There was no significant difference for CHM compared to RP in one study with 54 participants (MD 0.16, 95%CI [-0.38, 0.70]) (459), or for CHM compared to no treatment in one study with 62 participants (MD 0.06, 95%CI [-0.43, 0.56]) (424) (Figure 7.12).
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Huang 2002</td>
<td>0.65</td>
<td>0.35</td>
<td>500</td>
<td>0.77</td>
<td>0.37</td>
<td>300</td>
<td>0.22 [0.66, 0.78]</td>
<td>0.67</td>
</tr>
<tr>
<td>Wu(1) 2006</td>
<td>0.91</td>
<td>0.12</td>
<td>100</td>
<td>0.74</td>
<td>0.34</td>
<td>100</td>
<td>0.66 [0.39, 0.93]</td>
<td>0.67</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>900</td>
<td>400</td>
<td>900</td>
<td>3</td>
<td>0.63</td>
<td>0.00</td>
<td>0.68 [0.39, 0.93]</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.93 (P = 0.05)

7.12.2 CHM vs Pharmacotherapy

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2003</td>
<td>1.46</td>
<td>0.59</td>
<td>28</td>
<td>1.37</td>
<td>0.51</td>
<td>25</td>
<td>0.16 [0.00, 0.78]</td>
<td>0.16</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>29</td>
<td>25</td>
<td>54</td>
<td>100.0%</td>
<td>0.16</td>
<td>0.00</td>
<td>0.16 [-0.38, 0.70]</td>
<td>0.16</td>
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</table>

Test for overall effect: Z = 0.59 (P = 0.56)

7.12.2 CHM plus Pharmacotherapy vs Pharmacotherapy

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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Chen 2004</td>
<td>0.71</td>
<td>0.07</td>
<td>20</td>
<td>0.69</td>
<td>0.09</td>
<td>20</td>
<td>0.32 [0.16, 0.48]</td>
<td>0.32</td>
</tr>
<tr>
<td>Lu 2002</td>
<td>1.01</td>
<td>0.62</td>
<td>50</td>
<td>0.96</td>
<td>0.6</td>
<td>50</td>
<td>0.60 [0.47, 0.73]</td>
<td>0.60</td>
</tr>
<tr>
<td>Wang 2006</td>
<td>1.48</td>
<td>0.56</td>
<td>30</td>
<td>1.38</td>
<td>0.49</td>
<td>30</td>
<td>0.19 [0.32, 0.06]</td>
<td>0.19</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>80</td>
<td>25</td>
<td>105</td>
<td>100.0%</td>
<td>0.16</td>
<td>0.00</td>
<td>0.16 [-0.38, 0.70]</td>
<td>0.16</td>
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</table>

Test for overall effect: Z = 1.93 (P = 0.05)

7.12.2 CHM vs Other CHM

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun (2) 2007</td>
<td>59.21</td>
<td>10.362</td>
<td>18</td>
<td>53.37</td>
<td>3.330</td>
<td>18</td>
<td>100.0%</td>
<td>0.74 [0.60, 1.44]</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 2.21 (P = 0.03)

7.12.2 CHM vs no treatment

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<thead>
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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li(1) 2005</td>
<td>1.01</td>
<td>0.63</td>
<td>31</td>
<td>0.97</td>
<td>0.61</td>
<td>31</td>
<td>0.68 [0.42, 0.94]</td>
<td>0.68</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>31</td>
<td>31</td>
<td>62</td>
<td>100.0%</td>
<td>0.68</td>
<td>0.00</td>
<td>0.68 [-0.43, 0.58]</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 4.25 (P = 0.03)

Test for subgroups: CHM = 4.19, df = 4 (P = 0.02), P = 4.5%

---

Figure 7.12 Meta-analysis of CHM group versus control with MMEF (L/s) at the end of treatment as the outcome.
7.7.1.7 The maximum voluntary ventilation

MVV was measured and reported in 11 studies with 455 participants in the treatment groups and 378 participants in the control groups.

Meta-analysis showed a significant improvement in MVV when CHM plus pharmacotherapy was compared with pharmacotherapy in seven studies with 549 participants (MD 8.04, 95% CI [3.83, 12.24]) with high heterogeneity ($I^2 = 72\%$) ($p=0.0002$) (370, 372, 412, 418, 453, 456, 457).

In addition, a significant improvement in MVV was found for CHM versus placebo in one study with 60 participants (MD 7.59, 95% CI [2.79, 12.39]) (349).

There was no change in MVV for CHM versus no treatment in one study with 62 participants (MD 4.94, 95% CI [-5.01, 14.89]) (424), or for CHM versus pharmacotherapy in two studies with 162 participants (MD 9.92, 95% CI [-3.78, 23.63]) (455, 459) (Figure 7.13).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
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<tbody>
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<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
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<td>7.59 [2.79, 12.39]</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 3.10 (P = 0.002)</td>
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<tr>
<td>CHM Vs Pharmacotherapy</td>
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<tr>
<td>Wang 2006</td>
<td>56.13</td>
<td>8.79</td>
<td>54</td>
<td>40.60</td>
<td>6.10</td>
<td>54</td>
<td>55.6%</td>
<td>15.14 [13.61, 16.67]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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<td>15.14 [13.61, 16.67]</td>
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<tr>
<td>Heterogeneity: $I^2 = 72%$; df = 1 (P = 0.0002); P = 0.07</td>
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<tr>
<td>Test for overall effect: Z = 3.42 (P = 0.001)</td>
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<tr>
<td>CHM plus Pharmacotherapy Vs Pharmacotherapy</td>
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<tr>
<td>Lao 2006</td>
<td>56.13</td>
<td>8.79</td>
<td>54</td>
<td>40.60</td>
<td>6.10</td>
<td>54</td>
<td>55.6%</td>
<td>15.14 [13.61, 16.67]</td>
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</tr>
<tr>
<td>Lu 2006</td>
<td>52.22</td>
<td>12.63</td>
<td>62</td>
<td>42.17</td>
<td>11.65</td>
<td>62</td>
<td>17.6%</td>
<td>10.06 [7.77, 12.35]</td>
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<tr>
<td>Lu 2002</td>
<td>52.22</td>
<td>12.63</td>
<td>62</td>
<td>42.17</td>
<td>11.65</td>
<td>62</td>
<td>17.6%</td>
<td>10.06 [7.77, 12.35]</td>
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<tr>
<td>Wang 2006</td>
<td>51.72</td>
<td>16.07</td>
<td>30</td>
<td>56.80</td>
<td>16.19</td>
<td>30</td>
<td>11.6%</td>
<td>2.74 [6.16, 11.64]</td>
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<tr>
<td>Wu (2006)</td>
<td>43.55</td>
<td>14.11</td>
<td>36</td>
<td>37.20</td>
<td>11.11</td>
<td>36</td>
<td>0%</td>
<td>0.18 [0.5, 1.2]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td>Heterogeneity: $I^2 = 21.34%; df = 3 (P = 0.0005)$, $I^2 = 76%$</td>
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<tr>
<td>Test for overall effect: Z = 3.75 (P = 0.0002)</td>
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<tr>
<td>CHM Vs no treatment</td>
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<tr>
<td>Lao 2006</td>
<td>57.59</td>
<td>22.62</td>
<td>31</td>
<td>52.65</td>
<td>16.94</td>
<td>31</td>
<td>106.0%</td>
<td>4.94 [5.01, 14.83]</td>
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<td>4.94 [5.01, 14.83]</td>
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<tr>
<td>Test for subgroup differences: $I^2 = 42%; df = 2 (P = 0.04); P = 0.6$</td>
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</tbody>
</table>

Figure 7.13 Meta-analysis of CHM group versus control with MVV (L/min) at the end of treatment as the outcome.
7.7.1.8  The peak expiratory flow (%)

The PEF% was reported in two studies each having 60 participants. A significant change of PEF % was found for CHM versus other CHM in one study with 60 participants (MD 12.60, 95%CI [3.04, 22.16]) (434).

No change in PEF % was found for CHM plus RP versus RP in one study with 60 participants (MD 4.55, 95%CI [-2.32, 11.42]) (410) (Figure 7.14).

Figure 7. 14 Comparison of CHM plus RP versus RP, or CHM versus other CHM in patients with stable COPD: PEF (%) at the end of treatment
7.7.1.9 The peak expiratory flow (L/s)

The value of PEF (L/s) was reported in two studies with 76 participants in the treatment groups and 61 participants in the control groups. No change in FEF (L/s) was found for CHM compared with placebo in one study with 62 participants (MD 0.56, 95%CI [-0.05, 1.18]) (69); or for CHM plus pharmacotherapy (RP) compared with pharmacotherapy in one study with 75 participants (MD -2.60, 95%CI [-4.42, -0.78]) (446) (Figure 7.15).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Faced, 95% CI</th>
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</tr>
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<tbody>
<tr>
<td>7.16.3 CHM vs Placebo</td>
<td>2.576</td>
<td>1.041</td>
<td>31</td>
<td>2.012</td>
<td>0.227</td>
<td>31</td>
<td>0.56</td>
<td>0.05, 1.18</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td>31</td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.05, 1.18</td>
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</tr>
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<tr>
<td>Test for overall effect: Z = 1.80 (P = 0.07)</td>
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</tbody>
</table>

| 7.16.4 CHM plus Pharmacotherapy vs Pharmacotherapy | 12.9              | 2.5   | 46     | 15.5        | 4.2   | 30     | -2.60           | -4.42, -0.78               |        |
| Subtotal (95% CI)                          | 45                |     |       | 30           |       |       | -2.60           | -4.42, -0.78               |        |
| Heterogeneity: Not applicable               |                   |     |       |              |       |       |                 |                           |        |
| Test for overall effect: Z = 2.80 (P = 0.005) |                   |     |       |              |       |       |                 |                           |        |

Test for subcategory differences: CH² = 16.44, df = 1 (P = 0.001), f² = 96.4%

Figure 7.15 Comparison of CHM versus placebo or CHM plus RP versus RP in patients with stable COPD: PEF (L/s) at the end of treatment
7.7.1.10 The maximum inspiratory pressure

MIP was reported by one study with 60 participants and found no significant change between CHM and placebo (MD 0.55, 95%CI [-0.04, 1.14]) (349) (Figure 7.16).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.16 CHM vs Placebo</td>
<td>2.10</td>
<td>2.78</td>
<td>0.68</td>
<td>29</td>
</tr>
<tr>
<td>7.16 CHM vs Placebo (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>38</td>
<td>100.0%</td>
<td>0.55 (0.04, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.12 (P = 0.23)

Test for subsetor differences: Not applicable

Figure 7.16 Comparison of CHM versus placebo in patients with stable COPD: MIP at the end of treatment

7.7.1.11 Airway resistance

Raw was measured by one study on 54 participants and found no significant change when comparing CHM with pharmacotherapy (MD -0.12, 95%CI [-0.76, 0.52]) (459) (Figure 7.17).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.17 CHM vs Pharmacotherapy</td>
<td>2.05</td>
<td>1.12</td>
<td>-0.92</td>
<td>29</td>
</tr>
<tr>
<td>7.17 CHM vs Pharmacotherapy (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>29</td>
<td>100.0%</td>
<td>-0.12 (0.76, 0.52)</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subsetor differences: Not applicable

Figure 7.17 Comparison of CHM versus routine pharmacotherapy in patients with stable COPD: Raw at the end of treatment
7.7.2 Effectiveness of CHM on prevention of exacerbation of COPD

ECOPD involving acute exacerbation or relapse or hospitalizations were reported in 21 studies on 1,619 participants with 4 withdrawals in one study during the treatment period. Ten studies with 699 participants specifically indicated that ECOPD was observed over at least one year including the treatment period and follow up period. Two studies with 185 participants observed ECOPD for 2 month treatment and two seasons (half year) follow-up period (340, 381). One study with 69 participants observed ECOPD for three months treatment and half year follow up periods (376). The remaining studies did not state there was a follow up period in their studies.

ECOPD rate was reported in nine studies on 377 participants in the treatment groups and 319 participants in the control groups (Figure 7.18), while frequency of ECOPD was reported in eleven studies with 427 participants in the treatment groups and 421 participants in the control groups (Figure 7.19).

In addition, ECOPD leading to days of hospitalization was reported in three studies with 123 participants in the treatment groups and 122 in the control groups. Frequency of ECOPD and / or days of hospitalization due to ECOPD were reported in two studies with 124 participants (370, 376). However, the means and / or standard deviations of their measurements were not provided by authors, so these could not be analyzed by RevMan 5.1.

7.7.2.1 Reduction of ECOPD rate

A significant reduction in the number of ECOPDs was found for two studies with 154 participants when CHM was compared to pharmacotherapy (RR 0.68, 95%CI [0.52, 0.90]); when CHM was compared to no treatment in one study with 99 participant (RR 0.25, 95%CI [0.07, 0.85]) and when CHM plus RP was compared to RP in three studies with 179 participants (RR 0.53, 95%CI [0.38, 0.76]). However, no significant reduction in the percentage of ECOPD was found when CHM was compared to other CHM in three studies with 264 participants (RR 0.50, 95%CI [0.23, 1.13]) (Figure 7.18).
Figure 7.18 Meta-analysis of CHM group versus control with Number of ECOPD at the end of treatment as the outcome
7.7.2.2 Frequency of ECOPD

Significant reductions of the frequency of ECOPD per participant were found when:

- CHM was compared with placebo in two studies with 166 participants (MD \(-0.93, 95\%\text{CI }[-1.17, -0.70]\));
- CHM plus RP was compared with RP in six studies with 489 participants (MD \(-1.26, 95\%\text{CI }[-1.41, -1.12]\));
- CHM was compared with other CHM in three studies with 239 participants (MD \(-0.84, 95\%\text{CI }[-1.08, -0.60]\)); and
- CHM was compared with no treatment in one study with 60 participants (MD \(-1.20, 95\%\text{CI }[-1.14, -0.99]\)) (Figure 7.19).

The two studies which compared CHM plus pharmacotherapy to pharmacotherapy did not provide the Mean and Standard Deviation, so they were not included in the Meta-analysis. However, a significant reduction in the frequency of ECOPD was reported by each study.

![Figure 7.19](image-url)
7.7.2.3 Days of hospitalization and ECOPD occurrence

Significant reductions in days of hospitalization due to ECOPD occurrence were found for CHM compared to placebo in one study with 68 participants (MD -1.65, 95%CI [-3.12, -0.18]) (381); CHM plus RP compared to RP in one study with 60 participants (MD -3.70, 95%CI [-7.21, -0.19]) (366); and for CHM versus other CHM in one study with 109 participants (MD -5.44, 95%CI [-6.78, -4.11]) (Figure 7.20).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>7.20.1 CHM vs Placebo</td>
<td>-1.65</td>
<td>34</td>
<td>4.03</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>7.20.2 CHM plus RP vs RP</td>
<td>-3.70</td>
<td>30</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>7.20.3 CHM vs Other CHM</td>
<td>-5.44</td>
<td>58</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Test for subgroup differences: CHM vs 14.42, df = 2 (P = 0.0007); P = 59.1%.

Figure 7.20 Comparison of CHM versus placebo, CHM plus RP versus RP, or CHM versus other CHM in patients with stable COPD: days of hospitalization at the end of follow up.
7.7.3 Effectiveness of CHM for relieving symptoms

Measures of the relief of symptoms included percentage of effectiveness for the relief of symptoms; and reduction in the total scores for an individual’s symptoms and/or sub-scores for specific symptoms including: chronic cough, sputum production and dyspnea.

In addition, dyspnoea was assessed by the MMRC Dyspnea Scale.

Relief of symptoms was reported in 55 studies on 3,885 participants, with 24 withdrawals during the treatment period in four studies. Four studies reported assessments of the effectiveness for each symptom but did not provide total scores or percentage effectiveness for symptoms, so these aspects could not be entered into RevMan 5.1 and analyzed (363, 364, 452, 455).

7.7.3.1 Effectiveness rate for symptoms

Effectiveness rate for symptoms is calculated by the ratio of the total scores for symptoms before treatment minus the total scores for symptoms after treatment, divided by the total scores of symptoms before treatment. The percentage of effectiveness for symptoms can range from 0 to 100. Less than 30% means ‘no improvement’, greater than or equal to 70% means ‘symptoms remarkably relieved’ and greater than or equal to 90% means ‘symptoms completely relieved’. Percentage of effectiveness was reported in forty three studies with 1,673 participants in the treatment groups and 1,441 participants in the control groups. Six participants dropped out during the treatment period but their data were not analyzed by intent to treat. Meta-analysis indicated a significant improvement in effectiveness rate for symptoms was found for:

- CHM compared to placebo in two studies with 120 participants (RR 1.91 95% CI [1.01, 3.60]) with moderate heterogeneity (Chi² = 2.41, df = 1 (P =0.12); I² = 58 %) (p=0.05) (349, 375);
- CHM compared to RP in nine studies with 636 participants (RR 1.33 95% CI [1.15, 1.53]) with moderate heterogeneity (Chi² = 18.96, df = 8 (P =0.02); I² = 58 %) (p<0.0001) (80, 402, 403, 407, 421, 423, 428, 439, 445);
- CHM plus RP compared to RP in twenty two studies with 1,603 participants (RR 1.25 95% CI [1.16, 1.35]) with moderate heterogeneity (Chi² = 54.45, df = 21 (P < 0.0001); I²
CHM compared to other CHM in seven studies with 586 participants (RR 1.19 95% CI [1.07, 1.33]) with moderate heterogeneity ($\chi^2 = 12.72$, df = 6 (P =0.05); $I^2 = 53 \%$) (p=0.001) (340, 343, 399, 429, 434, 441, 461) and

CHM compared to no treatment in three studies with 169 participants (RR 2.03 95% CI [1.13, 3.66]) with moderate heterogeneity ($\chi^2 = 7.76$, df = 2 (P =0.02); $I^2 = 74 \%$) (p=0.02) (408, 413, 432) (Figure 7.21).
### Figure 7.21: Meta-analysis of CHM group versus control with effectiveness rate of symptoms at the end of treatment as the outcome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.21A CHM vs Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin 2003</td>
<td>26</td>
<td>30</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su 2009</td>
<td>17</td>
<td>30</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>60</td>
<td>120</td>
<td>100.0%</td>
<td>1.51 [1.09, 2.10]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.13, Chi^2 = 2.41, df = 1 (P = 0.11), P = 0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for overall effect: Z = 2.60 (P = 0.05)

<table>
<thead>
<tr>
<th>7.21B CHM vs RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2006</td>
</tr>
<tr>
<td>Hu 2005</td>
</tr>
<tr>
<td>Shi (2) 2006</td>
</tr>
<tr>
<td>Shi (2) 2006</td>
</tr>
<tr>
<td>Wu (2) 2006</td>
</tr>
<tr>
<td>Xiao 2005</td>
</tr>
<tr>
<td>Zhang 2006</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.03, Chi^2 = 10.96, df = 0 (P = 0.002), P = 0.0001</td>
</tr>
</tbody>
</table>
| Test for overall effect: Z = 2.60 (P = 0.0001)

<table>
<thead>
<tr>
<th>7.21C CHM plus RP vs RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao 2007</td>
</tr>
<tr>
<td>Chen (2) 2008</td>
</tr>
<tr>
<td>Fang 2006</td>
</tr>
<tr>
<td>Qiu 2008</td>
</tr>
<tr>
<td>Hu 2009</td>
</tr>
<tr>
<td>Jia 2007</td>
</tr>
<tr>
<td>Li (2) 2006</td>
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<tr>
<td>Lu 2007</td>
</tr>
<tr>
<td>Li 2010</td>
</tr>
<tr>
<td>Meng 2009</td>
</tr>
<tr>
<td>Qiu 2009</td>
</tr>
<tr>
<td>Shan 2007</td>
</tr>
<tr>
<td>Tang 2010</td>
</tr>
<tr>
<td>Wang 2009</td>
</tr>
<tr>
<td>Wu (2) 2006</td>
</tr>
<tr>
<td>Zhang 2006</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.02, Chi^2 = 54.45, df = 21 (P = 0.0001), P = 0.01</td>
</tr>
</tbody>
</table>
| Test for overall effect: Z = 7.56 (P < 0.0001)

<table>
<thead>
<tr>
<th>7.21D CHM vs Other CHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2) 2007</td>
</tr>
<tr>
<td>Chen 2008</td>
</tr>
<tr>
<td>Qiu 2008</td>
</tr>
<tr>
<td>Qiu 2010</td>
</tr>
<tr>
<td>Sun (2) 2009</td>
</tr>
<tr>
<td>Xu 1996</td>
</tr>
<tr>
<td>Zhang 2003</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.06, Chi^2 = 12.72, df = 9 (P = 0.05), P = 0.53</td>
</tr>
</tbody>
</table>
| Test for overall effect: Z = 3.20 (P = 0.001)

<table>
<thead>
<tr>
<th>7.21E CHM vs No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu 2005</td>
</tr>
<tr>
<td>Zhang 2005</td>
</tr>
<tr>
<td>Zhang 2005</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.18, Chi^2 = 7.79, df = 2 (P = 0.02), P = 0.24</td>
</tr>
</tbody>
</table>
| Test for overall effect: Z = 2.37 (P = 0.02)

Test for sub-group differences, Chi^2 = 2.76, df = 4 (P = 0.62), P = 0.30

Test for overall effect: Z = 2.77 (P = 0.006)
7.7.3.2  Reduction of the total scores of symptoms

The total scores were calculated as the average of the sum of the scores for each symptom including cough, dyspnea and sputum production. The score for each symptom ranged from 0 (no symptoms) to 3 (severe symptoms); higher scores denote greater distress and thus, worse symptoms, which was according to the *Guiding principle of Clinical Research on New Drugs of Chinese medicine* (308).

The reduction of the total scores of symptoms was reported in ten studies with 394 participants in the treatment groups and 326 participants in the control groups (Fig 7.22), and reduction in the score of each component such as chronic cough, production of sputum and dyspnea was reported in fourteen studies with 540 participants in the treatment groups and 466 participants in the control groups (Figs 7.23-5).

A significant reduction of the total scores for symptoms was found in the following studies which compared: CHM with placebo including 60 participants (MD -3.40, 95%CI [-5.19, -1.61]) (375); CHM with other CHM including 100 participants (MD -1.29, 95%CI [-1.77, -0.81]) (429); and CHM with no treatment including 74 participants (MD -3.90, 95%CI [-4.11, -3.69]) (420).

A meta-analysis comparing CHM plus RP with RP in six studies with 362 participants showed significant reduction in the total scores for symptoms (MD -1.36, 95%CI [-1.99, -0.74]) with moderate heterogeneity (Chi² = 45.07, df = 5 (P =0.00001); I² = 89%) (p<0.0001) (376, 380, 404, 410, 425, 427). However, reduction in the total scores for symptoms did not achieve significance when CHM was compared to RP in one study with 124 participants (MD -0.56, 95%CI [-1.13, 0.01]) (Figure 7.22) (439).
Figure 7.22 Meta-analysis of CHM group versus control with reduction of the total scores of symptoms at the end of treatment as the outcome.
7.7.3.3 Reduction of the scores for chronic cough, production of sputum and dyspnea

The reduction of scores for individual symptoms was reported by fourteen studies with 1,044 participants. Six participants dropped out in one study (407). The fourteen studies are as follows: CHM was compared to placebo in two studies with 128 participants, to RP in two studies with 182 participants; CHM plus RP compared to RP in five studies with 349 participants; CHM compared to other CHM in three studies with 220 participants; and CHM compared to no treatment in two studies with 127 participants.

Scores for chronic cough

A significant reduction in the score for chronic cough was found for:

- CHM compared to placebo in two studies (MD -1.49, 95%CI [-1.98, -1.00]) with high heterogeneity ($\chi^2 = 8.60$, df = 1 (P =0.003); $I^2 = 88\%$) (p<0.00001) (375, 381); and
- CHM compared to RP in two studies with 182 participants (MD -0.39, 95%CI [-0.62, -0.17]) with low heterogeneity ($\chi^2 = 1.44$, df = 1 (P =0.23); $I^2 = 30\%$) (p=0.0007) (407, 428);
- CHM plus RP compared to RP in five studies on 349 participants (MD -0.23, 95%CI [-0.36, -0.11]) with moderate heterogeneity ($\chi^2 = 8.08$, df = 4 (P =0.09); $I^2 = 50\%$) (p=0.0002) (345, 366, 376, 380, 410);
- CHM compared to other CHM in three studies (MD -0.33, 95%CI [-0.47, -0.20]) with moderate heterogeneity ($\chi^2 = 1.43$, df = 2 (P =0.49); $I^2 = 0\%$) (p<0.00001) (429, 434, 442) and
- CHM compared to no treatment in two studies with 127 participants (MD -0.42, 95%CI [-0.61, -0.22]) with moderate heterogeneity ($\chi^2 = 2.02$, df = 1 (P =0.16); $I^2 = 50\%$) (p<0.0001) (424, 432) (Figure 7.23).
Figure 7. 23 Meta-analysis of CHM group versus control with reduction of the scores of chronic cough at the end of treatment as the outcome
Scores for production of sputum

A significant reduction in the score for production of sputum was found for:

- CHM plus RP compared to RP (MD -0.37, 95% CI [-0.51, -0.23]) with low heterogeneity ($\chi^2 = 5.70, \text{df} = 4 (P = 0.22); I^2 = 30\%$) ($p < 0.00001$) (345, 366, 376, 380, 410);
- CHM compared to other CHM (MD -0.25, 95% CI [-0.40, -0.11]) with low heterogeneity ($\chi^2 = 1.47, \text{df} = 2 (P = 0.48); I^2 = 0\%$) ($p = 0.0004$) (429, 434, 442); and
- CHM compared to no treatment (MD -0.40, 95% CI [-0.58, -0.22]) with low heterogeneity ($\chi^2 = 0.05, \text{df} = 1 (P = 0.82); I^2 = 0\%$) ($p < 0.00001$) (424, 432).

However, no reduction in sputum scores was found when CHM was compared to placebo in two studies with 128 participants (MD -0.33, 95% CI [-0.84, 0.18]); or when CHM was compared to RP in two studies with 182 participants (MD -0.19, 95% CI [-0.40, 0.01]) (407, 428) (Figure 7.24).

**Figure 7.24** Meta-analysis of CHM group versus control with reduction of the scores of sputum production at the end of treatment as the outcome
Scores for dyspnoea

A significant reduction in the score for dyspnea was found for:

- CHM compared to placebo (MD -1.25, 95%CI [-1.70, -0.80]) with no heterogeneity (Chi² = 0.00, df = 1 (P =0.95); I² = 0%) (p<0.00001) (375, 381);
- CHM compared to RP (MD -0.32, 95%CI [-0.51, -0.14]) with low heterogeneity (Chi² = 0.92, df = 1 (P =0.34); I² = 0%) (p=0.0005) (407, 428);
- CHM plus RP compared to RP (MD -0.23, 95%CI [-0.39, -0.07]) with low heterogeneity (Chi² = 4.72, df = 4 (P =0.32); I² = 15%) (p=0.0005) (345, 366, 376, 380, 410);
- CHM compared to other CHM (MD -0.27, 95%CI [-0.40, -0.15]) with low heterogeneity (Chi² = 0.97, df = 2 (P =0.61); I² = 0%) (p<0.0001) (429, 434, 442); and
- CHM compared to no treatment (MD -0.50, 95%CI [-0.74, -0.25]) with low heterogeneity (Chi² = 0.05, df = 1 (P =0.82); I² = 0%) (p<0.0001) (424, 432) (Figure 7.25).

![Figure 7.25](image_url)
7.7.3.4  Reduction in the Modified Medical Research Council Dyspnea scale

This scale was administrated in three studies with 90 participants in each of the treatment and control groups (312, 375, 408).

A significant reduction in the Modified Medical Research Council Dyspnea scale was found in each study comparing CHM with placebo (MD -0.33, 95%CI [-0.66, 0.00]); CHM plus RP with RP (MD -0.45, 95%CI [-0.84, -0.06]); and CHM with no treatment (MD -0.49, 95%CI [-0.92, -0.06]) (Figure 7.26).

![Figure 7.26](image)

Figure 7.26 Meta-analysis of CHM group versus control with reduction of scores of MMRC dyspnoea at the end of treatment as the outcome

7.7.4  CHM impact on 6MWD and BODE index and BMI

6MWD test was reported in 10 studies with 366 participants in the treatment groups and 357 participants in the control groups. Duration of treatment included 1 month (28 days) in two studies (345, 452), three months in 5 studies (312, 347, 386, 408, 434), six months in 2 studies (415, 422) and one year in 1 study (420).

BODE index was measured in two studies with 68 participants in the treatment groups and 65 participants in the control groups, and the duration of treatment was 3 months in both (312, 408).
BMI was reported in four studies with 125 participants in the treatment groups and 107 participants in the control groups. Duration of treatment included one month in 2 studies (440, 454), two months in 1 study (417) and three months in 1 study (408). Results from these measurements are showed individually as follows.

### 7.7.4.1 6MWD

Meta-analysis found that a significant improvement in the exercise capacity and tolerance of participants assessed by 6MWD performance for:

- CHM plus RP compared to RP in five studies with 403 participants (MD 41.39, 95%CI [28.69, 54.10]) \((\chi^2 = 5.41, df = 4 (P = 0.25); I^2 = 26\%)\) (p<0.00001) (312, 345, 347, 386, 415);
- CHM compared to other CHM in three studies with 173 participants (MD 33.31, 95%CI [15.55, 51.07]) \((\chi^2 = 0.97, df = 2 (P = 0.88); I^2 = 0\%)\) (p<0.0002) (422, 434, 452) and
- CHM compared to no treatment in two studies with 147 participants (MD 67.54, 95%CI [58.65, 76.43]) \((\chi^2 = 1.36, df = 1 (P = 0.24); I^2 = 26\%)\) (p<0.00001) (408, 420).

The heterogeneity was consistent at \(I^2<50\%\) for each comparison, so a fixed effect model was used (Figure 7.27).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES</td>
<td>SD</td>
<td>Total</td>
<td>ES</td>
<td>SD</td>
</tr>
<tr>
<td>CHM plus Pharmacotherapy vs Pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen (2008)</td>
<td>412.11</td>
<td>79.53</td>
<td>50</td>
<td>364.47</td>
<td>71.82</td>
</tr>
<tr>
<td>Oke (2008)</td>
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<td>76.50</td>
<td>50</td>
<td>466.74</td>
<td>74.74</td>
</tr>
<tr>
<td>Hong (2005)</td>
<td>240.74</td>
<td>46.99</td>
<td>22</td>
<td>218.62</td>
<td>45.26</td>
</tr>
<tr>
<td>Liu (2010)</td>
<td>348.32</td>
<td>65.79</td>
<td>30</td>
<td>283.32</td>
<td>58.26</td>
</tr>
<tr>
<td>Zhang (2016)</td>
<td>420.80</td>
<td>80.00</td>
<td>40</td>
<td>401.74</td>
<td>78.40</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>202</td>
<td>201</td>
<td>100.0%</td>
<td>41.39 [28.69, 54.10];</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \(Chi^2 = 0.61, df = 4 (P = 0.75); I^2 = 9\%\) (p<0.0001)
Test for overall effect: \(Z = 2.09 (P < 0.0001)\)

| CHM vs Other CHM | | | | | | | | | |
|-------------------|--------------|---------|-----------------|-----------------|----------------|
| Liu (2002)        | 307.47 | 45.35 | 30 | 283.54 | 42.86 | 28 | 59.7% | 30.83 [11.55, 50.13]; | |
| Sun (2) (2008)    | 395.83 | 69.14 | 30 | 352.44 | 46.06 | 25 | 170.0% | 43.29 [3.59, 82.94]; | |
| Subtotal (95% CI) | 60 | 83 | 100.0% | 33.31 [15.65, 51.67]; | |

Heterogeneity: \(Chi^2 = 0.29, df = 2 (P = 0.89); I^2 = 9\%\) (p<0.0001)
Test for overall effect: \(Z = 2.68 (P < 0.0001)\)

| CHM vs No treatment | | | | | | | | | |
|---------------------|--------------|---------|-----------------|-----------------|----------------|
| Shao (2006)         | 412.65 | 17.56 | 36 | 343.66 | 22.38 | 38 | 93.3% | 68.90 [59.72, 78.08]; | |
| Zhang (2006)        | 329.76 | 72.86 | 39 | 282.74 | 92.2 | 35 | 6.2% | 46.97 [1.28, 92.98]; | |
| Subtotal (95% CI)   | 74 | 73 | 100.0% | 67.54 [58.65, 76.63]; | |

Heterogeneity: \(Chi^2 = 1.28, df = 1 (P = 0.24); I^2 = 26\%\) (p<0.0001)
Test for overall effect: \(Z = 14.80 (P < 0.0001)\)

Test for subvarious differences: \(Chi^2 = 37.77, df = 2 (P = 0.0001); I^2 = 89.7\%\)

Figure 7.27 Meta-analysis of CHM group versus control with improvement of 6MWD at the end of treatment as the outcome
7.7.4.2 BODE index

A significant decline in the mean of BODE index was found when comparing CHM plus RP with RP in one study with 60 participants (MD -1.21, 95%CI [-2.34, -0.08]) (312) and CHM versus no treatment in one study with 73 participants (MD -1.50, 95%CI [-2.68, -0.32]) (408) (Figure 7.28).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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<td>2.97</td>
<td>2.26</td>
<td>30</td>
<td>100.0%</td>
<td>-1.21</td>
<td>2.34, -0.08</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
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<td></td>
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Figure 7.28 Comparison of CHM plus RP versus RP or CHM versus no treatment in patients with stable COPD: BODE index at the end of treatment as the outcome

7.7.4.3 BMI index

Body-mass index (BMI) is a calculation using weight and height. It measures the level of nutrition represented as four classes of leanness or obesity, being < 20 kg/m² ‘underweight’; 20 to 24 kg/m² ‘normal’; 24 to 29 kg/m² ‘overweight’; >29 kg/m² ‘obese’. BMI was reported in four studies with 232 participants.

A significant increase of the mean BMI index was found for: CHM compared with placebo in one study with 60 participants (MD 1.59, 95%CI [0.79, 2.39]) (454); and for CHM plus RP compared with RP in one study with 54 participants (MD 2.13, 95%CI [1.84, 2.42]) (417). There was no difference in the mean BMI index when CHM was compared to RP in one study with 45 participants (MD -0.90, 95%CI [-2.25, 0.75]) (440) and CHM was compared to no treatment in one study with 73 participants (MD 0.94, 95%CI [-0.52, 2.40]) (408) (Figure 7.29).
### Figure 7. 29 Comparison of CHM group versus control groups in patients with stable COPD: BMI index at the end of treatment as the outcome

#### 7.7.5 Effect of CHM on arterial blood gas measurements

The arterial blood gas measurement includes multiple items such as arterial oxygen tension (PaO2), PaCO2, oxygen saturation (SaO2) and blood pH. This section focuses on analysis of PaO2 and PaCO2. Normally, the value of PaO2 ranges from 10.6 to 13.3KPa (80-100mmHg). PaO2 <80mmHg (10.6 KPa) suggests hypoxia; <60mmHg (8KPa): respiratory failure; <40mmHg severe hypoxemia; and <20mmHg non survival.

The value of PaCO2 ranges from 35 to 45 mmHg (4.67 to 6.0KPa). A PaCO2 >50 mmHg (6.67 KPa) suggests respiratory acidosis, and PaCO2 <35 mmHg (4.67 KPa) respiratory alkalosis. When considering the combination of PaO2 and PaCO2, a PaO2 <60mmHg (8KPa) combined with PaCO2 <50 mmHg (6.67 KPa) is diagnosed as stage I respiratory failure. If PaO2 <60mmHg (8KPa) is combined with PaCO2 >50 mmHg (6.67 KPa), it should be diagnosed as stage II respiratory failure.

Arterial blood gas measurement was measured and reported in ten studies with 706 participants. These studies involved the following intervention and duration: CHM compared with placebo in one study for 2-months, CHM compared with RP in one study for 3-months,
CHM compared with no treatment in one study for 6-months, CHM compared with other CHM in three studies for 3-months, and CHM plus RP compared to RP in four studies, with Wang 2006 lasting for 28-days and the others for 3-months. A 9-month follow-up was recorded in Zhao (2009) but data were not reported at completion of follow up (446).

7.7.5.1 PaO₂

A significant difference of PaO₂ was reported at completion of treatment for CHM versus placebo in one study with 60 participants (MD 0.68, 95%CI [0.23, 1.12]) (349), and for CHM versus no treatment in one study with 104 participants (MD 0.53, 95%CI [0.14, 0.93]) (367). However, no statistically significant increase in the level of PaO₂ for CHM versus RP was found in one study with 54 participants (MD 0.09, 95%CI [-0.65, 0.83]) (459).

A meta-analysis of four studies with 251 participants showed a significant change for: CHM plus RP compared to RP (MD 0.42, 95%CI [0.15, 0.69]) with no heterogeneity (I² = 0%) (p=0.002) (312, 446, 453, 457). However, significant increase in the level of PaO₂ with high heterogeneity was found in three studies with 237 participants that compared experimental CHM with other CHM (MD 0.77, 95%CI [0.02, 1.51]) (I² = 86%) (p=0.04) (340, 437, 461) (I²>50%, so random effects applied) (Figure 7.30).
Figure 7. 30 Comparison of CHM CHM group versus control groups in patients with stable COPD: PaO2 (KPa) at the end of treatment as the outcome

### 7.7.5.2 PaCO2

A meta-analysis indicated a significant decrease in the level of PaCO2 in three studies with 237 participants that compared CHM with other CHM (MD -0.34, 95%CI [-0.64, -0.04]) with consistent heterogeneity ($I^2 = 0\%$) ($p=0.02$) (340, 437, 461). In addition, a significant decrease in the level of PaCO2 was found at completion of treatment when CHM was compared with no treatment in one study with 104 participants (MD -1.59, 95%CI [-1.95, -1.23]) (367).

In contrast, meta-analysis showed no significant decrease in the level of PaCO2 in four studies with 251 participants that compared CHM plus RP to RP (MD -0.26, 95%CI [-0.59, 0.06]) (312, 446, 453, 457).

In addition, no change in the level of PaCO2 was found in one study on 60 participants which compared CHM to placebo in one study on 60 participants (MD -0.03, 95%CI [-0.63, 0.03]) (349), and CHM to RP in one study on 54 participants (MD -0.05, 95%CI [-0.41, 0.31]) (459).
Figure 7.31. Comparison of CHM group versus control groups in patients with stable COPD: PaCO2 (KPa) at the end of treatment as the outcome.

7.7.6 Effect of CHM on biomarkers

COPD is a complex disease with multiple pathogeneses. Airway inflammation plays an imperative role in pathogenesis of COPD and the level of inflammatory cells are associated with the phenotype of COPD, which needs descriptive measures through levels of biochemical biomarkers to provide a more comprehensive and clinically accurate assessment of COPD (464).

In this section, the results of biomarker measurements are analyzed for inflammatory chemokines and cytokines in sputum or in serum, T lymphocyte subsets and the level of immunoglobulins in serum as well as other measurements.

Inflammatory chemokines and cytokines and T lymphocyte subsets and immune globulin
were tested and reported in twenty three studies on 1,431 participants with four withdrawals during the treatment period. Although four studies with 254 participants reported the use of tests of IL-8, IL-1, IL-6, TNF-α, TGF-β (transforming growth factor) and/or C-reactive protein (CRP), the original data were not provided by the authors so it could not be analyzed by RevMan 5.1 (369, 398, 411, 463).

7.7.6.1 Measurements of IL-8 and TNF-α and IL-2

Inflammatory chemokines and cytokines including IL-8, IL-2 or TNF-α were tested in ten studies with 531 participants. The IL-8 and TNF-α levels were tested by sputum or serum examination. The level of IL-8 in sputum was reported in four studies with 158 participants. The level of IL-8 in serum was tested by two studies with 98 participants. The level of TNF-α was measured in three studies by sputum on 167 participants and in another three studies by serum on 146 participants. The level of IL-2 only was tested by serum in two studies with 175 participants.

Level of IL-8 in sputum

The level of the chemokine IL-8 in sputum was measured in four studies with 158 participants. A significant decrease of the level of IL-8 in sputum was found when comparing CHM with placebo in one study with 36 participants (MD -0.94, 95%CI [-1.70, -0.18]) (435), and CHM plus RP compared with RP in two studies with 86 participants (MD -2.43, 95%CI [-3.52, -1.34]) with low heterogeneity (Chi² = 0.03, df = 1 (P =0.85); I² = 0%) (405, 436). However, no significant change in the level of IL-8 in sputum was found in one study with 36 participants that compared CHM to no treatment (MD -1.18, 95%CI [-2.99, 0.62]) (346) (Figure 7.32).
Figure 7.32 Comparison of CHM group versus control groups in patients with stable COPD: IL-8 in sputum at the end of treatment as the outcome

**Level of IL-8 in serum**

There was a significant decrease in the mean level of serum IL-8 in the following two studies. When CHM was compared with RP in one study that included 60 participants (MD -10.35, 95%CI [-12.76, -7.94]) (80) and when an experimental CHM was compared to other CHM in one study that included 38 participants (MD -0.23, 95%CI [-0.32, -0.15]) (433) (Figure 7.33).

Enzyme-linked immunosorbent assay (ELISA) was applied in Xiong (2008) using ng/L as the unit of measurement. However, pg/ml was used as the unit of measurement in Sun (2007-a) with no description of the assay that was used to measure IL-8. Therefore the units of measurement were not the same in these two studies.
Comparison of CHM group versus control groups in patients with stable COPD: IL-8 in serum at the end of treatment as the outcome

There were three studies with 146 participants that found significant decreases in the level of TNF-α in sputum when comparing CHM plus RP with RP (MD -0.58, 95%CI [-0.68, -0.49]) with low heterogeneity (Chi² = 1.08, df = 2 (P =0.58); I² = 0%) (p<0.00001) (405, 425, 436) (Figure 7.34).

Comparison of CHM plus RP versus RP in patients with stable COPD: the level of TNF-α in sputum at the end of treatment as the outcome

There was a significant decrease in the level of serum TNF-α when CHM was compared to placebo in one study with 40 participants (MD -10.22, 95%CI [-18.60, -1.84]) (449); CHM compared to RP in one study with 60 participants (MD -7.96, 95%CI [-10.36, -5.56]) (80) and CHM plus RP compared to RP in one study with 67 participants (MD -4.56, 95%CI [-6.27, -2.85]) (447) (Figure 7.35).
Figure 7.35 Comparison of CHM group versus control groups in patients with stable COPD: TNF-α in serum at the end of treatment as the outcome

Level of serum IL-2

A significant increase in the mean level of serum IL-2 was found when CHM plus RP was compared with RP in one study with 67 participants (MD 21.40, 95%CI [15.60, 27.20]) (447), whereas no significant change was observed between CHM and RP in one study with 108 participants (MD 0.03, 95%CI [-0.01, 0.07]) (455)(Figure 7.36).

Figure 7.36 Comparison of CHM group versus control groups in patients with stable COPD: IL-2 in serum at the end of treatment as the outcome
7.7.6.2 Measurements of T lymphocyte subsets

Serum T lymphocyte subgroups were measured in eight studies with 323 participants in the treatment groups and 282 participants in the control groups.

Level of serum CD4

A meta-analysis found a significant increase in the level of CD4 when CHM plus RP was compared with RP in three studies with 239 participants (MD 6.23, 95%CI [3.44, 9.01]) with severe heterogeneity (Chi² = 11.04, df = 2 (P =0.004); I² = 82%) (p<0.0001) (372, 450, 455) and CHM compared to no treatment in two studies with 122 participants (MD 5.49, 95%CI [3.80, 7.18]) with low heterogeneity (Chi² = 0.19, df = 1 (P =0.66); I² = 0%) (p<0.0001) (383, 424).

In addition, a significant increase in the level of CD4 was found when CHM was compared to placebo in one study with 62 participants (MD 6.00, 95%CI [5.01, 6.99]) (69) and CHM compared to RP in one study with 80 participants (MD 8.67, 95%CI [6.37, 10.97]) (444).

However, no difference in the level of CD4 between experimental CHM and other CHM was observed in one study with 102 participants (MD 0.90, 95%CI [-1.13, 2.93]) (343) (Figure 7.37).
### Figure 7.37 Comparison of CHM group versus control groups in patients with stable COPD: CD4 in serum at the end of treatment as the outcome

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Test for subgroups: Chi² = 26.22, df = 4 (P < 0.0001), P = 65.9%
Level of serum CD8

There was significant decrease in the level of CD8 when CHM was compared to placebo in one study with 62 participants (MD -1.99, 95%CI [-2.66, -1.32]) (69).

However, no significant change in the level of CD8 was found when CHM was compared to RP in one study with 80 participants (MD -0.98, 95%CI [-2.27, 0.31]) (444); or CHM plus RP was compared to RP in three studies with 239 participants (MD -6.06, 95%CI [-20.33, 8.22]) (372, 450, 455); or CHM was compared to other CHM in one study with 102 participants (MD 2.51, 95%CI [0.40, 4.62]) (343); or CHM was compared to no treatment in two studies with 122 participants (MD -0.60, 95%CI [-2.20, 1.00]) (383, 424) (Figure 7.38).

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<td>54</td>
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<td>5.01</td>
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<td>24.02</td>
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<td>100.0%</td>
<td>2.51 [0.40, 4.62]</td>
<td>2.51 [0.40, 4.62]</td>
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<td>7.38.5 CHM Vs No treatment</td>
<td>Lin 2008</td>
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<td>5.62</td>
<td>31</td>
<td>26.11</td>
<td>6.08</td>
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<td>28.2%</td>
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<td>3.57</td>
<td>30</td>
<td>29.01</td>
<td>3.77</td>
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<td>100.0%</td>
<td>-0.60 [-2.20, 1.00]</td>
<td>-0.60 [-2.20, 1.00]</td>
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<td>Heterogeneity: Tau² = 8.00; Chi² = 20.0, df = 6 (P = 0.001); P = 6%</td>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
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Test for subarous differences; CHI² = 17.98, df = 4 (P = 0.001), P = 77.7%
Level of serum CD3

A meta-analysis indicated a significant increase in the level of CD3 when CHM plus RP was compared to RP in three studies with 239 participants (MD 5.88, 95%CI [2.99, 8.78]) with severe heterogeneity (Chi² = 10.28, df = 2 (P = 0.005); I² = 81%) (p<0.0001) (372, 450, 455).

In addition, a significant increase of the level of CD3 was found when CHM was compared with placebo in one study with 62 participants (MD 6.87, 95%CI [5.63, 8.11]) (69) and CHM compared with RP in one study with 80 participants (MD 5.17, 95%CI [3.07, 7.27]) (444).

However, no difference was found between experimental CHM and other CHM in one study with 102 participants (MD -0.34, 95%CI [-3.13, 2.45]) (343) and between CHM and no treatment control group in two studies with 122 participants (MD 1.75, 95%CI [-4.22, 7.91]) (383, 424) (Figure 7.39).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
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<td></td>
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<td>Mean SD Total</td>
<td>IV Random 95% CI</td>
<td>IV Random 95% CI</td>
</tr>
<tr>
<td>7.39.1 CHM Vs Placebo</td>
<td>Li (1) 2006</td>
<td>59.00 2.56 31</td>
<td>53.01 2.41 31</td>
<td>6.97 [6.6, 7.11]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>31</td>
<td>31</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 19.88 (P = 0.0001)</td>
</tr>
<tr>
<td>7.39.2 CHM Vs Pharmacotherapy</td>
<td>Chen (2) 2007</td>
<td>60.7 4.48 40</td>
<td>55.6 5.09 40</td>
<td>6.17 [3.07, 7.27]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>40</td>
<td>40</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 4.83 (P = 0.0001)</td>
</tr>
<tr>
<td>7.39.3 CHM Vs Placebo</td>
<td>Lin (1) 2005</td>
<td>56.7 4.59 32</td>
<td>54.5 5.95 32</td>
<td>2.21%</td>
</tr>
<tr>
<td></td>
<td>Xia 2000</td>
<td>55.6 4.66 54</td>
<td>53.8 8.08 54</td>
<td>27.4%</td>
</tr>
<tr>
<td></td>
<td>Xu 2005</td>
<td>59.00 2.56 33</td>
<td>53.01 2.41 33</td>
<td>30.5%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>119</td>
<td>120</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 5.16, Chi² = 10.48, df = 2 (P = 0.005); P = 81%</td>
<td></td>
<td>Test for overall effect: Z = 3.98 (P = 0.0001)</td>
<td></td>
</tr>
<tr>
<td>7.39.4 CHM Vs Other CHM</td>
<td>Xu 1996</td>
<td>52.5 5.78 72</td>
<td>53.8 6.84 72</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
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<td>72</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.24 (P = 0.81)</td>
</tr>
<tr>
<td>7.39.5 CHM Vs No treatment</td>
<td>Lin 2008</td>
<td>55.0 7.21 31</td>
<td>57.31 6.71 31</td>
<td>49.5%</td>
</tr>
<tr>
<td></td>
<td>Tang 2008</td>
<td>74.0 5.96 30</td>
<td>70.13 4.85 30</td>
<td>51.5%</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>61</td>
<td>61</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 7.25, Chi² = 7.74, df = 1 (P = 0.006); P = 87%</td>
<td></td>
<td>Test for overall effect: Z = 0.56 (P = 0.57)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 7.39 Comparison of CHM group versus control groups in patients with stable COPD: CD3 in serum at the end of treatment as the outcome.
Level of the ratio of serum CD4/CD8

A meta-analysis indicated a significant increase in the ratio of CD4/CD8 when CHM plus RP was compared to RP in two studies with 131 participants (MD 0.55, 95%CI [0.19, 0.91]) with severe heterogeneity (Chi² = 5.08, df = 1 (P =0.02); I² = 80%) (p=0.003) (372, 450); and CHM was compared to a no treatment control group in two studies with 122 participants (MD 0.20, 95%CI [0.08, 0.32]) with severe heterogeneity (Chi² = 3.49, df = 1 (P = 0.06); I² = 71%) (p = 0.0007) (383, 424).

In addition, a significant increase in the ratio of CD4/CD8 was also found when comparing CHM with placebo in one study with 62 participants (MD 0.36, 95%CI [0.11, 0.61]) (69); and when CHM was compared to RP in one study with 80 participants (MD 0.33, 95%CI [0.15, 0.51]) (444).

However, no significant change in the ratio of CD4/CD8 between experimental CHM and other CHM was observed in one study with 102 participants (MD -0.38, 95%CI [-0.56, -0.20]) (343) (Figure 7.40).

![Figure 7.40 Comparison of CHM group versus control groups in patients with stable COPD: CD4/CD8 in serum at the end of treatment as the outcome](image-url)
7.7.6.3 Measurements of immune globulins

Immune globulins include immune globulin A (IgA), immune globulin G (IgG) and immune globulin M (IgM), which were measured and reported in nine studies with 600 participants.

Level of serum IgA

A meta-analysis showed a significant increase of the level of IgA when CHM was compared to RP in two studies with 145 participants (MD 0.44, 95%CI [0.21, 0.66]) with low heterogeneity ($\chi^2 = 1.17$, df = 1 (P =0.28); $I^2 = 15\%$) (p=0.0001) (432, 444); and CHM plus RP was compared with RP in three studies with 191 participants (MD 0.44, 95%CI [0.27, 0.62]) with low heterogeneity (Chi$^2 = 3.20$, df = 2 (P =0.20); $I^2 = 38\%$) (p<0.00001) (372, 410, 450).

In addition, there was a significant increase in the level of IgA found when comparing CHM with placebo in one study with 62 participants (MD 0.54, 95%CI [0.27, 0.81]) (69).

However, no difference was observed between experimental CHM and other CHM in two studies with 140 participants (MD -0.11, 95%CI [-0.62, 0.39]) (343, 433); or for CHM compared with no treatment group in one study with 62 participants (MD -0.60, 95%CI [-1.21, 0.01]) (424) (Figure 7.41).
Level of serum IgM

There was no significant difference in the level of IgM when CHM was compared to placebo in one study with 62 participants (MD 0.09, 95%CI [-0.24, 0.42]) (69); or when CHM was compared to RP in two studies with 145 participants (MD 0.10, 95%CI [-0.68, 0.87]) (432, 444); or when CHM plus RP as compared with RP in three studies with 191 participants (MD 0.27, 95%CI [-0.20, 0.74]) (372, 410, 450); or when experimental CHM was compared to other CHM in two studies on 140 participants (MD 0.06, 95%CI [-0.02, 0.14]) (343, 433); or when CHM was compared to no treatment control group in one study on 62 participants (MD 0.01, 95%CI [-0.47, 0.49]) (424) (Figure 7.42).
Figure 7. 42 Comparison of CHM group versus control groups in patients with stable COPD: IgM in serum at the end of treatment as the outcome

Level of serum IgG

A meta-analysis found a significant increase of the level of IgG when CHM was compared to RP in two studies with 145 participants (MD 1.80, 95%CI [0.87, 2.73]) with low heterogeneity (Chi² = 0.03, df = 1 (P =0.86); I² = 0%) (p=0.0002) (432, 444); and CHM plus RP was compared to RP in three studies with 191 participants (MD 2.42, 95%CI [1.65, 3.18]) with low heterogeneity (Chi² = 3.15, df = 2 (P =0.21); I² = 38%) (p <0.00001) (372, 410, 450).

In addition, there was a significant increase in the level of IgG found when CHM was compared to placebo in one study with 62 participants (MD 2.32, 95%CI [1.13, 3.51]) (69).

However, there was no different change in the level of IgG between experimental CHM and other CHM in two studies with 140 participants (MD 0.03, 95%CI [-0.73, 0.79]) (343, 433).

On the other hand, a contrary result was found for CHM compared to no treatment control
group in one study with 62 participants (MD -3.19, 95%CI [-4.68, -1.70]) (424) (Figure 7.43).

![Figure 7.43 Comparison of CHM group versus control groups in patients with stable COPD: IgG in serum at the end of treatment as the outcome](image)

### 7.7.6.4 Measures of level of nutrition

The nutrition parameters consist of the level of serum ALB measured in four studies and Pre ALB (PALB) in five studies and Leptin in two studies. One study did not provide original data for PALB, so it could not be analyzed by meta-analysis (463).

**Level of serum albumin**

Serum ALB was tested in four studies with 219 participants. A significant increase in the level of serum ALB was found by one study with 60 participants when CHM was compared to placebo (MD 2.04, 95%CI [0.92, 3.16]) (454). However, no difference was found when CHM was compared to RP in one study with 45 participants (MD 1.00, 95%CI [-2.52, 4.52]) (440), and CHM plus RP was compared to RP groups in two studies on 134 participants (MD 0.65, 95%CI [-0.40, 1.71]) (410, 417) (Figure 7.44).
Figure 7.44 Comparison of CHM group versus control groups in patients with stable COPD: serum ALB at the end of treatment as the outcome

Level of serum Prealbumin

Serum PALB was tested in four studies with 230 participants. A significant increase in the level of serum PALB was found when CHM was compared to placebo in one study that included 60 participants (MD 14.90, 95%CI [8.97, 20.83]) (454), and CHM plus RP was compared to RP in 2 studies with 125 participants (MD 52.78, 95%CI [49.20, 56.36]) (398, 417), whereas no difference was found when CHM was compared to RP in one study with 114 participants (MD 20.00, 95%CI [-27.61, 67.61]) (440) (Figure 7.45).
A significant increase in the level of serum Leptin was found by one study with 60 participants when CHM was compared to placebo (MD 1.12, 95%CI [0.83, 1.41]) (454). However, no difference was found when CHM plus RP was compared to RP in one study with 54 participants (MD -0.19, 95%CI [-0.93, 0.55]) (417) (Figure 7.46).
7.7.6.5 Measurement of superoxidase dismutase and lipid peroxide

The level of serum superoxidase dismutase (SOD) and Lipid peroxide, which are the major relevant factors for maintaining the balance of oxidants and antioxidants, were reported by one study with 60 participants.

**Level of superoxidase dismutase**

A significant increase in the level of serum SOD was found by one study when CHM was compared to placebo with 60 participants (MD 20.31 95%CI [7.09, 33.53] (73) (Figure 7.47).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Weight</th>
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<td>7.47 CHM Vs Placebo</td>
<td>169.5</td>
<td>31.18</td>
<td>30</td>
<td>149.19</td>
<td>19.67</td>
<td>30</td>
<td>20.31</td>
<td>[7.09, 33.53]</td>
<td>70</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>160.0%</td>
<td>20.31</td>
<td>[7.09, 33.53]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.01 (# = 0.002)

**Figure 7. 47 Comparison of CHM versus placebo in patients with stable COPD: plasma SOD at the end of treatment as the outcome**

**Level of lipid peroxide**

A significant reduction in the level of serum LPO was found in one study when CHM was compared to placebo with 60 participants (MD -0.68 95%CI [-1.12, -0.24] (73) (Figure 7.48).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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</tr>
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<tbody>
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<td>7.48 CHM Vs Placebo</td>
<td>14.64</td>
<td>0.39</td>
<td>30</td>
<td>15.32</td>
<td>1.17</td>
<td>30</td>
<td>-0.68</td>
<td>[1.12, -0.24]</td>
<td>70</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>100.0%</td>
<td>-0.68</td>
<td>[1.12, -0.24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.03 (# = 0.002)

**Figure 7. 48 Comparison of CHM versus placebo in patients with stable COPD: plasma LPO at the end of treatment as the outcome**
7.7.6.7 Measurement of blood rheology parameters

Measurements of blood rheology, specifically plasma viscosity and hematocrit, were reported by three studies with 239 participants.

Level of plasma viscosity shear rate

A significant reduction of the level of plasma viscosity, measured as shear rate, was found when CHM plus RP was compared to RP with 59 participants (MD -0.60 95%CI [-0.81, -0.39] (384); and CHM was compared to no treatment in one study with 120 participants (MD -0.65 95%CI [-0.72, -0.58] (400). Whereas no difference was found when experimental CHM was compared to other CHM in one study with 60 participants (MD -0.06 95%CI [-0.14, 0.02] (441) (Figure 7.49).

![Comparison of CHM group versus control groups in patients with stable COPD: plasma viscosity at the end of treatment as the outcome](image)

Test for overall effect: Z = 5.72 (P < 0.00001)

Test for overall effect: Z = 1.65 (P = 0.10)

Test for overall effect: Z = 17.32 (P < 0.00001)

Test for subgroups differences: Chi² = 124.13, df = 2 (P < 0.00001), F = 98.4%
Level of plasma hematocrit

A significant reduction in the level of plasma hematocrit was demonstrated when CHM plus RP was compared to RP in one study with 59 participants (MD -15.00 95%CI [-20.88, -9.12] (384), and when CHM was compared to no treatment in one study with 120 participants (MD -5.87 95%CI [-7.41, -4.33] (400). Whereas, no difference was found in one study with 60 participants when experimental CHM was compared to other CHM (MD -1.13 95%CI [-5.00, 2.74] (441) (Figure 7.50).

Figure 7.50 Comparison of CHM group versus control groups in patients with stable COPD: plasma hematocrit at the end of treatment as the outcome

7.7.7 Adverse event recording

Among the 101 included studies (see Table from 4.7 to 4.12), 17 studies reported that no adverse events were observed during the treatment period (73, 79, 312, 340, 346, 375, 376, 380, 412, 424, 426, 428, 432, 435, 440, 452, 461); 4 studies reported minor adverse events were observed during the treatment period (347, 365, 405, 420); and adverse events were not mentioned in 80 studies.

In some of the studies, liver and kidney function as a measure of the safety of the CHM were tested using blood taken before and after treatment. There was no change between pre and post treatment which meant the CHM treatment had no adverse effect on liver and kidney function of patients in these six studies (375, 376, 380, 432, 440, 461). However, protocols that included observation of adverse events and blood tests involving liver and kidney function
function were set up in two studies but no results were reported (403, 404).

Minor adverse events were reported by 4 studies. In one study, five subjects had abdominal bloating during the treatment period but it was not mentioned which group they belonged to (405). Two participants who were in the treatment group had mild stomach symptoms, and then changed intake of the CHM to after meals and the symptoms disappeared (420). Five patients had mild stomach symptoms such as nausea, vomiting and diarrhea. One of them took ‘Live Bacillus Licheniformis preparation’ for two days and the symptoms disappeared. The others did not take any medications and recovered (365). Minor adverse events were recorded in Huang 2005 (347) and the details have been described in the Ginseng formulae section (SR1).

No severe adverse event was reported among the 101 studies. The participants who dropped out from the studies did not attribute their dropping out to adverse events of CHM.

7.8 Results of herbs and formulae from all clinical trials for stable COPD

7.8.1 Types of herbs

A total of 139 different herbs were used in this review. All of the herbs in the included studies were included under fourteen types according to the categories of Materia Medica as listed in Appendix 19.

Among these types of herbs, the most commonly used herbs belong to tonifying herbs.

7.8.2 Frequency of use of herbs in all 101 included studies

141 different herbs were used in these studies. The orders of frequency of use of herbs were ranked as following from high to low:

The 4 most commonly used herbs were each used in excess of 40 times as follows: Huang qi in 55 studies, Bai zhu in 54 studies and Fu ling in 45 studies and Dang shen in 40 studies (including repeats due to multiple formulae being used in the studies by Fang, 2008 and Shi, 2009).

4 herbs were used more than 30 times: Gan cao in 34 studies, Wu wei zi in 34 studies (including repeats due to multiple formulae being used in the studies by Fang, 2008 and Shi,
and Chen pi in 32 studies as well as Di huang in 30 studies (including Gan di huang, Sheng di huang and Shu di huang).

There are 6 herbs that were used in the range of 20 to 30 times: Ban xia in 25 studies (including Fa ban xia and Zhi ban xie); Dan shen and Mai dong in 24 studies each; Ge jie in 23 studies, Dang gui in 21 studies, and Ren shen (ginseng) in 20 studies (including Hong shen 3, Sheng shai shen 1, Gao li shen 1 and Xi yang shen 3).

There are five herbs for resolving phlegm and suppressing cough and two herbs for activating blood; the remaining herbs are for tonifying lung and kidney, and fortifying spleen.

The 18 herbs that were used from 10 to 20 times in individual studies were: Shan yao (19), Shan zhu yu (Shan yu rou) (19), Xing ren (17), Su zi (15) Kuan dong hua (14), Bei mu (14) (including Zhe bei mu and Chuan bei mu), Bu gu zhi, (13), Di long (13), Sang bai pi (13), Tao ren (13), Fang feng (12), Jie geng (12), Dong chong xia cao (11), Sha shen (11), Zi wan (11), Yin yang huo (Xian ling pi) (10), Tu si zi (10) and Zi he che (10) (see Table 7.1).

| Table 7.1 The top twenty herbs most frequently used in the 101 RCTs |
|---|---|
| 1 | Huang qi (Zhi) | 55 |
| 2 | Bai zhu | 54 |
| 3 | Fu ling | 45 |
| 4 | Dang shen | 40 |
| 5 | Wu wei zi | 34 |
| 6 | Gan cao (Zhi) | 34 |
| 7 | Chen pi | 32 |
| 8 | Di huang (Shu) | 30 |
| 9 | Ban xia | 25 |
| 10 | Mai men dong | 24 |
| 11 | Dan shen | 24 |
| 12 | Ge jie | 23 |
| 13 | Dang gui | 21 |
| 14 | Ren shen | 20 |
| 15 | Shan yao (Sheng) | 19 |
| 16 | Shan zhu yu | 19 |
| 17 | Xing ren (Bei) | 17 |
| 18 | Su zi (Zi) | 15 |
| 19 | Beimu | 14 |
| 20 | Kuandonghua | 14 |
Five herbs were used in 7 to 9 studies: Rou gui was used in 9 studies, Fu zi was used in eight studies (including Zhi fu zi and Shu fu zi); Bai jie zi, Chen xiang and Shui zhi were each used in seven studies.

5 herbs were used in six studies: Chai hu, Chuan xiong, Dan pi, Dong chong xia cao jun si, and Ma huang.

There are 8 herbs that were used in five studies: Bai bu, Gua lou, Gui zhi, Lu jiao jiao, Niu xi, Nu zhen zi and Sheng ma, and Tai zi shen.

In the 101 studies 79 herbs were used fewer than 5 times: Gou ji, Hong hua, Hou po, Huang qin, Hu tao ren, Lai fu zi, San qi, Yu zhu, Ze xie, Zhi qiao and Zi shi ying (4 times; Bai shao, Bai guo (Yin xing ye), Chi shao, E zhu, Gan jiang, Gui zhi, He tao rou, Huang jing, Ju hong, Kan qi, Qian hu, Xuan shen, Yi yi ren and Zhi mu (3 times); Bai ji tian, Chan tui, Da zao, Du zhong, Gua lou pi, Han lian cao, Jiao gu lan, Jin yin hua, Ling zhi, Mao dong qing, Pi ba ye, Quan xie (Quanchong), Rou cong rong (Yucongrong), Shi chang pu, Tian hua fen, Ting li zi, Wu zha long, Xuan fu hua (Jin fei cao), Yang fei, Yu xing cao, and Zhu ru (2 times);

There were 33 herbs that were applied only once in different formulae: Bai he, Ban lang en, Cang zhu, Che qian zi, Chuan shan long, Ci wu jia, E jiao, Fu pen zi, Gui ban jiao, Hai ge qiao, Hong jing tian, Ji nei jin, Jin qiao mai gen, Jin ying zi, Lian qiao, Ling ci shi, Bo he, Qing tian kui, Qi ye yi zhi hua, Sang shen, Shan yin hua, She gan, Sheng jiang, Shi gao, Tu bie chong, Wei jin, Wu gong, Xiang fu, Xian mao, Xi xin, Yi mu cao, Yi zhi ren and Yu jin.

In the sensitivity analysis conducted for the 59 studies with durations of three months or more, the five most commonly used herbs were Huang qi (33), Bai zhu (30), Dang shen (27), Fu ling (27), and Wu wei zi (26). This is the same set of herbs as for the 101 studies in total. Therefore, these herbs were not only frequently used in the studies as a whole, but also in the subset of studies most relevant to the treatment of stable COPD over a longer term.

A comparison of the most frequently used herbs in classical datasets and the herbs most commonly used in the RCTs can be found in Chapter 8.

7.8.3 Frequency of use of particular formulae

CHM formulae were used in the form of pills, capsules, granules, syrups or decoctions in the included studies. The individual formulae comprised from 1 to 27 different herbs. Extracts of
the single herbs Ren shen, Bai guo, Bai bu and Dong chong xia cao were applied in one study each (79, 380, 383, 415, 435). The most complex formulae was in Ji (2010) with 27 different herbs in the test formula (431).

7.8.3.1 Liu Jun Zi Tang

The most commonly used formulae was Liu Jun Zi Tang, with or without modification, which was used in 7 studies (73, 365, 408, 417, 419, 421, 440). The ingredients of each formula are shown in Appendices 14 to 17. In these 7 studies:

- CHM was compared to placebo in one study (Zhuan, 2006) with 60 participants with biomarkers as the outcome measure (73).
- CHM was compared to RP in two studies with 107 participants (421, 440); relief of symptoms was reported in Wu (2006); lung function and BMI as well as ALB were measured in Wu (2009).
- CHM plus RP was compared to RP in two study with 176 participants; relief of symptoms, BMI as well as ALB were measured in Chen (2) (2009); relief of symptoms was measured in Peng (2010).
- CHM was compared to no treatment in two studies with 204 participants; lung function, 6 MWD test and BODE index were measured in Zhang (2008), lung function and QoLQ were measured in Wu (2007).

Therefore, two pairs of Liu Jun Zi Tang studies were comparable but the lung function measures were different in Zhang 2008 and Wu 2007. For relief of symptoms both the Liu Jun Zi Tang studies show a small benefit for Liu Jun Zi Tang plus RP compared to RP alone (Figure 7.51).

Figure 7. 51 Comparison of CHM (Liu Jun Zi Tang) plus RP versus RP in patients with stable COPD: effective rate at the end of treatment as the outcome
7.8.3.2 Bu Fei Tang

Modified Bu Fei Tang was used in 3 studies (375, 437, 447). The ingredients of each formula are shown in Appendices 14, 16 and 18.

- CHM was compared to placebo in one study with 60 participants (Sun, 2009); lung function, QoLQ, and relief of symptoms were measured.
- CHM plus RP was compared to RP in one study (Hu, 2009) with 67 participants; lung function, biomarkers and relief of symptoms were measured.
- Experimental CHM was compared to other CHM in one study with 60 participants (Huang 2009); lung function and blood gas measurement were tested.

Lung function (FEV$_1\%$) was an outcome in three studies (see Figure 7.3) but since the comparators were different no pooling was possible.

7.8.3.3 Shen Ge Tang

Original or modified Shen Ge Tang was used in five studies (80, 342, 344, 422, 427); and both Bu Fei Tang and Shen Ge Tang were applied together in one study (373). The ingredients of each formula are shown in Appendices 14-16 and 18.

- CHM was compared to placebo in one study with 200 participants (Wu, 2006); lung function was an outcome measure.
- CHM was compared to RP in one study with 60 participants (Xiong, 2008); lung function, biomarkers and relief of symptoms were measured.
- CHM plus RP was compared to RP in three studies with 140 participants; lung function was tested in Chen (2004); lung function and relief of symptoms were measured in Pu (2010); lung function, QoLQ and relief of symptoms were measured in Mai (2009).
- Experimental CHM was compared to other CHM in Sun (2007a) with 45 participants; lung function, QoLQ, 6 MWD test and relief of symptoms were measured.

Significant improvement in FEV$_1\%$ predicted was reported in these five studies (see Figure 7.3); relief of symptoms including percentage of effectiveness and reduction of the total scores and the scores of each symptom (cough, dyspnea and sputum production) was found to be significantly improved in each study.
The most comparable studies were Chen (2004), Mai (2009) and Pu (2010) which found significant improvement in lung function in favour of CHM plus RP compared to RP (Figure 7.52). However, relief of symptoms with percentage of effectiveness and reduction of the total scores were incomparable in these studies.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>7.52 CHM plus Pharmacotherapy vs Pharmacotherapy</td>
<td>Chen 2004</td>
<td>74</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Mai 2009</td>
<td>54.9</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Pu 2010</td>
<td>58.55</td>
<td>9.01</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100</td>
<td>110</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Test for sub-group differences: Not applicable

Figure 7.52 Comparison of CHM (Shen Ge Tang) plus RP versus RP in patients with stable COPD: FEV₁% at the end of treatment as the outcome

7.8.3.4 Bu Zhong Yi Qi Tang

Bu Zhong Yi Qi Tang was used in 3 studies (65, 398, 402). The ingredients of each formula are shown in Appendices 14 and 16.

- CHM was compared to RP in one study (Hu 2005) with 62 participants; lung function and exacerbation COPD were measured.
- CHM plus RP was compared to RP in two studies with 106 participants; biomarkers including CRP, TNF-α and IL-6 as well as PALB were tested in both studies (398, 463). QoLQ was measured in Tatsumi (2009).

Significant decreases for CRP, TNF-α and IL-6 were reported in the Bu Zhong Yi Qi Tang groups but these were unchanged in the control groups in both studies; PALB level increased in the Bu Zhong Yi Qi Tang groups but was unchanged in the control groups. However, data suitable for pooling was not provided.

7.8.3.5 Multi syndrome differentiation

Two studies used syndrome differentiation according to CHM principles to select the most appropriate of four CHM treatment interventions (379, 382). Both of these two studies used very similar designs and formula selection (see Appendix 16). Feng (2008) was conducted in Jizhou Hospital in Hebei; and Shi (2009) was conducted in Tianjing Chest Hospital. Cai’s
QoLQ was used in both studies which compared CHM to RP. Lung function, including FEV$_1$ (L), FEV$_1$/FVC% and FVC (L), was only reported in the Feng study (Figure 7.6, Figure 7.9 and Figure 7.11). Since both studies reported data for the subscores but not for the total, they were not included in the pooled data in section 2 of chapter (see Figure 6.9). These QoL are pooled in Figure 7.53. In both studies the CHMs produced a greater improvement in all HRQoL sub-scores compared with RP.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2006</td>
<td>2.2 ± 0.68</td>
<td>0.0</td>
<td>2.2 ± 0.68</td>
<td>0.0</td>
</tr>
<tr>
<td>Chi, 2005</td>
<td>2.1 ± 0.68</td>
<td>0.0</td>
<td>2.1 ± 0.68</td>
<td>0.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>150</td>
<td>150</td>
<td>100.0%</td>
<td>-0.42 [-0.55, -0.29]</td>
</tr>
<tr>
<td>Social activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2006</td>
<td>2.2 ± 0.59</td>
<td>0.0</td>
<td>2.2 ± 0.59</td>
<td>0.0</td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>2.1 ± 0.54</td>
<td>0.0</td>
<td>2.1 ± 0.54</td>
<td>0.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>150</td>
<td>150</td>
<td>100.0%</td>
<td>-0.52 [-0.66, -0.39]</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2006</td>
<td>2.1 ± 0.67</td>
<td>0.0</td>
<td>2.1 ± 0.67</td>
<td>0.0</td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>2.1 ± 0.67</td>
<td>0.0</td>
<td>2.1 ± 0.67</td>
<td>0.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>150</td>
<td>150</td>
<td>100.0%</td>
<td>-0.54 [-0.68, -0.40]</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2006</td>
<td>2.2 ± 0.58</td>
<td>0.0</td>
<td>2.2 ± 0.58</td>
<td>0.0</td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>2.1 ± 0.58</td>
<td>0.0</td>
<td>2.1 ± 0.58</td>
<td>0.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>150</td>
<td>150</td>
<td>100.0%</td>
<td>-0.69 [-1.29, -0.13]</td>
</tr>
</tbody>
</table>

Test for sub-group differences: \( \chi^2 = 8.00, \ df = 3, P = 0.01 \); \( P = 50.3% \)

Figure 7.53: Comparison of CHMs (based on syndrome differentiation) versus RP in patients with stable COPD: Subscores of Cai’s QoLQ at the end of treatment as the outcome

7.8.3.6 Formulae used in multiple clinical trials

Five formulae were used in multiple clinical trials at the same sites but at different times.

Li Jin granule

Li Jin granule was used in two studies which compared CHM to RP (423, 444) in Ruikang Hospital Affiliated to Guangxi University of Chinese medicine (CM) (see Appendix 15). Lung function and relief of symptoms with significant improvements were reported in Chen (2006), whereas biomarkers with significant effectiveness were reported in the later study (444). Therefore there was no opportunity for pooling data.
Fei Kang Granule

Fei Kang Granule was used in two studies which compared CHM plus RP to RP (368, 369) and in one study which compared CHM to no treatment (411) in Dongzhimen Hospital Affiliated to Beijing University of CM (see Appendices 16-17). QoLQ was reported in Feng (2005); biomarkers were reported in Su (2005); QoLQ and biomarkers were reported in Feng’s later study (2007). The author’s reported significant improvement in QoLQ in both studies (Feng 2005 & 2007) and significant effectiveness in biomarkers in Su (2005) and Feng (2007). However, the data were not suitable for meta-analysis.

Man Zhi Ke Chuan Ning liquid

Man Zhi Ke Chuan Ning liquid was applied in the study by Lin 2008 which compared CHM to no treatment and Xiao 2000 which compared CHM to RP in Zhanjiang Second Hospital of TCM in Guangdong (424, 455). Lung function, relief of symptoms and biomarkers were reported in both of studies. The authors reported significant improvement in lung function and relief of symptoms as well as improvement in immune function in both studies when CHM groups were compared to control groups. Due to the difference in study design these data could not be pooled.

Jian Pi Yi Fei Granule

Jian Pi Yi Fei Granule was investigated by Lin 2003, Xu 2008 and Xu 2009 (349, 450, 454) in Guangdong Provincial Hospital of CM. Comparison of CHM with placebo was used in Lin (2003) and Xu (2008); comparison of CHM plus RP with RP was used in Xu (2009). Lung function, relief of symptoms and blood gas analysis were reported in Lin; BMI and nutrition outcome were reported in Xu (2008); and biomarkers were reported in Xu (2009). The authors reported significant effects for each outcome when CHM was compared to control groups in these studies. Due to the differences in outcome measures, data could not be pooled.

Zhou Fei Tang

Modified versions of Zhou Fei Tang were investigated in two studies (363, 364) which compared CHM to no treatment in Guangdong University of CM (see Appendix 17) lung function, QoLQ and relief of symptoms were reported in both studies. The comparable studies were Fang (2008) and Liu (2005) which found significant improvement in QoLQ (Figure 7.54).
in favour of CHM compared to no treatment, whereas no difference in FEV$_1$% was found (Figure 7.55). The authors also reported significant relief of symptoms of cough, dyspnea and sputum production etc. However, these data could not be pooled.

Figure 7. 54 Comparison of CHM (Zhou Fei Tang) versus no treatment in patients with stable COPD: the total scores of Cai’s QoI at the end of treatment as the outcome

Test for subgroups: Not applicable

Figure 7. 55 Comparison of CHM (Zhou Fei Tang) versus no treatment in patients with stable COPD: FEV$_1$% at the end of treatment as the outcome
### 7.9 Results of funnel plots

An obvious asymmetry was found in the funnel plot of the data based on the outcome of effectiveness rate of symptoms when CHM was compared to placebo, RP and CHM plus RP was compared to RP, and CHM was compared to no treatment, and experimental CHM was compared to other CHM, which indicated potential publication bias or bias due to other sources (Figure 7.56).

![Funnel plot comparison of CHM with control groups based on outcome: effectiveness rate of symptoms](image)

**Figure 7.56** Funnel plot comparison of CHM with control groups based on outcome: effectiveness rate of symptoms

Also, an asymmetry was found in the funnel plot of the data based on the outcome of reduction of ECOPD rate when CHM was compared to placebo, RP and CHM plus RP was compared to RP, and CHM was compared to no treatment, and experimental CHM was compared to other CHM, which indicated potential publication bias or bias due to other sources (Figure 7.57).
7.10 Discussion

7.10.1 Summary of the main results

This systematic review and analyses of RCTs set out to investigate the effects of oral CHM formulae and single herb extracts on clinical endpoints in patients with stable COPD using direct comparisons from all available randomized controlled trials. One hundred and one parallel trials, involving 8,014 participants were identified. All of the included studies were conducted and published in China from 2000 to 2010 except one study that was conducted in Israel and two studies in Japan. About 20 of articles were also indexed in MEDLINE.

Meta-analysis demonstrated that oral CHM formulae or single herb extracts were more effective than control in:

- Increasing FEV₁ and FEV₁/FVC from baseline compared to placebo, no treatment, RP etc (see Figures 7.3, 7.6 & 7.9);
- Reducing exacerbations of COPD compared to placebo, RP, no treatment and other CHM (Figures 7.18 & 7.19) and reducing related hospitalizations compared to placebo, RP and
other CHM (Figure 7.20);

- Relief of symptoms compared to placebo, no treatment, RP etc (Figures 7.21-7.25).
- Each of these outcomes is discussed in detail below (section 7.10.2). The results for quality-of-life were discussed in SR2 (chapter 6).

### 7.10.2 Discussion of the effects of CHM formulae on main outcomes

The main results are discussed below beginning with lung function, followed by effect on exacerbations and symptoms.

#### 7.10.2.1 Discussion of the effects of CHM formulae on pulmonary function

Various pulmonary function tests were performed and reported in 70 studies with 5,574 participants, with 89 participants withdrawing from 11 studies.

**Discussion of FEV1 % predicted**

This review found changes in spirometric parameters that appeared clinically significant, particularly in FEV1. Overall this review found a significant increase in FEV1% based on pooling 3,332 participants and FEV1(L) with pooled data from 3,475 participants when CHM was compared to placebo, RP, or other CHM as well as when CHM plus RP was compared to RP.

Improvements in FEV1% predicted were most evident when CHM plus RP was compared to RP in the meta-analysis of 20 studies (Figure 7.3). Eight studies showed clearest benefit (344, 370, 386, 401, 404, 425, 427, 460). The same RP of Salmeterol xinafoate/Fluticasone propionate was used by Chen (2009-1), Liu (2010), Pu (2010) and Zhu (2010); Theophylline was used by Feng (2006), Liang (2005), Liu (2006-1), Luo (2002), Wang (2006); Theophylline plus Salbutamol Sulfate was used by Hu (2009), Liu (2007) and You (2008); Ipratropium bromide was used in the study by Jia (2007) and Wu (2009-2); Salbutamol Sulfate was used Wang (2005) and Zhou (2007) (see Figure 7.58). However, Chen (2004), Qiu (2009) and Yang (2010) did not specify which RP was used. So it is difficult to evaluate whether the benefit found by Chen was due to the efficacy of the CHM used or the inefficacy of the RP; in Liang (2009) the RP used was based on the participant’s COPD stage. Overall, the pooled data suggest that the most consistent evidence for a benefit of the addition of CHM is for the combination with RP except Theophylline plus Salbutamol Sulfate in Hu (2005) and Liu
The participants employed in those studies were at severe COPD stage, so participants’ FEV$_1$% was worse than those in other studies. Therefore, CHM plus Theophylline and Salbutamol for treatment of patients with severe COPD needs further evaluation.

Among these 20 studies, Huang qi (12 studies), Ren shen (4 studies) and/or Dang shen (9 studies), Bai zhu (9 studies), Di long (7 studies), Wu wei zi (6 studies), Fu ling (6 studies) and Ge jie (5 studies) were used most frequently in the formulae. Although the ingredients of each formula are different, herbs that tonify qi play a key role in these formulae.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean SD</th>
<th>Total Mean SD</th>
<th>Total Weight IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2010</td>
<td>40.11</td>
<td>7.26</td>
<td>30 47.62 7.19 30 38.0% 1.06 (0.56, 4.94)</td>
<td></td>
</tr>
<tr>
<td>Liu 2010</td>
<td>59.45</td>
<td>14.06</td>
<td>30 59.62 13.40 30 17.1% 1.04 (0.31, 17.53)</td>
<td></td>
</tr>
<tr>
<td>Fu 2013</td>
<td>50.36</td>
<td>6.01</td>
<td>30 50.64 5.50 30 27.3% 1.00 (0.25, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Zhu 2010</td>
<td>87.45</td>
<td>6.01</td>
<td>28 55.49 8.57 27 27.2% 0.02 (0.47, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>116</td>
<td>127</td>
<td>100.0% 6.47 (2.41, 10.53)</td>
<td></td>
</tr>
<tr>
<td>Overall effect</td>
<td>104</td>
<td>104</td>
<td>100.0% 6.61 (3.41, 10.61)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 7. 58 Comparison of CHM plus RP versus RP in patients with stable COPD: FEV$_1$% at the end of treatment as the outcome
Discussion of FVE$_1$ (L)

Improvements in FVE$_1$ (L) were most evident in the meta-analysis of 18 studies in which CHM plus RP was compared to RP (Figure 7.6). Nine studies showed the greatest benefit (386, 404, 405, 418, 427, 430, 431, 447, 460). Among 18 studies, Che (2005), Feng 2008, Huang 2005 and Mai (2009) did not specify which RP was used so it is difficult to evaluate whether the benefit found was due to the CHM used or other factors. The same RP of Salmeterol xinafoate/Fluticasone propionate was used by Liu, Pu and Zhu; and Theophylline was used by Hao (2008), Ji (2010), Liang (2005), Liu (2006-1), Luo (2002) and Wang (2006); with the addition of Salbutamol sulfate aerosol in the studies by Hu and Liu (2008); Ipratropium bromide was used by Zhang (2010) (see Figure 7.59 below). Expectorant was used by Zhao (2009). The results of the pooled data are comparable except for Zhang (2010).

Among the 18 studies (see Figure 7.6), Renshen or Dangshen plus Huang qi were used by Feng (2008), Hu (2009), Huang (2005) and Ji (2010) and in both the studies by Liu (2008 & 2010). Ren shen or Dang shen as a key herb were used by Liang and Pu. Huang qi or Ren shen was used in Zhu based on the Chinese medicine syndrome. Huang qi was used in Che (2005) and Zhao (2009). On the other hand, herbs that diffuse the lung to resolve phlegm were used in Liu (2006-1) and Wang (2006). Therefore, tonify lung qi therapy was the main strategy applied in these studies, except for Hao (2009), which used tonify and warm kidney.
Comparison of CHM plus RP versus RP in patients with stable COPD: FEV$_1$ (L) at the end of treatment as the outcome

When a sensitivity analysis was applied for FVE$_1$% predicted and FEV$_1$ (L) based on duration of therapy (short term Vs longer term), the overall result remained the same. This suggested that CHM therapy may have a longer term potential for improving the level of FEV$_1$ or prevention of decline in FEV$_1$.

**Discussion of FEV$_1$/FVC**

Also, the meta-analyses showed significant increases in the ratio of FEV$_1$/FVC in 2,635 participants when CHM was compared to placebo, compared to RP, compared to no treatment, when experimental CHM was compared to other CHM, as well as when CHM plus RP was compared to RP (see Figure 7.9). Improvements in FEV$_1$/FVC were most evident in the meta-analysis of 20 studies in which CHM plus RP was compared to RP (Figure 7.9). The clearest benefit for improvement in FEV$_1$/FVC was demonstrated in seven studies (372, 373, 401, 404, 418, 427, 451). The same RP of Salmeterol xinafoate/Fluticasone propionate was used by Pu (2010) and Zhu (2010). Also, similar RP were evident in a number of studies with

Salbutamol was used in Wang (2005) and Zhou (2007). Ipratropium bromide was used in Jia (2007), Wu (2009-2) and Zhang (2010). However, Che (2005), Huang (2005), Feng (2008), Mai (2009), Qiu (2009) and Yang (2010) did not specify which RP was used. In Liang (2009) the RP used was based on the participant’s COPD stage, so the results of these studies are more difficult to evaluate.

Consequently, the two pairs of studies that were most comparable in terms of the RPs used were pooled (see Figure 7.60). The pooled data for Pu and Zhu are comparable with significant improvements in FEV$_1$ / FVC. Similar results were found for Theophylline and Theophylline plus Salbutamol. However due to high heterogeneity, the four studies are incomparable.

Among the twenty studies, the therapeutic approach of tonify lung qi was applied in most studies, with Ren shen, Dang shen and Huang qi being the key herbs in these formulae. Huang qi (12), Dang shen (5) or Ren shen (5), Bai zhu (8), Fu ling (7), Wu wei zi (6), Ge jie (5) and Di long (5) were used most frequently in the formulae. The therapeutic approach of diffuse the lung to suppress cough and calm panting was applied in one study which used Ma huang, Shi gao, Xing ren and Shan yin hua etc (Yang 2010).
Comparison of CHM plus RP versus RP in patients with stable COPD: FEV₁/FVC at the end of treatment as the outcome

Disscussion of other parameters of pulmonary function

Improvements in MVV were most evident when CHM plus RP was compared to RP in the meta-analysis of seven studies (344, 370, 412, 418, 453, 456, 457) (see Figure 7. 13).

The studies by Jia (2007), Li (2) 2006, Liu (2008) and Wu (2) 2009 showed the clearest benefit but only Jia and Wu used the same RP (Ipratropium Bromide). However, there were distinct similarities in the four CHMs. All aimed to strengthen ‘Lung qi’ with Huang qi being used in three (Liu, Li, Jia) with the addition of ginseng in Liu 2008, and with Wu (2) 2009 using Dangshen as the main herb. However the evidence for CHM plus RP compared to RP was mixed when MMEF was the outcome (Figure 7.12).

Of the three studies (Chen 2004, Lou 2002 and Wang 2006), only one (Chen 2004), which
used a ginseng-containing formula that aimed to tonify lung qi, showed a clear benefit for the addition of the CHM. In the other two studies the RP was theophylline but Chen (2004) did not specify which RP was used, so it is difficult to determine whether the benefit found by Chen was due to the efficacy of the CHM used or the inefficacy of the RP.

The outcomes, MIP and Raw were only reported in single studies so no comparisons were possible.

**Discussion of FEV\(_1\) and QoL**

FEV\(_1\) is the traditional metric used to define the progression of COPD as well as the strongest spirometric predictor of mortality in COPD patients (465). FEV\(_1\) as a primary spirometric test outcome is more usually used to assess respiratory function in clinical trials than other parameters (466). However, besides pulmonary functional abnormalities, COPD is also associated with significant systemic effects, so spirometry is not a unique outcome for the assessment of the severity and mortality of COPD. Therefore, the effects found in these studies may not be specific to COPD.

Moreover, Ries (2006) has pointed that reductions in objective pulmonary function measurements, such as FEV\(_1\), are not well-correlated with the patient's perception of symptoms and with HRQOL (467). Currently, health related QoL and BODE index are considered the main predictors for prognostic assessment in COPD (468). Therefore, any improvements in lung function found in these studies may not reflect discernible benefits on the part of the COPD sufferers. Nevertheless, as discussed in SR2, certain CHMs, appeared to also improve HRQoL.

In SR2, QoL and lung function were measured in 18 studies. Improvement of QoL was most evident when CHM plus RP was compared to RP in six studies that used SGRQ (312, 347, 366, 370, 376, 386) (Figure 6. 8). Huang (2005) and Tang (2010) did not specify the RP used, Jia (2007) used Ipratropium bromide, both Chen (2009-1) and Liu (2010) used Salmeterol xinafoate plus Fluticasone propionate, and You (2008) used Theophylline plus a \(\beta_2\) adrenergic receptor agonist.

The most comparable studies (Chen 2009-1 and Liu 2010) found the CHM plus RP to be superior to the RP alone in Liu (2010), but Chen (2009-1) found no benefit for the addition of the CHM. Positive results for both lung function (FEV\(_1\)) and QoL were found in Huang
(2005), Jia (2007) and Liu (2010). However, the further pooling data was not appropriate due to the different RP used, as discussed above (see section 7.5.2). Nevertheless, the CHMs used by Jia (2007) and Liu (2010) both aimed to tonify qi and move blood stagnation and were comparable in terms of their ingredients since both contained Huangqi, Dilong and Danshen.

7.10.2.2 Discussion of CHM formulae for reducing exacerbations of COPD

Frequent AECOPDs are associated with poor quality of life and more rapid decline in lung function, so for all clinical trials AECOPDs should be a key outcome measure for the evaluation of the clinical approach. The findings of this review indicated that CHM formulae were more effective in reducing exacerbation rate and frequency of exacerbations when CHM was compared to placebo, to RP, or to no treatment, and when CHM plus RP was compared with RP based on 21 studies on 1,619 participants. Due to the differences in duration and follow-up periods in the included trials, there was moderate heterogeneity, so a sensitivity analysis was performed and found no difference based on study duration.

Reduction of hospitalization days and cost were only reported in three studies with incomparable data due to different study designs. Also, the overall cumulative incidence of exacerbation-related hospitalizations and all-cause mortality were not measured in any of the included studies.

Of the various study designs, CHM plus RP compared with RP best reflects clinical practice and this design provided the best data for meta-analysis. Based on three studies (Ao 2007, Huang 2005, Luo 2002), the addition of the CHM reduced exacerbations from 50 to 30 incidents. The same RP (Theophylline) was used in both Ao (2007) and Luo (2002) so the pooled data are comparable, but the herbal therapeutics were different with different strategies, formulae and herbs. The formula Shao Yao San for smoothing liver and regulating qi (comprising Chai hu, Huang qin, Bai shao etc.) was applied in Ao while Tonify lung and spleen qi (using Dang shen, Huang qi, Mai dong etc.) was applied in Luo. Therefore the herbs used in these studies are incomparable. On the other hand, Huang (2005) used the strategy Tonify lung and spleen qi and used similar herbs to Luo (e.g Huang qi, mai dong) but did not specify which RP was used, so it is difficult to evaluate the effectiveness of the CHM in this study.

There was also a significant reduction on the mean number of exacerbations when data from six studies were pooled with the greatest decreases in the studies by Liang 2009 and Zhang
2010. In Liang (2009) the RP used was based on the participant’s COPD stage, whereas Zhang (2010) used Ipratropium bromide for all participants. However, similar herbs were used in the two studies, Dong chong xia cao plus Huang qi, Bai zhu and Fang feng were used in Liang 2009 and an extract of Dong chong xia cao was used in Zhang 2010, but due to the different kinds of bronchodilators used, the data were unsuitable for further pooling.

The number of days of hospitalization was found to have decreased in the study by You (2008) when CHM was combined with Salbutamol inhaler as the RP. You (2008) employed similar herbs to those used in other studies including Renshen, Fu ling and Bai zhu etc. However, only three studies in this review reported hospitalization days of patients due to acute onset of COPD, and You (2008) was the only study that included a comparison with RP. Therefore the question of whether CHM treatment may have an effect on reduction of hospitalization days that needs further investigation via more clinical studies.

The benefits observed with oral CHM formulae for exacerbations and related hospitalizations were not large but these aspects are clinically important. Acute exacerbations in COPD are increasing and these result in significant morbidity and mortality and drive significant health care costs due to increased physician visits and additional medications. Also, exacerbations are a leading cause of hospital admissions worldwide, with 35% of COPD patients having at least one admission a year and up to 40% of admitted patients having two or more readmissions a year (469-471). These acute hospital admissions contribute tremendously to the disease burden and account for the majority (52–84%) of the overall direct costs related to COPD (472). COPD exacerbation also leads to adverse impacts on quality of life and lung function and causes morbidity and mortality. So therapies that reduce their frequency or severity are a key aspect of any paradigm of COPD therapy.

7.10.2.3 Discussion of CHM formulae for relieving symptoms

Relieving symptoms was reported in 55 studies on 3,885 participants, with 24 withdrawals during the treatment period from four studies. It was assessed through symptom scores involving composites of symptoms or individual symptom scores for cough, dyspnoea and sputum. In addition, the degree of dyspnea was assessed by the Modified Medical Research Council Dyspnea Scale.

In this review, meta-analyses of the effective rate of symptom improvement, or reduction in the total symptom score, or the individual symptom score found that CHM formulae were
more effective in alleviating symptoms in patients with stable COPD when compared to any type of control group, regardless of whether short term or long term therapy was used.

**Discussion of Effective rate results for symptom improvement**

Positive results for the effective rate for symptom improvement were found when CHM was compared to placebo, no treatment and to RP, when CHM plus RP was compared to RP, and when experimental CHM was compared to other CHM in 3,114 participants.

In the meta-analysis of 22 studies that compared CHM plus RP to RP, which was the largest sub-group, a better effective rate for symptom improvement was found in 12 out of 22 studies (see Figure 7. 21). The RP used was not specified in Lang (2010), Mai (2007), Qiu (2009) and Tang (2010), and the use of RP was based on the patient’s COPD stage in Liang (2009). So these studies were unsuitable for further data pooling.

Theophylline was used in Ao (2007), Feng (2006), Hao (2008), Ji (2010) and Shan (2007), Theophylline plus β₂-adrenergic receptor agonist were used in Guo (2008), Hu (2009), Liu (2007), Tian (2005) and Wang (2009). Ipratropium bromide was used in Chen (2009-2) and Wu (2009-2), so the pooled data for these groups of studies were comparable.

The pooled data for the five studies that employed theophylline, found that the addition of the CHM improved the effective rate, especially in Shan (2007), Ao (2007) and Feng (2006). A similar result was found for the five studies that combined CHM with Theophylline plus β₂-adrenergic receptor agonist, especially the study by Wang (2009).

Theophylline plus Salmeterol xinafoate /Fluticasone were used in Peng (2010); Salmeterol xinafoate/Fluticasone propionate was used in Liu (2010) and Salmeterol was used in Zhou (2007) (Figure 7.61), so the pooled data for these studies are less comparable. An expectorant was used in Zhao (2009).

Among the twenty two studies, the therapeutic approach of tonify lung qi was applied in most studies with Ren shen, Dang shen and Huang qi being the key herbs in these formulae. Huang qi (12), Dang shen (11) or Ren shen (1) or Tai zi shen (1), Bai zhu (10), Fu ling (8), Wu wei zi (7), Ge jie (5) and Di long (5) were used most frequently in the formulae. The therapeutic approach of tonify qi was used in Shan (2007), Feng (2006) and Wang (2009) while Smooth the liver and regulate qi was applied in Ao (2007) with Chai hu, Bai shao, Huang qin and Bai
zhu etc. being used in combination with remove phlegm and suppress cough herbs.

Figure 7.61 Comparison of CHM plus RP versus RP in patients with stable COPD: Effective rate of symptom improvement at the end of treatment as the outcome
Discussion of CHM formulae for relieving Dyspnea

Dyspnea is a common symptom of COPD which manifests as sensations of respiratory discomfort. Relief from dyspnea is an important goal of pharmacotherapy. The degree of dyspnea has been demonstrated to influence and predict health related quality of life, as well as survival (310, 473). In COPD, dyspnea can be due to dynamic hyperinflation, neuromechanical dissociation, gas exchange abnormalities, and inspiratory muscle weakness, as well as cognitive and psychological factors. Therefore, the effective assessment of the degree of dyspnea is important for the monitoring of patients, guiding treatment and improving prognosis.

A variety of instruments are available to measure the degree of dyspnea during exercise, including: the visual analogue scale (VAS) (474); the Borg scale (475); Oxygen Cost Diagram (OCD) (476); Baseline Dyspnea Index (BDI) and Transition Dyspnea index (TDI) (477); as well as the Shortness Of Breath Questionnaire (SOBQ) (478). Each of these instruments has its strong points and weak points (467), but none of these instruments addresses all aspects of this symptom (479).

MMRC is one of the components of the BODE multidimensional index for assessment of level of functional dyspnea. It is a simple, easy-to-use grading system for the assessment of patients’ level of dyspnea, which is valid and reliable and commonly used. The MMRC dyspnea scale provides an independent dimension that is not measured by pulmonary function tests or by measuring dyspnea in an exercise laboratory. So it is widely used in patients with COPD (310) and as an outcome measure in clinical trials.

However, the MMRC dyspnea scale was only used in three of the studies located and none of the other established scales mentioned above were reported. In each case, the CHM formulae were found to be more effective in reducing dyspnea as measured by the MMRC Dyspnea Scale when compared with placebo in one study on 60 participants (375), no treatment in one study on 60 participants (408), or CHM plus RP compared to RP in one study on 60 participants (312). However, meta-analysis could not be performed due to the differences in study design. The greatest reduction of dyspnea in the three studies was in Chen (2009-1). The herbs included tonify lung and kidney herbs such as Dang shen, Huang qi, Bai zhu and Shan zhu yu etc. in combination with Salmeterol xinafoate/Fluticasone propionate which was the RP used.
Discussion of Symptom scores for individual COPD symptoms

Individual symptoms were reported by fourteen studies with 1,044 participants. Of these five studies with 349 participants compared CHM plus RP to RP and reported scores for dyspnea, chronic cough and sputum production. The RP used were not specified in Lang (2010), Qiu (2009) and Tang (2010). Theophylline plus β2 adrenergic receptor agonists were used in both You (2008) and Guo (2008).

For chronic cough, better reduction of the scores of chronic cough was found in three studies out of five when CHM plus RP was compared to RP (366, 376, 410) (see Figure 7.23). Theophylline plus β2 adrenergic receptor agonist was found to be superior to the RP alone in You (2008), but, Guo (2008) found no benefit for the addition of the CHM.

For sputum production, a greater reduction in symptom scores was found in four studies when CHM plus RP was compared RP (345, 366, 380, 383) (Figure 7.24), whereas Qiu 2009 showed no additional benefit. Both the studies that used Theophylline plus a β2 adrenergic receptor agonist (i.e. Guo 2008 and You 2008) found a benefit for the addition of the CHM.

For dyspnea, the best relief was reported in Lang (2010) but the RP was not specified. An extract of Bai bu was used in this study whereas the other studies used multi-herbs formulations. The most comparable studies (You 2008 and Guo 2008) found no additional benefit for the CHM for dyspnea (see Figure 7.25).

Although, pooling data was difficult due to the different RP used, two studies were directly comparable in terms of RP and similar therapeutics of Tonify Qi and strengthen spleen were used in four of the studies. The exception was Lang (2010) which aimed to stop cough and resolve sputum only.

Ren shen or Dang shen as key herbs were used in Qiu (2009), Tang (2010). You (2008) and Guo (2008), Fu ling and Bai zhu were also used in Qiu (2009) and You (2008), while Huang qi was only used in Tang (2010). The two most comparable studies in terms of RP, only had one herb in common (Ren shen) but they both showed benefit for sputum production, You (2008) also showed benefit for cough but neither showed benefit for dyspnea.
Discussion of the impact of CHM on BODE index, 6MWD and BMI index

Discussion of BODE index

The BODE index is a new tool incorporating measurements that reflect the multi component nature of COPD through assessment of nutrition, airflow limitation, dyspnea and exercise capacity, which has been established as multidimensional staging tool (480). In addition, it is useful in predicting and monitoring mortality and hospitalizations and in reflecting disease progression, and has been found to be very good surrogate outcome of mortality of COPD (481, 482). However, BODE index was only used in two studies in this review. The BODE index would be suggested to be primary outcome in further CHM clinical trials.

This review found that the CHM formulae were more effective in reducing the BODE index when CHM plus RP was compared with RP in one study with 60 participants (Chen 2009) or when CHM was compared to no treatment in one study with 73 participants (Zhang 2008). In both studies the duration of treatment was three months. Four patients withdrew in Zhang 2008 and intent to treat was applied in the data analysis.

The formula used in Zhang 2008 was Liu Jun Zi Wan, while it was Qi Wei Dou Qi Tang in Chen (2009-1). Liu Jun Zi Tang is the most commonly used formula overall but Qi Wei Dou Qi Tang is infrequent. Also, the principle of treatment for Liu Jun Zi Wan (strengthen spleen qi) is different than in Qi Wei Dou Qi Tang (strengthen kidney), but, three ingredients of these formulae, i.e. Dang shen, Bai zhu, Fu ling are the same in both studies. So the formulae are more similar than their names suggest. These three herbs are frequently used together to replenish spleen. This suggests that the strategy of replenish spleen plays an important role in the treatment for patients with stable COPD.

Discussion of the 6MWD Test

6MWD test is used to assess the functional exercise capacity of patients with moderate-to-severe heart or lung disease.

Meta-analysis in this review found that the CHM formulae were effective in improving exercise capacity as measured by the 6MWD test when compared to RP, other CHM or no treatment in ten studies on 723 participants with no statistical heterogeneity. Short term therapy was reported in 2 studies (345, 452), and long term therapy in eight studies (312, 347, 386, 408, 415, 420, 422, 434).
Most of the formulae employed the treatment principle of replenishing lung and tonifying spleen and kidney using modified Ren Shen Ge Jie San (345, 422), Qi Wei Du Qi Wan (312), Jian Pi Yi Fei granule (347), Gu Ben Ke Chuan Granule (434) as well as Bai Ling Capsules (415). The treatment principle of tonifying qi and activating blood was applied in two studies (386, 420).

Benefit was most evident in the five studies that compared CHM plus RP with RP (312, 345, 347, 386, 415). Of these Chen (2009-1) & Liu (2010) used the same RP (Salmeterol & Fluticasone), employed similar formulae, both of which contained Huang qi, Dang shen, Fu ling, and Bai zhu, and both trials found a benefit for the addition of the HMs (see Figure 7.27).

Also, Chen (2009-1), Liu (2010) and Huang (2005) used similar CHMs which all included Huang qi, Bai zhu and Fu ling. Ginseng was used in both Guo (2008) and Huang (2005), and Dang shen appeared in Liu 2010 and Chen 2009. Two studies used Dong chong xia cao capsules (Zhang 2010 and Huang 2005). Of these studies, the longest were Zhang (2010) and Liu (2010) (6 months) followed by Huang (2005) (3 months) so these studies would appear the most relevant to clinical practice.

**Discussion of BMI index**

Nutritional depletion and weight loss are features of COPD. The incidence of malnutrition is 24 to 23% in patients with moderate to severe COPD when using the criteria of weight <90% of ideal body weight or weight loss of 5 to 10% of initial body weight. BMI has been found to be an independent negative determinant of survival in patients with COPD (483). BMI index is also one of components of the BODE multidimensional index for assessment of nutrition status.

BMI index was reported in four studies (408, 417, 440, 454) with 232 participants, that found CHM to be effective when compared to placebo in Xu (2008) and CHM plus RP was more effective when compared to RP in Chen (2009-2). Although some herbs were different in the two studies, the major therapeutic strategy was fortifying spleen in both of them, and Dang shen or Ren shen plus Bai zhu and Fu ling were the key herbs.

In Chinese medicine, fortifying spleen is an important therapeutic strategy for strengthening muscle function and enhancing exercise tolerance. However, malnutrition and muscle weakness in patients with COPD are chronic conditions. Therefore, longer term treatment
with CHM therapy than the one or two months used in these trials is needed to clearly assess the effects on BMI.

7.10.2.5 Discussion of effects of CHM formulae on arterial blood gas measurements

Arterial blood gas (ABG) analysis provides information about oxygenation, ventilation and acid-base status of the body and is used in the clinical assessment of patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (317). Oxygen level and dynamic hyperinflation have also been demonstrated to be related to airway oxidative stress in stable patients with COPD by Garcia-RioF 2011 (484). Patients with severe COPD may present with resting hypoxaemia that is defined by arterial blood gas analysis. Hypoxaemia is associated with QoL and survival of patients with severe COPD, particularly in those with stable conditions. Therefore, therapies that can improve arterial blood gas parameters are clinically important.

Arterial blood gas was measured and reported in ten studies on 706 participants. Results from this review showed that oral CHM were more effective in increasing of the level of PaO₂ when compared with placebo in one study, or no treatment in one study, when CHM plus RP was compared with RP in four studies, and when experimental CHM was compared with other CHM in three studies. Conversely, when CHM was compared with RP, the effect was the same. With regard to the level of PaCO₂, a similar pattern of results was found with the greatest reduction being in the single study that compared CHM with no treatment, and a marginally significant reduction for the pooled data of the four studies that compared CHM plus RP to RP.

Increase in PaO₂ was most evident in the pooled results of four studies that compared CHM plus RP with RP (312, 446, 453, 457) (see Figure 7.30). Chen (2009-1) and Zhao (2009) showed the greatest increase in the level of PaO₂. The same RP (Theophylline) was used in Luo (2002) and Wang (2006) and neither study showed a clear benefit for the addition of the CHM. Salmeterol plus Fluticasone was used in Chen (2009-1) whilst the RP was not specified in Zhao (2009).

Tonify qi was the strategy applied in both Chen (2009-1) and Zhao (2009) over the same duration of treatment (12 weeks), and the herbs Huang qi and Bai zhu were used in both studies. The formula in Chen (2009-1) tended to strengthen spleen and tonify kidney with Huang qi and Bai zhu plus Dang shen, Fu ling, Wu wei zi and Shan zhu yu etc. whereas the
formula in Zhao (2009) focused on ‘diffuse lung and calming dyspnea’ using Huang qi and Bai zhu plus Bai guo, Ma huang, Su zi and Kuan dong hua etc. Also, Luo (2002) used a similar strategy to Chen (2009-1) with Dang shen, Huang qi and Yin yang huo etc for three months of treatment.

The herbs in Wang (2006) included Bai jie zi, Su zi, Bai qian and Jin fei cao which all belong to the category of herbs that remove phlegm. This formula did not contain tonifying herbs and had quite different ingredients to the other studies. Although, this formula has been demonstrated to reduce swelling of bronchial mucous membranes, reduce resistance in small airways and have anti-inflammatory effects (66), it appears to have been less clinically effective than the tonifying formulae used in the other three studies.

With regard to the clinical significance of these results, patients whose PaO$_2$ at sea level > 70 mmHg do not need oxygen supplementation as suggested by GOLD (174). In most of these studies, the levels of PaO$_2$ of participants were more than 60 mmHg whereas PaCO$_2$ levels were normal or slightly higher than normal, so these patients had hypoxemia without hypercapnia and were suitable for treatment by CHM in addition to RP without the use of oxygen therapy. The results from these studies showed that the addition of the CHM appeared to increase the level PaO$_2$ through improvement of ventilation function.

Improvement of hypoxemia is an important aspect of COPD therapy particularly in patients whose level of PaO$_2$ are less than 50 mmHg and who depend on long term oxygen therapy. Extended periods of oxygen therapy at a low flow rate are very important for the deceleration of disease progression. The included studies did not include patients receiving oxygen therapy, but the results for PaO$_2$ suggest that the addition of CHM to such patients’ therapy could produce a benefit. Therefore, future clinical trials that aim to evaluate the effects of CHMs on ABG should involve patients undergoing long term oxygen therapy and include measurements of the amount of oxygen therapy that patients receive in order to further investigate the effects of CHMs on ABG and produce clinically meaningful results.

7.10.2.6 Discussion of the effect of CHM formulae on biomarkers

A range of biomarkers identified in the serum of patients with COPD have be found to correlate with clinical variables known to predict disease outcome including degree of airflow limitation, lung transfer factor, functional capacity, BODE index and exacerbation frequency (485).
A number of biomarkers were measured in 23 studies. The biomarkers included chemokines, inflammatory cytokines, lymphocyte subsets, immune globulins, ALB and PALB and Leptin, SOD and LPO and blood rheology parameters.

**Discussion of Inflammatory markers**

COPD is a multi-component disease and systemic inflammation is one of the possible mechanisms underlying its systemic manifestations, including skeletal muscle weakness and cachexia, so changes in these aspects might be related to changes in biomarkers of systemic inflammation (486, 487).

Measures of inflammatory markers included: the serum levels of IL-2 in 2 studies (447, 455), IL-8 in 4 studies (80, 369, 411, 433), IL-6 in 2 studies (398, 463), TNF-α in 6 studies (65, 80, 369, 398, 447, 449), C-reactive protein (CRP) in 2 studies (398, 463); and measures of the sputum levels of IL-8 in four studies (346, 405, 435, 436) and TNF-α in three studies (405, 425, 436).

Pinto-plata (2007) found that serum levels of both TNF-α and IL-8 correlated with FEV1, BODE index and exacerbation rate (485). Increased systemic CRP, which is regulated by IL-6 (487), is also associated with poorer health status, comorbidities, hospitalisations and death (488, 489). Since increased levels of IL-8, TNF-α and CRP are correlated with worse disease severity, exacerbation rates, and lung function decline, they are not only proxy measures of inflammation but are also of clinical relevance.

The results found an increase in the serum level of IL-2 when CHM plus RP was compared to RP (1 study). A reduction in the serum level of TNF-α was found when CHM was compared to placebo (449) (1 study), or RP (80) (1 study), or when CHM plus RP was compared to RP (447) (1 study). However, there was no change in the level of TNF-α in sputum in the meta-analysis of three studies that compared CHM plus RP to RP (405, 425, 436).

A reduction in the serum level of IL-8 was found in one study that compared CHM to RP (80) and compared experimental CHM to other CHM (433). In addition, CHM was found to be more effective in reducing the level of IL-8 in sputum when compared to placebo (435) or when CHM plus RP was compared to RP (405) (one study each). Due to differences between studies, the pooled data were not comparable.
Ren shen and Ge jie were used in Xiong (2008) which was the longest study (half year). Huang qi plus Lian qiao, Huang qin, Zi wan and Kuan dong hua etc were used in Che (2005), Huang qi, Dang shen, Bai zhu, Fu ling and Kuan dong hua were used in Wang (2005), Huang qi, Jin yin hua, Su ye and Jie geng etc were used in Zhou (2007). The principle of Tonify Qi and Kidney was applied in Xiong (2008) and, the principles of tonify qi and diffuse the lung to resolve phlegm were applied in the other three studies. Huang qi was the key herb in the formulae used in the three shorter term studies (from 4 to eight weeks). These four studies showed reduced levels of IL-8 and TNF-α in serum or sputum in patients with stable COPD which suggests the formulae enhanced the immune function of the patients.

CRP was measured in one study (Tatsumi 2009) and IL-6 was measured in both Tatsumi (2009) and Shinozuka (2007) which implied that CHM may decrease the level of CRP and IL-6 in serum, but detailed data were not provided (398, 463). The authors reported that the CHM reduced the chances of common cold and consequent exacerbations and that the CHM may have antibacterial and/or antiviral effects.

Raised serum levels of TNF-α, IL-6 and CRP have been found in COPD patients compared to normal subjects. This supports their use as biomarkers of systemic inflammatory response in stable COPD patients (490). TNF-α and IL-6 were found to be higher in severe COPD and in those patients in an exacerbation stage (485, 491) but no relationship between CRP level and COPD severity was found (491). However, no change was detected in TNF-α or IL-6 following the remission of exacerbations (485, 490). Raised TNF-α level has also been found to be associated with weight loss in COPD patients by Karadag F et al. 2008 (490). CRP level has been found to predict death in COPD patients and is associated with exercise tolerance, health status and muscle strength (487).

Higher sputum levels of IL-8 and IL-6 have been found during exacerbations compared to periods of stable COPD, and raised IL-6 was associated with common cold symptoms (492), but the clinical significance of sputum levels of cytokines remains unclear since the use of liquefaction agents in sampling may affect results (493).

It has recently been shown by Sin (2008) that the use of inhaled corticosteroids (ICSs), with or without the long-acting β2-adrenergic agonist Salmeterol, does not affect serum IL-6 and CRP levels (494). However, theophylline was found to decrease the level of TNF-α and IL-8
in sputum in seventeen COPD patients with long-term treatment (495). Therefore, it appears plausible that the CHMs may also have this effect.

CRP is a surrogate marker that reflects the status of systemic inflammation (318). A higher level of CRP was found in COPD patients with lower BMI associated with malnutrition (491) and is also a marker of prognosis in patients with mild and moderate COPD and a predictor of higher risk of mortality (482, 496). Therefore, CRP is an important indicator of the progression and morbidity of COPD. In this SR, CRP was only tested in one study and needs to be examined in further clinical trials.

TNF-α and IL-8 in serum, plus measures of lung function and the effectiveness rate of improvement of symptoms were reported in Xiong (2009), which found that the CHM may decrease the level of TNF-α and IL-8 in serum, as well as improve lung function and relieve symptoms for moderate COPD patients. Also, lung function and TNF-α in sputum were reported in Che (2005), Wang (2005) and Zhou (2007) which found reductions in the level TNF-α in sputum was associated with improvements in lung function.

These results suggest that the levels of inflammatory markers are relevant to other outcomes of COPD, such as lung function and symptoms. However, due to different methods used to measure the inflammatory markers, the small number of studies, and the small population samples used, the effect of these CHMs on these inflammatory markers cannot be confirmed.

The findings of the studies in this analysis indicated that some CHM formulae appear to reduce systemic inflammatory response in patients with stable COPD.

**Discussion of lymphocyte subsets**

It is known that COPD is characterised by an abnormal inflammatory immune response in the lung in response to cigarette smoke or other particles (497). Both CD4 and CD8 T lymphocytes play key roles in the in the pathogenesis of COPD, but the complex procedure of systemic inflammation in the pathogenesis of COPD is not yet clear (498).

In subjects with COPD, the level of lymphocyte subsets CD3, CD4, and the ratio of CD4/CD8 in peripheral blood have been found to be lower, and the level of CD8 is higher compared to normal subjects (499). The level of CD4/CD8 is positively related to FEV1% predicted (500), CD8 is more closely correlated with GOLD stage in stable COPD than is CD4 (498), also,
CD4 level is correlated with FEV₁ in smokers with COPD (501). So changes in the levels of these lymphocytes appear to be related to clinical measures of COPD severity.

ICSs used for long-term therapy, such as fluticasone, in combination with salmeterol have been found to have anti-inflammatory actions through reduction of the level of neutrophils, macrophages and CD8 and CD4 lymphocytes in sputum and can attenuate decline in lung function in patients with moderate to severe COPD, but adding LABAs does not enhance these effects (502, 503). However, due to the risk of pneumonia, the use of ICSs for long term therapy in patients with COPD should consider this risk factor (197).

In a clinical trial that investigated the immunomodulatory actions of the synthetic dipeptide pidotimod in patients with exacerbation of COPD, found that pidotimod increased the level of CD4 in peripheral blood and increased the ratio of CD4/CD8 after 15 days treatment and decreased the level of CD8 after 30 days treatment (504).

In this SR, levels of CD3, CD4, CD8 and CD4/CD8 in blood were tested in 8 studies (Figs: 37-40). The CHM formulae were found to be potentially effective in increasing CD3 and CD4 as well the ratio of CD4/CD8 when compared to either placebo or RP, or when CHM plus RP was compared to RP, whereas no difference was found when the test CHM was compared with other CHM or no treatment. The most evidence was when CHM plus RP was compared to RP (3 studies). However, due to the different RP used, the pooled data was not comparable.

Dong chong xia cao, Huang qi, Bai zhu and Fang feng were used in Liang (2009) with 6 months treatment; Ren shen, Huang qi, Bai zhu and Fu ling etc were used in both Xiao (2000) with 2 months treatment and Xu (2009) with 3 weeks treatment. Therefore, tonify qi plus replenish spleen or tonify kidney herbs may have anti-inflammatory effects in patients with stable COPD.

However, these CHM formulae seemed to have no clear effect on CD8. In these studies, there was no healthy subject control group, so it was not possible to determine how much higher the level of CD8 was in the trial subjects compared to healthy subjects. Also, in Kim (2002), the level of CD8 was observed to be only slightly higher when compared to healthy smokers or to healthy non-smokers (319), and in Chen (06) changes in CD8 were only detected after 30 days of treatment (504). So a change in the level of CD8 between intervention and control groups after treatment may be difficult to detect.
Discussion of Immune globulins

The serum levels of Immune globulins IgA, IgM and IgG were found to be lower in stable COPD patients than in healthy subjects (505). IgG levels were found to be higher in epithelial fluid in COPD patients with recurrent stable versus normal control subjects with a history of tobacco consumption of 30 pack-years (506). Also, IgM was found to be slightly higher in stable COPD patients than in healthy subjects, but for IgA and IgG no differences were found between stable COPD patients and healthy subjects. This study suggested that IgA, IgM and IgG may not be sensitive outcome measures for stable COPD (507).

Immune globulins IgA, IgM and IgG were measured in 9 studies in this SR. The normal values for adults are in the following ranges: IgG 7.6-16.6g/L; IgA 0.71-3.35g/L; IgM 0.48-2.12g/L.

In all these studies the reported values were within the normal ranges and after treatment some were close to, but still lower than, maximum.

The results suggest that the CHM formulae were potentially effective in increasing IgA and IgG when CHM was compared to placebo (69), was compared to RP (433, 508), and when CHM plus RP was compared to RP (372, 410, 450), whereas no difference was found when a test CHM was compared with other CHM or no treatment. CHM formulae seemed to have no clear effect on IgM in the two studies with short-term treatment (2 months of treatment in Qiu 2009 and 3 weeks of treatment in Xu 2009), whereas a better effect on Ig M was found in Liang after 6 months of treatment (2009). So any effect may be related to duration of treatment.

Both Huang qi and Bai zhu were used in these six studies. Ren shen or Dang shen were used in four studies (Li 2006-1, Qiu 2009, Sun 2007-2 and Xu 2009), Dong chong xia cao, Mai dong and Fu ling were each used in three studies. Therefore, tonify qi plus replenish spleen or tonify kidney herbs may have an immunomodulation effect in patients with stable COPD.

Although immune deficiency has been postulated as a factor in COPD aetiology, this theory is not well-established and increases in IgA may reflect response to pathogens (509). Also, the roles of immunoglobulins in immune response are complex and there is contradictory evidence for the meaning of Ig levels (510). It appears that IgA levels may rise in exacerbations related to respiratory tract infections (511) but in stable COPD measures of
serum immune globulins are difficult to interpret and may not have clear clinical significance.

IgM that are specific for community-acquired pneumonia caused by various pathogens, including atypical types such as Mycoplasma and Legionella, show increased serum IgM levels in plasma and are predictive of the pathogens involved in the pneumonia (512). Therefore, changes in the level of IgM may be indicative of the type of bacterial infection in COPD patients at the exacerbation stage, but such measures do not appear useful for determining the progression in stable COPD.

The level of IgD in serum is a quite old measure but relevance to various diseases and conditions remains unclear (513). Also, it was found to be significantly higher in elderly patients with stable COPD than in normal controls (507). It appears to have immunomodulatory effects and the level seems to be higher or lower in disorders characterized by immunodeficiency with increases being associated with infection. Consequently, IgD level may be a useful measure of exacerbations of COPD but its significance in stable COPD remains unclear (514).

Discussion of albumin, Prealbumin and Leptin

Nutritional depletion is common in COPD patients. It is due to imbalance between low-energy intake and high-energy requirements, and affects morbidity and mortality (515). Therefore, nutritional support is generally implemented in pulmonary rehabilitation programmes (516). Nutritional status is assessed in various ways. However, nutritional depletion is represented as a loss of body weight, so body mass index (BMI) is the most commonly used measure in clinical practice either as a single measure or as part of a composite score such as BODE (517).

Serum ALB has been used as a proxy measure of nutritional status (518) and has been found to correlate with lung function (519). However, it is not typically used in contemporary clinical studies.

The level of serum Leptin was positively correlated with BODE index and a negatively correlated with Fat-free mass index (FFMI) in stable COPD patients (520), but it was found not to be related to anorexia and weight loss in COPD patients and no difference was found between COPD patients during stable and acute exacerbation stages (521). ALB, PALB and Leptin as markers for the assessment of nutritional status were measured in six studies (65,
The effect was most evident when CHM was compared to placebo (454), which found ALB, PALB and leptin all increased after one month treatment using Ren shen, Bai zhu, Fu ling, Mai dong, Sang bai pi, and Huang qi. PALB was increased in two studies which compared CHM plus RP with RP and used similar formulae (Liu Jun Zi Tang and Bu Zhong Yi Qi Tang) (398, 417). The results seem to be not correlated with the duration of treatment which was two months in Chen (2009-2) and six months in Tatsumi (2009).

Although these markers have been used as proxy measures of nutritional status, the clinical significance of changes appear less clear than direct measures such as BODE index. Therefore the results found in this review for these measures are difficult to interpret.

**Discussion of Superoxidase dismutase and Lipid peroxide**

Oxidative stress has an important role in the pathogenesis and progression of COPD (522). Impairment in oxidant-antioxidant balance was found in patients with stable or exacerbation of COPD and even in healthy smokers by Hanta L et al (523). SOD as a parameter of antioxidative defence was found to be decreased in patients with COPD when compared to healthy subjects, also, lipid peroxidation products acting as signalling molecules can induce release of inflammatory mediators from lung cells (524). Therefore, finding new therapeutic interventions to repair oxidant antioxidant imbalance in COPD may prevent the further progression of COPD (523).

Serum SOD and LPO were examined in one study that used Liu Jun Zi Tang (Dang shen, Bai zhu, Fu ling, Chen pi, Ban xia, Gan cao) taken for three months (73). The results from Zhuan (2005) showed that this CHM formula may rectify the imbalance of oxidation/anti-oxidation through increasing the level of SOD and decreasing the level of LPO.

**Discussion of blood rheology parameters**

Damage of pulmonary vessels is related to the progression of COPD and vascular change is present in endothelial and microvascular dysfunction (525). Also, the magnitude of changes in periferal circulation is related to the severity of COPD (321). Changes in hemorheology in COPD were found to be associated with hypoxemia (526). Hypoxia may lead to prothrombotic state or hypercoagulable state in COPD and also increase the risk of venous thromboembolism (527), which can be measured by Plasma D-dimer (528). The level of plasma D-dimer was observed to be slightly higher in stable COPD than in healthy subjects, but was
significantly higher in exacerbation of COPD (529). Therefore, plasma D-dimer is commonly used in exacerbation COPD and very important for treatment (529). Plasma D-dimer was not measured in any of the RCTs in this review; however a number of blood rheology parameters were used to assess blood viscosity.

Blood rheology parameters provide a measurement and assessment of the condition of the periferal circulation in various diseases (530). A study showed that changes in blood rheology parameters in patients with COPD were greater than in healthy subjects. Due to oxygen deficiency, repeated infection or respiratory acidosis, COPD may lead to changes in the quality and quantity of erythrocytes and increase blood viscosity (531), and polycythaemia may develop. Blood stasis syndrome is associated with the severity of COPD so blood rheology parameters are frequently used in China as an objective measurement of blood stasis syndrome (532).

Blood rheology parameters were tested in 3 studies. In two studies (Wang 2009, Cui 2008) measures of viscosity, shear rate and hematocrit level indicated that the CHM formulae were more effective in reducing plasma viscosity and erythrocyte aggregation when CHM plus RP was compared to RP (384), and when CHM was compared to no treatment (400).

The herbs Tai zi shen, Dan shen, Dang gui, Tao ren, Hong hua and Chi shao etc were used in Wang (2009); and Huang qi, E zhu and Tao ren etc were used in Cui (2008). Both formulae used the methods tonify qi and activate blood. Both included the blood activating and stasis-resolving herb Tao ren plus other herbs with similar effects such as Dan shen, Hong hua and E zhu.

In the study by Guo et al (2010), the comparison was between two CHMs. The test CHM formula comprised Sheng sha shen, Shu di huang, Dang gui, Zhi ban xia, Chen pi, Fu ling, Lu jiao pian, Zhi ma huang, Xing ren, Bai jie zi, Chuan xiong, E zhu, Wu wei zi, and Zhi gan cao whereas the control group used Gu Ben Ke Chuan Tablet (Dang shen, Bai zhu, Fu ling, Mai dong, Zhi gan cao, Wu wei zi, Bu gu zhi). There was a non-significant improvement in blood rheology in the test medication but it only included two blood stasis removing herbs i.e. Chuan xiong and E zhu. Therefore a large effect would not have been expected.

Dan shen (*Salvia miltiorrhiza*) belongs to the category of blood-activating and stasis-dispelling herbs. Pharmacological studies have demonstrated that Dan shen has effects on hemorheology (533). Also, a clinical trial showed that Dan shen injection may relieve airway
inflammation, improve pulmonary ventilation and immune function (534).

In Chinese Medicine, a recent study showed blood stasis syndrome to be more frequent as the severity of COPD increased, and increased COPD severity was associated with increased erythrocyte aggregation and higher hematocrit (532). Therefore, blood stasis plays an important role in the pathogenesis of COPD. Also, the incidence of pulmonary hypertension is very high in patients with COPD, and it was found that a high proportion of patients with pulmonary hypertension showed the CM syndrome of blood stasis (535). Although few studies measured blood rheology, the CHMs in numerous studies included herbs that have blood activating and stasis removing actions, for example Dan shen was used in 24 studies and Tao ren was used in 13 studies, as was Di long. Therefore removing blood stasis is an important strategy in managing COPD and in the prevention of co-morbidity. These studies demonstrated that certain CHMs may reduce blood viscosity and regulate blood flow and thereby prevent blood stasis forming in COPD. These actions may prevent or slow the disease progression.

7.10.3 Discussion on syndrome differentiation, formula use and main herbs

In CM, the selection of the most appropriate CHM treatment intervention is usually based on CHM principles that depend on syndrome differentiation. Of the 101 included studies, participants were diagnosed by Chinese medicine syndrome differentiation in 43 studies. In the majority of these studies the main syndromes identified involved ‘deficiency of lung’ (28 studies), with multiple deficiencies being identified in other studies such as: ‘deficiency of lung and kidney’, ‘deficiency of lung and spleen’ or ‘deficiency of lung and spleen and kidney’, with or without existing ‘phlegm’ (4 studies) or ‘blood stasis’ (4 studies). Therefore the principles of treatment are predominantly ‘reinforce qi’, especially ‘reinforce the spleen to benefit lung’, ‘supplement spleen to nourish lung’, or ‘tonify the kidney to improve inspiration’.

Also, even when a study did not explicitly state which syndrome was the focus of the intervention, the formula used may indicate what the treatment principle was, and from this the main syndrome can be inferred. For example, in Chen 2009, the selection criteria were set up but the Chinese medicine syndrome was not specified. Based on the formula used in treatment (Qi Wei Dou Qi Tang plus Dang shen, Huang qi and Bai zhu), it can be inferred that the patients included in this study were classified as deficiency of lung and kidney qi.
As introduced in Chapter three, the pathogenesis of COPD according to CM is associated with ‘deficiency’, ‘phlegm’ and ‘blood stasis’. Among the studies that reported on syndrome differentiation, the majority reported deficiency of qi, in particular deficiency of the qi of lung, lung and kidney, lung and spleen, or lung and spleen and kidney, which may be combined with phlegm or blood stasis.

Syndromes involving single organ deficiency versus multi organ deficiency may be representative of the progressive development of COPD and may also reflect the relationship between the degree of deficiency and the severity of COPD. It is very meaningful to further explore the pathogenesis of COPD in CM terms to determine the progression of syndromes and hence the appropriate treatment principles at different stages in this disease.

Based on the Chinese medicine syndromes identified and the formulae used in these studies, replenish qi and/or fortify spleen and/or tonify kidney were the predominant treatment strategies in most studies with the addition of resolve phlegm or activate blood in certain studies. The most commonly used formulae and herbs are as follows:

Formulae: Bu Fei Tang ( Tonify the lung), Liu Jun Zi Tang (Fortify the spleen and replenish qi), Shen Ge Tang (Tonify the lung and supplement the kidney) and Fei Kang Granule (Tonify qi and activate blood).

Among top twenty herbs, the majority of herbs are tonifying herbs, such as Huang qi (Tonify qi and upraise the middle qi, strengthen the defense and secure the exterior), Dang shen (Tonify and replenish the middle qi, engender fluid and nourish blood) or Ren shen (Greatly tonify the original qi, fortify the spleen and replenish the lung), Bai zhu (Tonify qi and fortify the spleen, induce diuresis to dry dampness), Fu ling (Fortify the spleen and replenish the middle qi), Wu wei zi (constrain the lung and enrich kidney, engender fluid and secure the exterior to check sweating), Ge jie (Tonify the lung and supplement the kidney), Shan yao (fortify spleen), Shan zhu yu (tonify kidney) and Mai men dong.

The next most frequent group were herbs used of resolving phlegm and suppressing cough: Ban xia, Bei mu, Kuan dong huan and Su zi and Xing ren. Followed by herbs for activating blood and dissipating stasis: Dan shen and Dang gui.

Gan cao was one of highest frequency herbs used in both the classical literature and the modern clinical trials. Its effects are resolving phlegm and suppressing cough and it also
regulates spleen and stomach.

**Study design, study quality and the meaningfulness of results**

The primary goals of the treatment for stable COPD are to prevent decline of lung function, improve HRQoL and reduce exacerbations. Five studies used QoL, lung function and exacerbations as outcomes (Huang 2005, Jia 2007, Ni, 2008, Tang 2009, Zhang 2006) (347, 370, 377, 381, 383). However, due to differences in the study designs, the pooled data were not comparable.

The best study design involving CHM plus RP was applied in Ni (2008) with 68 participants for two months treatment, since the control group used RP plus placebo. However, multiple types of RP were used in the Ni study which makes the results difficult to interpret.

CHM plus RP versus RP was applied in Huang (2005) with 63 participants for three months treatment and Jia (2007) with 55 participants for six months treatment, but information on the RP was not provided in Huang (2005). Therefore, the degree of effectiveness of the CHM could not interpreted in Ni or Huang. Ipratropium bromide was used in Jia (2007) which found a significant improvement of QoL and FEV1% and reduction of exacerbations of COPD in favour of the CHM.

QoLQ and lung function were measured in 20 studies. The best evidence was when CHM plus RP were compared to RP in 8 studies. RP including Salmeterol, Ipratropium bromide, Salmeterol Xinafoate/Fluticasone Propionate, theophylline Sustained-release were used in five studies (Chen 2009-1, Jia 2007, Liu 2006-1, Liu 2010 and You 2008) (312, 366, 370, 385, 386). RP was not provided by two studies (347, 379) and multi medicines were used in one study (372).

The best results from FEV1% and QoL assessed by SGRQ were found in Jia (2007) with 55 participants for six-month treatment and Liu (2010) with 60 participants with three months. Although the score of methodological quality assessed by Jadad’s scale was 2 in these two studies, most domains were judged as unclear risk of bias by the Cochrane method. Also, the diagnostic criteria, classification of severity of COPD, CM syndromes and set up of the outcome measures as well as the data analysis methods were described in both studies. The deficiencies of these two studies are small sample size, and lack of description of generation of randomisation and double blinding as well adverse events.
Qi-tonifying and blood-activating therapeutics were applied in two studies with similar formulae including the herbs Huang qi, Dang shen or Tai zi shen, Dan shen and Di long. In one study (Chen 2009) (312) with 60 participants for three months treatment, Salmeterol Xinafoate/Fluticasone Propionate was used in both the treatment group and control group. This study appears frequently in the results since it reported on many outcomes including pulmonary function, quality of life questionnaire, dyspnea scale by MMRC, BODE index and arterial gas measurement as well as adverse events. However, this study showed the same as the above-mentioned problems of methodological quality reporting. Nevertheless, the outcomes measured in Chen (2009-1) are recommended to be used in clinical trials for stable COPD, in particular BODE index. However, MMRC and BODE index were used in only a few of the 101 RCTs.

Surrogate biomarkers specific for COPD have not been found. However, some of the main biomarkers of inflammation such as IL-8 and TNF-α were tested in sputum or serum in several studies. These studies provided evidence that the level of IL-8 and TNF-α in sputum or serum were correlated with stable COPD patients and that the CHMs may have potential effects on anti-inflammation and reduction of inflammatory response in stable COPD patients.

Therefore, the oral CHMs used in these studies appear to have potential benefits for stable COPD sufferers but the evidence should be interpreted with caution due to the potential risks of bias due to the identified methodological issues.

7.10.4 Agreements and disagreements with other studies or reviews

A recent systematic review on RCTs of herbal medicines for COPD (536) included 14 RCTs, two of which were also included in these reviews (79, 343). The reasons for exclusion from this review are as follows: two studies were not on a CHM(537, 538); two involved intravenous injection (539, 540); one study included patients with COPD in children (541); one study included some patients who had COPD accompanied with pulmonary heart disease (542); and six studies included patients with acute chronic bronchitis or chronic bronchitis (543-548). Consequently, these studies have not been included in these three SRs on oral CHMs for stable COPD.

The electronic data search for the SR by Guo et al (2006) was limited to English language databases and this was a major factor in the relatively small number of included studies.
The outcome measures in the studies included in the SR by Guo et al (2006) involved pulmonary function, symptom scores, and health related quality of life (SGRQ) but the small number of included studies and the diversity in these studies meant that there were few opportunities for data pooling and meta-analyses were not undertaken. The conclusions of this review indicated that the effectiveness of herbal medicines for treating COPD was not established beyond reasonable doubt due to methodological weaknesses, based on scores on the Jadad scale, and possible publication bias in favour of positive studies.

In these three SRs, the methodological reporting of the study methods was inadequate in the majority of cases with the result that bias was judged as ‘unclear’ or ‘high’ in many studies. This is broadly consistent with the earlier review.

All of the 101 included studies reported at least some positive results for the experimental arms. This suggests the presence of publication bias, however, the meta-analyses of the reported data found a mix of positive and negative results.

7.10.5 Limitations to the evidence reported in this review

The observations reported above should be interpreted with caution considering that the results might be influenced by: 1) incompleteness in the data search and collection processes; 2) differences in the participants, size and duration of trials; 3) differences in study design and interventions; 4) weaknesses in the study methodology; 5) variability in the procedures for diagnosis and collecting outcome measure data; 6) reporting bias, since not all trials reported results suitable for inclusion in the meta-analysis for each outcome; and 7) variation in the form, composition and dosage of the CHMs used.

7.10.5.1 Overall completeness of the evidence

Although large and comprehensive searches were conducted in this review, only 101 studies were identified and included. Due to there being two phases of COPD, all of the studies on patients with exacerbations of COPD were excluded. Also, all of the studies of HM interventions that involved injections or administration routes other than oral were excluded. So, not all forms of CHM interventions are represented in the data.

Among the 101 trials, 98 were conducted and published in Chinese. Two were conducted in Japan and one in Israel and were published in English journals. To avoid language bias and
location bias, no potential studies were excluded based on publication language, but potential dissemination bias could not be excluded. Extensive searches for unpublished material were undertaken, but few of the trials identified qualified for inclusion. However, the possibility that trials with negative findings may remain unpublished cannot be disregarded.

7.10.5.2 Diversity in participants, sample size and duration of studies

Participants in the full range of the COPD trials were diverse in terms of age, whether they were in-patients or out-patients, their stage of COPD and in other aspects of their background and medical history. This diversity was limited in the SRs since only patients with stable COPD and without acute exacerbations were included. Since most of the participants were recruited from Chinese populations this contributed to the comparability between studies. On the other hand, this aspect could impact on the applicability of the interventions when used in other populations. Also, since stable COPD is one of the phenotypes of COPD, the results of these SRs may not be applicable to exacerbations of COPD.

Many of the trials had relatively small sample sizes. For example, six of the 101 trials included 40 or fewer participants. There are, however, 26 trials with sample sizes of 80 or more and there are a number of large studies, for example Huang et al (2002) had 600 participants. Small sample size reduces the reliability of the results, so this issue needs to be considered when interpreting results.

COPD is a chronic disease with progressive development, so long term therapy is better for treatment and the inclusion of short-term studies may affect the outcomes. Among the 101 included studies, the duration of treatment period was more than three months in 59 studies. Therefore a substantial proportion of the data was derived from longer studies. Also, no difference was found in the sensitivity analysis for lung function and for the most frequently used herbs. This suggests that the duration of study did not affect the overall outcome but sensitivity analyses were not conducted for other outcome measures due to the relatively fewer trials that used comparable measures.

7.10.5.3 Diversity in study design and interventions

There is variation in the design of studies and in the control interventions used. Placebo controls were used in 12 trials; CHM alone was compared to no treatment in 18 studies; CHM plus RP was compared with RP in 47 studies; and CHM alone was compared to RP in 13
studies.

Even when the same or similar herbal medicine is used as the test intervention, it is difficult to interpret the results when the study design is different. For example, when the CHM was compared with placebo in one study, but the same CHM plus RP was used in another. In the meta-analyses, this issue was addressed by conducting sub-group analyses based on study design, and the studies that combined CHM plus RP, further sub-group analyses were conducted based on the type of RP. However, while the general designs of these studies are comparable, other factors may differ. This limitation needs to be considered when interpreting the results of meta-analyses.

In addition to the conventional study designs mentioned above, a test CHM was compared to another CHM in 11 studies. Manufactured herbal medicines such as Guben Kechuan tablets have been used in China for 30 years for respiratory disorders and Bailing capsules have been used for over 10 years, so these CHMs could be considered a form of RP. Therefore, when these herbal medicines were used in the control groups they could be regarded as active controls, similar to the use of the RPs of Western medicine. Nevertheless, this sub-group of studies is considered separately in the meta-analyses.

In China, patients suffering with COPD are usually reluctant to participate in RCTs that employ a placebo, so placebo controls are not widely applied in clinical trials. Instead, active controls in the form of the Western or Chinese medicines that are frequently used for COPD are used in clinical trials, especially in those aiming at developing new medicines. In addition, numerous trials used combinations of medicines, such as Chinese plus Western medicine in the test arm. This approach allows all patients to receive an active treatment whilst evaluating the additive effect of the combination therapy. Such an approach is clinically relevant since it reflects actual practice but introduces complexity into the trial design which can make the results more difficult to interpret.

Even when the CHM formula interventions were same or similar, they may be administered using different treatment regimens with regard to the dosage, frequency and duration of treatment. This factor also limits the interpretability of pooled data. The sensitivity analysis that was performed on treatment duration did not find any significant differences based on this aspect but it was impractical to conduct sensitivity analyses on all variables.
7.10.5.4 Risk of bias and methodological quality of the evidence

1) Cochrane risk of bias

All the 101 RCTs in this SR had methodological weakness and potential risks of bias as assessed by Cochrane risk of bias. In most cases the risk of bias was unclear due to limited descriptions of the study design, methods of randomization, allocation concealment and blinding. Information about the method of generation of randomization was provided in only 23 studies and an unsuitable randomization method was used in one study. In a few studies there were large differences in the number of participants in each group, but the baseline data were considered by the researchers to be comparable. This design creates difficulties in the generation of randomization and is less likely to produce baseline comparability.

The use of double blinding was described in only three studies. However no further details were available on who were blinded, or which outcomes were blinded.

Many of the included trials were in heterogeneous populations that could include adults or elderly patients with mild to severe of COPD. Moreover, 44 studies did not report the stage of COPD, only that it was stable. This is likely to have been a major factor in the heterogeneity found in a number of the meta-analyses.

The selection criteria for participants were specified in 42 studies and the outcome measures were described and reported on in 72 studies, so these were considered free from selective reporting of results and were judged as low risk of bias, whereas any study that did not report all outcomes was judged as high risk.

Withdrawals were reported in only 11 studies and this represents a 1.22 percent withdrawal rate. As would be expected, the withdrawal rate was higher in the seven longer-term studies which ranged from three months to six months (withdrawal rate 1.48%). However, only one of these studies used intention-to-treat data analysis to control for the effect of withdrawals. Overall, the withdrawal rate was low, so the lack of ITT analysis is unlikely to have affected the overall outcomes.

2) Methodological quality assessed by Jadad’s scale

Jadad’s scale emphasizes the description of three aspects, randomization, double blinding and withdrawals. If the score is greater or equal to three, the methodological reporting can be
considered to be of good quality. Scores of 3 or more were found for 26 studies. The major reasons for the lower scores were: no double blinding performed, the authors did not describe whether there were withdrawals or not, as well no explanation of the reasons for withdrawals in the studies.

Published SRs of CHM clinical studies for the treatment of various diseases, have often found that the methodological quality as assessed by Jadad’s scale was low (549-551). The need to improve the design and methodological reporting of CHM clinical trials has been a concern for a number of years and the quality of studies appears to be improving (552).

Because of the high risk of bias of blinding and allocation concealment in the most included studies, the results for outcome measures that involve subjective assessment are less reliable and must be interpreted with caution. These include symptom scores, effective rate, exacerbation rates and adverse events which are subject to interpretation by physicians and Qol questionnaires which may be affected when patients know their group allocation. On the other hand, measures such as lung function and the results of laboratory tests should be less affected by blinding issues.

Although, methodological shortcomings such as inadequate generation of the randomization code, insufficient concealment of random allocation and lack of blinding are likely to have contributed to discrepancies among the results of these trials, the following other factors also may impact on the reliability of the results of these analyses.

The relatively small sample sizes and short lengths of duration of treatment may impact on the reliability of the outcomes and on the generalisability of the results to a clinical setting in which long-term therapy is a necessity. Amongst the 101 studies only 4 were for one year (363, 403, 420, 460).

Therefore, besides proper trial design and methodological reporting, large sample size, long-term duration of treatment and patients at a consistent COPD stage, preferably stage one or two, are strongly recommended in future clinical trials.

These SRs have also provided evidence to suggest a difference in exacerbation rates or frequencies between COPD patients treated by CHM alone or CHM plus RP and those treated by RP alone. However, since patients with exacerbations were excluded from these studies at randomization, this outcome does not indicate that the CHMs were effective for treating
exacerbations, only that they may have reduced the incidence of exacerbation in patients with stable COPD.

7.10.5.5 Variability in the procedures for diagnosis and collecting outcome measure data

Diagnostic criteria

Among the one hundred and one included trials, most of the participants were diagnosed as COPD by either the guideline for the diagnosis and management of COPD produced by the CSRD in 1997, 2002, 2007 or by GOLD. In addition, a few of trials set up selection and diagnostic criteria based on books on internal medicine. However, ten studies did not indicate how the participants were diagnosed.

In the latest version (2007), the national standard for the diagnosis and management of COPD issued by CSRD is in accordance with the the GOLD international standard, and earlier versions were similar to the GOLD guidelines. Therefore, guidelines similar or equivalent to GOLD are not only widely used in clinical practice and trials, but are also recommended as the criterion for the definition of COPD in China. Consequently, variations in diagnosis and inclusion criteria appear to be less variable that might be expected given the use of different standards.

Classification of the severity of COPD was described in 57 studies. However, most of these studies did not report a description of the performance of pulmonary function tests except in one study in which the performance of a spirometric test was based on the standard procedure in the GOLD guideline. Therefore, there may be variation in the way in which the severity of COPD was assessed. This may have impacted on results and may limit comparability between trials.

The majority of included studies were from China and all used Chinese herbal medicines, but only 43 studies characterized participants according to the syndrome differentiation procedure used in Chinese medicine. Since the specific syndromes are the basis for the selection of formulae and herbs used in treatment, the lack of syndrome differentiation is a major shortcoming in a clinical trial and the inappropriate use of a formula may affect results. One reason for not using or not reporting the use of syndrome differentiation is the lack of a national standard. Therefore, it is very important that a standard for for the CM diagnostic
criteria and syndrome differentiation for COPD be set up and for this to be linked to the stages of COPD progression.

**Procedures for collecting and reporting outcome measure data**

As mentioned above, the procedures for performing pulmonary function tests were seldom described in the articles. Also, few trials reported that procedures were based on the guidelines developed by GOLD.

Especially when multiple spirometric indices are measured, it is important that the performance procedures be clear, since variation in procedures within a trial can affect results and when different procedures are used between trials this can affect the comparability of the results. This aspect is less of an issue when a standardized test such as QoL using SGRQ or Cai’s questionnaire are used.

**7.10.5.6 Reporting bias**

Duplicated publication of articles on the same RCTs may result in bias since such articles tend to each report on specific outcome measures only. This issue was identified at the beginning of the SRs and any multiple publications were counted as a single RCT and any selective outcome measure reporting issues were identified and assessed under Risk of Bias.

Another aspect of reporting bias is exclusion of unpublished material. Efforts were made to identify such material in the extensive searches, but few of the trials identified qualified for inclusion. However, it remains possible that trials with negative findings may remain unpublished. This may be due to the lack of awareness of the need to register clinical trials in China and/or journal editors rejecting the negative trials. The evidence suggests there is publication bias in favour of positive studies in China and other countries [202, 203]. In the future, it is important that both positive and negative studies be reported.

There are also deficiencies in the reporting of safety aspects, ethics approval, the use of consent forms signed by subjects with these being reported in only a few of the published articles. Also, most articles did not provide a protocol so it was difficult to determine whether there was selective reporting.

When only symptom scores are reported as outcome measure, there is the potential for subjectivity in measurement especially when blinding is inadequate. All of these aspects need
to be considered and improved in future trials.

### 7.10.5.7 Variation in the form, composition and dosage of the CHMs used and adverse event reporting

There are wide variations among the tested Chinese herbal medicines. These may involve formulae or single herb extracts that may be used the form of pills, capsules, granules, syrups or decoctions.

Furthermore, in most of the studies information on the quality standards for the production of the CHM preparations or the manufacture of the CHM products is lacking. This limits the comparability of trials and the meaningfulness of dosage specifications. Future trials should provide information about product standardization including composition, quality control, concentration of key phytochemicals, and detailed dose regimen.

There was inadequate reporting on adverse events in the included trials. Eighty trials did not mention any results about adverse effects. 4 trials reported inconsistent minor adverse effects which were not related to the herbal medicine and 17 trials reported that no adverse event was observed in their studies. These results suggest that the herbal medicines were well tolerated, but they may also reflect inadequate data collection on this aspect and/or inconsistent methods for interpreting what consists an adverse event, a serious adverse event or which adverse event is a result of the intervention.

In some studies, the safety of the herbal medicine was demonstrated through pre and post blood tests including liver function and kidney function that indicated no adverse effect of the CHM on the blood test results for these functions in six studies. In future studies, adequate reporting on adverse events is needed and the safety of the herbal medicines needs to be monitored and reported in the published results of the clinical trial.

### 7.10.6 Interpreting the meaning of outcome measures and meta-analysis results

#### 7.10.6.1 Lung function

The best method of evaluating the effectiveness of a therapeutic approach is measuring changes in spirometric parameters. Due to the stability of measurement, repeatability and high resolution, FEV$_1$ and FVC as well as the ratio of FEV$_1$/FVC are commonly used in clinical trials for COPD. FEV$_1$ is an important spirometric parameter which is most relevant to the
diagnosis and classification of the severity of COPD. It may be increased by 12% (200 ml) soon after inhalation of a Beta-2 agonist such as Salbutamol (10, 174).

In two studies of CHM versus placebo over 2 months, there was an average increase of FEV₁% predicted of 13% in Wu (2006) (342) with 200 participants and 10.88% in Li (2006-1) with 62 participants (69). In a longer study in which CHM was compared to no treatment, a relative benefit of 11.49% was found in Zhang (2006) with 46 participants for six months, with participants in the no treatment group showing little change and those in the CHM group improving (377). In Hong (2005) in which 38 participants were given CHM or no treatment for six months, the FEV₁ increased slightly from a baseline of 0.982 (L) to 0.998 (L) at six months follow up (i.e. one year later) in the treatment group, whereas there was a decline from 0.987 (L) to 0.911 (L) in the control group. These four studies suggest the CHM alone was effective improving and/or reducing decline in lung function in the short to medium term when compared to control groups. However, patients with FEV₁ % predicted of 40% to 50%, may not benefit from oral CHM.

When CHM was used in conjunction with theophylline was compared to theophylline, Feng (2006) reported an improvement of FEV₁% predicted of 7.42% in 69 participants over 30 days (401) and an improvement of 8.22% was found in Liang (2005) with 63 participants for one year (460) (Fig 7.3). Also, an increase in FEV₁% of 22.35% was reported by He (2010) for CHM plus theophylline sustained-release vs placebo plus theophylline sustained-release with 98 participants over six months (426).

Improvements in FEV₁% predicted ranging from 7.95% to 10.43% were reported in three studies of CHM plus Salmeterol Xinafoate/Fluticasone Propionate versus Salmeterol Xinafoate/Fluticasone Propionate, with 60 participants for six months in Liu (2010) (386) and Pu (2010) (427), and with 58 participants for two months in Zhu (2010) (404). Similarly, an improvement of 12.46% was found in Jia (2007) for CHM plus Ipratropium bromide vs Ipratropium bromide with 55 participants over 6 months.

Although these studies demonstrated improvements in FEV₁, a considerable number of studies found no significant benefit (Fig 7.3). These differences in effect may have been related to the severity of the COPD of the participants, the particular CHMs and dosages used, or other factors. These issues require further clinical evaluation.
7.10.6.2 Symptoms

The results suggest that oral CHMs can markedly relieve symptoms including chronic cough, sputum production and dyspnea. However, most studies used subjective scales so the magnitude of the effect is difficult to assess. In the 3 studies that used the MMRC dyspnea scale there was a significant improvement (p<0.05) in dyspnea scores, but in each of the 3 studies that the relative benefit was less than 0.5. While this is a modest effect, considering the distress that dyspnea produces, relief of this symptom is clinically important.

7.10.6.3 Quality of Life

Scores on the SGRQ range from 0 to 100 with a higher score indicating a decline in quality of life. A change of 4 units or more is considered to be clinically meaningful (553). The change in SGRQ score was more than 4 units when CHM was compared to placebo in one study with 60 participants for over one month (375); and when CHM was compared to no treatment in Zhang (2009-1) (367) with 104 participants for over six months and in Wu (2007) with 122 participants for over 4 months (365); and when CHM was compared to Ipratropium Bromide with 67 participants for over six months (Zhu 2007).

Also, when CHM plus Salmeterol Xinafoate/Fluticasone Propionate was compared to Salmeterol Xinafoate/ Fluticasone Propionate in Liu (2010) with 60 participants for six months, an average improvement of 6 points was found (386).

In other studies, the effectiveness of the CHM was difficult to interpret. For example, the RP was not provided in Huang (2005) (347); multiple medicines were used in You (2008) (366). However, based on the overall results, oral CHM may improve QoL, particulary when used as long-term therapy.

7.10.6.4 Exacerbation incidence

The meta-analysis found that oral CHM plus ipratropium bromide or theophylline may reduce COPD exacerbation frequency in the range MD -0.34 to -1.80 (95% CI) (p<0.01) in one year based on three studies (412, 415, 460) and when CHM alone was compared to no treatment in one study the reduction was MD -1.20 (95% CI) (p<0.00001) (383).

According to GOLD, patients with Moderate COPD have 0.7-0.9 exacerbations per year, Severe COPD patients have 1.1-1.3 exacerbations per year and Very Severe COPD patients
have 1.2-2.0 exacerbations. In the included studies, the level of COPD severity was not clearly defined and patients may have different levels, so it is unclear whether the reduction of around one exacerbation found in the studies was related to a sub-group of the COPD patients. Nevertheless, since exacerbations are associated with morbidity and mortality, any reduction is clinically significant and the potential benefit of CHM treatment on this aspect of COPD warrents further research.

7.10.6.5 6MWD

The best results were an average increase of 40 meters or more when CHM plus RP was compared to RP (312, 345, 347, 386, 415), and when CHM was compared to no treatment (408, 420). For example, CHM plus Salmeterol Xinafoate/Fluticasone Propionate versus Salmeterol Xinafoate/Fluticasone Propionate was used in Chen (2009-1) and in Liu (2010), both with 60 participants over three months with relative increases of 47 and 66 meters respectively.

CHM plus Ipratropium Bromide versus Ipratropium Bromide was used in Zhang (2010) with 120 participants over six months with a difference of 35 meters. However, the RP was not provided in Huang (2005) or Guo (2008) so the results are difficult to interpret.

In Shao (2006), the value for 6WMD was slightly lower after one year compared to baseline in the no treatment control group which suggests that the CHM prevented decline over the year.

Overall, oral CHM plus Salmeterol Xinafoate/Fluticasone Propionate or Ipratropium Bromide, as well as CHM alone appeared to produce a clinically significant improvement in the exercise tolerance of patients with stable COPD.

7.10.6.6 Surrogate outcomes

BODE index was used as a surrogate outcome in two studies which reported reductions of about 1.3-1.5 (p=0.04 or p=0.01). When the BODE index is decreased by one, the survival rate will be increased by 1.6 times (480), so the decline found was clinically significant. Since the BODE index is an internationally recognized measure that is associated with clinical outcomes it is recommended to be included in future clinical trials.

Inflammation is an important feature of COPD, so a number of surrogate outcomes for
systemic inflammation were measured including inflammatory cytokines, lymphocyte subsets, and CRP. Due to the small number of studies, the effectiveness of the oral CHMs could not be assessed by meta-analysis and the significance of the changes reported is difficult to interpret. None of the biomarkers measured are specific for COPD but recent studies tend to favour measures of CRP, IL-8 and TNF-α since these are correlated with lung function and may even be predictors of the severity of COPD (482, 496). Therefore, these are useful outcome measures for future clinical trials.

The levels of immunoglobulins were included in some trials on the basis that they reflect the immune status of patients with COPD. However, these are not sensitive outcomes for patients with stable COPD.

In this SR, D-dimer antigen test was not measured in any studies. It is useful outcome measure for patients with moderate or severe COPD, particularly in the acute exacerbation stage. Whether it is correlated with syndrome of blood stasis or not could be evaluated in future studies.

7.10.6.7 Other outcome measures

Blood gas analysis

In the studies that used P02 as an outcome, the best result was an average increase of 0.68 KPa (5.1 mmHg) in Lin et al 2003 for CHM vs placebo over 2 months (Fig 7.30). Although this change was not large, it is clinically significant. A similar change (0.64 KPa / 4.8 mmHg) was found in Chen et al (1) 2009, for the combination of CHM plus Salmeterol & Fluticasone over 3 months. However, in some studies the change was too small to be clinically useful. Also, it appears unlikely that this level of improvement would be evident in the longer term.

Blood rheology parameters

The effectiveness of the oral CHMs on blood rheology could not interpreted by meta-analysis due to the small number studies that measured the level of plasma viscosity, shear rate and hematocrit. Increase in blood viscosity reflects the progression of COPD. Also, in Chinese medicine, increased blood viscosity it is regarded as relevant to the syndrome of blood stasis and can be used to guide the selection of herbs and formulae. Hematocrit levels of over 55% can indicate polycythemia in response to low oxygen availability, so hematocrit reductions in these patients are clinically important. However, in the few trials that measured hematocrit, it
was not clear how many patients achieved hematocrit reductions.

Further research is required on the effects of blood activating herbs on blood rheology and also which herbs can reduce elevated hematocrit levels in COPD patients.

**Nutrition status**

Nutritional status is of particular concern in patients with COPD so relevant outcome measures should be included in clinical trials. BMI index was measured in four studies. It is a component of the BODE Index and is important measure of nutritional status in COPD studies. Other proxy measures of nutritional status included the level of serum ALB in four studies, PALB in five studies and Leptin in two studies. However, as discussed above, each of these proxy measures presents data interpretation difficulties in COPD. Therefore the evidence of CHM action on nutrition provided by this SR remains unclear. Further studies that focus on nutritional status and include outcome measure such as BODE Index and fat free mass are needed.

**7.10.7 Authors’ conclusions**

This evidence should be interpreted with caution due to the potential risks of bias in many of the included trials. Larger, longer-term trials are necessary to assess the validity of these results, which would be of major clinical relevance if replicated in well designed, adequately powered RCTs. The use of CHMs that employ the principal strategies identified in this SR appear to benefit a majority of stable COPD patients. However, their usefulness in exacerbations remains unclear, and it is difficult to determine whether these benefits would be evident with long term treatment.

Few instances of adverse effects were reported and none were severe AEs, so it appears that the safety profile of the CHMs used in the 21 studies that reported AEs was good. However, 80 studies did not report these important data, so the safety profile of the CHMs used in these studies remains unclear.
8 Chapter Eight: General Discussion

This chapter summarises, compares and contrasts the main results from the two parts of this thesis and discusses how the commonly used formulae and herbs may function in the treatment of COPD from both the experimental and traditional perspectives. Finally, the strengths and weaknesses of this study are discussed and directions for further research are identified.

8.1 Summary of results from the analyses of classical literature and modern clinical trials

This project included two main parts: an analysis of the Chinese classical literature and an analysis of the results of modern clinical trials of herbal medicines. These two parts employed different methodologies and criteria to investigate the use of Chinese herbs and herbal formulae for treating stable COPD. Prior to searching the Chinese classical literature, COPD was defined. Several disease and symptom names used in the classical medical literature that were considered relevant to COPD were selected as search terms for the classical literature. Herbs and formulae recorded in classical books to treat these COPD-related diseases were searched using these terms in the Zhong Hua Yi Dian (ZHYD CD). In the second part, an analysis of the modern clinical trial literature was conducted according to the guidelines of the Cochrane Review Airway Group. This analysis evaluated the effectiveness and safety of oral Chinese herbal medicines (CHMs) for treating patients with stable COPD using SRs and meta-analyses.

8.1.1. Main findings from the analyses of the classical literature

When the findings of the two main parts of this study were compared, distinct differences were evident in the concepts of COPD-related disorders that were found in the classical literature and COPD in the clinical trials, even though both employed the conceptual framework of TCM. Related to these differences, differences were found in the herbal formulae used and in the primary herbs used between the citations in classical books and the RCTs. Each of these three aspects is discussed below.
8.1.1.1 Traditional terminology relevant to COPD

COPD as a medical condition has a short history of only several decades; thus, there was no mention in the classical literature of a term that corresponded directly to COPD. The aetiology and pathogenesis of this disease are very complex. As discussed in Chapter 2, COPD can develop from chronic bronchitis, asthma, emphysema or other respiratory diseases. In modern TCM, COPD is commonly known as Fei zhang (251, 332).

In the classical Chinese medical literature, because no particular disease name could be assumed to correspond to COPD, respiratory disorders that shared similar symptoms and signs with COPD needed to be identified. Based on the descriptions of the symptoms and signs of these respiratory conditions used in the classical texts, it was very difficult to make a diagnosis or to assess the stage, length, severity or acuity of disease development. Nevertheless, in order to identify citations on conditions that may have been COPD, a quantitative and qualitative system was established to assess each respiratory disease mentioned in the sample of 1,000 classical books in order to best exclude those medical conditions that were unlikely to have been COPD and to identify diseases that were possibly or likely to have been conditions that would now be considered COPD.

Seven search terms were identified as being relevant to COPD-related diseases in the classical literature. These were: Jiu ke sou (long-term cough); Ke chuan (cough and dyspnoea); Chuan sou (dyspnoea and sputum); Chuan zheng (dyspnoea); Fei zhang (lung distension); Tanyin kesou (phlegm-fluid with cough); and Zhi yin (thoracic fluid retention). They were all used to search the ZHYD, with each citation extracted to a database and analysed for its specific relevance to the modern concepts of stable COPD and COPD exacerbations. The period ranging from the 11th century (Song dynasty) to the early 20th century (late Qing dynasty) produced the highest number of citations.

Based on its presentation, COPD may be classified as either being in the stable stage or in the acute stage. Different stages exhibit different symptoms and require different treatment plans. At the stable stage, COPD patients mostly display the clinically observable symptoms of sputum production and shortness of breath upon exercise or chronic cough and sputum production. It is at the exacerbation stage when the symptoms of dyspnoea and chest tightness become more evident.

When only a few symptoms are present, the clinical differentiation of chronic bronchitis,
emphysema, asthma, heart failure and a variety of other disorders is difficult; this is particularly so when the descriptions of the symptoms are brief. Consequently, to find the closest correspondences to COPD in the classical literature, combinations of ‘non-acute’, ‘no haemoptysis’, ‘cough’, ‘sputum production’, ‘dyspnoea’ and ‘chest tightness’ were the main criteria used to limit the data set. However, the result of this was to find conditions that were possible COPD at the severe stage and/or COPD exacerbations. At the same time it was not possible to screen out all other severe lung disorders, because decisions could only be made based on the information included in the citations, which may have been incomplete.

Therefore, even when all selection criteria were applied, citations were likely to include some respiratory conditions that were not COPD. Also, citations that referred to possible examples of stable COPD and were likely to be in the data set were not identified when all selection criteria were applied, because these were much more difficult or impossible to distinguish from other related conditions due to their lack of distinctive clinical manifestations.

Among the search terms used, some were more or less closely aligned with the main symptoms of COPD. Zhi yin was found to be an unlikely term, whereas Fei zhang was found to be associated with all of the main symptoms. This did not mean that Fei zhang was the classical term for COPD; rather, this term was only used for conditions that were consistent with severe COPD and/or COPD exacerbations. It could have been used for other conditions as well, but this issue was not explored. Similarly, Tanyin kesou and Chuan sou were used to refer to conditions that were consistent with severe COPD, but may also have been used for disorders like chronic bronchitis and other respiratory diseases.

Therefore, among the search terms, Fei zhang (lung distension), Tanyin kesou (phlegm-fluid with cough) and Chuan sou (dyspnoea and sputum) were found to be the most similar to COPD, although not all of the citations found under these search terms were analogous to COPD.

Modern TCM books consider that Fei zhang was analogous to COPD and also mention that COPD was classified under Tanyin. During the search, Tanyin was too broad a term to be considered, although a number of citations identified under Tanyin kesou were consistently likely to be COPD (248). In contrast, Chuan sou is not mentioned in modern TCM books as a classical term for COPD and is generally not included as a disease category, although it is listed in Zhong Yi Da Ci Dian (中医大辞典) (554).
8.1.1.2 Aetiology and pathogenesis of COPD

Although COPD was not mentioned in the classical literature, there were discussions on the aetiology and pathogenesis of various types of cough, dyspnoea and lung distension (Fei zhang). In the book *Mu Jing Da Cheng* (目经大成) (c 1741), the term Ke sou, which now refers to ‘cough’, was divided into the terms Ke (咳), which had ‘sound’ but was unproductive, and Sou, which was productive but without ‘sound’ (嗽) (555). From the modern perspective, Sou is a symptom that is typical of stable COPD. However, these two terms were generally combined as Ke sou (cough with sputum) so the separate searching of Sou was not feasible.

Ke sou could be due to external factors, such as wind and heat, or to phlegm or food and were mainly treated with formulae and herbs that eliminated these pathogenic factors. In modern TCM, these kinds of cough are mainly associated with acute respiratory infections. However, these kinds of cough can also appear as complications and exacerbations of chronic conditions, including COPD.

In addition to the external pathogenic types of cough mentioned above, the *Mu Jing Da Cheng* (目经大成) said that cough could also be caused by qi deficiency and explained that this cough was due to lung weakness that failed to produce water and resulted in the production of heat. Therefore, it was treated by formulae like Bu Fei Tang, which included Ren shen and Huang qi for tonifying the lung, Zi wan and Sang bai pi for clearing the lung, and Di huang and Wu wei zi for replenishing the lung (555). This type of cough is closer to the symptoms of stable COPD and the aetiological explanation is consistent with modern TCM concepts of some types of COPD (333, 556).

The *Zheng Yin Mai Zhi* (症因脉治) (c 1641) explained that qi deficiency cough could be due to damage to the lung qi or to excess food and drink that damaged the spleen qi, which would lead to lung damage with shortness of breath and Sou (sputum production). These types belong to the syndrome category of Qi deficiency cough (qi xu ke sou). The treatment should aim to strengthen the spleen and lung using formulae like Si Jun Zi Tang, Shen Zhu Gao, Bu Zhong Yi Qi Tang, Qiong Yu Gao or Sheng Mai San (557). In modern TCM, a similar approach is also used and formulae based on Si Jun Zi Tang and Bu Zhong Yi Qi Tang were evident in the RCTs.
In modern TCM, the pathogenesis of COPD involves turbid phlegm accumulation in the lung, which impairs lung function, together with qi deficiency associated with prolonged illness. This combination of qi deficiency that fails to promote the movement of blood, and phlegm that blocks the circulation of blood can lead to blood stasis. Blood stasis is considered an important factor in the modern TCM concept of COPD, but it was seldom referred to in the classical citations. Consequently, herbs that aim to remove blood stasis (e.g. Dan shen, Tao ren) appear frequently in the RCT formulae, but are infrequent in the classical formula lists.

Blood stasis as an aspect of aetiology is prominent in modern TCM, but it is not absent in the classical literature. Zhu Danxi (ca. 1281-1358) in the Dan Xi Xin Fa (丹溪心法) mentioned blood stasis as an aspect of the pathogenesis of lung distension (Fei zhang). He said that ‘people with Fei zhang have sputum and cannot sleep, not on their right or left side, this disease is due to phlegm (tan) combined with blood stasis (yu xue 瘀血) obstructing the qi. The treatment should nourish the blood (yang xue 养血) and promote the flow (liu dong 流动) of qi, subdue fire and course liver (jiang huo shu gan 降火疏肝) to clear the phlegm.’ He suggested using Si Wu Tang plus Tao ren, He zi, Qing pi, Zhi li, ginger juice and others (558). The condition described here was more like an acute exacerbation than a stable condition, although the combination of phlegm and blood stasis was similar to the modern TCM concept of COPD aetiology.

This was not a typical example of the treatment for Fei zhang in the classical literature, so the frequency of the herbs mentioned was not high. Nevertheless, it provides an early illustration of the principle of removing blood stasis that has become a more standard approach in modern CHM. As can be seen in the lists of higher frequency herbs in the RCTs, herbs like Dang gui, Di huang and Tao ren are all included, whereas none of these herbs are high in the classical lists (see table 8.1).

Modern Chinese medicine considers that the aetiology and pathogenesis of COPD has a deficiency at its root (ben) and an excess in its branch (biao). Its nature is phlegm, deficiency and stasis and its development is due to turbid phlegm accumulation in the lung that impairs lung function. Because it is a prolonged illness, this causes qi deficiency and a further failure to promote and circulate the movement of blood, which leads to blood stasis (559). This view is more detailed than the descriptions found in the classical literature, although it is based on the classical understanding of chronic respiratory diseases.
8.1.1.3 Investigations into the nature and pathogenesis of COPD in modern Chinese medicine

Since the 1980s, research into the concept that COPD has a deficiency at its root (ben) and an excess in its branch (biao) has gradually progressed. Phlegm was regarded as characteristic of an excess in the branch, which manifested as various syndromes involving phlegm, such as heat-phlegm, cold-phlegm, phlegm-dampness and phlegm-dryness. These phlegm syndromes were shown to be correlated to the level of damage to neutrophils and ciliated columnar epithelium as well as to changes in the concentration of cAMP and the cAMP/cGMP ratio, particularly in the heat-phlegm syndrome.

With regard to research on the concept that the root of COPD was deficiency, research has focused on exploring correlations between deficiency and immune functions, endocrine functions, energy metabolism and autonomic nervous system functions (560).

Investigations using chest X-rays and measures of pulmonary function have shown differences between the lung deficiency, spleen deficiency and kidney deficiency types of COPD, which indicates that these syndromes represent a change from a mild to a severe condition.

For lung deficiency syndromes, chest X-rays displayed lung markings with the diaphragm position and activity in their normal ranges, although there was a decline in the PEF that indicated pulmonary dysfunction in the small, medium and large airways. In lung and spleen deficiency, chest X-rays displayed increased lung markings of the blur, net and/or spot shadow types, the diaphragm position was slightly lowered and there were declines in FVC, VC and IC, which implied that lung elasticity had diminished and Raw had increased.

When kidney deficiency was also present, the lung markings appeared slender and sparse, the diaphragm was lower and its mobility had decreased. The X-ray appeared bright as in emphysema or there were pulmonary bullae, and the functional residual capacity was increased (561).

Other correlations between deficiency syndromes and disease deterioration were reported in a study by Zhu et al. (2008), in which they found that phlegm turbidity, deficiency and blood stasis reflected the progressive development of COPD (e.g. from mild to severe). Significant interrelationships were found between the changes in pulmonary function of COPD patients
who had turbid phlegm accumulation, deficiency and/or blood stasis. This study showed that patients with turbid phlegm accumulation only had better pulmonary function, whereas worse pulmonary function was correlated with increased levels of deficiency and blood stasis (562).

8.1.1.4 Progression of disease between organs

The initial site of disease in COPD is in the lung. Prolonged illness then affects the spleen and, later, the kidney. This disease progression has been verified by research. A study by Tang at al. (2005) showed that there was a very close relationship between the five organs in Chinese medicine and the progression of COPD at different developmental phases. This study collected clinical case reports and established a database.

At the earlier stages, chronic bronchitis was related to the lung and liver, and the combination of chronic bronchitis and emphysema was associated with the lung, spleen and kidney. With further development of emphysema involving heart disease, the organs affected then included the lung, spleen, heart and kidney or the lung, spleen, heart and liver, as well as the kidney (563). In the RCTs, the subjects tended to be in the middle stages of the disease, whereas many of the citations on Fei zhang and other COPD-related disorders found in the classical books appeared to belong to the later phases of the disease.

8.1.1.5 Syndrome differentiation in modern TCM and the RCTs

In Chinese medicine practice, disease assessment involves diagnosis (of the disease), syndrome identification (of the pattern) and assessing the symptoms and signs (the presentation), followed by a treatment plan. In the classical literature, however, only the symptoms and signs were described in the majority of citations. Few of these combined differentiation of the syndrome with the description of the presenting symptoms and signs. By comparison, the modern TCM literature usually includes the following: diagnosis, syndrome identification and symptoms and signs, followed by the herbal formula with or without modifications.

A study by Fu et al [15] investigated CM syndromes in patients with stable COPD or ECOPD using a large sample size (99 cases). This study showed that the incidence rates of excess syndromes in stable COPD were (in decreasing order): blood stasis; phlegm heat accumulation in the lung; followed by phlegm dampness retention in the lung. By comparison, the incidence rates of deficiency syndromes in stable COPD were (in decreasing order):
deficiency of lung qi; deficiency of spleen qi; followed by deficiency of kidney yang.

Another study collected information from six hospitals for patients with COPD at the stable stage (774 cases) and analyzed the syndrome elements in a database using the latent structure method (564). These results identified syndromes of the lung, spleen, kidney, stomach and heart, which had the features of yin deficiency, yang deficiency, qi deficiency, phlegm (dampness), blood stasis, qi stagnation and heat. The authors concluded that these were similar to the syndromes identified in clinical settings (565).

Shang et al. (2004) analysed correlations between CM syndromes and the four stages of COPD severity. Their results indicated that lung deficiency and spleen qi were the main types of deficiency syndrome at all COPD stages, deficiency of kidney yang was mostly present in severe and very severe conditions, blood stasis also appeared in both severe and very severe conditions with a few cases at the moderate stage, and there were a few cases of phlegm retention at all stages (566). Therefore, both qi deficiency and phlegm appeared at all stages, whereas blood stasis was more evident at the more severe stages.

The 101 RCTs distinguished numerous syndromes in the following descending order: 1. lung and kidney qi deficiency; 2. lung and spleen qi deficiency; 3. lung, spleen and kidney qi deficiency; 4. lung qi deficiency; 5. qi deficiency and blood stasis; and 6. spleen and kidney deficiency with phlegm, and lung and spleen with phlegm stagnation. These syndromes were similar to those reported in the studies cited above, although syndrome differentiation was not mentioned in more than half of the included RCT studies. Thus, we could not make comparisons between studies based on syndrome differentiation and the severity of the COPD. Also, there are still no standard COPD syndromes in modern TCM.

### 8.1.2. Main findings from the clinical trials

The main findings from the analysis of the clinical trials were reported in the results of three systematic reviews: 1. oral ginseng formulae for stable COPD, which were included in 12 randomized control trials (RCTs); 2. oral CHM for improving the quality of life of patients with stable COPD, which was included in 27 RCTs; and 3. oral CHM for stable COPD with physiological and symptomatic outcome measures, which was included in 101 RCTs.

#### 8.1.2.1 Oral ginseng formulae for stable COPD

Twelve ginseng formulae from 12 RCTs that met the inclusion and exclusion criteria were
included (see chapter 6.1). It was found that ginseng formulae had possible effects for improving lung function, quality of life, alleviating symptoms and reducing COPD exacerbation rates (84). However, most of the included studies had a high or an unclear risk of bias as assessed by the Cochrane risk of bias and had low methodological quality as assessed by Jadad’s scale.

8.1.2.2 CHM for improving Quality of Life

As one of the outcome measures used in clinical trials, a quality of life questionnaire was used in 27 RCTs that matched the selection criteria. A meta-analysis found that oral CHMformulae may be beneficial for improving the QoL of patients with stable COPD (85). However, the weak methodological quality of these trials limits the strength of this conclusion.

8.1.2.3 CHM for physiological and symptomatic outcome measures

A total of 101 RCTs that studied patients with stable COPD were included in this review. All were parallel group studies that involved oral administration of CHM formulae or extracts of a single herb. Twelve RCTs compared CHM with placebo, 15 RCTs compared CHM with RP, 46 RCTs compared CHM plus RP with RP, 16 RCTs compared CHM with no treatment and 12 RCTs compared CHM with other CHM. The outcomes included spirometric parameters, symptom scores, exacerbation frequency or rate, BODE index, BMI, 6MWD, blood gas analysis and biomarkers.

Assessments of risk of bias for all the included studies were judged using the six Cochrane domains for risk of bias. Of 101 studies, no study was judged as having a low risk of bias for all six domains, and only two studies (79, 461) provided adequate descriptions for both randomization and blinding. Zhang et al (2003) conducted a trial that compared two CHMs and Gross et al (2002) found that a ginseng extract significantly improved lung function after three months when compared with placebo.

When the methodological quality was assessed by Jadad’s scale, only 26 studies received a score of ≥3 and could be regarded as having higher methodological quality, while the remaining studies were assessed as having low or weak methodological quality.

A meta-analysis of these reviews found that oral CHMs (including ginseng formulae) may have promising effects for improving lung function, improving QoL, reducing exacerbation
rates or frequencies, alleviating symptoms and improving exercise tolerance as determined by
the 6 minute walk distance test when CHM was compared with the control groups,
particularly when CHM plus RP was compared with RP. No serious adverse events were
found in any of these studies.

8.2 Comparisons of the formulae used in classical books and in RCTs

8.2.1. Frequently occurring herbs in classical books and RCTs

The most frequent formulae in the total classical data set, after the general exclusions (898
formulae) and excluding 187 unnamed formulae, were Xiao Qing Long Tang, Xiao Ban Xia
Tang, Yue Bi Jia Ban Xia Tang, Xiao Qing Long Jia Shi Gao Tang, Xiao Ban Xia Jia Fu Ling
Tang, Mu Fang Ji Tang, Wu Ling San, Zao Jiao Jian Wan and Ma Huang Gan Cao Jia Xing
Ren Sheng Jiang Tang (see Table 5.22). Six of the high frequency formulae were also found to
appear at step 2 (dyspnoea plus cough) of the step-wise hierarchical combinations (Table 5.26)
and in the list of formulae identified using the global scoring system (Table 5.33).

Ma Huang San, Zi Wan Tang and Ting Li Da Zao Tang became relatively more frequent when
the global scoring system was used, while Xiao Ban Xia Jia Fu Ling Tang, Wu Ling San and
Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang became less frequent.

The overall lists of formulae were strikingly similar. However, of the top frequency formulae,
only Zao Jiao Jian Wan remained among the 21 formulae included at step 7. Thus, when the
four symptoms were combined together, only a small number of formulae remained and these
tended to differ from the formulae in the more general lists.

One reason for these differences is the large number of different formula names in the total
data set. This meant that many formulae had similar compositions. However, due to the
different names, they only appeared at low frequencies in the data set. Consequently, the
‘individual herb’ was considered a more appropriate level of analysis for comparisons.

The main functions of the above formulae are dispersing the lung and suppressing wheezing,
dispersing the lung and resolving phlegm as well as suppressing wheezing and stopping
cough. They mainly target the acute stages of respiratory conditions.

The following nine formulae were used frequently in the 101 RCTs: Liu Jun Zi Tang; Bu Fei
Tang; Shen Ge Tang; Bu Zhong Yi Qi Tang; Jian Pi Yi Fei granule; Zhou Fei Tang; Li Jin granule; Man Zhi Ke Chuan Ning liquid; and Fei Kong Tang. These formulae mainly tonify the lung and/or fortify the spleen and/or tonify the kidney, with the addition of herbs to activate blood or relieve cough or dyspnoea.

8.2.2. Reasons for the use of different formulae in the RCTs and classical books

None of the top ten frequently appearing formulae was the same when comparing the classical and modern reviews.

For treating COPD, the contemporary formulae found in the RCTs tended to focus on tonifying the lung and fortifying the spleen. Typical formulae included Liu Jun Zi Tang, Bu Fei Tang, Zhou Fei Tang and others. These formulae all originated from the classical literature, but they did not appear among the high frequency formulae in the classical literature data. The main reason was that the RCTs focused on stable COPD patients with particular emphasis on the stable phase without any exacerbations or complications, such as heart or kidney disorders. Consequently, the symptoms of cough and dyspnoea may be relatively mild in these patients and may be partially managed with pharmaceutical medicines. Therefore, the focus of the CHMs used in the RCTs was not on symptom management but on strengthening the body.

In contrast, the principal focus of the formulae identified in the classical literature was on the management of cough and dyspnoea and the resolution of phlegm, with strengthening of the lung and spleen as secondary aims. In the modern context, the high frequency formulae found in the classical literature were considered to be more applicable to the acute exacerbation stage of a chronic lung disorder than to the stable stage. This difference in focus might partly explain the different usages of formulae.

8.3 Comparisons of herbs occurring at high frequencies in the RCT and classical data sets

8.3.1 Herbs occurring at high frequency in classical books

The included COPD-related classical citations provided a total data set of 5,858 herbs, which were included in 898 formulae. The herb with the highest frequency was Gan cao, which was included in 372 formulae. Other commonly used herbs mentioned in formulae in decreasing order (with the frequency in parentheses) were: Ban xia (266); Xing ren (249); Ren shen (217);
Fu ling (209); Wu wei zi (181); Chen pi (170); Sang bai pi (142); Sheng jiang (127); Kuan dong hua (124); Ma huang (117); Zi wan (114); Rou gui (113); Bei mu (102); Jie geng (99); Gan jiang (92); Mai men dong (87); Zhi shi (87); Bai zhu (82); and Da zao (78) (see Tables 5.23 & 8.1).

A series of step-wise hierarchical combinations of the principal symptoms of COPD, cough, dyspnoea, sputum production and chest tightness were used to select groups of citations that satisfied these criteria. At step 2, all of the herbs were included in formulae for dyspnoea plus cough; at step 5, all formulae were for dyspnoea plus cough and sputum; while at step 7, all were for dyspnoea plus cough, sputum and chest tightness (see Table 5.43). Also, citations were classified according to the three main global score categories of ‘most likely COPD’, ‘possible complication of COPD’ and ‘possible COPD’ (see Table 5.43).

The herbs that appeared in the top ten most frequent herbs at steps 2, 5 and 7 and in citations scored as ‘most likely COPD’ were: Gan cao; Ban xia; Xing ren; Ren shen; Fu ling; Wu wei zi; Chen pi; Sang bai pi; and Kuan dong hua. The remaining herbs in the lists of the top 20 most frequent herbs showed variations in their relative frequencies based on the inclusion criteria.
Table 8.1 Comparisons of high frequency herbs: RCT and Classical data sets

<table>
<thead>
<tr>
<th>Rank</th>
<th>Total of 101 RCTs</th>
<th>The total data set</th>
<th>Step 2.1</th>
<th>Step 5.1</th>
<th>Step 7</th>
<th>Global score 4</th>
<th>Global score 3</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
<td>Gan cao</td>
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<td>2</td>
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<td>Ban xia</td>
<td>Ban xia</td>
<td>Ban xia</td>
<td>Ren shen</td>
<td>Xing ren</td>
<td></td>
</tr>
<tr>
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<td>Xing ren</td>
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</tr>
<tr>
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<td>Xing ren</td>
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<td>Fu ling</td>
<td>Fu ling</td>
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<td>Kuan dong hua</td>
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<td>Kuan dong hua</td>
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<td>Fu ling</td>
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<td>Ying su ke</td>
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<td>Rou gui</td>
<td>Mai men dong</td>
<td>Chen pi</td>
</tr>
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<td>14</td>
<td>Ren shen</td>
<td>Bei mu</td>
<td>Xi xin</td>
<td>Mai men dong</td>
<td>Jie geng</td>
<td>Rou gui</td>
<td>Bei mu</td>
</tr>
<tr>
<td>15</td>
<td>Shan yao</td>
<td>Jie geng</td>
<td>Bei mu</td>
<td>E jiao</td>
<td>Zi wan</td>
<td>Zhi mu</td>
<td>Xi xin</td>
</tr>
<tr>
<td>16</td>
<td>Shan zhu yu</td>
<td>Gan jiang</td>
<td>Jie geng</td>
<td>Xi xin</td>
<td>Sheng jiang</td>
<td>Shi gao</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Xing ren</td>
<td>Mai men dong</td>
<td>Gan jiang</td>
<td>Ying su ke</td>
<td>Xi xin</td>
<td>Jie geng</td>
<td>Gan jiang</td>
</tr>
<tr>
<td>18</td>
<td>Su zi</td>
<td>Zhi shi</td>
<td>Mai men dong</td>
<td>Zi wan</td>
<td>Zao jiao</td>
<td>E jiao</td>
<td>Jie geng</td>
</tr>
<tr>
<td>19</td>
<td>Bei mu</td>
<td>Bai zhu</td>
<td>Zhi mu</td>
<td>Shan yao</td>
<td>Bai fan</td>
<td>Xi xin</td>
<td>Da zao</td>
</tr>
<tr>
<td>20</td>
<td>Kuan dong hua</td>
<td>Da zao</td>
<td>Zao jia</td>
<td></td>
<td></td>
<td>Ma huang</td>
<td>Fang ji</td>
</tr>
<tr>
<td>21</td>
<td>Bu gu zhi, Di long, Sang bai pi, Tao ren</td>
<td>Xi xin</td>
<td></td>
<td>Ying su ke</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Herbs appearing in both the RCT and classical data sets are in **bold**.
Total data set: Total classical data set (after general exclusions); Step 2.1: dyspnoea + cough; Step 5.1: dyspnoea + cough + sputum; Step 7: dyspnoea + cough + sputum + chest tightness; Global score 4: ‘likely COPD’; Global score 3: ‘complication of COPD’

At step 7 of the step-wise hierarchical combinations, there were five herbs that were different when compared to the total data set. Ying su ke, Xi xin, E jiao, Ban fan and Zao jiao were included, while Ma huang, Gan jiang, Zhi shi, Da zao and Mai men dong did not appear. There were only three different herbs when the global score category of ‘most likely COPD’ was compared with the total data set. Ying su ke, Xi xin and E jiao were included, while Gan jiang, Zhi shi, Da zao were not in the high frequency list.

Consequently, using the step-wise hierarchical combinations and the global score category ‘most likely COPD’ produced very similar lists of high frequency herbs. These did not differ

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greatly from the total list of herbs based on the combinations of search terms. Although
greater consistency in the results had been expected for the herbs compared with the formulae,
it appeared that many of the formulae located under the search terms tended to use similar
herbs.

Even though many of the herb entries were eliminated by the step-wise procedures,
consistency remained in the list. One likely reason was that, due to the brevity of the symptom
descriptions in the classical literature, formulae intended for persistent conditions that
combined the main symptoms did not necessarily include complete descriptions and were
consequently eliminated at early steps, while similar formulae were retained due to the greater
level of detail provided in the citations.

8.3.2 Frequently occurring herbs in the RCTs

The top 20 frequently occurring herbs in the RCTs were ranked as follows: Huang qi (used in
55 RCTs); Bai zhu (54); Fu ling (45); Dang shen (40); Gan cao (35); Wu wei zi (34); Chen pi
(32); Di huang (Gan/Sheng/Shu) (30); Banxia (Fabanxia/Zhibanxia) (25); Dan shen (24); Mai
dong (24); Ge jie (23); Dang gui (21); Ren shen (20, including Hong shen in 3, Sheng shai
shen in 1, Gao li shen in 1, Xi yang shen in 3); Shan yao (19); Shan zhu yu (19); Xing ren
(17); Su zi (15); Kuan dong hua (14); Bei mu (Zhebeimu/Chuanbeimu) (14); Bu gu zhi (13);
Di long (13); Sang bai pi (13); and Tao ren (13).

Huang qi, Dang shen and Ren shen are the major herbs used to tonify qi and Shan yao, Fu
ling, Chen pi, Bai zhu, Mai men dong, Shan zhu yu, Wu wei zi, Ge jie and Di huang are the
major herbs used to fortify the spleen and tonify the kidney. Also, Dan shen and Dang gui are
often used to activate blood, while Gao cao, mostly Zhi gan cao, is commonly used for
regulating the spleen and stomach. Five other frequently used herbs are the expectorants,
antitussives and anti-asthmatics Xing ren, Ban xia, Su zi, Kuan dong hua and Bei mu.
Therefore, in contrast to the results from the classical books, tonifying herbs were
predominantly used in modern clinical trials to treat stable COPD.

8.3.3 Comparisons of the herbs in the RCT and classical data sets

Among the top 20 or so high frequency herbs, 11 were common to both the classical and RCT
data sets. These included Gan cao, Xing ren, Ban xia, Ren shen, Fu ling, Wu wei zi, Chen pi,
Kuan dong hua, Mai men dong, Bei mu and Bai zhu (see Appendix 20).
Ren shen, Bai zhu and Mai men dong are tonic herbs. Fu ling induces diuresis and excretes dampness, Wu wei z is an astringent and Chen pi regulates qi. The herbs, Xing ren, Ban xia, Kuan dong hua and Bei mu are expectorants, antitussives and anti-asthmatics. Gan cao has diverse uses, including tonic effects, regulating the spleen and stomach and is also frequently included in formulae to harmonise the effects of other herbs; therefore, it is likely to be frequently included in formulae for a wide range of diseases and symptoms.

The analyses of the classical books showed that the following nine herbs were among the higher frequency herbs that were not common in the RCTs: Sheng jiang; Ma huang; Zi wan; Rou gui; Jie geng; Gan jiang; Zhi shi; Da zao; and Xi xin. Ma huang and Xi xin focus on relieving dyspnoea and Zi wan and Jie geng focus on cough (see Appendix 21). There were only four tonifying herbs among the higher frequency herbs in the classical data: Ren shen; Bai zhu; Wu wei zi and Rou gui. However, three of these were also frequently found in the RCT data set.

In the RCT formulae there were numerous herbs for qi deficiency (Huang qi, Dang shen, Ren shen and Ge jie), herbs to resolve phlegm (Chen pi, Ban xi, Bei mu and Su zi) and to stop cough (Xing ren, Kuan dong hua). Similarly, the formulae in the classical literature included herbs for qi deficiency (Ren shen, Bai zhu, Shan Yao), for resolving phlegm (Ban xia, Chen pi, Bei mu) and for clearing the lung and stopping cough (Xing ren, Kuan dong hua, Zi wan). There were also more herbs for activating blood and removing stasis (Dan shen, Dang gui and Di huang) (see Appendix 22).

Overall, the focus of the classical formulae was more on resolving phlegm and stopping cough, whereas for the RCT formulae the focus was more towards strengthening qi. Dang shen and Huang qi tend to have replaced Ren shen in modern formulae, but this is likely to be largely due to the high cost of Ren shen. Another difference was the greater focus on blood stasis in the RCTs. However, as mentioned earlier, addressing blood stasis was not entirely absent in the classical literature.

Although the emphases for treating COPD are different between the classical and modern approaches, they both recognize the essential nature of the disease involving a deficiency at the root and an excess at the branch.
8.4 Mechanisms of the formulae and herbs used for treating COPD

8.4.1 Pharmaceutical activities of formulae

This section will explore the pharmaceutical properties of the high frequency formulae found in the modern RCTs.

8.4.1.1 Bu Fei Tang

Bu Fei Tang was used in three RCTs (375, 437, 447). It was derived from the book entitled Yong Lei Ling Fang (永类铃方) compiled by Li Zhongnan and the book entitled Yi Fang Kao (医方考) compiled by Wu Kun during the Ming dynasty. Bu Fei Tang consists of Huang qi, Ren shen, Shu di huang, Wu wei zi, Sang bai pi and Zi wu an.

A number of formulae with the name Bu Fei Tang appeared in the classical data set, but these were different from those in the RCTs, and Huang qi did not appear among the top frequency herbs in the classical data set. However, Bu Fei Tang and Huang qi were commonly used in modern clinical trials. Bu Fei Tang was also commonly used for treating qi deficiency cough in the classical books, as discussed earlier. In the experimental literature, Bu Fei Tang was found to enhance superoxide dismutase (SOD) activity and reduce malondialdehyde (MDA) levels in the blood plasma in a rat model of lung deficiency COPD. Thus, Bu Fei Tang might have protective effects for the airway mucosa and reduce lung injury, and may also clear free radicals and have anti-lipidperoxidation effects (567).

In Chapter 2, (MMPs were also indicated as having an important role in the pathogenesis of COPD. MMP-9 is the largest and most structurally complex member of the MMP family. Both MMP-9 and the tissue inhibitor of matrix metalloproteinases (TIMP)-1, play important roles in airway inflammation and remodelling (568). In addition, when MMP-9 was used as a biomarker, the levels of MMP-9 in serum were related to declines in FEV1 (569). MMPs have also been therapeutic targets. An oral MMP-9 and MMP-12 inhibitor was used in a clinical trial for treating patients with moderate and severe COPD, although it did not produce any significant effects during a six week trial (570).

Among the 101 RCTs, none measured the serum levels of MMP-9. However, an experimental study showed that Bu Fei Tang may have downregulated NF-κB activity and the protein expressions of MMP-9 and TIMP-1 and attenuated the airway remodelling in COPD in a rat
model with lung-Qi deficiency syndrome (571). This provided evidence that this CHM had
effects on MMP-9 and TIMP-1. Also, Bu Fei Tang was found to significantly reduce the
levels of TNF-α and IL-8 in BALF in a COPD rat model in study by Zhang et al. (2008). This
suggested that Bu Fei Tang may relieve airway inflammation and may have beneficial effects
on COPD with lung qi deficiency (572). Another study found that Bu Fei Tang may have
inhibited airway remodelling and prevented the decline in lung function in COPD rats with
lung qi deficiency (573). These results were consistent with those of two RCTs (375, 447).

8.4.1.2 Bu Zhong Yi Qi Tang

Bu Zhong Yi Qi Tang was used in three RCTs (65, 398, 402), but only appeared once in the
classical data set for Ke chuan. Bu Zhong Yi Qi Tang consists of Huang qi, Ren shen, Bai zhu,
Dang gui, Chai hu, Sheng ma, Gan cao and Chen pi. It was created by physician Li Dongyuan
and recorded in the Pi Wei Lun (脾胃论处)(1249).

No experimental studies of Bu Zhong Yi Qi Tang for COPD could be found, although Bu
Zhong Yi Qi Tang has been shown to have the pharmaceutical actions of enhancing immunity
and have anti-tumour anti-inflammatory effects. It can ameliorate the side effects of cancer
drugs and is an effective biological response regulator (574). Bu Zhong Yi Qi Tang has also
been found to increase T-lymphocyes division and increase the amounts of IL-2 in mice with
spleen deficiency. Thus, it could positively increase lymphoid immune function in these mice
(575). Similar results were found in two RCTs that showed that Bu Zhong Yi Qi Tang may
have regulated the levels of IL-6 in serum (398, 463).

Liu Jun Zi Tang

Liu Jun Zi Tang was used in seven RCTs (73, 365, 408, 417, 419, 421, 440) and variations on
this formula appeared in the classical data set. It consists of Ren shen (or Dang shen), Fu ling,
Bai zhu, Gan cao, Chen pi and Ban xia. Its source was the book Shi Yi De Xiao Fang (世医得
效方) written over a period of 10 years by Wei Yilin and published during the Yuan dynasty
(1345).

An experimental study found that Liu Jun Zi Tang reduced the levels of IL-8, TNF-α and IL-4
in a COPD rat model, so Liu Jun Zi Tang may relieve inflammation and improve immunological function (576). However, relevant biomarkers were not measured in the RCTs
that used Liu Jun Zi Tang.
8.4.1.3 Shen Ge San

Shen Ge San (also called Ren Shen Ge Jie San) was used in five RCTs (80, 342, 344, 422, 427), but only appeared twice in the classical data set. Ren Shen Ge Jie San was found in the text Pu Ji Fang (普济方) complied by Zhu Li in 1406. The original formula included Ren shen, Ge jie, Fu ling, Xing ren, Bei mu, Sang bai pi and Zhi mu.

Shen Ge San was found to reduce the serum levels of IL-8 and TNF-α in a rat COPD model, which indicated that it suppressed inflammation (577). It was also observed to reduce IL-8 and TNF-α levels in one RCT (80).

8.4.1.4 Li Jin Fang

Li Jin Fang was used in two RCTs (423, 444). It was found to reduce IL-8, TNF-α and LTB4 levels in the blood and BALF; thus, it appeared to inhibit airway inflammation, which may be its mechanism of action for treating COPD (578, 579). IL-8 and TNF-α were not measured in RCTs that used Li Jin Fang for stable COPD patients.

8.4.1.5 Xiao Qing Long Tang

Xiao Qing Long Tang was not used in any of the 101 RCTs; however, it was the most frequent formula in the classical data set. It has been found to reduce the levels of IL-8 and TNF-α and increase the IFN-γ/IL-4 ratio, so it may inhibit inflammation and regulate immune function (580). Xiao Qing Long Tang did not appear in the RCTs for stable COPD patients, but it was used in RCTs for ECOPD patients and might have relieved symptoms and had effects on airway inflammation and remodelling (581, 582).

Using a rat model of COPD, an experimental study used different formulae, including Xiao Qing Long Tang, Ma Xing Shi Gan Tang, Yu Ping Feng San, Liu Jun Zi Tang and Shen Ge San, based on the syndrome differentiation for rats with the syndromes of cold phlegm retention in the lung, heat phlegm accumulation in the lung, lung qi deficiency, spleen qi deficiency and kidney deficiency to explore the effects of these formulae on the levels of NF-κB expression in the airways and in inflammatory cells. It was found that these formulae might regulate the balance between oxidants and antioxidants (583).
8.4.2 Pharmaceutical actions of key herbs

This section will explore the pharmaceutical actions of the main herbs used in the classical books and in modern RCTs. In the analysis of the classical literature, Ren shen was the most frequently used (257 times) tonifying qi herb in the formulae. Ginseng was not ranked at the top position, yet all of the high frequency formulae contained Ginseng. Thus, Ginseng played an important role in the classical formulae. Also, Ginseng, a key herb used for tonifying qi, is still used for treating chronic diseases, including COPD (584-586). Therefore, to evaluate the effectiveness of Ginseng formulae for treating stable COPD, a systematic review of oral Ginseng formulae for stable COPD was conducted at the first stage of the analysis of the modern RCTs.

Unlike Ren shen, Dang shen was used in only 11 formulae in the classical books. However, it was one of the most frequently used herbs in the formulae in modern RCTs. The modern trend is to employ Dang shen to replace Ren shen for treating stable COPD. For example, in Liu Jun Zi Tang, Ren shen was one of ingredients in the classical formula, whereas Dang shen was used instead in the Liu Jun Zi Tang found in six RCTs (73, 365, 417, 419, 421, 440). There were two reasons for replacing Ren shen with Dang shen: 1. Ren shen is much more expensive than Dang shen; and 2. Ren shen is warmer than Dang shen and may induce phlegm-dampness retention in the lung, which can then change to phlegm heat, more readily than can Dang shen.

While Ren shen was widely used, Dang shen was hardly mentioned in ancient Chinese materia medica texts. It appeared as another name for Ren shen in the Ming dynasty materia medica, but the earliest mentions of Dang shen as a separate herb appear to be in medical books from the Qing dynasty, such as Ben Cao Zheng Yi (本草正义) (587) and Shen Xian Ji Shi Liang Fang (神仙济世良方) (588). However, Dang shen rather than Ren shen is now more widely used. Due to their differences in chemical compositions and pharmaceutical actions, Dang shen cannot simply be regarded as a replacement for Ren shen. Whether Dang shen is superior to or should be used to replace Ren shen deserves further investigation.

8.4.2.1 Ren shen

In the classical literature, Ren shen played a very important role in treating COPD-related diseases as well as other lung diseases that were excluded from data analysis, such as Fei wei
and Fei lao. The book entitled Zhong Guo Ren Shen Fang Ji (中国人参方集) written by Song Chenji (2006) includes 3,521 Ren shen formulae. This book comprehensively classifies Ren shen prescriptions into 17 categories. Of these, one was under the heading of Expelling Sputum (Qu Tan Prescriptions), which contains 175 COPD-relevant formulae. The large number of classical formulae containing Ren shen attests to the importance of this herb in the development of Chinese medicine.

Its earliest use appeared in the Treatise of Febrile Diseases written by Zhang Zhongjing and these classical Ren shen formulae are still being used clinically for treating various chronic conditions. Furthermore, Ren shen extracts are also used singly and Ren shen is not only widely used in China, but also all over the world. There has been extensive research on the properties of the active ingredients of Ren shen, which provides the scientific basis for using Ren shen for treating COPD.

The majority of components of Ren shen are ginsenosides and ginseng polysaccharides, the pharmacological actions of which have been widely investigated worldwide. Ginseng has been found to have effects on multiple physiological systems. Therefore, Ren shen has been widely used for a variety of diseases, such as diabetes, lung cancer (589) and others. Also, compounds extracted from Ginseng have been extensively investigated in experimental and human studies (590). In mice, an extract was found to ameliorate airway inflammation (591) and a different extract was found to improve the oxidative stress status in aged rats (592). A recent study of a polysaccharide extract of Red Ginseng found that its immunostimulatory effects were via the molecular activation of macrophages (593) and a ginseng polysaccharide extract was found to have anti-fibrotic actions in mouse cell-line (594). Clinical trials have shown that Ginseng extracts may be effective for preventing respiratory symptoms in community dwelling adults (595) and upper respiratory infections (596), as well as improving lung function in patients with moderate COPD (79).

8.4.2.2 Huang qi

In the classical data set, only 30 formulae included the combination of Huang qi and Ren shen. However, in modern RCTs, Huang qi combined with Ren shen and Huang qi combined with Dang shen are among the top pairs of herbs used in clinical treatments.

Experimental studies on extracts of Huang qi found that airway hyper-responsiveness and remodelling in mice were inhibited by astragaloside IV (387) and an aqueous extract of
Huang qi (injection) decreased inflammatory infiltration and mucus secretion in lung tissues, which suggested that Astragalus membranaceus may have had an effect on preventing airway hyperreactivity in mice related to Th2 response inhibition (388). Astragalus was also found to modify responses of lipopolysaccharide-stimulated macrophages and had an effect of reducing the production of TNF-α, IL-6, IL-10 and IL-12 in a dose-dependent manner. This suggested that Astragalus may regulate macrophage-associated immune responses and reduce pro-inflammatory responses (597). Furthermore, an extract of Astragalus was shown to have potent activity as an immunological adjuvant when administered in a mouse cancer model (598).

8.4.2.3 Dang shen

There is experimental evidence in humans to suggest that Dang shen can improve respiratory symptoms in acute altitude sickness (389). An extract of Dang shen (Codonopsis lanceolata) was found to suppress the release of NO and TNF-α, which indicated that it had anti-inflammatory actions (599). Dang shen was also found to have an immunological adjuvant effect on the immune responses to ovalbumin in mice (600).

8.4.2.4 Bai zhu

Extracts of Bai zhu were found to have anti-inflammatory effects on TNF-α and NO production by peritoneal macrophages in acute and chronic animal models (390) and in a rat lung cell membrane chromatography model (391). Lactone I, a component of Bai zhu, has also been found to reduce serum IL-1 and TNF-α levels and improve the appetite of cachectic cancer patients (601).

8.4.2.5 Fu ling

Fu ling was shown to have anti-inflammatory effects on experimentally induced irritant contact dermatitis (ICD) in a repeated sodium lauryl sulphate (SLS) irritation model (393) and in an inflammation model in mice (602). A protein isolated from Poria cocos, PCP, was found to have immunomodulatory activities by activating the NF-κB signalling pathway to activate murine macrophages through a Toll-like receptor 4 (TLR4)-dependent mechanism (392).

8.4.2.6 Wu wei zi

Wu wei zi is considered an ‘adaptogen’ with stress protective effects (395). Schisandrin, a
compound isolated from the fruit of Schisandra chinensis, has been shown to have anti-inflammatory activity by inhibiting the production of NO and the release of PGE2 in mice (396). Furthermore, Schisandrin B appears to exert anti-inflammatory actions by downregulating the production of pro-inflammatory mediators, including NO, TNF-α, PGE2, IL-1β and IL-6. It also inhibited the production of ROS (603).

8.4.2.7 Ge jie

A Gecko peptide extract may have improved immune functions in a mouse model of immune suppression (604). Gecko was shown to have anti-tumour effects in both in vitro and in vivo experiments by inducing tumour cell apoptosis and downregulating the protein expressions of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (605).

8.4.2.8 Mai men dong

Although Mai men dong (Radix Ophiopogon) was mentioned for moistening the lung and relieving cough in Chinese medicine, these antitussive and expectorant effects have not manifested in studies of its pharmacological actions. However, Mai men dong was shown to contribute to improving airway mucociliary clearance, which may be attributed to ameliorating airway mucus secretion in a quail model (606). In addition, an extract of the polysaccharides from Mai men dong had an antagonistic effect on acetylcholine and histamine induced bronchial smooth muscle contraction in a guinea pig model (607).

8.4.2.9 Dan shen

Dan shen was found to reduce IL-8 levels and the white blood cell and neutrophil counts in BALF in a rat COPD model and significantly suppressed airway inflammation (608). This was consistent with the results of RCTs. Dan shen injection significantly improved FEV1 and reduced the levels of IL-6 and TNF-α in sputum and increased the levels of IgG and CD3 T cells, CD4 T cells and the CD4/CD8 T cell ratios in the blood of patients with stable COPD. This indicated that Dan shen might relieve airway inflammation and improve pulmonary and immunological functions (609). Dan shen injection was also found to maintain the balance between MMP-9 and TIMP-1 in the sera of patients at the acute stage of COPD, which suggested that Dan shen might inhibit MMP production, have a protective effect on the bronchial membrane and have a role in treating COPD patients (610).
**8.4.2.10 Tao ren**

Tao ren was found to reduce TNF-α and IL-2 levels and stimulate humoral immune responses in mice (611). Another study showed that the total protein of Tao ren (Prunus persica) had an immuno-modulatory effect by regulating the ratio of CD4/CD8 T cells and promoting apoptosis in S180 mouse cells (612).

Overall, experimental studies have found immunomodulatory or immunostimulatory effects for Ren shen, Huang qi, Dang shen, Fu ling, Ge jie and Tao ren. A number of herbs have also demonstrated anti-inflammatory actions, including Huang qi, Ren shen, Dang shen, Bai zhu, Fu ling, Wu wei zi, Dan shen and Mai men dong, based on their effects on modulating cytokine expressions *in vitro* and/or in animal studies (613). However, these herbs warrant further investigation to determine their specific activities in COPD.

**8.4.3 Mechanisms of action of herbs and formulae for treating COPD**

Experimental and clinical research on the mechanisms of action of single herb extracts and CHM formulae provide evidence that CHMs, as adjunct therapies, may be promising for treating COPD patients and for preventing or slowing the progression of this disease.

Biomarkers that were measured in the RCTs and in experimental studies on formulae and herbs included cytokines (e.g., IL-6, IL-8 and TNF-α), immunoglobulins and SOD activity, as well as T lymphocyte subsets (CD3, CD4), B lymphocytes (LTB4) and inflammatory cell types.

The results of these studies suggest several mechanisms of action for the CHMs used for treating COPD: 1. effects on cytokine levels and suppressing airway inflammation; 2. improving immune functions; 3. maintaining the oxidant-antioxidant balance; and 4. regulating an imbalance between proteases and anti-proteases. All of these are very important factors in the pathogenesis of COPD.

In conclusion, by building on the knowledge in the ancient literature, modern Chinese medicine has increased our understanding of and improved treatment methods for COPD. In modern Chinese medicine, research on COPD is multi-faceted. It systematically investigates the aetiology, pathogenesis, syndrome differentiation and principles for treating COPD, as well as the clinical effects and the pharmacological mechanisms of herbs. To date, some
Chinese medicines have been shown to be effective and additional research is being done to establish a definitive system for syndrome differentiation and treatment methods for COPD (614).

8.5 Strengths of this project

This project is the first of its kind to combine a systematic analysis of modern literature (including Chinese medicine and Western medicine) with analyses of RCTs and classical literature with the aim of evaluating CHM for treating COPD. The SRs of the RCTs and analyses of the CHMs used in these studies indicated that, as an adjunct therapy to pharmacotherapy, CHM is well-tolerated and has potential benefits for patients with stable COPD. Furthermore, these SRs are more comprehensive and analytical than earlier reviews of CHM RCTs for COPD. In a review by Guo et al (2006) (536), only 14 RCT studies were included that used CHM for treating COPD. CHM was either administered orally or by intravenous injection for stable COPD, acute COPD exacerbations and chronic bronchitis.

In contrast, the SRs in this project focused solely on subjects with stable COPD, and excluded RCTs that studied patients with acute COPD exacerbations. This made the comparisons between studies more meaningful and valid. In the future, it would be appropriate to conduct a separate review on COPD cases that involve exacerbations. In addition, the analyses of 101 RCTs identified the main herbs and formulae used for COPD, all of which warrant further experimental and clinical investigation.

As is well known, COPD can follow two courses: stable and with exacerbations. The management strategies for these are completely different. The essential goals for managing stable COPD are to reduce the incidence of exacerbations and prevent the progressive development of COPD. The analyses of the RCTs showed that certain CHMs appeared to have benefits for reducing the acute exacerbation rate during the treatment period and, in some RCTs, over the entire follow-up period. The results of the RCTs and experimental studies also suggested that CHMs may have effects on inflammatory cytokines, which provides evidence for exploring the pharmacological actions of CHMs further for treating COPD.

Much research attention has been given to COPD and clinical investigations have been conducted in China during the last ten years that have resulted in a large amount of clinical
evidence for treating COPD with CHM. However, the level of interest has been lower in other countries, including Western countries. More scientific research, especially on the pharmacological and biochemical properties of CHMs, is needed to elucidate the mechanisms of CHMs’ actions in COPD treatment. Therefore, the findings of these reviews may provide an evidentiary basis for the roles of CHM for treating patients with stable COPD and stimulate additional studies to better understand the mechanisms of CHMs’ actions for treating this disease.

This analysis of classical literature is also the first to use an electronic database that included 1,000 classical Chinese medical books and extract the references that contained information relevant to the treatment of COPD. These results summarized the extensive ancient experiences on the use of herbs and formulae for treating lung diseases that manifested the symptoms and signs that are now associated with COPD.

Combining the experiences of the classical and modern approaches may provide for a better understanding of this disease and also aid in identifying the appropriate herbs and formulae for treating patients with COPD in clinical practice.

8.6 Limitations

During the searches for the systematic reviews, languages were restricted to English and Chinese. Other languages, such as German, Japanese and Korean, were excluded because of a lack of accessibility to databases and a lack of language proficiency by the author. In effect, most of the included studies were conducted in China. Only 3 of the 101 studies were done in other countries. Therefore, a potential language of publication bias may affect the results of this study and may affect the generality of the conclusions. Other limitations for the methods used for analysing the clinical trials for COPD were discussed in Chapter 7.

In the analysis of the classical literature, because there were no exact disease names in ancient Chinese medicine that matched the contemporary term COPD, search terms that were considered to be the most appropriate and relevant to COPD were determined and were used based on examination of the symptoms and signs of classical diseases. This may have resulted in incomplete data collection. Thus, the search terms used is a matter for further discussion.

In addition, 187 unnamed formulae were excluded from the analysis of the formulae, although these were included in the herb-level analyses. Also, due to limitations in terms of human
resources and time, a great deal of content relevant to the symptoms of COPD in the classical Chinese medical books may be not have been explored. The use of frequencies and combinations of symptoms and signs is only one option for analyzing the large data set derived from the classical books. Furthermore, there were no criteria for evaluating the effectiveness of formulae in classical Chinese medical books. Specific information on this aspect is generally lacking; an assumption was made that the authors believed that their recommendations were effective unless they specifically stated otherwise. Because there is no plausible method for retrospectively evaluating the methods used in classical books, the herbs and formulae identified require further experimental and/or clinical evaluation.

8.7 Implications for further study on CHMs for COPD

Based on the findings of the analyses of the RCTs, more rigorous, higher methodological quality clinical trials on CHM for stable COPD are needed. The following are recommendations for addressing certain issues.

8.7.1 RCT design

8.7.1.1 Methodologies

The methodological reporting quality of the majority of included studies in the SRs was weak largely with respect to the procedures used for blinding, randomization sequence generation and allocation concealment.

The paucity of reporting of methodology, herbal quality and other details required by the CONSORT statement in clinical trials of CHMs has been a point of criticism (329). In 2006, a published review indicated that the overall methodological quality of RCTs on CHM treatments for COPD were poor based on the author’s assessments of clinical trial designs and RCT methodologies in CHM research; this author recommended that RCT design should be improved in future studies (536). Poor methodological quality of RCTs on CHM used for treating diseases other than COPD was also reported by most SRs (615).

The major weaknesses in methodology are the lack of attention paid to specific details for randomization and blinding for allocation concealment. This can lead to ineffective blinding and increase biases during observations (616, 617). Double blinding means that neither the patients nor the treating physicians know which intervention will be given to each participant.
In addition, randomization methods and allocation concealment are considered to be necessary interrelated processes for successfully achieving a properly blinded RCT (619). These three domains were found to be weak in the risk of bias assessments. Adequate methodology and proper reporting should be addressed in future RCTs that investigate CHM.

8.7.1.2 Control groups

The types of controls used were quite varied, including placebo, RP, no treatment and other CHM. Aside from the concerns of ethics and limiting bias, how to choose a reasonable control group for RCTs has been discussed by Bian et al (2006)(620). In the investigations of CHM for COPD, the types of RP used in the RCTs varied. This lack of standardized RP usage may result in differences in determining effectiveness. Therefore, for future RCTs that investigate COPD, this concern should be addressed and a standardized pharmacotherapy for stable COPD should be decided upon based on the GOLD guidelines.

Additionally, comparing one CHM with another CHM is not suggested as a suitable design for a RCT. RCTs for CHM are a recent development in China and a placebo is not easily accepted by local people, which leads to the problems of participant compliance and invalid results. To overcome the unwillingness of participants to accept a placebo, Chinese researchers have decided to compare a test CHM formula with another CHM used as control, in which the test CHM was based on syndrome differentiation and appropriate herbal prescription, whereas the control CHM formula was not. The control formula was difficult for the participants to recognize as being a placebo. Although this approach may overcome the participant compliance problem, it may compromise the findings of any significant differences between the two CHM formulae because it would not be entirely clear what effect the control CHM formula had on the disease condition.

8.7.1.3 Outcome measure selection

Lung function testing (LFT; spirometry) was performed in the majority of the RCTs. However, this is not currently perceived to be the most suitable predictor of COPD severity and mortality. Therefore, the choice of LFT as the outcome measure for the majority of RCTs was rather inappropriate. BODE has replaced LFT as the main outcome measure for COPD used in RCTs; however, this was measured in only two of the studies in the SRs. QoLQ and exacerbation rates were more commonly used in RCTs that investigated the effectiveness of CHM intervention for COPD, which was in line with international practices (621).
Although there are currently no surrogate outcome measures that can be definitively used for COPD, a number of biomarkers have potential as surrogate measures for the diagnosis of COPD, as outcome measures in clinical trials and in drug development pharmacogenomics. Chemokine and cytokine levels, such as for IL-8, IL-4 and TNF-α, were determined in both serum and sputum samples in some studies in the SRs. Yet, CRP, a remarkable inflammatory endpoint in COPD (622), was not measured in any of the RCTs. Thus, these more appropriate outcome measures should be adopted in future clinical trials for investigating the effects of CHMs on COPD (623).

Safety of CHM is also an important aspect in CHM RCTs. Therefore, adverse events should be observed and reported in CHM RCTs.

### 8.7.1.4 Identifying participants

Selection criteria, both inclusion criteria and exclusion criteria, are necessary for recruiting participants. These criteria should be adequately described in CHM RCTs. None of the RCTs in the SRs made mention of or described adherence to the standardized procedures of the GOLD guidelines with regard to measuring FEV₁. Similarly, there was no mention of standard procedures for making spirometric measurements. A lack of standardization when using these procedures may result in inaccurate applications of the inclusion and exclusion criteria.

In most of the RCTs, patients were recruited who had varying stages of COPD. Because the different stages of COPD require different treatment principles and CHMs, these study designs could compromise the true effects of the intervention. Therefore, for future trials, it is advisable that recruiting COPD patients should be based on stricter inclusion and exclusion criteria such that only patients who have the same COPD stage will be included in the RCT. Because COPD is a rather complex disease and treatment principles can differ according to the different syndromes involved, future RCTs should include syndrome differentiation in their selection criteria. The patients should also be informed of their COPD severity in terms of its stage of development.

### 8.7.1.5 Data analysis

Missing data were not accounted for properly in the studies in which participants dropped out. Intention to treat (ITT) is broadly applied to data analysis for dealing with missing data.
Explaining the reasons for withdrawals and using ITT can reduce the bias in trials and their impacts on the results.

### 8.7.1.6 Sample size calculations

There was a large amount of variation in the numbers of participants across the studies. The methods used for calculating sample sizes were not provided in any of the RCTs and no rationales were given for the sample size choices. A small sample size can result in a study that is underpowered to detect a real effect. Without any sample size calculations, it is difficult to determine which studies were likely to have been underpowered and which had adequate power with regard to the outcome measures.

### 8.7.1.7 Limitations of the RCT approach

The SRs of the RCTs were guided by the Cochrane airway group and meta-analyses were performed for specific outcome measures when suitable data were provided by the authors. The included studies were all identified as randomized and controlled trials (RCTs), which belong to the classification level 2 of Cochrane reviews. Because the RCT is widely considered to be the gold standard design for determining the efficacy of an intervention in a clinical study, it is widely used in clinical trials, including investigations of CHMs. RCT results reflect the mean response of a population to an intervention rather than the responses of individuals. Due to the difference between individuals, an individual’s reaction to the same treatment for a chronic disease may be different. Thus, effectiveness may also vary.

One characteristic of treatments used in Chinese medicine are that herbal formulae are designed to suit the individual. Among the included RCTs, some had made syndrome differentiations. However, this could not completely reflect the essence of Chinese medicine treatments. Thus, there is the issue of the degree to which an RCT can provide a reasonable evaluation of the efficacy of a CHM formula for treating patients with stable COPD.

### 8.7.2 Research on CM syndromes of COPD relevant to COPD severity

There are various CM syndromes of COPD, whereas Western medicine classifies COPD into four stages based on severity or disease progression. There is a need to clearly determine the correlations between Chinese medicine syndromes and the stages of COPD defined in Western medicine. Zhang, et al (2004) examined 318 COPD patients at varying stages of the
disease, performed a CM analysis of the differentiation of syndromes and graded them according to one of the four stages of COPD (i.e., early stage I, moderate stage II, severe stage III and late stage VI). They did a correspondence analysis using multivariate statistical methods. These results indicated that both early stage I and early stage IIa of COPD corresponded strongly to the syndromes of Lung qi deficiency and Spleen qi deficiency.

According to CM principles, the spleen is the source of phlegm and the lung is the receptacle for phlegm. After a prolonged deficiency in lung and spleen qi, COPD progresses to severe stage III and the syndrome becomes predominantly one of phlegm turbidity. When the condition further develops to late stage III, yin and yang are usually damaged and leads to blood stasis with the resulting syndromes of either kidney yin or kidney yang deficiency, or even syndromes of blood stasis. This multivariate statistical method provided an analysis of the correlations between CM syndromes and the COPD grades, which could possibly provide a more objective basis for a CM diagnosis and treatment principles. The use of such objective approaches should be considered when selecting participants for inclusion in future RCTs.

Among the published Chinese medicine clinical trials, only a few specifically included COPD patients at stages I and II. Most trials recruited COPD patients with varying degrees of severity that ranged from mild to moderate to severe. These inclusion criteria are inappropriate because different degrees of severity require different treatment plans. In addition, according to the Chinese medicine principles of aetiology and pathogenesis, COPD at different stages affects different visceral organs (zang organs) and, consequently, the selection of herbs is also different. Therefore, in future clinical trials, the study designs should consider separating their cohorts based on different degrees of severity and also use appropriate treatments based on an objective method of syndrome differentiation. This should minimize variations due to differences in COPD stages and syndromes.

By aligning the severity of the symptoms and signs (i.e., classification) with the syndromes during selection, or using stratification based on these factors at baseline, it may be possible to maximize the selection of the appropriate herbs and, thereby, obtain optimal, clinically relevant results. Nevertheless, all sources of variation may be difficult to control for in this complex disease. Thus, large sample sizes may be needed to detect treatment effects, especially when CHM plus RP is compared to RP plus placebo.
8.7.3 **Experimental research**

There is a need to investigate the pharmacological and biochemical roles of Chinese herbal medicines used for treating COPD from different aspects. For example, Dang shen and Huang qi used as a pair for treating stable COPD should be further investigated in terms of their pharmacological mechanisms. By comparison, the effectiveness of Ren shen has already been widely confirmed. Nevertheless, the comparative functions and effectiveness of Ren shen, Dang shen and Huang qi need to be further investigated to provide a scientific basis for their clinical use for COPD.

8.7.4 **Further clinical practice**

These analyses of the modern and classical literature provide data and discussions on the pathogenesis of COPD, syndrome differentiation in COPD and the mechanisms of CHMs used for treating COPD. In addition, these analyses explored which herbs and formulae were frequently used to treat COPD in classical and modern CM. It is hoped that these data and the associated discussions may aid practitioners to apply more evidence-based and more effective approaches for the use of herbs and formulae for treating patients with COPD.
9 References


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218. Martinez FJ, Donohue JF, Rennard SI. The future of chronic obstructive pulmonary disease


257. Lai SL. Clinical research design, measurement, evaluation (DME) special lectures on the basic principles of clinical research design and programs. China Journal of Traditional Chinese Medicine 1987(03):57-60.


402. Hu ZM, Ding YD. Clinical observation of Bu Zhong Yi Qi Tang in treatment stable chronic


Paats MS, Bergen IM, Hoogsteden HC, van der Eerden MM, Hendriks RW. Systemic CD4+ and CD8+ T cell cytokine profiles correlate with GOLD stage in stable COPD. Eur Respir J. 2011 Dec 19.


537. Hauke W, Kohler 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


567. Li X. Effect Of decoction for reinforcing Jung on the activity of SOD and the content MDA in blood plasma of rats model which have chronic obstructive pulmonary disease (COPD) and TCM syndrome such as 'lung deficiency'. Journal of practical traditional Chinese internal medicine. 2008;22(11):20-2.


571. Zhang K, Zhang Y, Cheng YJ, Lu L. Effects of Shenqi Bufeitang on expressions of NF-kappaB,


## 10 APPENDICES

### Appendix 1 Table: Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/prevention, Aetiology/harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1a</td>
<td>Systematic reviews (SRs) with homogeneity of randomised clinical trials (RCTs)</td>
</tr>
<tr>
<td>Level 1b</td>
<td>Refers to individual RCTs with narrow confidence intervals</td>
</tr>
<tr>
<td>Level 2a</td>
<td>Denotes homogeneous SRs of cohort studies</td>
</tr>
<tr>
<td>Level 2b</td>
<td>Includes individual cohort studies and ‘low-quality’ RCTs (e.g. with &lt;80% follow-up)</td>
</tr>
<tr>
<td>Level 3a</td>
<td>Refers to systematic homogeneous reviews of case-control studies</td>
</tr>
<tr>
<td>Level 3b</td>
<td>Principally represented by individual case-control studies</td>
</tr>
<tr>
<td>Level 4</td>
<td>Denotes case series with poor-quality cohort-based and case-control studies</td>
</tr>
<tr>
<td>Level 5</td>
<td>‘Expert opinion’ without explicit critical appraisal or first-hand generation of data</td>
</tr>
</tbody>
</table>

Ref: Oxford Centre for Evidence-Based Medicine Levels of Evidence
### Appendix 2 Table: Summary of differential diagnosis of COPD and other lung diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Onset Age</th>
<th>Symptoms</th>
<th>Signs</th>
<th>History</th>
<th>Chest x-ray or CT</th>
<th>Spirometry</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Middle age</td>
<td>chronic cough, sputum, shortness of breath,</td>
<td>Smoking history</td>
<td>X-ray or HRCT</td>
<td>Spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dyspnoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Early life (childhood)</td>
<td>Wheezing</td>
<td>Family history</td>
<td></td>
<td>Spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Severe infection in childhood</td>
<td>Cough with large volumes of purulent sputum, haemoptysis</td>
<td>Crackles and wheezes</td>
<td>Rhinosinusitis</td>
<td>HRCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis (TB)</td>
<td>All ages (infants)</td>
<td>Fever, haemoptysis</td>
<td>X-ray</td>
<td></td>
<td></td>
<td></td>
<td>TST, Sputum exam</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>Onset in younger age</td>
<td>Shortness of breath, cough</td>
<td>Early inspiratory crackles or 'squeaks'</td>
<td>History of rheumatoid arthritis or fume exposure</td>
<td>HRCT scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse panbronchiolitis (DPB)</td>
<td></td>
<td></td>
<td>Chronic sinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (CHF)</td>
<td></td>
<td>Dyspnoea, ankle or pulmonary oedema, fatigue, heart palpitations</td>
<td>Fine basilar crackles</td>
<td>Chest X-ray: DH, PE</td>
<td>Volume restriction, not airflow limitation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; CT, computed tomography; HRCT, high-resolution computed tomography; PE, pulmonary oedema; DH, dilated heart; TST, tuberculin skin test.
## Appendix 3 Table: Syndromes and treatment of Cough, Dyspnoea, Feizhang, Zhiyin and Xiaozheng

<table>
<thead>
<tr>
<th>Terms</th>
<th>Syndromes</th>
<th>Treatment principles</th>
<th>Formulae and ingredients</th>
</tr>
</thead>
</table>
| Ke sou                     | Stagnation of phlegm-dampness    | Invigorate the spleen & eliminate dampness       | Er Chen Tang or San Zi Yang Qin Tang  
                          | in the lung                      |                                                   | Ban xia, Chen pi, Fu ling Gan cao (Zhi) or Su zi, Bai jie zi, Lai fu zi |
|                            | Accumulation of phlegm and heat  | Remove heat to resolve phlegm                    | Qing Jin Hua Tan Tang  
                          | in the lung                      |                                                   | Huang qin, Shan zhi, Jie geng, Mai dong, Sang bai pi, Bei mu, Zhi mu, Gua lou ren, Ju hong, Fu ling, Gan cao |
|                            | Invasion of the lung by live-fire| Remove the liver-fire and clear the lung        | Dai Ge San & Xie Bai San  
                          |                      |                                                   | Qing dai, Hai ge qiao, Gan cao, Sang bai pi, Di gu pi, Jing mi |
|                            | Lung qi deficiency               | Tonify lung qi                                   | Bu Fei Tang  
                          |                      |                                                   | Ren shen, Huang qin, Zi wan, Di huang (Shu), Wu wei zhi, Sang bai pi |
|                            | Lung yin deficiency              | Nourish yin and moisten the lung                 | Sha Shen Mai Dong Tang  
                          |                      |                                                   | Shashen, Maidong, Yuzhu, Sangye, Gancao, Tianhuafeng, Biandou, |
| Chuan zheng (deficiency)    | Deficiency of the lung           | Invigorate the lung                              | Shenmai San & Bufei Tang  
                          |                      |                                                   | Renshen, Maidong, Wuwei  
                          |                      |                                                   | Plus Ren shen, Huang qin, Di huang (Shu), Wu wei zhi, Zi wan, Sang bai pi |
|                            | Deficiency of the kidney         | Tonify the kidney                                | Qi Wei Dou Qi Wan  
                          |                      |                                                   | Di huang, Shan zhu yu, Shan yao, Fu ling, Dan pi, Ze xie, Wu wei zhi |
|                            | Deficiency of the lung and kidney| Tonify the lung and kidney                       | Ren Shen Ge Jie San modified  
                          |                      |                                                   | Ren shen, Ge jie |
| Fei zhang                  | Yang deficiency of the spleen    | Fortify the spleen and tonify the kidney to warm| Jin Gui Shen Qi Wan  
                          | and kidney                     | yang and promote qi absorption                 | Rou gui, Fu zi, Di huang (Shu), Shan yao, Shan zhu yu, Fu ling, Dan pi, Ze xie |
|                            | Cold-fluid in the lung           | Warm the lung to remove fluid retention          | Xiao Qing Long Tang  
                          |                      |                                                   | Ma huang, Gui zhi, Shao yao, Gan cao, Gan jiang, Xi xin, Ban xia, Wu wei zhi |
|                            | Yang deficiency of the spleen    | Warm and invigorate the spleen and kidney to     | Jin Gui Shen Qi Wan  
                          | and kidney                     | remove fluid retention                      | Rou gui, Fu zi, Di huang (Shu), Shan yao, Shan zhu yu, Fu ling, Dan pi, Ze xie |
| Zhi yin                    | Deficiency of the lung           | Tonify lung qi                                   | Yu Ping Feng San  
                          |                      |                                                   | Huang qi, Bai zhu, Fang feng |
|                            | Deficiency of the spleen         | Strengthen the spleen to resolve phlegm          | Liu Jun Zi Tang  
                          |                      |                                                   | Ren shen, Fu ling, Bai zhu, Chen pi, Ban xia (Zhi), Gan cao (Zhi) |
|                            | Deficiency of the kidney         | Tonify the kidney to promote qi absorption       | Jin Gui Shen Qi Wan or Qi Wei Dou Qi Wan  
                          |                      |                                                   | Rou gui, Fu zi, Di huang (Shu), Shan yao, Shan zhu yu, Fu ling, Dan pi, Ze xie Or |

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<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Di huang, Shan zhu yu, Shan yao, Fu ling, Dan pi, Ze xie, Wu wei zi</th>
</tr>
</thead>
</table>
## Appendix 4 Table: Traditional disease names related to COPD found in books on TCM internal medicine and respiratory diseases

<table>
<thead>
<tr>
<th>First Author, date</th>
<th>Book name in English</th>
<th>Book name in Chinese</th>
<th>Disease names relevant to COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACM, 2008</td>
<td>Guidelines for the Diagnosis and Treatment of Common Internal Medicine Diseases in Chinese Medicine</td>
<td>中医内科常见病诊疗指南 (西医疾病部分)</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Chao, 2011</td>
<td>Contemporary Chinese Internal Medicine</td>
<td>今日中医内科</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Fan, 2008</td>
<td>Manual of Diagnosis and Treatment of Internal Medicine Diseases by Integrative Chinese and Western Medicine</td>
<td>中西医结合内科疾病诊疗手册</td>
<td>Fei zhang</td>
</tr>
<tr>
<td>Feng, 2000</td>
<td>The Clinical Diagnosis and Treatment of Respiratory Diseases in TCM</td>
<td>呼吸科专病中医临床诊治</td>
<td>Ke sou, Fei zhang</td>
</tr>
<tr>
<td>Han, 2005</td>
<td>Contemporary Respiratory Medicine in Traditional Chinese Medicine</td>
<td>现代中医呼吸病学</td>
<td>Ke sou, Chuan zheng, Fei zhang, Tan yin</td>
</tr>
<tr>
<td>Hong, 1995</td>
<td>The Practice of Chinese Respiratory Medicine</td>
<td>实用中医呼吸病学</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Li, 2009</td>
<td>Respiratory Diseases: Essentials of Clinical Treatment in TCM</td>
<td>呼吸病·中医临床精要</td>
<td>Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Ouyang, 1997</td>
<td>Chinese Respiratory Medicine</td>
<td>中医呼吸病学</td>
<td>Ke sou, Chuan zheng</td>
</tr>
<tr>
<td>Pan, 1997</td>
<td>Compendium of the Treatment of Internal Medicine Diseases in Chinese Medicine</td>
<td>中医内科治疗大成</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Wang, 1999</td>
<td>Chinese Internal Medicine</td>
<td>中医内科学</td>
<td>Ke sou, Chuan zheng, Fei zhang</td>
</tr>
<tr>
<td>Wang, 2009</td>
<td>The Practice of Chinese Internal Medicine</td>
<td>实用中医内科学</td>
<td>Ke sou, Chuan zheng, Fei zhang, Tan ke, Tan sou</td>
</tr>
<tr>
<td>Wu, 2001</td>
<td>Chinese Internal Medicine Diagnosis and Therapy</td>
<td>中医内科诊断治疗学</td>
<td>Jiu ke, Fei zhang, Zhi yin</td>
</tr>
<tr>
<td>Zhu, 2011</td>
<td>Diagnosis and Treatment of Diseases in Chinese Internal Medicine (National Standard Application)</td>
<td>中医内科疾病诊疗常规 (国家标准应用)</td>
<td>Jiu ke, Fei zhang</td>
</tr>
</tbody>
</table>

CACM: China Association of Chinese Medicine
Appendix 5 SGRQ

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and affecting your life. We want to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick one box which best describes your present health:

[ ] Very good  [ ] Good  [ ] Fair  [ ] Poor  [ ] Very poor

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Fax +44 (0) 20 8725 5955
**St. George’s Respiratory Questionnaire**

**PART 1**

These questions are about how much chest trouble you have had over the last 4 weeks.

Please tick (✓) one box for each question:

<table>
<thead>
<tr>
<th></th>
<th>most days a week</th>
<th>several days a week</th>
<th>a few days a month</th>
<th>only with chest infections</th>
<th>not at all</th>
</tr>
</thead>
</table>

1. Over the last 4 weeks, I have coughed: [ ] [ ] [ ] [ ] [ ]

2. Over the last 4 weeks, I have brought up phlegm (sputum): [ ] [ ] [ ] [ ] [ ]

3. Over the last 4 weeks, I have had shortness of breath: [ ] [ ] [ ] [ ] [ ]

4. Over the last 4 weeks, I have had attacks of wheezing: [ ] [ ] [ ] [ ] [ ]

5. During the last 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had? Please tick (✓) one:
   - more than 3 attacks [ ]
   - 3 attacks [ ]
   - 2 attacks [ ]
   - 1 attack [ ]
   - no attacks [ ]

6. How long did the worst attack of chest trouble last? (Go to question 7 if you had no severe attacks) Please tick (✓) one:
   - a week or more [ ]
   - 3 or more days [ ]
   - 1 or 2 days [ ]
   - less than a day [ ]

7. Over the last 4 weeks, in an average week, how many good days (with little chest trouble) have you had? Please tick (✓) one:
   - No good days [ ]
   - 1 or 2 good days [ ]
   - 3 or 4 good days [ ]
   - nearly every day is good [ ]
   - every day is good [ ]

8. If you have a wheeze, is it worse in the morning? Please tick (✓) one:
   - No [ ]
   - Yes [ ]
St. George’s Respiratory Questionnaire

PART 2

Section 1

How would you describe your chest condition?

Please tick (✔) one:

- The most important problem I have
- Causes me quite a lot of problems
- Causes me a few problems
- Causes no problem

If you have ever had paid employment.

My chest trouble made me stop work altogether

My chest trouble interferes with my work or made me change my work

My chest trouble does not affect my work

Section 2

These questions are about what activities usually make you feel breathless these days.

For each activity, please tick (✔) one box as it applies to you these days:

<table>
<thead>
<tr>
<th>Activity</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Getting washed or dressed</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking around the home</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking outside on level ground</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up one flight of stairs</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking up hills</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Playing sports or active games</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
St. George’s Respiratory Questionnaire
PART 2

Section 3
Some more questions about your cough and breathlessness these days.
For each situation, please tick (✓) one box as it applies to you these days:

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough hurts</td>
<td></td>
</tr>
<tr>
<td>My cough makes me tired</td>
<td></td>
</tr>
<tr>
<td>I am breathless when I talk</td>
<td></td>
</tr>
<tr>
<td>I am breathless when I bend over</td>
<td></td>
</tr>
<tr>
<td>My cough or breathing disturbs my sleep</td>
<td></td>
</tr>
<tr>
<td>I get exhausted easily</td>
<td></td>
</tr>
</tbody>
</table>

Section 4
These are questions about other effects that your chest trouble may have on you these days.
For each situation, please tick (✓) one box as it applies to you these days:

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough or breathing is embarrassing in public</td>
<td></td>
</tr>
<tr>
<td>My chest trouble is a bother to my family, friends or neighbours</td>
<td></td>
</tr>
<tr>
<td>I get afraid or panic when I cannot get my breath</td>
<td></td>
</tr>
<tr>
<td>I feel that I am not in control of my chest problem</td>
<td></td>
</tr>
<tr>
<td>I do not expect my chest to get any better</td>
<td></td>
</tr>
<tr>
<td>I have become frail or an invalid because of my chest</td>
<td></td>
</tr>
<tr>
<td>Exercise is not safe for me</td>
<td></td>
</tr>
<tr>
<td>Everything seems too much of an effort</td>
<td></td>
</tr>
</tbody>
</table>

Section 5
These are questions about your medication. If you are receiving no medication go straight to
For each situation please tick (✓) one box as it applies to you these days:

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My medication does not help me very much</td>
<td></td>
</tr>
<tr>
<td>I get embarrassed using my medication in public</td>
<td></td>
</tr>
<tr>
<td>I have unpleasant side effects from my medication</td>
<td></td>
</tr>
<tr>
<td>My medication interferes with my life a lot</td>
<td></td>
</tr>
</tbody>
</table>
St. George’s Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

For each situation, please tick (✓) the correct box that applies to you because of your breathing:

- I take a long time to get washed or dressed
- I cannot take a bath or shower, or I take a long time
- I walk slower than other people, or I stop for rests
- Jobs such as housework take a long time, or I have to stop for rests
- If I walk up one flight of stairs, I have to go slowly or stop
- If I hurry or walk fast, I have to stop or slow down
- My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening (e.g. weeding), dance, play bowls or play golf
- My breathing makes it difficult to do things such as carry heavy loads, dig the garden, jog or walk fast (8 km/hr), play tennis or swim laps
- My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports

Section 7

We would like to know how your chest trouble usually affects your daily life.

For each situation, please tick (✓) the correct box that applies to you because of your chest trouble:

- I cannot play sports or active games
- I cannot go out for entertainment or recreation
- I cannot go out of the house to do the shopping
- I cannot do housework
- I cannot move far from my bed or chair
Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

- Going for walks or walking the dog
- Doing things at home or in the garden
- Sexual intercourse
- Going out to church or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

........................................................................................................................................................
........................................................................................................................................................
........................................................................................................................................................

Now, would you tick the box (one only) which you think best describes how your chest trouble affects you:

- It does not stop me doing anything I would like to do
- It stops me doing one or two things I would like to do
- It stops me doing most of the things I would like to do
- It stops me doing everything I would like to do

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.
Appendix 6 Dyspnea scale

Dyspnea was assessed by the MMRC Scale that consists of five levels of dyspnoea as follows:

- Grade 0: I only get breathless with strenuous exercise;
- Grade 1: I get short of breath when hurrying on level ground or walking up a slight hill;
- Grade 2: on level ground, I walk slower than people of the same age because of breathlessness, or have to stop for a breath when walking at my own pace;
- Grade 3: I stop for a breath after walking about 100 yards or after a few minutes on level ground;
- Grade 4: I am too breathless to leave the house or I am breathless when dressing.
Appendix 7 Search terms of RCTs

The search terms for PubMed were done using the following steps:

1. Pulmonary disease, chronic obstructive [MeSH]
2. Bronchitis, chronic [MeSH]
3. Emphysema [MeSH]
4. (Chronic obstructive pulmonary disease [Text word] OR Chronic obstructive airway disease [Text word] OR Chronic obstructive lung disease [Text word] OR Chronic obstructive bronchitis disease [Text word])
5. Chronic Airflow Limitation* [Text word]
6. Chronic Airflow Obstruction* [Text word]
7. Chronic Airways Obstruction* [Text word]
8. (COPD [Text word] OR COAD [Text word] OR COBD [Text word])
9. Chronic bronchitis [Text word]
10. Chronic obstructive bronchitis [Text word]
11. Emphysema [Text word]
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. Clinical trials [MeSH]
14. Clinical trial [pt]
15. Controlled clinical trial [pt]
16. Randomized controlled trials [MeSH]
17. Randomized controlled trial [pt]
18. Random allocation [MeSH]
19. Double-blind method [MeSH]
21. Placebos [MeSH]
22. Clin* trial* [TIAB]
23. (Randomized clinical trial* [TIAB] OR Randomised clinical trial* [TIAB])
24. Placebo [TIAB]
25. (singl* blind* [TIAB] OR doubl* blind* [TIAB] OR tripl* blind* [TIAB] OR trebl* blind* [TIAB])
26. (singl* Mask* [TIAB] OR doubl* Mask* [TIAB] OR tripl* Mask* [TIAB] OR trebl* Mask* [TIAB])
27. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28. Animal/ NOT (human/ and animal/)
29. #27 NOT #28
30. Complementary Therapies [MeSH]
31. Plants, Medicinal [MeSH]
32. Medicine, Chinese traditional [MeSH]
33. Medicine, traditional [MeSH]
34. Plant extracts [MeSH]
35. Phytotherapy [MeSH]
36. Drugs, Chinese herbal [MeSH]
37. Drugs, Non-Prescription [MeSH]
38. Acupuncture [MeSH]
39. Massage [MeSH]
40. (Complementary Therap* [TIAB] OR Complementary medicine [TIAB] OR Alternative therap* [TIAB] OR Alternative medicine [TIAB] OR Traditional medicine [TIAB])
41. (Plant extract* [TIAB] OR Herb* [TIAB] OR Phytotherap* [TIAB])
43. #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44. #12 AND #29 AND #43
## Appendix 8 Table: Ten most frequent formulae in total data set following general exclusions*

<table>
<thead>
<tr>
<th>Formula code &amp; name</th>
<th>Freq.</th>
<th>Terms</th>
<th>Action</th>
<th>Ingredients</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unnamed</td>
<td>187</td>
<td>various</td>
<td>various</td>
<td>various</td>
<td>various</td>
<td>various</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>10</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ma huang, Gan cao, Gui zhi, Shao yao, Gan Jiang, Ban xia, Xi xin, Wu wei zi</td>
<td>Bing Yin Mai Zhi</td>
<td>1706</td>
</tr>
<tr>
<td>59 Xiao Ban Xia Tang</td>
<td>9</td>
<td>Zhi yin</td>
<td>Invigorate the spleen and eliminate fluid retention</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>7</td>
<td>Fei zhang</td>
<td>Clear heat and resolve phlegm to stop wheezing</td>
<td>Ban xia, Ma huang, Shi gao, Gan cao</td>
<td>Shen Ji Zong Lu</td>
<td>1117</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi Gao Tang</td>
<td>6</td>
<td>Fei zhang</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing, clear interior heat</td>
<td>Shi gao, Ma huang, Shao yao, Gui, Xi Xin, Gan cao, Gan Jiang</td>
<td>Shen Ji Zong Lu</td>
<td>1117</td>
</tr>
<tr>
<td>57 Xiao Ban Xia Jia Fu Ling Tang</td>
<td>6</td>
<td>Zhi yin</td>
<td>Invigorate the spleen and eliminate fluid retention</td>
<td>Ban xia, Sheng jiang, Fu ling</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>54 Mu Fang Ji Tang</td>
<td>5</td>
<td>Zhi yin</td>
<td>Promote the circulation of fluid, restore qi and remove heat</td>
<td>Fang ji, Gui zhi, Ren shen, Shi gao</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>63 Wu Ling San</td>
<td>5</td>
<td>Zhi yin</td>
<td>Move qi to drain water</td>
<td>Ze xie, Zhu ling, Fu ling, Bai zhu, Rou gui</td>
<td>Bing Yin Mai Zhi</td>
<td>1706</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>5</td>
<td>Tanyin kesou</td>
<td>Tonify qi and resolve phlegm to calm dyspnea</td>
<td>Zao jiao, Ren shen</td>
<td>Ye Shi Lu Yan Fang</td>
<td>1186</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren, Sheng Jiang Tang</td>
<td>5</td>
<td>Tanyin kesou</td>
<td>Warm lung to dispel cold, resolve phlegm to suppress cough</td>
<td>Ma huang, Gan cao, Xing ren, Sheng jiang</td>
<td>Zheng Zhi Zhai Yao</td>
<td>1862</td>
</tr>
</tbody>
</table>
### Appendix 9 Table: Twenty formulae rated as used for ‘possible’, ‘most likely’ or ‘possible complication’ of COPD

<table>
<thead>
<tr>
<th>Formula code &amp; name</th>
<th>Terms</th>
<th>Actions</th>
<th>Ingredients</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 no name</td>
<td>various</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Ma huang, Shi gao, Gan cao</td>
<td>various</td>
<td>various</td>
</tr>
<tr>
<td>3 Yue Bi Jia Ban Xia Tang Fang</td>
<td>Fei zhang</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing, clear interior heat</td>
<td>Shi gao, Ma huang, Chi yao, Gui, Xi Xin, Gan cao, Gan Jiang</td>
<td>Shen Ji Zong Lu</td>
<td>1117</td>
</tr>
<tr>
<td>5 Xiao Qing Long Jia Shi Gao Tang</td>
<td>Fei zhang</td>
<td>Invigorate the spleen and eliminate fluid retention</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>59 Xiao Ban Xia Tang</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>54 Mu Fang Ji Tang</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>61 Xiao Qing Long Tang</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>144 Zao Jiao Jian Wan</td>
<td>Tanyin kesou</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Ma huang, Shi gao, Gan cao</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>4 Ma Huang Tang</td>
<td>Fei zhang</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>8 Zi Wan Tang</td>
<td>Fei zhang</td>
<td>Warm lung to dispel cold, resolve phlegm to stop wheezing</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>162 Ma Huang Gan Cao Jia Xing Ren Sheng Jiang Tang</td>
<td>Tanyin kesou</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>337 Su Zi Jiang Qi Tang</td>
<td>Chuan Zheng</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>21 Zi Wan San Jia Jian</td>
<td>Fei zhang</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>55 Shi Zao Tang</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>57 Xiao Ban Xia Jia Fu ling Tang</td>
<td>Zhi yin</td>
<td>Warm lung to dispel cold, resolve phlegm to calm dyspnea</td>
<td>Ban xia, Sheng Jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eliminate fluid retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---------------------------</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>58 Ze Xie Tang</td>
<td>Zhi yin</td>
<td>Eliminate fluid retention</td>
<td>Ze xie, Bai zhu</td>
<td>Pu Ji Fang</td>
<td></td>
</tr>
<tr>
<td>66 Mu Fang Ji Tang Jia Jian</td>
<td>Zhi yin</td>
<td>Promote the circulation of fluid, restore qi and remove</td>
<td>Fang ji, Rou gui, Ren shen, Fu ling, Mang xiao</td>
<td>Wai Tai Mi Yao</td>
<td></td>
</tr>
<tr>
<td>127 Jiu Xian San</td>
<td>Tanyin kesou</td>
<td>Constrain the lung to suppress cough</td>
<td>Ren shen, Jie geng, E jiao, Wu mei Kuan dong hua, Sang bai pi, Wu wei zi, Bei mu, Ying su ke</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td></td>
</tr>
<tr>
<td>226 Ren Shen Kuan Dong Hua San</td>
<td>Chuan sou</td>
<td>Fortify spleen to resolve phlegm</td>
<td>Ren shen, Zhi mu, Kuan dong hua, Bei Mu, Ying su ke, Ban xia</td>
<td>Pu Ji Fang</td>
<td></td>
</tr>
<tr>
<td>477 Jiu Sou Wan Zi</td>
<td>Jiu ke sou</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Hai ge fen, Dan xing, Xing ren, He zi, Qing dai, Zao jiao</td>
<td>Yi Xue Gang Mu</td>
<td></td>
</tr>
</tbody>
</table>

Ref: Peng (2003) Zhong Guo Ming Yi Fang Ji Da Quan (中国名医方剂大全).
Appendix 10 Table: Formulae occurring in the data set at step 7 and also ranked as ‘most likely COPD’

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Terms</th>
<th>Actions*</th>
<th>Ingredients</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Ban Xia Yin Fang</td>
<td>Fei zhang</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Ban xia, Mai men dong, Sheng ma, Qian hu, Bing lang, Chen pi, Zhe ye, Sheng di huang, Da huang</td>
<td>Shen Ji Zong Lu</td>
<td>1117</td>
</tr>
<tr>
<td>21 Zi Wan San Jia Jian</td>
<td>Fei zhang</td>
<td>Moisten the lung to suppress cough</td>
<td>Zi wan, Ren shen, Jie geng, Mai men dong, Fu ling, E jiao, Bei mu, Wu wei zi, Gan cao, Dan pi, Sheng jiang, Da zao</td>
<td>Zhang Shi Yi Tong</td>
<td>1695</td>
</tr>
<tr>
<td>92 Run Fei Wan</td>
<td>Tanyin kesou</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Ren shen, Kuan dong hua, Xi xin, Xing ren, Gan cao, Zhi mu, Rou gui, Jie geng</td>
<td>Tai ping hui min he ji ju fang</td>
<td>1078</td>
</tr>
<tr>
<td>96 Kuan Dong Hua San</td>
<td>Tanyin kesou</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Kuan dong hua, Zhi mu, Sang ye, Ban xia, Gan cao, Ma huang, E jiao, Xing ren, Bei mu</td>
<td>Tai ping hui min he ji ju fang</td>
<td>1078</td>
</tr>
<tr>
<td>97 Xi Xin Wu Wei Zi Tang</td>
<td>Tanyin kesou</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Xi xin, Ban xia, Gan cao, Wu mei, Wu wei zi, Ying su ke, Sang bai pi</td>
<td>Tai ping hui min he ji ju fang</td>
<td>1078</td>
</tr>
<tr>
<td>98 Yang Zhong Tang</td>
<td>Tanyin kesou</td>
<td>Diffuse the lung to resolve phlegm and suppress cough</td>
<td>Ban xia, Gan cao, Rou gui, Ying su ke, Sheng jiang</td>
<td>Tai ping hui min he ji ju fang</td>
<td>1078</td>
</tr>
<tr>
<td>112 Wen Fei Wan</td>
<td>Tanyin kesou</td>
<td>Warm the lung resolve phlegm and suppress cough</td>
<td>Xi Xin, Rou gui, Ban xia, Fu zhi, Kuan dong hua, Zi wan, Gan jiang, Xing ren, Chen pi, Gan cao, Ren shen</td>
<td>Tai ping hui min he ji ju fang</td>
<td>1078</td>
</tr>
<tr>
<td>213 Shen Su Ban Xia Tang</td>
<td>Chuan sou</td>
<td>Diffuse the lung to resolve phlegm</td>
<td>Ren shen, Rou gui, Gan cao, Mu xiang, Wu wei zi, Sang bai pi, Chen pi, Bai zhu, Zi su, Ban xia</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>220 Shen Ying Dan</td>
<td>Chuan sou</td>
<td>Diffuse the lung to resolve phlegm and calm dyspnea</td>
<td>Bo he, Gan cao, Ba dou, Wu ling zhi, Pen xiao, Qing fen, Dou chi</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>258 Ren Shen Ding Chuan Tang</td>
<td>Chuan sou</td>
<td>Diffuse the lung to suppress cough and calm dyspea, tonify lung qi</td>
<td>Ren shen, Ma huang, Gan cao, E jiao, Ban xia, Sang bai pi, Wu wei zi, Ying su ke</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>259 Chen Sha Li Ge Wan</td>
<td>Chuan sou</td>
<td>Resolve phlegm to move phlegm-fluid retention</td>
<td>Tian nan xing, Fu ling, Gan sheng jiang, Sheng xi (生犀), Ban xia, Bai Fan, Shan yao, Zao jiao</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>273 Dao Tan Wan</td>
<td>Chuan sou</td>
<td>Resolve phlegm to move phlegm-fluid retention</td>
<td>Tian nan xing, Ban xia, Bai fan, Zao jiao, Sheng jiang</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>454 Jin Bu Huan San</td>
<td>Jiu kesou</td>
<td>Warm the lung and stomach to dispel cold and resolve phlegm</td>
<td>Ying su ke, Xing ren, Gan cao, Zhi ke</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>484 Qing Jin Tang</td>
<td>Jiu kesou</td>
<td>Fortify spleen to resolve phlegm and suppress cough</td>
<td>Ying su ke, Ren shen, Gan cao, Chen pi, Fu ling, Xing ren, E jiao, Wu wei zi, Sang bai pi, Yi yi ren, Zi su, Bai he, Bei mu, Ban xia, Kuan dong hua</td>
<td>Pu Ji Fang</td>
<td>1584</td>
</tr>
</tbody>
</table>

Ref: Peng (2003) Zhong Guo Ming Yi Fang Ji Da Quan (中国名医方剂大全).
Appendix 11 Table: Frequency of formulae occurring in the data set at step 7: ‘possible complications of COPD’

<table>
<thead>
<tr>
<th>Formula name</th>
<th>Terms</th>
<th>Actions</th>
<th>Ingredients</th>
<th>Book name</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No name</td>
<td>Fei zhang</td>
<td>various</td>
<td>Ke zi, Hai fen, Huang qin, Qing dai, Xing ren, Wu wei zi</td>
<td>Ji Yang Gang Mu</td>
<td>1626</td>
</tr>
<tr>
<td>8 Zi Wan Tang Fang</td>
<td>Fei zhang</td>
<td>Resolve phlegm and regulate qi</td>
<td>Zi wan, Gan cao, Bing lang, Fu ling, Ting li zi</td>
<td>Pu Ji Fang</td>
<td>1406</td>
</tr>
<tr>
<td>33 Jia Wei Si Wu Tang</td>
<td>Fei zhang</td>
<td>Regulate qi and resolve phlegm and activate blood stasis</td>
<td>Dang gui, Chuan xiong, Shao yao, Di huang, Ke zi, Tao ren, Qing pi</td>
<td>Ji Yang Gang Mu</td>
<td>1626</td>
</tr>
<tr>
<td>83 Ban Xia Wan</td>
<td>Tanyin kesou</td>
<td>Invigorate the spleen and eliminate fluid retention</td>
<td>Ban xia, Bai fan, Sheng jiang</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1078</td>
</tr>
<tr>
<td>108 Ren Shen Yang Fei Wan</td>
<td>Tanyin kesou</td>
<td>Tonify qi and fortify spleen to resolve phlegm and suppress cough</td>
<td>Huang qi, Ren shen, Fu ling, Gua lou, Xing ren, Ban xia, Zi su, Sang bai pi</td>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
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<td>278 Ting Li San</td>
<td>Chuan Sou</td>
<td>Diffuse the lung to resolve phlegm and calm dyspnea, tonify qi</td>
<td>Ting li zi, Ge jie, Sang bai pi, Zhi zi, Ren shen, Jing jie, Bo he, Fu ling, Jie geng, Xing ren, Gan Cao</td>
<td>Pu Ji Fang</td>
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<td>144 Zao Jiao Jian Wan</td>
<td>Tanyin kesou</td>
<td>Tonify qi and resolve phlegm to calm dyspnea</td>
<td>Zao jiao</td>
<td>Ye Shi Lu Yan Fang</td>
<td>1186</td>
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Ref: Peng (2003) Zhong Guo Ming Yi Fang Ji Da Quan (中国名医方剂大全) (336)
Appendix 12 Table: The characteristics of the 101 studies included in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>First author, date</th>
<th>Location, Design [duration / follow up]</th>
<th>Out /in patients</th>
<th>No. subjects (R/A)</th>
<th>M/F</th>
<th>Age Mean SD (years)</th>
<th>Severity of COPD: No. subjects</th>
<th>CM Syndrome Differentiation</th>
<th>COPD history (years)</th>
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<td>NS</td>
<td>21±NS</td>
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<td>C: 35/35</td>
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<td>C: 40/40</td>
<td>T: 58.6 ± 6.1</td>
<td>NS</td>
<td>Lung Qi deficiency</td>
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<td>C: 30/30</td>
<td>T: &gt;30</td>
<td>NS</td>
<td>NS</td>
<td>T: 3-30</td>
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<td>C: &gt;30</td>
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<td>C: 3-38</td>
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<td>T: 30/30 C: 30/30</td>
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<td>T: 27/27 C: 27/27</td>
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<td>T: 60/60 C: 60/60</td>
<td>T: 38/22 C: 42/18</td>
<td>T: 50-75 C: 50-75</td>
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<td>NS</td>
<td>NS T: 3-20 C: 3-20</td>
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<td>T: 26/4 C: 23/3</td>
<td>T: 68.0±5.70 C: 68.0±4.96</td>
<td>T: I 18, II 22 C: I 16, II 20</td>
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<td>Beijing, China RCT [3 mths/NS]</td>
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<td>T: 0 8, I 9, II A 9, II B 9 C: 0 8, I 12, II A 9, II B 8</td>
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<td>T: 36/36 C: 33/36</td>
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<td>T: 17/13</td>
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<td>T: I 26, II 15</td>
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<td>COPD history (years)</td>
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<td>T: 7.20±4.40 C: 8.50±3.60</td>
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<td>T: 16.2± NS C: 15.8± NS</td>
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<td>NS</td>
<td>T: 15± NS C: 18± NS</td>
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<td>62.0±NS C: 60.5±NS</td>
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<td>Both</td>
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<td>Guangdong, China RCT [6 mths / NS]</td>
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<td>T: 30/26</td>
<td>T: 22/4</td>
<td>T: 68.0± 5.70</td>
<td>T: I 4, II 22</td>
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<td>T: 30/30</td>
<td>T: 25/5</td>
<td>T: 67.37±6.03</td>
<td>T: I 4, II 26</td>
<td>NS</td>
<td>T: 3.62±2.07</td>
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<td>T: 30/30</td>
<td>T: 18/12</td>
<td>T: 65.12±5.36</td>
<td>T: 0.5, 1.9, II 16</td>
<td>Qi deficiency and phlegm stasis</td>
<td>T: 17.32±2.36</td>
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<td>T: 23/10</td>
<td>T: 39-74</td>
<td>T: I 12, II 15, III 6; Lung qi deficiency</td>
<td>T: I 12, II 15, III 6; Lung qi deficiency</td>
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<td>CM Syndrome Differentiation</td>
<td>COPD history (years)</td>
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<td>T: 40/40 C: 40/40</td>
<td>T: 22/18 C: 24/16</td>
<td>T: 67.70±6.80 C: 66.89±5.87</td>
<td>T: II 12, III 28 C: II 10 III 30</td>
<td>NS</td>
<td>T: 13.05±6.84 C: 14.53±6.05</td>
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<td>T: 34/34 C: 34/34</td>
<td>T: 19/15 C: 20/14</td>
<td>T: 64.35±6.77 C: 64.62±7.05</td>
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<td>T: 11.24±5.02 C: 10.50±4.56</td>
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<td>T: 17/13 C: 18/12</td>
<td>T: 64.5±8.5 C: 63.5±9.0</td>
<td>II &amp; III</td>
<td>NS</td>
<td>T: 9.8±4.2 C: 10±3.5</td>
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<td>T: 73.6± NS C: 72.9± NS</td>
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<td>T: 100/94 C: 30/30</td>
<td>T: 44/56 C: 14/16</td>
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<td>T: 15.64±10.51 C: 18.55±12.38</td>
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<td>T: 31/14 C: 29/16</td>
<td>T: 69± NS C: 68.5± NS</td>
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<td>T: 16/19 C: 18/17</td>
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<td>Qi deficiency &amp; blood stasis NS</td>
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<td>Moderate Lung Qi &amp; Kidney Qi deficiency NS</td>
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<td>T: 11/8 C: 12/7</td>
<td>T: 60.97±8.97 C: 59.54±10.87</td>
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<td>II &amp; III: NS NS</td>
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<td>T: 24/6 C: 24/6</td>
<td>T: 64.67±8.54 C: 68.30±7.68</td>
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<td>CM Syndrome Differentiation</td>
<td>COPD history (years)</td>
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<td>T: 34/37 C: 34/37</td>
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<td>T: 32/18 C: 29/20</td>
<td>T: 60.17±6.87 C: 61.12±6.85</td>
<td>NS</td>
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<td>T: 10.7±0.51 C: 10.59±0.52</td>
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<td>Hangzhou, Zhejiang RCT [3 mths / NS]</td>
<td>Out patients</td>
<td>T: 29/29 C: 25/25</td>
<td>T: 20/9 C: 18/7</td>
<td>T: 61.3± NS C: 61.3± NS</td>
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<td>T: 18/2 C: 19/1</td>
<td>T: 59.4±7.5 C: 60.9±7.9</td>
<td>T: IIA 8, IIB 9 III 3; C: IIA 9, IIB 9, III 2</td>
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<td>T: 11.2±4.1 C: 11.8±4.5</td>
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<td>T: 19/11 C: 20/10</td>
<td>T: 49.38±NS C: 47.62±NS</td>
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<td>In patients</td>
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<td>T: 24/6 C: 25/7</td>
<td>T: 70.5±6 NS C: 69.8±6 NS</td>
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<td>T: 68/32 C: 72/28</td>
<td>T: 71.87±4.37 C: 69.33±5.71</td>
<td>T: mild 21, moderate 48, severe 31 C: mild 23, moderate 51, severe 26</td>
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<td>T: 18.70±3.72 C: 17.81±4.57</td>
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<td>Dongyang, Zhejiang</td>
<td>In patients</td>
<td>T: 32/32 C: 30/30</td>
<td>T: 19/13 C: 21/9</td>
<td>T: 63-89 C: 62-88</td>
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<td>M/F</td>
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<td>CM Syndrome Differentiation</td>
<td>COPD history (years)</td>
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<td>T: 13.36±NS</td>
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<td>C: 28/28</td>
<td>T: 58.5± NS</td>
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<td>T&amp;C: 72.00±NS</td>
<td>Average of FEV₁ T: 52.3%; C: 56.8%</td>
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<td>T: 54/54</td>
<td>C: 45/45</td>
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<td>C: 30/30</td>
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<td>T: 18/6</td>
<td>T: 66.70±6.60</td>
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<td>T: 14.05±6.54</td>
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<td>T1: 17/3</td>
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<td>T: 63.5±10.08 C: 63.55±10.42</td>
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T: treatment group; C: control group; NS: not specified
Appendix 13 Table: Methodological quality of the 101 studies assessed by Jadad’s scale in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

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<td>Xu, 2009</td>
<td>1</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
<td>2</td>
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<td>Yang, 2010</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>You, 2008</td>
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<td>1</td>
<td>NS</td>
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<tr>
<td>Zhai, 2009</td>
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<td>NS</td>
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<tr>
<td>Zhang, 2008</td>
<td>1</td>
<td>NS</td>
<td>1 (reason)</td>
<td>NS</td>
<td>NS</td>
<td>2</td>
</tr>
<tr>
<td>Zhang (1), 2009</td>
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<td>NS</td>
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<td>NS</td>
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<tr>
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<td>Zhang, 2010</td>
<td>1</td>
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<td>NS</td>
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<td>Zhao, 2008</td>
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<td>NS</td>
<td>1</td>
<td>1</td>
<td>NS</td>
<td>3</td>
</tr>
<tr>
<td>Zhu, 2007</td>
<td>1</td>
<td>NS</td>
<td>1</td>
<td>1</td>
<td>NS</td>
<td>3</td>
</tr>
<tr>
<td>First author, date</td>
<td>Randomisation</td>
<td>Double blinding</td>
<td>Description of withdrawals</td>
<td>Adequate description of randomization</td>
<td>Blinding adequately carried out</td>
<td>Total scores</td>
</tr>
<tr>
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<tr>
<td>Zhu, 2010</td>
<td>1</td>
<td>1</td>
<td>1 (reason)</td>
<td>NS</td>
<td>NS</td>
<td>3</td>
</tr>
<tr>
<td>Zhuan, 2006</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
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</tbody>
</table>
Appendix 14 Table: Comparison of CHM (formulae and ingredients) and placebo control groups in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du, 2006</td>
<td><em>Yinxingye extract tablet: 2 tablets, Tid</em> Ginkgo biloba extract.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Gross, 2002</td>
<td><em>Ginseng extract capsule: 100 mg Bid</em> Renshen</td>
<td>Bronchodilator (not specified)</td>
<td>Placebo + Bronchodilator (not specified)</td>
</tr>
<tr>
<td>He, 2010</td>
<td><em>Buzhong Yiqi Tang /granule: 6g Bid</em> Huangqi, Dangshen, Baizhu, Shashen, Banxia, Chenpi, Sangbaipi, Yuzhu</td>
<td>Theophylline Sustained-release Tablets 0.2g Bid</td>
<td>Placebo + Theophylline Sustained-release Tablets 0.2g Bid</td>
</tr>
<tr>
<td>Huang, 2002</td>
<td><em>Bufei Guben granule: 10g Tid</em> Renshen, Gejie, Yinyanghuo, Hutaorou, Buguzhi, Wuweizi, etc.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Li (1), 2006</td>
<td><em>Bufei Yishen granule: 10g Tid</em> Renshen, Huangqi, Baizhu, Fangfeng, Maidong, Buguzhi, Wuweizi, Gejie, Shanyurou, Dongcongxiacao, Zhebeimu, Chenxiang, Weijin, Quanchong, Xingren, Chuanxiong.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Lin, 2003</td>
<td><em>Jiapi Yifei granule: 10g Tid</em> Rehshen, Baizhu, Fuling, Maidong, Sangbaipi, Huangqi.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Ni, 2008</td>
<td><em>Bushen Naqi granule: 10g Tid</em></td>
<td>Theophylline, Inhaler of Salbutamol</td>
<td>Placebo (Shanzha granule) +</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Plus RP</td>
<td>Control</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Buguzhi, Yinyanghuo, Fupenzi, Wuweizi.</td>
<td>Theophylline, Inhaler of Salbutamol</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Sun (1), 2009</td>
<td><em>Bafei granule</em>: 16g Bid&lt;br&gt;Dangshen, Shudihuang, Danggui, Shanzhuyu, Mahuang, Sangbaipi, Chenpi, Ziyuan.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wu (1), 2006</td>
<td><em>Shenge granule</em>: 1 bag Tid&lt;br&gt;Renshen, Gejie, Xingren, Zhigancao, Fuling, Chuanbeimu, Sangbaipi, Dongcongxiao. Baizhu, Huangqi, Chuanxiong, Dilong.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Xu, 2008</td>
<td><em>Jianpi Yifei granule</em>: 10g, Tid&lt;br&gt;Hongshen, Baizhu, Fuling, Maidong, Sangbaipi, Huangqi.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Zhang, 2007</td>
<td><em>Sanzi Yangqin Decoction</em>: 200ml Bid&lt;br&gt;Dangshen, Baizhu, Yunling, Suzi, Baijiezi, Laifu, Juhong, Fabanxia.</td>
<td>No</td>
<td>Placebo</td>
</tr>
<tr>
<td>Zhuan, 2006</td>
<td><em>Liujunzi Tang/Decoction</em>: one packet once daily, 300ml, Bid&lt;br&gt;Dangshen, Chaobaizhu, Fuling, Chenpi, Zhibanxia, Gancao.</td>
<td>No</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

RP: routine pharmacotherapy
**Appendix 15 Table: Comparison of CHM (formulae and ingredients) and RP groups in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures**

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Plus RP</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2006</td>
<td><em>Lijin granule/decoction: one packet once daily, 100ml, Bid</em> Dangshen, Huangqi, Maidong, Wuweizi, Ziyuan, Chuanbaimu, Gejie, Baizhu, Fangfeng, Fuling, Chenpi, Gancao.</td>
<td>No</td>
<td>Theophylline Tablets: 0.1g Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Chen (2), 2007</td>
<td><em>Lijin granule/decoction: one packet once daily, 150ml, Bid</em> Dangshen, Huangqi, Maidong, Wuweizi, Ziyuan, Chuanbaimu, Gejie, Baizhu, Fangfeng, Fuling, Chenpi, Gancao.*</td>
<td>No</td>
<td>Theophylline Tablets: 0.1g Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Hu, 2005</td>
<td><em>Bazhong Yiqi Decoction: NS</em> Huangqi, Dangshen, Baizhu, Zhigancao, Danshen, Cheng, Chaihu.</td>
<td>No</td>
<td>Ipratropium Bromide Aerosol, Pulmicort Aerosol, Theophylline</td>
<td>NS</td>
</tr>
<tr>
<td>Jin, 2008</td>
<td><em>Jinpi Bufei Decoction: NS</em> Renshen, Fuling, Baizhu, Danshen, Fabanxia, Zhuru, Gualoupi, Houpo, Zhiquiao, etc.</td>
<td>No</td>
<td>Bronchodilator</td>
<td>NS</td>
</tr>
<tr>
<td>Ma, 2009</td>
<td><em>Yuquingfeng pill: 6g, Bid</em> Huangqi Baizhu Fangfeng</td>
<td>No</td>
<td>Mannatide tablets: 5mg Tid</td>
<td>NO</td>
</tr>
<tr>
<td>Shi (1) 2008</td>
<td><em>Bushen Yifei capsule: 6 Tid</em> Gandihuang, Shanyurou, Wuweizi, Yinyanghuo, Tusizi, Nvzhenzi, Huainiuxi, Gejie</td>
<td>No</td>
<td>Nucleotide and Casein Oral Solution: 10ml Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Shi (2), 2008</td>
<td><em>Yonggui Yin/Decoction</em> <em>Shenqi pill: 1 Bid; Xuesaitong tablet: 2# Tid Yongchongcaoju capsule: 3 Tid</em> Shudihuang, Shanyao, Shanzhuyu, Gouji, Zhigancao, Duzhong, Rougui, Zhifuzi</td>
<td>No</td>
<td>Stage I: Salmeterol 100-200 μg; Stage II-III: Salmeterol Xinafoate/Fluticasone Propionate: 50 μg, Bid; OR Compound Aminophylline Tablets: 1# p.r.n</td>
<td>NS</td>
</tr>
<tr>
<td>Wang, 2003</td>
<td><em>Xiazhi Number I granule: 15g Tid</em> Huangqi, Ezhu, Tusizi, Zhiyiing, Qiyezi, Zhuhua, etc.</td>
<td>No</td>
<td>Theophylline Controlled Release Capsules: 0.2g Bid</td>
<td>NS</td>
</tr>
<tr>
<td>Wu (2), 2006</td>
<td><em>Liujuzi Tang/Decoction: one packet once daily, 150ml, Bid</em> Dangshen, Fuling, Zhigancao, Chenpi, Jiangbanxia, Ziyuan, Kuandonghua, Taoren, Honghua, Danggui, etc.</td>
<td>No</td>
<td>Diastase Pancreat in and Pepsin Tablet: 4# Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Wu (1), 2009</td>
<td><em>Liujuzi granule: 15g Tid</em> Dangshen, Baizhu, Fuling, Zhihanxa, Chenpi, Zhigancao.</td>
<td>No</td>
<td>Diastase Pancreat in and Pepsin Tablet: 2# Tid</td>
<td>NO</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------</td>
<td></td>
</tr>
<tr>
<td><strong>Xiao, 2000</strong></td>
<td><em>Manzhi Kechuanning oral liguid:</em> 10ml Bid Renshen, Huangqi, Baizhu, Fuling, Shanyao, Hongzao</td>
<td>0.9% saline 30ml + Dexamethasone 3mg + Theophylline 0.125g: as Ultrasonic atomizing inhalation Bid; Theophylline Controlled Release Tablets: 0.1g p.r.n</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Xin, 2010</strong></td>
<td><em>Yiqi Xiaotan Huayu formula/decoction:</em> one packet once daily (400ml, Bid) Huangqi, Dangshen, Fuling, Baizhu, Gancao, Chenpi, Banxia, Gualou, Xingren, Zhiqiao, Chaihu, Taoren, Honghua, Huangqin, Danshen</td>
<td>Theophylline Sustained-release Tablets: 0.2g Bid; Ambroxol Hydrochloride: 30mg Bid</td>
<td>NO</td>
<td></td>
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<tr>
<td><strong>Xiong, 2008</strong></td>
<td><em>Shenge granule:</em> 5g Bid Gaolishen, Gejie</td>
<td>Salmeterol Xinafoate/Fluticasone Propionate: 1 puff Bid</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Zhai, 2009</strong></td>
<td><em>Bufei Nashen Tang/Decoction:</em> one packet once daily Huangqi, Gejie, Baizhu, Fuling, Shudihuang, Shanzhuyu, Danggui, Wuweizi, Chenpi, Chenxiang, Rougui, Dilong, Danshen, Zhigancao, etc.</td>
<td>Theophylline, Salbutamol and ipratropium bromide: p.r.n</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Zhu, 2007</strong></td>
<td><em>Tianlong Kechuanning capsule:</em> 4 capsules, Tid Qingtiankui, Kuandonghua, Fabanxia, Shufuzi, Wuweizi.</td>
<td>Compound Ipratropium Bromide Aerosol: 2 puffs, Qid</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

RP: routine pharmacotherapy; I, II, III (severity of COPD): Stage I, Stage II, Stage III
Appendix 16 Table: Comparison of CHM (formulae and ingredients) plus RP and RP groups in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula name (form): Dose / Ingredients</strong></td>
<td><strong>Plus RP</strong></td>
<td><strong>Control</strong></td>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ao, 2007</td>
<td>Xiaoyaosan /decoction: one packet once daily. 150ml, Tid Danggui, Baishao, Chaifu, Fuling, Baizhu, Bohe, Huangqin, Gualou, Qianhu, Shegan, Pipaye.</td>
<td>Theophylline Tablets: 0.1g Tid</td>
<td>Theophylline Tablets: 0.1g Tid</td>
</tr>
<tr>
<td>Che, 2005</td>
<td>Zhike Qingfei oral liquid: 2 ml, Tid (QC) Jinyinhua, Huangqin, Lianqiao, Banlangen, Kuandonghua, Ziyuan, Yuxingcao, Jiegeng, Mahuang, Pipaye, Huangqi, Gancao.</td>
<td>RP</td>
<td>RP</td>
</tr>
<tr>
<td>Chen, 2004</td>
<td>Yiqi pill: 2 pills Tid Renshen, Gejie Buguzhi</td>
<td>RP</td>
<td>RP</td>
</tr>
<tr>
<td>Chen (1), 2009</td>
<td>Qiwei Duqi Tang (decocition): 250 ml Bid Shanzhuyu, Shanyao, Shudihuang, Mudanpi, Zexie, Fuling, Wuweizi, Huangqi, Dangshen, Baizhu.</td>
<td>Salmeterol 50μg &amp; Fluticasone 500μg inhaled Bid</td>
<td>Salmeterol 50μg &amp; Fluticasone 500μg inhaled Bid</td>
</tr>
<tr>
<td>Chen (2), 2009</td>
<td>Liujunzi Tang /Decocition: one packet once daily Dangshen, Chaobaizhu, Fuling, Chenpi, Zhibanxiao, Gancao.</td>
<td>Ipratropine 40 μg inhaled Tid; Theophylline Tablets: 0.1g Bid</td>
<td>Ipratropine 40 μg inhaled Tid; Theophylline Tablets: 0.1g Bid</td>
</tr>
<tr>
<td>Feng, 2005</td>
<td>Yiqihuoxuehuatang (decocition): one packet once daily Huangqi, Shuizhi, Beimu, Guangdilong etc. Plus Bailing capsule: 4 capsules, Tid Or Feikang granule: 10g once daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc.</td>
<td>Stage 0: no treatment I: short-acting bronchodilator II: one or multi bronchodilators or inhaled glucocorticosteroid</td>
<td>Stage 0: no treatment I: short-acting bronchodilator II: one or multi bronchodilators or inhaled glucocorticosteroid</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
</tr>
<tr>
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<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Formula name (form): Dose / Ingredients</strong></td>
<td><strong>Plus RP</strong></td>
<td><strong>Control</strong></td>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td><strong>Plus Bailing capsule: 4 capsules, Tid</strong></td>
<td></td>
<td>Doxofylline Tablets: 400mg Bid</td>
<td>NS</td>
</tr>
<tr>
<td>Feng, 2006</td>
<td><em>Jianpi Bufei Tang</em>/decoction: 150 ml, Bid Taizishen, Huangqi, Gejie, Baizhu, Shengma, Chaihu, Danggui, Kuandonghua, Tusizi, Shuizhi.</td>
<td>Doxofylline Tablets: 400mg Bid</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Plus Bailing capsule: 4 capsules, Tid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Or</em> Feikang granule: 10g once daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc.</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Feng, 2007</td>
<td><em>YiqihuoXuehuaTang</em> (decoction): one packet once daily Huangqi, Shuizhi, Beimu, Guangdilong etc.</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td><em>Plus Bailing capsule: 4 capsules, Tid</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Or</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feikang granule: 10g once daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Plus Bailing capsule: 4 capsules, Tid</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng, 2008</td>
<td><em>Bufei Tang</em> (decoction): one packet once daily Dangshen, Huangqi, Baizhu, Shanyao, Wuweizi, Maidong, Yuzhu, Zimiu, Jiegeng, Chenpi, ZhiBaibu, Zhigancao.</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td><em>Qiweidiquwan &amp; Shengmaisan</em> (decoction): one packet once daily Shudihuang, Shanzhu, Shengshanyao, Fuling, Danpi, Gouji, Wuweizi, Taizishen, Maidong, Nvzhenzi, Huaniuacao.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Or</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Or</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suzijiangqi Tang (decocction): one packet once daily Zisuzi, Banxia, Qianhu, Houpo, Danggui, Chenpi, Rougui, Gancao.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo, 2008</td>
<td><em>Jianfei capsule: 2-3 capsules Tid</em> Renshen, Gejie, Jinqiaomaigeng, Dilong, Chuanbeimu, Xingren, etc.</td>
<td>Theophylline Tablets &amp; Mucosolva &amp; inhaled long-acting β₂-agonists</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Note:** RP denotes ‘Respiratory Hyperreactivity’.
<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hao, 2008</td>
<td><em>Pingchuanfang/Decoction: one packet once daily</em> Shufuzi, Danshen, Fuling, Buguzhi, Yinyanghuo, Dilong, Wuweizi, Zhigancao, Chenpi, Xixin.</td>
<td>Theophylline Sustained-release Tablets</td>
<td>NS</td>
</tr>
<tr>
<td>Hu, 2009</td>
<td><em>Bufei Tang/Decoction: one packet once daily</em> Danshen, Huangqi, Xuanshen, Maidong, Buguzhi, Bajitian, Tusizi, Baibu, Sangbaipi, Chenpi, Jiegeng, Danshen.</td>
<td>Ambroxol hydrochloride: 30mg Tid, Salbutamol sulfate Aerosol: 200 μg, Tid, Theophylline Sustained-release Tablets: 0.2g Bid</td>
<td>NS</td>
</tr>
<tr>
<td>Huang, 2005</td>
<td><em>Yupingfeng granule</em>: 5g Tid Huangqi, Baizhu, Fangfeng. <em>Plus Jianpiyifei granule</em>: 10g Tid Renshen, Baizhu, Fuling, Maidong, Sangbaipi, Huangqi. <em>Plus Bailing capsule</em>: 5 capsules Tid</td>
<td>RP</td>
<td>Yes</td>
</tr>
<tr>
<td>Ji, 2010</td>
<td><em>Yuchuan Zhisheng Syrup: one spoon Bid</em> Danshen, Zhihuangqi, Shanyao, Chaobaizhu, Hutaorou, Shudihuang, Huangjing, Danggui, Nanshashen, Fuling, Ziwan, Kuandonghua, Baibu, Suzi, Fabanxia, Baiyezi, Beimu, Taoren, Xingren, Ganjiang, Chenpi, Zhimahuang, Wuweizi, Baiguo, Chenxiang, Zhigancao, Zheche, Gejie.</td>
<td>Theophylline Tablets: 0.1g, Bid</td>
<td>NS</td>
</tr>
<tr>
<td>Jia, 2007</td>
<td><em>Yiqihuoxue formula (decoction): one packet once daily</em> Huangqi, Dilong, Xuanshen, Danshen, Taizishen, Danggui, etc. Ipratropium bromide: 40 μg Tid (inhaled)</td>
<td>Ipratropium bromide: 40 μg Tid (inhaled)</td>
<td>NS</td>
</tr>
<tr>
<td>Jian, 2008</td>
<td><em>Pingchuan capsule</em>: 4 capsules Tid Renshen, Gejie, Tianqi etc. Ipratropium Bromide: 2 puffs, Bid</td>
<td>Ipratropium Bromide: 2 puffs, Bid</td>
<td>NS</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
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</tr>
</tbody>
</table>
| Lang, 2010 | **Baibu Yangfei Paste: NS**  
Baibu | RP | RP | NO |
| Li (2), 2006 | **Decoction: one packet once daily, 200ml, Bid**  
Chishao. Honghua. Chenpi. Xingren. Maidong | Theophylline or Albuterol | Theophylline or Albuterol | NS |
| Liang, 2005 | **Jianpi Yifei Capsule & Bushen Peiyuan capsule: 3 capsules/per Bid**  
Dongcongxiacao. Yucongrong. Shudihuang. Hetao | Theophylline Sustained-release Tablets: 0.1g, Bid  
Plus Bromhexine Hydrochloride Tablets: 16mg, Tid | Theophylline Sustained-release Tablets: 0.1g, Bid  
Plus Bromhexine Hydrochloride Tablets: 16mg, Tid | NS |
| Liang, 2009 | **Dongping Tang (powder in decoction): one packet once daily**  
Dongchongxiacao, Huangqi, Baizhu, Fangfeng. | Stage 1: Salmeterol inhaler, 200μg up to Tid  
Stage 2: Theophylline tablets: 0.1-0.2g Tid OR terbutaline sulfate tablets 2.5mg Bid OR salmeterol inhaler, 200μg up to Qid (if dyspnoea severe)  
Stage 3: Theophylline tablets: 0.1-0.2g Tid OR terbutaline sulfate tablets 2.5mg Tid OR salmeterol inhaler, 200μg up to 6 times/day (if dyspnoea severe) | Stage 1: Salmeterol inhaler, 200μg up to Tid  
Stage 2: Theophylline tablets: 0.1-0.2g Tid OR terbutaline sulfate tablets 2.5mg Bid OR salmeterol inhaler, 200μg up to Qid (if dyspnoea severe)  
Stage 3: Theophylline tablets: 0.1-0.2g Tid OR terbutaline sulfate tablets 2.5mg Tid OR salmeterol inhaler, 200μg up to 6 times/day (if dyspnoea severe) | NS |
| Liu (1), 2006 | **Huoxuehuayu formula (decoction): one packet once daily**  
Chenpi, Fabanxia, Laifuzi, Zisuzi, Zhebeimu, Xingren,  
Taoren, Fuling, Maodongqing, Baijiezhi, Gancao. | Theophylline Sustained-release Tablets: 0.2g Bid | Theophylline Sustained-release Tablets: 0.2g Bid | NS |
<p>| Liu, 2007 | <strong>Pingchuan III: Decoction: one packet once daily</strong> | Combivent: 80μg, Bid | Combivent: 80μg, Bid | NS |</p>
<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Plus RP</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2008</td>
<td><strong>Fuzheng Guben Tang/Decoction: one packet once daily</strong>&lt;br&gt;Hongshen, Huangqi, Maidong, Wuweizi, Danshen, Buguzhi, Ziheche, Chuanxiong, Chenpi, Jiegeng, Sangbaipi</td>
<td>Bambuterol Hydrochloride: 10mg once daily&lt;br&gt;Theophylline Sustained-release Tablets: 0.4g p.r.n</td>
<td>Bambuterol Hydrochloride: 10mg once daily&lt;br&gt;Theophylline Sustained-release Tablets: 0.4g p.r.n</td>
<td>NS</td>
</tr>
<tr>
<td>Liu, 2010</td>
<td><strong>Yiqi Huatan Huoxue Tongluo formula/decoction: one packet once daily</strong>&lt;br&gt;Huangqi, Danshen, Fuling, Baizhu, Chuanbeimu, Dilong, Danshen, Xixin, Baijiezhi, Zishiyi, Hongjingtian</td>
<td>Carbocisteine Tablets: 0.5g Tid&lt;br&gt;Theophylline Sustained-release Tablets: 0.2g Bid&lt;br&gt;Salbutamol inhaler: 200μg Tid</td>
<td>Carbocisteine Tablets: 0.5g Tid&lt;br&gt;Theophylline Sustained-release Tablets: 0.2g Bid&lt;br&gt;Salbutamol inhaler: 200μg Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Luo, 2002</td>
<td><strong>Baofei dingchuan granule: 15g/bag, 2 bag, Bid</strong>&lt;br&gt;Dangshen, Huangqi, Danshen, Danggui, Shengdihuang, Maidong, Jiegeng, Gancao, Dilong, Yinyanghuo, etc.</td>
<td>Theophylline Controlled Release Tablets: 0.2g Bid&lt;br&gt;Carbocisteine Tablets: 0.5g Tid</td>
<td>Theophylline Controlled Release Tablets: 0.2g Bid&lt;br&gt;Carbocisteine Tablets: 0.5g Tid</td>
<td>NS</td>
</tr>
<tr>
<td>Peng, 2010</td>
<td><strong>Jinshui Liujun decoction: one packet once daily (Tid)</strong>&lt;br&gt;Dangshen, Danshen, Yinyanghuo, Maidong, Shichangpu, Wuweizi, Danggui, Shudihuang, Baizhu, Fuling, Chenpi, Fabanxia, Tinglizi, Gancao.</td>
<td>Theophylline Tablets+β₂ agonist inhaler+Glucorticosteroid inhaler</td>
<td>Theophylline Tablets+β₂ agonist inhaler+Glucorticosteroid inhaler</td>
<td>NS</td>
</tr>
<tr>
<td>Pu, 2010</td>
<td><strong>Shenge capsule: 4 capsules Tid</strong></td>
<td>Salmeterol xinafoate/ Fluticasone</td>
<td>Salmeterol xinafoate/ Fluticasone</td>
<td>NS</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
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<tr>
<td>Qiu, 2009</td>
<td><em>Guben Shengjin decoction: 200ml Bid</em>&lt;br&gt;Dangshen, Yunling, Baizhu, Shudihuang, etc.</td>
<td>RP</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shan, 2007</td>
<td><em>Peitu Shengjin Tang</em> (decoction): one packet once daily&lt;br&gt;Dangshen, Wuzhualong, Fuling, Baizhu, Shanyao, Wuweizi, Kuandonghua, Xingren, Taoren, Suzi, Jineijin.</td>
<td>Theophylline Sustained-release Tablets: 0.2g Bid</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shi, 2009*</td>
<td><em>Bufei Tang</em> (decoction): one packet once daily&lt;br&gt;Huangqi, Dangshen, Baizhu, Jiegeng, Chenpi, Zhigancao, Chaoshanyao, Zhihu, Wuweizi, Maidong, Yuzhu, Zhibai</td>
<td>RP</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>OR <em>Qiweiduqiwian + Shengmaisan</em> (decoction): as above&lt;br&gt;Shudi, Shanyou, Shengshanyao, Gouji, Maidong, Nvzhenzi, Hanliancao, Fuling, Danpi, Wuweizi, Taizishen</td>
<td>RP</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>OR <em>Jinguishenqiwian</em> (decoction): as above&lt;br&gt;Shudi, Danshen, Yiyiren, Shanyouro, Chaoshanyao, Fuling, Dangshen, Baizhu, Huainiuxi, Shufuzi, Tusizi, Rougui, Lujiaojiao</td>
<td>RP</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shi, 2009</td>
<td>OR <em>Suzijiangqitang</em> (decoction): as above&lt;br&gt;Zisuzi, Banxia, Qianhu, Houpo, Chenpi, Danggui, Rougui, Gancao.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Shinozuka, 2007</td>
<td><em>Buzhong Yiqi extraction: 2.5g Tid</em>&lt;br&gt;Huangqi, Dangshen, Baizhu, Chenpi, Shengma, Danggui, Chaihu, Zhigancao.</td>
<td>Bronchodilators</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tang, 2010</td>
<td><em>Jianpi Yishen formula/decoction: one packet once daily</em>&lt;br&gt;Bronchodilators &amp; Glucocorticosteroid inhaler</td>
<td>Bronchodilators &amp; Glucocorticosteroid inhaler</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
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<td></td>
</tr>
<tr>
<td><strong>Formula name (form): Dose / Ingredients</strong></td>
<td><strong>Plus RP</strong></td>
<td><strong>Bronchodilators</strong></td>
<td><strong>Bronchodilators</strong></td>
<td></td>
</tr>
<tr>
<td>Huangqi, Dangshen, Baizhu, Shashen (Nan), Shashen (Bei), Buguzhi, Baijitian, Danggui</td>
<td>Buzhong Yiqi extraction: 2.5g Tid Huangqi, Dangshen, Baizhu, Chenpi, Shengma, Danggui, Chaihu, Zhigancao.</td>
<td>Bronchodilators</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Bronchodilators</strong></td>
<td><strong>Theophylline Sustained-release Tablets or Terbutaline Sulfate Tablet</strong></td>
<td><strong>Theophylline Sustained-release Tablets or Terbutaline Sulfate Tablet</strong></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Yifei Tang/Decoction:one packet once daily, 200ml, Tid</strong></td>
<td><strong>Salbutamol inhaler: p.r.n</strong></td>
<td><strong>Salbutamol inhaler: p.r.n</strong></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Huangqi, Dangshen, Baizhu, Fuling, Huangqi, Shudihuang, Yinyanghoo, Ziyuan, Kuandonghua, Fabanxia, Ziheche, Baijiezi, Laifuizi, Suzi, Taoren, Gancao, etc.</td>
<td>Ambroxol Hydrochloride Tablets: 16mg Tid</td>
<td>Ambroxol Hydrochloride Tablets: 16mg Tid</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Wang, 2005</strong></td>
<td><strong>Yifei Jianpi/Decoction:one packet once daily</strong></td>
<td><strong>Theophylline Tablets: 0.1g, Bid</strong></td>
<td><strong>Theophylline Tablets: 0.1g, Bid</strong></td>
<td></td>
</tr>
<tr>
<td>Huangqi, Dangshen, Baizhu, Fuling, Fangfeng, Banxia, Chenpi, Dilibin, Kuandonghua, Gancao.</td>
<td>Salbutamol inhaler: p.r.n</td>
<td>Salbutamol inhaler: p.r.n</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Wang, 2006</strong></td>
<td><strong>Huatang Jiangqi capsule: 2g, Tid</strong></td>
<td><strong>Theophylline Tablets: 0.1g, Bid</strong></td>
<td><strong>Theophylline Tablets: 0.1g, Bid</strong></td>
<td></td>
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<tr>
<td>Baijiezi, Zisuzi, Baiqian, Jinfecao, etc.</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Wang, 2009</strong></td>
<td><strong>Sanshen Jianpi Tang (decoction): one packet once daily</strong></td>
<td><strong>Salbutamol inhaler or Theophylline Tablets</strong></td>
<td><strong>Salbutamol inhaler or Theophylline Tablets</strong></td>
<td></td>
</tr>
<tr>
<td>Taizishen, Danshen, Shashen, Fuling, Baizhu, Honghua, Danggui, Taoren, Jiegeng, Chishao, Tianhuafen, Zhibanxia, Shenggancao, Sharen, Xiangfu, Juhong.</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Wu (2), 2006</strong></td>
<td><strong>Liujuzi Tang/Decoction:one packet once daily, 150ml, Bid</strong></td>
<td><strong>Diastase Pancreatin and Pepsin Tablet: 4# Tid</strong></td>
<td><strong>Diastase Pancreatin and Pepsin Tablet: 4# Tid</strong></td>
<td></td>
</tr>
<tr>
<td>Huangqi, Fuling, Zhigancao, Chenpi, Jiangbanxia, Ziyuan, Kuandonghua, Taoren, Honghua, Danggui,etc.</td>
<td>Diastase Pancreatin and Pepsin Tablet: 4# Tid</td>
<td>Diastase Pancreatin and Pepsin Tablet: 4# Tid</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Wu (2), 2009</strong></td>
<td><strong>Bufei Huoxue Huayu Tang/Decoction:one packet once daily</strong></td>
<td><strong>Ipratropium Bromide Aerosol: 40 μg, Tid</strong></td>
<td><strong>Ipratropium Bromide Aerosol: 40 μg, Tid</strong></td>
<td></td>
</tr>
<tr>
<td>Huangqi, Chuanxiong, Dilibin, Wuweizi, Dongcongxicao, etc.</td>
<td></td>
<td></td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Plus RP</td>
<td>Control</td>
<td>Adverse event</td>
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</tr>
<tr>
<td>Xu, 2009</td>
<td>Jianpi Yifei granule: 10g, Tid Renshen, Fuling, Baizhu, Maidong, Sangbaipi, Huangqi,</td>
<td>RP</td>
<td>RP</td>
<td>NS</td>
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<tr>
<td>Yang, 2010</td>
<td>Maxuan Zhike Liquid (Mixture): 20ml Tid Mahuang, Shigao, Xingren, Gancao, Shanyinhua, Xuanshen, Maidong, Jiegeng, Baiqian, Yuxingcao</td>
<td>RP</td>
<td>RP</td>
<td>NS</td>
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<tr>
<td>You, 2008</td>
<td>Yifei Mixture: 100ml Bid Yinyanghuo, Xianmao, Renshen, Fuling, Baizhu, Danshen, Fabanxia, Zhurui, Gualoupi, Houpo, Zhiquiao, Gancao</td>
<td>Salbutamol or becotide inhaler &amp; Theophylline Tablets</td>
<td>Salbutamol or becotide inhaler &amp; Theophylline Tablets</td>
<td>NS</td>
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<tr>
<td>Zhang, 2010</td>
<td>Bailing capsule: 5 capsules Tid Dongchongxiaocao Ipratropium Bromide Aerosol:</td>
<td>Ipratropium Bromide Aerosol: 2 puffs, Tid</td>
<td>Ipratropium Bromide Aerosol: 2 puffs, Tid</td>
<td>NS</td>
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</tr>
<tr>
<td>Zhou, 2007</td>
<td>Feisaitong Mixture/liquid: 100 ml,Tid Huangqin, Danshen, Jiegeng, Laifuzi, Zisuzi, Chantui, Dilong, Jinyinhua, Beishashen, Yiypiren, Shenggancao.</td>
<td>Salbutamol Sulfate Tablets: 2.4mg, Tid</td>
<td>Salbutamol Sulfate Tablets: 2.4mg, Tid</td>
<td>NS</td>
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<td></td>
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<tr>
<td>Zhu, 2010</td>
<td>Shengmai Yin or Zhenwu Tang: NS Nanshashen, Maidong, Wuweizi, Yuzhu, Shengdihuang, Tianhuafen, Huangqí etc. OR Hongshen, Fuzi, Rougui, Baizhu, Ganjiang, Fuling, Chenxiang, Shudihuang etc.</td>
<td>Salmeterol xinafoate 50ug/Fluticasone propionate 500 ug: 1 puff Bid</td>
<td>Salmeterol xinafoate 50ug/Fluticasone propionate 500 ug: 1 puff Bid</td>
<td>NO</td>
</tr>
</tbody>
</table>

RP: Routine Pharmacotherapy; 0, I, II, III (severity of COPD): Stage 0, Stage I, Stage II, Stage III

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### Appendix 17 Table: Comparison of CHM (formulae and ingredients) with no treatment groups in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
</table>
| Cui, 2008          | *Yiqi Huayu recipe/Decoction: one packet once daily; 100ml, Bid*  
Huangqi, Shenma, Jiegeng, Zhimu, Jiaogulan, Ezhu, Taoren, Wuzhualong.  
*Zoufei granule*: 10g Tid  
Huangqi, Ziyuan, Kuandonghua, Wuweizi, Xingren, Taoren, Chenxiang, Zhiyiying, Goat lung. | No | No treatment | NS |
| Fang, 2008         | *Zoufei granule*: 10g Tid  
Dangshen, Guizhi, Ziyuan, Kuandonghua, Wuweizi, Xingren, Taoren, Chenxiang, Zhiyiying, Goat lung. | No | No treatment | NS |
| Hong, 2005         | *Yufeining pill*: 6g Bid  
Renshen, Huangqi, Baizhu, Fangfeng, Ziheche, Hetaorou, Tusizi, Shanzhuyu, Wuweizi, Xingren, Gualou, Danshen, Taoren. | No | No treatment | No |
| Li, 2007           | *Pingchuan Guben Tang/Decoction: one packet once daily*  
Dangshen, Wuweizi, Dongcongxiacao, Hutaorou, Chenxiang, Lingcishi, Kanqi, Suzi, Kuandonghua, Fabanxia, Juhong. | No | No treatment | NS |
| Liu, 2005          | *Manzi Kechuangling (oral liquid)*: 10ml Bid  
Renshen, Huangqi, Baizhu, Fuling, Shanyao, Buguzhi, Lujiaojiao, Ziheche, Ejiao, Hetaoren, Gejie, Zisuzi, Chuanbeimu, Yimucao, Taoren, Gancao. | No | No treatment | NS |
| Liu (2), 2006      | *Gushen Dingchuan pill*: 2g Tid  
Shudihuang, Fuzi, Buguzhi, Niuxi, Cheqianzi, Rougui, Jinyingzi, Yizhi, Fuling. | No | No treatment | NS |
| Shao, 2006         | *Tongxinluo capsule*: 2-4 capsules, Tid  
Quanxie, Shuizhi, Wugong, Tubiechong, Chuantui. | No | No treatment | Yes |
| Su, 2005           | *Feikang granule*: 10g, Tid  
Huangqi, Shuizhi, Haigejiao, etc. | No | No treatment | NS |
| Tang, 2009         | *Bailing capsule*: 3 capsules Tid  
Dongchongxiacao. | No | No treatment | NS |
| Wu, 2007           | *Liujunzi Tang* (decoction): 100ml Bid  
Dangshen, Baishu, Fuling, Chenpi, Zhibanxia, Gancao. | No | No treatment | NS |
| Xiong, 2010        | *Bifei Yishen granule*: 10g Tid  
Shengdi, Shanyrou, Nvzhengi, Niuxi, Yinyanghuo, Tusizi | No | No treatment | NS |
<p>| Zhang, 2006        | <em>Jiapí Yifei Bushen formula</em> (decoction): one packet once daily | No | No treatment | NS |</p>
<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2008</td>
<td>Huangqi, Dangshi, Baizhu, Fuling, Maidong, Shashen, Buguzhi, Tusizi, Nvzhenzi, Gejie, Xingren, Gualou, Beimu, Danshen, Chuanxiong,</td>
<td>No</td>
<td>No treatment</td>
</tr>
<tr>
<td>Zhang (1), 2009</td>
<td><em>Liujuanzi Pill:</em> 9g, Bid Renshen, Baizhu, Fuling, Zhigancao, Chenpi, Banxia, Dazao, Shengjiang.</td>
<td>No</td>
<td>No treatment</td>
</tr>
<tr>
<td>Zhang (2), 2009</td>
<td><em>Yifei Yangyin Tang</em> (decoction): 300ml Bid Baihe, Shengdihuang, Shudihuang, Chuanbei, Jiegeng, Zhqiiao, Maidong, Baishao, Danggui, Shashen, Weishanyao, Fuling, Huangqi, Shenggancao.</td>
<td>No</td>
<td>No treatment</td>
</tr>
<tr>
<td>Zhang (2), 2009</td>
<td><em>Wenshen Bufei Tang/Decoction:</em> one packet once daily, 100ml, Bid Dangshen, Wuweizi, Fuling, Huangqi, Ziyuan, Sangbaipi, Shudihuang, Shanzhuyu, Huaishanyao, Zexie, Danpi, Buguzhi, Rougui.</td>
<td>No</td>
<td>treatment</td>
</tr>
</tbody>
</table>

RP: routine pharmacotherapy
Appendix 18 Table: Comparison of test CHM (formulae and ingredients) with other CHM (formulae and ingredients) groups in review of Chinese herbal medicine for stable COPD with physical and symptomatic outcome measures

<table>
<thead>
<tr>
<th>First author, date</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (1), 2007</td>
<td>Feikangning capsule: 3 capsules, Tid Renshen, Buguzhi, Dongcongxiacojinsi, Danshen, etc.</td>
<td>Jinshuibao capsule Extract of Dongcongxiacao</td>
<td>NO</td>
</tr>
<tr>
<td>Chen 2008</td>
<td>Guben Pingchuan pill: 6g, Tid Huangqi, Renshen, Zheche, Lujiaoqiao, Giubianjiao, Bajitian, Shudihuang, Shanzhuyu, Huashanyao, Tusizi, Maidong, Wuweizi, Suzi, Xingren, Chenpi, Danshen, Gejie.</td>
<td>Zhenqi Fuzheng capsule: 2 capsules, Bid Nuzhenzi, Huangqi</td>
<td>NS</td>
</tr>
<tr>
<td>Gao, 2008</td>
<td>Zoufei Pingchuan capsule: 4 capsules, Tid Shudihuang, Huangqi, Kuandonghua, Wuweizi, Xuanfuhua, Dongcongxiacao, Shuiishi.</td>
<td>Jinshuibao capsule: 3 capsules, Tid Extract of Dongcongxiacao</td>
<td>NS</td>
</tr>
<tr>
<td>Huang, 2009</td>
<td>Bufei tablet: 3#, Tid Huangqi, Danshen, Fangfeng, Baizhu, Jiaogulan, Gejie, Jiegeng, Wuweizi etc.</td>
<td>Jinshuibao capsule: 3 capsules, Tid Extract of Dongcongxiacao</td>
<td>NS</td>
</tr>
<tr>
<td>Lei, 2006</td>
<td>Sheng Qi Feibao: NS Huangqi, Danshen, Fangfeng, Buguzhi, Danshen, Baibu, Sangbaipi.</td>
<td>Zhike Huatan Pingchuan CHM</td>
<td>NS</td>
</tr>
<tr>
<td>Liu, 2002</td>
<td>Feikang II granule: 8g, Tid Renshen, Baizhu, Zhigancao, Shudihuang, Shanzhuyu, Shanyao, Moadongqing, Quangualou, Danpi, Zexie, Fuling, Maidong, Tinglizi, Wuweizi.</td>
<td>Feikang I granule: 8g, Tid</td>
<td>NO</td>
</tr>
<tr>
<td>Sun (1), 2007</td>
<td>Shenge YiFei capsule: 4 Tid Xiyangshen, Gejie, Congcaojusi, Zheche, Chuanbaimu, Shensanqi.</td>
<td>Jinshuibao capsule: 3 capsules, Tid Extract of Dongcongxiacao</td>
<td>NS</td>
</tr>
<tr>
<td>Sun (2), 2009</td>
<td>Guben Kechuan granule: 1 bag, Bid (QC) Dangshen, Fuling, Baizhu, Shashen, Shihuangqi, Guizhi, Baishao, Fangfeng, Baibu, Suzi, Shudihuang, Shanyurou, Goujiji, Kanqi.</td>
<td>Gu Ben Ke Chuan tablet:4#, Tid</td>
<td>NS</td>
</tr>
<tr>
<td>First author, date</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse event</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>Formula name (form): Dose / Ingredients</td>
<td>Plus RP</td>
<td></td>
</tr>
</tbody>
</table>
| Xu, 1996          | *Yiqi Mianyi granule: 20g Tid*  
Renshen, Fuling, Baizhu, Ciwujia, Shanzhuyu. | No | *Zhen Qi Fu Zheng granule: 15g Bid*  
NS |
| Zhang, 2003       | *Tiaobu Feishen capsule: 4 capsules, Tid*  
Xiyangshen, Dongcongxiacao, Shanyurou, Danshen, Fuling, etc. | No | *Guben Kechuan tablet: 3 tablets, Tid*  
NO |
|                   | Ganjiang, Wuweizi. |         |               |

RP: routine pharmacotherapy
# Appendix 19 Table: Herbs included in the formulae used in the 101 RCTs by functional category

<table>
<thead>
<tr>
<th>No.</th>
<th>Categories of Materia Medica</th>
<th>Name of herbs</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Release the Exterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warm and acrid herbs</td>
<td>Ma huang, Gui zhi, Fang feng, Sheng jiang, Su ye, Xi xin</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cool and acrid herbs</td>
<td>Chai hu, Chan tui, Bo he, Sheng ma</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Clear the Heat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>drain fire,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shí gào, Tian hua fen, Wei jin, Zhi mu, Zhi zi</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cool the blood</td>
<td>Chi shao, Dan pi, Sheng di huang, Xuan shen</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>clear heat and dry dampness</td>
<td>Huang lian, Huang qín</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>clear heat and relieve toxicity</td>
<td>Ban lan gen, She gan, Jin qiao mai gen, Lian qiao, Jin yin hua, Qi ye yi zhi huá, Jin qiao mai, Qing tian kui, Yu xing cao</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Drain dampness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry dampness</td>
<td>Cang zhú, Hou po, Shà rèn</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Transform dampens</td>
<td>Fu líng, Che qian zì, Yi yí ré, Ze xíe</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Activate the blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activate blood</td>
<td>Chúan xióng, Dans hén, È zhú, Nìu xí, Hóng huá, Máo dòng qíng, Shuí zhí,</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Stop bleeding</td>
<td>Su mù, Táo rén, Yú jīn, Yí mù cáo</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Tonify</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tonify qí</td>
<td>Bai zhú, Cí wú jiá, Dá zào, Dāng shèn, Gāo cáo, Gào lí shén, Hóng jíng tián, Xì yáng shén, Hútao rùn, Jiáo gū lán, Hóng shèn, Rén shèn, Táí zhí shén, Ling zhí, Huang qí, Shàn yáo, Shèng shāi shén, Yáng fēi (Goat lung)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Replenish blood</td>
<td>Bai shào, Dāng guì, Yī jiāo, Zhī hé ché, Dí huáng</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Tonify yang</td>
<td>Bai ji tián, Dōng chōng xiá cáo, Kán qí, Bú gu zhí, Hè táo rén, Lú jiāo jiāo, Dú zhòng, Dōng chōng xiá cáo jùn sì, Róng kōng róng, Sāng shèn, Xiān mào, Shān zhū yú, Tú sì zhí,</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Replenish yín</td>
<td>Huán jíng, Huán lián cáo, Gōu jí, Guī bàn jiāo, Mǎi dōng, Shā shèn, Nú zhēn zhí, Yuan zhí, Yúzhú</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Resolve Phlegm and suppress cough</td>
<td>Banxiá, Bái jié zì, Gúalóu, Gúa lóu pí, Chúan bèi mù, Hāi gé qíáo, Zhū rú, Xuān fú huá,</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Suppress cough</td>
<td>Zhè běi mù</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>Warm the Interior and Expel Cold</td>
<td>Fu zhí, Gān jiāng, Róu guì</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Regulate the Qi</td>
<td>Chen pí, Chen xiàng, Jú hóng, Xiāng fù, Xíe bái, Zhī qiáo</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>Tranquilizers</td>
<td>Ling cì shí, Zhì shí yǐng</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Astringents</td>
<td>Fu pén zì, Jīn yíng zì, Wú wèi zì, Yí zhí rén</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Removing food stagnation</td>
<td>Ji nèi jìn, Lài fú zì</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>Dispelling Wind-Dampness</td>
<td>Wu xiāo shè, Chūan shān lónɡ, Xu chānɡ qínɡ</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>Extinguishing Wind and Stopping Tremors</td>
<td>Dí lónɡ, Quán xíe, Wú gònɡ, Wú zhá lónɡ, Tū bǐe chónɡ</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>Opening orifices</td>
<td>Shí chānɡ pú</td>
<td>1</td>
</tr>
<tr>
<td>over all</td>
<td></td>
<td></td>
<td>139</td>
</tr>
</tbody>
</table>
### Appendix 20 Table: Comparisons of high frequency herbs common to classical literature and modern clinical trials

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Botanical name</th>
<th>Properties</th>
<th>Channels entered</th>
<th>Effects</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao</td>
<td><em>Glycyrrhiza uralensis</em> Fisch</td>
<td>Neutral &amp; sweet</td>
<td>Heart, lung, spleen &amp; stomach</td>
<td>Invigorates spleen &amp; replenishes qi or eliminates phlegm &amp; arrests cough</td>
<td>Deficiency of spleen qi &amp; stomach qi or cough &amp; dyspnoea</td>
</tr>
<tr>
<td>Ban xia</td>
<td><em>Pinelliae ternate</em> (Thunb.) Breit</td>
<td>Warm, acrid &amp; toxic</td>
<td>Lung, spleen &amp; stomach</td>
<td>Eliminates dampness &amp; resolves phlegm</td>
<td>Profuse sputum, cough, adverse upward flow of qi</td>
</tr>
<tr>
<td>Xing ren</td>
<td><em>Prunus armeniaca</em> L.</td>
<td>Slightly warm, bitter &amp; slightly toxic</td>
<td>Lung &amp; large intestine</td>
<td>Relieves cough &amp; asthma</td>
<td>Multiple kinds of cough and dyspnoea</td>
</tr>
<tr>
<td>Ren shen</td>
<td><em>Panax ginseng</em> C.A. Mey.</td>
<td>Neutral, sweet &amp; slightly bitter</td>
<td>Spleen, lung &amp; heart</td>
<td>Replenishes primordial qi &amp; tonifies spleen &amp; lung</td>
<td>Prostration syndromes due to deficient qi, chronic illness &amp; shortness of breath</td>
</tr>
<tr>
<td>Fu ling</td>
<td><em>Poria cocos</em> (Schw.) Wolf</td>
<td>Neutral, sweet &amp; tasteless</td>
<td>Heart, spleen &amp; kidney</td>
<td>Induces diuresis, excretes dampness, invigorates spleen &amp; resolves phlegm</td>
<td>Phlegm retention &amp; deficiency of spleen</td>
</tr>
<tr>
<td>Wu wei zi</td>
<td><em>Schisandra chinensis</em> (Turcz.) Baill</td>
<td>Warm, sour &amp; sweet</td>
<td>Lung, kidney &amp; heart</td>
<td>Astringes lungs &amp; nourishes kidney</td>
<td>Chronic cough and asthma due to deficiency</td>
</tr>
<tr>
<td>Chen pi</td>
<td><em>Citrus tangerine</em> Hort. et Tanaka</td>
<td>Warm &amp; pungent</td>
<td>Spleen &amp; lung</td>
<td>Regulates qi, normalizes the function of middle-Jiao, eliminates dampness &amp; resolves phlegm</td>
<td>Cough, profuse sputum &amp; full and oppressed feeling in chest due to accumulation of phlegm-dampness in the lung</td>
</tr>
<tr>
<td>Kuan dong hua</td>
<td><em>Tussilago farfara</em> L.</td>
<td>Acrid &amp; warm</td>
<td>Lung</td>
<td>Directs qi downward and suppresses cough</td>
<td>Coughing due to different types of cold in lung</td>
</tr>
<tr>
<td>Bei mu</td>
<td><em>Fritillaria cirrhosa</em> D.Don</td>
<td>Bitter, sweet &amp; slightly cold</td>
<td>Heart &amp; lung</td>
<td>Clears heat and transforms phlegm</td>
<td>Cough, chiefly chronic cough, with signs of fire due to yin deficiency</td>
</tr>
<tr>
<td>Mai men dong</td>
<td><em>Ophiopogon japonicus</em> Ker-Gawl</td>
<td>Slightly cold, sweet &amp; slightly bitter</td>
<td>Lung, heart &amp; stomach</td>
<td>Moistens lung &amp; nourishes yin</td>
<td>Dry cough with sticky sputum</td>
</tr>
<tr>
<td>Ba zhu</td>
<td><em>Atractylodis Macrocephala</em> Koidz</td>
<td>Warm, bitter &amp; sweet</td>
<td>Spleen &amp; stomach</td>
<td>Replenishes qi, reinforces the spleen, eliminates dampness &amp; induces diuresis</td>
<td>Phlegm retention due to deficiency of spleen</td>
</tr>
<tr>
<td>Herb name</td>
<td>Botanical name</td>
<td>Properties</td>
<td>Channels entered</td>
<td>Effects</td>
<td>Indications</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sang bai pi</td>
<td><em>Morus alba</em> L.</td>
<td>Sweet &amp; cold</td>
<td>Lung &amp; spleen</td>
<td>Suppresses cough and calms panting, clears and resolves heat-phlegm</td>
<td>Coughing and wheezing due to lung heat</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td><em>Zingiber officinale (Wild.) Rosc.</em></td>
<td>Acrid &amp; warm</td>
<td>Lung, spleen &amp;</td>
<td>Disperses cold and suppresses cough</td>
<td>Exterior cold patterns or cough due to both acute wind-cold cough patterns and chronic disorders with phlegm</td>
</tr>
<tr>
<td>Ma huang</td>
<td><em>Ephedra sinica</em> Stapf., <em>E. equisetina</em> Bunge.</td>
<td>Warm, pungent &amp; bitter</td>
<td>Lung &amp; bladder</td>
<td>Promotes the flow of lung qi</td>
<td>Cough with dyspnœa due to dispersion of lung qi</td>
</tr>
<tr>
<td>Zi wan</td>
<td><em>Aster tartaricus</em> L.f.</td>
<td>Bitter &amp; slightly warm</td>
<td>Lung</td>
<td>Suppresses cough and expels phlegm</td>
<td>For chronic cough, especially cold-induced cough with copious sputum</td>
</tr>
<tr>
<td>Rou gui</td>
<td><em>Cinnamomum cassia</em> Presl.</td>
<td>Hot, acrid &amp; sweet</td>
<td>Kidney, spleen, heart &amp; liver</td>
<td>Supplements fire &amp; strengthens yang</td>
<td>Syndromes of yang deficiency</td>
</tr>
<tr>
<td>Jie geng</td>
<td><em>Platycodon grandiflorum (Jacq.) A. DC.</em></td>
<td>Neutral, pungent &amp; sweet</td>
<td>Lung</td>
<td>Ventilates lung &amp; resolves phlegm</td>
<td>Cough due to wind-heat or wind-cold exopathogens</td>
</tr>
<tr>
<td>Gan jiang</td>
<td><em>Zingiber officinale Rosc.</em></td>
<td>Hot &amp; pungent</td>
<td>Spleen, stomach, heart &amp; lung</td>
<td>Warms lung and resolves phlegm retention</td>
<td>Cough &amp; dyspnœa due to retention of cold phlegm in the lung</td>
</tr>
<tr>
<td>Zhi shi</td>
<td><em>Citus aurantium</em> L.</td>
<td>Slightly cold, bitter &amp; pungent</td>
<td>Spleen, stomach &amp; large intestine</td>
<td>Relieves stagnation of qi &amp; resolves phlegm</td>
<td>Stiffness &amp; fullness in the chest due to obstruction of flow qi by phlegm</td>
</tr>
<tr>
<td>Da zao</td>
<td><em>Ziziphus jujuba</em> Mill.</td>
<td>Sweet &amp; neutral</td>
<td>Spleen &amp; stomach</td>
<td>Fortifies spleen and replenishes qi; Nourishes the blood and calms the spirit</td>
<td>Weakness, shortness of breath, lassitude, reduced appetite and loose stools due to spleen and stomach deficiency</td>
</tr>
<tr>
<td>Herb name</td>
<td>Botanical name</td>
<td>Properties</td>
<td>Channels entered</td>
<td>Effects</td>
<td>Indications</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>------------</td>
<td>------------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>Huang qi</td>
<td>Astragalus membranaceus</td>
<td>Sweet &amp; slightly warm</td>
<td>Lung &amp; spleen</td>
<td>Fortifies spleen &amp; replenishes qi; Increases yang qi of the spleen and stomach; tonifies qi and blood</td>
<td>Lack of appetite, fatigue and diarrhoea due to spleen deficiency; prolapse disorders; post partum fever due to qi and blood deficiency</td>
</tr>
<tr>
<td>Dang shen</td>
<td>Codonopsis pilosula (Franch.) Nannf.</td>
<td>Sweet &amp; neutral</td>
<td>Lung &amp; spleen</td>
<td>Tonifies middle qi and lung; strengthens qi and nourishes fluids</td>
<td>Chronic illness, such as lack of appetite, fatigue and diarrhoea due to spleen deficiency; or chronic cough and shortness of breath, or copious sputum.</td>
</tr>
<tr>
<td>Di huang</td>
<td>Rehmannia glutinosa Libosch (dried root)</td>
<td>Sweet &amp; slightly warm</td>
<td>Heart, kidney &amp; liver</td>
<td>Tonifies blood, nourishes yin, nourishes the blood and tonifies essence</td>
<td>Blood deficiency (irregular menstruation), kidney yin deficiency (night sweats, wasting and thirsting) and low back pain.</td>
</tr>
<tr>
<td>Dan shen</td>
<td>Salvia miltiorrhiza Bge</td>
<td>Bitter &amp; slightly cold</td>
<td>Heart, pericardium &amp; liver</td>
<td>Invigorates the blood and breaks up blood stasis</td>
<td>Lower abdomen, such as dysmenorrhoea, &amp; chest or epigastric pain</td>
</tr>
<tr>
<td>Ge jie</td>
<td>Gekko gecko Linnaeus</td>
<td>Salty &amp; neutral</td>
<td>Lung &amp; kidney</td>
<td>Tonifies the kidney and the lung, assists kidney yang and augments the essence and blood</td>
<td>Wheezing, consumptive cough or with streaked sputum, urinary frequency due to kidney yang deficiency</td>
</tr>
<tr>
<td>Dang gui</td>
<td>Angelica sinensis (Oliv.) Diels</td>
<td>Sweet, acrid, bitter &amp; warm</td>
<td>Heart, liver &amp; spleen</td>
<td>Tonifies the blood and regulates menses, invigorates and harmonises the blood and disperses cold ect.</td>
<td>Blood deficiency, stop pains due to blood stasis</td>
</tr>
<tr>
<td>Shan yao</td>
<td>Dioscorea opposita Thunb.</td>
<td>Sweet &amp; neutral</td>
<td>Kidney, lung &amp; spleen</td>
<td>Tonifies and augments the spleen and stomach, tonifies lung qi and replenishes lung yin, tonifies kidney, etc.</td>
<td>Lack of appetite, fatigue and diarrhoea due to deficiency of spleen or stomach; chronic cough and wheezing due to lung deficiency; frequent urination, vaginal discharge</td>
</tr>
<tr>
<td>Shan zhu yu</td>
<td>Cornus officinalis Sieb. &amp; Zucc.</td>
<td>Sour &amp; slightly warm</td>
<td>Kidney &amp; liver</td>
<td>Tonifies kidney yang and stabilises the kidney and retains the essences, stops excessive sweating Tonifies and augments the kidney and liver.</td>
<td>Leakage of fluids due to weak essence (excessive urination); excessive sweating; light-headedness, dizziness, Sore and weak lower back and knees due to liver and kidney deficiency; excessive uterine bleeding and prolonged menstruation due to deficiency pattern.</td>
</tr>
<tr>
<td>Su zi</td>
<td>Perilla frutescens (L.) Britt.</td>
<td>Acrid &amp; warm</td>
<td>Large intestine &amp; lung</td>
<td>Suppresses cough and calms panting, directs downward qi and resolves phlegm</td>
<td>Coughing and wheezing with copious phlegm; constipation due to intestine</td>
</tr>
</tbody>
</table>
### Appendix 23 Table: The Pharmacological activities of herbs used frequently in the classical literature

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Pharmaceutical name</th>
<th>Chemical Constituents</th>
<th>Pharmacological activities</th>
<th>Clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gancao</td>
<td>Radix Glycyrrhiza Uralensis</td>
<td>Glycyrrhizin, Glycyrrhizic acide Liquiritigenin</td>
<td>Mineralocorticoid effect; Glucocorticoid effect; Anti-inflammatory effect Anti-allergic effect</td>
<td>Chronic bronchial asthma Use in gastroenterology</td>
</tr>
<tr>
<td>Banxia</td>
<td>Rhizoma Pinelliae Ternatae</td>
<td>Beta-sitosterol, conine, protoanemonin, homogentisic acid, aspartic acid Essential oils Polysaccharide Amylose</td>
<td>Antitussive effect Antiemetic effect</td>
<td>Respiratory disorder</td>
</tr>
<tr>
<td>Xingren</td>
<td>Semen pruniArmeniacae</td>
<td>Amygdalin, amygdalase, prunase, Emulsin, fatty acid</td>
<td>N/A</td>
<td>Pulmonary diseases</td>
</tr>
<tr>
<td>Renshen</td>
<td>Radix ginseng</td>
<td>Panaxosides, Saponins, Polysaccharide etc.</td>
<td>Central nervous system effect, Peripheral nervous system effect, Cardiovascular effect, Metabolic effect, Endocrine effect, Immunologoical effect, gastrointestinal effect etc.</td>
<td>N/A</td>
</tr>
<tr>
<td>Fuling</td>
<td>Sclerotiom poriae cocos</td>
<td>β-pachyman, Triterpenoid, Pachymic-acid, fats, glucose, protein, etc.</td>
<td>Urinary effect, Central nervous system effect, Effect on smooth muscle, Endocrine effect.</td>
<td>N/A</td>
</tr>
<tr>
<td>Wuweizi</td>
<td>Fructus schisandrae chinensis</td>
<td>Sesquicarene, lignans, Schisandrin Gomisin A, etc.</td>
<td>Central nervous system effect, Respiratory effect, Peripheral nervous system effect, Cardiovascular effect</td>
<td>Anicteric infectious hepatitis, neurasthenia.</td>
</tr>
<tr>
<td>Chen pi</td>
<td>Pericarpium Citri Reticulatae</td>
<td>Limonene, Hesperdin, isopropenyltoluene, elemene, etc.</td>
<td>Effect on smooth muscle, Cardiovascular effect, anti-inflammatory effect</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Sangbaipi</td>
<td>Cortex Mori Albae Radicis</td>
<td>Mulberrin, Scopoletine mulberrochomene, morusin, cyclomulberrin, etc.</td>
<td>Diuretic effect, Effect on blood pressure, Central nervous system effect.</td>
<td></td>
</tr>
<tr>
<td>Shengjiang</td>
<td>Rhizoma Zingiberis Officinalis Recens</td>
<td>Naphtha, Gingerol, diphenyleptanes, Zingiberol, zingiberene, etc.</td>
<td>Effect on the gastrointestinal system, etc.</td>
<td>Bacillary dysentery</td>
</tr>
<tr>
<td>Kuandonghua</td>
<td>Flos Tussilaginis Farfarae</td>
<td>Faradiol, Butin, triterpenoid saponins etc.</td>
<td>Respiratory effect, Cardiovascular effect</td>
<td>Pulmonary diseases; Rise in blood pressure</td>
</tr>
<tr>
<td>Mahuang</td>
<td>Herma Ephedrae</td>
<td>L-ephradine, D- pseudoephradine, I-N.</td>
<td>Diaphoretic effect, Bronchodilation effect, Antiviral etc.</td>
<td>Pulmonary diseases; influenza</td>
</tr>
<tr>
<td>Herb</td>
<td>Common Name</td>
<td>Ingredients</td>
<td>Effects</td>
<td>Conditions</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Ziwan</td>
<td>Radix Asteris Tatarici</td>
<td>Methylephedrine, Astersaponin, Shionone, quercetin, etc.</td>
<td>Respiratory effect, Antimicrobial effect.</td>
<td>Pulmonary diseases;</td>
</tr>
<tr>
<td>Rougui</td>
<td>Cotex Cinnamomi cassiae</td>
<td>Cinnamaldehyde, Cinnamyl acetate, Phenylpropyl acetate.</td>
<td>Central nervous system effect, Cardiovascular effect, Effect on temperature regulation, Antibiotic effect</td>
<td>Asthma</td>
</tr>
<tr>
<td>Beimu</td>
<td>Bulbus, fritillariae cirrhosae</td>
<td>Sipeimine, fritidine, chinpeimine</td>
<td>Effect on smooth muscle.</td>
<td>N/A</td>
</tr>
<tr>
<td>Jiegu</td>
<td>Radix Platycodi Grandiflori</td>
<td>Platycodigenin, polygalain-acid, Platycodonin, etc.</td>
<td>Strong expectorant effect, Antifungal effect, Endocrine effect.</td>
<td>Pulmonary diseases; lowered plasma glucose levels.</td>
</tr>
<tr>
<td>Ganjiang</td>
<td>Rhizoma Zingiberis officinalis</td>
<td>α-zingiberene, 6-gingesulfonicacid, gingeralicylopinid, phellandrene, etc.</td>
<td>Central nervous system effect.</td>
<td>N/A</td>
</tr>
<tr>
<td>Maimendong</td>
<td>Tuber Ophiopogonis Japonici</td>
<td>Ophiopogonin, ruscogenin, Beta-sitosterol, stigmasterol.</td>
<td>Endocrine effect.</td>
<td>N/A</td>
</tr>
<tr>
<td>Zhishi</td>
<td>Fructus immaturus citri auranti</td>
<td>Hesperidin, Neohesperidin, Naringenin-7-rutinoside, α-pinene, etc.</td>
<td>Effect on uterus, Effect on intestines, Cardiovascular effect. Etc.</td>
<td>N/A</td>
</tr>
<tr>
<td>Baizhu</td>
<td>Rhizoma Atractylodis Macrocephalae</td>
<td>Atractylon, Butenolide A, Butenolide B, Acetoxyatractylon, hydroxyatractylon, vitamin A.</td>
<td>Urinary effect, Endocrine effect, Hematologic effect etc.</td>
<td>N/A</td>
</tr>
<tr>
<td>Dazao</td>
<td>Fructus Zizyphi Jujubae</td>
<td>Ziziphussaponin I,II,III, Jujuboside B, cAMP, cGMP, vitamin A, vitamin B2, vitamin C, calcium, phosphorous, iron.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Appendix 24 Table: The Pharmacological activities of herbs used frequently in the RCTs

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Pharmaceutical name</th>
<th>Chemical Constituents</th>
<th>Pharmacological activities</th>
<th>Clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huangqi</td>
<td>Radix Astragali Membranaceous</td>
<td>Astragalosides, 6-dimethoxyisoflavane, calycosin</td>
<td>Vasodilatory effect; Prolonged diuretic effect; Effect on endurance, Endocrine effect</td>
<td>Reduction of blood pressure</td>
</tr>
<tr>
<td>Dangshen</td>
<td>Radix Codonopsis pilosulae Ternatae</td>
<td>Saponins, alkaloids, taraxerylacetate, glucose, friedelin etc.</td>
<td>Hematologic effect, Endocrine effect, Vasodilatory effect, Immunologic effect.</td>
<td>N/A</td>
</tr>
<tr>
<td>Dihuang</td>
<td>Radix Rehmannia glutinosae conquitae</td>
<td>Beta-sitosterol, Mannitol, stigmasterol, campesterol etc.</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Danshen</td>
<td>Radix Salviae Miltiorrhiza</td>
<td>Tanshinone, cryptotanshinone, salbiol, isotanshinone</td>
<td>Vasodilatory effect</td>
<td>Reduction of blood pressure</td>
</tr>
<tr>
<td>Gejie</td>
<td>Gecko</td>
<td>Carnoside, carnitine, guanine, albumen.</td>
<td>Hormonal effect</td>
<td>prostate</td>
</tr>
<tr>
<td>Danggui</td>
<td>Radix angelicae sinensis</td>
<td>Butylidene phthalide, ligustilide,sequiterpenes, Beta-sitosterol etc.</td>
<td>Cardiovascular effect, Antibiotic effect, Effect on smooth muscle.</td>
<td>Effect of lower blood pressure, pain</td>
</tr>
<tr>
<td>Shanyao</td>
<td>Radix dioscorea oppositae</td>
<td>Saponins, choline, d-abscisin vitamin C, mannan, phytic acid, allantoin</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Shanzhuyu</td>
<td>Fructus corni officinalis</td>
<td>Verbenaolin, saponins, morroniside, loganin, cornusin A and B, ursolic acid, tannin, vitamin A.</td>
<td>Antibiotic effect, general effect (diuretic effect, lowered blood pressure, little effect on serum glucose)</td>
<td>Inhibitory effect against bacteria; Lowered blood pressure</td>
</tr>
<tr>
<td>Suzi</td>
<td>Fructus Perillae Frutescentis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Appendix 25: Names of Chinese medicinal substances

<table>
<thead>
<tr>
<th>Pinyin name</th>
<th>Chinese</th>
<th>Botanical/Scientific name</th>
</tr>
</thead>
<tbody>
<tr>
<td>An xi xiang</td>
<td>安息香</td>
<td>Styrax tonkinensis</td>
</tr>
<tr>
<td>Ba dou</td>
<td>巴豆</td>
<td>Croton tiglium L.</td>
</tr>
<tr>
<td>Bai bian dou</td>
<td>白扁豆</td>
<td>Dolichos lablab L.</td>
</tr>
<tr>
<td>Bai bu</td>
<td>百部</td>
<td>Stemona sessilifolia</td>
</tr>
<tr>
<td>Bai dou kou</td>
<td>白豆蔻</td>
<td>Amomum krervanh Pierre ex Gagnep.</td>
</tr>
<tr>
<td>Bai fán</td>
<td>白矾</td>
<td>Alumen</td>
</tr>
<tr>
<td>Bai fú zǐ</td>
<td>白附子</td>
<td>Typhonium giganteum Engl.</td>
</tr>
<tr>
<td>Bai he</td>
<td>百合</td>
<td>Lilium lancifolium Thunb.</td>
</tr>
<tr>
<td>Bai jí</td>
<td>白芨</td>
<td>Tribulus terrestris L.</td>
</tr>
<tr>
<td>Bai jiao xiang</td>
<td>白胶香</td>
<td>Liquidambar taiwaniana Hance</td>
</tr>
<tr>
<td>Bai jí zì</td>
<td>白芥子</td>
<td>Brassica juncea (L.) Czern. &amp; Coss.</td>
</tr>
<tr>
<td>Bai shào</td>
<td>白芍</td>
<td>Paeonia lactiflora Pall.</td>
</tr>
<tr>
<td>Bai shí yíng</td>
<td>白石英</td>
<td>White quartz</td>
</tr>
<tr>
<td>Bai zhi</td>
<td>白芷</td>
<td>Angelica dahurica (Fisch.ex Hoffm.) Benth.</td>
</tr>
<tr>
<td>Bai zhù</td>
<td>白术</td>
<td>Atractylodes macrocephala Koidz.</td>
</tr>
<tr>
<td>Bai zuí ren</td>
<td>柏子仁</td>
<td>Platycladius orientalis (L.) Franco</td>
</tr>
<tr>
<td>Ban xia (zhi)</td>
<td>半夏</td>
<td>Pinellia ternata (Thunb.) Breit.</td>
</tr>
<tr>
<td>Bei mu</td>
<td>贝母</td>
<td>Fritillaria cirrhosa D.Don</td>
</tr>
<tr>
<td>Bi qí</td>
<td>芪荠</td>
<td>Eleocharis dulcis (Burm.f.)Trin.ex Henschel</td>
</tr>
<tr>
<td>Bi xíè</td>
<td>草薢</td>
<td>Dioscorea colletitii Hook.f.var:hypoglauca Palibin</td>
</tr>
<tr>
<td>Bie jíá</td>
<td>鳖甲</td>
<td>Trionyx sinensis Wiegmann</td>
</tr>
<tr>
<td>Bing lang</td>
<td>槟榔</td>
<td>Areca catechu L.</td>
</tr>
<tr>
<td>Bo hé</td>
<td>薄荷</td>
<td>Mentha haplocalyx Briq.</td>
</tr>
<tr>
<td>Bu gu zhí</td>
<td>补骨脂</td>
<td>Psoralea corylifolia L.</td>
</tr>
<tr>
<td>Cang zhú</td>
<td>苍术</td>
<td>Atractylodes lancea (Thunb.)DC</td>
</tr>
<tr>
<td>Cha yè</td>
<td>茶叶</td>
<td>Camellia sinensis O.Ktze (leaf)</td>
</tr>
<tr>
<td>Chái hu</td>
<td>柴胡</td>
<td>Bupleurum chinense DC.</td>
</tr>
<tr>
<td>Chan tui</td>
<td>蝉蜕</td>
<td>Cyptotympana pastulata Fabricius.</td>
</tr>
<tr>
<td>Che qían zì</td>
<td>车前子</td>
<td>Plantago asiatica L.</td>
</tr>
<tr>
<td>Chen pí</td>
<td>陈皮</td>
<td>Citrus reticulata Blanco</td>
</tr>
<tr>
<td>Chen xiàng</td>
<td>沉香</td>
<td>Aquilaria sinensis (Lour.) Gilg.</td>
</tr>
<tr>
<td>Chi shí zhí</td>
<td>赤石脂</td>
<td>Halloysitum rubrum</td>
</tr>
<tr>
<td>Chi xiáo dou</td>
<td>赤小豆</td>
<td>Phaseolus calcaratus Roxb.</td>
</tr>
<tr>
<td>Chu shí zhì</td>
<td>楂实子</td>
<td>Broussonetia papyrifera (L.)Vent.</td>
</tr>
<tr>
<td>Chuan jiào</td>
<td>川椒</td>
<td>Zanthoxylum bungeanum Maxim.</td>
</tr>
<tr>
<td>Chuan lián zì</td>
<td>川楝子</td>
<td>Melia toosendan Sieb. &amp; Zucc.</td>
</tr>
<tr>
<td>Chuan wù</td>
<td>川乌</td>
<td>Aconitum carmichaeli Debx.</td>
</tr>
<tr>
<td>Chuan xiong</td>
<td>川芎</td>
<td>Ligusticum chuanxiong Hort.</td>
</tr>
<tr>
<td>Ci huáng</td>
<td>雌黄</td>
<td>Realgar</td>
</tr>
<tr>
<td>Ci shí</td>
<td>磁石</td>
<td>Magnetite</td>
</tr>
<tr>
<td>Cong bái</td>
<td>葱白</td>
<td>Allium fistulosum L.</td>
</tr>
<tr>
<td>Da dou huáng juàn</td>
<td>大豆黄卷</td>
<td>Glycine max (L.) Merr.</td>
</tr>
<tr>
<td>Da fù pí</td>
<td>大腹皮</td>
<td>Areca catechu L.</td>
</tr>
<tr>
<td>Da huáng</td>
<td>大黄</td>
<td>Rheum palmatum L.</td>
</tr>
<tr>
<td>Da jí</td>
<td>大戟</td>
<td>Euphorbia pekinensis Rupr.</td>
</tr>
</tbody>
</table>
Huang lian | 黄连 | Coptis chinensis Franch.
Huang qi | 黄芪 | Astragalus membranaceus Fisch.
Huo ma ren, | 火麻仁 | Cannabis sativa L.
Huo xiang | 霍香 | Pogostemon cablin (Blanco) Benth.
Jiang can | 淫羊藿 | Bombyx mori L.
Jiang huang | 姜黄 | Curcuma longa L.
Jie geng | 桂枝 | Schizonepeta tenuifolia Briq.
Jing mi | 冬虫草 | Oryza sativa L.
Ju hong | 橘红 | Citrus reticulata Blanco
Ku lian | 苦楝 | Melia spp.
Kuan dong hua | 款冬花 | Tussilago farfara L.
Lai fu zi | 莱菔子 | Raphanus sativus L.
Lei wan | 雷丸 | Polyporus militaris Cook.et Mass.
Li lu | 黎芦 | Veratrum spp.
Lian qiao | 连翘 | Forsythia suspensa (Thunb.)Vahl
Lian xu | 莲须 | Nelumbo nucifera Gaertn. (stamen)
Lian zi | 莲子 | Nelumbo nucifera Gaertn. (dried seed)
Lian zi xin | 莲子心 | Nelumbo nucifera Gaertn.
Liang Jiang | 良姜 | Alpinia officinarum Hance
Ling yang jiao | 羚羊角 | Saiga tatarica L.
Liu huang | 硫黄 | Sulfur
Long dan cao | 龙胆草 | Gentiana scabra Bge.
Long gu | 龙骨 | Fossilia ossis mastodi
Long nao | 龙脑 | Dryobalanops aromatica Gaertn.
Lu feng fang | 蜂房 | Vespa nippon Temminck
Lu jiao jiao | 鹿角胶 | Cervus nippon Temminck
Lv dou | 绿豆 | Phaseolus radiatus L.
Ma dou ling | 马兜铃 | Aristolochia debilis Sieb.et Zucc.
Ma huang | 麻黄 | Ephedra sinica Stapf
Ma ya xiao | 马牙消 | Mirabilite (with long crystals)
Mai men dong | 麦门冬 | Ophiopogon japonicus (Thunb.) Ker-Gawl.
Man jing zi | 蔓荆子 | Vitis trifolia L. var. simplicifolia Cham.
Mang xiao | 芒硝 | Natrii sulfas
Mao gen | 茅根 | Imperata cylindrica Beauv.var.major(Nees)C.E.Hubb
Meng shi | 磷石 | Chlorite-schist
Mi tuo seng | 密陀僧 | Lithargyrum
Mo yao | 没药 | Commiphora myrrha Engl.
Mu dan pi, Dan pi | 牡丹皮 | Paeonia suffruticosa Andr.
Mu gua | 木瓜 | Chaenomeles speciosa (Sweet)Nakai
Mu li | 牡蛎 | Ostrea gigas Thunb.
Mu tong | 木通 | Akebia quinata (Thunb.) Decne.
Mu xiang | 木香 | Aucklandia lappa Deane.
Nan mu xiang | 南木香 | Aristolochia yunnanensis Franch.
Niu ru | 牛乳 | Cow’s milk
Niu xi | 牛膝 | Achyranthes bidentata Blume
Nuo mi | 糯米 | Oryza sativa L.
Peng sha | 硼砂 | Borax

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<table>
<thead>
<tr>
<th>Chinese Name</th>
<th>English Name</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pi pa ye</td>
<td>李叶</td>
<td>Eriobotrya japonica (Thunb.) Lindl.</td>
</tr>
<tr>
<td>Pu huang</td>
<td>蒲黄</td>
<td>Typha angustifolia L.</td>
</tr>
<tr>
<td>Qian cao</td>
<td>茜草</td>
<td>Rubia cordifolia L.</td>
</tr>
<tr>
<td>Qian dan</td>
<td>铅丹</td>
<td>Lead oxide</td>
</tr>
<tr>
<td>Qian hu</td>
<td>前胡</td>
<td>Peucedanum praeruptorum Dunn.</td>
</tr>
<tr>
<td>Qian niu zi</td>
<td>牵牛子</td>
<td>Pharbitis nil (L.) Choisy</td>
</tr>
<tr>
<td>Qian shi</td>
<td>尖实</td>
<td>Euryale ferox Salisb.</td>
</tr>
<tr>
<td>Qiang huo</td>
<td>香活</td>
<td>Notopterygium incisum Ting ex H.T. Chang</td>
</tr>
<tr>
<td>Qin jiao</td>
<td>秦艽</td>
<td>Gentiana macrophylla Pall.</td>
</tr>
<tr>
<td>Qing dai</td>
<td>青黛</td>
<td>Isatis indigotica Fort.</td>
</tr>
<tr>
<td>Qing fen</td>
<td>青皮</td>
<td>Calomelans</td>
</tr>
<tr>
<td>Qing pi</td>
<td>青皮</td>
<td>Citrus reticulata Blanco</td>
</tr>
<tr>
<td>Quan xie</td>
<td>全蝎</td>
<td>Bathus Martensii Karsch</td>
</tr>
<tr>
<td>Ren ru zhi</td>
<td>乳腺汁</td>
<td>Human milk</td>
</tr>
<tr>
<td>Ren shen</td>
<td>人参</td>
<td>Panax ginseng C.A. Mey.</td>
</tr>
<tr>
<td>Rou cong rong</td>
<td>肉苁蓉</td>
<td>Cistanche deserticola Y.C. Ma</td>
</tr>
<tr>
<td>Rou gui</td>
<td>甘草</td>
<td>Cinnamomum cassia Presl.</td>
</tr>
<tr>
<td>Ru xiang</td>
<td>乳香</td>
<td>Boswellia carterii Birdw.</td>
</tr>
<tr>
<td>Sang bai pi</td>
<td>桑白皮</td>
<td>Morus alba L.</td>
</tr>
<tr>
<td>Sang ye</td>
<td>桑叶</td>
<td>Morus alba L.</td>
</tr>
<tr>
<td>Sha ren</td>
<td>砂仁</td>
<td>Amomum volosum Lour.</td>
</tr>
<tr>
<td>Sha shen</td>
<td>沙参</td>
<td>Adenophora tetraphylla (Thunb.) Fisch</td>
</tr>
<tr>
<td>Sha yuan zi</td>
<td>沙苑子</td>
<td>Astragalus complanatus R. Br.</td>
</tr>
<tr>
<td>Shan yao</td>
<td>沙苑子</td>
<td>Dioscorea opposita Thunb.</td>
</tr>
<tr>
<td>Shan zha</td>
<td>沙苑子</td>
<td>Crataegus pinnatifida Bge.</td>
</tr>
<tr>
<td>Shan zhu yu</td>
<td>沙苑子</td>
<td>Cornus officinalis Sieb. &amp; Zucc.</td>
</tr>
<tr>
<td>Shang lu</td>
<td>商路</td>
<td>Phytolacca acinosa Roxb.</td>
</tr>
<tr>
<td>She gan</td>
<td>射干</td>
<td>Belamcanda chinensis (L.) DC.</td>
</tr>
<tr>
<td>She xiang</td>
<td>石香</td>
<td>Massa medicata fermentica</td>
</tr>
<tr>
<td>Shen qu</td>
<td>神曲</td>
<td>Rehmannia glutinosa Libosch</td>
</tr>
<tr>
<td>Sheng di huang</td>
<td>生地中黄</td>
<td>Rehmannia glutinosa Libosch</td>
</tr>
<tr>
<td>Sheng jiang</td>
<td>生姜</td>
<td>Zingiber officinalis (Willd.) Rosc.</td>
</tr>
<tr>
<td>Sheng ma</td>
<td>升麻</td>
<td>Cimicifuga foetida L.</td>
</tr>
<tr>
<td>Shi chang pu</td>
<td>石菖蒲</td>
<td>Acorus tatarinowii Schott.</td>
</tr>
<tr>
<td>Shi gao</td>
<td>石膏</td>
<td>Crystalline gypsum</td>
</tr>
<tr>
<td>Shi hu</td>
<td>石斛</td>
<td>Dendrobiun loddigesii Rolfe.</td>
</tr>
<tr>
<td>Shi jue ming</td>
<td>石决明</td>
<td>Haliotis diversicolor Reeve</td>
</tr>
<tr>
<td>Shi zhong ru</td>
<td>石钟乳</td>
<td>Stalactitum tubuliform</td>
</tr>
<tr>
<td>Shu di huang</td>
<td>熟地黄</td>
<td>Rehmannia glutinosa Libosch</td>
</tr>
<tr>
<td>Su geng</td>
<td>苏梗</td>
<td>Perilla frutescens (L.) Britt.</td>
</tr>
<tr>
<td>Su he xiang</td>
<td>苏合香</td>
<td>Liquidambar orientalis Mill.</td>
</tr>
<tr>
<td>Su mu</td>
<td>苏木</td>
<td>Caesalpinia sappan L.</td>
</tr>
<tr>
<td>Tan xiang</td>
<td>檀香</td>
<td>Santalum album L.</td>
</tr>
<tr>
<td>Tao ren</td>
<td>桃仁</td>
<td>Prunus persica (L.) Batsch</td>
</tr>
<tr>
<td>Tian hua fen</td>
<td>天花粉</td>
<td>Tirchosanthes kirilowii Maxim.</td>
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<td>天南星</td>
<td>Arisaema erubescens (Wall.) Schott.</td>
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<td>Pinyin</td>
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<td>藜丝子</td>
<td>Cuscuta chinensis Lam.</td>
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<td>五加皮</td>
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<td>犀角</td>
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