Panax ginseng for Chronic Obstructive Pulmonary Disease (COPD)

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Johannah L. Shergis _____

Date _____

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Publications

Published manuscripts

1. An, X., Zhang, A.L., Yang, A.W., Lin, L., Wu, D., Guo, X., Shergis, J.L., Thien, F.C.K., Worsnop, C.J., & Xue, C.C. Oral ginseng formulae for stable chronic obstructive pulmonary disease: A systematic review. *Respiratory Medicine*. 2011, 105 (2):165-176.

2. Xue, C.C., Shergis, J.L., Zhang, A.L., Worsnop, C.J, Fong, H., Story, D., Da Costa, C., & Thien, F.C.K. *Panax ginseng* C.A Meyer root extract for moderate Chronic Obstructive Pulmonary Disease (COPD): study protocol for a randomised controlled trial. *Trials*. 2011 Jun 30;12(1):164.

3. Shergis J.L., Zhang A.L., Zhou W., & Xue C.C. *Panax ginseng* in Randomised Controlled Trials: A Systematic Review. *Phytotherapy research*. Epub 2012/09/13, DOI: 10.1002/ptr.4832.

4. Shergis, J.L., Zhang, A.L., Zhou, W., & Xue, C.C. The methodological quality and risk of bias of *Panax ginseng* randomized controlled trials: a review. *The American Journal of Chinese Medicine*. 2013, 41(2):231-252.

5. Shergis, J.L., Parker, S., Coyle, M.E., Zhang, A.L., & Xue, C.C. Key considerations for conducting Chinese medicine clinical trials in hospitals. *Chinese medicine*. 2013, 8:3.

Manuscripts in preparation

1. Shergis, J.L., May, B.H., Zhang, A.L., & Xue, C.C. Evaluating the traditional Chinese literature for herbal formulae and individual herbs used for COPD (in preparation).

2. Shergis, J.L., Di, YM., Zhang, A.L., & Xue, C.C. The mechanisms and key pathways of *Panax ginseng* and its potential as a treatment for COPD (in preparation).

Conference abstracts

1. Shergis, J.L., Parker, S., Coyle, M., Zhang, A.L., & Xue, C.C. Perspectives on conducting Chinese medicine clinical trials in hospitals. Presented at RMIT University College of Science Engineering and Health Higher Degrees by Research Student Conference, 19 October 2012.

2. Zhang, A.L., Shergis, J.L., & Xue, C.C. Chinese herbal medicine for chronic obstructive pulmonary disease (COPD). Presented at International Scientific Acupuncture and Meridian Symposium (iSAMS). Sydney, Australia, 5-7th October 2012.

3. Shergis, J.L., Zhang, A.L., Zhou, W., & Xue, C.C. *Panax ginseng* in randomised controlled trials: a systematic review. Poster presented at the International Research Congress on Integrative Medicine and Health Portland, Oregon, 16 May 2012. Published in *BMC Complementary and Alternative Medicine*, 12(Suppl 1):P297 (12 June 2012).

4. Shergis, J.L., Zhang, A.L., & Xue, C.C. Can a natural herbal extract improve quality of life and lung function? Presented at RMIT University College of Science Engineering and Health Higher Degrees by Research Student Conference, 21 October 2011.

5. Shergis, J.L., Zhang, A.L., Thien, F.C.K., Worsnop, C.J., & Xue, C.C. Chinese Herbal Medicine in the Management of Chronic Obstructive Pulmonary Disease (COPD). Poster presented at Australian Acupuncture & Chinese medicine Annual Conference. Adelaide, Australia, 22 May 2010.

Abbreviations

ACTH	Adrenocorticotropic hormone
AMSTAR	Assessment of multiple systematic reviews
ANOVA	Analysis of variance
ANZCTR	Australian and New Zealand Clinical Trials Registry
ARTG	Australian Register of Therapeutic Goods
CAM	Complementary and alternative medicine
CAT	COPD Assessment Test
CHM	Chinese herbal medicine
CM	Chinese medicine
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case record form
CRQ	Chronic respiratory questionnaire
CT	Computed tomography
EBM	Evidence based medicine

ESCOP	European Scientific Cooperative on Phytotherapy
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good clinical practice
GEARS	Ginseng Extract and Respiratory Symptoms
GMP	Good manufacturing practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
GSH	Glutathione
HPLC	High performance liquid chromatography
HREC	Human Research Ethics Committee
HRQoL	Health related quality of life
iAUC	Incremental area under the glucose curve
ICS	Inhaled corticosteroids
IIEF-5	International Index of Erectile Function questionnaire
IL	Interleukin
MAPK	Mitogen activated protein kinase
MD	Mean difference

MeSH	Medical subject heading
MMP	Matrix metalloproteinases
MRC-D	Medical Research Council dyspnoea scale
MRI	Magnetic resonance imaging
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHLBI	National Heart, Lung and Blood Institute
NHMRC	National Health and Medical Research Council
NICM	National Institute of Complementary Medicine
NK	Natural killer
PDE	Phosphodiesterase
QoL	Quality of life
RCT	Randomised controlled trial
RMIT	Royal Melbourne Institute of Technology
ROS	Reactive oxygen species
RR	Relative risk
SAE	Serious adverse events
SERP	Streamlined ethical review process
SF-36	Short Form Health Survey

SGRQ	St. George's Respiratory Questionnaire
TGA	Therapeutic Goods Administration
TNF-α	Tumour necrosis factor α
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
WHOQOL-BREF	World Health Organization Quality of Life- Brief
WM	Western medicine
ZYFJDCD	Zhong Yi Fang Ji Da Ci Dian

Summary

Chronic obstructive pulmonary disease (COPD) is characterised by shortness of breath, cough and excess sputum production. The most common conditions included in COPD are chronic bronchitis (inflammation in the airway) and emphysema (destruction of lung tissue) resulting in irreversible airflow restriction. COPD is a major cause of morbidity and mortality and predicted to be the third leading cause of death by 2030. COPD is more prevalent in the older population. In those over 40 years of age in western countries, it is estimated that >10% of the population is affected by COPD. COPD is associated with substantial loss of productivity and significant direct and indirect costs.

The causes of COPD are the long-term exposure to toxic substances and gases such as cigarette smoke, which induce an amplified inflammatory response in the lung, particularly in the small airway. The resultant tissue destruction is irreversible and without cure.

Due to the irreversible nature of the condition, available treatments only provide symptomatic relief and management of exacerbations. The commonly used treatments are bronchodilators, corticosteroids (for severe cases), and antibiotics (for exacerbations). These treatments are limited in their effectiveness and are associated with a range of adverse events.

Patients with COPD have increasingly used complementary and alternative medicines (CAM), particularly herbal medicines. In Australia, 17.3% or nearly one in five COPD

sufferers have used some form of CAM therapy. There have been randomised controlled trials (RCT) evaluating the benefits of herbal medicines for COPD. *Panax ginseng* is one herb, which shows promise for a number of health conditions including COPD. However, existing *Panax ginseng* studies have produced inconsistent evidence on efficacy due to a range of methodological issues including inadequate reporting of participant allocation methods, small sample sizes, inappropriate outcome measures and inadequate information of the herbal preparation. Under the framework of evidence-based healthcare, all interventions need to be evaluated systematically to provide high-level clinical evidence to support the rational use of such interventions. In the case of Chinese herbal medicine, both modern and classical literature on relevant herbs needs to be reviewed to investigate efficacy and clinical relevance.

Study objectives:

1) Search and analyse the classical literature on Chinese herbal medicine for symptoms associated with COPD.

2) Review the extant systematic reviews of *Panax ginseng* for any health condition.

3) Systematically review the English and Chinese literature of *Panax ginseng* in RCTs for any health condition.

4) Review the potential mechanisms of *Panax ginseng* on reducing inflammation and oxidative stress.

5) Design and implement an RCT that addresses the identified methodological short falls identified in the literature and evaluate the efficacy and safety of *Panax ginseng* for patients with moderate COPD.

A comprehensive search and analysis of the Zhong Yi Fang Ji Da Ci Dian (ZYFJDCD) fulfilled the first objective. The ZYFJDCD is the largest compendium of Chinese herbal formulae with over 96,592 entries. The search resulted in 1,147 citations relevant to COPD. The results confirmed the use of Chinese herbal formulae and herbs similar to what is used in the modern setting for COPD.

To achieve the second objective, a review of systematic reviews on Ginseng for any health condition was completed. The methods of the overview are in line with the Cochrane Collaboration. Thirteen systematic reviews were included. These evaluated 11 broad health areas and showed promise of efficacy for lung diseases, disorders of glucose metabolism, angina pectoris, and erectile dysfunction.

To achieve the third objective, a systematic review guided by the 'Cochrane Handbook for Systematic Reviews of Interventions' was completed. The review identified 65 English and two Chinese RCTs. The most promising findings from this review supported the value of *Panax ginseng* for use in moderating the immune response, particularly cell-mediated immunity with implications for chronic respiratory diseases. However, the review also identified methodological issues that need to be addressed in future studies such as information on quality control of the *Panax ginseng* products, allocation concealment, sample size calculation and the use of intention-to-treat approach.

To address the fourth objective, a review was conducted to identify the potential mechanisms of *Panax ginseng* for reducing inflammation and oxidative stress relevant

to COPD. Findings revealed *Panax ginseng* and its active components, the ginsenosides, exert multiple actions. *Panax ginseng* possesses actions including regulation of immune cell activity and numbers, modulation of cytokine and mediator production, reduction in oxidative stress, and regulation of their related pathways.

To achieve the fifth objective, a randomised, double blind, placebo controlled clinical trial was designed and implemented. The study evaluates the efficacy and safety of *Panax ginseng* for moderate COPD, that is, $FEV_1/FVC < 0.70$, $FEV_1 \geq 50\%$ and $< 80\%$ predicted. Outcome measures include quality of life, lung function, use of relief medication, exacerbations and adverse events. The study integrates contemporary clinical research methodology guided by Chinese medicine principles and theory for clinical practice (ANZCTR: ACTRN12610000768099).

A stepwise approach was developed to identify candidate herbal medicines for COPD through systematic reviews on classical and modern literature, and then prioritise the key herb for further investigation with respect to its efficacy, potential mechanisms of action and evaluation of its efficacy and safety through an RCT. Although there is extensive literature, methodological flaws often limit the acceptance and applicability of results. This highlights the importance of improving standards and reporting in future research. Rigorous clinical trials focusing on specific health conditions and indications would improve the body of evidence. The clinical trial presented here will provide critical clinical data and build on previous RCTs and systematic reviews. Although the results of the clinical trial are not yet available the rigorous trial design and the use of a well-characterised high quality Ginseng product will ensure reliable results. Given the

increasing prevalence and burden associated with COPD, particularly in the elderly, this research is timely to explore alternatives that may help patients to improve their quality of life and lung function.

This thesis applies a systematic "whole evidence" approach in investigating a Chinese herb for the management of a major health condition that is triggered by smoking. There is no cure in modern medicine for COPD, and thus an investigation such as this is of significant value. This thesis revealed promising benefits of *Panax ginseng* for the treatment of COPD. Our multi-centre RCT will provide a conclusive answer to this well-characterised Ginseng product for the management of moderate level COPD patients.

Chapter 1: General introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is a common, incurable and disabling respiratory condition (1). William Briscoe is believed to be the first person to use the term “COPD” in his discussions on airflow obstruction and the slow spaces in the lung in 1965 (2). Well-known as the "smoker's cough”, COPD symptoms include breathlessness, persistent cough and excess sputum production. COPD is characterised by the pulmonary diseases emphysema and chronic bronchitis. These two diseases produce similar symptoms and are both causes of COPD. After onset symptoms are persistent over a lifetime.

COPD is ranked as the fourth leading cause of death worldwide and is predicted to rank third by 2030 (3). COPD has a high prevalence in Australia, reported to be one in five aged over 40 years (4). This disease often affects adults in the prime of their life and results in high social and economic costs.

The pathophysiology of COPD is due to a complex cascade of chronic inflammation leading to airway narrowing and alveolar wall destruction. The inflammation seen in COPD is often a response to cigarette smoke coupled with genetic susceptibility (5).

COPD is an incurable progressive disease. Current treatments are unsatisfactory and only nominally effective. Treatments include bronchodilators and corticosteroids and they are associated with a number of limitations. Treatments are based on drugs

effective for asthma however in COPD there is limited evidence of benefit particularly at the early stage of the disease. These medications, particularly inhaled steroids also pose a risk of long-term side-effects such as cataracts and osteoporosis (1). Subsequently there is an unmet need to provide effective relief of symptoms, slow the progression and improve quality of life (QoL).

Complementary and alternative medicines (CAM) including Chinese medicine are gaining popularity in western countries including Australia (6). Patients with COPD are increasingly using CAM. A recent study in Australia, reported that 17.3% of COPD patients had used CAM (7). Chinese medicine (CM) including herbal medicine are particularly popular (7).

Chinese medicine (CM) is a unique medical system developed over millennia in China. The basic theories of yin, yang, five elements and Qi guide the diagnosis, prevention and treatment of disease. Long periods of clinical practice and knowledge support the use of CM for chronic lung diseases like COPD. This knowledge is useful in the modern setting for understanding the application of herbal medicines.

Herbal medicines are important sources for drug discovery. However, the traditional drug discovery pathway has been associated with a number of concerns such as low success rate from investigative new drug candidates to new therapeutics, it is time consuming, and costly. Hence, there has been an increasing emphasis of a more targeted approach in drug discovery involving the use of classical literature such as those of CM. This trend is coupled with the increasing use of CAM including Chinese herbal

medicine (CHM). Objectively and scientifically evaluating its use under controlled environments and using scientific methods enriches the application of CM. The knowledge generated can improve understanding and potentially expand its application for diseases like COPD.

Recently, research has provided data for the safety and efficacy of herbal medicines for COPD (8, 9). Specific CHM may be effective for COPD however, quality data is limited.

In CM, *Panax ginseng* has been used for thousands of years to treat breathlessness, fatigue as well as debilitation and reduced mental and physical capacities due to chronic illness. *Panax ginseng* shows a promising effect on COPD and immune function. Recent laboratory studies have indicated that *Panax ginseng* possesses a broad range of pharmacological actions (10).

A recent review concluded that *Panax ginseng* improves the immune response, particularly cell-mediated immunity with implications for chronic respiratory diseases (11). Additionally, a recent RCT evaluated *Panax ginseng* for COPD, results indicated improved lung function and a good safety profile with no adverse events (12).

Although studies have evaluated *Panax ginseng*, they often lack rigour and consistency (11). Results from systematic reviews and individual RCTs are often promising but inconclusive and methodological flaws compromise their validity.

To date, despite frequent use, the role of CHM including *Panax ginseng* in treating COPD is not clear. The research presented in this thesis reviews *Panax ginseng* in modern and classical literature. It also evaluates the efficacy and safety of *Panax ginseng* for COPD with a focus on QoL improvements in a rigorous RCT.

1.2 Objectives

The objectives are:

- Conduct systematic reviews of the existing literature on *Panax ginseng* for any health condition.
- Search the classical CM literature to establish formulae and herbs often used to treat conditions consistent with COPD.
- Evaluate the potential of *Panax ginseng* to reduce inflammation and oxidative stress.
- Design and implement an RCT evaluating the safety and efficacy of *Panax ginseng* for moderate COPD.

1.3 Significance of the research

This research concerns the systematic gathering, evaluation and further investigation of efficacy and safety of *Panax ginseng* for COPD involving systematic reviews and an RCT. It explores theories and knowledge from CM and conventional medicine. The research summarises the existing literature and develops a novel clinical trial. The results aim to determine if CHM, specifically *Panax ginseng* is safe and effective for the treatment of COPD.

Systematic reviews identify, evaluate and summarise data from individual studies and provide information to guide health care decision makers (13). RCTs are the gold standard of clinical trials and they evaluate the efficacy and safety of interventions in a population of patients. To inform the design of the RCT presented in this thesis, comprehensive systematic reviews of *Panax ginseng* were undertaken. The reviews were guided by the Cochrane Handbook (13).

This research evaluated the classical CM literature to identify CHM for COPD. Classical CM literature provides a source of information for herbal medicine use over millennia. The information identifies particular herbal formulae and herbs used for specific conditions.

Exploring the plausible mechanisms of herbal medicines can aid in understanding suitable indications. *Panax ginseng* has multiple actions and exerts a wide range of effects on reducing inflammation and oxidative stress (10). To this end, a review was conducted to evaluate the potential mechanisms of *Panax ginseng*.

To inform the design of the RCT the preceding research listed above was undertaken. The RCT entitled 'Ginseng Extract and Respiratory Symptoms (GEARS)' is rigorous and aims to evaluate the effect of a standardised *Panax ginseng* extract for patients with moderate COPD.

The specific research questions of the trial are:

1. Does *Panax ginseng* produce beneficial effects/symptomatic relief in subjects with moderate COPD, in terms of improved QoL and/or improved respiratory function?

2. Does *Panax ginseng* reduce the use of conventional symptom-relief medication in subjects with moderate COPD?

3. With six months treatment and six months follow-up, what are the time courses of onset and persistence of any beneficial effects of *Panax ginseng* in subjects with moderate COPD?

4. What adverse effects does *Panax ginseng* produce in subjects with moderate COPD?

1.4 Organisation of the thesis

This thesis consists of seven chapters, as follows:

Chapter One introduces the background of the research. The objectives, significance and scope of the research are highlighted, and an overview of the thesis structure is included.

Chapter Two describes the literature relevant to COPD. The chapter begins with a detailed background of the disease including definitions, prevalence, pathophysiology, risk factors, diagnosis, assessment, treatment and management. The latter part of the chapter introduces CM concepts relevant to COPD with detailed information on CM diagnosis, existing research, and introduces the herbal medicine *Panax ginseng*.

Chapter Three provides details of *Panax ginseng*, including its species identification, historical use, constituents, pharmacology, safety, efficacy, and clinical research in this area.

Chapter Four presents an original search and analysis of the classical Chinese literature for COPD. The first two sections discuss the rationale and method of searching and establish the novelty of this type of review. The second section presents detailed results of the herbal formulae and herbs identified including frequencies and citation ranking. The final section provides a general discussion integrating results and opinion and elaborating on citations consistent with COPD.

Chapter Five presents three systematic reviews. Firstly, a review of systematic reviews summarising the existing published reviews of *Panax ginseng* for any health condition. Secondly, a systematic review of published *Panax ginseng* RCTs and finally, the mechanism of *Panax ginseng* relevant to reducing inflammation and oxidative stress in experimental and clinical research, is presented.

Chapter Six presents the protocol development and implementation of the 'Ginseng Extract for Respiratory Symptoms' (GEARS) clinical trial. The design of the clinical trial is to the highest scientific rigour and is the first of its kind in Australia.

Chapter Seven discusses and summarises the research findings and conclusions. It also discusses strengths and limitations of the project and includes recommendations for future research.

Chapter 2: Literature review of COPD

2.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a common, incurable and disabling respiratory condition encompassing two main pathologies, emphysema and chronic bronchitis. Symptoms include breathlessness, persistent cough and excess sputum production. Throughout the course of disease acute infective exacerbations are common and can exponentially deteriorate lung function and lead to considerable morbidity and reduced quality of life (QoL) (1). COPD is preventable, however, exposure to risk factors (chiefly cigarette smoking) contribute significantly to the disease.

COPD is highly prevalent and is the fourth leading cause of death worldwide (3). The onset of COPD is often in the prime of one's working life, has a significant impact on productivity, and imposes an economic burden on individuals, communities and governments (4).

2.2 Definition of COPD

COPD is a disease of the lungs. It is an umbrella term used to describe the overlapping conditions, chronic bronchitis and emphysema. COPD is characterised by airflow obstruction that is not fully reversible. Symptoms include dyspnea, cough and sputum production.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as *'a common preventable and treatable disease that is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Exacerbations and comorbidities contribute to the overall severity in individual patients'* (1).

2.3 Prevalence of COPD

The World Health Organisation (WHO) estimates that COPD affects 127 million people worldwide (14). COPD increases an individuals' risk of death 3.2 times compared with the general population (4). COPD deaths occur primarily in low and middle income countries and it is predicted to rank as the third leading cause of death by 2030 (3). The worldwide prevalence of COPD in adults is approximately 9–10% (15). Estimates of prevalence from around the world are summarised in Table 1.

Table 1: Prevalence of COPD among adults aged over 40 years

County	% of population over 40 years with COPD	Reference	County	% of population over 40 years with COPD	Reference
Australia	18.6%	(4)	Japan	10.9%	(16)
China	8.2%	(17)	South Korea	17.2%	(18)
Finland	9.4%*	(19)	UK	4.7%*	(20)
Greece	8.4%	(21)	USA	5.1%*	(22)

* In these countries prevalence of COPD is among adults aged over 18 years.
Note: Estimates were calculated from survey self-reports and conservative approximation of undiagnosed cases.

2.3.1 Prevalence of COPD in Australia

In Australia, COPD affects over 2 million people (4). Of these, it is estimated almost 1 million are undiagnosed and untreated (4). Individuals aged over 40 years are most commonly affected, estimated at 18.6% or approximately one in five (4). The majority are women aged over 60 years (56.5%). Despite reduced rates of smoking, it is predicted that COPD will affect 4.5 million Australians by 2050 (4).

2.3.2 Economic impact of COPD

The socio-economic impact of COPD is substantial. COPD has significant direct and indirect costs to individuals, society and the government. In Australia, it is estimated to cost $8.8 billion per annum, with individuals bearing costs of up to $7,446 annually (4). Figure 1 presents the bearers of financial costs.

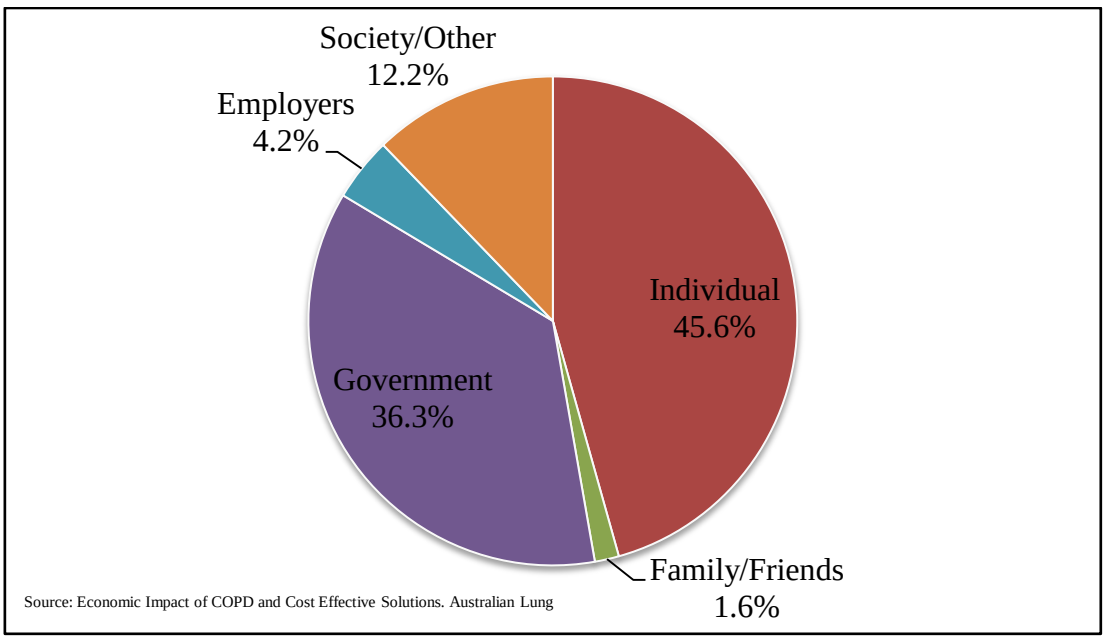


Figure 1: Financial costs of COPD

2.4 Mechanisms of COPD

Exchanging oxygen and carbon dioxide maintains life. In a normal lung, air travels down the trachea into the bronchi entering progressively smaller tubes until it terminates in the bronchioles and alveoli. The alveoli facilitate delivery of oxygen to the blood and removal of carbon dioxide.

The pathogenesis of COPD involves a complex process associated with an abnormal and amplified immune response and lung tissue repair and remodelling (23). Long-term inflammation in the lung leads to airway narrowing, fibrosis, mucous plugging and airway closure. The characteristic airflow limitation is caused by a combination of emphysema and chronic bronchitis (24).

2.4.1 Emphysema

The pathogenesis of emphysema involves alveolar destruction. Chronic inflammation in the lungs causes permanent dilation of the peripheral air spaces accompanied by destruction of the walls of the bronchioles, alveolar ducts, and alveoli. There is loss of elastic recoil and gas exchange surfaces as well as airway wall collapse, leading to hyperinflation and air trapping (24). Figure 2 presents the pathogenesis of emphysema.

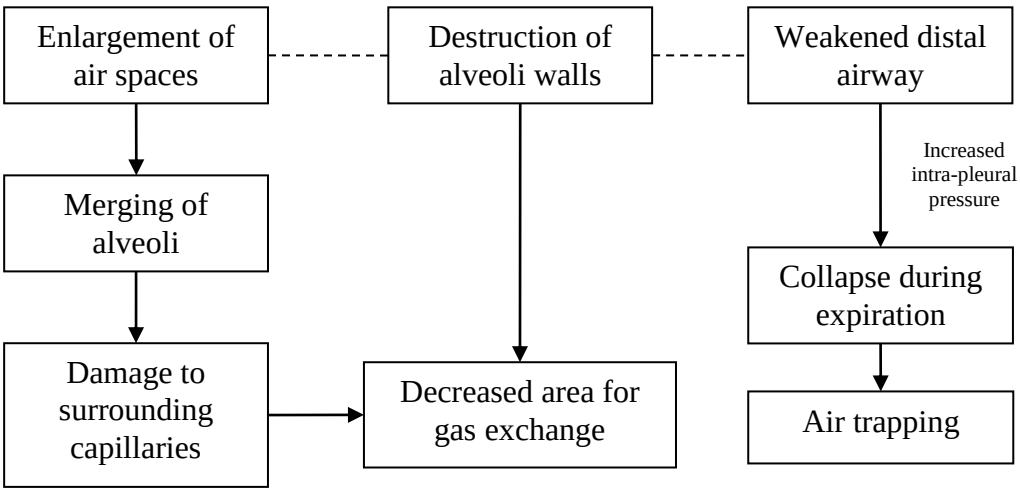


Figure 2: Pathogenesis of emphysema

2.4.2 Chronic bronchitis

Chronic bronchitis is caused by inflammation of the bronchial tubes and excess mucus production. The tiny cilia in the lungs are unable to clear the build-up of mucus leading to narrowing and/or blockage of the airway lumen and thickening due to fibrosis. Clinically, chronic bronchitis is defined as a productive cough for over three months and for more than two successive years. Figure 3 presents the pathogenesis of chronic bronchitis.

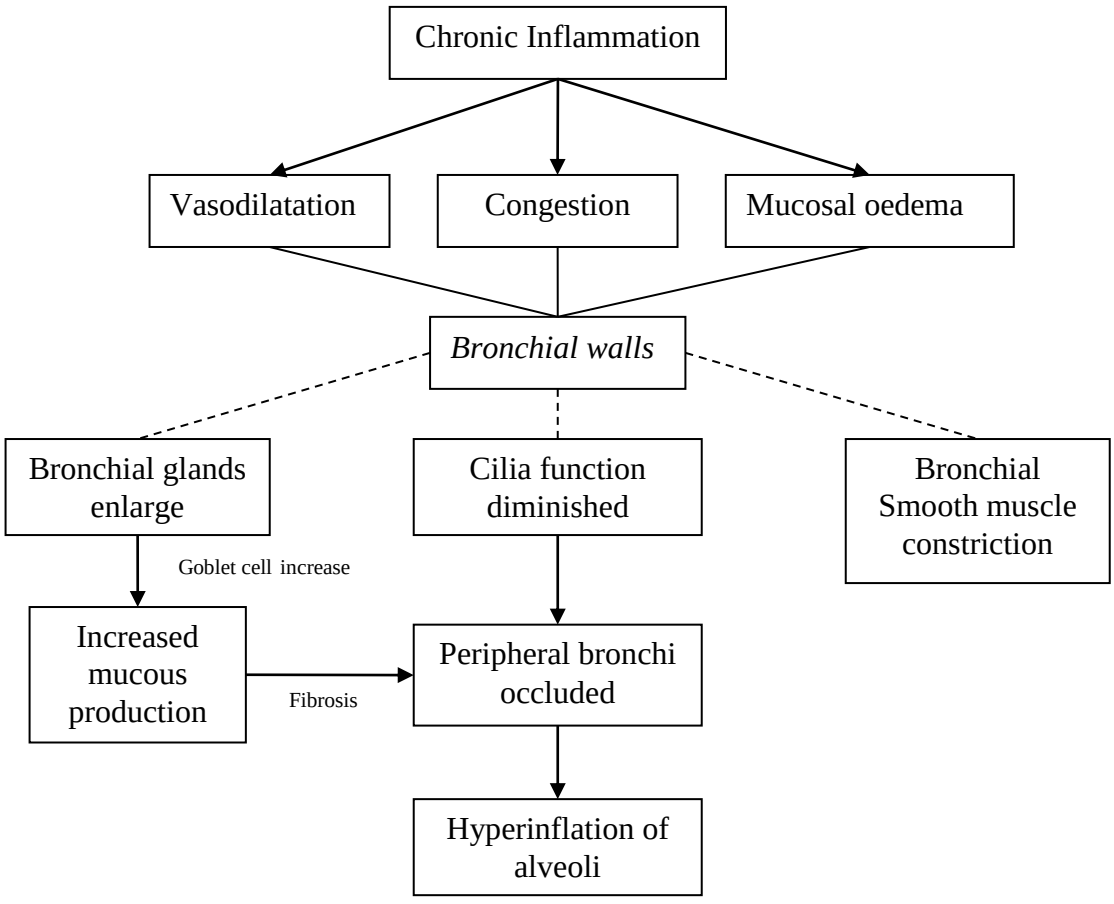


Figure 3: Pathogenesis of chronic bronchitis

2.4.3 Comorbidities of COPD

Comorbidities of COPD may include cardiovascular disease, cachexia, osteoporosis, anaemia, gastrointestinal disease, metabolic disease and depression (1). These conditions often contribute to diminished QoL and need to be monitored with the primary pulmonary component of COPD.

2.5 Risk factors for the development of COPD

Lifestyle choices, environmental factors and genetic predisposition contribute to the risk of developing COPD. Cigarette smoking is the foremost risk factor, however, other factors can cause and contribute to COPD, including environmental pollution, occupational irritants as well as genetics and age (1). COPD is a slow progressing disease. The incidence increases with age as the cumulative inhalation of noxious particles over years results in irreversible lung damage. Table 2 presents an overview of the risk factors for the development of COPD.

Table 2: Risk factors for COPD

Smoking (e.g., cigarettes, pipe, cigar, marijuana and hashish)
Environmental air pollution (indoor and outdoor)
Occupational irritants
Genes (e.g., alpha–1 antitrypsin deficiency)
Age

Cigarette smoking accounts for an estimated 80–90% of all COPD cases (5). In Australia, 23%, or approximately one in four adults smoke (25). Smoking prevalence is similar in other countries. In the United Kingdom (UK) it is estimated at 21% (26), in the United States of America (USA) 19.3% (27) and in China 28.1% (28).

Environmental air pollution, both indoor and outdoor has been identified as a risk factor and contributing factors for developing COPD (29). Indoor air pollution includes passive smoking, and heating or cooking with biomass fuels in unventilated dwellings. Living in urban cities contributes to outdoor air pollution.

Occupational exposure to irritants including chemical fumes, dusts and gases may increase the risk of developing COPD. For example, COPD has been identified in coal workers as an occupational disease causing significant loss of lung function and disability (30).

Genetic variations may contribute to an individual's susceptibility in the development of COPD. About 10–15% of cigarette smokers develop clinically significant COPD that is symptomatic enough to require therapeutic intervention (31). One specific genetic risk factor for COPD is alpha–1 antitrypsin deficiency. About 1–4% of COPD suffers have alpha–1 antitrypsin deficiency (32). This protein is a serine protease inhibitor (e.g., neutrophil elastase). When alpha–1 antitrypsin is deficient, proteolytic activity goes unchecked and the extracellular matrix and elastin are destroyed leading to alveolar wall apoptosis and collapse (emphysema).

2.6 Pathology of COPD

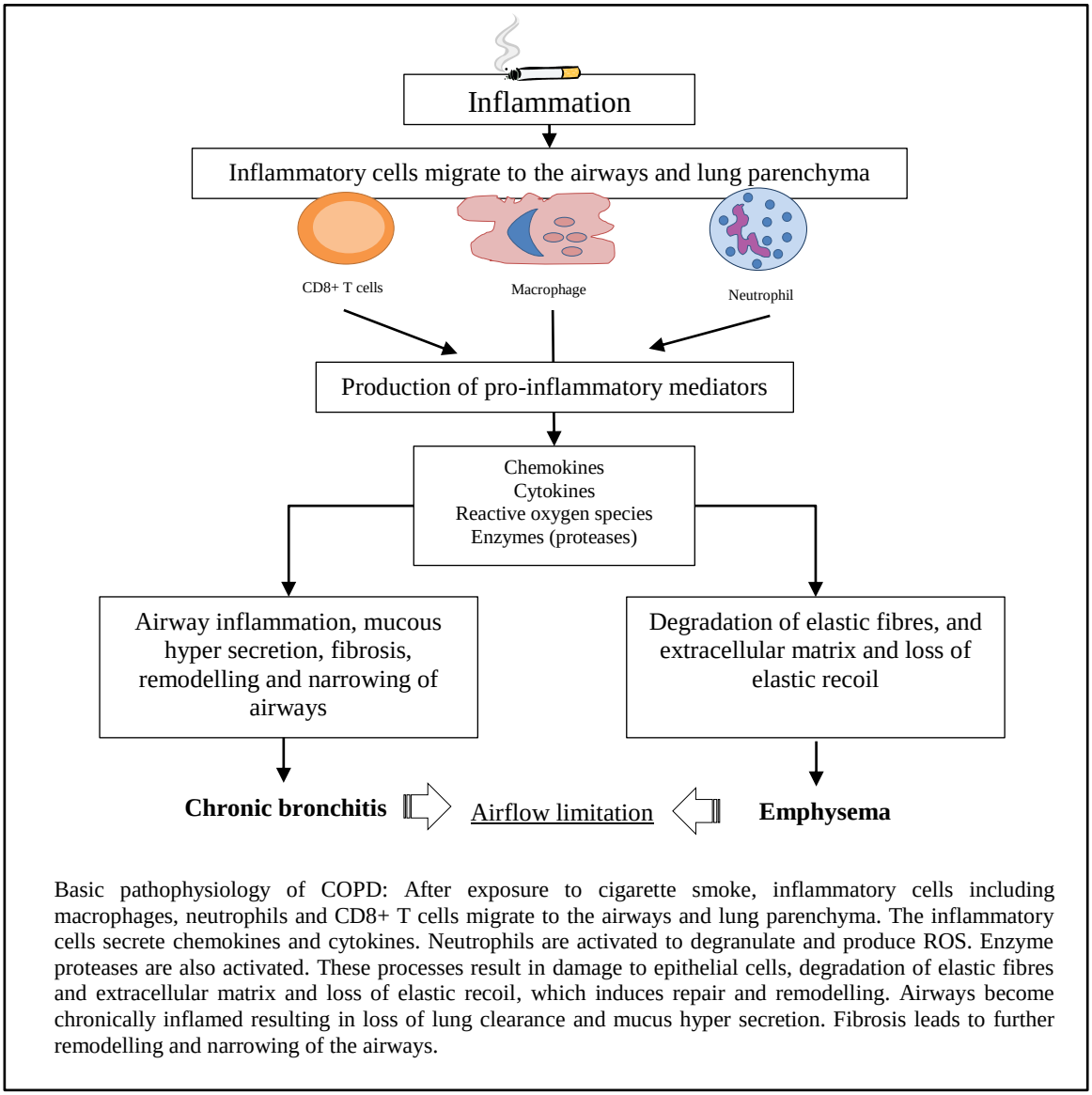
Inhaled irritants activate chronic inflammation in COPD and cause an influx of inflammatory cells into the central and peripheral airways and lung parenchyma (23). Inflammation normally subsides however, in COPD a cyclical cascade of inflammatory cells migrate to the lungs and cause chronic inflammation. The inflammatory cells include neutrophils, macrophages and CD8-positive T lymphocytes. The migrated cells release chemotactic factors, interleukin (IL) 8, pro-inflammatory cytokines, tumour necrosis factor (TNF) α, reactive oxygen species (ROS) and protease enzymes. These mediators facilitate the recurrent inflammatory response as well as tissue repair and remodelling.

Figure 4 presents the basic pathophysiology of COPD.

Neutrophils are the first inflammatory cells to enter the lungs. Activated epithelial cells produce chemotactic factors such as IL-8 that recruit neutrophils. The neutrophils then release pro-inflammatory mediators including serine proteases and neutrophil elastase. Anti-protease becomes imbalanced resulting in significant levels of protease that cannot be counteracted (33). These enzymes destroy the extra-cellular matrix components (elastin) cause mucus hyper secretion and emphysematous change.

Oxidative stress amplifies inflammation and plays a key role in COPD. Markers such as hydrogen peroxide and 8-isoprostane are increased in the exhaled breath of patients with COPD (34). Oxidative stress can facilitate inflammation by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which in turn stimulates transcription of DNA to produce the pro-inflammatory mediators TNF-α and IL-8.

Systemic changes are evident in patients with COPD. Oxidative stress factors induce the release of ROS and circulating cytokines (e.g., TNF-α and IL-8) leading to systemic inflammation causing cachexia, weight loss and wasting of skeletal muscle (33).



Basic pathophysiology of COPD: After exposure to cigarette smoke, inflammatory cells including macrophages, neutrophils and CD8+ T cells migrate to the airways and lung parenchyma. The inflammatory cells secrete chemokines and cytokines. Neutrophils are activated to degranulate and produce ROS. Enzyme proteases are also activated. These processes result in damage to epithelial cells, degradation of elastic fibres and extracellular matrix and loss of elastic recoil, which induces repair and remodelling. Airways become chronically inflamed resulting in loss of lung clearance and mucus hyper secretion. Fibrosis leads to further remodelling and narrowing of the airways.

Figure 4: Basic pathophysiology of COPD

2.7 Diagnosis of COPD

COPD develops over many years and often presents symptomatically in middle to late life. Early diagnosis and intervention can slow disease progression improve lung health and prevent further damage (1). Clinical assessment of COPD begins with effective communication between the patient and the health care provider. Diagnosis of COPD requires subjective evaluation of symptoms and overall health, combined with lung function tests (spirometry).These include post-bronchodilator forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the ratio, FEV_1/FVC (1). Early diagnosis of COPD combined with a treatment plan may delay or prevent the progression of airflow limitation, improve QoL and long term outcomes (1).

In 2001, scientists from the United States National Heart, Lung and Blood Institute (NHLBI) and the World Health Organisation (WHO) formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to standardise the diagnosis and management of COPD. They produced a report 'Global strategy for the diagnosis, management and prevention of COPD' under the guidance of a panel of international experts. A full revision was undertaken in 2006 and the report is now revised annually, providing an up to date summary of the field (1). Many national respiratory societies have followed the GOLD recommendations. In Australia and New Zealand, the Thoracic Society and the Australian Lung Foundation provide information for clinical practice based on both the GOLD report and systematic reviews and meta-analyses. These guidelines are disseminated as 'The COPD-X Plan' (35).

The GOLD report recommends a diagnosis of COPD should be considered in patients with a history of risk factors, most notably tobacco smoking, and presenting with dyspnea, chronic cough and/or sputum production. The diagnosis should be confirmed by lung function spirometry, that is, post-bronchodilator FEV_1/FVC <0.70 [Table 3].

Table 3: Diagnosis of COPD

History	Symptoms	Confirmation
✓ Aged over 40 years ✓ Expose to risk factors (e.g., tobacco smoke)	✓ Dyspnea ✓ Chronic cough ✓ Chronic sputum production	✓ Spirometry: post–bronchodilator FEV_1/FVC <0.70

2.8 Classification of COPD

COPD severity is based on the patient's symptoms, the level of spirometric deficiency, and other factors including frequency of exacerbations, overall health status and comorbidities. Diagnosis of COPD is confirmed by post-bronchodilator FEV_1/FVC <0.70 and severity classification is based on FEV_1 and divided into four stages; mild, moderate, severe and very severe [Table 4]. Mild, stage I COPD often presents as very mild cough and sputum production or no symptoms. Patients may be unaware of any abnormal lung function at this stage. Moderate, stage II COPD presents with shortness of breath particularly on exertion as well as coughing and sputum production. Patients often seek medication to treat symptoms and exacerbations. Severe, stage III COPD presents with increased airflow limitation, worsening shortness of breath at rest and during exercise and fatigue. Patients often experience frequent exacerbations. Very severe, stage IV COPD presents as extreme airflow limitation and often respiratory failure. Other complications may include cor pulmonale and exacerbations may jeopardise a patient's life.

Table 4: Severity classification of COPD

Stage	Lung function indices
Stage I: **Mild**	- $FEV_1/FVC < 0.70$ - $FEV_1 \geq 80\%$ predicted
Stage II: **Moderate**	- $FEV_1/FVC < 0.70$ - $FEV_1 \geq 50\%$ and $< 80\%$ predicted
Stage III: **Severe**	- $FEV_1/FVC < 0.70$ - $FEV_1 \geq 30\%$ and $< 50\%$ predicted
Stage IV**: Very Severe**	- $FEV_1/FVC < 0.70$ - $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second, FVC: forced vital capacity.
Note: Severity classification of COPD based on GOLD criteria (1). All values refer to post-bronchodilator spirometry.
Predicted refers to predicted values that are calculated with reference to the expected range of normal lung capacity of an individual with similar characteristics including gender, height, age and ethnicity.

2.9 Exacerbations

Exacerbations of COPD are *'an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications'* (1). There is acute symptom worsening and increased volume and purulence of sputum. Treatments include bronchodilators, systemic glucocorticoids, antibiotics, and supplemental oxygen (1). Exacerbations can be caused by respiratory infection (viral or bacterial), air pollution or the cause of exacerbation may be unknown. Repeated exacerbations can worsen the prognosis by accelerating decline in lung function and worsen QoL. Individuals who experience an exacerbation are encouraged to participate in pulmonary rehabilitation and develop self-management plans to reduce the risk of recurrence (1).

2.10 Differential diagnosis of COPD

COPD should be differentiated from other diseases with similar symptoms. These diseases may include; asthma, congestive heart failure, lung carcinoma, bronchiectasis, tuberculosis, lung abscess, and pneumonia. Table 5 presents the differential diagnosis of COPD.

2.10.1 Differential diagnosis with asthma

Asthma is a difficult condition to distinguish from COPD and a co-diagnosis may be considered. Asthma causes the airways to become narrow and swell, producing a thick mucous due to a cascade of events triggered by inhaled irritants or allergens. Unlike asthma, COPD does not involve the whole airway but is generally isolated to the bronchioles and lung parenchyma (35). In people with asthma, sputum samples and bronchoalveolar-lavage fluid contains eosinophils, whereas in COPD sputum samples mainly contain macrophages and neutrophils (33). Asthma often presents earlier in life with day-to-day fluctuations in symptoms, whereas COPD is commonly seen in older individuals with a history of smoking and constant and progressively worsening symptoms. Cough and wheeze may be seen in both conditions and cannot be used alone to differentiate. The major difference between asthma and COPD is the reversibility in airflow obstruction. To test for this spirometry is performed before and after inhalation of a bronchodilator medication. Largely reversible obstruction is seen in asthma, but in COPD, it is largely irreversible (36).

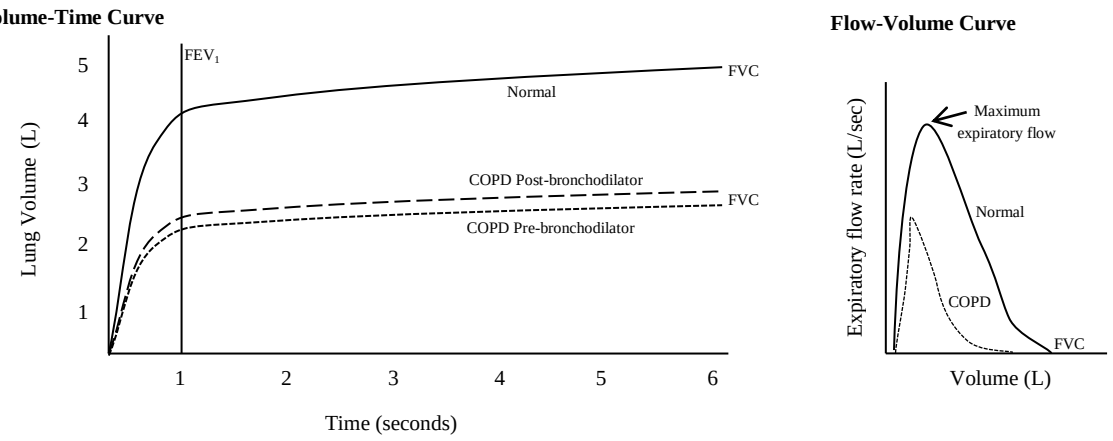
Table 5: Differential diagnosis of COPD

Condition	Symptoms	Common symptoms for all conditions
COPD	Onset in mid-life (people aged over 40 years)	Fatigue Wheezing Panting Weight loss Hoarseness or changing voice
	History of smoking or exposure to other types of smoke	
	Chronic constant symptoms, that progressively worsen	
	Dyspnea	
	Chronic cough (productive or non–productive)	
	Sputum production	
	Limitation of activity and exercise (often to avoid getting breathless)	
	Pursed lip breathing	
	Barrel chest	
	Irreversible airflow limitation	
Asthma	Onset earlier in life (often in childhood)	
	Symptoms fluctuate and are variable from day to day	
	Predominant night time cough or early morning	
	Allergy, rhinitis and eczema also present	
	Family history of asthma	
	Reversible airflow limitation	
Cardiac (congestive heart failure)	Chest pain and or heaviness sensation in the chest	
	Ankle oedema	
	Dyspnea while lying flat (sleeping)	
Lung carcinoma	Haemoptysis	As above plus fever
	Chest pain	
Bronchiectasis	Chronic cough with large volumes of thick, tenacious, purulent sputum	
	Haemoptysis	
Pulmonary tuberculosis	Haemoptysis	
Lung abscess	Subacute onset	
	Purulent sputum and/or blood–streaked sputum	
Pneumonia	Acute to subacute cough	
	Chest pain	

2.11 Assessment of COPD

2.11.1 Lung function – spirometry

Spirometry, 'the measure of breath', is the GOLD standard for assessing lung function. It is useful for screening at risk patients, diagnosing, classifying severity, assessing interventions and monitoring COPD (37). It can provide reproducible and standard objective evaluations in confirming airflow limitation that is not fully reversible. Spirometry is performed using an instrument called a spirometer. Functionally, it is easy to use and there are many devices on the market. Tests measure the flow-rate and volume during forced exhalation after a maximal deep inspiration [Figure 5]. For COPD, three spirometry values are commonly measured, these are $FEV_{1,}$ FVC and FEV_1/FVC ratio. Table 6 presents the values.



The volume-time curve presents the FEV_1 and FVC values. The lung volume is presented in litres expired per second. Normal lung volume is much greater than that of a person with COPD and after the administration of a bronchodilator the lung volume will often improve slightly. The flow-volume curve represents the expiratory flow rate in litres per second with the curve peaking at the maximal expiratory flow. COPD patients will have a deflated curve and limited maximal expiratory flow.
Note: Volume-time curves and flow-volume curves based on GOLD data (1).

Figure 5: Spirogram of volume-time curves and flow-volume curves

Table 6: Spirometry values used to measure lung function

Values	Definition	Expected outcome in COPD patients
Forced Vital Capacity (FVC)	The total volume of air that can be forcibly exhaled after a full inspiration.	Normal or slightly reduced
Forced Expiratory Volume in One Second (FEV_1)	The volume of air that is exhaled in the first second of forced expiration.	Reduced
Ratio of FEV_1 to FVC expressed as a percentage (FEV_1 /FVC)	Percentage of the vital capacity which is expired in the first second of maximal expiration	Reduced (< 70%)

Lung function values should be measured post-bronchodilator, that is, after the inhalation of a suitable bronchodilator (e.g., salbutamol) (38). Spirometry values are compared to predicted normal values that have been determined through comprehensive analysis of healthy populations using variables including age, height, gender, and ethnicity (35). This method is used to avoid over-diagnosis of COPD, especially in the aged. Spirometry is globally recognised as an essential tool for assessing COPD, yet there are limitations. The full impact of COPD cannot be measured by FEV_1 alone. It is able to classify the severity of disease and predict outcomes. However, it cannot accurately predict dyspnea symptoms, the impact on QoL, or mortality. To perform the tests and interpret results, a certain level of technical ability is required. Some patients find the effort to perform the inhalation and/or expiration problematic and readings may be invalid. Furthermore, an over-estimation of diagnosis using spirometry in the older population is a concern. Lung function deteriorates with age and normal limits for individuals over 70 years are lower, therefore results need to be interpreted with caution (36).

2.11.2 Radiology

Imaging technologies such as x-ray, computed tomography (CT) and magnetic resonance imaging (MRI) are not diagnostic for COPD. They assist treatment and management and are useful in differential diagnosis and identifying comorbidities, such as cardiac failure and infection.

2.11.3 Symptom questionnaires

Symptom questionnaires can often provide useful information on the impact of disease. Examples include the Medical Research Council Dyspnea scale (MRC-D) (39) and the COPD assessment test (CAT) (40). These tools can supplement history taking and lung function tests in the clinical and research setting.

2.11.4 Quality of life

Assessing QoL particularly health-related QoL (HRQoL) can reflect a treatment's effect on overall health including aspects of physical, psychological and social wellbeing. Questionnaires are particularly useful in research trials to highlight the possible clinical significance of interventions. A good number of generic and disease specific questionnaires have been developed. They often differ in numerous ways such as goals, contents, scaling methods and cultural factors.

Generic questionnaires can be used across different diseases, ethnicities, and cultures. They measure broad domains of health and wellbeing, such as general, physical and mental health. Validated examples include the Short Form Health Survey (SF-36) (41) and the World Health Organization Quality of Life Brief (WHOQOL-BREF) (42).

When evaluating HRQoL in COPD, two disease specific questionnaires are most commonly utilised, the St. George's Respiratory Questionnaire (SGRQ) (43) and the Chronic Respiratory Questionnaire (44). These disease specific questionnaires have an advantage over generic varieties as they can measure impact on various COPD domains, including symptoms and activities. When evaluating HRQoL in COPD it is often appropriate to use a disease specific questionnaire complemented by a generic instrument to provide a more complete representation of overall QoL (45).

2.11.5 Exercise capacity

Rehabilitation programs and some clinical trials evaluate the impact of COPD by using bicycle ergometry, treadmill exercise and/or timed walking tests, e.g., the 6-minute walk test. These activities can assess changes in functional exercise capacity following pulmonary rehabilitation and are useful prognostic tools (1).

2.11.6 Other

BODE index

The BODE index is often used for predicting mortality in COPD (46). BODE stands for and evaluates 1) Body mass index, 2) degree of airflow Obstruction, FEV_1, 3) Dyspnea using a modified MRC-D scale, and 4) Exercise capacity measured by the 6-minute walk test. This index is a practical tool in the clinical setting where higher scores correlate to an increased risk of mortality (46).

Blood gas

Blood gas measurements can assist in monitoring potential lung and heart failure in severe COPD. Particularly when oxygen saturation is extremely low, and the acid-base balance is compromised.

Blood tests

Blood tests are undertaken at intervals throughout the treatment of COPD for identifying secondary conditions such as infections and neoplasms. Further to this, blood tests verify cases of COPD caused by alpha–1 antitrypsin deficiency.

Nitric oxide

Exhaled nitric oxide is commonly used to evaluate asthma. In COPD the results are often inconsistent, therefore it is seldom used.

Biomarkers

Currently biomarkers have not been established to predict or monitor COPD. Potential targets include inflammatory cells and oxidative markers in bronchial fluid, exhaled breath and blood. However, heterogeneity within and between sufferers has hindered developed and limited clinical relevance (47).

2.12 Treatment and management of COPD

There is no cure for COPD. Therefore a multifaceted approach including pharmacologic and non-pharmacologic interventions is required. Smoking cessation is the only intervention proven to reduce the decline in lung function (48). However, drug therapies are also required as smoking cessation alone is not enough to reduce lung inflammation. Current pharmacological treatments include bronchodilators and corticosteroids. They are nominally effective, and primarily intended to control and alleviate symptoms and prevent complications (1). Management of COPD aims to reduce risk factors, alleviate symptoms, prevent progression, improve exercise tolerance, improve QoL, prevent and treat exacerbations, and reduce mortality (1). However, there is currently an unmet need to optimise the management of COPD. Figure 6 presents the treatments for COPD according to severity.

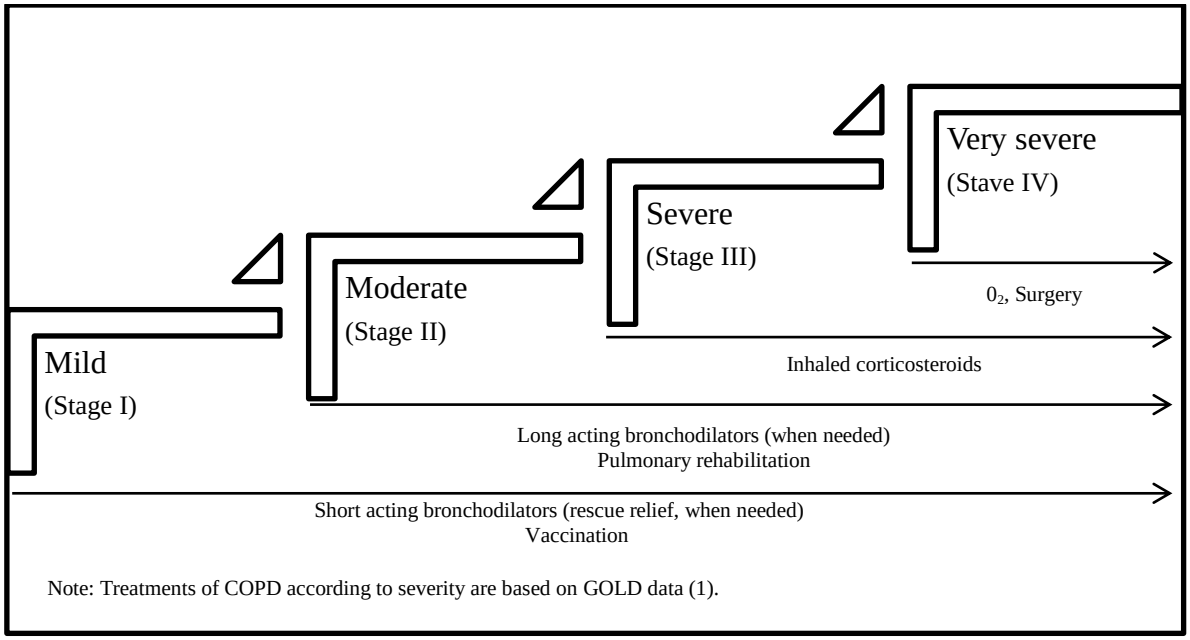


Figure 6: Treatments for COPD according to severity

2.13 Pharmacologic agents for COPD

2.13.1 Bronchodilators

Bronchodilator medications are fundamental in managing symptoms of COPD (1). Inhaled bronchodilators provide symptomatic relief by reducing hyperinflation and dyspnea. However, they do not slow the progression of COPD (35). Bronchodilators include anticholinergics, β2-agonists and methylxanthines. Table 7 presents the pharmacologic interventions for COPD.

Bronchodilators are prepared as short acting or long acting and can improve lung function. They are the first line therapy for COPD and prescribed throughout all stages (1). Long acting bronchodilators include the previously mentioned drug classes, anticholinergics and β2-agonists. They can improve breathlessness, lung function (FEV_1), QoL, and decrease frequency of exacerbations (33). They are more effective and convenient than short acting bronchodilators (35). Although bronchodilators are useful for symptom relief they do not improve lung function or reduce inflammation in the lungs or systemically.

Methylxanthines including theophylline are smooth muscle relaxants serving as bronchodilators. Their full mechanism is not defined however they are considered non-selective phosphodiesterase inhibitors and are thought to reduce muscle fatigue. Unfortunately, adverse effects have limited their therapeutic application in COPD (49).

Table 7: Pharmacologic interventions for COPD

Category	Class	Generic names	Stage of COPD prescribed
Short acting bronchodilators	Anticholinergics	Ipratropium bromide	I to IV
	β_2-agonists	Salbutamol	
Long acting bronchodilators	Anticholinergics	Tiotropium Aclidinium bromide	II to IV
	β_2-agonists	Salmeterol Indacaterol Eformoterol	
Oral Bronchodilators	Methylxanthines	Theophylline	IV
Anti-inflammatories	ICS	Budesonide Fluticasone Prednisolone (Oral)	III and IV Exacerbations
	PDE-4 inhibitors	Cilomilast Roflumilast	
Combination medications	ICS and β_2-agonists	Budesonide and Eformoterol Fluticasone and Salmeterol	II to IV

ICS: Inhaled corticosteroids

Note: Stages of COPD; Stage I mild ($FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ predicted); Stage II moderate ($FEV_1/FVC < 0.70$, $FEV_1 \geq 50\%$ and $< 80\%$ predicted); Stage III severe ($FEV_1/FVC < 0.70$, $FEV_1 \geq 30\%$ and $< 50\%$ predicted); Stage IV very severe ($FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure)

2.13.2 Anti-inflammatories

Inhaled corticosteroids (ICS) reduce inflammation and COPD exacerbations. However they do not improve lung function and are not recommended for long term use (35). In severe cases of COPD, ICS are combined with bronchodilator treatment (50). Oral glucocorticoids are also used for short periods throughout disease progression, particularly during exacerbations (51).

Recently, phosphodiesterase 4 (PDE-4) inhibitors have been approved as new drugs for severe COPD. They increase cyclic AMP levels and exert a wide range of anti-inflammatory actions. They can prevent decline in lung function, improve QoL and decrease the frequency of exacerbations (52). Unfortunately, adverse effects have limited the clinical usefulness of PDE-4 inhibitors (1) and despite approval in Europe and the USA they are not approved in Australia.

2.13.3 Other

During acute exacerbations of COPD, antibiotics are often prescribed due to bacterial infections. Additionally, annual vaccinations for influenza may reduce or prevent exacerbations (53).

2.14 Non-pharmacologic interventions for COPD

2.14.1 Pulmonary rehabilitation

Rehabilitation programs are recommended in the management of COPD. Activities are structured to include exercise programs to improve skeletal and respiratory muscles, as well as behavioural, psychosocial, and educational support (54). Pulmonary

rehabilitation programs encourage sufferers to develop self-care and self-management plans, aiding to reduce dyspnea, anxiety, depression and improve exercise capacity and QoL.

2.14.2 Oxygen therapy

Oxygen supplementation is prescribed in advanced disease and aids to improve QoL and survival especially for individuals with hypoxemia (55).

2.14.3 Lung volume reduction surgery

Surgical removal of emphysematous tissue or bullectomy is reported to be beneficial in some patients with severe COPD. It reduces hyperinflation and improves breathing efficiency (1). Lung volume reduction carries substantial risks and is only suitable for individuals with advanced symptoms.

2.14.4 Lung transplantation

Transplantation may be considered in sufferers in the advanced stages of COPD (56). The scarce number of available donor organs and resources limits this method.

2.15 Novel treatment approaches

Current drug therapies for COPD only provide modest benefit and no single treatment sufficiently prevents or treats COPD. Improved understanding of the mechanisms involved in COPD has allowed some novel approaches to be investigated. Emerging treatments focus on broad inflammatory candidates including anti-TNF and IL-10 agonists. Anti-TNF drugs have application in other chronic inflammatory diseases, such

as rheumatoid arthritis and Crohn's disease, and may be useful for COPD (57). Other potential drug candidates include matrix metalloproteinase inhibitors. Pre-clinical studies have indicated that inhibition of these enzymes could prevent extracellular matrix degradation and slow lung tissue destruction (58). Mucolytic agents may be useful for COPD patients, however, the clinical value has not been determined and further research is needed (59). Antioxidant therapies may also be useful to counter oxidative stress and subdue inflammation. These novel therapies present opportunities for drugs however their development is in the early stages and widespread availability is not expected for many years. Furthermore their clinical application is often restricted by significant side effects and it is still unclear if inhibiting a single mediator or process will have a significant clinical effect (33).

2.16 Complementary therapies for COPD

Complementary and alternative medicines (CAM), particularly herbal medicines have been increasingly used for the management of COPD (7, 60). CAM interventions include natural products, dietary supplements and body-based practices including acupuncture and massage. A recent survey in Australia suggested that nearly one in five individuals with moderate to severe COPD had used some form of CAM therapy and one in six used herbal medicine (7).

The effectiveness and safety of CAM for COPD has not been wholly established. Evidence suggests that several interventions including herbs and acupuncture may be effective for improving symptoms of dyspnea and lung function (9, 12, 61).

2.17 Chinese medicine for COPD

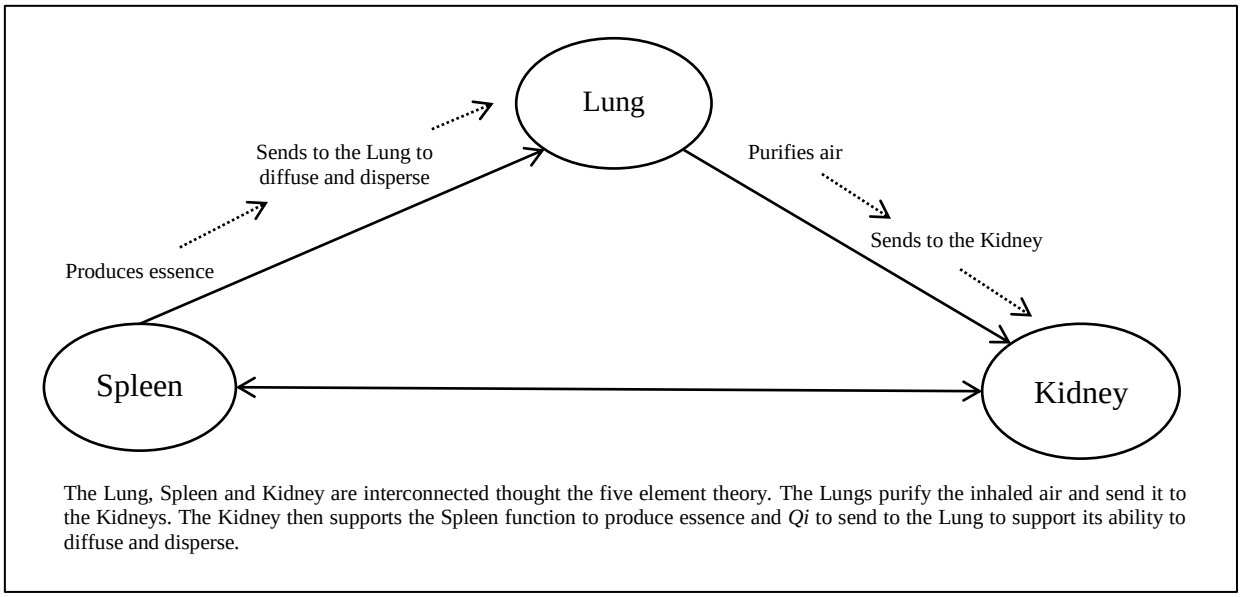
2.17.1 Introduction

Chinese medicine (CM) has a long history of use for chronic lung diseases like COPD. It is a system of health care that conceptualises disease and health uniquely and presents a holistic picture of the patient and their illness. Traditionally, CM relies on patient reported symptoms and observation of the tongue and pulse in formulating a diagnosis. Other factors such as the environment, seasons, emotions, diet, and lifestyle are acknowledged as influencing an individual's health.

The fundamental theories of CM include yin, yang, five elements and *Qi*. These theories were conceptualised through observation of the laws of nature and applied to the human body and disease to guide diagnosis and treatment (62). The internal organs, *Zang* (solid) and *Fu* (hollow) are interconnected and able to generate and control each other. They have unique functional activities rather than anatomical and pathophysiological paradigms. The dynamic balance between yin and yang is impaired during disease causing imbalance in the body. The treatment goals of CM are to regulate and harmonise the relationship between yin and yang and the *Zang Fu*, therefore encouraging salubrious balance.

2.17.2 Chinese medicine diagnosis of COPD

Modern CM texts refer to COPD as two characteristic patterns *fei zhang* (肺胀) (Lung distension) and *chuan zheng* (喘症) (Panting pattern). *Man xing zu sai xing fei bing* (慢性阻塞性肺病) is the translation for COPD. COPD in CM is understood using different theories to western medicine (WM). It is based on the history and observation of the patient and does not require any specialised WM testing. In CM, COPD is related to three organs, these are the Lung, Spleen and Kidney [Figure 7]. The Lungs dominate *Qi* and respiration and governs diffusion and depurative down bearing, as well as regulating the waterways. The Spleen maintains the transportation and transformation of food, upbearing and raising the *Qi* and supporting the flow of blood in the vessels. The Kidneys store the vital essence promoting growth and development and supporting the respiratory system (63). These concepts do not equate to WM functions of the organs.



The Lung, Spleen and Kidney are interconnected thought the five element theory. The Lungs purify the inhaled air and send it to the Kidneys. The Kidney then supports the Spleen function to produce essence and *Qi* to send to the Lung to support its ability to diffuse and disperse.

Figure 7: Lung, Spleen and Kidney interconnectivity in Chinese medicine

The Lung dominates the *Qi* of the body. Pollutants in the air inhibit the Lung's ability to separate the clean and turbid air and impede diffusing and dispersion. The Lung *Qi* becomes deficient causing cough and dyspnea. When the Lungs are dysfunctional, they fail to support the Spleen and Kidneys. The Kidneys then become deficient and they are unable to receive *Qi*. In turn the Kidneys are then unable to support the Lung and Spleen function and lead to further *Lung and Spleen Qi deficiency* [Figure 7].

The diagnosis of COPD in CM often involves phlegm. This is due to the inhibited regulation of waterways by the Lungs and Kidneys and failure of the Spleen to transport and transform, leading to phlegm accumulation in the Lung. The phlegm can narrow and block the airways leading to dyspnea and mucous hyper-secretion. Figure 8 presents the pathomechanisms of COPD in CM.

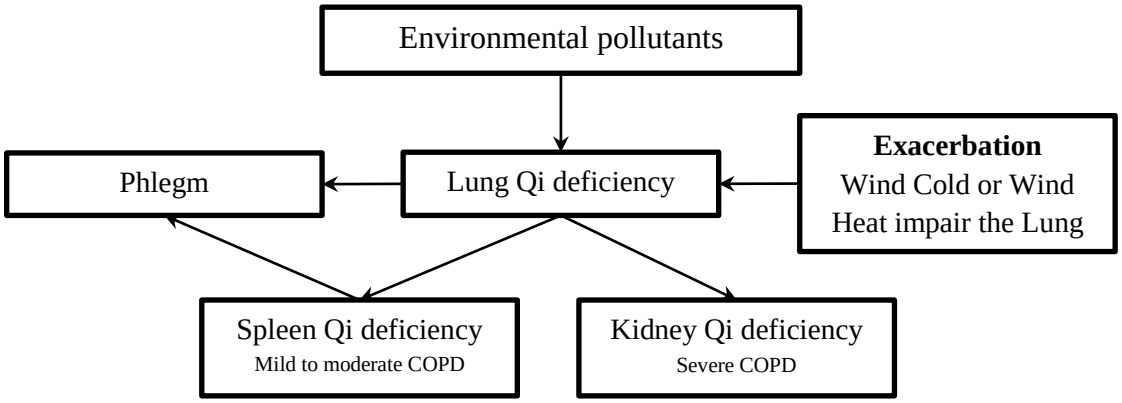


Figure 8: Pathomechanisms of COPD in Chinese medicine

2.17.3 Chinese medicine differentiation of COPD

According to CM theory, COPD can be differentiated into three syndromes, *Lung Qi deficiency, Lung and Spleen Qi deficiency or Lung, Spleen and Kidney Qi deficiency* (64). Table 8 summarises the CM differential diagnosis of COPD. *Lung Qi deficiency* symptoms include coughing, wheezing excessive sputum production and a propensity to catch a cold. The tongue is pale and possibly depressed in the anterior third and the pulse is thready. The Spleen controls digestion and nourishes the Lung. When there is *Spleen Qi deficiency* symptoms include tiredness, heavy limbs, poor appetite, swollen tongue and a therapy pulse. Kidneys function to support and warm the body, they receive *Qi* from the Lungs and support the respiratory function. *Kidney Qi deficiency* includes cold limbs, weakness and pain in the back and knees, nocturnal enuresis, shortness of breath after slight exertion, a pale dry tongue and a deep and weak pulse. During acute exacerbations of COPD wind-cold or wind-heat may be diagnosed. In CM, these pathogenic factors invade the susceptible Lungs and cause increased sputum purulence, chills and/or fever, sweating, a yellow tongue coating and a superficial and rapid pulse.

Table 8: Chinese medicine differential diagnosis of COPD

Syndrome	Key symptoms	Tongue	Pulse
Lung Qi deficiency	1. Sweating easily 2. Catch a cold easily 3. Difficulty to recover from a cold 4. Dyspnea, wheezing and cough	Pale and swollen tongue body with a depressed anterior third	Thready
Spleen Qi deficiency	1. Tiredness or exhaustion 2. Heavy limbs 3. Poor appetite and fullness in the stomach without eating 4. Loose bowel motions 5. Headache or heavy head	Pale and swollen tongue body with a white tongue coating	Thready
Kidney Qi deficiency	1. Aversion to cold 2. Cold limbs 3. Weakness or pain in the lower back or knee 4. Nocturnal enuresis (> 2 times per night) 5. Shortness of breath after slight exertion	Pale and dry tongue body	Deep Weak
Wind-cold or wind-heat	1. Increased sputum purulence 2. Chills and/or fever 3. Sweating	Thin and yellow tongue coating	Superficial Rapid

2.17.4 Chinese medicine treatments for COPD

Chinese medicine (CM) theories of health and healing differ from WM. Therapies are individualised based on CM differentiation and the imbalance that disease creates. Treatment principles in CM set out to recreate balance by strengthening deficiencies and reducing excesses. In CM, unlike WM, the stages of COPD are not clearly defined and the diagnosis requires consideration of the signs and symptoms, including severity of dyspnea and cough, the amount and colour of the phlegm and other systemic symptoms. COPD can be treated with herbal medicines, acupuncture, diet therapy, massage (*Tui na*), and exercise (*Tai chi*). Principles of treatment in CM include tonification of the Lung, Spleen and Kidney as well as clearing phlegm and eliminating wind-cold or wind-heat when applicable. These concepts do not equate to WM functions of the organs.

2.17.5 Chinese herbal medicine for COPD

In the clinical setting CHM is selected based on the differentiation of disease and herbal formulae are prescribed and modified to account for individual patient differences. Table 9 highlights common CM treatments for COPD. Chinese herbal medicine (CHM) has been used for over 2,000 years to treat respiratory conditions and may offer new approaches to more effectively treat COPD. Panax ginseng is one of the commonly used herbs for treating respiratory conditions due to Qi deficiency, which includes COPD. Recent preclinical and clinical research has shown beneficial effects of herbal medicine for treating COPD, with the most promising being *Panax ginseng* (9, 11, 65).

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2.17.6 Acupuncture for COPD

Acupuncture is used to treat COPD. It involves the insertion of needles into specific points on the body according to CM theory. Table 9 highlights common CM treatments for COPD.

Table 9: Chinese medicine treatments for COPD

Syndrome	Herbal formulas	Acupuncture points
Lung Qi deficiency	**Name: *Bu Fei Tang*** Herbal ingredients: *Ren Shen, Huang Qi, Shu Di, Wu Wei Zi, Zi Wan, Sang Bai Pi* **Name: *Yu Ping Feng San*** Herbal ingredients: *Huang Qi, Bai Zhu, Fang Feng*	Tai yuan (LU 9) Fei shu (BL 13) Lie que (LU 7)
Spleen Qi deficiency	**Name: *Bu Zhong Yi Qi Tang*** Herbal ingredients: *Ren Shen, Huang Qi, Bai Zhu, Gan Cao, Dang Gui, Chen Pi, Sheng Ma, Chai Hu* **Name: *Liu Jun Zi Tang*** Herbal ingredients: *Ren Shen, Zhi Gan Cao, Fu Ling, Bai Zhu, Chen Pi, Ban Xia*	Zu san li (ST 36) Pi shu (BL 20)
Kidney Qi deficiency	**Name: *Shen Qi Wan*** Herbal ingredients: *Shu Di, Shan Zhu Yu, Shan Yao, Fu Ling, Mu Dan Pi, Fu Zi, Rou Gui* **Name: *Sheng Mai San*** Herbal ingredients: *Ren Shen, Wu Wei Zi, Mai Dong*	Tai xi (KI 3) Shen shu (BL 23)
Wind-Cold or Wind-Heat	**Name: *Ma Huang Tan*** Herbal ingredients: *Ma Huang, Gui Zhi, Xing Ren, Gan Cao* **Name: *Gui Zhi Tang*** Herbal ingredients: *Gui Zhi, Bai Shao, Sheng Jiang, Da Zao, Gao Cao*	Feng chi (GB 20) Lie que (LU 7) Chi ze (LU 5) Da zhui (GV 14)
Phlegm accumulation	**Name: *Er Chen Tang*** Herbal ingredients: *Ban Xia, Chen Pi, Fu Ling, Gan Cao* **Name: *Ping Wei San*** Herbal ingredients: *Cang Zhu, Hou Po, Chen Pi, Gan Cao, Sheng Jiang, Da Zao*	Feng long (ST 40)

2.17.7 Chinese medicine research for COPD

Chinese herbal medicine and acupuncture are commonly used by COPD suffers (7). However, an evidence-based approach for selecting treatments has not been established.

The effectiveness of CHM for COPD has been evaluated in several systematic reviews (8, 9, 66). A number of herbal medicines were investigated and results indicated that *Panax ginseng, Salvia miltiorrhiza* and *Hedera helix* had a good effect on pulmonary function, including FEV_1 (9). CHM formulae were investigated for their effect on

HRQoL in patients with COPD (8). The included studies used the SGRQ or Cai's QoL questionnaire. The results showed improvement in overall HRQoL scores. The efficacy and safety of CHM formulae containing Ginseng for COPD has been reviewed (66). Results indicate that Ginseng formulae can improve lung function FEV_1 and QoL. Ginseng formulae were considered safe overall and no serious adverse events were reported in the included studies (66). Results from these reviews were limited by small sample sizes and poor methodological quality. Additionally, there were no replicated RCTs and results could not be pooled.

Other CM treatments for COPD includ acupuncture and *Tai chi.*They have been evaluated in randomised controlled trials (RCTs). Acupuncture reduced pulmonary medications in a recent review and was effective in reducing dyspnea on exertion in patients with COPD (61, 67). *Tai chi 'Qigong'* was found to be effective in improving respiratory function and activity tolerance in COPD sufferers (68).

The current evidence of CM for COPD reveals promising results despite some methodological weaknesses in study design. Further investigation of CM treatments may provide novel therapies for COPD.

2.17.8 *Panax ginseng* as a treatment for COPD

Panax ginseng has demonstrated benefit on a number of health conditions (11). The systematic review presented in Chapter 5 reveals that *Panax ginseng* had the most promising evidence for moderating the immune response, particularly cell-mediated immunity and clinical applicability for chronic respiratory diseases.

It is plausible that *Panax ginseng* can benefit COPD given its multiple activities on reducing inflammation and oxidative stress. These actions include the regulation of TNF-α and IL-8 and suppression of the NF-κB pathway. The mechanisms of action are described in Chapter 5. Ginseng also has antioxidant capacity and can increase nitric oxide and decrease reactive oxygen species (ROS). Furthermore, Ginseng also possesses anti-protease properties (69, 70).

Similar to the newly developed PDE-4 drugs, Ginseng has been shown to elevate intracellular cAMP levels (71). Side effects of the PDE-4 drugs are common and Ginseng may be a safer alternative.

One study evaluated *Panax ginseng* for COPD (12). *Panax ginseng* extract, G115 at 100 mg twice a day or placebo was administered for three months. Lung function and exercise capacity improved in the G115 group but not placebo. The study had several methodological shortcomings, including inadequate sample size (n=92), short follow-up period and lack of assessment of QoL.

Ginseng may be most beneficial for COPD sufferers in the mild to moderate stages. These individuals are often prescribed inhaled steroids without any evidence of benefit, but are at risk of long-term side-effects (1). The therapeutic potential of *Panax ginseng* in the management of COPD remains inconclusive. While the results from pre-clinical and clinical trials are encouraging, rigorous trials with high quality methodological design will provide further information about the potential usefulness of *Panax ginseng* as a treatment for COPD.

Chapter 3: Literature review of *Panax ginseng*

3.1 Introduction

Panax species from the Araliaceae family are the most researched herbal medicines (72, 73). Many Panax species have been recognised with morphometric and constituent diversity [Table 10] (74). Of these, *Panax ginseng* is the most researched for medicinal purposes (75). Panax is a composite Greek word, *pan* meaning 'all' and *axos* 'cure', denoting a 'cure-all'. *Panax ginseng* is commonly used in Chinese medicine (CM) and the name Ginseng originates from the Chinese '*Ren shen*' or man-root due to its fork shape, which resembles a human body and legs. The Russian scientist Carl Anton Meyer identified and named *Panax ginseng* C.A. Meyer in 1843 (74). For the purposes herewith *Panax ginseng* C.A Meyer will be referred to as Ginseng.

Table 10: Botanical classification of Araliaceae, Panax and the main species

Family	Genus	Main Species
Araliaceae	Panax	*Panax ginseng* C.A. Mey.
		Panax japonicas C.A.Mey.
		Panax notoginseng (Burkill) C.Y.Wu & Feng
		Panax pseudoginseng Wall.
		Panax quinquefolius L.
		Panax stipuleanatus Tsai & Feng
		Panax trifolius L.
		Panax wangianus S.C.Sun
		Panax zingiberenseis C.Y.Wu & Feng

3.2 Prevalence of Ginseng use

For millennia, CM practitioners have used Ginseng. In the West it has become one of the most commonly used herbs (76). Ginseng accounts for 24.1% of herbal use in America, only behind Echinacea (40.3%) (72). In Australia, Ginseng accounts for 5.9% of herbal use (73). Although Ginseng is one of the most expensive herbs it remains a top seller. Korean Ginseng is often purported to be the most potent and therefore fetches the highest prices. Products on the market include wild roots, cultivated roots, granulated powders, standardised extracts, tablets, teas, and lollies.

3.3 Identification of Ginseng

Ginseng is naturally found in a cool climate of the temperate zone in Northern Korea, Northeast China and Far East Russia. Due to diminished wild sources, Ginseng is cultivated for commercial use in Korea, China and North America. It is a perennial plant with branched roots 2.5–20 cm in length and 0.5–3.0 cm wide, verticillate leaves and a central umbel with small green flowers and clusters of red berries. The roots are 'human like' in appearance with small roots and rootlets branched off the centre. The roots are the main part of the plant used for medicinal purposes and they are harvested after 4–6 years of growth. Figure 9 presents an image of a mature Ginseng plant. Figure 10 provides samples of different forms of Ginseng, including slices, rootlets, whole root and capsules.

Ginseng is a very valuable herb and wild roots can be sold for thousands of dollars. Over time several Panax species have been sold as *Panax ginseng* often due to similarities in appearance but at times for profitability. Other species, although similar

in appearance have different constituent contentand their therapeutic effect and function differ (77). Similar species include *Panax quinquefolius* (American Ginseng), *Panax notoginseng* and *Eleutherococcus senticosus* (Siberian Ginseng). *Panax quinquefolius (Pin yin: Xi yang shen)* is not a native species of China. It was imported in the 1700's from America and is now part of the Chinese materia medica having similar functions as *Panax ginseng*. In Chinese medicine theory, *Panax notoginseng (Pin yin: San qi)* functions to stop bleeding, reduce swelling and alleviate pain, for conditions such as angina or traumatic pain. Its constituent profile is similar to *Panax ginseng* but the root does not have the typical 'man-root' appearance. Siberian Ginseng, *Eleutherococcus senticosus (Pin yin: Ci wu jia)* from the Araliaceae family is often substituted for *Panax ginseng.* It is similar in appearance however, it does not contain the active constituents, ginsenosides.

Source, Court W.E. Ginseng, the Genus Panax: CRC Press; 2000

Figure 9: Mature Ginseng plant

Selection of Ginseng samples. From left; steamed (Red Ginseng) cut into slices, steamed (Red Ginseng) rootlets, air dried whole root, and Ginseng capsules.
Source: iStock Photo.

Figure 10: Ginseng samples

3.4 Ginseng use in Chinese medicine

In CM, Ginseng, is highly valued and has been used for thousands of years as a tonic for improving stamina and vitality. It has supposed adaptogenic properties making it useful for many conditions (78). The earliest recorded account of Ginseng is in the *Shen Nong Ben Cao Jing* (Farmer God's Materia Medica), compiled between 206 B.C. – A.D. 220. The reference describes Ginseng as a multipurpose medicinal with the ability to strengthen the body (79). The most famous traditional reference to Ginseng is from the *Ben Cao Tu Jing* (Atlas of Materia Medica) c. A.D. 1061, Song Dynasty (80).

It says:

'It was said that in order to evaluate the effect of genuine Shangdang ginseng, two persons were asked to run together. One was given the ginseng while the other ran without. After running for approximately three to five Li [equivalent to 1,500 to 2,500 meters], the one without the ginseng developed severe shortness of breath, while the one who took the ginseng breathed evenly and smoothly'.

This reference highlights the early historical use of Ginseng and places it as an important medicinal plant used over centuries. Figure 11 presents two images of Ginseng from traditional CM texts.

A

B

A: Ren shen plant, [wood block print]. *Image source:* Jing Shi Zheng Lei Bei Ji Ben Cao (c. 1082), in the Complete Collection of Traditional Texts in Chinese Material Medica, Volume 7, pg. 361. **B:** Ren shen plant, [drawing]. *Image source:* Yu Zhi Ben Cao Pin Hui Jing Yao (c. 1505), in the Complete Collection of Traditional Texts in Chinese Material Medica, Volume 29, Pg. 877.

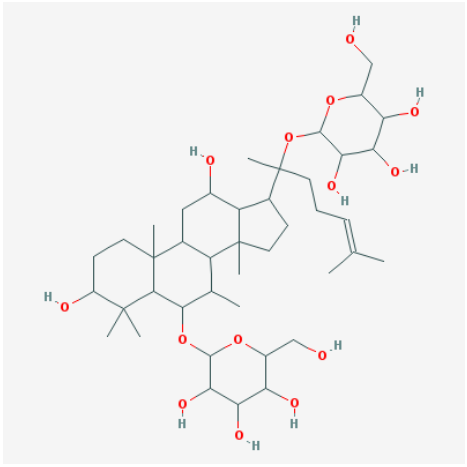
Figure 11: Traditional images of Ginseng

3.4.1 Chinese medicine properties of Ginseng

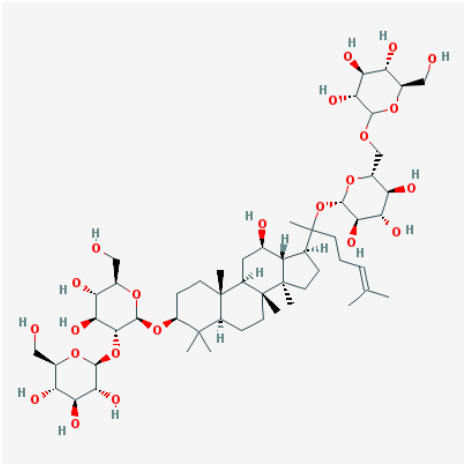
Chinese medicine classifies Ginseng as a tonifying herb, it is sweet, slightly bitter, slightly warm and enters the Heart, Lung and Spleen channels (81). The nature of Ginseng is slightly warm therefore it relates to yang and it is able to warm the yang and disperse cold. It is also sweet in nature and can repair and supplement. Ginseng is indicated for use in *Qi* deficiency conditions, specifically for *Lung and/or Spleen Qi deficiency*. Other functions include the generation of body fluids and calming the spirit. It is often prescribed alone or in combination with other herbs for shortness of breath, wheezing, general weakness, lack of appetite, forgetfulness, thirst and impotence.

3.5 Constituents of Ginseng

The therapeutic activity of Ginseng relies on a unique mix of triterpenoid saponins called ginsenosides. Ginsenosides consist of a steroid nucleus with carbon atoms arranged in a four-ring structure with various sugar attachments. Figure 12 shows the chemical structure of the ginsenosides Rg1 and Rb1. Over 150 ginsenosides have been identified from two main groups, dammarane and oleanane. Dammerane includes protopanaxadiols, for example, Rb_1, Rb2, Rc, Rd, and protopanaxatriols, for example, Rg1, Rg2, Re, and Rf. Oleanane includes oleanolic acid for example Ro (82). Ginsenosides are named as R*x* based on their structure, where R refers to the root and *x* denotes chromatographic polarities in alphabetical order. That is, Rb is more polar than Rc which is even more polar than Rd.



Ginsenoside Rg1



Ginsenoside Rb1

Source: National Centre for Biotechnology Information. PubChem Compound Database; CID=441923 and 73148, http://pubchem.ncbi.nlm.nih.gov/ (accessed Sept. 27, 2012).

Figure 12: Chemical structure of ginsenoside Rg1 and Rb1

Ginsenosides are measured using spectrophotometry and high performance liquid chromatography (HPLC). Rg1 is commonly used as the marker ginsenoside calculated as no less than 1.5% (83). Ginsenoside content will chiefly rely on the species of Ginseng. There are some ginsenosides unique to individual species, for example Rf is present in *Panax ginseng* but not in *Panax quinquefolius*. Within species variability can also exist due to factors such as geographic source, climate, time of harvest and processing techniques (84).

Ginsenosides are concentrated in the roots of Ginseng and different theories exist regarding the best part of the root to use, for example the main root, lateral sections or the rootlets. Most often the main root is desirable for medicinal purposes. Ginseng also contains polysaccharides, peptides, polyacetylenic alcohols, fatty acids, sugars, and

trace elements (10, 78). The pharmacokinetics of Ginseng and ginsenosides have not been fully established. Ginsenosides are large compounds and have poor membrane permeability. The absorption and bioavailability of ginsenosides and their metabolites are extremely low, particularly after oral administration (85). Some studies have detected serum ginsenosides (Rb1) as low as 0.64% (86). Ginsenosides are quickly absorbed from the digestive tract and their peak time is between 1–2 hours and total elimination varies between 24 and 72 hours (87). Several ginsenosides are hydrolysed after ingestion and undergo bio-transformation to form new compounds, for example compound K is a metabolite of Rb1. Evidence suggests that ginsenosides may be pro-drugs requiring bio-activation though deglycosylation and fatty acid esterification in the intestines (88).

3.6 Standardisation and quality control

Chinse herbal medicines (CHM) are often processed after harvest to produce an enhanced therapeutic effect, reduce toxicity and/or change their properties. Methods may include frying with honey or vinegar or stir baking or steaming. After harvest, Ginseng roots are traditionally air-dried and peeled (White Ginseng) or steamed which turns the root a deep red colour (Red Ginseng). The steaming process changes Ginseng's properties from slightly warm to hot and supposedly increases its therapeutic effect. The recommended daily dose of Ginseng is 0.5–2 g of dried root per day or 200–600 mg for extracts.

Standardised Ginseng extracts are preferred among researchers as they ensure consistency between batches and therapeutic advantage. The most commonly referenced

standardised extract is G115, manufactured by Ginsana SA. This product has been evaluated in over 46 studies over 35 years (89, 90). The manufacturers of G115 select raw plant material aged 5 to 7 years from Korea and Northern China. The processing method involves a 20 step standardisation procedure yielding a total ginsenoside content of 4% (4mg) (Rg1, Rb1, Re, Rf, Rg2, Rc, Rb2, Rd). Quality control and standardisation methods are essential when using Ginseng for therapeutic purposes. Differences in chemical composition and concentration will affect efficacy and have implications for safety. Figure 13 presents the interconnectivity between quality, efficacy and safety of Ginseng.

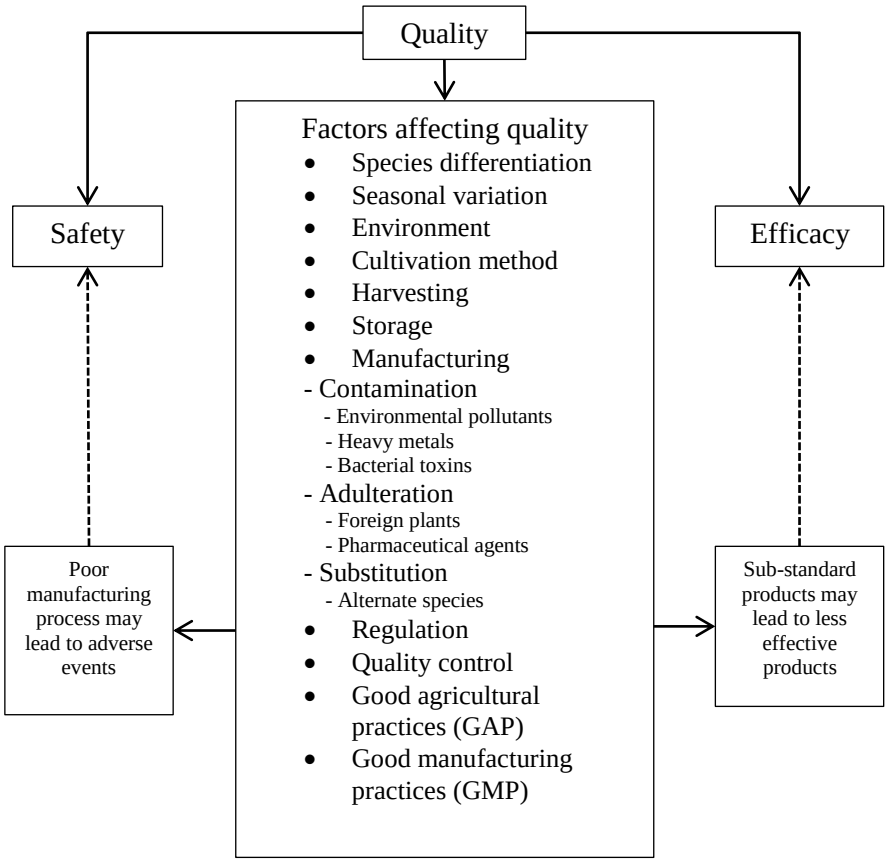


Figure 13: Quality, efficacy and safety of Ginseng

3.7 Ginseng products on the market

Many forms of Ginseng are on the market, these include: raw plant material; granulated extracts; liquids extracts; and standardised extracts. Ginseng is one of the top selling herbs with sales in the USA worth over $7,000,000 annually (91). The quality of Ginseng products is variable and reports have indicated ginsenoside content between 0% and 9% (92). A search of the Therapeutic Goods Administration's (TGA) Australian Register of Therapeutic Goods (ARTG) on 27 September 2012 identified 395 listed products containing *Panax ginseng* as an active ingredient. Of these, only 14 products contained *Panax ginseng* alone. The other items were combinatorial products containing Ginseng with other herbal medicines and/or vitamins and minerals. The 14 Ginseng products listed on the ARTG are presented in Table 11.

3.8 Ginseng research

Ginseng is one of the most researched herbs and there is a significant body of literature evaluating its effect for many health conditions (75). Chapter 5 presents the results from RCTs evaluating Ginseng. Briefly, Ginseng was found to have the most promising effect for moderating the immune response particularly cell mediated immunity, and for glucose metabolism. These results may have implications for several diseases such as chronic respiratory conditions and type 2 diabetes (11).

Table 11: Ginseng products listed on the ARTG

Product	% ginsenosides	Recommended dose	Effect and indications
Blackmores® Korean Ginseng	1.86%	500 mg bid	Improves mental and physical capacities.
Ginsana® G115	4%	100 mg bid	Improves energy and fights fatigue. Strengthens the immune system.
Ginsana® Tonic Oral Liquid (also listed as Pharmaton Ginsana G115 Oral Liquid)	4%	15 mL qd	Helps relieve nervous tension and stress. Can increase the oxygen intake capacity and reduce blood lactate levels.
GNC Ginseng Gold™	3%	500 mg qd	Improves mental and physical vitality.
KGAC Co Cheong-Kwan-Jang, powders, pills and tablets (5 products)	Not specified	1 g bid or tid	Enhances stamina and endurance. Strengthens the immune system.
Nutra-Life® Korean ginseng 2500	1.67%	2.5 g qd	Helps relieve nervous tension and stress. Enhances stamina and endurance.
Korean Ginseng 500 mg Super Strength	Not specified	500 mg qd	Improves general well-being.
Nature's Own® Korean Ginseng	Not specified	500 mg bid	Helps relieve stress. Enhances stamina.
Nature's Path standardised Korean Ginseng	Not specified	150 mg bid	Enhances stamina and endurance.
Nature's Sunshine™ Korean Ginseng	Not specified	410 mg qid	Improves general well-being. Improves energy and fights fatigue.
Well Herb *Panax ginseng* (capsules and liquid)	Not specified	240 mg bid 80 mg/ml	Improves energy and fights fatigue. Strengthens the immune system.
Peking *Panax ginseng* extract	Not specified	10 mL bid	Improves general well-being. Enhances endurance.
RPS ANG COX GINSENG 150MG *Panax ginseng*	Not specified	150 mg	No specific indications

Note: Product information, % ginsenosides, recommended dose and indications are taken from the product label and company webpages.

3.9 Safety of Ginseng

Ginseng has an overall good safety profile. The WHO monograph, the Chinese pharmacopoeia and the European Scientific Cooperative on Phytotherapy (ESCOP) indicate Ginseng is safe with no contraindications (83, 93, 94). Systematic reviews indicate Ginseng is safe at the recommended dose of 0.5–2 g/ day (90, 95). Clinical trials and case studies have reported rare occurrences of minor transient adverse events including diarrhoea, sleeplessness, palpitations, headache and nausea (95). The systematic review in Chapter 5 presents events from RCTs.

There is a need to establish the safety of Ginseng during pregnancy and lactation. The current literature is scarce and recommendations of caution are based on isolated case reports of hormonal activity and results from animal and *in vitro* studies (96).

Ginseng has been shown to interact with cytochrome P450 (97). This enzymes is involved in the metabolism of many drugs and caution needs to be taken when Ginseng is combined with other medications (97). There are four documented cases of Ginseng-drug interaction in humans. The monoamine oxidase inhibitor, phenelzine interacted in three cases and the anti-coagulant, warfarin in another [Table 12]. The significance and clinical implications of these interactions is hard to determine.

Table 12: Reported cases of Ginseng-drug interaction

Drug	Number of cases	Ginseng product	Dose of Ginseng	Adverse effects	Outcome of the event
Phenelzine (98)	1	NatrolHigh: Combination product containing Ginseng and other ingredients	Unspecified	Trembling, headache and insomnia	Resolved after discontinuation of Ginseng containing product
Phenelzine (98)	1	Ginseng tea	Unspecified	Trembling, headache and insomnia	Resolved after discontinuation of Ginseng containing product
Phenelzine (99)	1	Ginseng unspecified (Patient was also taking triazolam, lorazepam and bee pollen)	Unspecified	Hypomania, and worsening depression	Depression not improved after cessation of Ginseng product
Warfarin (100)	1	G115 (*Panax ginseng* standardised product manufactured by Ginsana SA)	3 capsules daily	Decline in INR which was previously stable	INR returned to normal after cessation of ginseng

INR: International normalised ratio

3.10 Pharmacology of Ginseng

Ginseng exerts a range of complex pharmacological activities on the immune, endocrine, cardiovascular and central nervous systems (10). Cellular processes and activities of Ginseng are diverse due to the complex mix of compounds. The extent of its actions and mechanisms has not been fully elucidated however it is described as an "adaptogen", increasing the body's defence and enhancing stamina and endurance (83).

Ginseng's major active components, the ginsenosides, have demonstrated ability on numerous tissues as well as initiating multiple actions within the same tissue (10). The diverse actions of Ginseng are thought to rely on its ability to influence the

hypothalamic-pituitary-adrenal axis and target plasma membrane receptors as well as intracellular steroid receptors (10). Ginseng is a functional ligand of the glucocorticoid receptor and displays synergistic effects with cyclic AMP (101, 102). Evidence suggests it has glucocorticoid-like activity and can regulate gene transcription. Ginseng may have an effect on inflammatory diseases, diabetic conditions, steroid resistance, and cancers.

3.10.1 Immune system

Ginseng has anti-inflammatory and immune-modulatory actions. Ginseng may modulate inflammation through multiple immune system components including regulation of cell mediated and humoral immune response increasing phagocytosis and reducing mediators (103). These effects may have implications for local and systemic inflammation.

Ginseng has multiple actions on inflammatory pathways. Predominantly, Ginseng affects NF-κB and TNF-α production. Ginseng can regulate DNA binding, transcriptional activity, release of cytokines, and regulation of intracellular cAMP pathways (71). Ginseng can down regulate the expression and release of TNF-α (65), IL-6, and IL-8 (104) as well as increase T-cell numbers and natural killer cell activity (105). Anti-inflammatory effects of Ginseng also relate to its ability to act as an anti-oxidant. *In vitro* studies have found that ginsenosides can activate antioxidant enzymes (106), protect cells from free radical damage (107) and inhibit lipid peroxidation (108).

Furthermore, animal studies have found that ginsenosides were able to increase adrenocorticotropic hormone (ACTH) from the pituitary and increase serum

corticosterone (109). This may have implications for inflammation, as corticosterone is an anti-inflammatory agent. The activation of these mediators and pathways has been linked to several inflammatory diseases, including COPD, rheumatoid arthritis, and inflammatory bowel disease (59, 110). Figure 14 highlights the potential effects of Ginseng on inflammatory pathways.

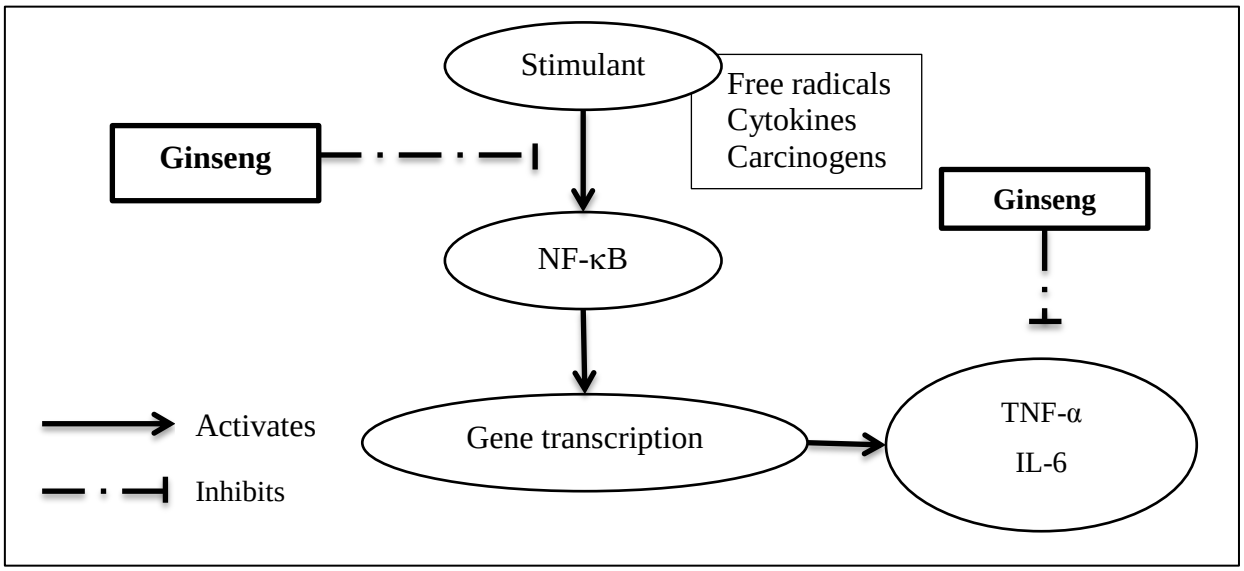


Figure 14: Potential effects of Ginseng on inflammatory pathways

Anti-carcinogenic and anti-neoplastic effects of Ginseng are thought to rely on its ability to suppress inflammatory pathways. *In vitro* and *in vivo* studies have shown several ginsenosides including Rh2 and Rg3 can inhibit tumour cell growth (10). Clinical trials have also indicated that Ginseng can reduce the incidence and recurrence of cancer in at risk individuals (111, 112).

3.10.2 Glucose metabolism

Ginseng lowers blood glucose by regulating glucose metabolism, improving insulin sensitivity, and stimulating hepatic glucose utilisation (113). Clinical trials evaluating the effect of Ginseng on healthy individuals and in type 2 diabetics have demonstrated a decrease in circulating glucose. These actions have implications for reducing hyperglycaemia and treating diabetes. However, conclusive results have not been established (11). The specific mechanisms and anti-diabetic actions are complex and still under investigation. Most notably, Ginseng can improve glucose homeostasis (114), activate pancreatic β-cells, increase insulin secretion, improve metabolic rate and glucose removal (113). Another mechanism of ginsenosides may be their ability to increase cellular energy. They are able to increase the capacity of muscles to oxidize free fatty acids instead of glucose therefore yielding more energy and endurance (115).

3.10.3 Cardiovascular system

The full extent of Ginseng's effect on the cardiovascular system is unclear. Ginseng is thought to modulate vasomotor function, reduce platelet adhesion, influence ion channels (Ca^{2+} and K^{+}), reduce vascular smooth muscle dysfunction and dilate blood vessels (116). Furthermore, oxidative stress is a factor in cardiovascular disease. Ginseng can ameliorate damage and reduce oxidative stress as well as enhancing nitric oxide production leading to vasodilation (117, 118). Clinical studies have yet to demonstrate a significant effect of Ginseng on any of the promising mechanisms found *in vitro* and in animal studies.

3.10.4 Central nervous system

Ginseng may modulate neurotransmission and improving memory (10). The beneficial effects are thought to involve nitric oxide and scavenging of free radicals, reducing central nervous system cell apoptosis and inflammation and preventing the detrimental effects of aging (119, 120). Specifically, Ginseng and ginsenosides (Rb1, Rg1, Rg3) can affect the hippocampus, increasing acetylcholine and corticosterone (109, 121). Clinical trials are yet to conclusively demonstrate Ginseng's effect on memory enhancement or neurodegenerative disorders such as Alzheimer's disease and dementia (122). Some positive effects have been noted but clinical implications are difficult to interpret (11).

3.11 Summary

Ginseng is one of the most popular herbal medicines worldwide. It is used for an array of health conditions including respiratory and gastrointestinal diseases and general well-being. It is safe and generally well tolerated. The current literature is diverse and there are a comprehensive array of pharmacological actions of Ginseng and ginsenosides. Diverse mechanisms of individual ginsenosides and whole root extracts may explain non-specific effects and the multitude of actions. Positive results from pre-clinical and clinical research indicate that Ginseng may have potential application in many diseases.

Chapter 4: Search and analysis of classical literature on Chinese herbal medicine for COPD

4.1 Foreword

Chinese medicine (CM) theories and treatments have been widely used and preserved for over 2,000 years. There is a growing body of clinical evidence for the efficacy of CM, particularly Chinese herbal medicine (CHM) for certain disorders including respiratory, metabolic and cardiovascular conditions (8, 11). However, evidence-based CM practice is still undergoing development.

The classical literature is voluminous, offering a diverse range of references based on the practice of healers over many centuries. These works offer a range of CHM treatments for a diversity of health conditions and continue to inform the use of CM in the contemporary setting.

There term ‘classical’ applies to ancient works that formed the foundation of CM theory and practice. It generally relates to works written and/or published in dynastic China compared to works produced in modern China. The shift from classical to modern cannot be dated exactly. The fall of the Qing Dynasty and the beginning of the Republic of China (1911) marks the political end of the traditional period but the modernisation of CM occurred following the establishment of the People’s Republic of China in 1949. In this study the literature was considered to belong to the ‘classical’ period of Chinese medicine up until 1949.

The earliest extant CM works arose in the period up to and including the Han Dynasty (206 B.C. – A.D. 220). The principal works include the *Huang Di Nei Jing* 'Yellow Emperor's Internal Classic', *Nan Jing* 'Classic of Difficulties' and the *Shen Nong Ben Cao Jing* 'Farmer God's Materia Medica' all of which are of unknown authorship (79, 123).

The most influential herbal medicine work is considered to be the *Shen Nong Ben Cao Jing* 'Farmer God's Materia Medica' compiled between 206 B.C. – A.D. 220. It was named in attribution to the renowned deity *Shennong* who is believed to have taught agriculture practices and herbal medicine to the ancient people of China. The *Shen Nong Ben Cao Jing* includes details of herbal medicines coupled with their application and indications. The book summarises 365 plant, animal and mineral medicines (79).

Over the ensuing millennia, the materia medica grew exponentially creating a vast body of knowledge. Significant texts include the *Ben Cao Jing Ji Zhu* 'Annotations on Materia Medica' and the *Ben Cao Gang Mu* 'Compendium of Materia Medica'(124). Modern CM practices have maintained the fundamental theories and concepts presented in ancient texts and enhanced early understanding by incorporating up to date scientific knowledge.

4.2 Introduction

Search and analysis of the classical literature in a systematic and organised way is an approach to selecting herbs and herbal formulae with potential efficacy for inclusion in drug discovery efforts and/or in clinical trials (125-127). Classical literature citations may lead to new drug development similar to that which lead to the anti-malarial drug, artemisinin (128).

Chronic obstructive pulmonary disease (COPD) is a modern disease and classical CM literature does not refer to this condition as it is understood today. Therefore, the terms COPD, chronic bronchitis and emphysema cannot be found in the classical texts. The terms used in CM are more general than in modern medicine with less specificity for a particular disease. However, classical Chinese manuals include conditions broadly similar to the modern conception of COPD. Typical terms for such conditions include: *fei zhang* 'Lung distension'; *jiu ke* 'chronic cough'; *jiu chuan* 'long-term dyspnea '; *zhi yin* 'chest tightness'; *chuan zheng* 'dyspnea'; and *ke chuan* 'cough and dyspnea' (129). Within these concepts it is conceivable that some of the conditions treated would now be considered COPD and the herbal treatments used may have contained herbs that were efficacious for the relief of the condition. In this study, a large sample of the classical literature was searched for instances of the use of herbal formulae for treating a condition that was most likely COPD. Within this subgroup of references the most commonly used formulae and herbs are identified and form a basis for selecting herbs requiring further investigation to inform future drug development (125).

In this section ‘formula’ refers to a prescription or recipe of a combination of herbal ingredients. These may include herbs from plant, animal and/or mineral origin. Formulae are usually constructed by combining a number of herbs that address different aspects of a health condition. Traditionally formula are prepared by decoction, that is, by boiling the herbs in water, used as powders or formed into pills.

The Chinese names for formula, herbs and books have been transliterated into pin yin and are italicised (except in tables where they are in regular text). Chinese characters are not included in the text. Chinese terms and names are presented as follows:

- Chinese terms are written in lower case, for example *fei zhang*
- Herb names are written in lower case, for example *ren shen*
- Herbal formula are written in sentence case, for example *Shen qi wan*
- Book names are written in title case, for example, *Jin Gui Yao Lue*

The classical literature is often combined into compendia that comprise extracts from many CM books. They provide a convenient body of data that can be searched and linked to original references. There is no complete collection of the classical CM literature however several large collections and compendia are available that cover a wide variety of publications (130, 131).

The *Zhong Yi Fang Ji Da Ci Dian* (ZYFJDCD) is a collection of formulae citations derived mainly from classical books. The formulae have been categorised and indexed against diseases and symptom names. The ZYFJDCD includes extracts from at least 685 books. In 11 volumes, it is the largest collection of Chinese herbal formulae. It contains 96,592 entries, each referring to at least one herbal formula, Figure 15 (131).

The Nanjing Chinese Medicine Institute compiled the ZYFJDCD and first published it in 1993.

The ZYFJDCD was selected in this search as it is easy to access, comprehensive and includes CM literature spanning over 2,000 years (c. 206 B.C. – A.D. 1985).

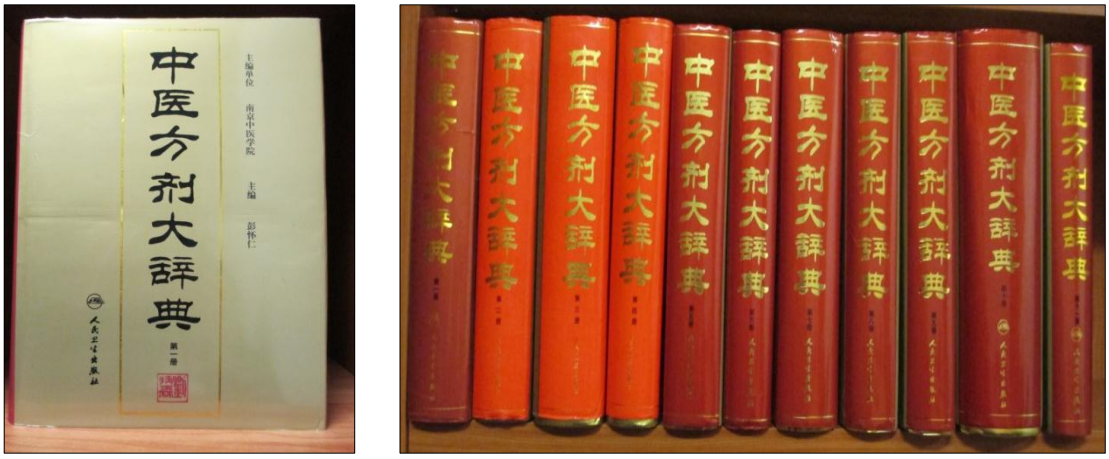


Photo at left, the ZYFJDCD volume 1 front cover. Photo at right, the ZYFJDCD 11 volumes. Image source © Johannah Shergis

Figure 15: Zhong Yi Fang Ji Da Ci Dian

4.3 Aims and hypothesis

The aim of the study was to search and analyse the classical literature to identify herbs and CHM formulae that had been referenced and indicated for the treatment of conditions analogous to COPD. Additionally, the study aimed to reveal the most frequently used CHM formulae and individual herbs for conditions similar to COPD.

It is hypothesised that the six search terms: *fei zhang, jiu ke, jiu chuan, zhi yin, chuan zheng,* and *ke chuan* are good matches for COPD and at least some of the extracted citations are consistent with COPD.

4.4 Methods

4.4.1 Search strategy

The search method was based on previously published procedures (125). COPD is a modern classification of disease and identical classical terms are not available. Classical CM texts do not refer to COPD specifically, however similar terms include *fei zhang* (Lung distension) and *chuan zheng* (panting pattern). These terms alone were not sufficient to search the traditional literature. Therefore, it was necessary to develop a set of terms based on key symptoms. The terms were developed by consulting an authoritative CM dictionary, *Zhong Xi Yi Bing Ming Dui Zhao Da Ci Dian* (132). Additionally respiratory experts and medical manuals were consulted. The ZYFJDCD was searched using the following terms.

- *fei zhang* 'Lung distension'
- *jiu ke* 'chronic cough'
- *jiu chuan* 'long-term dyspnea '
- *zhi yin* 'chest tightness'
- *chuan zheng* 'dyspnea'
- *ke chuan* 'cough and dyspnea'

The classical literature search was restricted to the dynastic and republican periods and included books written and published up until 1949.

The ZYFJDCD is written in Chinese, therefore experienced researchers who were native Chinese speakers and proficient in English language undertook extraction of data. The contribution of Xiankun Chen and Nicole Chang is acknowledged.

4.4.2 Data extraction

Each search term was indexed in the ZYFJDCD. In most cases, one reference was associated with a single herbal formula but in some cases a reference referred to more than one formula, additionally some references were not relevant to their indexed term. Therefore, only the references that were specific to the index term and included an herbal formula were considered an ‘entry’. One ‘entry’ contains one formula. Entries were given an identification number and the details of each entry were entered onto Microsoft® Excel spread sheets.

Extracted data included:

- index term
- formula name
- name of individual herbs in the formula
- instructions for preparation and/or use
- syndrome or disorder for which the formula was intended
- book title where formula was found
- authorship of the book (when available)

- year the book was written.

Issues with inconsistent and unclear data were addressed by comparing them with other classical CM literature sources.

4.4.2.1 Dating classical books

Classical books were dated according to the listing of books in the ZYFJDCD (volume 11). If the year of publication was not clear other CM sources were consulted (124, 133). If the year could still not be determined, it was assigned the year of the author's death and if this was unavailable the last year of the historical period (dynasty).

4.4.3 Classification of citations

Citations fall broadly into two types, those that refer to a particular case or series of cases, and information on the general use of the formula. In some cases, the type is unclear.

4.4.4 Classification of symptoms

The search terms selected reflect the main symptoms of COPD. However, there is no certainty that the condition listed in the citation is consistent with the modern understanding of the disease so the search will find references that are not relevant. Citations are often brief and the information provided does not give enough insight to draw firm conclusions as to the application of the formula. In other cases, the description is detailed enough to allow inference as to the identity of the condition.

To identify citations likely to refer to COPD, a set of inclusion and exclusion criteria were developed. The symptoms selected were those that would be observed when making a clinical diagnosis of COPD. To develop the inclusion and exclusion criteria as well as the related scoring system expert opinion was sought and modern medical literature and clinical manuals were consulted (1, 134).

The selected COPD symptoms were:

- dyspnea, including *shang qi* 'difficulty breathing'
- cough
- sputum production
- chest tightness, including *fei zhang* 'Lung distension'.

4.4.5 Exclusion criteria

Excluded citations were:

- citations in books published after 1949
- citations specifically relating to women's disorders
- citations specifically indicated for postpartum conditions
- citations specifically indicated for children
- citations indicated for acute disorders, trauma or other disorders unrelated to COPD
- citations indicated for haemoptysis

In cases where there was an acute complication of a chronic condition the citation was included. Table 13 presents the scoring system for excluding citations.

Table 13: Scoring system for excluding citations

Children or women at childbirth or postpartum	Code
1. No mention	0
2. Specific for Children	1
3. Specific for women and/or disorders at childbirth or postpartum	2
Acute disorder	
1. No mention	0
2. No, chronic disorder	1
3. Yes, acute disorder	2
4. Yes, injury or trauma	3
5. Yes, *shang han* (generally refers to acute conditions)	4
Haemoptysis	
1. No mention	0
2. No haemoptysis	1
3. Yes, indicated for haemoptysis	2

4.4.6 Global score

Citations were judged as a whole with reference to all the details, including index and entry terms, formula ingredients, use, indication and any other information. They were given a global score to rank their likelihood of being similar to COPD [Table 14]. The scores were: 0 ‘not enough information to decide’; 1 ‘other disease unlike COPD’; 2 ‘possibly COPD’; 3 ‘possible complication of COPD’; or 4 ‘most likely COPD’.

Two independent reviews judged the citations. One reviewer was an experienced Chinese medicine practitioner and the other an experienced researcher in Classical Chinese literature.

Table 14: Scoring system for the global score

Description	Global score
1. Not enough information to decide	0
2. Other disease unlike COPD	1
3. Yes, possible COPD	2
4. Yes, possible complication of COPD (for example right heart failure, lower limb oedema, cyanosis, or weight loss)	3
5. Yes, most likely COPD	4

4.4.7 Data analysis

Source data was entered into Microsoft® Excel spread sheets. The data was then prepared and entered into SPSS (IBM® SPSS® Statistics Version 20, 2010) for statistical analysis. Descriptive data was converted to numeric entries and each formula and herb was identified by a code. For example, the herbal formula *Da fu pi san* was assigned the code 343 as per existing data sets developed by Dr Brian May, RMIT University (unpublished). The century and dynasty of the citation was also coded.

Frequencies of formulae and herbs were evaluated from the total data set. Duplicate entries and those from modern books (post 1949) were excluded from further analysis.

Citations that were not consistent with COPD were excluded in a stepwise fashion. Citations referring to women's disorders, postpartum conditions or children were excluded, followed by citations referring to acute conditions. Finally, citations referring to haemoptysis were excluded.

Frequencies of formulae and herbs were calculated at each step and evaluated against the six COPD symptoms. The six search terms referred to in the search strategy were also cross-linked to the six COPD symptoms.

Citations were grouped in levels of specificity according to their strength and likelihood of being consistent with COPD. The levels were then compared with the global scores. To ensure consistency lists of the most frequent formulae and herbs were generated from citations showing higher levels of consistency with COPD.

4.5 Results

4.5.1 Search results

In total 1,557 entries were extracted from the ZYFJDCD. After exclusion of modern books (post 1949) and duplications (*n*= 65), there were 1,492 formulae citations and 513 distinct herbs within the formulae. Two hundred and seven (207) distinct books located the citations, written from A.D. 206 to 1949. The earliest book was the *Shang Han Lun* c. A.D. 206 and the most recent book was the *Xiao Er Zhu Re Bian* published in 1949.

The search term *ke chuan* located the majority of citations (*n*=796), followed by *chuan zheng* (*n*=500), *jiu ke* (*n*=127), *zhi yin* (*n*=35), *fei zhang* (*n*=27) and *jiu chuan* (*n*=7) [Table 15]. On inspection of the citations, dyspnea was mentioned in 982 citations, the term s*hang qi* in 294, cough in 862, sputum production in 319, chest tightness in 297 and *fei zhang* in 32.

Table 15: Number of citations located by each search term

Search term	Number of citations
ke chuan	796
chuan zheng	500
jiu ke	127
zhi yin	35
fei zhang	27
jiu chuan	7
Total	1,492

4.5.2 Results after exclusions

To refine the data set it was necessary to exclude citations not consistent with COPD, these were:

- women's disorders, postpartum conditions or children's disorders (*n*=119)
- acute or other unrelated disorders (*n*= 156)
- haemoptysis (*n*= 70).

After exclusions, the total number of formulae citations was 1,147 derived from 180 books written from A.D. 206 to 1937. The included formulae were composed of 455 distinct herbs, with an average of 8.6 herbs per formula.

Figure 16 presents the flowchart of citation selection.

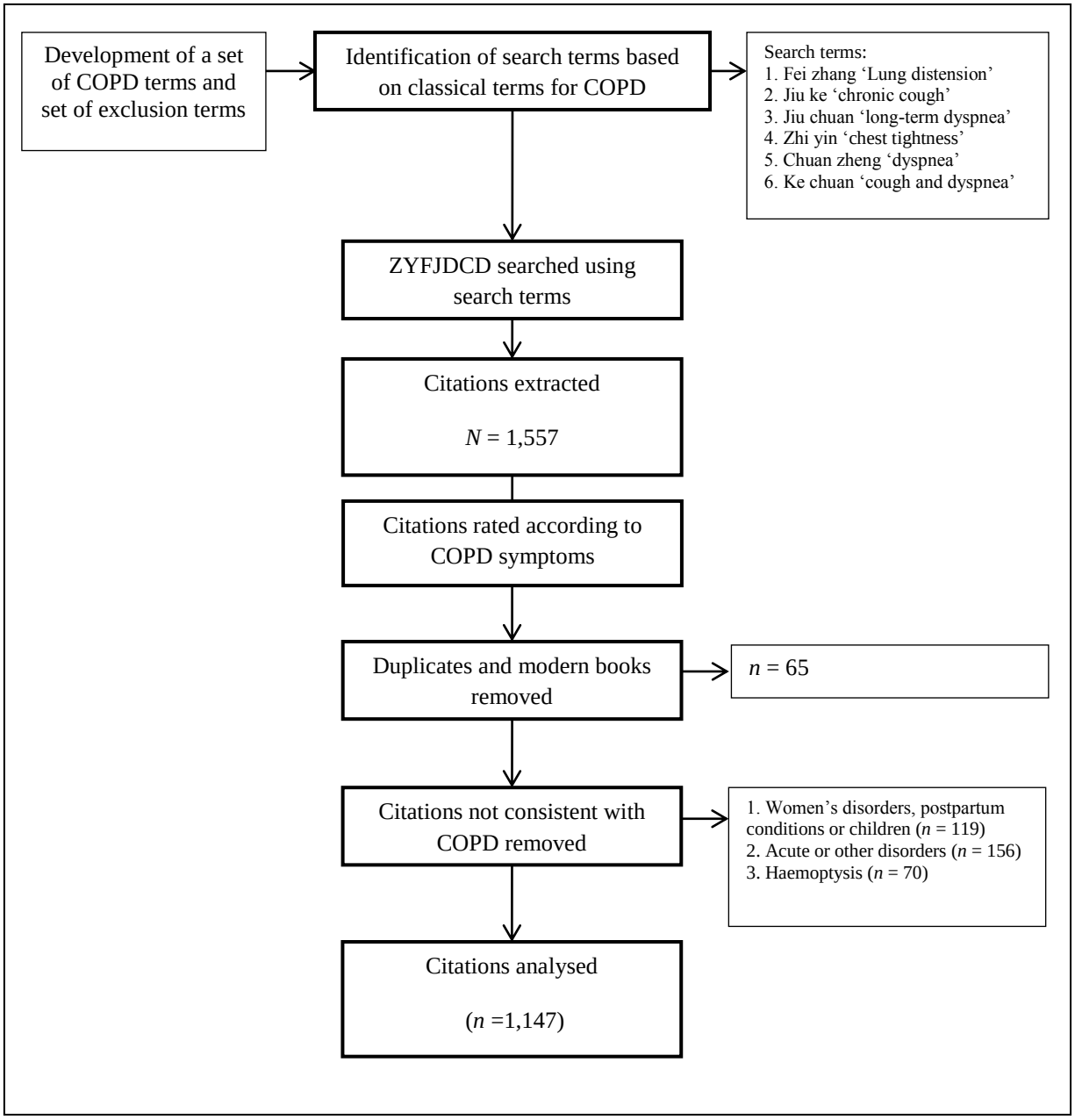


Figure 16: Flowchart of citation selection

4.5.3 Characteristics of citations

The data set after exclusions comprised 1,147 citations each comprising a single formula that was indexed as applicable when treating at least one of the search terms. There were 902 distinct formulae and 426 distinct herbs within the formulae. Table 16 presents the data.

Table 16: Characteristics of citations after exclusions

Total number of formulae	Number of distinct formulae[a]	Number of herbs	Number of distinct herbs[a]	Search term frequencies					
				fei zhang	jiu ke	jiu chuan	zhi yin	chuan zheng	ke chuan
1,147	902	9,863	426	22	105	6	35	413	566

[a] Distinct formulae and herbs refers to the number of different formulae and herbs represented.

4.5.3.1 Frequency of formulae

The frequency of formulae are summarised in Table 17. The formulae are listed with their ingredients and the number of citations. The top three formulae were referenced on 10 or more occasions. Shen qi wan(2) was the most frequent formula (n=16). It was first mentioned in the Jin Gui Yao Lue c. A.D. 206. It contains eight herbs and treats chronic conditions, with the ability to warm the body and tonify the Kidney. The second most frequently used formulae were Mai men dong tang(1) (n=10) and Xiao qing long tang(2) (n=10). Mai men dong tang(1) first appeared in Wai Tai Mi Yao c. A.D. 752 it is used to treat the Lung and is indicated for cough, wheezing, and phlegm. Xiao qing long tang(2) first appeared in the Shang Han Lun c. A.D. 206. It is used for coughing and descends the flow of Qi and warms the Lung, although it is commonly used for acute conditions it can also be used for chronic conditions (81).

Table 17: Most frequent formulae

Rank	Formula name	Name of herbs in the formula	Frequency
1	Shen qi wan (2)	Gan di huang, Shan yao, Shan zhu yu, Ze xie, Fu ling, Mu dan pi, Gui zhi, Fu zi. Cooked with honey and taken with rice wine.	16
2	Mai men dong tang (1)	Mai men dong, Ban xia, Ren shen, Gan cao, Ji mi, Da zao	10
3	Xiao qing long tang (2)	Ma huang, Shao yao, Xi xin, Gan jiang, Gan cao, Gui zhi, Wu wei zi, Ban xia	10
4	Wu ji san	Cang zhu, Jie geng, Zhi qiao, Chen pi, Shao yao, Bai zhi, Chuan xiong, Dang gui, Gan cao, Rou gui, Fu ling, Ban xia, Hou pou, Gan jiang	6
5	Ze xie tang	Ze xie, Bai zhu	5
6	Si mo tang	Ren shen, Bin lang, Chen xiang, Wu yao	5
7	Si mo yin	Wu yao, Zhi shi, Bin lang	5
8	Guan yin ren shen hu tao tang	Ren shen, Hu tao rou	5
9	Jiu bao san	Da fu pi, Rou gui, Gan cao, Zi su, Xing ren, Sang bai pi, Ma huang, Chen pi, Bo he, Wu mei, Gan jiang.	5
10	Ze xi tang (1)	Ban xia, Zi shen, Ze qi, Sheng jiang, Bai qian, Gan cao, Huang qin, Ren shen, Gui zhi	5
11	Du qi wan	Shu di huang, Shan yao, Shan zhu yu, Mu dan pi, Ze xie, Bai Fu ling, Wu wei zi	5
12	Yi shi li yu tang	Xing ren, Bei mu, Rou gui, Ju pi, Ren shen, Zhi gan cao, Zhi hou po, Ma huang, Fu ling, Hu ma, Bai qian, Sheng jiang, Ban xia. Cook carp together with herbs and take out the fish in the end.	4
13	Sheng xian tang	Huang qin, Zhi mu, Chai hu, Jie geng, Sheng ma	4
14	Liu mo yin	Zhi qiao, Bin lang, Wu yao, Ren shen, Mu xiang, Chen xiang	4
15	An shen wan (1)	Rou gui, Wu yao, Tao ren, Bai ji li, Ba ji tian, Shan yao, Fu ling, Zhi Rou cong rong (soaked in rice wine), Zhi shi hu, Bi xie, Bai zhu, Po gu zhi. Cook with honey.	4
16	Zhen wu tang	Fu ling, Shao yao, Sheng jiang, Bai zhu, Fu zi	4
17	Wu hu tang	Ma huang, Xing ren, Gan cao, Shi gao	4
18	Zi su zi tang (2)	Zi su zi, Ban xia, Qian hu, Hou po, Gan cao, Dang gui, Ju pi, Da zao, Sheng jiang, Rou gui	4

Note: To distinguish formulae with the same name but different herbal ingredients a number has been placed next to them. For example, the data set contained four formulae named Mai men dong tang, all with different ingredients. Therefore, they are distinguished by placing a number next to their name.

4.5.3.2 Frequency of herbs

Table 18 presents the top 20 most frequently cited herbs. The citations did not indicate which herbs in a formula were specific for COPD and which were used for other reasons. The highest frequency items were ginger, *jiang (Zingiber officinale)* and licorice, *gan cao (Glycyrrhiza uralensis).* Although these herbs were commonly used in the citations, they were not necessarily specific for Lung conditions.

Certain herbs are added during the preparation of formulae but are not part of the main ingredients. The data were further analysed to evaluate the most frequently cited herbs after the exclusion of added herbs, results are presented in Table 19. From the table it is clear that excluding added herbs changed the order of their frequencies. It revealed that *feng mi* 'honey' was no longer included in the top 20 herbs. Honey is often used in the preparation of herbal pills and is not part of the formula itself. Additionally *da zao* was no longer in the top 20 herbs, which is often added during the decoction process in many formulae. The high frequency of *gan cao* may be due to its generic use in most formulae. Traditionally it is used to harmonise the other ingredients and often does not have a specific action for the condition being treated (81). Typically *ban xia* is used with ginger, *sheng jiang*, they are combined to harmonise each other. Therefore the use of *sheng jiang* for respiratory conditions may not be specific (81).

Therefore after the removal of non-specific herbs the six most frequently cited herbs were *xing ren* (*n*=386), *ban xia* (*n*=314), *ren shen* (*n*=283), *sang gen bai pi* (*n*=256), *wu wei zi* (*n*=214) and *ma huang* (*n*=202).

Xing ren, dried apricot seed (*Prunus armeniaca*) was first mentioned in formulae in the *Shang Han Lun* c. A.D. 206. It is indicated for coughing and is able to dissipate phlegm. The second most frequent herb was *ban xia*, (*Pinellia ternate*) its main function is to remove phlegm and is indicated for cough with copious sputum (81). *Ban xia* is slightly toxic in the raw form and is therefore processed into *zhi ban xia*. *Ren shen*, Ginseng root (*Panax ginseng*) was the third most frequent herb. It was first mentioned in formulae in the *Jin Gui Yao Lue* c. A.D. 206. In comparison to *Xing ren* and *ban xia, ren shen* functions to tonify the Lung and strengthen the body, therefore it is indicated for Lung conditions, particularly chronic Lung conditions (81). Other frequently cited herbs include *sang gen bai pi,* mulberry bark (*Morus alba*) which is indicated for cough and wheeze and is particularly useful for phlegm and heat in the Lung (81). *Wu wei zi*, (*Schisandra chinensis*) is used to treat cough, particularly chronic cough and finally *ma huang,* ephedra stem (*Ephedra sinica*) which is predominantly indicated for wheezing and asthma.

Table 18: The 20 most frequently cited herbs

Rank	Scientific name	Chinese name	Frequency
1	*Zingiber officinale* (fresh or dried rhizome)	Gan jiang/Sheng jiang	642
2	*Glycyrrhiza uralensis* or *G. glabra* (dried root)	Gan cao	538
3	*Prunus armeniaca* (dried seed)	Xing ren	386
4	*Pinellia ternata* (dried processed rhizome)	Ban xia (zhi)	314
5	*Poria cocos* (dried sclerotium)	Fu ling	294
6	*Citrus reticulata* or *C. tangerine* (dried peel)	Chen pi	289
7	*Panax ginseng* (dried root)	Ren shen	283
8	*Morus alba* (dried bark)	Sang gen bai pi	256
9	*Cinnamomum cassia* (dried bark)	Rou gui/Gui zhi	246
10	Honey	Feng mi	217
11	*Schisandra chinensis* (dried fruit)	Wu wei zi	214
12	*Perilla frutescens* or *P. crispa* (dried herb)	Zi su geng/Zi su zi/Zi su ye	203
13	*Ephedra sinica* (dried herb)	Ma huang	202
14	*Ziziphus jujuba* (dried fruit)	Da zao	182
15	*Platycodon grandiflorum* (dried root)	Jie geng	156
16	*Tussilago farfara* (dried flower)	Kuan dong hua	148
17	*Aster tartaricus* (dried root)	Zi wan	146
18	*Fritillaria cirrhosa* (dried rhizome)	Bei mu	143
19	*Citrus aurantium* (dried fruit)	Zhi shi	140
20	*Ophiopogon japonicus* (dried rhizome)	Mai men dong	130

Table 19: The 20 most frequently listed herbs after exclusion of added herbs

Rank	Scientific name and part used	Chinese name	Frequency
1	*Glycyrrhiza uralensis* or *G. glabra* (dried root)	Gan cao	533
2	*Prunus armeniaca* (dried seed)	Xing ren	382
3	*Pinellia ternata* (dried processed rhizome)	Ban xia (zhi)	314
4	*Zingiber officinale* (fresh or dried rhizome)	Gan jiang/Sheng jiang	303
5	*Poria cocos* (dried sclerotium)	Fu ling	293
6	*Citrus reticulata or C. tangerine* (dried peel)	Chen pi	285
7	*Panax ginseng* (dried root)	Ren shen	277
8	*Cinnamomum cassia* (dried bark)	Rou gui/Gui zhi	246
9	*Morus alba* (dried bark)	Sang gen bai pi	231
10	*Schisandra chinensis* (dried fruit)	Wu wei zi	213
11	*Ephedra sinica* (dried herb)	Ma huang	202
12	*Perilla frutescens* or *P. crispa* (dried herb)	Zi su geng/Zi su zi/Zi su ye	192
13	*Platycodon grandiflorum* (dried root)	Jie geng	156
14	*Tussilago farfara* (dried flower)	Kuan dong hua	148
15	*Aster tartaricus* (dried root)	Zi wan	144
16	*Fritillaria cirrhosa* (dried rhizome)	Bei mu	142
17	*Citrus aurantium* (dried fruit)	Zhi shi	140
18	*Ophiopogon japonicus* (dried rhizome)	Mai men dong	127
19	*Atractylodes macrocephala* (dried rhizome)	Bai zhu	117
20	*Rehmannia glutinosa* (dried root)	Di huang/ Shu di huang/ Sheng di huang/ Gan di huang	102

Note: Herbs were 'recoded' to combine cases that were the same species, yet prepared differently. For example, gan jiang is the dried form of sheng jiang therefore they were grouped. Scientific names are referenced from: Bensky, *Chinese herbal medicine: materia medica*, 2004 (81).Added herbs are those that are not included in the core herbal formula however are added during or at the end of decoction. For example, da zao is generically used in many formulae to harmonise the other ingredients and often it does not have a specific action for the condition being treated.

4.5.4 Botanical identity of herbs

The citations extracted from the ZYFJDCD are from classical texts. The scientific names of the herbs are not listed in the classical literature therefore the scientific names were referenced from modern CM materia medica books (81). Accurately describing the botanical identity is not always straightforward. For instance, *Perilla frutescens* and the variety *Perilla crispa* are difficult to distinguish when referencing the classical literature alone. To alleviate the confusion, herbs that were from a similar species or from the same species but prepared differently were combined and recoded in the data set. For example, dried *jiang* (*gan jiang*) and fresh *jiang* (*sheng jiang*) were grouped and recoded into one item. In Table 18 and Table 19, the herbs are listed together if they are from the same species but prepared differently.

4.5.5 Distribution of data by historical period

The frequency of formulae citations and books are grouped according to dynastic period in Table 20, and by century in Figure 17. In the early periods, a small number of books dominated and located many of the formulae citations. For instance before the Tang Dynasty the 67 citations were from three books, *Shang Han Lun, Jin Gui Yao Lue* and the *Zhou Hou Bei Ji Fang*. This was expected as large classical books predominated over certain periods (133).

Table 20: Number of formulae citations and books grouped by dynastic period

Dynastic period[a]	Number of formula citations		Number of distinct books
	Full data set	After exclusions	
Before Tang Dynasty (before 618)	78	67	3
Tang and 5 Dynasties (618–960)	127	90	4
Song and Jin Dynasties (961–1271)	666	503	36
Yuan Dynasty (1272–1368)	39	32	9
Ming Dynasty (1369–1644)	340	267	50
Qing Dynasty (1645–1911)	206	161	69
Republic of China (1912–1949)	37	27	10
Modern (1950 onwards)	64	0	0
Total	1,557	1,147	181

[a] The dynastic periods were allocated a historical period to remove overlapping years.

The majority of formulae were cited from the Song Dynasty (961–1271) followed by the Ming Dynasty (1369–1644). During the Song Dynasty medical publishing expanded. Major medical classics were edited and published for wide-spread distribution (135). Most notably the Song Dynasty delivered the first official medical encyclopaedia the *Sheng Ji Zong Lu*, covering diverse aspects of medicine with references to approximately 20,000 formulae (135). After the Song Dynasty new medical works dropped off until the Ming Dynasty when a number of works were produced, including the famous *Ben Cao Gang Mu* (124).

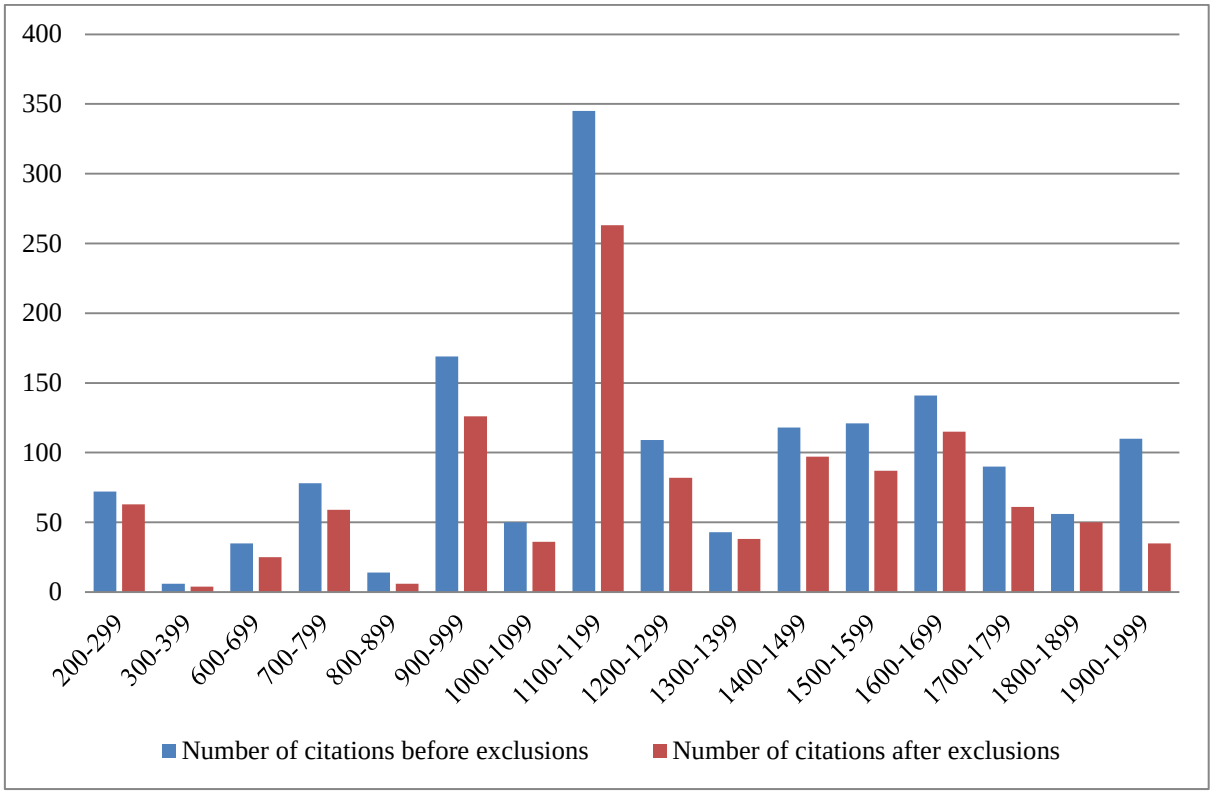


Figure 17: Formula grouped by century of publication before and after exclusions

The years 1100–1199 produced the most citations. This period includes the Song and Jin Dynasties. As mentioned above, during this period medical publishing expanded. There was no real difference between the data set before and after exclusions. One noteworthy difference was in the period from 1900–1999. Citations after 1949 were excluded, therefore the number of formulae after exclusions was greatly reduced compared to before exclusions.

4.5.5.1 Search terms

All the search terms were productive in locating citations. *Ke chuan* located the majority of citations, followed by *chuan zheng, jiu ke, zhi yin, fei zhang* and *jiu chuan.* The frequency and use of the search terms has changed over time. Figure 18 presents the distribution of terms.

Ke chuan 'cough and dyspnea' was the most productive in locating relevant citations and it was used throughout the whole data set. *Chuan zheng* 'dyspnea' was seldom used before A.D. 800. After this time, it peaked until 1200 then peaked again after 1400. *Zhi yin* 'chest tightness' was first mentioned in 200–299 but not again until 900–999 and then seldom used in the remaining centuries. *Jiu chuan* 'long-term dyspnea' was not used until 1100–1199. *Jiu ke* 'chronic cough' was similarly used from A.D. 800 onwards. Then use dropped off from 1700 in favour of *ke chuan* and *chuan zheng.*

Fei zhang 'Lung distension' and *chuan zheng* 'Panting pattern' are considered the translational terms for COPD (129). It was thought these terms would match the classical literature and be able to locate citations similar to what is known today as COPD. This was not the case for *fei zhang,* which was rarely used. It located only a minimal number of citations predominantly from 1400 onwards. *Chuan zheng* was more successful in locating relevant citations and was used throughout the historical periods.

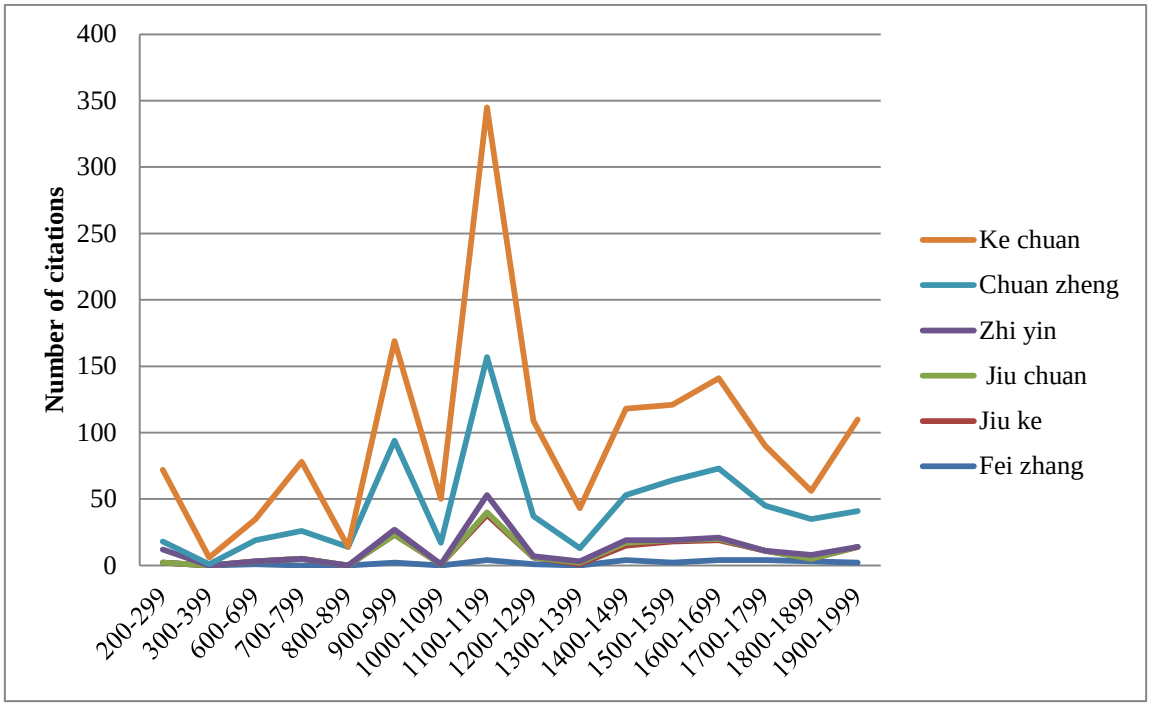


Figure 18: Distribution of search terms by century

4.5.5.2 Frequency of search terms and symptoms

Table 21 presents the frequencies of the six search terms and six symptoms. Dyspnea and cough were the most frequent symptoms. Dyspnea was referenced in 776 out of the 1,147 citations (67.7%), cough 648 (56.5%), sputum production 252 (21.9%), chest tightness 236 (20.6%), *shang qi* (19.9%), and *fei zhang* 23 (2%). *Shang qi* appears to have a similar meaning to 'dyspnea'. In the case of *fei zhang*, its meaning as a symptom is less clear. 'Lung distension' is the term provided by modern medical references however the meaning appears similar to 'chest tightness' (129).

Table 21: Frequency of search terms against symptoms

Symptom	Number of citations					
	Fei zhang	Jiu ke	Jiu chuan	Zhi yin	Chuan zheng	Ke chuan
1. Dyspnea						
No mention	8	91	1	24	96	151
No	0	0	0	0	0	0
Dyspnea	12	14	5	11	315	414
Worse with exercise	2	0	0	0	2	1
Severe dyspnea	0	0	0	0	0	0
2. *Shang qi* 'difficulty breathing'						
No mention	17	96	5	30	304	466
Yes	5	9	1	5	109	100
3. Cough						
No mention	11	1	5	25	374	83
No	0	0	0	0	0	0
Yes	11	2	0	10	37	462
Chronic or long term cough	0	102	1	0	2	21
4. Sputum production						
No mention	20	92	5	33	326	380
No	0	1	0	0	0	1
Yes	0	6	1	1	69	165
Chronic sputum production	0	6	0	0	1	3
CM phlegm syndrome	2	0	0	1	17	17
5. Chest tightness						
No mention	17	98	6	21	321	448
No	0	0	0	0	0	0
Yes	5	7	0	14	92	118
6. *Fei zhang* 'Lung distension'						
No mention	2	105	6	35	410	563
Disease	9	0	0	0	0	0
Symptom	9	0	0	0	3	2
Not sure	2	0	0	0	0	1
Total	132	630	36	210	2478	3396

The data was consistent with the expectation that when a search term located a formula the indications of that formula would match the search term. However, there were some anomalies. For example, one citation was indexed under the term *jiu chuan* 'long-term dyspnea' yet the indication for use made no mention of dyspnea. However it was

indicated for '*shang qi'* which is a similar term for dyspnea. Furthermore, 96 citations indexed under *chuan zheng* 'dyspnea' did not mention dyspnea as an indication. Fifty-six (56) did mention *shang qi.* The reasons for the remaining 40 citations indexed under *chuan zheng*, may include variations in the indexing authors' definitions and interpretation of terms, predominately overlap with terms such as choking (*zhi xi*, 窒息) or throat blockage (*yan hou zu sai*, 咽喉阻塞) and tachypnea (*hu xi ji cu*, 呼吸急). These terms could be broadly defined as relating to dyspnea but such terms were not included within the scope of 'dyspnea' in our scoring system. There were two occasions when the search term *fei zhang* did not mention the 'symptom' *fei zhang.* Similarly, one citation was indexed under *jiu ke* 'chronic cough' yet it did not mention cough as an indication.

4.5.6 Global score

A global score was used to rank the citations. Forty-nine (49) were ranked as '0', that is, they did not provide enough information to decide, 311 were classified as 'other diseases unlike COPD', 27 were 'possible complications of COPD', 735 were 'possibly COPD' and 25 were 'most likely COPD'.

Table 22 presents the citations ranked as 'possibly COPD' against the search terms that located the citations and the symptoms mentioned in the citations. Table 23 presents the citations ranked as 'complications of COPD' and Table 24 presents the citations ranked as 'most likely COPD'.

The 25 citations that were most likely COPD all referred to different formula. They were derived from 15 books written between c. 992 and 1933. The formulae were made up of 104 distinct herbs and the top 20 herbs are presented in Table 25. *Ke chuan* was the best predictor of the citation being ranked as 'most likely COPD' with 16 out of the 25 (64%) being located by this search term. Dyspnea and cough were better predictors and were referenced in 24 and 22 citations, respectively. *Shang qi* and *fei zhang* were less commonly used, referenced in two and one citations, respectively [Table 24].

Table 22: Citations ranked as 'possibly COPD' by search term and symptom frequency

Search term	Number of citations, (%)	Symptoms[a]	Number of citations, (%)
Fei zhang	17 (2.3%)	Dyspnea	543 (36%)
Jiu ke	89 (12.1%)	Shang qi	150 (10%)
Jiu chuan	5 (0.7%)	Cough	468 (31%)
Zhi yin	13 (1.8%)	Sputum production	180 (12%)
Chuan zheng	249 (33.9%)	Chest tightness	160 (10%)
Ke chuan	362 (49.3%)	Fei zhang (as a symptom)	20 (1%)
Total citations	735	Total citations	735

[a] Several symptoms were often referred to in the one citation.

Citations ranked as 'possibly COPD' (*n*=735) were mostly located by the search term *ke chuan*, 49.3%. *Jiu chuan* was the least successful in locating citations, 0.7%. The majority of citations referenced dyspnea and cough, 36% and 31%, respectively. *Fei zhang* was the least referenced 1%.

Table 23: Citations ranked as 'complications of COPD' by search term and symptom frequency

Search term	Number of citations, (%)	Symptoms[a]	Number of citations, (%)
Fei zhang	1 (4%)	Dyspnea	22 (38%)
Jiu ke	1 (4%)	Shang qi	4 (7%)
Jiu chuan	0 (0%)	Cough	17 (29%)
Zhi yin	5 (18%)	Sputum production	6 (10%)
Chuan zheng	7 (26%)	Chest tightness	8 (14%)
Ke chuan	13 (48%)	Fei zhang (as a symptom)	1 (2%)
Total citations	27	Total citations	27

[a] Several symptoms were often referred to in the one citation.

Ke chuan located the most citations ranked as 'complications of COPD'. Complications include symptoms of right heart failure (*you xin shuai jie*, 右心衰竭), lower limb oedema (*xia zhi shui zhong*, 下肢水肿), cyanosis (*zi gan*, 紫绀), and weight loss (ti zhong xia jiang, 体重下降). The search term *jiu chuan* expectedly did not locate citations in this category as it refers to long-term dyspnea. Similar to citations ranked as 'possibly COPD' [Table 22], the majority of citations referenced dyspnea and cough, 38% and 29%, respectively.

Table 24: Citations ranked as 'most likely COPD' by search term and symptom frequency

Search term	Number of citations, (%)	Symptoms[a]	Number of citations, (%)
Fei zhang	1 (4%)	Dyspnea	24 (33%)
Jiu ke	4 (16%)	Shang qi	2 (3%)
Jiu chuan	0 (0%)	Cough	22 (30%)
Zhi yin	0 (0%)	Sputum production	15 (21%)
Chuan zheng	4 (16%)	Chest tightness	9 (12%)
Ke chuan	16 (64%)	Fei zhang (as a symptom)	1 (1%)
Total citations	25	Total citations	25

[a] Several symptoms were often referred to in the one citation.

Citations ranked as 'most likely COPD' were located by the search term *Ke chuan* in 16 out of the 25 citations, 64%. *Jiu chuan* and *zhi yin* did not locate any of these citations. Although *ke chuan* and *chuan zheng* located the most citations, the hit rate for these terms was not as high as for *fei zhang*. *Fei zhang* had the highest hit rate, from 22 citations in the full data set one was 'most likely COPD', 4.5%, compared to *jiu ke* four from 105, 3.8%, *ke chuan* 16 from 566, 2.8% and *chuan zheng* 4 from 413, 0.9%.

All of the citations referenced dyspnea and 22 out of the 25 referenced cough. This is not surprising as these are the main symptoms associated with COPD. Modern CM texts refer to COPD as two characteristic patterns *fei zhang* and *chuan zheng*. However, the classical literature did not reflect these terms, *fei zhang* only located one citation, and *chuan zheng* located four, much less than expected.

Table 25: The 20 most frequently cited herbs from the 25 citations ranked as 'most likely COPD' and after exclusion of added herbs

Rank	Scientific name and part used	Chinese name	Frequency
1	*Glycyrrhiza uralensis or G. glabra* (dried root)	Gan cao	12
2	*Prunus armeniaca* (dried seed)	Xing ren	11
3	*Zingiber officinale* (fresh or dried rhizome)	Gan jiang/Sheng jiang	7
4	*Citrus reticulata or C. tangerine* (dried peel)	Chen pi	7
5	*Pinellia ternata* (dried processed rhizome)	Ban xia (zhi)	7
6	*Panax ginseng* (dried root)	Ren shen	6
7	*Ephedra sinica* (dried herb)	Ma huang	6
8	*Perilla frutescens* or *P. crispa* (dried herb)	Zi su geng/Zi su zi/Zi su ye	6
9	*Tussilago farfara* (dried flower)	Kuan dong hua	6
10	*Angelica sinensis* (dried root)	Dang gui	4
11	*Poria cocos* (dried sclerotium)	Fu ling	4
12	*Anemarrhena asphodeloides* (dried rhizome)	Zhi mu	4
13	*Citrus aurantium* (dried fruit)	Zhi shi	4
14	Alunite	Bai fan	4
15	*Arisaema heterophyllum* or *A. consanguineum* (prepared rhizome)	Dan nan xing/Tian nan xing	3
16	*Paeonia lactiflora* (dried root)	Bai shao	3
17	*Platycodon grandiflorum* (dried root)	Jie geng	3
18	*Asarum heterotropoides* (dried rhizome)	Xi xin	3
19	*Terminalia chebula* (dried herb)	He zi R	3
20	*Atractylodes macrocephala* (dried rhizome)	Bai zhu	2

Note: Herbs were 'recoded' to combine cases that were the same species, yet prepared differently. For example gan jiang is the dried form of sheng jiang therefore they were grouped. Scientific names are referenced from: Bensky, *Chinese herbal medicine: materia medica*, 2004 (81).
Added herbs are those that are not included in the core herbal formula however are added during or at the end of decoction. For example, da zao is generically used in many formulae to harmonise the other ingredients and does not have a specific action for the condition being treated.

The 20 most frequently listed herbs from the 25 citations ranked as 'most likely COPD' were comparatively different to the full data set after exclusions [Table 19]. Restricting the data set cut the frequency of herbs. Thirteen (13) herbs were the same however ranked slightly different. The remaining seven herbs were not included in the full data set top 20. Several herbs relevant to COPD were no longer included, these were, *sang gen bai pi, wu wei zi, zi wan, bei mu,* and *mai men dong.* The herbs included in their place were still applicable for the treatment of COPD. *Dang gui* and *bai shao* are tonics used for chronic conditions, *zhi mu* nourishes the Lung, *bai fan, nan xing, xi xin* and *he zi* remove phlegm and *he zi* stops cough. Therefore, the herbs included in Table 25 are similar to what would be used in modern CM for the treatment of COPD.

4.5.7 Ranking the formulae citations

The citations were organised into levels of strength of specificity according to the four key COPD symptoms: dyspnea, cough, sputum production, and chest tightness. The formula were not ranked using *shang qi* and *fei zhang*. These terms were seldom used in the citations and are often included under the other key symptom terms. A stepwise process was used to ranked the citations and create levels of increasing strength, that is, if they contained dyspnea plus one other symptom, followed by dyspnea plus two other symptoms, and finally dyspnea plus three other symptoms. The levels were refined by limiting the citations to 'chronic' cough or sputum production. Table 26 presents the levels of strength and likelihood the citation refers to COPD.

Table 26: Analysis of strength and likelihood the citation refers to COPD

Level	Inclusion criteria	Number of formulae	Number of distinct formulae	Number of herbs	Number of distinct herbs	Citation year(s)	Global score 4 'most likely COPD' (%)
1	dyspnea + cough	441	426	4,147	363	206-1936	21 (4.8%)
2	dyspnea + sputum production	201	193	1,943	277	206-1929	11 (5.5%)
3	dyspnea + chest tightness	175	170	1,545	211	206-1924	8 (4.6%)
4	dyspnea + cough + sputum production	141	137	1,462	258	206-1892	13 (9.2%)
5	dyspnea + cough + chest tightness	98	97	941	172	206-1863	7 (7.1%)
6	dyspnea + sputum production + chest tightness	54	54	515	133	206-1863	6 (11.1%)
7	dyspnea + chronic cough + sputum production	8	8	84	54	1078-1753	8 (100%)
8	dyspnea + cough + chronic sputum production	4	4	43	34	1172-1687	4 (100%)
9	dyspnea + cough + chronic sputum production + chest tightness	1	1	9	9	1406	1 (100%)
10	dyspnea + chronic cough + chronic sputum production + chest tightness	1	1	17	16	1186	1 (100%)

4.5.7.1 Description of the levels of formulae citations

Levels 1, 2 and 3 capture 441, 201 and 175 formulae citations, respectively. These citations include dyspnea plus one other symptom. The formulae at these levels were numerous however many were not specific for COPD. At level 4, citations included dyspnea plus two other symptoms. Levels 5 and 6 revealed a similar number of citations to level 4. However level 4 was considered to be a more appropriate judge of consistency with COPD as it contained the three key COPD symptoms, dyspnea, cough and sputum production. Changing the second symptom to chest tightness instead of sputum production at level 5 reduced the number of citations but did not increase the specificity. Similarly, at level 6 the number of citations was knocked down yet the specificity did not increase substantially. At these levels, it was difficult to draw any conclusions about the citations consistency with COPD. The citations from levels 1 to 6 had limited consistency with COPD as judged by a global score of 4, 'most likely COPD', at these levels the consistency was below 12%.

At level 4 there was a large number citations, 141 formulae and 258 distinct herbs. The data spanned from c. 206 to 1892 and the top 20 most frequently listed herbs are presented in Table 27. The consistency of citations ranked as a global score of 4, 'most likely COPD' was moderately low, 9.2%. When comparing the frequency of cited herbs at level 4 with the full data set after exclusions [Table 19] the herbs were essentially the same. However at level 4 the frequency was reduced and the 20 herbs were ranked in a different order. When compared to the top 20 herbs ranked as 'most likely COPD' [Table 25] the herbs at level 4 were closer to the full data set.

Table 27: The 20 most frequently listed herbs at level 4 and after the exclusion of added herbs

Rank	Scientific name and part used	Chinese name	Frequency
1	*Glycyrrhiza uralensis* or *G. glabra* (dried root)	Gan cao	75
2	*Pinellia ternata* (dried processed rhizome)	Ban xia (zhi)	59
3	*Prunus armeniaca* (dried seed)	Xing ren	57
4	*Zingiber officinale* (fresh or dried rhizome)	Gan jiang/Sheng jiang	44
5	*Citrus reticulata or C. tangerine* (dried peel)	Chen pi	43
6	*Panax ginseng* (dried root)	Ren shen	39
7	*Schisandra chinensis* (dried fruit)	Wu wei zi	35
8	*Morus alba* (dried bark)	Sang gen bai pi	35
9	*Poria cocos* (dried sclerotium)	Fu ling	33
10	*Perilla frutescens* or *P. crispa* (dried herb)	Zi su geng/Zi su zi/Zi su ye	30
11	*Platycodon grandiflorum* (dried root)	Jie geng	29
12	*Fritillaria cirrhosa* (dried rhizome)	Bei mu	27
13	*Cinnamomum cassia* (dried bark)	Rou gui/Gui zhi	25
14	*Anemarrhena asphodeloides* (dried rhizome)	Zhi mu	25
15	*Ephedra sinica* (dried herb)	Ma huang	23
16	*Atractylodes macrocephala* (dried rhizome)	Bai zhu	22
17	*Tussilago farfara* (dried flower)	Kuan dong hua	22
18	*Aster tartaricus* (dried root)	Zi wan	18
19	*Citrus aurantium* (dried fruit)	Zhi shi	18
20	*Angelica sinensis* (dried root)	Dang gui	17

Note: Herbs were 'recoded' to combine cases that were the same species, yet prepared differently. For example gan jiang is the dried form of sheng jiang therefore they were grouped. Scientific names are referenced from: Bensky, *Chinese herbal medicine: materia medica*, 2004 (81).

Added herbs are those that are not included in the core herbal formula however are added during or at the end of decoction. For example, da zao is generically used in many formulae to harmonise the other ingredients and does not have a specific action for the condition being treated.

4.5.7.2 Description of level 7 formulae citations

The data set was limited as the levels increased and citations became more consistent with COPD. Level 7 refined the citations by specifying ‘chronic’ cough. This produced 100% specificity as measured by the global score but greatly reduced the data set to eight formulae. These citations were consistent with COPD, having symptoms of dyspnea, chronic cough and sputum production. All of the eight formulae were given a global score for 4 ‘most likely COPD’. Table 28 presents the details of the eight formulae. Additionally, Table 29 presents the herbs included in the eight formulae.

There were 50 distinct herbs used in the eight formulae at level 7. They were seldom used more than once. The top 10 herbs are similar to the top 10 at level 4, Table 27. Level 7 is more specific than Level 4, as all citations are ranked as a global score 4 ‘most likely COPD’. However, for herb selection the data set at level 4 is more useful. The frequency of herb references is higher at level 4 and at level 7 only four herbs are referenced more than three times.

Table 28: Analysis of formulae consistent with COPD and satisfying level 7 criteria

Formula	Book title	Book year	Search term	Symptoms	Global score	Indications
Hua lao tang (modified Liu jun zi tang)	Bian Zheng Lu	1687	jiu ke	1. Dyspnea 2. Chronic cough 3. Chronic sputum production	4	This formula is used for disease caused by phlegm. The symptoms are, chronic cough, phlegm that is yellow in colour and congealed in the throat, the airways are not clean and it is hard to expectorate the phlegm.
E jiao san (4)	Yi Xue Ru Men	1575	jiu ke	1. Dyspnea 2. Chronic cough 3. Sputum production	4	This formula is used for symptoms of deficiency of the Lung Qi caused by chronic cough, rapid breathing with phlegm and nausea.
Kuan qi wan (1)	Su Wen Bing Ji Qi Yi Bao Ming Ji	1186	jiu ke	1. Dyspnea 2. Chronic cough 3. Chronic sputum production 4. Chest tightness	4	The formula is used for symptoms of chronic cough and dyspnea with phlegm and oedema caused by lung diseases.
Ren shen run fei wan	Tai Ping Hui Min He Ji Ju Fang	1078	ke chuan	1. Dyspnea 2. Chronic cough 3. Sputum production 4. Chest tightness	4	The formula is used for four indications: 1) deficiency of Lung Qi with cough, dyspnea, rapid breathing, chest fullness, anxiety, thick sputum production and dry mouth; 2) dizziness with loss of vitality; 3) deficiency of Lung and Stomach Qi with chronic cough, weakness, emaciation, chest fullness, shortness of breath, dyspnea with exercise and reduced appetite; 4) chronic or acute cough.
Xian ren zhi wan	Huang Di Su Wen Xuan Ming Lun Fang	1172	ke chuan	1. Dyspnea 2. Chronic cough 3. Sputum production 4. Chest tightness	4	This formula is used for sputum production and dyspnea with chest fullness. It is also used for chronic cough caused by birthing, no matter cold or heat factor.
Ning sou bai hua gao	Huo Ren Fang	1753	ke chuan	1. Dyspnea 2. Chronic cough 3. Sputum production	4	This formula is used for cold phlegm in the Lung with constant phlegm and cough. It is used for chronic paroxysmal dyspnea with cough.
Zhong ru wan (5)	Shi Yi De Xiao Fang	1328	ke chuan	1. Dyspnea 2. Chronic cough 3. Sputum production	4	This formula is used for chronic or acute cough and dyspnea with thick phlegm. The symptoms persist day and night and it is difficult for the patient to lie down.
Xin tian ban xia gua lou wan	Huang Di Su Wen Xuan Ming Lun Fang	1172	ke chuan	1. Dyspnea 2. Chronic cough 3. Chronic sputum production	4	This formula is used for chronic or acute cough with phlegm. There is also non-stop dyspnea with anxiety.

Table 29: Herbs listed at level 7

Number	Chinese name (pin yin)	Frequency
1	Gan cao	5
2	Xing ren	5
3	Ren shen, Zi tuan shen	5
4	Kuan dong hua	4
5	Zhi mu	3
6	Bai zhu	2
7	Fu ling	2
8	Rou gui/Gui zhi	2
9	Chen pi	2
10	Ma huang	2
11	Ma dou ling	2
12	Dan nan xing/Tian nan xing	1
13	Gou qi zi	1
14	Chai hu	1
15	Dang gui	1
16	Shu di huang/sheng di huang/gan di huang	1
17	Ze xie	1
18	Ban xia (zhi)	1
19	Mai men dong	1
20	Di gu pi	1
21	Dan shen	1
22	Bai shao	1
23	Mu li	1
24	E jiao	1
25	Mu xiang	1
26	Jie geng	1
27	Zi wan	1
28	Xuan shen	1
29	Yu li ren	1
30	Bai jie zi	1
31	Xi xin	1
32	Jiang mi	1
33	Qing pi	1
34	Wu mei	1
35	Shi zhong ru	1
36	Fang ji	1
37	Qian niu zi	1
38	Bai fan	1
39	Ge jie	1
40	Qian hu	1
41	Bing lang	1
42	Zi su geng/Zi su zi/Zi su ye	1
43	Nan sha shen/bei sha shen	1
44	Sang gen bai pi	1
45	Hua shi	1
46	E zhu	1
47	Ting li zi	1
48	Gua lour en/ gua lou pi	1
49	Ying su ke	1
50	Shi di	1

4.5.7.3 Description of levels 8 to 10 formulae citations

Four formulae were identified at level 8, dyspnea, plus cough, plus chronic sputum production. The four formulae were given a global score for 4 ‘most likely COPD’. Level 8 contained the formulae identified at level 7 minus four formulae that did not mention chronic sputum production.

Only one formula was associated with level 9, dyspnea, plus cough, plus chronic sputum production, plus chest tightness. The global score was ranked as 4 ‘most likely COPD’. The formula is named *Qing jin dan* which contains nine herbs. It is indicated for ‘cough and dyspnea with sputum, chronic phlegm accumulation, stabbing pain in the chest and hypochondria as well as epigastric distension and a choking sensation in the throat’.

At level 10 one formula was identified, it was ranked as 4 ‘most likely COPD’. The formula is named *Kuan qi wan* and contains 17 herbs. The formula is indicated for ‘chronic cough and dyspnea with phlegm and oedema caused by *Lung Qi deficiency*’.

4.6 Discussion

Search and analysis of the classical literature is a relatively new approach developed in the last few years (125). The method was developed at RMIT University by experts in the field.

The search revealed a considerable number of classical literature citations for conditions consistent with COPD. The exclusion criteria were effective in removing non-specific citations and the search terms accurately located relevant formulae. *Ke chuan* and *jiu ke* were successful in locating many citations that were most likely COPD. *Fei zhang* is considered the modern term for COPD, however the search terms *ke chuan* and *jiu ke* located the most citations. When evaluating the hit rate of the terms against those that were ranked as 'most likely COPD', *fei zhang* had the highest hit rate, followed by *jiu ke, ke chuan,* and *chuan zheng*. *Jiu chuan* and *zhi yin* did not locate any citations that were most likely COPD. At level 7 there were eight citations consistent with COPD, they were located by *ke chuan* and *jiu ke.* This confirms that these terms were the most productive in the classical literature for identifying citations that were most likely COPD.

Duplicate formulae were seldom found and it was difficult to analyse the formulae data in detail or draw any firm conclusions for which formulas were more or less commonly used. The analysis of the individual herb frequencies was more productive in informing the researchers of what treatments were used for conditions broadly consistent with COPD. The citations did not include which herbs were specifically used for COPD, therefore pharmacopoeias were used to reference the indications of the herbs (81). The

formulae and herbs are similar to what is in modern use (81, 136). According to pharmacopoeias, many of the 20 highest frequency herbs are indicated for COPD. These include *xing ren, ban xia, ren shen, kuan dong hua and sang gen bai pi.*

While, a number of formulae were indicated for conditions broadly consistent with COPD, the classical literature is limited in its description of symptoms and detailed information is not provided. For example, details of the severity and stage of symptoms and the possible cause are not included. Therefore, the citations could not be aligned to stable COPD or exacerbated COPD and there was no way to decipher if the citations referred to comorbid conditions such as asthma or tuberculosis. The inferences made in the retrospective analysis of the classical literature is limited, however conditions broadly consistent with COPD were treated throughout the historical period from c. A.D. 206 –1949.

Smoking is the major risk factor for COPD and although citations were broadly consistent with COPD it is difficult to find any representative data of the possible rates of smoking historically. Smoking is prevalent today, however an assumption cannot be made regarding its ancient use. Indoor air pollution including biomass smoke from stoves run by wood, coal or animal dung may be a more likely risk factor in ancient times. This may be an explanation of citations consistent with COPD, despite limited knowledge of smoking rates.

4.6.1 Limitations

The classical literature is vast. This search and analysis was only conducted on one published collection and the type and scope of the search was limited to six select terms. The ZYFJDCD is comprehensive and representative of a wide range of books across the span of eras yet it is not all-inclusive and the data does not represent all the possible books available.

Searching classical literature is productive if the disease has identifiable classical terms. Defining search terms can be an issue as terms change over time. The search terms used in this review are the best match and aligned with classical terms. However, citations may have been missed or incorrectly included due to interpretation when indexing the ZYFJDCD.

The formulae citations listed in the ZYFJDCD are often brief. Some data including book titles and year were difficult to determine. Two experienced reviewers manually extracted the data. This offered a buffer for mistakes however misinterpretation or mistakes may have occurred. Overall these limitations should be few and not affect the data in a significant way or change the overall data set.

4.6.2 Summary of findings

The search terms were able to locate citations in the ZYFJDCD that were consistent with COPD. The data was distributed throughout the classical literature from A.D. 206 to 1949. The majority of citations were extracted from books written/published in the Song and Jin Dynasties (961–1271). However, each term also located numerous citations that were inconsistent with COPD.

After the application of exclusion criteria, 1,147 citations remained. Three formulae were frequently used, *Shen qi wan, Mai men dong tang and Xiao qing long tang* with the remaining not being used on more than five occasions. The top 20 herbs were sometimes non-specific for lung conditions however after the removal of herbs that were non-specific, six herbs recurred frequently: *xing ren, ban xia, ren shen, sang gen bai pi, wu wei zi* and *ma huang.*

Twenty-five (25) citations were most likely COPD as judged by the global score. After ranking citations into levels of specificity, eight were broadly consistent with COPD. These approaches agreed in that all eight citations located using the ranking method were also classified as 'most likely COPD' using the global scoring method. Terms for dyspnea and cough were referenced in all these citations. The relevant citations were mostly located by the search terms *ke chuan* and *jiu ke.*

Formulae and herbs identified in this review are similar to what is used in modern clinical manuals and in clinical trials for COPD (8, 129). Recent systematic reviews identified herbal formulae effective in treating COPD (8, 9, 66). The formulae names

are different to what was identified in this review however there were commonalities in the herbal ingredients, including: *ren shen, wu wei zi, xing ren, ban xia, and sang bai pi.*

Ren shen was one of the most commonly used herbs in the classical literature for COPD. It is one of the most commonly researched CHM for COPD (8, 9). Studies have shown a promising effect on improving lung function and quality of life (9, 66). Combined with herbs such as *xing ren* and *wu wei zi, ren shen* has often been used in clinical trials (66).

Huang qi is recommended for use in COPD (129). The search of the classical literature did not identify *huang qi* as a common herb for conditions consistent with COPD. *Huang qi* is often a substitute for *ren shen*, it grows quicker, is hardier and is thus less expensive (83). In the historical periods *ren shen* may have been more readily available and cheaper compared to today, therefore a substitute such as *huang qi* was not needed.

4.7 Conclusions and implications

The search and analysis of the traditional literature revealed many citations that were broadly consistent with COPD. The method used was rational and systematic and the search terms were able to locate relevant formulae and herbs. The results indicate that the formulae and herbs used in the classical literature were broadly similar to what is used in the modern setting. This group of herbs may guide further clinical and experimental research.

Chapter 5: Systematic reviews on *Panax ginseng* for COPD

5.1 Foreword

This chapter provides three reviews. These include, an overview of preceding systematic reviews, a systematic review of *Panax ginseng* in RCTs, and a review of the effect of *Panax ginseng* on reducing inflammation and oxidative stress and the possible implications for COPD.

5.2 Introduction

Health care policy makers, practitioners and consumers require evidence to make informed choices. Systematic reviews are important in health care to provide a snapshot of the evidence as well as identifying limitations in the literature.

Standardised methods are applied when systematically reviewing the literature to limit bias, critically appraise, synthesise, and address specific questions. Commonly systematic reviews include a set of predefined inclusion criteria used to search databases and literature sources. Studies are identified, analysed and judged for their quality and risk of bias. Synthesis and précis of results often include meta-analysis to combine studies (137).

Poor reporting in systematic reviews is common (137). Organisations and collaborations have endeavoured to guide and standardise the processes of conducting systematic reviews, one well regarded method is the Cochrane Collaborations Handbook for systematic reviews of interventions (13). It also includes a risk of bias tool that is

comprehensive and addresses six domains of bias and is more rigorous than other published tools, particularly those that use a scoring system.

5.3 Overview of systematic reviews on Ginseng

5.3.1 Objective

The objective of this overview was to review systematic reviews and evaluate the effects of *Panax ginseng* for any health condition.

5.3.2 Search strategy

A literature search was conducted to identify systematic reviews of the effectiveness and safety of *Panax ginseng* for any health condition. Databases searched were MEDLINE, EMBASE and the Cochrane Library. The search period ranged from the databases' inception until 5 October 2012. Search terms used were *Panax ginseng*, Ginseng, Panax, Red Ginseng, Korean Red Ginseng and review, systematic review, meta-analysis.

Studies published in English were included. Systematic reviews were defined as articles that included a clear and repeatable methodology. Non-systematic reviews were excluded.

5.3.3 Data extraction

Details from the included studies were extracted onto data collection forms set up in Microsoft® Excel.

5.3.4 Quality assessment

The quality of the included systematic reviews was assessed using the assessment of multiple systematic reviews tool (AMSTAR) (138). There are more than 20 tools that assess systematic review methodology (139). Many are not used widely as they are complicated, lengthy and out of date. The AMSTAR was developed to improve shortfalls in previous tools and limit bias, therefore it was selected in this review (138). Each systematic review was evaluated against the 11 items. The items were recorded as; included, not included or cannot answer. Overall quality was evaluated as a percentage, where higher percentage equates to better quality, that is, 100% indicates all items were reported.

5.3.5 Results

The search revealed 247 articles, of which 234 were excluded. Thirteen (13) systematic reviews met the inclusion criteria [Figure 19]. Health conditions examined were COPD (66), cardiovascular risk factors (140), quality of life (141), cognition (122), blood pressure (142), ischemic heart disease (143), erectile dysfunction (144), type 2 diabetes (145), Alzheimer's disease (146), any health condition (11, 147, 148) and safety (95). Table 30 presents the systematic reviews.

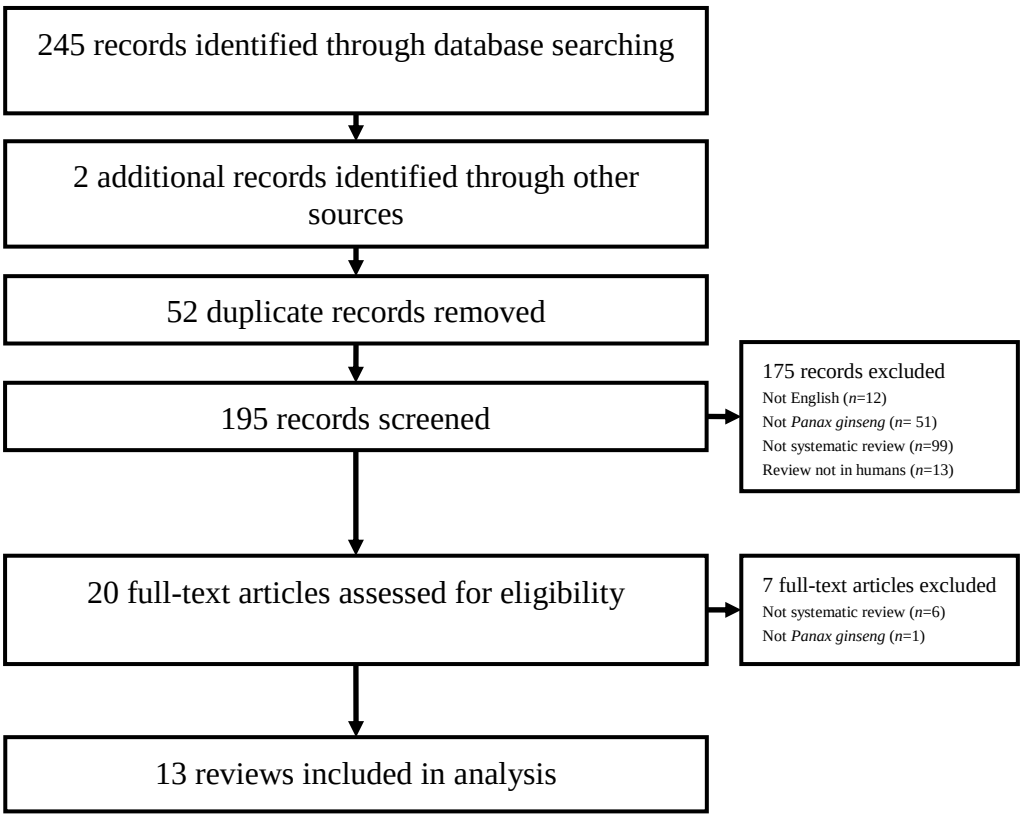


Figure 19: Flow diagram of study selection

Table 30: Systematic reviews of *Panax ginseng*

Author, year (reference)	Health condition	Number of studies	AMSTAR quality score*, %	Conclusion
Jia, 2012 (143)	Ischemic heart disease (angina pectoris)	18	9, 82%	Promising evidence that Ginseng is more effective than nitrates for treating angina pectoris. However studies included in the review had small sample sizes and poor methodological quality.
Shergis, 2012 (11)	Any condition	65	8, 73%	Promising evidence for glucose metabolism and moderating the immune response.
An, 2011 (66)	COPD	12	7, 64%	Promising evidence of lung functions and quality of life improvement. However studies were low quality.
Kim, 2011c (145)	Type 2 diabetes mellitus	4	6, 55%	No compelling evidence despite some positive results.
Lee, 2011 (147)	Any condition	57	4, 36%	Promising evidence for glucose metabolism, psychomotor function, and pulmonary disease, but not for physical performance enhancement.
Geng, 2010 (122)	Cognition	9	11, 100%	Lack of convincing evidence.
Hur, 2010 (142)	Blood pressure in patients with hypertension	5	6, 55%	Limited evidence for the treatment of high blood pressure.
Lee, 2009 (146)	Alzheimer's Disease	2	7, 64%	No compelling evidence.
Jang, 2008 (144)	Erectile dysfunction	7	7, 64%	Promising evidence however no definitive conclusions could be drawn due to small sample sizes and poor methodological quality.
Buettner, 2006 (140)	Cardiovascular risk factors	34	3, 27%	No compelling evidence despite some small reductions in blood pressure.
Coleman, 2003 (141)	Quality of life	9	2, 18%	No compelling evidence despite some positive results.
Coon, 2002 (95)	Safety and adverse events	146	2, , 18%	*Panax ginseng* is rarely associated with adverse events or drug interactions.
Vogler, 1999 (148)	Any condition	16	5, 55%	No compelling evidence for any particular condition.

*Quality score is based on the 11 item AMSTAR tool. High percentage (%) indicates higher quality, where 100% indicates all items were reported.

Three reviews evaluated Ginseng for any health condition or indication (11, 147, 148). All three authors concluded promising findings for Ginseng however, the evidence was not compelling due to poor methodological quality and small sample sizes. One review evaluated Ginseng for COPD (66). The authors reported some promising evidence of improved lung functions and QoL. However, the quality of the RCTs was poor.

Cardiovascular conditions were reviewed in three studies (140, 142, 143). The evidence was limited and the majority of studies had methodological short falls. Type 2 diabetes mellitus was evaluated in one review and the authors reported some positive results however the included studies were heterogeneous prohibiting conclusive results (145). Alzheimer's disease was evaluated in one review (146) and cognition (122) in another. There was a lack of convincing evidence in both reviews despite some positive results. Erectile dysfunction (144) and QoL (141) were evaluated in one review each. Authors' concluded some promising evidence however poor methodological quality prohibited definitive conclusions. Safety of Ginseng was evaluated and Ginseng was rarely associated with adverse events or drug interactions (95).

5.3.5.1 Quality of the included systematic reviews

The quality of the included systematic reviews was variable**.** The AMSTAR ratings ranged from two to 11 (out of a maximum of 11). The mean percentage score was 47%.

The majority of systematic reviews did not report a priori design methods and only two articles reported the likelihood of publication bias (122, 143). However, it should be noted that the majority of authors did not conduct a meta-analysis. All authors provided characteristics of the included studies. A comprehensive literature search was performed in all studies except for one which did not disclose the keywords or terms used to perform the search (147). Only one study provided the list of excluded studies (122). Table 31 presents the AMSTAR analysis of the systematic reviews.

Table 31: AMSTAR analysis of the systematic reviews

AMSTAR items	Jia 2012 (140)	Shergis 2012 (10)	An 2011 (65)	Kim 2011c (142)	Lee 2011 (144)	Geng 2010 (121)	Hur 2010 (139)	Lee 2009 (143)	Jang 2008 (141)	Buettner 2006 (137)	Coleman 2003 (138)	Coon 2002 (93)	Vogler 1999 (145)
1. Was an 'a priori' design provided?	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No
2. Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes
3. Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	Yes
5. Was a list of studies (included and excluded) provided?	No	No	No	No	No	Yes	No	No	No	No	No	No	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
10. Was the likelihood of publication bias assessed?	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No
11. Was the conflict of interest stated?	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No

Note: Yes indicates the item was included in the publication and no indicates the item was not included.

5.3.5.2 Quality of evidence in the RCTs

From the primary data RCTs, the risk of bias and methodological quality was evaluated using the Jadad scale in four reviews (140, 146-148), using the Cochrane risk of bias assessment tool in two (11, 122) and using both the Jadad and Cochrane tools in five (66, 142-145). Risk of bias was not evaluated in two reviews (95, 141). Methodological quality was poor in the majority of RCTs and the risk of bias was mostly unclear or high.

5.3.6 Discussion

This research provides an overview of systematic reviews. *Panax ginseng* has been studied for a broad range of health conditions and indications. From the 13 systematic reviews included, five presented promising efficacy, six lacked convincing evidence and one showed no significant effect. *Panax ginseng* was considered safe. Overall, the included systematic reviews were unable to establish conclusive results.

Pooling of data from RCTs and meta-analysis was not possible in the majority of reviews. Heterogeneity and inconstancy between studies limited the ability to draw firm conclusions.

The methodological quality of the included studies was variable, they were all considered systematic reviews and their methodology was explicit. However, five reviews were considered to have major flaws in that they did not report more than five of the AMSTAR items, seven had minor flaws, reporting between 6–9 items and one review had minimal or no flaws reporting all 11 items.

The methods used to conduct this overview of systematic reviews is in line with the recommendations of The Cochrane Collaboration (13). However, the analysis may have limitations. This overview identified systematic reviews with some methodological shortfalls. Comprehensive searches were conducted however, there is no guarantee that all the relevant systematic reviews were located. Additionally only articles published in English were included. Panax species and *Eleutherococcus senticosus* were combined with *Panax ginseng* in several of the reviews. This approach does not engender conclusive results as different species contain different chemical compositions. Promising finding from several reviews needs careful interpretation due to methodological weaknesses' and risks of bias of the included RCTs. Reviewers found flaws in research design including inadequate reporting of allocation methods, small sample sizes, undisclosed power calculations and inadequate information of the herbal intervention. The extant systematic review literature does not establish the efficacy of Ginseng for a particular health condition or indication. Ginseng does appear to have a good safety profile and is rarely associated with adverse events or drug interactions.

5.3.7 Conclusions and implications

Many systematic reviews have evaluated Ginseng. Despite this, clear indications for clinical use have not been established. The majority of systematic reviews revealed a lack of convincing evidence of efficacy. However, Ginseng was considered safe. Future research should focus on rigorous clinical trial methods for well defined health conditions.

5.4 *Panax ginseng* in randomised controlled trials: a systematic review

5.4.1 Objective

The objective of this systematic review was to summarise the current evidence of *Panax ginseng* in RCTs. *Panax ginseng* was evaluated to determine its efficacy and safety. The methodological quality and risk of bias was also evaluated. The review was designed to identify the most promising areas for future *Panax ginseng* research.

5.4.2 Review protocol

The search and analysis of the literature was predefined by the reviewers. The databases and dates were selected to capture a comprehensive list of articles and the search strategy was designed and tested for sensitivity by two independent reviewers. The eligibility criteria were designed by three reviewers to ensure precision and confidence in the results. The methods presented here are in line with protocol set out prior to implementation.

5.4.3 Method

5.4.4 Search strategy

A systematic search was conducted on four English databases and two Chinese databases.

English databases:

- MEDLINE
- CINAHL

- PsychINFO
- Cochrane library

Chinese databases:

- Wei Pu, www.cqvip.com
- CNKI, www.cnki.net

The search period ranged from the databases' inception until 17 January 2012. Reference lists from the included studies were also searched to identify further publications. Full text articles as well as abstracts were included. Search terms were developed in MEDLINE using medical subject headings (MeSH) and keywords. These terms were modified for the other databases. A combination of synonyms for *Panax ginseng* and RCTs were used, presented in Table 32.

Table 32: Search strategy to identify *Panax ginseng* RCTs in MEDLINE

1.	Panax* or ginseng.tw or *Panax ginseng*.tw or Radix ginseng.tw or ginsan.tw or jen shen.tw or shinseng.tw or renshen.tw or schinseng.tw or ninjin.tw or ginsenoside* or gingilone.tw or protopanaxadiol.tw or protopanaxatriol.tw or ginsenol.tw
2.	*Panax notoginseng** or Eleutherococcus* or Siberian ginseng.tw or American ginseng.tw or *Panax quinquefolium*.tw
3.	1 not 2
4.	Clinical Trials* or Controlled Clinical Trials* or Randomized Controlled Trials* or Clinical Trial.pt or Controlled Clinical Trial.pt or randomized controlled trial.pt or random allocation* or double blind method* or placebos* or randomised clinical trial.tw
5.	3 and 4
(* = MeSH, medical subject heading; tw = text word; pt = publication type [and, or, not are Boolean operators]	

5.4.5 Eligibility of studies

Specific inclusion criteria were:

- randomised studies
- *Panax ginseng* sole preparations as the intervention
- studies using a control group, for example placebo, conventional intervention or no intervention
- studies that stated the intervention was administered orally including capsules liquids or powders

Specific exclusion criteria were:

- *Panax ginseng* combinatorial products
- non-oral preparations, for example injected compounds or suppositories
- compounds extracted from *Panax ginseng*, for example individual ginsenosides.

Studies' outcome measures and design were not restricted. The included studies were published in English or Chinese.

The Chinese databases were searched and translated by an experienced researcher from RMIT University, the contribution of Dr Wenyu Zhou is acknowledged.

5.4.5.1 Participants

Participants were healthy or diagnosed with any type of disease. No restriction was placed on age, gender or other demographics.

5.4.6 Selection of studies

One reviewer assessed all titles and abstracts against pre-defined inclusion criteria, the second reviewer verified the information. A third reviewer resolved any disagreements over a study inclusion.

5.4.7 Data extraction

Details from the included studies were extracted using a standard form (Appendix 1):

Details included:

- first author, year of publication, country where study was conducted
- title
- source of participants
- trial design
- condition treated
- number of participants
- age and gender of participants
- intervention and control
- dosage and treatment duration
- outcomes
- results (mean and standard deviation or number of events)
- adverse events
- authors conclusions

One reviewer extracted the data and the other verified the data against the standard form. Any disagreements were resolved by consensus.

5.4.8 Assessment of risk of bias

For each study, risk of bias was evaluated using the Cochrane Collaboration's Risk of Bias tool, with reference to the Cochrane Handbook (13).

Two reviewers independently extracted information on the six domains of bias (selection, performance, detection, attrition, reporting and other) from seven sources of bias [Table 33]. A third reviewer resolved any disagreements on risk of bias.

For 'other' bias, the chief focus was on the risk of bias due to sources of funding and other support, such as supply of drugs and the role of the funders. Authors were contacted where publications did not provide enough information to judge risk of bias. Nine authors were contacted and three responded (149-151).

Table 33: The Cochrane Collaborations domains and sources of bias

Domain	Source of bias
Selection bias	Random sequence generation Allocation concealment
Performance bias	Blinding of participants and personnel
Detection bias	Blinding of outcome assessment
Attrition bias	Incomplete outcome data
Reporting bias	Selective reporting
Other bias	Other (including baseline imbalance and source of funding)

5.4.9 Assessment of quality method

5.4.9.1 Introduction

As the gold standard of research, RCTs should minimise selection and allocation bias and increase the generalisability of the findings. The reporting of methodology in herbal RCTs is often inadequate (152).

The Consolidated Standards of Reporting Trials (CONSORT) statement and checklist were developed to help improve RCT methodology (153). Published RCTs should address checklist items. The first version, published in 1996, included a checklist of 21 items and a flow diagram (154). In 2001, a new item was added and the flow diagram was updated (155). It was revised again in 2010, with wording changes and 25 items, including new items and modifications from previous checklists (153). The CONSORT statement was not developed as a specific evaluation tool however, it can highlight the reporting quality of RCTs.

Further to the CONSORT statement and checklist, an extension was developed to address underreporting in herbal medicine RCTs. The extension includes specific items relevant to herbal interventions (156).

5.4.9.2 Objective of quality assessment

The objective of the quality assessment was to evaluate the methodological and reporting quality of *Panax ginseng* RCTs. Specific examination was undertaken to determine quality changes relating to time, outcomes, preparation type, sample size and geographic origin.

5.4.9.3 Eligibility of studies

The eligibility of the studies is detailed in section 5.4.4 above. However, quality assessment was only performed on full text articles.

5.4.9.4 Data extraction

The two independent reviewers entered each item from the two checklists onto spread sheets. Checklist items were scored as 1– included in the report, 0 – not included in the report, or N/A – not applicable to the study. A third reviewer resolved any disagreements.

5.4.9.5 Data analysis

Studies were grouped according to their primary outcome(s). Mean difference and 95% confidence intervals were calculated between groups at the end of treatment for continuous data. Relative risk (RR) was calculated for dichotomous data. Where insufficient information was provided, results were recorded as not estimable.

Meta-analysis was planned using RevMan 5.0 software. Studies that featured similar health conditions, outcome measures, *Panax ginseng* dose and lengths of treatment were combined. However, due to the high level of heterogeneity in the studies reviewed, data synthesis was limited and meta-analysis could not be performed.

Each study's methodological quality was assessed using the CONSORT checklist 2010 (153), and the extension for herbal interventions checklist (156). Studies were grouped and compared according to publication date, that is, before CONSORT (pre 1995), after

its publication and review (from 1996–2006), and after 2007. The CONSORT extension for herbal interventions checklist was published in 2006, and manuscripts were compared with those published before and after 2006.

The CONSORT checklist was designed primarily to guide two-group parallel RCTs however, it can be applied to any design by making allowances for specific items (155). Therefore, one item was added, 'Cross-over studies should be justified, why was this design used?' Including this item was necessary as several studies used cross-over designs.

Each item was categorised as reported, not reported, or not applicable and presented as a percentage of the overall for that section.

Publications were grouped and assessed according to:

- publication period (before or after CONSORT)
- outcomes
- type of *Panax ginseng* preparation
- sample size
- whether or not the article was published in a CONSORT promoter journal
- location where the research was undertaken

Mean, standard deviation, and percentage were calculated for the grouped studies. Potential group differences were examined using analysis of variance (ANOVA), with $p < 0.05$ indicating significance.

5.4.10 Results

5.4.11 Identification of Studies

Searches identified 1,778 studies, 183 were duplicates, and therefore 1,595 were screened for eligibility. One thousand five hundred and twenty-five (1,525) studies were excluded. Seventy (70) full-text articles were assessed and three were excluded as they were not RCTs (157-159). Finally, 65 English and two Chinese studies were identified. Figure 20 illustrates study selection.

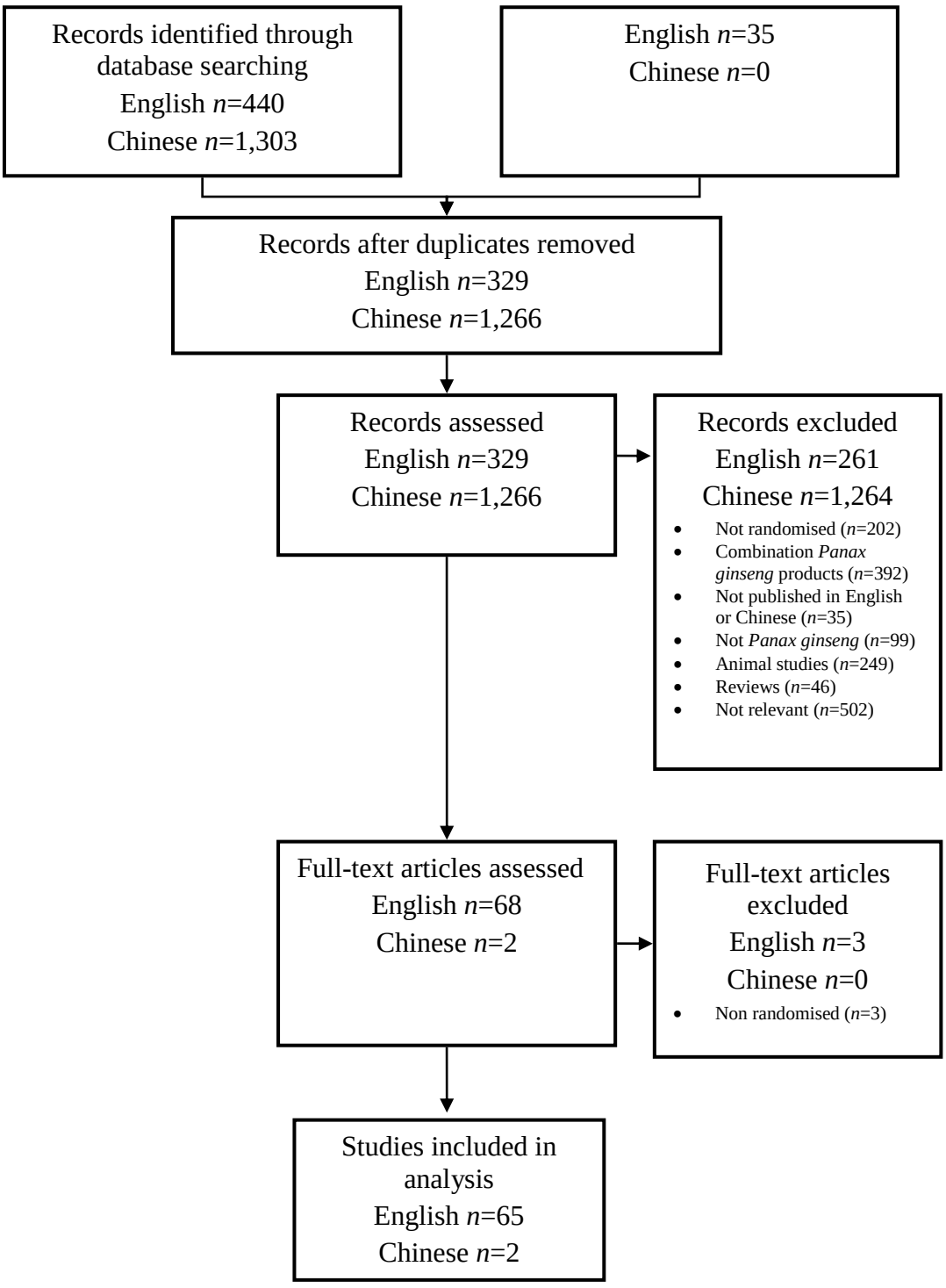


Figure 20: Flow diagram of study selection

5.4.12 Description of the Studies

The data from the 67 studies is presented in Table 34. The included studies investigated the following 13 health related areas:

- psychomotor performance (17 studies)
- physical performance (10 studies)
- circulatory conditions (9 studies)
- glucose metabolism (6 studies)
- respiratory conditions (5 studies)
- erectile dysfunction (4 studies)
- immunomodulation (4 studies)
- quality of life and mood (4 studies)
- antioxidant function (2 studies)
- cancer (2 studies)
- menopausal symptoms (2 studies)
- dry mouth (1 study)
- ulcerative colitis (1 study)

All 67 studies were described by the authors as ‘randomised’, 57 were labelled ‘double blind’, three were labelled ‘single-blind’, four were described as ‘open-label’ and three studies didn’t state blinding. Most studies (*n*=44) were designed as parallel and 23 were cross-over studies. Twenty-nine (29) studies were conducted in Asia, a further 20 in Europe/UK, 15 in North America, and one from each, Australia, Israel and Brazil.

Studies were published between 1983 and 2011.

5.4.12.1 Participants

In total 3,961 participants were involved in these studies. The sample size ranged from 6–643, with a median sample of 32.

Thirty-nine (39) studies assessed the use of *Panax ginseng* among healthy people. The remaining studies assessed 15 conditions: COPD/chronic bronchitis (3 studies), erectile dysfunction (4 studies), menopausal women (3 studies), type 2 diabetes (3 studies), Alzheimer's disease (2 studies), cancer (2 studies), hypertension (2 studies), myocardial infarction (2 studies), allergic rhinitis (1 study), cardiac valve replacement (1 study), chronic atrophic gastritis (1 study), dry mouth (1 study), glaucoma (1 study), ischemic stroke (1 study) and ulcerative colitis (1 study).

The age range of participants was between 18 and 80 years.

5.4.12.2 Interventions

The interventions in all 67 studies used the root of *Panax ginseng* for oral administration.

Twelve (12) different types of preparations or extracts were used across the studies: Ginsana G115 (24 studies); undeclared preparation types (16 studies); Red Ginseng extract (15 studies); Korean Red Ginseng (4 studies); Gerimax™ (2 studies); Cheong Kwan Jang™ (2 studies). The following six preparations were each used in one study: Korean Red Ginseng rootlet; fermented Red Ginseng; Sun Ginseng; tissue-cultured mountain Ginseng extract; 60% ethanolic extract and PKC 169/79. Two studies

included two different preparations of *Panax ginseng*: Ginsana G115 plus Cheong Kwan Jang™ (160), and Ginsana G115 plus PKC 169/79 (161). Therefore, 69 preparations were used in total.

In 60 studies, *Panax ginseng* preparations were given as capsules. In four studies, they were given as loose powder and in one study as liquid. Four studies did not state preparation type. *Panax ginseng* dosage ranged from 100–600 mg per day for standardised extracts, 1–60 g per day for powdered extracts and 4 mL per day for liquid extracts.

Table 34: Characteristics of the included studies

Psychomotor performance						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions Intergroup difference MD [95% CI]**
D'Angelo, 1986, Italy (162)	DB, PG	Healthy individuals	T: 16 C: 16	G115/ P 200 mg/ 12 weeks	1. Psychomotor performance 2. Auditory reaction time 3. Visual reaction time 4. Adverse events	Improved mental arithmetic only. 1. NE 2. NE 3. NE 4. T: 0 C: 0
Fulder, 1984, Korea (163)	DB, CO	Healthy elderly individuals	T&C: 49	KRG/ P 15 g/ 10 days	1. Psychomotor performance 2. Adverse events	Certain aspects of psychomotor performance improved. 1. NE 2. 1 (group not specified)
Heo, 2008, Korea (164)	OL, PG	Alzheimer's disease	T(4.5g): 15 T (9g): 15 C: 31	RG/ SC 4.5, 9 g / 12 weeks	1. ADAS 2. MMSE 3. CDR battery 4. Adverse events	9g dose improved the ADAS and CDR. 1. -3.59[-10.01,2.83] 2. 2.71[0.32,5.10] 3. -0.03[-0.37,0.31] 4. $T_{(4.5g)}$:2 $T_{(9g)}$:2 C:3
Kennedy, 2001, UK (165)	DB, CO	Healthy individuals	T&C: 20	G115/ P 200, 400, 600 mg/ 1 day	1. Quality of memory 2. Accuracy of attention 3. CDR battery 4. Bond-Lader VAS-alert 5. Adverse events	400mg dosage improved quality of memory. 1. 0.12[-45.06,45.30] 2. -9.10[-11.38,-6.82] 3. NE 4. -30.38[-35.89,-24.87] 5. NS
Kennedy, 2002, UK (166)	DB, CO	Healthy individuals	T&C: 20	G115/ P 400 mg/ 1 day	1. Quality of memory 2. CDR battery 3. Bond-Lader VAS-alert 4. Mental arithmetic tasks 5. Adverse events	Improved secondary memory, speed of performance, memory tasks and accuracy of attention. 1. 14.12[-18.92,47.16] 2. 17.33[4.26,30.40] 3. -1.51[-11.68,8.66] 4. -0.83[-2.63,0.97] 5. NS
Kennedy, 2003, UK (167)	DB, CO	Healthy individuals	T&C: 15	G115/ P 200 mg/ 1 day	1. EEG 2. Adverse events	Modulation of cerebro-electrical activity. 1. NE 2. NS
Kennedy, 2007, UK (150)	DB, CO	Healthy individuals	T&C: 18	*Panax ginseng*/ P 200 mg/ 8 weeks	1. Quality of memory 2. Accuracy of attention 3. Bond-Lader VAS-alert 4. HbA1c 5. WHOQOL BREF-psyc 6. Adverse events	Improved working memory and rating of mood and QoL. 1. -0.72[-33.93,32.49] 2. 0.86[-6.91,8.62] 3. 8.94[-3.44,21.32] 4. 0.17[0.01,0.33] 5. 0.08[-0.70,0.86] 6. NS

Table 34: Characteristics of the included studies continued						
Lee, 2008(b), Korea (168)	OL, PG	Alzheimer's disease	T: 58 C: 39	*Panax ginseng*/ SC 4.5 g/ 12 weeks and 12 weeks follow-up	1. ADAS 2. MMSE 3. Adverse events	Improved cognitive performance on both scales. 1. -1.75[-4.80,1.30] 2. 1.33[-0.26,2.92] 3. T: 7 C: 6
Reay, 2005, UK (169)	DB, CO	Healthy individuals	T&C: 30	G115/ P 200, 400 mg/ 1 day	1. Mental arithmetic tasks 2. RVIP reaction time 3. Blood glucose 4. Rate of fatigue 5. Adverse events	Some improvement in cognitive performance and subjective feelings of mental fatigue. Decreased blood glucose. 1. -0.13[-2.00,1.74] 2. 0.01[-0.01,0.04] 3. -0.10[-0.65,0.45] 4. -10.77[-22.52,0.99] 5. NS
Reay, 2006, UK (170)	DB, CO	Healthy individuals	T&C: 27	G115/ P 200 mg/ 1 day	1. Mental arithmetic tasks 2. RVIP reaction time 3. Blood glucose 4. Rate of fatigue 5. Adverse events	Enhanced cognitive performance and decreased blood glucose. 1. -0.78[-1.70,0.14] 2. 0.02[-0.02,0.06] 3. 0.25[-0.08,0.57] 4. -7.37[-20.45,5.71] 5. NS
Reay, 2008, UK (151)	DB, CO	Healthy individuals	T&C: 25	G115/ P 200 mg/ 8 weeks	1. CDR battery 2. Blood glucose 3. Adverse events	Improved working memory and aspects of cognitive performance and mood. 1. NE 2. NE 3. NS
Reay, 2010, UK (171)	DB, CO	Healthy individuals	T&C: 30	G115/ P 200, 400 mg/ 8 days	1. Bond-Lader VAS-alert 2. Adverse events	No significant effect. 1. -1.15[-11.99,9.69] 2. NS
Scholey, 2002, UK (172)	DB, CO	Healthy individuals	T&C: 20	G115/ P 200, 400, 600 mg/ 1 day	1. CDR battery 2. Adverse events	400mg improved subtraction tasks. 1. NE 2. NS
Sorensen, 1996, Denmark (173)	DB, PG	Healthy individuals	T: 55 C: 57	Gerimax/ P 400 mg/ 8 to 9 weeks	1. Auditory reaction time 2. Visual reaction time 3. Finger tapping test 4. Adverse events	Improved simple reactions and abstract thinking. 1. -13.00[-24.87,-1.13] 2. -10.00[-21.69.1.69] 3. -1.60[-5.12,1.92] 4. T: 0 C: 0
Sotaniemi, 1995, Finland (174)	DB, PG	NIDDM	T (100mg): 12 T (200mg): 12 C: 12	Gerimax/ P 100, 200 mg/ 8 weeks	1. Psychomotor performance 2. Total cholesterol 3. OGTT 4. HbA1c 5. Adverse events	Improved mood, physiological performance and reduced fasting blood glucose (100mg only). 1. -9.20[-15.55,-2.85] 2. 0.20[-0.76,1.16] 3. -0.60[-1.49,0.29] 4. 0.00[-1.40,1.40] 5. T: 0 C: 0

Table 34: Characteristics of the included studies continued						
Sunram Lea, 2005, UK (175)	DB, CO	Healthy individuals	T&C: 30	G115/ P 400 mg/ 1 day	1. Quality of memory 2. Adverse events	Improved speed of attention. 1. -5.14[-30.56,20.28] 2. NS
Ziemba, 1999, Poland (176)	DB, PG	Healthy individuals	T: 7 C: 8	*Panax ginseng*/ P 350 mg/ 6 weeks	1. Visual reaction time 2. Heart rate 3. Adverse events	Improved psychomotor performance during exercise. 1. -10.10[-12.54,-7.46] 2. 2.00[-6.57,10.57] 3. 3. NS
Physical performance						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Allen, 1998, USA (177)	DB, PG	Healthy individuals	T:13 C:15	*Panax ginseng*/ P 200 mg/ 3 weeks	1. $VO_{2\ peak}$ 2. Adverse events	No significant effect. 1. 2.90[1.26,4.54] 2. T: 2 C: 0
Cherdrungsi, 1995, Thailand (178)	DB, PG	Healthy individuals	T:20 C:21	*Panax ginseng*/ P 300 mg/ 8 weeks	1. VO_{2max} 2. Heart rate 3. Adverse events	No significant effect. 1. 0.70[-0.95,2.35] 2. -1.10[-1.71,-0.49] 3. T: 2 C: 0
Engels, 1996, USA (179)	DB, PG	Healthy individuals	T:10 C:9	G115/ P 200 mg/ 8 weeks	1. VO_{2max} 2. Heart rate 3. Adverse events	No significant effect. 1. -1.00 [-7.98, 5.98] 2. -2.80 [-10.26, 4.66] 3. T: 2 C: 0
Engels, 1997, USA (180)	DB, PG	Healthy individuals	$T_{(200mg)}$:12 $T_{(400mg)}$:12 C:12	G115/ P 200, 400 mg/ 8 weeks	1. VO_{2max} 2. Heart rate 3. Adverse events	No significant effect. 1. 1.50 [-4.90,7.90] 2. -1.30[-2.88,0.28] 3. T_{200mg}:0 T_{400mg}:3 C:0
Engels, 2001, USA (181)	DB, PG	Healthy individuals	T:12 C:12	G115/ P 400 mg/ 8 weeks	1. Peak power output 2. Rate of fatigue 3. Adverse events	No significant effect. 1. -0.04[-1.00,0.92] 2. -2.54[-9.18,4.10] 3. T: 1 C: 0
Engels, 2003, USA (182)	DB, PG	Healthy individuals	T:19 C:19	G115/ P 400 mg/ 8 weeks	1. Peak power output 2. Absolute s-IgA 3. Adverse events	No significant effect. 1. 0.20[-0.36,0.76] 2. -20.00[-54.51,14.51] 3. T: 0 C: 0
Knapik, 1983, USA (183)	DB, PG	Healthy individuals	T:5 C:6	*Panax ginseng*/ P 2 g/ 4 weeks	1. VO_{2max} 2. Adverse events	No significant effect. 1. NE 2. NS
Kulaputana, 2007, Thailand (184)	DB, PG	Healthy individuals	T:30 C:30	KRG/ P 3 g/ 8 weeks	1. Lactate threshold 2. Adverse events	No significant effect. 1. 7.20[-4.43,18.83] 2. T: 0 C: 0

Table 34: Characteristics of the included studies continued						
Ping, 2011, Malaysia (185)	DB, CO	Healthy individuals	T&C: 9	*Panax ginseng*/ P 200 mg/ 1 day	1. Time to exhaustion 2. Plasma glucose 3. Plasma insulin 4. Heart rate 5. Adverse events	No significant effect. 1. 0.20[-0.15,0.55] 2. -0.15[-0.53,0.23] 3. -0.40[-1.27,0.47] 4. -1.00[-8.12,6.12] 5. T: 0 C: 0
Teves 1983, USA (186)	DB, PG	Healthy individuals	T:6 C:6	*Panax ginseng*/ P 2 g/ 4 weeks	1. VO_{2max} 2. Adverse events	No significant effect. 1. NE 2. NS
Circulatory conditions						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Ahn, 2011, Korea (187)	SB, PG	Myocardial infarction	T:25 C:25	RG/ P 3 g/ 8 weeks	1. CFR 2. Angiogenic cells 3. IL-6 4. TNFa 5. Total cholesterol 6. Adverse events	Increased CFR and angiogenic cells. Decreased inflammatory markers. 1. 0.24[-0.23,0.71] 2. NE 3. -0.78[-1.58,0.02] 4. -0.83[-2.41,0.75] 5. 0.09[-0.44,0.62] 6. T:1 C:1
Caron, 2002, USA (188)	DB, PG	Healthy individuals	T:15 C:15	G115/ P 200 mg/ 4 weeks	1. ECG parameters 2. BP- diastolic 3. Adverse events	Modulation of certain ECG intervals and decreased diastolic BP at certain time intervals only. 1. 0.01[-0.01,0.02] 2. 3.10[-2.11,8.31] 3. T:1 C:0
Chen, 1993, China (189)	NS, PG	Silent myocardial ischemia	T:30 C:28	RG/ SC 6g/ 15 days	1. (ECG Monitor) Minutes lasted each time of MI 2. (ECG Monitor) Times of MI occurred in 24 hrs 3. Level of MI (mV) by ECG Monitor 4. 15 days MI improvement 5. 6 month MI improvement 6. Adverse events	1. NE 2. NE 3. NE 4. RR 2.71 [1.64, 4.47] 5. RR 2.59 [1.48, 4.55] 6. NS
Jovanovski, 2010, Canada (190)	DB, CO	Healthy individuals	T&C:17	RG/ P 3 g/ 1 day	1. Augmentation Index 2. Diastolic BP 3. Adverse events	Lowered Augmentation Index. 1. -5.19[-6.58,-3.80] 2. NE 3. T:0 C:0
Kim, 2010, Korea (191)	DB, CO	Glaucoma	T&C:36	Cheong Kwan Jang / P 4.5 g/ 12 weeks	1. Visual ocular blood flow 2. Adverse events	Improved retinal peri-papillary blood flow. 1. NE 2. T:1 C:2

Table 34: Characteristics of the included studies continued						
Lee, 2008(a), Korea (192)	OL, PG	Ischemic stroke	T:17 C:17	*Panax ginseng*/ SC 1.5 g/ 2 weeks	1. Prothrombin time 2. INR – peak 3. Adverse events	No significant effect. 1. 0.81[-1.72,3.34] 2. 0.11[-0.19,0.41] 3. T: 0 C: 0
Lee, 2010, Korea (193)	DB, CO	Cardiac valve replacement	T&C:31	RG/ P 1 g/ 6 weeks	1. Prothrombin time 2. Adverse events	Ginseng could be used in patients who take warfarin. 1. -0.39[-0.91,0.13] 2. NS
Rhee, 2011, Korea (194)	DB, PG	Essential hypertension	T:40 C:40	RG/ P 3 g/ 12 weeks	1. Diastolic BP 2. Total cholesterol 3. Adverse events	No significant effect. 1. 3.00[-1.69,7.69] 2. -11.00[.32.15,10.15] 3. T: 5 C:2
Sung, 2000, Korea (195)	DB, PG	Essential hypertension	T:10 C:10	RG/ No treatment 4.5 g/ 21 to 27 months	1. Vascular endothelial function 2. Adverse events	No significant effect. 1. NE 2. T:0 C:0
Glucose metabolism						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
De Souza, 2011, Canada (196)	DB, CO	Healthy individuals	T&C:16	*Panax ginseng*/ P 3 g/ 1 day	1. Glycaemic response iAUC 2. Peak postprandial glycaemia 3. Adverse events	Reductions of overall glycaemic response. 1. -33.42[-41.04,-25.80] 2. 0.27[0.15,0.39] 3. T:0 C:0
Ma, 2008, Hong Kong (197)	DB, CO	Type 2 diabetes	T&C:20	KRG/ P 2.2 g/ 4 weeks	1. OGTT 2. Plasma glucose 3. Lipid peroxidation - MDA 4. HOMA-IR 5. Adverse events	Decreased HOMA-IR and fasting glucose. 1. 0.60[-0.91,3.40] 2. -2.10[-4.52,0.32] 3. 0.10[-0.18,0.38] 4. NE 5. T:2 C:0
Reay, 2009, UK (160)	DB, CO	Healthy individuals	Study1 T&C:25 Study2 T&C:18	Study1:G115/ P 200 mg/ 8 weeks Study2: Cheong Kwan Jang / P 200 mg/ 8 weeks	1. Plasma insulin 2. HbA1c 3. Adverse events	No significant effect. 1. 0.47[-5.51,6.45] 2. 0.08[-0.16,0.32] 3. NS
Sievenpiper, 2003, Canada (198)	SB, CO	Healthy individuals	Study 1 T&C:14 Study 2 T&C:11	*Panax ginseng*/ P 1, 2, 3, 6, 9 g/ 1 day	1. OGTT 2. Adverse events	Higher two hour plasma glucose. 1. NE 2. Study1: T:1 C:0; Study2: NS
Sievenpiper, 2006, Canada (199)	DB, CO	Healthy individuals	Study 1 T&C:7 Study 2 T&C:12	*Panax ginseng*/ P 2, 4, 6 g/ 1 day	1. OGTT 2. Adverse events	2 g rootlets reduced postprandial glycaemia. 1. NE 2. NS
Vuksan, 2008, Canada (200)	DB, CO	Type 2 diabetes	T&C:39	RG/ P 6 g/ 12 weeks	1. OGTT 2. Plasma glucose 3. HbA1c 4. Adverse events	No significant effect. 1. -0.61[-1.26,0.05] 2. -0.33[-0.97,0.32] 3. 1.96[-0.16,1.14] 4. T:1 C:2

Table 34: Characteristics of the included studies continued

Respiratory conditions						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Gross, 2002, Israel (12)	DB, PG	COPD	T:51 C:43	G115/ P 200 mg/ 12 weeks	1. FEV_1 2. FVC 3. VO_{2max} 4. Adverse events	Improved lung function tests and $VO_{2max.}$ 1. 20.00[15.62,24.38] 2. -8.50[-11.00,-6.00] 3. 9.50[4.19,14.81] 4. T:0 C:0
Jung, 2011(b), Korea (149)	DB, PG	Allergic rhinitis	T:33 C:33	Fermented RG/ P 1.5 g/ 4 weeks	1. TNSS 2. Overall RQoL 3. Total IgE 4. Adverse events	Improved nasal congestion and reduced skin reactivity to allergens. 1. -0.30[-0.64,0.04] 2. -0.76[-2.26,0.74] 3. 16.39[-11.41,44.19] 4. T:1 C:2
Scaglione, 1994, Italy (201)	DB, PG	Chronic bronchitis	T:20 C:20	G115/ P 200 mg/ 8 weeks	1. Phagocytosis index 2. Intra cellular killing 3. Adverse events	Improved immune response. 1. 0.38[0.24,0.52] 2. 0.20[0.08,0.32] 3. NS
Scaglione, 1996, Italy (202)	DB, PG	At risk of influenza	T:114 C:113	G115/ P 200 mg/ 12 weeks	1. NK cell activity 2. Number of common colds 3. Anti-body titres 4. Adverse events	Improved immune response and decreased common colds. 1. 16.70[13.83,19.57] 2. RR 0.35 [0.21, 0.60] 3. 52.70[33.74,71.66] 4. T:8 C:1
Scaglione, 2001, Italy (203)	OL, PG	Chronic bronchitis	T:38 C:37	G115/ Antibiotics 200 mg/ 9 days	1. Bacterial count 2. Adverse events	Improved bacterial count. 1. -0.80 [-0.94, -0.66] 2. NS
Erectile dysfunction						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Choi, 1995, Korea (204)	SB, PG	Erectile dysfunction	T: 30 C(P):30 C(SC):30	RG/ P or SC 200 mg/ 12 weeks	1. Erection and sexual satisfaction 2. Adverse events	Rigidity, girth, libido and satisfaction improved. 1. NE 2. T:0 C:0
de Andrade, 2007, Brazil (205)	DB, PG	Erectile dysfunction	T:30 C:30	*Panax ginseng*/ P 3000 mg/ 12 weeks	1. IIEF-5 2. Testosterone 3. Total cholesterol 4. GAS 5. Adverse events	IIEF-5 total score improved 1. 3.30[0.28,6.32] 2. 51.20[-3.38,105.78] 3. -10.00[-33.06,13.06] 4. 0.30[-0.16,0.76] 5. T:3 C:0
Hong, 2002, Korea (206)	DB, CO	Erectile dysfunction	T&C:45	RG/ P 2.7 g/ 8 weeks	1. IIEF-5 2. RigiScan 3. Adverse events	IIEF-5 total score improved, RigiScan showed improvement. 1. 2.37[-0.08,4.82] 2. 4.09[-8.11,16.29] 3. T:1 C:0

Table 34: Characteristics of the included studies continued

Kim, 2009, Korea (207)	DB, PG	Erectile dysfunction	T:75 C:68	Tissue cultured mountain Ginseng extract/ P 2 g/ 8 weeks	1. IIEF-5 2. Testosterone 3. Adverse events	IIEF-5 erectile function and overall satisfaction improved. 1. 6.53[0.81,12.25] 2. 0.53[-0.36,1.42] 3. T:3 C:NS
Immunomodulation						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Gaffney, 2001, Australia (208)	DB, PG	Healthy individuals	T:10 C:10	*Panax ginseng*/ P 4 mL/ 6 weeks	1. Lymphocyte count 2. Testosterone 3. Adverse events	No significant effect. 1. -0.01[-0.53,0.51] 2. 0.00[-5.83,5.83] 3. NS
Jung, 2011(a), Korea (209)	DB, PG	Healthy individuals	T:9 C:9	RG/ P 60 g/ 10 days	1. CK 2. IL-6 3. OGTT 4. Adverse events	Decreased CK, IL-6 and glucose levels. 1. -39.50[-65.98,-13.02] 2. -0.07[-0.18,0.04] 3. 1.40 [0.52, 2.28] 4. NS
Scaglione, 1990, Italy (161)	DB, PG	Healthy individuals	Study1 T:20 C:20 Study2 T:20 C:20	Study1: G115/ P 200 mg/ 8 weeks Study2: PKC/ P 200 mg/ 8 weeks	1. Chemotaxis 2. Intra cellular killing 3. Total lymphocytes 4. Adverse events	Stimulation of an immune response, G115 was more active. 1. G115 0.53[0.19,0.87] 1. PKC 0.52 [0.19, 0.85] 2. G115 -3.65 [-12.26, 4.96] 2. PKC-12.95[-21.31,-4.59] 3. G115 5.74 [-0.20, 11.68] 3. PKC 5.82 [0.89, 10.75] 4. NS
Srisurapanon, 1997, Thailand (210)	DB, PG	Healthy individuals	T:10 C:10	*Panax ginseng*/ P 300 mg/ 8 weeks	1. Leukocyte counts 2. Lymphocyte count 3. Total WBC 4. Adverse events	No significant effect. 1. NE 2. NE 3. NE 4. NS
Quality of life and mood						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Cardinal, 2001, USA (211)	DB, PG	Healthy individuals	T (200mg):22 T (400mg):27 C:34	G115/ P 200, 400 mg/ 8 weeks	1. PANAS 2. POMS 3. Adverse events	No significant effect. 1. NE 2. NE 3. NS
Ellis, 2002, USA (212)	DB, PG	Healthy individuals	T:15 C:15	G115/ P 200 mg/ 8 weeks	1. SF-36 – physical 2. SF-36 – mental 3. Adverse events	Improved aspects of mental and social functioning after 4 weeks of treatment. 1. -1.70[-4.69,1.29] 2. 2.10[-3.42,7.62] 3. T:4 C:2

Table 34: Characteristics of the included studies continued						
Kim, 2006, Korea (213)	DB, PG	Cancer	T:32 C:21	Sun Ginseng/ P 3 g/ 12 weeks	1. WHOQOL BREF – psychological 2. GHQ-12 3. Adverse events	Improved psychological and physical health domains of the WHOQOL-BREF. Improved GHQ-12 total score. 1. -0.50[-3.00,2.00] 2. 0.00[-3.66,3.66] 3. T:0 C:0
Wiklund, 1999, Sweden (214)	DB, PG	Post-menopausal women	T:193 C:191	G115/ P 200 mg/ 12 weeks	1. PGWB 2. WHQ 3. Menopause symptoms VAS 4. Adverse events	Improved sub scales of depression and well-being. 1. 0.40[-2.72,3.52] 2. -1.20[-4.08,1.68] 3. 0.50[-2.29,3.29] 4. T:2 C:2
Antioxidant function						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Kim, 2001, Korea (215)	DB, PG	Healthy smokers	T:3 C:3	RG/ P 1.8 g/ 4 weeks	1. Triacylglycerol 2. Lipid peroxidation - MDA 3. Total cholesterol 4. Adverse events	No significant effect. 1. 12.49[-27.48,52.46] 2. 0.07[-0.69,0.83] 3. 2.61[-12.19,17.41] 4. NS
Kim, 2011(a), Korea (216)	DB, PG	Healthy individuals	T(1g):27 T(2g):28 C:27	*Panax ginseng*/ P 1, 2 g/ 4 weeks	1. Lipid peroxidation - MDA 2. Serum levels ROS 3. SF-36-mental 4. Adverse events	Some antioxidant properties. 1. -1.50[-2.97,-0.03] 2. -17.00[-35.30,1.30] 3. -3.40[-9.63,2.83] 4. T(1g):0 T(2g):2 C:0
Cancer						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Suh, 2002, Korea (111)	NS, PG	Stage III gastric cancer	T:22 C:20	RG/ P 4.5 g/ 6 months and 4.5 years follow-up	1. Recurrence of cancer 2. Total leukocytes 3. Total lymphocytes 4. Adverse events	Increased five year survival rate. 1. RR 0.49 [0.25, 0.98] 2. 1.60[0.33,2.87] 3. -0.50[-6.56,5.56] 4. T:0 C:0
Yun, 2010, China (112)	DB, PG	Chronic atrophic gastritis	T:325 C:318	RG/ P 1 g per week/ 3 years and 8 years follow-up	1. Incidence of cancer 2. Adverse events	Preventive effects on cancer in males only. 1. RR 0.49 [0.21, 1.13] 2. T:19 C:23
Menopausal Symptoms						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Kim, 2011(b), Korea (217)	DB, PG	Menopausal women	T:36 C:36	RG/ P 3 g/ 12 weeks	1. Kupperman index 2. Serum estradiol 3. Total cholesterol 4. Adverse events	Kupperman index improved, Cholesterol decreased. 1. NE 2. NE 3. NE 4. NS

Table 34: Characteristics of the included studies continued						
Oh, 2010, Korea (218)	DB, CO	Menopausal women	T&C:32	RG/ P 3 g/ 8 weeks	1. GAQ 2. FSFI – arousal level 3. Testosterone 4. Adverse events	Improved GAQ and FSFI. 1. NE 2. 0.10[-0.01,0.21] 3. NE 4. T:2 C:0
Dry Mouth						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Park, 2010, Korea (219)	DB, PG	Subjective dry mouth	T:50 C:50	KRG/ P 6 g/ 8 weeks and 2 weeks follow-up	1. Dry mouth VAS 2. Salivary flow rate 3. Adverse events	No significant effect. 1. 0.24[-0.66,1.14] 2. -0.02 [-0.08, 0.04] 3. T:7 C:9
Ulcerative Colitis						
Author, Year, Country	**Design**	**Condition**	**No. of Subjects T / C**	**T/ C Daily dose/ Duration**	**Outcomes**	**Author's conclusions. Intergroup difference MD [95% CI]**
Lu, 2009, China (220)	NS, PG	Severe ulcerative colitis	T:30 C:30	*Panax ginseng*/ SC 15-20g/ 15 days	1. Carbon Dioxide Combining Power 2. Blood electrolytes (K+) 3. Blood electrolytes (Na+) 4. End of treatment improvement 5. Deaths 6. Adverse events	1. 1.75 [0.01, 3.49] 2. 1.03 [0.79, 1.27] 3. 10.28 [9.44, 11.12] 4. RR 2.17 [1.37, 3.43] 5. RR 0.27 [0.10, 0.71] 6. T:0 C:0

ADAS: Alzheimer's Disease Assessment Test, BP: Blood Pressure, C: Control, CDR: Clinical Dementia Rating, CFR: Cardiac Flow Reserve, CI: Confidence Interval, CK: Creatine Kinase, CO: Cross Over, COPD: Chronic Obstructive Pulmonary Disease, DB: Double Blind, ECG: Electrocardiogram, EEG: Electroencephalogram, FEV_1: Forced expiratory volume in 1 second, FSFI: Female Sexual Function Index, FVC: Forced Vital Capacity, GAQ: Global Assessment Questionnaire, GHQ-12: Global Health Questionnaire, HOMA-IR: Homeostatic Model Assessment –Insulin Resistance, iAUC : Incremental Area Under the Curve, IgE: Immunoglobulin-E, IIEF-5: International Index of Erectile Function questionnaire, IL-6: Interleukin-6, INR: International Normalised Ratio, K+: Potassium , KRG: Korean Red Ginseng, MD: Mean Difference, MMSE: Mini Mental Status Examination, Na+: Sodium , NE: Not Estimable, NIDDM: Non-Insulin Dependent Diabetes Mellitus, NK: Natural Killer, NS: Not Stated, OGTT: Oral Glucose Tolerance Test, OL: Open Label, P: Placebo, PANAS: Positive and Negative Affect Schedule, PG: Parallel Group, PGWB: Physiological General Wellbeing Index, PKC: *Panax ginseng* extract manufactured by Pharmaton, POMS: Profile Of Mood States, QoL: Quality of Life, RG: Red Ginseng, RQoL: Rhinitis Quality of Life Questionnaire, SB: Single Blind, SC: Standard Care, SD: Standard Deviation, SF-36: Short Form (36) health survey, T: Treatment, TNSS: Total Nasal Symptom Score, VAS: Visual Analogue Scale, WBC: White Blood Cell, WHOQOL-BREF: World Health Organisation quality of life-BREF questionnaire, WHQ: Women's Health Questionnaire

5.4.13 Risk of bias

Risk of bias was judged using the Cochrane Collaboration's Risk of Bias tool. The results are summarised in

Figure 21. From the 67 studies, 402 potential sources of bias were judged. The majority were categorised as unclear (209, 52%), low (176, 44%) and high (17, 4%). These are outlined below.

• Random sequence generation: high in one study; low in 22 studies; and unclear in 44 studies.

• Allocation concealment: high in four studies; low in 13 studies; and unclear in 50 studies.

• Blinding of participants and personnel: high in eight studies; low in 52 studies; and unclear in seven studies.

• Blinding of outcome assessment: high in no studies; low in six studies; and unclear in 61 studies.

• Incomplete outcome data: high in three studies; low in 26 studies; and unclear in 38 studies.

• Selective reporting: high in one study; low in 57 studies; and unclear in nine studies.

Other sources of bias were not included in

Figure 21. However, authors in six studies (160, 169-171, 173, 214) reported industry sponsorship by the manufacturer of the interventional product and the risk of bias was unclear. One study (175) was co-authored by an employee of the manufacturer of the interventional product and the risk of bias was judged as unclear.

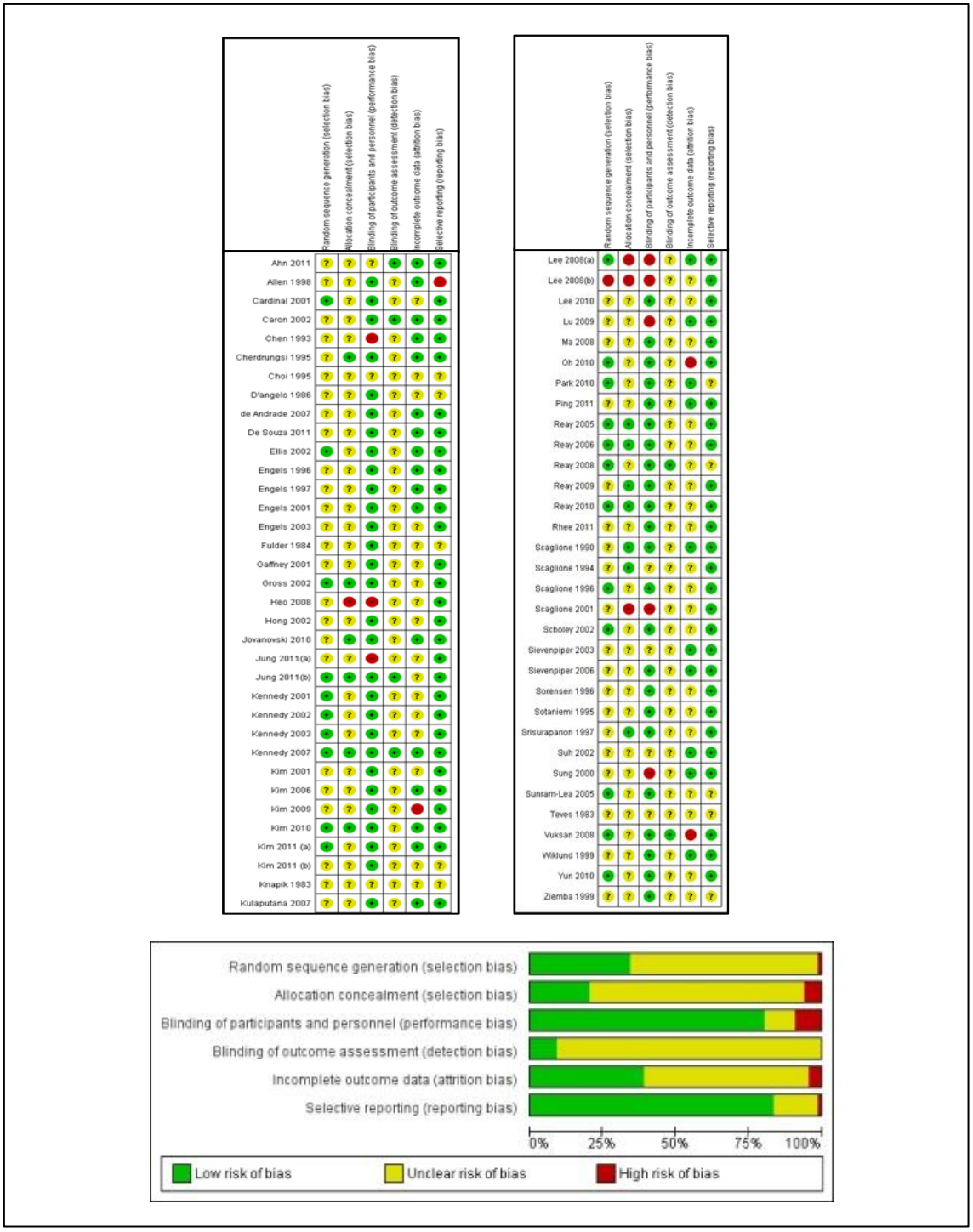


Figure 21: Risk of bias summary and graph

5.4.14 Quality assessment

Data from 60 out of the 67 studies were assessed for quality. Seven studies (151, 162, 163, 183, 186, 204, 217) did not have full text articles available and could not be included.

The studies included in this review were inherently randomised. However, only 33 (55%) mentioned randomisation in the title or abstract as recommended in the CONSORT checklist. Fifty-one (51) studies were described as double blind, two as single-blind, four as open-label and three didn't describe randomisation. Thirty-seven (37) studies were designed as parallel studies, and 23 as cross-over studies.

5.4.14.1 Methodological quality using the CONSORT checklist

The CONSORT checklist sections are summarised in Table 35 and the individual CONSORT items are described in Table 36. Analysis of the included studies showed that on average 47.9% of the recommended items were reported. Kim et al 2010 reported the highest percentage of recommended items, 78% and Sotaniemi et al 1995 reported the lowest percentage of recommended items, 19%. Twenty-six (26) studies reported between 50% and 75%, and 32 reported between 20% and 49% of the recommended items.

Abstracts were structured appropriately in 74.2% of included studies and introductions were structured appropriately in 81.7%. Seventeen (17) items were recommended to be reported in the methods sections, overall these items were under reported. They were reported in just 40.9% of included studies [Table 35].

The results section included a participant flow diagram in five studies (8.3%), mentioned analysis by originally assigned groups and intention-to-treat in nine (15.0%), losses and exclusions after randomisation in 24 (40.0%), and adverse event reporting in 33 (55.0%).

Three items relate to the discussion section. These items were reported in 53.9% of the included studies [Table 35]. Information regarding trial registration number was reported in 5.0% of the studies, availability of the full protocol in 0% and funding source in 38.3%. Justification for using a cross-over design was reported in 21 out of the 23 relevant studies.

Studies published after the CONSORT checklist was disseminated in 1996 reported more items. Specifically, until 1995, 10.3 ± 4.9 (32.8%); from 1996–2006, 14.6 ± 3.3 (32.8%); and from 2007 onwards, 16.9 ± 4.5 (53.5%), ($p = 0.005$, ANOVA $F = 5.73$). Significance identified in ANOVA is due to a difference between studies published up until 1995 and those published from 2007 onwards, mean difference 6.7, $p=0.009$.

The studies reporting the items were those that evaluated QoL and mood, had sample sizes between 51 and 100, were conducted in North America and published in journals that promote the CONSORT [Table 38].

Table 35: CONSORT items reported in the 60 studies

CONSORT				
Section	Number of items	Reported	Not reported	Not applicable
Title and abstract	2	74.2%	25.8%	0.0%
Introduction	2	81.7%	18.3%	0.0%
Methods	17	40.9%	41.9%	17.2%
Results	10	30.9%	41.8%	27.3%
Discussion	3	53.9%	46.1%	0.0%
Other information	3	14.4%	85.6%	0.0%
Additional	1	35.0%	3.3%	61.7%
Total	38	40.0% **(47.9%)**[a]	43.2%	16.8%
CONSORT extension for herbal interventions				
Section	Number of items	Reported	Not reported	Not applicable
Title and abstract	1	46.7%	53.3%	0.0%
Introduction	1	85.0%	15.0%	0.0%
Methods	17	26.8%	59.4%	13.8%
Results	1	15.0%	85.0%	0.0%
Discussion	3	40.5%	59.5%	0.0%
Total	23	31.4% **(35.0%)**[a]	58.5%	10.1%

% was calculated from all 60 studies. The total number of items reported from each section (numerator) was divided by the total possible number of items that could be reported (denominator).

[a] % was calculated from the total number of items reported (numerator) divided by the total number of items that could be reported (denominator). Some items aren't relevant to all studies, so the total number of items that could be reported is less than the total possible number of items. For example, for 60 studies, the total number of individual CONSORT items (38) would be multiplied by 60, which equals 2280. If 1000 items were reported and 100 items weren't relevant, the % would be calculated as 1000 divided by 2280 (2280 – 100), which equals 45.9%.

Table 36: Individual CONSORT items and number of studies reporting items

Section	Item number	Item description	Number of studies reporting items and % [a]
Title/Abstract	1	Study was identified as a randomised trial in the title.	33, 55.0%
	2	Included a structured summary of trial design, methods, results and conclusions.	56, 93.3%
Introduction	3	Included a scientific background and explained the rationale for the study.	43, 71.7%
	4	Included specific objectives or hypotheses.	55, 91.7%
Methods	5	Described trial design (such as parallel or factorial), including allocation ratio.	59, 98.3%
	6	Stated important changes to methods after the trial started (such as eligibility criteria), with reasons.	N/A
	7	Listed eligibility criteria for participants.	46, 76.7%
	8	Stated settings and locations where data were collected.	36, 60.0%
	9	Described interventions for each group, including how and when they were administered, with enough detail to let researchers replicate the study.	50, 83.3%
	10	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed.	56, 93.3%
	11	Stated any changes to trial outcome measures after the trial started, with reasons.	N/A
	12	Stated how the sample size was determined.	11, 18.3%
	13	When applicable, explained any interim analyses and guidelines for stopping the study.	N/A
	14	Described the method used to generate the random allocation sequence.	14, 23.3%
	15	Described the type of randomization and any restrictions (such as blocking and block size).	20, 33.3%
	16	Described how the random allocation sequence was implemented (such as by using sequentially numbered containers), including any steps taken to conceal the sequence until interventions were assigned.	15, 25.0%
	17	Stated who generated the random allocation sequence, enrolled participants and assigned participants to interventions.	3, 5.0%
	18	If relevant, stated who was blinded after interventions were assigned (such as participants, care providers and/or people assessing outcomes) and how.	18, 30.0%
	19	If relevant, described how interventions were similar.	31, 53.4%
	20	Described statistical methods used to compare groups for primary and secondary outcomes.	55, 91.7%
	21	Described methods for further analyses, such as sub-group and adjusted analyses.	4, 44.4%
Results	22	Included a participant flow diagram showing the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome for each group.	5, 8.3%
	23	Listed losses and exclusions after randomisation and the reasons for these, for each group.	24, 40.7%
	24	Listed dates of recruitment and follow-up periods.	16, 26.7%
	25	Stated why the trial ended.	N/A

	Table 36 Continued		
Section	**Item number**	**Item description**	**Number of studies reporting items and % [a]**
Results	26	Included a table showing the baseline demographic and clinical characteristics for each group.	27, 45.0%
	27	Stated how many participants (denominator) were included in each analysis and if participants were analysed in originally assigned groups.	9, 15.0%
	28	For each primary and secondary outcome, gave results for each group and estimated effect size and precision (such as 95% confidence interval).	45, 75.0%
	29	For binary outcomes, stated absolute and relative effect sizes.	1, 14.3%
	30	Gave results from any other analyses, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory.	2, 50.0%
	31	Listed all important harms or unintended effects in each group.	33, 55.0%
Discussion	32	Listed trial limitations (such as addressing sources of potential bias, imprecision and, if relevant, multiplicity of analyses).	21, 35.0%
	33	Trial findings were generalisable (such as external validity and applicability).	36, 60.0%
	34	Interpretation was consistent with results, balanced benefits and harms, and considered other relevant evidence.	40, 66.7%
Other information	35	Stated registration number and the name of the trial registry.	3, 5.0%
	36	Stated where the full trial protocol can be accessed, if available.	0, 0.0%
	37	Listed sources of funding and other support (such as supply of drugs), and the role of funders.	23, 38.3%
Additional	38	Cross-over studies should be justified. Including explanation of why they used this design.	21, 91.3%

[a] % was calculated from the total number of studies reporting the item (numerator) divided by the total number of studies (denominator). Some items aren't relevant to all studies, so the total number of studies may be less. If the number of studies is originally 60, and the particular item isn't relevant in 3 studies. The % would be calculated as the total number of studies reporting the item. For example 26 divided by the total number of studies where item is relevant, that is, 57 (60–3), which equals 45.6%.
N/A = Not applicable

5.4.14.2 Methodological quality using the CONSORT extension for herbal interventions

Overall, the checklist items were not satisfactorily reported. On average only 35.0% of the 23 items were reported [Table 35]. The individual CONSORTextension for herbal medicine items are described in Table 37.

It is recommended that the title or abstract states the herbal medicine's Latin binomial name, part of the plant used and preparation type. This was reported in only 28 (46.7%) of the included studies. Introductions satisfied the criteria in 85.0% of the studies. Research methods were poorly described, on average only 26.8% of the items were reported. In particular, three items were never reported, these are:

- a description of how traditional theories and concepts were maintained
- outcomes that reflect these traditional theories and concepts
- a description of any special or purity testing (e.g., heavy metal)

Items in the results and discussion sections were also under reported. In particular, those relating to the generalisability of results and use in self-care and clinical practice were reported in just eight studies (13.3%). After the CONSORT extension for herbal interventions was published in 2006, RCT quality improved, although not significantly. Until 2005, 7.3 ± 3.2, 35.2% of the items were reported, and from 2006 onwards, 7.6 ± 2.3, 37.3% were reported (p=0.64). The studies reporting the most recommended items were those that investigated G115 or Cheong Kwan Jang extracts, were conducted in North America and published in CONSORT promoting journals. Table 38 presents the characteristics of the included studies.

Table 37: Individual CONSORT checklist items for herbal interventions and number of studies reporting items

Section	Item #	Item description	Number of studies reporting items and % [a]
Title/ Abst	1	The title or abstract, or both, state the herbal medicinal product's Latin binomial, and part of the plant and preparation type used.	28, 46.7%
Introducti on	2	Includes a brief explanation of the reasons for the trial, which refers to the specific herbal medicinal product being tested and, if applicable, whether new or traditional indications are being investigated.	51, 85.0%
Methods	3	If a traditional indication is being tested, describes how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.	0, 0.0%
	4	States the Latin binomial, botanical authority, family and common names for each herbal ingredient.	22, 36.7%
	5	States the proprietary product name (i.e. brand name) or extract name (e.g. EGb-761) and the name of the manufacturer of the product.	30, 69.8%
	6	States if the product used is authorised (e.g. licensed or registered) in the country in which the study was conducted.	4, 6.7%
	7	States the part(s) of plant used to produce the product or extract.	20, 33.3%
	8	States the type of product used (e.g. raw – fresh or dry – extract).	49, 81.7%
	9	States the type and concentration of extraction solvent used (e.g. 80% ethanol, 100% H_2O, 90% glycerine) and ratio of herbal drug to extract (e.g. 2 to 1).	14, 23.3%
	10	States how the raw material was authenticated and by whom; the lot number of the raw material; if a voucher specimen (i.e. retention sample) was kept, and if so, where it is and what its reference number is.	5, 8.8%
	11	States the product's dose and duration of administration, and how these were determined.	60, 100.0% [+]
	12	Lists the content (e.g. as weight or concentration – may be given as range where appropriate) of all quantified herbal product constituents, native and added, per dose unit form. Added materials, such as binders, fillers and other excipients (e.g. 17% maltodextrin, 3% silicon dioxide per capsule), are also listed.	2, 3.3%
	13	For standardized products, states the quantity of active/marker constituents per dose unit form.	15, 25.0%
	14	States the product's chemical fingerprint, how this was analysed (e.g. equipment and chemical reference standards) and by whom (e.g. laboratory name). Also states if a sample of the product (i.e. retention sample) was kept, and if so, where it is.	1, 1.7%
	15	Describes any special testing/purity testing (e.g. heavy metal or other contaminant testing) done, which unwanted components were removed and how.	0, 0.0%
	16	Describes what was standardised (e.g. which chemical components of the product) and how (e.g. chemical processes or biological/functional measures of activity).	6, 10.0%
	17	Includes the rationale for the control or placebo type used.	45, 75.0%
	18	Describes the practitioners (including their training and practice experience) who were part of the intervention.	5, 8.3%
	19	Outcome measures reflect the intervention and indications tested, and consider, where applicable, underlying theories and concepts.	0, 0.0%
Results	20	Baseline data includes concomitant medicines, including herbal and complementary medicines.	9, 15.0%
Discussion	21	Results are interpreted in light of the product and dose regimen used.	38, 63.3%
	22	Where possible, herbal products and the dose regimen used are discussed in relation to what is used in self-care and/or practice.	8, 13.3%
	23	Trial results are discussed in relation to trials of other available products.	27, 45.0%

[a] % was calculated from the total number of studies reporting the item (numerator) divided by the total number of studies (denominator). Some items aren't relevant to all studies, so the total number of studies may be less. If the number of studies is originally 60, and the particular item isn't relevant in 3 studies. The % would be calculated as the total number of studies reporting the item. For example 26 divided by the total number of studies where item is relevant, that is, 57 (60–3), which equals 45.6%.

[+] All studies reported product dose and duration of administration. However, only 33 out of 60 (55%) reported how the dose and duration were determined.

Table 38: Characteristics of included studies, evaluated using the CONSORT checklist and extension for herbal interventions

Study element	Number of studies, %	CONSORT items reported[a] Mean (SD), %	Extension for herbal interventions items reported[b] Mean (SD), %
Publication period of the CONSORT checklist			
Up to 1995 (before CONSORT)	5, 8.3%	10.3 (4.9), 32.8%	-
1996–2006 (CONSORT published and revised)	30, 50.0%	14.6 (3.3), 46.1%	-
2007–present (CONSORT revised)	25, 41.7%	16.9 (4.5), 53.5%	-
Publication period of the extension for herbal interventions			
Up to 2005 (before extension)	35, 58.3%	-	7.3 (3.2), 35.2%
2006–present (after extension)	25, 41.7%	-	7.6 (2.3), 37.3%
Health-related sub-categories			
Psychomotor performance	14, 23.3%	13.6 (4.5), 42.6%	7.6 (2.4), 36.6%
Physical performance	8, 13.3%	15.8 (1.6), 50.2%	9.3 (3.1), 44.3%
Circulatory system	9, 15.0%	18.1 (4.6), 57.8%	7.5 (2.7), 37.0%
Glucose metabolism	6, 10.0%	16.5 (5.8), 51.0%	8.2 (2.8), 40.2%
Respiratory system	5, 8.3%	13.2 (4.8), 42.6%	5.4 (2.1), 25.7%
Immunomodulation	4, 6.7%	13.5 (1.7), 42.9%	7.8 (2.9), 37.3%
Quality of life/Mood	4, 6.7%	17.5 (4.0), 55.6%	6.5 (3.7), 31.7%
Erectile dysfunction	3, 5.0%	14.0 (2.0), 43.8%	5.0 (2.6), 23.8%
Anti-oxidant function	2, 3.3%	13.0 (4.2), 41.3%	6.5 (4.9), 31.7%
Cancer	2, 3.3%	15.0 (5.7), 46.9%	6.5 (3.5), 31.7%
Menopausal symptoms	1, 1.7%	NA, NA, 50.0%	NA, NA, 30.0%
Dry mouth	1, 1.7%	NA, NA, 69.7%	NA, NA, 45.5%
Ulcerative colitis	1, 1.7%	NA, NA, 34.2%	NA, NA, 4.3%
Panax ginseng* preparation			
G115™	22, 35.5%	15.3 (3.9), 48.3%	8.4 (2.8), 40.3%
Panax ginseng (undeclared)	14, 22.6%	15.1 (3.6), 47.5%	7.3 (2.3), 35.3%
Red Ginseng extract	13, 21.0%	14.8 (3.9), 46.7%	5.9 (2.5), 29.1%
Korean Red Ginseng	3, 4.8%	16.0 (8.2), 50.0%	7.3 (3.8), 35.5%
Gerimax™	2, 3.2%	10.5 (6.4), 33.3%	4.5 (3.5), 21.4%
Cheong Kwan Jang™	2, 3.2%	21.5 (4.9), 67.2%	8.5 (2.1), 40.5%
Korean Red Ginseng rootlet	1, 1.6%	NA, NA, 75.0%	NA, NA, 42.8%
Fermented Red Ginseng	1, 1.6%	NA, NA, 55.1%	NA, NA, 42.8%
Sun Ginseng	1, 1.6%	NA, NA, 43.8%	NA, NA, 20.0%
Tissue-cultured mountain extract	1, 1.6%	NA, NA, 43.8%	NA, NA, 40.0%
60% ethanolic extract	1, 1.6%	NA, NA, 43.8%	NA, NA, 57.1%
PKC 169/79 (Pharmaton)	1, 1.6%	NA, NA, 35.5%	NA, NA, 33.3%
Sample size			
0–10	2, 3.3%	13.0 (4.2), 40.6%	4.5 (2.1), 21.4%
11–50	38, 63.3%	15.1 (4.8), 47.6%	7.8 (2.9), 37.6%
51–100	15, 25.0%	15.8 (3.4), 50.2%	7.2 (2.9), 34.8%
101+	5, 8.3%	16.2 (2.2), 51.6%	6.6 (2.1), 32.0%
Journal			
Promotes CONSORT	13, 21.7%	15.8 (4.3), 50.1%	7.7 (3.5), 37.2%
Does not promote CONSORT	47, 78.3%	15.1 (4.3), 47.8%	7.4 (2.6), 35.5%
Geographical location where study was conducted			
Asia	26, 43.3%	15.7 (4.2), 49.7%	6.5 (2.6), 31.9%
Europe	18, 30.0%	13.3 (4.4), 41.9%	7.2 (2.4), 34.1%
North America	13, 21.7%	17.5 (3.6), 54.9%	9.6 (2.4), 46.9%
Other	3, 5.0%	14.7 (3.1), 46.3%	6.7 (1.2), 30.8%

a The CONSORT statement includes 38 items, **b** The CONSORT extension for herbal interventions includes 23 items.

% was calculated from the total number of items reported (numerator) divided by the total possible number of items that could be reported (denominator). For example, if 5 studies were included, the maximum number of CONSORT items would be 38 multiplied by 5, which equals 190. Some items aren't relevant to all studies. For example, if 20 items from these 5 studies weren't relevant, the total possible number of items equals 170 (190 – 20). If the numbers of items reported by these five studies were 10, 20, 20, 30 and 30, the total reported items would be 110. The % would be calculated as 110 divided by 170 (64.7%).

* Two studies reported on two different *Panax ginseng* preparations, so there are 62 preparations.

5.4.15 Adverse events

Information on adverse events was reported in 41 studies. Information on adverse events was not reported for 26 studies. Of the 41 studies where adverse events were reported, 17 studies had no reported adverse events and 24 studies had 135 minor events. Minor events included headache, insomnia, diarrhoea and mild hepatic dysfunction. Table 39 presents a summary of the adverse events from the included studies. Thirty-three (33) people withdrew from studies due to adverse events, 22 of these people were taking an intervention at the time of withdrawal and 11 people were taking a placebo. The numbers of events are outlined in Table 34.

Table 39: Adverse events from the included studies

Type of event	Number of cases	References
Headache and insomnia	19	(112, 168, 202, 205, 207, 212, 216)
Diarrhoea	7	(168, 177, 180, 219)
Nausea and vomiting	7	(164, 168, 188, 202, 212)
Mild feverish sensation	6	(164, 168, 191, 219)
Itching sensation or rash	5	(112, 219)
Increased blood pressure	4	(112)
Mild hepatic dysfunction (ALT increased)	4	(149, 187)
Dyspepsia	3	(219)
Nasal bleeding	3	(112)
Sweating	3	(112, 219)
Epigastric discomfort	2	(202, 219)
Gastrointestinal discomfort	2	(181, 194)
Increased heart rate	2	(112)
Vaginal bleeding	2	(218)
Allergic reaction	1	(198)
Anorexia	1	(168)
Anxiety	1	(202)
Dizziness	1	(168)
Flushing	1	(194)
Hypoglycemia	1	(200)
Irritability	1	(212)

The table includes specific references to reported adverse events. Some studies mentioned adverse events however group and type of event were not explicit, they were not included.

5.4.16 Effect of interventions

5.4.16.1 Psychomotor performance

Psychomotor performance and cognitive function were evaluated in 17 studies (150, 151, 162-176). These studies measured 13 different outcomes, which were broadly categorised as reaction times, arithmetic tasks, memory and attention, psychological status, and subjective feelings. Of these 17 studies, two evaluated *Panax ginseng's* effect on people with Alzheimer's disease, one evaluated its effects on people with non-insulin dependent diabetes mellitus, and the remaining 14 evaluated its effects on healthy people.

In 16 studies, certain aspects of psychomotor performance improved after *Panax ginseng* treatment. Intergroup differences were only observed in four of these studies (166, 173, 174, 176). One study reported a difference in immediate word recall after using a 400 mg single dose of G115 (MD 17.33 [4.26, 30.40]) (166). In another study, auditory reaction time improved after 8 weeks' treatment with 400 mg of Gerimax (MD –13.00 [–24.87, –1.13]) (173). In Ziemba's study, visual reaction time improved at the end of 6 weeks' treatment with 350 mg *Panax ginseng*, (MD –10.10 [–12.54, –7.46]). Sotaniemi et al investigated psychomotor performance in people with non-insulin dependent diabetes mellitus. They observed an intergroup difference on overall psychomotor performance after 8 weeks' of 100 mg Gerimax (MD –9.20 [–15.55, –2.85]). Although psychomotor performance seemed to improve in people given *Panax ginseng* the clinical significance of these results is difficult to interpret.

5.4.16.2 Physical performance

Physical performance was evaluated in 10 studies (177-186). Oxygen consumption (VO_2) was the main outcome measure in six studies, peak power output measured in two studies, and lactate threshold and time to exhaustion primarily measured in one study each. All studies recruited healthy people and treatment durations ranged from 1 day to 8 weeks. An intergroup difference for VO_{2peak} was seen in one study (MD 2.90 [1.26, 4.54]) (177). However, a baseline imbalance was present. Therefore, *Panax ginseng* had no significant effect on physical performance in these studies.

5.4.16.3 Circulatory conditions

Panax ginseng's effect on the circulatory system were evaluated in 9 studies (187-195). The characteristics of these studies varied. Participants included healthy people or people with conditions such as myocardial infarction, stroke, hypertension or glaucoma. *Panax ginseng* doses also differed, ranging from 200 mg per day to 4.5 g per day. This made it difficult to pool results.

Authors from three studies reported that *Panax ginseng* has no significant effect on prothrombin time (192), blood pressure (194), or vascular endothelial function (195). However, it reportedly did affect outcomes in four studies (187, 188, 191, 193), although intergroup differences at the end of treatment were not significant. Jovanovski et al compared the effect of a single dose of 3 g of Red Ginseng with placebo in healthy people. The Augmentation Index improved by MD –5.19 [–6.58, –3.80]. Lowering the Augmentation Index may help to reduce arterial stiffness and risk of cardiovascular disease, despite it not significantly lowering blood pressure.

5.4.16.4 Glucose metabolism

Six studies evaluated *Panax ginseng's* effects on glucose metabolism (160, 196-200). Two of these studies enrolled people with type 2 diabetes, and four enrolled healthy people. Authors from four studies reported positive results for *Panax ginseng* (196-199). No significant results were reported from the other two studies (160, 200).

Outcomes from five studies showed no intergroup differences at the end of *Panax ginseng* treatment. However, De Souza et al observed that a single 3 g dose of *Panax ginseng* significantly lowered the incremental area under the glucose curve (iAUC). This may indicate that *Panax ginseng* can help to decrease circulating glucose, which is often high in people with type 2 diabetes.

5.4.16.5 Respiratory conditions

Five studies evaluated *Panax ginseng's* effects on the respiratory system (12, 149, 201-203). One study used 1.5 g of fermented Red Ginseng for 4 weeks to treat allergic rhinitis (149). The authors reported reduced nasal congestion and skin reactivity to allergens, however intergroup differences were insignificant.

Scaglione et al investigated the effects of 200 mg of G115 on chronic bronchitis in two studies. The first compared with placebo for 8 weeks (201) and the second compared with antibiotics for 9 days (203). The phagocytosis index (MD 0.38 [0.24, 0.52]), intra cellular killing (MD 0.20 [0.08, 0.32]) and bacterial clearance (MD –0.80 [–0.94, –0.66]) improved in both studies, indicating that *Panax ginseng* may improve the immune response and quicken recovery after infection.

Scaglione et al also investigated the effects of 200 mg of G115 administered for 12 weeks after an anti-influenza vaccination. Results showed that *Panax ginseng* improved the immune response by increasing the natural killer cell activity (MD 16.70 [13.83, 19.57]). It also decreased the incidence of common colds (RR 0.35 [0.21, 0.60]). Anti-body titres also improved (MD 52.70 [33.74, 71.66]) in people given G115, suggesting it has a synergistic effect with vaccination. Giving people with COPD 200 mg of G115 for 12 weeks improved their lung function (FEV_1 MD 20.00 [15.62, 24.38], FVC MD –8.50 [–11.00, –6.00]), and exercise performance (VO_{2max} MD 9.50 [4.19, 14.81]) (12). However, these results were only observed after 4 weeks of treatment and by 8 weeks of treatment, there was no longer any statistical significance. This indicates that *Panax ginseng* may reduce respiratory inflammation and infection, and improve lung function and respiratory muscle strength.

5.4.16.6 Erectile dysfunction

Four studies investigated *Panax ginseng's* effect on erectile dysfunction (204-207). These studies used different *Panax ginseng* formulations. Two studies examined Red Ginseng, one at 200 mg for 12 weeks (204) and the other at 2.7 g for 8 weeks (206). Authors reported improved erectile function however there were no intergroup differences at the end of treatment. In the other two studies, participants reported significant improvement on the International Index of Erectile Function questionnaire (IIEF-5). One study (205) prescribed 3 g of *Panax ginseng* for 12 weeks, with improvements of MD 3.30 [0.28, 6.32]. The other prescribed 2 g of tissue-cultured mountain Ginseng extract for 8 weeks, with improvements of MD 6.53 [0.81, 12.25] (207).

5.4.16.7 Immunomodulation

Panax ginseng's effect on immunomodulation was investigated in four studies (161, 208-210). Gaffney et al administered a 4 mL 60% *Panax ginseng* ethanolic extract to healthy endurance athletes for 6 weeks. The athletes' lymphocyte counts and endocrine function were examined, but no significant effects were observed.

Jung et al investigated post-exercise muscle damage and inflammation after administration of 60 g of Red Ginseng to healthy people for 10 days. In that time, creatine kinase significantly deceased (MD –39.50 [–65.98, –13.02]) indicating reduced muscle damage. Insulin sensitivity also improved (MD 1.40 [0.52, 2.28]) possibly due to reduced muscle damage.

Scaglione et al conducted two studies that followed the same protocol, using 200 mg G115 or PKC for 8 weeks. Immune cell activity and numbers were measured at the end of treatment. Significance for G115 and PKC was observed, chemotaxis (G115, MD 0.53 [0.19, 0.87] and PKC, MD 0.52 [0.19, 0.85]), and total lymphocytes (PKC, MD 5.82 [0.89, 10.75]).

In another study, blood leukocytes and lymphocytes were measured in healthy people after 300 mg of *Panax ginseng* was administered for 8 weeks. However, no significant changes were reported (210).

5.4.16.8 Quality of life and mood

Three studies evaluated quality of life (212-214), and one evaluated mood (211). Studies used validated questionnaires, including the Short Form Health Survey (SF-36), World Health Organisation quality of life questionnaire (WHOQOL-BREF), Global Health Questionnaire, Physiological General Wellbeing Index, and for mood, the Positive and Negative Affect Schedule and Profile of mood states. Three authors reported improvements in certain domains of the questionnaires (212-214). However, intergroup differences at the end of treatment were insignificant.

5.4.16.9 Antioxidant function

Two studies evaluated *Panax ginseng's* antioxidant effects (215, 216). Kim & Lee studied healthy smokers taking 1.8 g of Red Ginseng or placebo for 4 weeks. However, no significant effect was reported.

Kim et al investigated the effect of *Panax ginseng* at 1 or 2 g per day on healthy people for 4 weeks. Lipid peroxidation decreased with low and high doses MD –1.50 [–2.97, –0.03] and MD –1.80 [–3.20, –0.40], respectively. These studies provide some evidence of *Panax ginseng's* antioxidant effect. However, other measured components, including total reactive oxygen species and antioxidant capacity were not significant.

5.4.16.10 Cancer

Cancer recurrence was monitored in people diagnosed with stage III gastric cancer who were given 4.5 g per day of Red Ginseng for 6 months (111). People were followed up for 4.5 years after treatment and there was a significant reduction in cancer recurrence (RR 0.49, [0.25, 0.98]).

Incidence of cancer was monitored in people with chronic atrophic gastritis who were given 1 g per week of Red Ginseng for 3 years (112). Participants were followed up for 8 years after treatment and there was a notable reduction in incidence of cancer (RR 0.49, [0.21, 1.13]).

5.4.16.11 Menopausal symptoms

Two studies investigated *Panax ginseng's* effects on menopausal symptoms (217, 218). One study used the Kupperman Index to evaluate menopausal symptoms and secondary outcomes of serum estradiol and cholesterol (217). The authors reported that Red Ginseng at 3 g per day for 12 weeks reduced symptoms. However, intergroup differences could not be analysed. Oh et al used the Global Assessment Questionnaire, the Female Sexual Function Index and testosterone levels to evaluate sexual arousal in menopausal women. Increased sexual arousal was reported. However, there were no significant intergroup differences at the end of treatment.

5.4.16.12 Dry mouth

One study evaluated *Panax ginseng's* effect on subjective dry mouth (219). Authors reported it had no significant effect and there were no intergroup differences for any outcome.

5.4.16.13 Ulcerative colitis

One study evaluated *Panax ginseng's* effect on severe ulcerative colitis (220). *Panax ginseng* was compared to standard care for 15 days. Electrolyte levels were improved (RR 2.17 [1.37, 3.43]). The clinical relevance of this result is difficult to interpret.

5.4.17 Discussion

This review identified 67 studies with very different designs and methodologies. This is not surprising as *Panax ginseng* has been investigated in RCTs for more than 28 years with 95 outcomes explored and 12 different types of *Panax ginseng* preparations used.

Results from the included studies indicate that *Panax ginseng* has promising therapeutic effects on immunity and glucose metabolism. It moderated the immune response, particularly cell-mediated immunity, in several of the included studies. This could have significant implications for people with health conditions like COPD (12, 201, 203). When combined with results from pre-clinical studies, results from clinical studies in the sub-categories of immunomodulation and antioxidant function may give insight into how the immune system may be moderated by *Panax ginseng.*

Although evidence supporting *Panax ginseng's* use to help balance glucose metabolism is limited, the positive results from the included studies give some indication of its effects on the overall glycaemic response and ability to lower circulating glucose. This area warrants further investigation, specifically looking at its mechanisms and clinical applicability for people with type 2 diabetes.

Psychomotor performance was the most commonly investigated outcome, results were positive but not compelling. The most interesting psychomotor performance results related to improved cognitive function and glucose metabolism. Psychomotor and cognitive function is impaired in people with diabetes (221). Future research that aligns psychomotor performance and glucose control will be valuable.

5.4.18 Summary of adverse events

Authors included information on adverse events in 41 out of the 67 studies reviewed. Adverse events most often included headache, insomnia, and diarrhoea. However, a particular dose or preparation relating to adverse events could not be identified.

From this review, it appears that *Panax ginseng* has a good safety profile. This result re-confirms other reports of *Panax ginseng's* safety (95). Interestingly, two studies (192, 193) noted no drug-herb interaction between *Panax ginseng* and warfarin, which has been reported in other studies (95, 100).

5.4.19 Comparison with other systematic reviews

The broad clinical benefit of Ginseng has been evaluated in two previous systematic reviews (147, 148). This review identified areas of promising findings that were similar to earlier reviews. However, this review clearly aligned important disease areas with clinical outcomes including; chronic respiratory diseases (e.g., chronic bronchitis) with cell-mediated immune outcomes; type 2 diabetes with circulating glucose levels, and psychomotor and cognitive performance.

Panax ginseng was the only species included in this review. The previous two reviews did not evaluate *Panax ginseng* alone, but combined data on several Ginseng species including *Panax quinquefolium* and *Eleutherococcus senticosus*. Combining results from different plants is inappropriate. Each plant has unique active constituents, which potentially have different actions making results difficult to interpret.

Previous reviews are out of date, Vogler's review published in 1999 and Lee's review only searched for literature published until 2009. Furthermore, Lee and Vogler used the Jadad scale to evaluate study quality. The Cochrane Collaboration's Risk of Bias tool was used in the current review and evaluates six domains of potential bias and more critically evaluates studies than the Jadad Scale.

Finally, Vogler and Lee did not report results as mean differences at the end of treatment preferring to interpret results subjectively. By using the mean differences, the conclusion and interpretation of efficacy are more reliable.

5.4.20 Heterogeneity of the Studies

Data synthesis for this review was limited by heterogeneity between studies. Pooling results would introduce confounding, so it was inappropriate. The lack of high quality and appropriately powered studies means it is difficult to make data relevant and able to be generalised. To further highlight this problem, 44 out of the 67 studies stated positive findings, but strong conclusions were not reported.

Included studies looked at a wide variety of outcomes and participant characteristics. Even after grouping studies into health related sub-categories, their differences were still significant. *Panax ginseng* preparations were also diverse, with the manuscripts including little information about manufacturing processes. This made it difficult to compare studies and decide if their recommendations for dosage and length of administration seemed appropriate.

5.4.21 Summary of risk of bias

A number of tools are available to evaluate risk of bias (222). Many researchers use the controversial and often misleading scoring system tools, for example the Jadad scale (223). In this review the Cochrane Risk of Bias tool was used despite potential limitations. The main limitation being its relative newness where studies published prior to its dissemination are at a disadvantage (13).

Classification of risk of bias in most studies was judged as “unclear”. The key issues identified in the studies include inadequate randomisation, allocation concealment procedures and blinding of outcome assessment. This does not necessarily mean the

authors of the studies used inappropriate research methods, but based on an evaluation of published studies alone, without access to full trial protocols it is difficult to properly judge the risk of bias in these studies with so little information provided.

5.4.22 Summary of quality assessment

This is the first time the CONSORT checklist, CONSORT extension for herbal interventions and risk of bias have been simultaneously used to determine the quality of clinical reports for a specific single herb intervention.

This review revealed that less than 50% of CONSORT items were reported in *Panax ginseng* RCTs. Therefore, results need to be interpreted with caution and the value of results from these studies, either positive or negative, may be compromised.

The major methodological issues include lack of information about participant and intervention allocation, insufficient statistical power and little detail about the intended treatment assignment. However, the context and time frame of publications needs to be kept in mind. For instance, trial registration before 2005 wasn't compulsory, but is now mandatory (224), and intention-to-treat analysis is a relatively new method.

Methodological deficiencies seen in this review have been identified in other herbal medicine and drug RCTs (225, 226). Herbal medicine RCTs are more challenging than western drug RCTs, because the herbal compounds are often in their natural form and quality control including authentication of constituents can be variable (227, 228).

Furthermore, effective application and interpretation of traditional medicine theory to ensure data validity is difficult.

Several independent and overlapping reasons could cause under reporting of trial methods. For example, publishing journals often do not strictly enforce the CONSORT checklists. Elements of the CONSORT extension for herbal interventions may be difficult to address, particularly in the areas of quality control, chemical fingerprinting and standardisation and researchers may be inexperienced in trial design and/or have little understanding of herbal quality control (229).

Evaluating herbal medicine RCTs using the CONSORT checklist, CONSORT extension for herb interventions and risk of bias simultaneously provides a detailed picture of the methodological quality. There are similarities in the evaluation methods, including the CONSORT checklist having components of randomisation and allocation concealment similar to that in the Cochrane Risk of Bias tool. The CONSORT checklist covers the fundamental methodological considerations however the CONSORT extension for herb interventions covers additional items. The risk of bias tool is most useful for determining internal validity and bias retrospectively however the CONSORT checklists are more appropriately applied in the guidance of prospective clinical studies.

5.4.23 Limitations of the review

The review was limited to clinical trials published in journals in English and Chinese. To overcome this, planned future reviews on Korean literature may help to draw firm conclusions about *Panax ginseng's* efficacy and safety in treating various health conditions. Also no included RCT protocols were tested more than once, which limited the strength of evidence and prevented the planned meta-analysis.

Results from these studies are difficult to interpret, as the use of *Panax ginseng* is unjustified. Aspects of the studies varied considerably, most notably, the preparation method of *Panax ginseng* and the justification for dose and standardisation of active ingredients.

The methodological component of this review may have some limitations. Specifically, 35 studies were published before the CONSORT extension for herbal interventions. Additionally, the results may not represent other types of herbal interventions.

5.4.24 Conclusions and implications

This is the most comprehensive and up-to-date systematic review of *Panax ginseng* in RCTs. *Panax ginseng* appeared to have some positive therapeutic effects on various health conditions. However, caution needs to be taken when interpreting results due to risks of bias, particularly for random sequence generation and allocation concealment. There were several different study designs and limited information on how *Panax ginseng* was prepared. There were also several methodological issues, notably small sample sizes with undisclosed sample calculations.

A diverse range of studies evaluatimg various health conditions were found. The most promising evidence supports *Panax ginseng's* use in moderating glucose metabolism and the immune response, particularly cell-mediated immunity with implications for chronic respiratory diseases and type 2 diabetes.

Variable findings from the included studies may be attributed to inconsistency in the quality of the *Panax ginseng* products investigated, particularly in respect to the ginsenoside content. Future clinical studies should focus on the most promising outcomes identified in this review. Additionally, quality methodology and standardised *Panax ginseng* products should be used in future studies and particular attention paid to establishing the mechanisms of *Panax ginseng*.

5.5 Effect of *Panax ginseng* on reducing inflammation and oxidative stress and its prospective as a treatment of COPD: a review of the experimental and clinical literature

5.5.1 Introduction

Chronic inflammation in COPD is activated by exposure to cigarette smoke leading to inflammation. Inflammatory cells including macrophages, neutrophils and CD8+ T cells migrate to the airways and lung parenchyma (33). The inflammatory cells secrete chemokines and cytokines. Neutrophils degranulate and produce reactive oxygen species (ROS) and enzyme proteases are activated. These processes result in damage to epithelial cells, degradation of elastic fibres and extra cellular matrix and loss of elastic recoil, which induces repair and remodelling. Airways become chronically inflamed resulting in loss of lung clearance and mucus hyper secretion. Fibrosis occurs leading to further remodelling and narrowing of the airways. Chapter 2 describes the details.

Panax ginseng has multiple actions and exerts a wide range of effects on inflammation and oxidative stress (10). *Panax ginseng* may have an effect on several areas including regulation of inflammation and oxidative stress related pathways; modulation of cytokines and mediators; reducing oxidative stress; and reducing the activity and numbers of immune cells. Understanding these actions may aid in the development of Ginseng products for the management of COPD.

5.5.2 Objective

The objective of this review was to summarise and evaluate the existing literature on *Panax ginseng* in experimental, *in vitro, in vivo* and clinical studies, RCTs. The focus was to evaluate the mechanisms of *Panax ginseng* on reducing inflammation and oxidative stress relevant to COPD.

5.5.3 Methods

5.5.4 Search strategy

A systematic search was conducted on five English databases: MEDLINE, EMBASE, CINAHL, PsychINFO and the Cochrane library. The search period ranged from the databases' inception until 20 August 2012. Reference lists for further publications were also searched. Table 40 presents the search strategy.

Table 40: Search strategy to identify *in vitro, in vivo* and RCTs in MEDLINE

In vitro	
1.	*Panax ginseng*.tw or ginsenoside.MeSH
2.	Cell.MeSH or cell.tw or *in vitro*.MeSH
3.	Inflammation.MeSH or inflammation.tw or anti-inflammatory.tw
4.	Oxidative stress.MeSH or oxidative stress.tw or antioxidant.tw
5.	1 and 2 and 3
6.	1 and 2 and 4
7.	5 or 6
In vivo	
1.	*Panax ginseng*.tw or ginsenoside.MeSH
2.	*In vivo*.tw
3.	Inflammation.MeSH or inflammation.tw or anti-inflammatory.tw
4.	Oxidative stress.MeSH or oxidative stress.tw or antioxidant.tw
5.	1 and 2 and 3
6.	1 and 2 and 4
7.	5 or 6
RCTs	
1.	*Panax ginseng*.tw or ginsenoside.MeSH
2.	Inflammation.MeSH or inflammation.tw or anti-inflammatory.tw
3.	Oxidative stress.MeSH or oxidative stress.tw or antioxidant.tw
4.	Randomized controlled trial.MeSH or randomized clinical trial.tw or clinical trial. MeSH or controlled clinical trial.pt
5.	1 and 2 and 4
6.	1 and 3 and 4
7.	5 or 6

MeSH = medical subject headings, tw = text word, pt = publication type. Boolean operators: and, or, not are

5.5.5 Eligibility of studies

Specific inclusion criteria were:

- *in vitro, in vivo* and RCTs
- *Panax ginseng* or ginsenoside(s) as the intervention

Specific exclusion criteria were:

- *Panax ginseng* combinatorial products
- non English publications

5.5.6 Data extraction

Two reviewers searched the databases. Any disagreements were resolved by consensus. The second reviewer was an experienced researcher from RMIT University, the contribution of Dr Yuan Ming Di is acknowledged.

5.5.7 Results

Searches identified 880 studies [Figure 22]. Of these, 35 met the inclusion criteria; 14 were *in vitro* studies (104, 230-242) [Table 41], 10 *in vivo* (243-252) [Table 42], and 11 were randomised controlled trials (12, 161, 187, 201-203, 208-210, 215, 216) [Table 43].

The main effects of *Panax ginseng* and ginsenosides included regulation of immune cell activity and numbers, modulation of cytokine and mediator production, reduction in oxidative stress, and regulation of inflammation and oxidative stress related pathways. Figure 23 presents an overview.

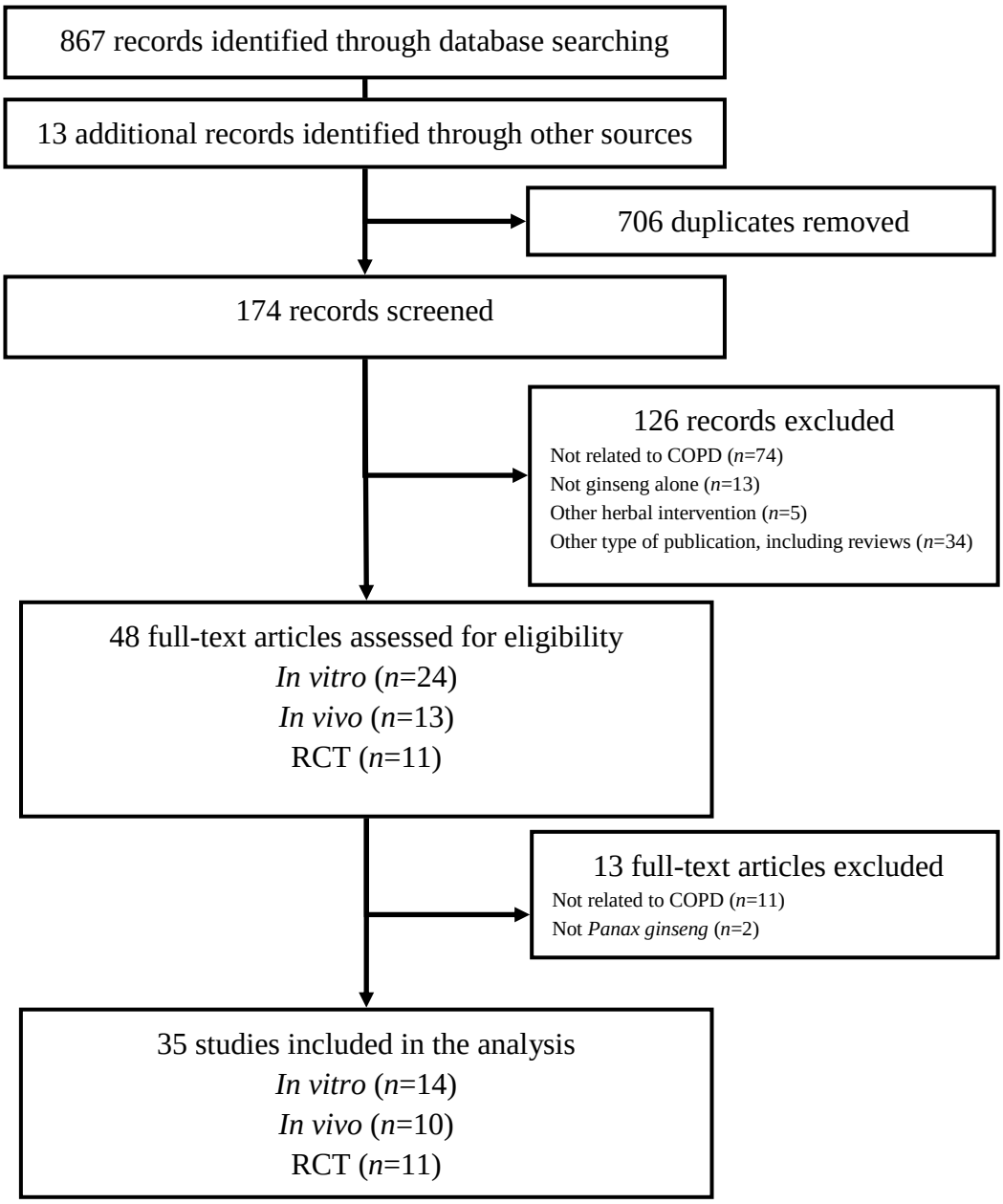


Figure 22: Flow diagram of study selection

Table 41: Characteristics of *in vitro* studies

***In vitro* studies**				
Test agent	**Cell line**	**Result**	**Conclusion and proposed mechanism**	**Reference**
INFLAMMATION				
Rb1	HUVECs and human lung microvascular endothelial cells	1. Decreased TNF-α 2. Blocked THP-1 adhesion 3. Decreased superoxide anion	Rb1 reduced TNF-α-induced MAPKs and NF-κB activation. May be effective for controlling inflammation	Chai, 2008, Japan (230)
Rb1, Rb2, Rc	human (U937) macrophages and (Maurine) RAW264.7 macrophage	1. Decreased TNF-a	Hypothesised decreased in TNF- α through suppression of cAMP PDE and regulate cGMP cell balance	Cho, 2001, Korea (233)
Re and PPT	Human umbilical vein endothelial cells (HUVECs)	1. Reduced IP-10 2. Increased cell viability 3. Decreased apoptosis and DNA damage	Re and PPT decreased influenza-induced inflammation and apoptosis	Chan, 2011, China (231)
Transgenic *Panax ginseng* root extract	Human mast cell line 1 (HMC-1)	1. Decreased TNF-α, IL-6, and IL-8 2. Decreased COX-2 expression 3. Inhibited intracellular Ca2+ levels	Ginseng can down regulate inflammation by inhibiting cytokine production. Mast cell activation was also turned down indicting *Panax ginseng* has an anti-inflammatory effect.	Kim, 2007, Korea (104)
Panax ginseng root extract	THP-1 monocytic leukemia cells	1. Decreased cytokine expression including TNF-α, IL-1β, IL-6, IL-8, IL-10, and TGF-β	Ginseng down regulated cytokine production and inflammation. Ultrafine granules of *Panax ginseng* were more potent inhibitors.	Lee, 2008, China (239)
Panax ginseng extract	Human monocytic cells (U937)	1. Reduced IP-10	Ginseng can supress signalling proteins of cytokines, possible correlated with the inactivation of ERK1/2 pathways	Lee, 2009, China (238)
Panax ginseng extract	Human mast cell line 1 (HMC-1)	1. Decreased IL-6 and COX-2 2. Suppression of NF-κB and MAPK	Ginseng modulates the production of IL-6 and the expression of COX-2 through the regulation of NF-κB activation	Choi, 2011(A), Korea (234)
Rh1	THP-1 monocytic leukemia cells	1. Decreased MCP-1 and CCR2 2. Attenuated the phosphorylation of MAPK 3. Reduced adhesion of monocytes	Rh1 inhibited the expression of both MCP-1 and its receptor CCR2, which are key mediators in monocyte and macrophage recruitment	Choi, 2011(B), Korea (235)
Panax ginseng root extract	Not specified	1. Inhibition of cAMP	May be related to biological activities	Nikaido, 1984, Japan (240)

ADP: adenosine diphosphate, ATP : adenosine triphosphate, cAMP : cyclic adenosine monophosphate, CCR2: chemokine receptor 2, cGMP: cyclic guanosine monophosphate, COX-2: cytochrome c oxidase subunit II, DNA: deoxyribonucleic acid, eNOS: endothelial nitric oxide synthase, ERK1/2: extracellular Signal-Regulated Kinases 1 and 2, GPx: glutathione peroxidase, GR: glutathione reductase, GSH: glutathione, GSSG: oxidized glutathione, Hcy: homocysteine, HMC-1: human mast cell line 1, HUVEC: Human umbilical vein endothelial cell, H_2O_2: hydrogen peroxide, IL: interleukin, IP-10: interferon-Inducible Protein 10, JNK: c-Jun N-terminal kinases, LDH: lactate dehydrogenase), MAPK: Mitogen activated protein kinase, MCP-1: monocyte chemotactic protein-1, MPP+: 1-methyl-4-phenylpyridinium, mRNA: messenger ribonucleic acid, NAD: nicotinamide adenine dinucleotide, NF-κB : nuclear factor kappa-light-chain-enhancer of activated B cells, NO: nitric oxide, PARP-1: poly [ADP-ribose] polymerase 1, PDE: phosphodiesterase, ROS: reactive oxygen species, TGF-β: transforming growth factor beta, THP-1: Tamm-Horsfall protein 1, TNF-α: tumour necrosis factor-alpha, t-PA: tissue-type plasminogen activator

Table 41: Characteristics of *in vitro* studies continued

***In vitro* studies**				
Test agent	**Cell line**	**Result**	**Conclusion and proposed mechanism**	**Reference**
OXIDATIVE STRESS				
Rg1	SHSY5Y human neuroblastoma cells	1. Reduced cell apoptosis 2. Attenuate ROS	Rg1 may exert protective effect and reduced cell apoptosis by inhibiting the production of ROS, activation of JNK and caspase-3.	Chen, 2003, China (232)
Rb1	HUVECs	1. Decreased LDH activity 2. Increased eNOS mRNA and t-PA mRNA 3. Increased NO	Reduce endothelial dysfunction by reducing LDH activity, increase vascular relaxation by increased NO and prevent thrombus fibrinolysis and formation.	He, 2007, China (236)
PPT	HUVECs	1. PPT reversed H_2O_2 induced cell death and LDH release. 2. PPT reversed the depleted GSH level and total GSH (GSH+GSSG) levels. 3. Partially reduce the formation of DNA strand breakage induced by H_2O_2. 4. PARP-1 activity significantly reduced NAD+ levels partially prevented. 5. ATP and ADP levels maintained.	Modulates glutathione level by affecting related enzymes. Prevents H_2O_2 induced cell death. Antioxidant effects by up regulating GPx and GR activities.	Kwok, 2010, China (237)
Rb1	HUVECs and SVEC4-10 (mouse endothelial)	1. Inhibition of Hcy	Hcy can suppress endothelial cell proliferation or viability by inhibition the production of NO and Rb1 10 μM blocks Hcy-induced inhibition of cell proliferation.	Ohashi, 2006, USA (241)
Rg1	Fibroblasts	1. Rg1 has a dose-dependent anti-senescence capacity. 2. Rg1 protects telomeres.	Rg1 has antioxidant activity by protecting telomeres.	Zhou, 2012, China (242)

ADP: adenosine diphosphate, ATP : adenosine triphosphate, cAMP : cyclic adenosine monophosphate, CCR2: chemokine receptor 2, cGMP: cyclic guanosine monophosphate, COX-2: cytochrome c oxidase subunit II, DNA: deoxyribonucleic acid, eNOS: endothelial nitric oxide synthase, ERK1/2: extracellular Signal-Regulated Kinases 1 and 2, GPx: glutathione peroxidase, GR: glutathione reductase, GSH: glutathione, GSSG: oxidized glutathione, Hcy: homocysteine, HMC-1: human mast cell line 1, HUVEC: Human umbilical vein endothelial cell, H_2O_2: hydrogen peroxide, IL: interleukin, IP-10: interferon-Inducible Protein 10, JNK: c-Jun N-terminal kinases, LDH: lactate dehydrogenase), MAPK: Mitogen activated protein kinase, MCP-1: monocyte chemotactic protein-1, MPP+: 1-methyl-4-phenylpyridinium, mRNA: messenger ribonucleic acid, NAD: nicotinamide adenine dinucleotide, NF-κB : nuclear factor kappa-light-chain-enhancer of activated B cells, NO: nitric oxide, PARP-1: poly [ADP-ribose] polymerase 1, PDE: phosphodiesterase, ROS: reactive oxygen species, TGF-β: transforming growth factor beta, THP-1: Tamm-Horsfall protein 1, TNF-α: tumour necrosis factor-alpha, t-PA: tissue-type plasminogen activator

Table 42: Characteristics of *in vivo* studies

***In vivo* studies**				
Test agent	**Animal and tissue**	**Result**	**Conclusion and proposed mechanism**	**Reference**
INFLAMMATION				
Panax ginseng root extract	Balb/C, C57 B1/6J and C57 B1/6J nu/nu, spleen cells	1. Elevated immunoglobulin production IgM and IgG 2. Enhanced NK cell activity 3. Enhanced immune interferon production 4. Inhibited lymphocyte proliferation	Enhanced interferon production leading to stimulated NK cell activity.	Jie, 1984, Switzerland (244)
Rb1 and compound K	male ICR mice, peritoneal macrophage cells	1. Decreased TNF-α IL-1, IL-1β, IL-6 and 2. Blocked expression of COX-2 and iNOS 3. Increased IL-10	Inhibition of pro-inflammatory cytokines and enzymes and increased anti-inflammatory cytokines. Anti-inflammatory effect by blocking NF-kB and MAPK.	Joh, 2011, Korea (245)
Panax ginseng root extract	Female B6C3f1 mice, spenocytes/ monocytes	1. Increased NK cell activity 2. Unchanged T and B cell response 3. Unchanged IgM antibody production 4. Improved host resistance	Ginseng has some immune-modulatory properties, mainly associated with NK cell activity.	Kim, 1990, USA (246)
Ginsenoside Rg5	Male C57BL/6 mice, alveolar macrophages	1. Decreased TNF-α and IL-1β 2. Inhibition of iNOS and COX-2 3. Decreased protein and neutrophils in broncho-alveolar lavage	Rg5 decreased TNF-a, IL-1β, iNOS and COX-2 through inhibition of NF-kB. It also prevented the binding of bacterial molecules to macrophage receptors and therefore decreased lung inflammation.	Kim, 2012, Korea (247)
Panax ginseng root extract	pathogen-free mice, spleen cells	1. Elevated immunoglobulin production IgM, IgG 2. Elevated cytokine production IL-2, IFN-γ and IL-4 and IL-10	Ginseng can regulate antibody production by augmenting Th1- (IL-2, IFN-γ) and Th2-type (IL-4, IL-10) cytokine production	Liou, 2004, Taiwan (249)
Panax ginseng root extract	male BALB/c mice, sera and spleen cells	1. Decreased IgG, increased IgA, IgM unchanged 2. Elevated IL-2, IFN- γ, IL-10 3. Increased NK cell activity 4. Reduced T-lymphocytes (CD3+, CD4+, CD8+)	Ginseng enhances Th1-type cytokine production. This may enhance the immune response.	Liou, 2006, Taiwan (248)
Korean Red Ginseng powder extract	female BALB/c mice, blood samples	1. Increased levels of virus specific antibodies 2. Increased IL-4 and IL-5 3. Decreased IL-6	Ginseng modulates cytokine production and enhances the humoral immune responses. Enhanced effect when co-administered with influenza vaccination.	Quan, 2007, USA (250)
Panax ginseng root extract	female Lewis rats, blood samples and lung histopathology	1. Improved pulmonary bacterial clearance 2. Decreased severity of lung pathology 3. Reduced mast cell numbers 4. Decreased IgG	Ginseng regulated the immune response and shifted the altered the response by lowering serum IgG to improve bacterial clearance.	Song, 1997, Denmark (251)
Panax ginseng root extract	Female CBA/J mice	1. Increased IFN- γ & TNF- α 2. Decreased IL-4 3. Decreased severity of lung pathology	Ginseng induced at Th1-type immune response.	Song, 2003, Denmark (252)
OXIDATIVE STRESS				
Re	Streptozotocin-induced diabetic rats	1. Increased glutathione levels 2. Decreased malondialdehyde levels	Ginseng can prevent the onset of oxidative stress in some tissues	Cho, 2006, China (243)

COX-2: cytochrome c oxidase subunit II, IFN-γ: interferon-gamma, IgG: immunoglobulin G, IgM: immunoglobulin M, IL: interleukin, iNOS: inducible nitric oxide synthetase, NF-κB : nuclear factor kappa-light-chain-enhancer of activated B cells, NK: natural killer, MAPK: mitogen activated protein kinase , Th1/2: T-helper cells 1 and 2, TNF-α: tumour necrosis factor-alpha

Table 43: Characteristics of clinical trials

Clinical trials				
Intervention/ control/ dosage	**Condition treated**	**Outcomes and Results**	**Conclusions and implications**	**Reference**
INFLAMMATION				
Red Ginseng/ Placebo/ 3 g/d	Myocardial Infarction (MI)	1. Decreased IL-6 and TNF- α 2. Increased cardiac flow reserve (CFR)	Ginseng decreased inflammation in MI patients, thereby improving CFR and quickening recovery.	Ahn, 2001, Korea (187)
Panax ginseng (60% ethanolic extract)/ Placebo/ 4 mL/d	Healthy	1. Unchanged lymphocyte count 2. Unchanged Hormone levels - testosterone	No significant effect.	Gaffney, 2001, Australia (208)
G115/ Placebo/ 200 mg/d	COPD	1. Increased lung function - FEV1, FVC 2. Increase VO_2 Max	Ginseng increased lung function and exercise performance.	Gross, 2002, Israel (12)
Red Ginseng/ Placebo/ 60 g/d	Healthy	1. Decrease IL-6 2. Decreased creatine kinase 3. Decreased glucose levels	Ginseng blunted high intensity exercise muscle damage and inflammation.	Jung, 2011(a), Korea (209)
G115 or PKC/ Placebo/ 200 mg/d	Healthy	1. Increased chemotaxis 2. Increased total lymphocytes neutrophil, CD4+ and NK cells 3. Increased phagocytosis index	Ginseng improved the immune response.	Scaglione, 1990, Italy (161)
G115/ Placebo/ 200 mg/d	Chronic Bronchitis	1. Increased phagocytosis index 2. Increased intra cellular killing	Ginseng improved the immune response.	Scaglione, 1994, Italy (201)
G115/ Matching Placebo and influenza vaccination/ 200 mg/d and influenza vaccine	At risk of influenza infection	1. Increased NK cell activity 2. Reduced incidence of common cold	Ginseng improved the immune response.	Scaglione, 1996, Italy (202)
G115/ Antibiotics (Amoxicillin and clavulonic acid)/ 200 mg/d and antibiotics	Chronic Bronchitis	1. Improved bacterial count	Ginseng improved bacterial clearance.	Scaglione, 2001, Italy (203)
Panax ginseng/ Placebo/ 300 mg/d	Healthy	1. Unchanged lymphocyte count, CD4+ T cell counts and total WBCs	No significant effect.	Srisurapanon, 1997, Thailand (210)
OXIDATIVE STRESS				
Red Ginseng/ Placebo/ 1.8 g/d	Healthy smokers	1. Elevated vitamin concentrations/plasma antioxidants 2. Decreased lipid peroxidation using MDA concentrations 3. Unchanged plasma lipids	Ginseng increased antioxidants	Kim, 2001, Korea (215)
Panax ginseng/ Placebo/ 1 or 2 g/d	Healthy	1. Decreased serum ROS and MDA levels 2. Unchanged serum TAC, SOD and catalase activities 3. Increased total glutathione and GSH-Rd activity	Ginseng shows antioxidant effects by decreasing ROS and MDA	Kim, 2011a, Korea (216)

CFR: cardiac flow reserve, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, GSH: glutathione, IL: interleukin, MDA: malondialdehyde, MI: myocardial infarction, NK: natural killer, ROS: reactive oxygen species, SOD: superoxide dismutase, TAC: total antioxidant capacity, TNF-α: tumour necrosis factor-alpha, VO2: oxygen consumption, WBC: white blood cells

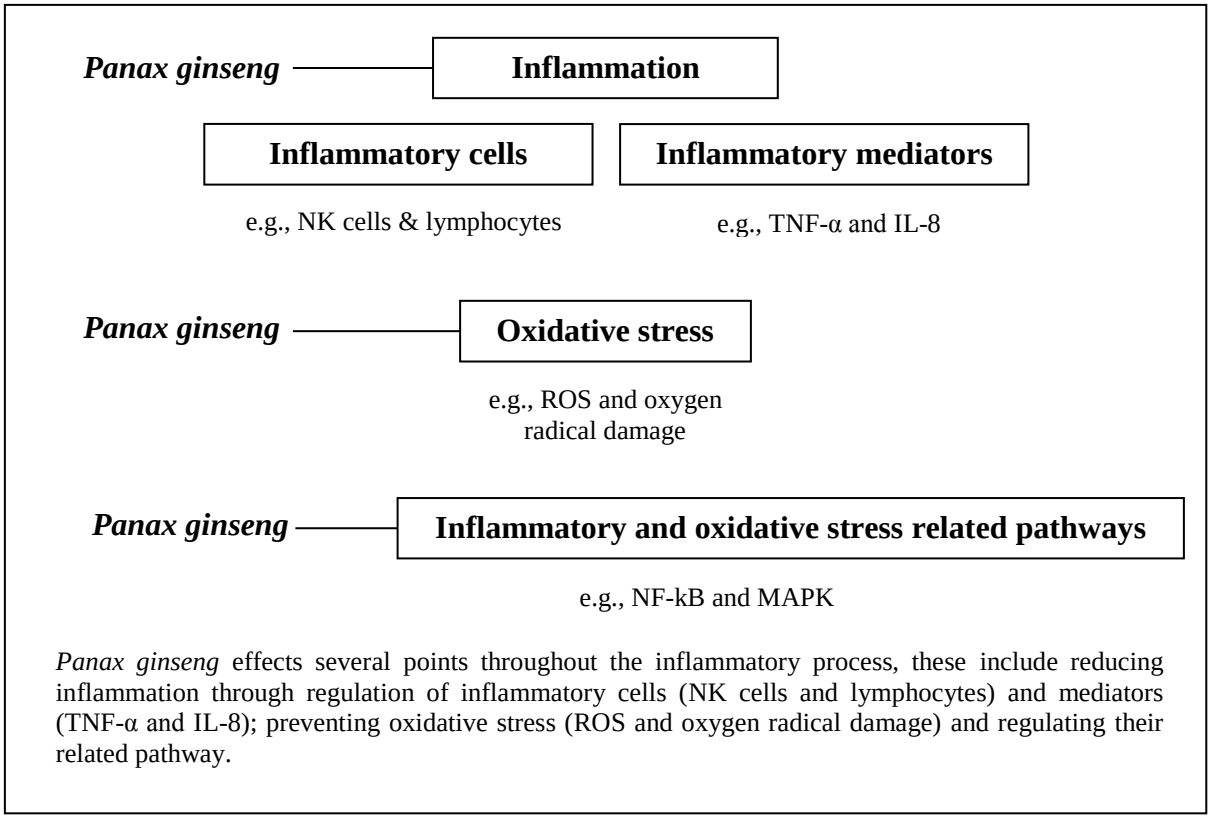


Figure 23: Effect of *Panax ginseng* on inflammation, oxidative stress and related pathways

5.5.8 Inflammatory cells

Results from *in vivo* studies

Panax ginseng root extract can moderate inflammation (244). Jie and colleagues reported enhanced interferon production, antibody formation, natural killer (NK) cell activity and the inhibition of lymphocyte proliferation by *Panax ginseng* (244). In this mouse model the results demonstrate an immune stimulatory effect by enhancing NK cell activity and an immune inhibitory effect by impeding lymphocyte proliferation. In another study, Kim et al (1990) showed that *Panax ginseng* increased NK cell activity (246). Results indicate that *Panax ginseng* has the ability to boost resistance against infection (246).

Previous *in vitro* studies show that ginsenosides can decrease influenza induced inflammation and apoptosis (231). *In vivo* studies have found a similar effect. Quan et al (2007) investigated the effect of Korean Red Ginseng on influenza infected mice (250). Korean Red Ginseng modulated cytokine production, interleukin (IL) 4, 5, 6 and increased influenza specific antibodies.

Song and colleagues in 1997 and 2001 evaluated the effect of *Panax ginseng* extracts on bacterial clearance and the immune response (251, 252). In both studies *Pseudomonas aeruginosa* infected mice showed an improved response. It was hypothesised that *Panax ginseng* may decrease the level of IgG and induce a Th-1 type response, therefore regulating the inflammatory process and reducing the bacterial load in the lung. For optimal immune function there needs to be a balance between the Th1 and Th2 type responses (253). *Panax ginseng* may regulate the axis of Th1 and Th2 and facilitate immune regulation.

Results from clinical trials

Immune cell activity and numbers including chemotaxis, total lymphocytes and leukocytes were evaluated in three studies (161, 208, 210). Scaglione et al (1990) reported improved chemotaxis and total lymphocytes in healthy people (161). However, Srisurapanon et al (1997) did not report a change in lymphocytes or blood leukocytes in a similar population (210). Gaffney et al (2001) reported no significant changes in lymphocyte counts after administration of an ethanol extract of *Panax ginseng* (208). Overall, the effect of *Panax ginseng* was variable.

Chronic bronchitis and related COPD were evaluated in three studies (12, 201, 203). In COPD sufferers, 200 mg day of a *Panax ginseng* extract (G115) increased lung function (FEV_1) and exercise performance (12). These findings are valuable for COPD sufferers as lung function and exercise capacity is severely reduced in COPD and even slight improvements can offer improved QoL. Scaglione and colleagues (1994 and 2001) evaluated 200 mg day of G115 for chronic bronchitis in two studies (201, 203). The immune response was improved in both studies, including intra cellular killing, bacterial clearance and the phagocytosis index.

In another study the effects of G115 was evaluated on the immune response after influenza vaccination (202). Several pre-clinical studies have indicated that *Panax ginseng* may reduce the severity of influenza infection particularly when used as an adjunct to the influenza vaccination (231, 250). Scaglione et al reported that G115 improved NK cell activity and lowered the incidence of common colds. These results indicate that *Panax ginseng* may improve the immune response and quicken recovery after infection.

5.5.9 Inflammatory mediators

Results from *in vitro* studies

During the pathogenesis of COPD, cytokines and mediators are increased. Tumour necrosis factor alpha (TNF-α) is a potent pro-inflammatory agent that promotes the migration of inflammatory cells into tissues. Cho et al (2001) evaluated the ability of ginsenosides Rb1, Rb2, and Rc to reduce cytokine production in U937 cells (233). Ginsenosides strongly decreased TNF-α production, implicating their use in TNF-α mediated disease. Furthermore, Lee et al (2008) found that ultra-fine granules of Red Ginseng inhibited cytokine production (TNF-α, IL- 6, 8, 10, 1β, TGF-β) in lipopolysaccharide stimulated THP-1 cells (239). These studies reveal that ginsenosides can down regulate the production and release of TNF-α.

Inhibiting cyclooxygenase-2 (COX-2) will turn down inflammation. Kim et al (2007) evaluated the effect of transgenic *Panax ginseng* on mast cell activation (104). *Panax ginseng* down regulated cytokine production (TNF-α, IL- 6, 8) inhibited COX-2 and decreased Ca_2+ levels.

Phosphodiesterases (PDE) are a family of enzymes responsible for the regulation of cAMP and cGMP. In this section the focus is on cAMP selective phosphodiesterases, such as PDE-4, 7 and 8. Nikaido et al (1984) found that protopanaxadiol ginsenosides, Rb1 and Rb2 had a high inhibitory effect on cAMP PDE (240). PDE is a principal enzyme in cAMP degradation. Inhibiting PDE will elevate the second messengers' cAMP and turn down inflammation (254).

Results from *in vivo* studies

Further to results shown in the *in vitro* studies, Kim et al (2012) found that ginsenoside Rg5 inhibits TNF-α, IL-1β, iNOS and COX-2 through inhibition of NF-kB (247). In this study C57BL/6 mice alveolar macrophages were stimulated with lipopolysaccharide and treated with Rg5. The results showed that Rg5 reduced pro-inflammatory mediators by preventing the binding of lipopolysaccharide to macrophage receptors and decreasing lung inflammation.

Liou et al (2004) injected healthy mice with an ethanol extract of *Panax ginseng*. Results demonstrated a regulation of antibody production (IgG, IgA and IgM) and enhanced cytokine production, IL-4, IL-10 IL-2, IFN-γ (249). Following on from this, Liou's group orally administered *Panax ginseng* root extracts to male BALB/c mice (248). Antibody production was regulated, that is, IgG was reduced, IgA was increased, yet IgM was unchanged. Cytokine production was elevated, IL-2, IF- γ, IL-10 (Th1-type) (248). Although these studies were not definitively conclusive, they reveal that *Panax ginseng* may have the ability to enhance and regulate inflammation.

Results from clinical trials

Panax ginseng's effect on cytokines was evaluated in two clinical studies (187, 209). One study evaluated post myocardial infarction (187) and the other looked at healthy people (209). Ahn et al (2011) found that 3 g day of Red Ginseng for 8 weeks reduced the release of IL-6 and TNF-α and improved recovery after myocardial infarction (187). Although the pathogeneses of myocardial infarction is different to respiratory inflammation, the ability of *Panax ginseng* to reduce cytokines may have implications

for COPD. Jung and colleagues evaluated post-exercise muscle damage and inflammation after 10 days of Red Ginseng administration (209). They observed a decrease in IL-6 and muscle damage. IL-6 is elevated during exercise and also plays a significant role in chronic inflammation. The results from this study support *Panax ginseng* as a cytokine regulator.

5.5.10 Oxidative stress

Results from *in vitro* studies

Reactive oxygen species (ROS) initiate oxidation of biological structures, and contribute to amplification of the inflammatory response. Chan et al (2011) evaluated the ability of Re and its metabolite PPT to protect endothelial cells from inflammation and apoptosis after influenza infection (231). Interferon gamma-induced protein 10 (IP-10) was supressed and cell viability was increased. These results indicated that the cells had a lessened infective burden and decreased influenza induced inflammation and apoptosis. The mechanism is thought to rely on the reduction of oxidative stress by enhancing the level of glutathione (GSH) that can stabilise ROS (231).

He et al (2007) showed that ginsenoside Rb1 at high doses could prevent oxidative stress by decreasing nitric oxide and serine proteases (t-PA and PAI-1) (236). These results taken together with other studies show ginsenosides seem to reduce oxidative stress.

Chen et al (2003) found Rg1 protected cells from MPP^+ induced apoptosis (232). In addition, MPP^+ induced ROS production was attenuated by Rg1. Further investigation

found that Rg1 can partially prevent the activation of JNK and caspase-3. These results are comparative to the commonly used antioxidant N-acetylcysteine (NAC). Suggesting Rg1 may exert protective effects by inhibiting ROS production and increasing defence against free radical damage.

Glutathione (GSH) is an important endogenous antioxidant enzyme that directly scavengers free radicals. Kwok et al (2010) found that PPT a metabolite of Re changed GSH metabolism by significantly increasing the activity of GSH reductase and GSH peroxidase (237). As a result, depleted levels of GSH and oxidised GSH were reversed, therefore preventing hydrogen peroxide (H_2O_2) induced change in GSH metabolism. Further, PPT protected HUVECs against H_2O_2 induced cell injury (237).

Plasma homocysteine (Hcy) can suppress endothelial cell proliferation by oxidative stress (255). Oshani et al (2006) effectively blocked Hcy induced inhibition of cell proliferation using Rb1 (241). Additionally, Rb1 blocked the effect of Hcy by increasing superoxide anion production in mouse cell lines (241). Rb1 shows effective antioxidant properties by protecting endothelial cells from Hcy induced damage.

Telomeres are specialised structures at the ends of linear eukaryotic chromosomes. Human telomeres are rich in guanine (TTAGGG) and are preferential targets of oxidative damage (256). Ultraviolet A (UVA) causes oxidative stress and shortens telomeres leading to premature aging (242). Zhou et al (2012) showed that after UVA irradiation and the photosensitising drug 8-MOP, fibroblasts had significantly shorter telomere length than the control (no UVA). Rg1 and the UVA groups were significantly

different to the 8-MOP group. 8-oxo-dG is a sensitive marker for oxidative DNA damage (242). In this study, increased concentrations of Rg1 reduced 8-oxo-dG concentrations, in turn protecting the telomere from oxidative DNA damage. Therefore, in oxidative damage by UVA, Rg1 demonstrates antioxidant properties by protecting telomeres. In the same study, in a stress induced premature senescence (growth arrest) model, Rg1 protected human fibroblasts from senescence in a dose-dependent manner (242). Age related biomarker SA-β-gal expression was significantly less in the Rg1 treated group compared to the control. These finding demonstrate that Rg1 can significantly antagonise premature senescence in human fibroblasts.

Results from *in vivo* studies

The antioxidant effects of ginsenoside Re were tested in the vascular tissues of streptozotocin-induced diabetic rats (243). GSH is an important endogenous antioxidant and malondialdehyde (MDA) is an oxidative product from lipid peroxidation. Cho et al (2006) evaluated if Re could prevent oxidative stress in vascular tissues of diabetic rats, in particular kidney, eye and the aorta. Re significantly increased GSH levels and decreased MDA levels (243). Authors summarised that Re can improve antioxidant status.

Results from clinical trials

Two clinical trials evaluated the effect of *Panax ginseng* on oxidative stress (215, 216). Kim et al (2001) evaluated antioxidant effects on smokers (215), whilst Kim et al (2011) tested healthy people (216). In smokers, 4 weeks of Red Ginseng increased plasma antioxidant levels and decreased MDA (215). MDA is a marker of oxidative

stress which is commonly seen in smokers compared to non-smokers (257). These findings suggest that Red Ginseng might protect smokers from oxidative stress (215). This is a valuable finding for COPD sufferers as smoking is the most common risk factor of disease, increased antioxidant levels in the body will offer defence against oxidative stress. In the other study, after 4 weeks of *Panax ginseng* a significant decrease in serum ROS and MDA levels was found (216). *Panax ginseng* showed antioxidant properties and enhanced antioxidant defence.

5.5.11 Inflammation and oxidative stress related pathways

The pathogenesis of COPD involves many mechanisms. The inflammatory and oxidative stress pathways are particularly important, including NF-kB and mitogen activated protein kinases (MAPK), for example ERK1/2 and p38.

Results from *in vitro* studies

NF-κB and MAPK activation orchestrates the release of down-stream products such as cytokines. In chronic conditions like COPD, these pro-inflammatory proteins facilitate the recurrent inflammatory response as well as tissue-repair and re-modelling (258).

Chai et al (2008) showed that Rb1 could reduce THP-1 monocyte adhesion and decrease superoxide anions. It is hypothesised that these effects were caused by a deactivation of NF-κB and MAPK gene transcription pathways and a reduction in TNF-α (230).

MAPK promotes transcriptional factors inducing monocyte chemotactic protein-1 (MCP-1) synthesis and stimulates the migration of monocytes and macrophages to the site of tissue injury. Choi et al (2011) and Lee et al (2009) revealed that *Panax ginseng* can reduce IL-6 and COX-2 through the deactivation of MAPK pathways (ERK1/2) (234, 238). Choi et al (2011) also showed that ginsenoside Rh1 inactivated the MAPK pathway and decreased MCP-1 (235).

Results from *in vivo* studies

MAPK and NF-kB promote cytokine release and amplify inflammation. Joh et al (2011) found that ginsenoside Rb1 and its metabolite compound K could inhibit TNF-α, IL-1β, iNOS, and COX-2. The mechanism was revealed to be through the regulation of the NF-kB and MAPK pathways (245).

5.5.12 Discussion

This review presents details of *Panax ginseng's* effect on reducing inflammation and oxidative stress. The search identified diverse actions of *Panax ginseng* and ginsenosides and highlights key areas including modulation of inflammatory cells and mediators, reduction of oxidative stress, and regulation of their related pathways.

TNF-α and NF-κB are intricately linked through bidirectional inducement (259). These factors play a significant role in the chronic inflammatory process seen in COPD. Cytokine inhibitors such as anti-TNF-α drugs are on the market and prescribed for chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease (57). For the treatment of COPD cytokine inhibitors are under investigation for use as drug therapy. The most promising targets are TNF-α inhibitors and IL-10 agonists (59). NF-κB and MAPK are involved in the pathogenesis of COPD (260). From the studies included in this review, evidence suggests *Panax ginseng* can inhibit TNF-α and regulate several steps along the gene signalling and transcription pathway via inhibition of NF-κB and MAPK. Individual ginsenosides, Rb1, Rb2, Rc, Rg5 as well as whole Ginseng extracts can reduce TNF-α, IL- 4, 6, 8, 1β through deactivation of the NF-κB pathway and subsequent gene and/or protein transcription. *Panax ginseng* also blocked other pathways including MAPK (245). The results show that Ginseng can reduce TNF-α in experimental and clinical studies. This is significant as experimental research often does not hold up in the clinical setting. Compared to drug based cytokine inhibitors *Panax ginseng* may offer an advantage in that it is considered safe and well tolerated. Cytokine inhibitors impair defence mechanisms and often cause adverse effects such as hypersensitivity reactions, serious infections, and malignancies (59, 261).

Oxidative stress is increased in patients with COPD (262). Several antioxidants such as GSH and iNOS are under investigation for clinical use in COPD (59). Ginseng and ginsenosides may also be potent antioxidants with the ability to regulate oxidant/antioxidant imbalance and reduce cell apoptosis. Ginsenoside Rg1 reduced ROS *in vitro* (232) and Kim et al reported a similar effect in a clinical trial (216). GSH which is an important antioxidant was reported to be increased by Ginseng in several studies. The specific cellular targets of Ginseng are still inconclusive however these important results indicate the need for further research.

Panax ginseng regulates NF-κB, consequently regulating inflammation, oxidation and subsequent cell apoptosis and degradation of extracellular matrix. NF-κB promotes iNOS that produces nitric oxide and supports inflammation. Ginsenoside Rg1 increases and decreases nitric oxide (236, 241). Rg1 at 10 μg/mL induced vascular relaxation by increasing nitric oxide in one study and Rg1at 10 μM inhibited endothelial cell damage by reducing nitric oxide in another (236, 241). The variable outcomes may relate to differences in dosage of Rg1, or the chemical reagents used, or other unknown factors. At a low level nitric oxide is important for normal bodily functions however it is also a free radical. When secreted as an inflammatory response it can cause oxidative damage. Variable results in this example highlight the complexity of *Panax ginseng's* effect and argue the need to undertake further studies to determine the precise mechanisms of action.

5.5.13 Limitations of the review

Results were promising however, pathophysiological insight including specific cellular targets and explicit detail regarding *Panax ginseng* and ginsenosides function was limited. This detail would help to improve understanding in the future.

5.5.14 Summary of findings

Panax ginseng and ginsenosides exert complex actions. These actions are due to multiple ginsenoside compounds and multiple targets. The results from this review are diverse. *Panax ginseng* affects several processes including inflammation and oxidative stress by down regulating the activity of NF-kB and MAPK, reducing the activity and numbers of inflammatory cells including NK cells and lymphocytes, modulation of inflammatory mediators particularly TNF-α and IL-8, and reducing oxidative stress by reducing ROS and oxygen radical damage. The results showed the most beneficial effects through the inhibition of inflammation through TNF-α and NF-κB as well as improving antioxidant status.

5.5.15 Conclusions and implications

There is substantial evidence in the literature that *Panax ginseng* and ginsenosides are capable of reducing inflammation and oxidative stress. Much of the literature focuses on experimental studies however, there is also evidence from clinical trials. The results highlight the need for further investigation into *Panax ginseng's* use in COPD in the view to develop new therapeutic treatments.

Chapter 6: A randomised controlled trial protocol on *Panax ginseng* for COPD

6.1 Foreword

The classical and modern literature reviews presented in Chapters 4 and 5 informed the design of the RCT protocol on *Panax ginseng* for COPD. The knowledge and insight generated from the reviews shaped a greater understanding on the topic and ensured the design and methodological undertakings would be to the highest quality. Previous shortfalls identified in the extant literature were addressed and new scope was created.

6.2 Introduction

Over the past two decades COPD has become one of the leading causes of death worldwide (14). The socio-economic impact of the disease is substantial, involving both direct costs to the individual and the healthcare system as well as indirect costs due to loss of productivity (4).

Current conventional therapy for COPD offers only modest benefit and adverse events are common (1). Therefore, there is an unmet need to provide effective and safe medications that provide symptomatic relief and improve the quality of life (QoL) of sufferers.

The RCT detailed in this chapter examines the efficacy and safety of a standardised Ginseng extract in the clinical management of patients with moderate COPD. The study is a multi-centre, randomised, placebo-controlled, double blind, and parallel clinical trial.

The trial will provide critical clinical data of the effect of Ginseng on QoL and pulmonary function. Findings from this study may lead to new therapeutic development for a range of chronic inflammatory diseases, particularly chronic respiratory diseases.

The effect of *Panax ginseng* on COPD and related conditions has been evaluated in preclinical and clinical studies (Refer to Chapter 5). There is promising evidence of effect however previous clinical trials have been limited by methodological shortcomings including small sample sizes and unclear risk of bias (12, 201, 203).

This chapter presents the design and methodology of the Ginseng for COPD clinical trial. The study is entitled '*The effect of a standardised ginseng extract in patients with moderate COPD: a randomised, double blind, placebo controlled trial'*, and the short title is '*Ginseng extract and respiratory symptoms (GEARS)*'. Recruitment began in October 2010 and will continue until December 2013.

Study timeline:

- Ethical approval, May 2010
- Recruitment commenced, October 2010
- Anticipated completion date, December 2013
- Data analysis and dissemination of findings, June 2014

The objective of the study is to evaluate the therapeutic value and safety profile of a standardised root extract of '*Panax ginseng* C.A Meyer' for symptomatic relief, with a

focus on QoL improvements in individuals with moderate (Stage II) COPD. The full trial protocol has been published in an international peer-reviewed journal (11).

6.3 Research funding

The study is funded by a project grant from the National Health and Medical Research Council (NHMRC), project grant number 616609. The National Institute of Complementary Medicine (NICM) has also contributed to the funding.

The Guangdong Provincial Academy of Chinese Medical Sciences and the Guangdong Provincial Hospital of Chinese Medicine, China, have provided additional funding through an international research grant.

6.4 Ethical approval

Ethics approval was granted from the Human Research Ethics Committees (HREC) of the participating clinical trial centres. Participating centres are the Austin Hospital, Box Hill Hospital, Northern Hospital and Frankston Hospital in Melbourne. Approval was granted in May 2010. The study was approved under the Streamlined Ethical Review Process (SERP). The SERP system was developed by the State government of Victoria, Australia to provide faster and more efficient ethical review for multi-site clinical trials (263). Austin Health was nominated as the reviewing HREC and individual site HRECs confirmed approval for conduct. The study also received full ethical approval from RMIT University's HREC.

HREC reference numbers are: Austin Health HREC/10/Austin/8 (H2010/03892), Eastern Health E90/0910, Northern Hospital SSA/12/NH/12, Frankston Hospital SSA/12/PH72 and RMIT University E31/10.

6.5 Trial registration

The trial is registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR Number: ACTRN12610000768099). Clinical trial notification has been filed with the Australian Government's Therapeutic Goods Administration under the Clinical Trial Notification Scheme.

6.6 Research team

The research team consists of an international collaborative group with experts in Chinese medicine, respiratory medicine and clinical trials.

6.7 Study justification

There is an unmet need to optimise treatment of COPD, particularly for individuals with moderate COPD. Quality of life dramatically declines in sufferers and they often seek complementary and alternative therapies, including herbal medicine (7). *Panax ginseng* is an herbal medicine that may be effective for COPD. The evidence of *Panax ginseng's* effectiveness in treating COPD symptoms is promising but not conclusive. A previous study suggested that *Panax ginseng* may be more effective than placebo for improving lung function and exercise capacity however the study was limited by methodological and design limitations (12).

6.8 Aims and hypothesis

The specific aims are to evaluate the effectiveness of *Panax ginseng* for treating moderate COPD and to achieve symptomatic improvement, enhance QoL and determine the safety profile for this condition.

It is hypothesised that *Panax ginseng* will alleviate some significant symptoms of COPD and improve QoL for individuals with moderate COPD.

6.9 Research questions

The research questions are:

1. Does *Panax ginseng* produce beneficial effects/symptomatic relief in people with moderate COPD, in terms of improved QoL?
2. Does *Panax ginseng* produce beneficial effects in people with moderate COPD, in terms of improved respiratory function?
3. Does *Panax ginseng* reduce the use of conventional symptom-relief medication in people with moderate COPD?
4. With six months treatment and six months follow-up, what are the time courses of onset and persistence of any beneficial effects of *Panax ginseng* in people with moderate COPD?
5. Does *Panax ginseng* have any adverse effects in people with moderate COPD, and if so, what is the nature of the adverse effect?

6.10 Trial design

This study is a randomised, multi-centre, double blind, placebo-controlled, two-armed parallel clinical trial comparing a standardised Ginseng extract to placebo. The study will proportionately randomise 168 participants at a ratio of 1:1 into the *Panax ginseng* group or placebo group. The design of the study will integrate contemporary clinical research methodology in accord with principles set out in the Declaration of Helsinki and the Good Clinical Practice guidelines with the theory that guides the appropriate use of traditional Chinese medicine in clinical practice (264-266).

6.10.1 Participants

The trial centres will proportionately randomise volunteer participants from the local community in Melbourne, Australia.

6.10.2 Inclusion criteria

Subjects must meet the following inclusion criteria to be eligible to participate.

1. Both males and females aged 40 to 80 years (inclusive).
2. Ex-smokers (ceased smoking at least three months prior trial entry), and agree to refrain from smoking throughout the trial.
3. Satisfy the diagnostic criteria for moderate (stage II) COPD, defined by GOLD as post-bronchodilator spirometry, $FEV_1/FVC < 0.70$ and FEV_1 50%–80% predicted.
4. Are clinically stable, that is, did not experience an acute infective exacerbation of COPD from at least 4 weeks prior to trial entry.
5. Meet the Chinese medicine diagnostic criteria for *Lung Qi deficiency* or *Lung and Spleen Qi deficiency*.
6. Give written informed consent to participate.

6.10.3 Exclusion criteria

Subjects with any of the following exclusion criteria will not be eligible to participate.

1. Current smokers.
2. Those with a diagnosis of alpha–1 antitrypsin deficiency.
3. A history of asthma or chronic systemic infections or inflammatory conditions in the last three months.
4. Women who are pregnant or breast-feeding, or intending to become pregnant during the course of the study.
5. Serious illnesses such as heart, liver or kidney disease.
6. Individuals who are unable to adequately perform spirometry tests.
7. Individuals taking long-term immunosuppressive agents or immune-stimulants.
8. Individuals who have an allergic history to Ginseng products.
9. Individuals currently using a Ginseng containing product or have used a Ginseng product within the last three months.
10. Individuals currently using anticoagulants, anti-hyperglycaemics or monoamine oxidase inhibitor anti-depressants.
11. Individuals who have undertaken pulmonary rehabilitation within three months of the commencement of the study, or intend to enter pulmonary rehabilitation during the study.

6.10.3.1 Chinese medicine diagnostic criteria

Chinese medicine (CM) theory requires that, to be effective, its therapies must be individualised based on CM syndrome differentiation. Ginseng is prescribed for the CM syndromes of *Lung Qi deficiency* and *Lung* and *Spleen Qi deficiency*. It is likely that, in the absence of an acute exacerbation and exclusion of severe cases, under the CM syndrome framework, most individuals with moderate COPD would be classified as either *Lung Qi deficiency* or *Lung* and *Spleen Qi deficiency*.

Participants must meet the CM syndrome criteria of *Lung Qi deficiency* or *Lung and Spleen Qi deficiency*. If they do not meet either of these they will not be eligible to participate. Table 44 presents the CM diagnositic criteria.

Table 44: Chinese medicine diagnostic criteria of Lung and Spleen Qi deficiency

Lung Qi deficiency	*Spleen Qi deficiency*
• Cough • Shortness of breath • Clear sputum • Wheezing • Catch a common cold easily • Difficult to recover from a common cold • Sweat easily	• Tired or exhausted • Heavy limbs • Loss of appetite • Loose bowels • Headache or heavy head • Full in the stomach even without eating

To determine the CM syndrome a qualified CM practitioner will examine the participant's symptoms based on the CM Syndrome Differential Diagnosis Form and take a digital photo of the participants tongue. The tongue photo ensures a comprehensive evaluation of the individual in line with the traditional style of CM (Appendix 2).

6.11 Recruitment

Departments of respiratory medicine at the participating hospitals will recruit participants. Methods of recruitment will include electronic and printed media promotion, advertising in clinic rooms, letters to general practice clinics and physician referrals [Table 45]. Examples of media promotion and advertising are displayed in Appendix 3.

Interested individuals will telephone or email the trial co-ordinators at the corresponding hospitals for further information. Potential participants are sent a Participant Information and Consent Form (Appendix 4).

Interested individuals will attend one of the hospitals for baseline assessment and preliminary screening for eligibility at visit 1. If the individual continues to stay stable in regards to their COPD during the 4 week run-in period they will be randomly assigned to one of the two treatment groups, *Panax ginseng* or placebo.

Continued suitability requires that they do not experience an acute infective exacerbation of COPD during the run-in period and that their post-bronchodilator spirometry values stay within the moderate (Stage II) range. If an individual does not meet all of the inclusion criteria they will not be randomised and their participation in the trial will be discontinued.

Table 45: Media promotion and advertising

Media type	Source
Newsletter	• Australian Lung Foundation • Fifty Plus News • RMIT University updates (Email sent to RMIT staff)
Web site	• RMIT University www.rmit.edu.au/chinese-med/gears • Australian Lung Foundation (www.lungfoundation.com.au) • Trial spotting (www.trialspotting.com.au) • Google Adwords
Newspaper	• Local 'Leader newspapers' • Herald Sun – Health noticeboard • The Senior • The Age
Magazine	• Nova Holistic Journal
TV	• Channel 7 News
Radio	• Eastern FM Radio • Plenty Valley FM Radio • Inner FM Radio • RPP FM

6.11.1 Randomisation

The study uses a simple randomisation ratio of 1:1. To minimise risk of imbalance between groups, two different sizes of block randomisation sequences will be used. The randomisation list is computer generated by an independent researcher and stratified by site. Treatment allocation numbers are entered into individually sealed opaque envelopes and provided to each site. At the time of randomisation, participants will draw an envelope. Each envelope contains a number that is concealed to the treatment allocation. A non-investigator independent at RMIT University holds the password protected list. In the event of an emergency medical situation, the participant's randomisation code and group allocation can be identified.

6.11.2 Blinding

This study is double blind in design. The randomisation sequence and allocation will be unknown to all study participants, research staff, investigators and pharmacists. The data will be analysed by blind assessors.

At the final visit the credibility of participant blinding will be assessed by asking the question, 'which treatment do you believe you have received, real, placebo or not sure?'

6.12 Trial procedures

Consenting eligible participants are enrolled for 52 weeks and will be required to attend 6 visits in total. Figure 24 presents the participation flow chart.

Trial phases:

Phase 1: Four weeks run-in

Phase 2: Twenty-four (24) weeks treatment

Phase 3: Twenty-four (24) weeks follow-up

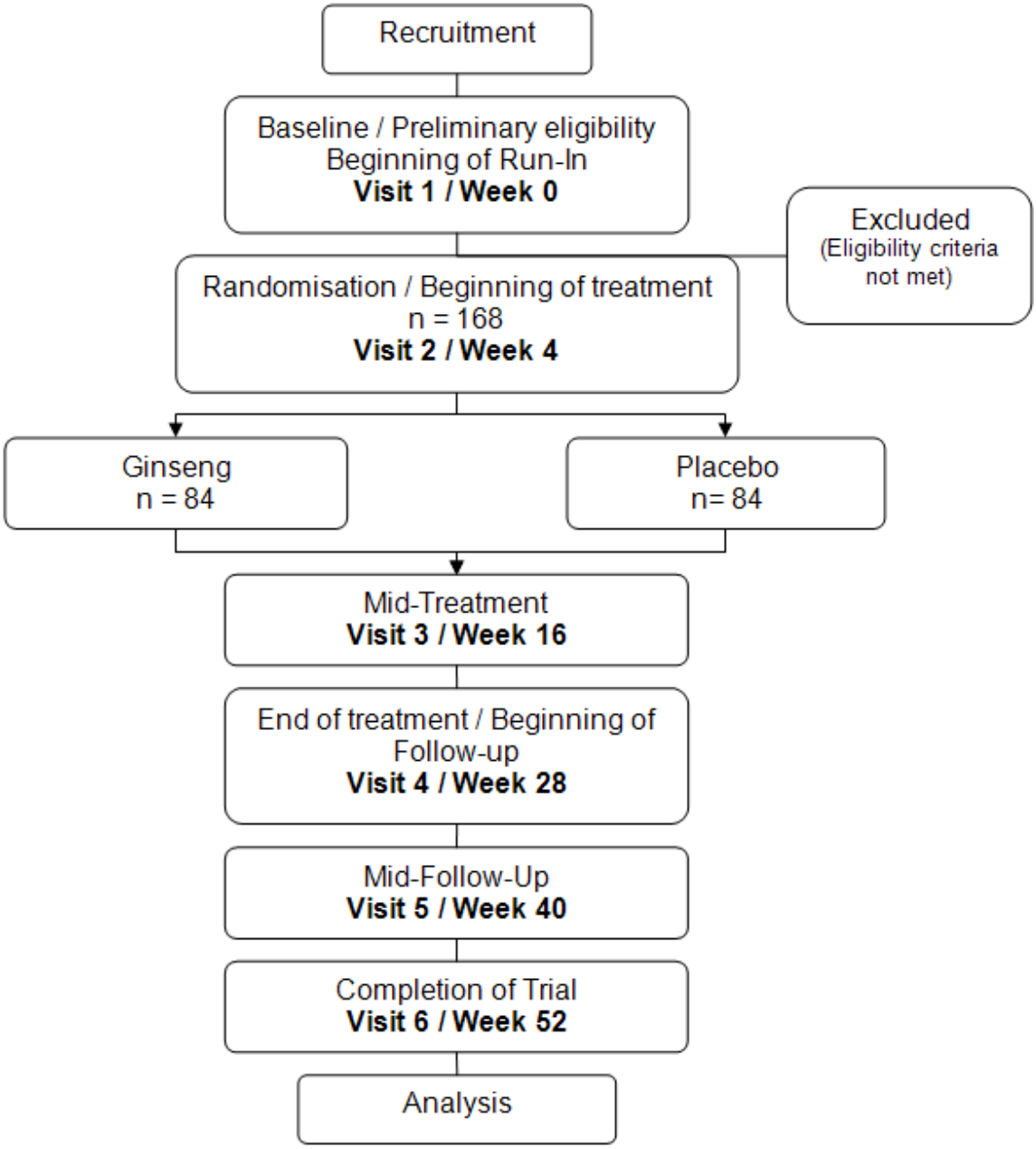


Figure 24: Participation flow chart

6.12.1 Initial assessment

Individuals wishing to participate in the study will be assessed at one of the hospital trial sites. After signing the consent form, individuals will be assigned a participant number.

Unique participant numbers combine the site initials, the site prefix number and a sequentially numbered suffix. For example, the first individual at the Austin Hospital will be assigned AH1001. Site initials and the prefix numbers are as follows: Austin Hospital (AH10xx); Box Hill Hospital (BH20xx); Northern Hospital (NH30xx); and Frankston Hospital (FH40xx). If an individual fails to be randomised the number will not be re-used.

All trial information is recorded on the Case Record Form (CRF) (Appendix 5). The participant visit schedule is outlined in Table 46.

Table 46: Participant visit schedule

Period	Initial Assessment	Randomisation	Treatment		Follow Up	
Visit	1	2	3	4	5	6
Week	0	4	16	28	40	52
Procedures to be undertaken						
Informed consent	©					
Full medical assessment	✓					
Current medication review	✓					
Chinese medicine diagnosis	×					
Confirm eligibility	©	©				
Smoking history and status	©	©	©	©	©	©
Lung function testing (spirometry)	©	©	©	©	©	©
Blood collection	©			©		
Randomisation		©				
Complete Case Record Form	©	©	©	©	©	©
Symptom Assessment	©	©	©	©	©	©
Dispense trial medication		©	©			
Dispense relief medication (if needed)	©	©	©	©	©	
Issue questionnaires (SGRQ, SF-36, CAT)	©	©	©	©	©	©
Issue Questionnaire (Opinion of Chinese Medicine)						©
Issue Participant Diary	©	©	©	©	©	
Review Participant Diary		©	©	©	©	©
Current condition and medication review						✓
Individual conducting procedure: © - Trial co-ordinator ✓ - Respiratory doctor × - Associate researcher						

6.12.2 Screening

Visit 1 (week 0)

The initial assessment requires participants to perform a lung function test, have a sample of their blood taken and complete several questionnaires. These questionnaires are:

- General information questionnaire
- Screening questionnaire (Appendix 6)
- St Georges Respiratory Questionnaire (SGRQ) (Appendix 7)
- Short Form Health Survey (SF-36) (Appendix 8)
- COPD Assessment Test (CAT) (Appendix 9)
- Chinese medicine syndrome differential diagnosis form (Appendix 2)

The study doctor will carry out a full medical assessment and review medications. Participants will be advised not to take certain COPD medications throughout the trial. These medications are presented in Table 47 and include short acting anti-cholinergics, long acting beta2-agonists, theophylline, inhaled corticosteroids (ICS) and combination ICS/beta2-agonists. Participants who are on any of these medications will be asked to discontinue use. These medications are recommended for patients with more advanced COPD and with repeated exacerbations (1). To assess the potential safety and efficacy of Ginseng versus placebo it is necessary for participants to cease using ICS and certain long acting bronchodilator therapy. Cessation of medications will be done under the advice of a study doctor over a 24–48 hour period. Participants will be allowed to use Ventolin® as rescue medication throughout the trial.

Table 47: Medications not to be used throughout the trial

Medication class	Generic name	Brand name
Short acting anti-cholinergics	Ipratropium	Atrovent
Long acting β_2-agonists	Salmeterol Efermoterol Indacaterol	Serevent Foradile/ Oxis Onbrez
Methylxanthines	Theophylline	Nuelin
Inhaled corticosteroids (ICS)	Budesonide Beclomethasone Fluticasone Ciclesonide	Pulmicort Qvar Flixotide Alvesco
Combination ICS/ β_2-agonists	Fluticasone/ Salmeterol Budesonide/Eformoterol	Seretide Symbicort
Oral corticosteroids	Prednisolone	Panafocortelone/ Solone
Monoamine oxidase inhibitors (anti-depressant)	Phenelzine Tranylcypromine	Nardil Parnate
Anti-hyperglycaemic	Pioglitazone Glimepiride Rosiglitazone Glibenclamide Metformin Gliclazide	Actos Amaryl Avandia Daonil, Glimel Diabex/Diaformin/ Glucophage Diamicron/ Minidiab
Anti-coagulant	Warfarin Phenindione	Coumadin/ Marevan Dindevan
Immunotherapy	-	-

Participants will be dispensed Ventolin® to be used as 'relief medication' when needed. Participants will be given a diary to take home to complete details of their daily use of Ventolin® and/or any other concomitant medications (Appendix 10). After the initial assessment, the trial co-ordinator will inform the participants' usual treating doctor of their participation in the study.

6.12.3 Run-in period

Participants will be required to undertake a four week run-in period prior to randomisation. This period will ensure participants are clinically stable in regards to their COPD and allow for baseline data gathering. If participants deteriorate during the

run-in period, that is, they have an exacerbation of COPD or there is a 4 point or more worsening of the SGRQ and/or deterioration in lung function (FEV_1 greater than 12% or 200 mL) they will be ineligible for randomisation. One further run-in period may be considered if a participants' condition re-stabilises.

6.12.4 Treatment phase

Visit 2 (week 4)

After the four week run-in period the participants will return for visit two. The trial co-ordinator will confirm eligibility of the participant and they will be randomised. Participants will undergo lung function testing and complete the three questionnaires, SGRQ, SF-36, and the CAT.

The participants will be dispensed their first pack of trial medication (sufficient for 12 weeks) and the relief medication (if needed). The diaries from the run-in period will be collected. Participants will be issued a new diary and they will be required to complete the diary every day after taking the trial medication and any other concomitant medications. Participants will be asked to return the completed diary and any leftover capsules at their next visit.

Visit 3 (week 16)

Similar to visit 2, at visit 3 the participants will undertake lung function testing and complete three questionnaires (SGRQ, SF-36 and the CAT). They will be given a new diary and dispensed the second pack of trial medication (sufficient for 12 weeks) and relief medication (if needed).

Visit 4 (week 28)

Week 28 marks the end of the treatment phase. At visit 4 participants will undergo lung function testing and complete three questionnaires (SGRQ, SF-36 and the CAT). Additionally they will have a blood sample taken. They will not be dispensed any trial medication however they will receive a new diary to document concomitant medication use and dispensed relief medication (if needed).

6.12.5 Follow-up phase

Visit 5 (week 40)

Participants will be required to undertake lung function testing and complete three questionnaires (SGRQ, SF-36 and the CAT). Participants will be given their final diary to document concomitant medication use and they will be dispensed relief medication (if needed).

Visit 6 (week 52)

The end of the follow-up phase and completion of the trial will be at week 52. At the final visit participants will be required to undertake lung function testing and complete three questionnaires (SGRQ, SF-36 and the CAT). They will also complete an additional questionnaire, 'Participant opinion of Chinese medicine questionnaire' (Appendix 11).

6.13 Treatment

6.13.1 Intervention

A standardised root extract of *Panax ginseng* will be used as the treatment. The extract, G115 and matching lactose-based placebo which is identical in appearance, taste and odour will be dispensed as 100 mg gel-filled capsules for oral intake [Table 48]. Two capsules will be taken daily, one with breakfast and one with dinner, for a total of 24 weeks.

Panax ginseng, G115 Ginsana™ is listed for use as an herbal medicine with the Therapeutic Goods Administration (TGA), Australian Register of Therapeutic Goods (ARTG), number 169069.

Table 48: Investigational product information, G115 and placebo

Details	Intervention	Placebo
Approved name	*Panax ginseng* G115 extract	Placebo
Trade name	Ginsana™ G115	Not applicable
Active compounds	30–55% *Panax ginseng* extract (4% ginsenosides)	Nil
Excipients	2% silica colloidal anhydrous, 43–68% lactose monohydrate, <2% mannitol	Lactose monohydrate, silica colloidal anhydrous, lecithin, soya lecithin, wax mixture, rapeseed oil, ethyl vanillin, gelatine, glycerol 85%, iron oxide black, iron oxide red, dried substance from Anidrisorb 85/70 (85% solution), soya-bean oil, soya oil
Indications	No standard indications included on the TGA ARTG record	Nil
Usage	Maintains stamina and endurance by improving the recovery rate after intense physical effort. A natural stress reliever of benefit during times of physical stress. Helps relieve nervous tension, anxiety and stress. Can increase the oxygen uptake capacity and reduce blood lactate levels.	Nil
Dosage regime	100 mg per capsule	100 mg per capsule
Administration	Oral, 100 mg (one capsule) twice daily	Oral, 100 mg (one capsule) twice daily
Known contraindications	Hypersensitivity or allergy to any of the ingredients	Hypersensitivity or allergy to any of the ingredients
Known adverse effects	Diarrhoea (from literature)	Nil
Concurrent drugs to be avoided	Warfarin and monoamine oxidase inhibitors (from literature)	Nil

TGA ARTG: Therapeutic Goods Administration Australian Register of Therapeutic Goods

6.13.2 Dosage

The dosage of G115 was determined by referencing previous clinical trials for the same indication (12, 203) and by recommendations from the manufacturer (267). Ginsana SA manufactures the standardised *Panax ginseng* extract, G115, and placebo in Switzerland (Appendix 12: Analytical reports of G115 and placebo). Each capsule contains approximately 4% (4 mg) ginsenosides, equivalent to dry root 212.5 mg. Table 49 presents the specific ginsenoside content of G115 used in the clinical trial. The full method of extraction and the process of standardisation of *Panax ginseng* roots into G115 are not available outside of the company. However, the process follows Good Manufacturing Practice (GMP) [Table 50].

Table 49: The ginsenoside content of G115

Ginsenoside	% amount
Rb1	0.91%
Re	0.70%
Rb2	0.65%
Rc	0.60%
Rg1	0.40%
Rf	0.33%
Rd	0.33%
Rg2	0.08%
Total ginsenosides	4.00%

Table 50: The process of standardising *Panax ginseng* into G115

Step	Process	Method
1	Cultivation	Controlled cultivation and monitoring, including growing conditions and treatment after harvest.
2	Selection of raw material	Roots aged 5–7 years are selected according to botanical and physical characteristics. The content of aflatoxins, heavy metals and pesticide residues are measured.
3	Analysis	A quali-quantitative determination of ginsenosides is measured using high performance liquid chromatography (HPLC).
4	Extraction	Hydro-alcoholic solvent: ethanol 96%: water (40:60 v/v). The ratio of the herb to extract is 5:1.
5	Concentration	After extraction a liquid extract is produced. It is concentrated and sterilised (UHT) and then spray-dried. The individual ginsenoside content is measured and checked for quality.
6	Standardisation	Twenty-step standardisation process. Specific ginsenosides are not standardised however the total content of ginsenosides is adjusted to 4%.

HPLC: high performance liquid chromatography, UHT: ultra-heat treated

6.13.3 *Panax ginseng* G115

Routine quality control checks will be undertaken on the packaging and contents of the G115 batch to ensure stability and quality. G115 capsules and the placebo will be supplied in glass bottles containing 60 capsules per bottle and dispensed in two lots at visit 2 and at visit 3. Six bottles will be dispensed in total, three bottles each time.

Figure 25 presents images of the study medication capsules and bottles.

Figure 26 presents the study medication labels and Figure 27 shows the study medication being packaged and boxed for distribution to the trial sites.

Source © Johannah Shergis

Figure 25: Study medication capsules and bottle

KEEP OUT OF REACH OF CHILDREN

Clinical Trial Medication
Project Title: GEARS
Sponsor: RMIT University

Ginseng or Placebo Capsules 100mg

Instructions: Take one capsule in the morning with breakfast & one capsule with dinner (or as advised).

Keep capsules dry, at room temperature

Randomisation No: 001
Bottle Number: 1/6
Manufacturer: Ginsana SA **Expiry:** 12/2013
Quantity: 60 capsules

Figure 26: Study medication label

From left, medications labelled and grouped and medications boxed for distribution.
Source © Johannah Shergis

Figure 27: Study medication packaged and boxed for distribution

6.13.4 Other treatments

Throughout the trial, participants will be supplied with a short acting beta2-agonist salbutamol, Ventolin®. This medication provides symptomatic relief and is used to provide rescue relief on an as needed basis. Ventolin® is a bronchodilator and rapidly opens the airways, giving relief from difficulty breathing. Table 51 presents the Ventolin® product information.

Table 51: Ventolin® product information

Items	Details
Active compound	salbutamol sulfate
Trade name	Ventolin®
Indication	Relief of bronchospasm
Dosage regime	1–2 inhalations every 4 hours if required (100 mcg per inhalation)
Known contraindications	Caution should be taken with patients with hypertension, hyperthyroidism, myocardial insufficiency, or diabetes mellitus.
Known adverse effects	Fine tremor, increase in cardiac output, tachycardia, increase in heart rate, headaches, nausea and palpitations. Potentially serious hypokalaemia may result from beta-2 agonist therapy.
Concurrent drugs to be avoided	Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.

6.13.4.1 Dispensing medications

The pharmacy departments of the participating hospitals will dispense medications. Participants are instructed to take one capsule twice daily, preferably with breakfast and dinner. The exact time of administration is not critical however participants are required to have a minimum of 4 hours between the two doses. The trial co-ordinators record compliance of medication dose on the ‘medication accountability form’ in the CRF. Participants will be given an information sheet detailing trial medication frequently asked questions (Appendix 13).

6.14 Outcomes

6.14.1 Primary outcome measures

The primary outcome measures are based on QoL improvement assessed using three validated questionnaires.

1. St Georges Respiratory Questionnaire (SGRQ)
2. Short Form Health Survey (SF-36)
3. COPD Assessment Test (CAT)

Participants will complete the three questionnaires at each visit, 6 times in total (Week 0, 4, 16, 28, 40 and 52).

6.14.1.1 St Georges Respiratory Questionnaire (SGRQ)

This questionnaire was designed to measure health impairment in patients with COPD. It consists of two parts, part one covers the patients' recollection of their symptoms and part two addresses the patients' current state of health. The questions are weighted individually for scoring and higher scores indicate poorer QoL.

The SGRQ is the standard COPD specific QoL questionnaire used in COPD trials. It has a higher discriminatory power in predicting lung function impairment (268). However, as it is disease specific it has limitations.

6.14.1.2 Short Form Health Survey (SF-36)

The SF-36 is used to assess more general QoL. It covers eight domains, broadly categorised as physical, emotional, general health and wellbeing. It also provides a summary of physical and mental health.

6.14.1.3 COPD Assessment Test (CAT)

This questionnaire measures health status impairment in COPD. It consists of eight scaled questions and is a recommended tool to assess symptoms of COPD (1).

6.14.2 Secondary outcome measures

Secondary outcome measures include efficacy and safety components.

1. Lung function using spirometry indices of FEV_1 and FEV_1/FVC ratio
2. Use of relief medication short-acting bronchodilator (beta2-agonist salbutamol)
3. Frequency, nature and severity of exacerbations
4. Emergency department presentations and medical practitioner visits
5. Full blood examination and blood biochemistry for liver and renal function
6. Adverse events

Relying on one outcome measure to demonstrate efficacy runs the risk of over interpreting the results of the study. Therefore, the secondary outcome measures were selected. Spirometry, is a standard measure of intervention efficacy for COPD (268). Measuring the amount of relief medication is an indirect measure of the efficacy of the intervention. It helps to validate the other outcome measures if they show a similar sort of response.

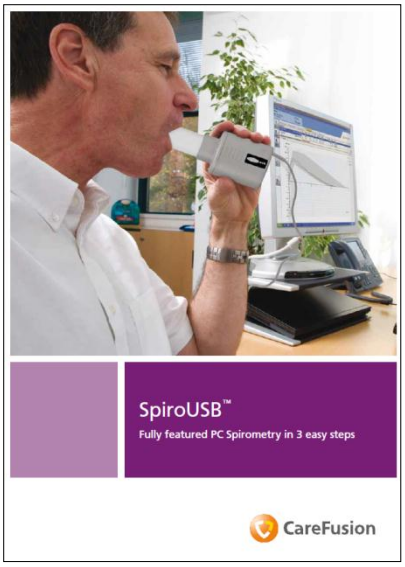
Exacerbations and emergency visits are a major health burden in COPD and the evaluation of treatment effects will require this measure (1). Blood tests and monitoring adverse events are essential to assess safety.

Spirometry

Spirometry will be conducted at all sites using the SpiroUSB™ and Spirometry PC software (CareFusion UK 232 Ltd) [Figure 28]. Participants will perform spirometry at each visit, 6 times in total (Week 0, 4, 16, 28, 40 and 52).

The SpiroUSB™ spirometer is convenient to use and plugs into the USB port of a computer. This apparatus requires minimal maintenance and cleaning and is ideal for use in any setting (269). Standard operating procedures set out by the manufacturer will be followed at each site, including calibration. The predicted normal values will be referenced against NHANES III (270) as these values have been extensively used in clinical trials (271).

Participants are advised not to take any inhaled respiratory medications for several hours prior to their spirometry testing, as this may alter the result. During testing, a participant places their mouth over the mouthpiece, takes a deep breath in, and then exhales forcefully and completely. Participants are required to complete three consistent blows and the 'best blow' is used. Two sets of blows are required, that is, pre-bronchodilator and post-bronchodilator (10 to 15 minutes after 400 μg of inhaled Ventolin®, salbutamol). Results are recorded on the spirometry PC software where information is presented on the quality of blows, absolute values and flow-volume loops. A respiratory doctor will check the results at each visit.



From left: SpiroUSB ™ user manual front cover and spirometry equipment including storage case, spirometry turbine, mouth piece and filter.
Source © Johannah Shergis

Figure 28: SpiroUSB ™ user manual and spirometry equipment

6.15 Adverse events

Adverse events are documented in the CRF by the trial co-ordinators. Adverse event details will be scored by the trial co-ordinators using a three-point scale: 1 = mild, easily tolerated by patient, causing minimal discomfort; 2 = moderate, discomfort significant enough to interfere with daily activities; or 3 = severe incapacitating and/or requiring therapeutic intervention. Participants will be able to report adverse events anytime throughout the trial and will receive advice from the trial co-ordinators. However, they will be referred to their usual treating doctor for any treatment. Serious adverse events (SAE) are defined as the potential to result in death, are life threatening, permanently incapacitating or resulting in hospitalisation. Serious adverse events will be reported to the HRECs, the manufacturer of the intervention and to the TGA.

Throughout the study period trial co-ordinators will contact the participant's usual treating doctor to record relevant data on hospital presentations and exacerbations.

6.15.1 Exacerbations

Exacerbations of COPD have been defined by Anthonisen et al as at least a two day persistence of at least two major symptoms (such as worsening dyspnea and an increase in sputum purulence, volume, or both), or of any single major symptom plus more than one minor symptom (upper airway infection, unexplained fever, increased wheezing) (272). Change of medication may be necessary, including an increased dose and/or frequency of existing short-acting bronchodilator therapy, such as a beta2-agonist, and may include a dose of 30 to 40 mg prednisolone per day for 7 to 10 days. Evidence of bacterial infection such as increased sputum volume and purulence may indicate the need for antibiotics.

If a participant experiences an exacerbation of COPD during the study they will be treated as deemed appropriate by their usual treating doctor. All relevant details will be recorded by the trial co-ordinators in the CRF. Following treatment for the exacerbation the participant will be expected to continue in the study. A review by the study doctor will be required if the participant requires the addition of new concomitant COPD medication that are listed as treatments not to be used throughout the study [Table 47]. They will also be reviewed if their use of the study medication is interrupted for more than three consecutive days.

6.16 Data collection and storage

The research team will collect data and record results on the relevant questionnaires and the CRF. Source data will be entered onto Microsoft® Excel spread sheets by staff blinded to group allocation. The data will then be prepared and entered into SPSS (IBM® SPSS® Statistics Version 20, 2010) for further analysis. For reporting purposes, de-identified and aggregated results will be used.

Information collected for, and used in this study will be stored in secure facilities, in locked cabinets at the trial sites until the completion of the study. After completion, all paper files will be stored in secure cabinets at RMIT University for 15 years. Electronic files will be held on RMIT University password protected computers for 15 years. All records will be disposed of after 15 years. The paper files will be shredded at a secure location, the electronic files will be erased permanently, and an appropriate IT expert will reformat the hard disk.

6.17 Sample size calculation

The sample size calculation has been determined on the basis of existing clinical data and power calculation. It is based on the effect size of QoL changes in COPD subjects, in an RCT of one of the most commonly used long-acting beta2-agonists salmeterol (273). In the study, the mean score change on the SGRQ was significantly higher ($p < 0.05$) in the treatment group (-6.8 ± 13.2) than in the placebo group (-1.4 ± 11.7). For the GEARS study, to achieve a similar difference between the *Panax ginseng* and placebo treatment groups with an 80% power and a two-tailed significance level of 5%, it is estimated that a sample size of 84 per group will be required, that is, 168 in total.

6.18 Withdrawal

Participants may withdraw from the study for any reason, at any time, without repercussion. Investigators will only withdraw them if it is deemed medically unsafe for them to continue. Dropouts will not be replaced.

6.18.1 Dropouts

The research team will strive to minimise dropouts. Intention-to-treat analysis will be applied to minimise bias due to dropouts. Researchers will endeavour to limit false inclusions. Nevertheless, if they are included they will remain in the study and analysed in their original assigned groups irrespective of what occurred.

6.18.2 Missing data

An intention-to-treat analysis will be applied. Missing responses will be imputed using the last observation carried forward method. Missing data in the SGRQ and SF-36 will be dealt with using the standard method according to the developers' instructions.

6.19 Data analysis

The trial data will be analysed by an independent biostatistician who will be blinded to the subject allocation. Data will be summarised as mean and standard deviations.

Primary outcome measures, SGRQ, SF-36 and the CAT will be assessed at baseline, start of treatment, mid-treatment, end of treatment, mid follow-up and at the end of follow-up. Analysis of covariance with the baseline as covariate will be used to assess differences in treatment outcomes between the two groups at each of these time points.

To correct for inflated risk of Type 1 error, multiple comparison procedures suggested by Ludbrook et al will be used (274, 275).

Comparability between baseline demographics in the two groups will be analysed using Chi-square or t-test and the number of adverse events will be analysed using Chi-square. Baseline measures will be used as a covariate. Differences in outcome measures will be assessed between the two treatment groups using ANCOVA at four time points (mid-treatment, end of treatment, mid follow-up and at the end of follow-up). Probability value of less than 0.05 is considered statistically significant.

The use of relief medication will be evaluated for its effect on the outcome measures as a covariate in the statistical analysis.

A data safety and monitoring board has been established to assess the progress of the trial, particularly safety endpoints.

6.20 Early termination of the trial

The trial will be terminated if it becomes apparent that the treatment procedure is associated with any significant adverse events. Based on current literature, there is no evidence of significant adverse events associated with the use of Ginseng products (Refer to Chapter 3.7, Safety of Ginseng).

6.21 Reimbursements

Participants will not be paid for any aspect of this research. The study medication, visits, and procedures will provided at no cost to the participant. Participants will be reimbursed for attending study visits. This includes parking, public transport and/or petrol costs.

6.22 Reporting

Reporting will be guided by the CONSORT statement (153) as well as its extension for herbal interventions (156). The results from the study will be presented at professional conferences and published in national and international peer-reviewed medical journals.

A final report will be submitted to the funding bodies, the HRECs and the administering institution, RMIT University.

6.23 Preliminary analysis of trial progress

6.23.1 Recruitment

The trial has been open for recruitment since October 2010. As of February 13, 2013 the following participants had been screened and recruited:

Total screenings: 152

Total randomisations: 45

Total completions: 29

The screening to randomisation translation is approximately three to one. A brief review of the screen failures revealed the majority were unable to be randomised due to lung function being within the normal range, that is $FEV_1/FVC > 0.70$.

Enrolment has been steady, however, presupposed targets have not been met. Initially it was estimated six to seven participants would be randomised per month over 27 months. Currently the average recruitment rate is 3 randomisations per month.

Reasons for dilatory recruitment have not been fully defined. However, several reasons may have contributed. These are:

- inclusion and exclusion criteria
- availability of suitable participants
- awareness of the study

To remedy these inhibiting factors and expedite recruitment, discussions were undertaken within the research team. The main ideas to improve recruitment were to:

- include new trial sites
- obtain more referrals from general practitioner (GP) clinics
- increase media presence

Changes have been implemented after discussions. Two new sites at the Northern Hospital and the Frankston Hospital will recruit participants. Melbourne and inter-state hospitals were examined for their suitability as new trial sites. These two sites have the best potential to meet trial requirements. They have large patient numbers and experienced research staff.

Study doctors and local GP clinics have referred patients to the trial. Four patient lists have been supplied with over 400 names. Trial co-ordinators at the hospitals have followed up with these lists and it has translated into approximately 30 screenings. Additional GP clinics are being approached to refer patients and updated lists are being investigated.

Advertising throughout 2010–2012 included an ad mixture of TV, newsletter, internet web sites, newspapers, and radio. The trial is ongoing, therefore the most effective recruitment strategy is unknown. Nevertheless, the majority of enquiries have come from the Channel 7 news story aired in June 2011. Table 52 presents the number of enquiries from different media. To increase media presence, newspaper and radio advertising is being implemented and several newspaper stories have been published in late 2012 and early 2013.

Table 52: Advertising enquiries from different media

Media type	Source	Number of enquiries
TV	Channel 7 news	287
Newsletters	Australian Lung Foundation, Fifty Plus News	74
Web sites	RMIT University, Australian Lung Foundation, Trial spotting, Google Adwords	32
Newspapers	Leader newspaper, the Herald Sun (health noticeboard), The Senior, The Age	164
Radio	Eastern FM, Plenty Valley FM and Inner FM	25

6.23.2 Monitoring

The hospital sites have been monitored throughout the trial. The trial co-ordinator at each site submits a fortnightly update including:

- number of screening visits
- number entered the run-in phase
- reasons for screen failures
- number randomised
- number of new enquiries
- number of follow-up calls
- number of return visits
- other tasks, including advertising and community engagement

A communication strategy between the trial sites and administrating centre was discussed early. Regular telephone and email communication was part of the overall monitoring strategy and onsite visits were scheduled every two months. Four key areas were reviewed at the sites:

- proper implementation of the protocol
- review of standard operating procedures
- adequate and accurate records
- review of adverse events

The funding bodies and the HRECs require annual reports. The funding bodies require information on the progress of the study, any changes to the research team or direction, and achievements related to the project. The HRECs require an annual report detailing the progress of the trial, any extensions required, any unanticipated issues, and assurance the study is being conducted in accordance with the protocol. Annual reports were submitted at the end of 2010, 2011 and 2012. A final report will be submitted at the end of 2013.

6.23.3 Serious adverse events

As of February 13, 2013, seven serious adverse events had been reported. All events required hospitalisation, however, no causal relationship between the events and the intervention were noted. Table 53 presents a summary of the serious adverse events.

All events were reported to the relevant agencies, including the TGA, the HRECs, and the intervention manufacturer. In view of the nature of the events no further follow up was required.

Table 53: Serious adverse event summary

Event	Length	Reason for severity	Outcome of event	Causal relationship to intervention	Brief description
Dyspnea and left sided chest pain	52 days	hospitalisation	recovered	no	All tests were negative and there was no ischemia present.
Perforated bowel	3 days	hospitalisation	recovered	no	Perforated bowel post super-pubic catheter replacement.
Pneumonia and exacerbation of COPD	5 days	hospitalisation	recovered	no	Exacerbation of COPD and pneumonia.
Acute respiratory infection	2 days	hospitalisation	recovered	no	Acute infection of the lower respiratory tract and exacerbation of COPD.
Mild stroke	3 days	hospitalisation	recovered	no	Tingling and weakness in the left arm.
Creutzfeldt-Jakob disease	31 days	fatal	fatal	no	Deteriorating cognitive function, mobility and gait disturbance. Principal diagnosis on hospital report states Creutzfeldt-Jakob disease.
Pancreatitis	2 days	hospitalisation	recovered	no	Pancreatitis.

6.23.4 Ongoing monitoring and operation

The trial has been conducted to the highest standards as per the protocol. Ongoing rigorous monitoring will ensure the protocol continues to be followed, and operation is successful. The key objectives for the coming year will require focused efforts on participant recruitment and completion of follow-up.

6.24 Discussion

Over the next decade, COPD will become the third most common cause of death worldwide (3). COPD is a disease of the elderly, and an ageing population is a significant factor in its increasing prevalence. Currently, conventional therapy for COPD is unsatisfactory. New therapies are being developed. However, there is a critical need to provide effective symptomatic relief and interventions that improve the QoL of sufferers (35).

Ginseng may be beneficial for COPD sufferers in the mild to moderate stages, $FEV_1/FVC < 0.70$ and $FEV_1 \geq 50\%$. This group is often prescribed inhaled steroids without any evidence of benefit, but are at risk of long term side effects such as cataracts and osteoporosis (1). It is in this group of patients that the GEARS clinical trial may offer an alternative and safer treatment approach. The GEARS trial presented in this chapter examines the efficacy and safety of a standardised Ginseng extract for moderate COPD. The study employs rigorous RCT methodology with sufficient statistical power to detect any treatment effects.

This is the first trial of its kind in Australia with novelties in design and implementation. Novelties include WM diagnosis of COPD and a CM differential diagnosis as part of the inclusion criteria. Additionally QoL and lung function are being evaluated together which has not been examined in previous Ginseng studies and recruitment will be through multiple hospital sites.

6.24.1 Challenges

Researchers often face additional challenges when conducting herbal medicine studies (276). Researchers in the GEARS study addressed and overcame common challenges, discussed below.

6.24.1.1 Managing bias and confounding

The researchers have strived to minimise bias in the trial design. Selection bias has been minimised by generating the random sequence by computer and allocation concealment has been maintained using opaque sealed envelopes. Blinding of participants, personnel and outcome assessment is also ensured. The study will be analysed by intention-to-treat. Confounding factors are minimised by the selection criteria. Participants with moderate COPD are selected according to lung function as per the GOLD standard of classification. Other stages of COPD i.e., severe or very severe were not selected as they are often taking corticosteroids and the intervention *Panax ginseng* may not be suitable for these cases. Individuals with other severe medical disorders were excluded as these disorders may affect their QoL independent of COPD. Concomitant medications such as corticosteroids and some bronchodilators may confound results and were therefore not allowed during the study.

6.24.1.2 Quality interventions

Ensuring quality herbal medicine interventions can be difficult due to the paucity of standardised herbal extracts. Additionally, many herbal studies use a combination of substances that are difficult to standardise. Conflicting findings in previous Ginseng clinical trials may be attributed to inconsistency in the quality of the Ginseng products investigated. In the GEARS study a quality certified internationally recognised standardised *Panax ginseng* extract (G115) is used.

6.24.1.3 Placebo

The placebo must match the intervention. The manufacturer of the trial intervention developed the placebo in the GEARS study. Encapsulating the herbs in gel not powder ensured better consistency between the capsules and maintained the integrity of blinding.

6.24.2 Limitations

This study employs several outcome measures to evaluate the diverse aspects of the disease. However there is a risk of data dredging with an emphasis on the most statistically impressive findings (277). To counter multiplicity issues the statistical analysis will be properly handled through pre-planned evaluation to limit bias of results.

The CM syndrome differentiation is not as comprehensive as that in the clinical setting. The CM practitioner performing the diagnosis is not face to face with the participants and the diagnosis is based on a form and a photo of the tongue. Although the cameras used are of the highest quality, some textural components may be lost in the image.

6.24.3 Progress

The GEARS clinical trial has been implemented for the last 2 years. Over this period the project has proceeded on schedule. The trial co-ordinators at each site have undertaken their day-to-day duties under the monitoring and guidance of the lead institution, RMIT University.

There have been no major emerging issues and the project has been conducted in compliance with the protocol. The procedures and the direction of the project have remained on task. Recruitment has been laggard however new strategies have been implemented (Refer to Chapter 6.23.1 Recruitment).

One protocol amendment was required soon after recruitment commenced. The initial protocol excluded individuals taking antidepressant medication. This exclusion was built into the protocol due to previous reports of interactions between Ginseng and phenelzine, a monoamine oxidase inhibitor antidepressant (98, 99). On review of participant recruitment, several individuals were taking antidepressant medications and were subsequently excluded. The research team considered this exclusion was unnecessarily restrictive. Several experts were consulted including an herbal pharmacologist, Ginseng experts and respiratory physicians to review the appropriateness of exclusion of antidepressant medication users. No reports or concerns were raised for potential interaction between Ginseng and other classes of antidepressants, for example selective serotonin reuptake inhibitors and tricyclic antidepressants. It was concluded that individuals taking monoamine oxidase inhibitor antidepressants would be excluded however, individuals taking any other class of

antidepressants would be eligible to participate. The HREC approved the protocol amendment in March 2011.

6.25 Conclusions

Upon successful completion, this trial will provide critical clinical data and build on previous RCTs and systematic reviews to answer the research questions in determining the efficacy and safety of *Panax ginseng* for moderate COPD. The study was designed by a multidisciplinary and international collaborative team and provides a novel approach in integrating rigorous RCT methodologies and theory that guides appropriate use of CM for translation into clinical practice. Findings from this study may lead to new therapeutic development for a range of chronic inflammatory diseases, particularly chronic respiratory diseases.

Chapter 7: General discussion and conclusions

7.1 Overview

COPD is one of the major health challenges in the developed and developing worlds (14). Despite a decline in cigarette smoking, the burden of COPD is likely to increase for some years (14). An ageing population means prevalence and health care costs will continue to rise.

Treatment options for COPD are still relatively limited and patients continue to experience poor QoL. Therefore, there is an unmet need for new therapeutic treatments for patients with COPD.

Panax ginseng is known as a "precious tonic", with particular benefits for lung and digestive functions. It has been used over centuries for improving stamina and vitality. In addition, clinical observation indicates potential benefit for patients with COPD.

Pre-clinical investigations showed *Panax ginseng* possesses a range of pharmacological actions such as anti-inflammatory and anti-oxidative stress (Refer to Chapter 5.5). Current clinical evidence is promising, however there is an overall paucity of high-level clinical evidence that supports the routine use of *Panax ginseng* for moderate COPD patients.

This research investigated the use *Panax ginseng* for COPD by:

- Searching and analysing the classical Chinese literature to identify references to formulae and herbs used to treat conditions consistent with COPD.
- Evaluating the systematic review literature for *Panax ginseng.*
- Systematically reviewing the English and Chinese literature for *Panax ginseng* in RCTs.
- Reviewing the literature specific to *Panax ginseng's* potential pharmacological mechanisms relevant to COPD.
- Designing and implementing an RCT to determine the efficacy and safety of *Panax ginseng* for COPD.

The research presented in this thesis employs a "whole evidence" approach to systematically searching, reviewing and analysing traditional and modern literature to identify candidates for further therapeutic evaluation. Through this process, critical data will be gathered to determine the role of one of the most commonly used herbs, *Panax ginseng,* in the management of COPD.

7.2 Summary of the research

7.2.1 Summary of classical literature on Chinese herbal medicine for COPD

The classical literature was searched and analysed to reveal citations of Chinese herbal medicine (CHM) for COPD. The *Zhong Yi Fang Ji Da Ci Dian* (ZYFJDCD) compendium was searched and 1,557 citations were extracted. After data checking and exclusion of irrelevant entries and repetitions, 1,147 citations were analysed. Nine hundred and two (902) formulae and 426 different herbs were identified. The search terms *ke chuan* 'cough and dyspnea' and *chuan zheng* 'dyspnea' located the most citations, 566 and 413 respectively.

When the formulae were ranked, 141 were broadly consistent with COPD. Twenty-five (25) citations had a global score of 4, that is 'most likely COPD' and the remainder were, 'possibly COPD' (*n*=735), 'other diseases unlike COPD' (*n*=311), 'possible complications of COPD' (*n*=27), and 'not enough information to decide' (*n*=49).

The three most frequently cited formulae were *Shen qi wan, Mai men dong tang* and *Xiao qing long tang.* The frequently cited herbs were *xing ren, ban xia, ren shen, kuan dong hua* and *sang gen bai pi.*

These results indicate that the use of formulae and herbs in the classical literature is similar to what is used in the modern setting. This research provides a novel approach and rationale for identifying formulae and herbs from classical literature. The method and results are in the process of being written up for submission to an international peer review journal (Refer to Publications, Manuscripts in preparation, number 1).

7.2.2 Summary of the overview of systematic reviews

Search and evaluation of the extant systematic review literature on *Panax ginseng* was conducted. Two hundred and forty-five (245) articles were located and 13 systematic reviews were eligible. The systematic reviews showed promising results for several health conditions including disorders of glucose metabolism, angina pectoris, lung function, and erectile dysfunction. However the extant literature does not establish the efficacy of *Panax ginseng* for a particular health condition or indication. It does appear to have a sound safety profile and is rarely associated with adverse events or drug interactions.

The overview of systematic reviews identified that *Panax ginseng* research is diverse yet often conducted using less than rigorous methods. Rigorous clinical trials focusing on specific conditions and indications are needed to further investigate *Panax ginseng's* evidence of efficacy.

7.2.3 Summary of the systematic review on *Panax ginseng* in RCTs

Panax ginseng has been extensively researched in RCTs. The systematic review evaluated *Panax ginseng* for any type of health condition, aiming to summarise the current evidence, evaluate the methodological quality and risks of bias and identify promising areas for future research.

Searches of English and Chinese databases revealed 1,778 potentially relevant studies, with 67 meeting the inclusion criteria. Thirteen (13) broad health areas were evaluated, these were psychomotor performance, physical performance, circulatory conditions,

glucose metabolism, respiratory conditions, erectile dysfunction, immunomodulation, quality of life and mood, anti-oxidant function, cancer, menopausal symptoms, dry mouth, and ulcerative colitis. Data synthesis was limited due to heterogeneity between studies and the planned met-analysis could not be performed.

The systematic review is the most comprehensive and up-to-date. *Panax ginseng* appeared to have some positive therapeutic effects. However, caution needs to be taken when interpreting results due to poor methodological quality and risks of bias, particularly for random sequence generation and allocation concealment. The most promising evidence supports *Panax ginseng* for use in moderating the immune response, particularly cell-mediated immunity with implications for chronic respiratory diseases. *Panax ginseng* has a good safety profile with limited minor adverse events and no serious adverse events reported. Future clinical studies should focus on the most promising outcomes identified in this review. Quality methodology and standardised Ginseng products should be used and particular attention should be given to elucidating the mechanisms of action for specific conditions such as chronic respiratory diseases.

This systematic review was published in an international peer review journal (11). The review of methodology was published separately (278).

7.2.4 Summary of *Panax ginseng's* effect on reducing inflammation and oxidative stress and its prospective as a treatment for COPD

Panax ginseng and its active constituents, ginsenosides, exert diverse actions. The experimental and clinical trial literature was analysed to explore *Panax ginseng's* effect on reducing inflammation and oxidative stress with a focus on research relevant to COPD.

The search identified 880 studies, 35 met the inclusion criteria. Fourteen (14) were *in vitro*, 10 *in vivo* and 11 were RCTs. *Panax ginseng* was found to have several effects including modulation of inflammation and oxidative stress by down regulating the activity of NF-kB and MAPK, reducing the activity and numbers of inflammatory cells including NK cells and lymphocytes, modulating inflammatory mediators particularly TNF-α and IL-8, and reducing oxidative stress by down regulating ROS and oxygen radical damage. *Panax ginseng* showed its most beneficial effects by inhibiting inflammation through TNF-α and NF-κB as well as improving antioxidant status. These results highlight the need for further investigation into *Panax ginseng's* use in COPD with the view to develop new therapeutic treatments.

The research is in the process of being written up for submission to an international peer review journal (Refer to Publications, Manuscripts in preparation, number 2).

7.2.5 Summary of a clinical trial protocol on *Panax ginseng* for COPD

There is an unmet need to optimise treatment for COPD, particularly for individuals with moderate COPD. The GEARS study is a randomised, multi-centre, double blind, placebo-controlled, two-armed parallel clinical trial comparing a standardised *Panax ginseng* extract to placebo.

The literature reviews presented in Chapters 4 and 5 informed the design of the GEARS study, which addresses methodological issues identified and creates new scope. The study received ethical approval in May 2010 and recruitment commenced in October 2010 (ANZCTR registration number: ACTRN12610000768099). Currently 152 individuals have been screened for the study and 45 participants have been randomised. The anticipated completion date is in December 2013 with analysis and dissemination of findings by June 2014.

This is the first trial of its kind in Australia. The study was designed by a multidisciplinary and international collaborative team and provides a novel approach by integrating rigorous RCT methodologies and theory that guides appropriate use of CM for translation into clinical practice. Findings from this study may lead to new therapeutic development for a range of chronic inflammatory diseases, particularly chronic respiratory diseases.

The clinical trial protocol was published in an international peer reviewed journal (279).

7.3 Overall strengths of the research

Structured research aids in informing choices and facilitating quality results. This research was informed by searching and evaluating the modern and classical literature and using the information gathered to help design a rigorous clinical trial. The specific approach was to evaluate the state of the current evidence including a search and analysis of the classical literature, an overview of systematic reviews, a systematic review, a review of the mechanisms of action of the test intervention (ginseng), and a clinical trial.

This study identified gaps in the literature and weaknesses in the existing trials and facilitated the refinement of the methodology for the clinical trial. The clinical trial is of the highest standard with the intent to limit biased estimates of treatment effect. The trial evaluates 6 months of treatment and 6 months of follow-up. It is important to evaluate the time course of effects in a chronic disease like COPD. The outcomes were selected in accord with international recommendations and specifically address shortfalls in the design of previous studies (1, 12, 268).

Herbal medicine RCTs can be challenging due to herbal compounds often lacking quality control standards and variable constituents (228). The GEARS trial used an internationally recognised and standardised *Panax ginseng* extract. The extract, G115 has been used in over 24 RCTs and is considered the best quality standardised product for research and clinical use (90).

Reviewing the extant literature enhanced the design of the clinical trial and directly contributed to the evidence on *Panax ginseng* and the relevance of its use in COPD. The findings are reliable and conclusions valuable for both the research and clinical settings.

7.4 Overall limitations of the research

The reviews only included English and Chinese language studies. Studies in other languages are not included. To overcome this, planned future reviews of the Korean literature may help to make firm conclusions about *Panax ginseng's* efficacy and safety in treating various health conditions.

The methodological component of the systematic review may be limited by retrospectively analysing studies using new evaluation tools, such as the Cochrane risk of bias tool and the CONSORT statements. This is difficult to prevent and results were therefore interpreted with caution to overcome this limitation.

Classic literature searches are productive if the disease has comparable classical terms. The terms used in this review were the best match, however citations may have been missed or incorrectly excluded due to terminology variations.

When reviewing and discussing the potential mechanisms of action of *Panax ginseng* and the relevance to the treatment of COPD, the search may have missed some studies as the pathophysiology of COPD is yet to be fully elucidated. Results were promising but pathophysiological insight regarding the functions of Ginseng and ginsenosides is

not fully understood. Future studies will aid in improving understanding and overcoming the limitations of previous research.

The GEARS clinical trial was not preceded by a pilot study. Although this was not essential it may have aided in polishing the protocol and testing feasibility. This may have highlighted potential issues and given a better understanding of the participant population and ability to achieve recruitment. In addition, the delivery of *Panax ginseng* alone and not in combination with other herbal medicines is not the typical style of herbal prescription in China. The results from the clinical trial may have limited immediate applicability, however understanding the effect of a single herb is essential in developing effective formulations in future research.

7.5 Implications for future research

Future research will be enhanced by understanding the limitations and reflecting upon existing trials. The strategy for future studies should be focused on the most promising outcomes identified in the systematic review presented in Chapter 5. Rigorous methodology and standardised Ginseng preparations should be used and particular attention should be paid to designing adequately powered trials.

The activity of *Panax ginseng* and ginsenosides is diverse. Evidence suggests *Panax ginseng* is capable of regulating inflammation and oxidative stress, however, the mechanisms of action have not been fully established. There is a need for further investigation into *Panax ginseng's* use in COPD with the view to develop new therapeutic treatments.

Other areas of future research should include improving understanding of the best route of administration of *Panax ginseng*, establishing the most effective dose and selecting the relevant end points to establish efficacy.

The clinical trial presented in Chapter 6 represents a quality RCT on herbal medicine. The study protocol has been published and other researchers may use this study as a key reference. Since publication, new trials have emerged that are similar in design to the GEARS study (280).

7.6 Implications for clinical practice

COPD is a significant health burden leading to reduced QoL. The findings of this study will contribute to the use of *Panax ginseng* for COPD in the clinical setting. The research will improve clinical practice, assist in the development of scientific investigation of CM, and facilitate evidence-based medicine to improve health outcomes.

The results from the clinical trial, when available, will contribute towards the determination of the efficacy and safety of *Panax ginseng* that will inform future use of herbal medicine for COPD sufferers. Translation of results from this thesis into clinical practice is reliant on the dissemination of findings. Several publications have arisen and more are in the process of being finalised. This thesis is comprehensive, it includes reviews of both modern and classical literature that adds weight and verifies the use of *Panax ginseng* for COPD. This is further enhanced by the GEARS clinical trial that is methodologically rigorous.

7.7 Overall conclusions

This thesis evaluates *Panax ginseng* and its potential efficacy and and safety for COPD. The systematic review was conducted under the Cochrane systematic review guidelines and the design of the clinical trial was conducted in accord with the principles set out in the Declaration of Helsinki and the Good Clinical Practice guidelines. The work emerged in a stepwise fashion, starting with the evaluation of the extant modern and classical literature. This evaluation informed the design of the clinical trial, addressing limitations in previous studies. Although there is extensive literature, methodological flaws often limit the generalisability and applicability of the results. Outcomes from this study highlight the importance of improving standards and reporting in future research on CM. The body of evidence would be improved by rigorous evaluation of existing evidence and quality clinical trials focusing on specific health conditions and indications. The clinical trial will provide critical clinical data and build on previous RCTs and systematic reviews. Although the RCT results are not yet available, the rigorous design foreshows successful completion and significant contributions to the development of an evidence base for *Panax ginseng* in treating COPD.

References

1. The Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis Management and Prevention of COPD [Internet] 2010 [updated 2013 Feb; cited 2013 March 01]. Available from: http://goldcopd.org.
2. Briscoe WA, Nash ES. The slow space in chronic obstructive pulmonary diseases. Ann N Y Acad Sci. 1965;121:706-22. PubMed PMID: 14309579. Epub 1965/03/24. eng.
3. World Health Organisation. World Health Statistics [Internet] 2008 [cited 2012 July 03]. Available from: http://www.who.int/gho/publications/world_health_statistics/EN_WHS08_Full.pdf.
4. The Australian Lung Foundation. Economic Impact of COPD and Cost Effective Solutions; . 2008 Oct.
5. US Department of Health and Human Services.The health consequences of smoking: chronic obstructive lung disease: a report of the Surgeon General. DHHS Publication No. PHS 84-50204. Public Health Service, Office on Smoking and Health. Rockville, Maryland; : 1984.
6. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007;13(6):643-50.
7. George J, Ioannides-Demos LL, Santamaria NM, Kong DCM, Stewart K. Use of complementary and alternative medicines by patients with chronic obstructive pulmonary disease. Med J Aust. 2004;181(5):248-51.
8. An X, Zhang AL, May BH, Lin L, Xu Y, Xue CC. Oral Chinese Herbal Medicine for Improvement of Quality of Life in Patients with Stable Chronic Obstructive Pulmonary Disease: A Systematic Review. J Altern Complement Med. 2012;18(8):1-14. PubMed PMID: 22803654. Eng.
9. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of COPD: a systematic review. Eur Respir J. 2006 Aug;28(2):330-8. PubMed PMID: 16880367. Epub 2006/08/02. eng.
10. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: Multiple constituents and multiple actions. Biochem Pharmacol. 1999;58(11):1685-93.
11. Shergis JL, Zhang AL, Zhou W, Xue CC. Panax ginseng in Randomised Controlled Trials: A Systematic Review. Phytother Res. 2012 Sep 12 DOI: 10.1002/ptr.4832. PubMed PMID: 22969004. Epub 2012/09/13. Eng.
12. Gross D, Shenkman Z, Bleiberg B, Dayan M, Gittelson M, Efrat R. Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Monaldi Archives for Chest Disease - Pulmonary Series. 2002;57(5-6):242-6.
13. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Internet]: The Cochrane Collaboration; March 2011 [cited 2012 January 10]. Available from: www.cochrane-handbook.org.
14. World Health Organisation. The Global Burden of Disease [Internet] 2008 [updated 2004; cited 2012 July 04]. Available from: www.who.int/healthinfo/global_burden_disease/en/.

15. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: Systematic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.
16. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan: The Nippon COPD Epidemiology study. Respirology Journal. 2004;9(4):458-65.
17. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, et al. Prevalence of chronic obstructive pulmonary disease in China: A large, population-based survey. Am J Respir Crit Care Med. 2007;176(8):753-60.
18. Kim DS, Kim YS, Jung KS, Chang JH, Lim CM, Lee JH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: a population-based spirometry survey. Am J Respir Crit Care Med. 2005;172(7):842-7. PubMed PMID: 15976382. Epub 2005/06/25. eng.
19. Kotaniemi JT, Sovijärvi A, Lundbäck B. Chronic obstructive pulmonary disease in Finland: Prevalence and risk factors. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005;2(3):331-9.
20. Consultation on a Strategy for Services for Chronic Obstructive Pulmonary Disease (COPD) in England [Internet] 2010 [cited 2012 September 13]. Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_128426.pdf.
21. Tzanakis N, Anagnostopoulou U, Filaditaki V, Christaki P, Siafakas N. Prevalence of COPD in Greece. Chest. 2004;125(3):892-900.
22. National Center for Health Statistics. Chronic Obstructive Pulmonary Disease Among Adults Aged 18 and Over in the United States, 1998–2009 [Internet] 2011 [cited 2012 September 13]. Available from: http://www.cdc.gov/nchs/data/databriefs/db63.htm.
23. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. Annual Review of Pathology: Mechanisms of Disease. 2009;4:435-59.
24. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Eur Respir J. 2003;22(4):672-88.
25. Australian Bureau of Statistics. National Health Survey 2008, Summary of results, cat no. 4364.0. Canberra, Australia; : 2008.
26. Office for National Statistics. General lifestyle survey overview: A report on the 2010 general lifestyle survey. London, UK; : 2012.
27. Current Cigarette Smoking Prevalence Among Working Adults. United States, 2004-2010 [Internet] 2011 [cited 2012 September 11]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6038a2.htm.
28. Li Q, Hsia J, Yang G. Prevalence of smoking in China in 2010. N Engl J Med. 2011;364(25):2469-70. PubMed PMID: 21696322. eng.
29. Liu Y, Lee K, Perez-Padilla R, Hudson NL, Mannino DM. Outdoor and indoor air pollution and COPD-related diseases in high- and low-income countries. Int J Tuberc Lung Dis. 2008;12(2):115-27.
30. Coggon D, Newman Taylor A. Coal mining and chronic obstructive pulmonary disease: a review of the evidence. Thorax. 1998;53(5):398-407. PubMed PMID: 9708233. Pubmed Central PMCID: 1745225. Epub 1998/08/26. eng.
31. Fletcher C, Peto R, Tinker C, Speizer F. The natural history of chronic bronchitis and emphysema. London: Oxford University Press; 1976.

32. American Thoracic Society and European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003 Oct 1;168(7):818-900. PubMed PMID: 14522813. eng.
33. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med. 2000;343(4):269-80.
34. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;156(2 I):341-57.
35. McKenzie D, Abramson M, Crockett A, Glasgow N, Jenkins S, McDonald C, et al. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease v2.30. Australia. On behalf of The Australian Lung Foundation; 2011.
36. The Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD Spirometry Guide [Internet] 2010 [updated 2010; cited 2012 June 19]. Available from: www.goldcopd.org/other-resources-gold-spirometry-guide.html.
37. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
38. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.
39. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6.
40. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.
41. Ware J, Jr, Snow K, Kosinski M, Gandek B. SF-36 Health Survey manual and interpretation quide. The Health Institute, Boston USA; 1993.
42. Harper A, Power M, Orley J, Herrman H, Schofield H, Murphy B, et al. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med. 1998;28(3):551-8.
43. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85(Supplement 2):25-31.
44. Guyatt GH, Berman LB, Townsend M. A measure of quality of life for clinical trials in chronic lung disease. Thorax. 1987;42(10):773-8.
45. Kanervisto M, Saarelainen S, Vasankari T, Jousilahti P, Heistaro S, Heliövaara M, et al. COPD, chronic bronchitis and capacity for day-to-day activities: Negative impact of illness on the health-related quality of life. Chron Respir Dis. 2010;7(4):207-15.
46. Celli BR, Cote CG, Marin JM, Golis JA. The BODE index predicted death in chronic obstructive pulmonary disease. Evid Based Med. 2004;9(5):156.
47. Barnes PJ, Chowdhury B, Kharitonov SA, Magnussen H, Page CP, Postma D, et al. Pulmonary biomarkers in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;174(1):6-14.
48. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: The lung health study. JAMA. 1994;272(19):1497-505.

49. Ram FSF, Jardin JR, Atallah A, Castro AA, Mazzini R, Goldstein R, et al. Efficacy of theophylline in people with stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. Respir Med. 2005;99(2):135-44.
50. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.
51. Wood-Baker R, Walters EH, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2001 (2):CD001288. PubMed PMID: 11405984. Epub 2001/06/19. eng.
52. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009;374(9691):695-703.
53. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane database of systematic reviews [Internet] 2000 [cited 2012 October 2]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002733.pub2/abstract.
54. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane database of systematic reviews [Internet] 2006 [cited 2012 November 14]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003793.pub2/abstract.
55. Ringbaek TJ, Viskum K, Lange P. Does long-term oxygen therapy reduce hospitalisation in hypoxaemic chronic obstructive pulmonary disease? Eur Respir J. 2002;20(1):38-42.
56. Lahzami S, Bridevaux PO, Soccal PM, Wellinger J, Robert JH, Ris HB, et al. Survival impact of lung transplantation for COPD. Eur Respir J. 2010;36(1):74-80.
57. Feldman M, Taylor P, Paleolog E, Brennan FM, Maini RN. Anti-TNFα therapy is useful in rheumatoid arthritis and Crohn's disease: Analysis of the mechanism of action predicts utility in other diseases. Transplant Proc. 1998;30(8):4126-7.
58. Ohnishi K, Takagi M, Kurokawa Y, Satomi S, Konttinen YT. Matrix metalloproteinase-mediated extracellular matrix protein degradation in human pulmonary emphysema. Lab Invest. 1998;78(9):1077-87. PubMed PMID: 9759652. Epub 1998/10/06. eng.
59. Barnes PJ, Hansel TT. Prospects for new drugs for chronic obstructive pulmonary disease. Lancet. 2004;364(9438):985-96.
60. Currie GP, Douglas JG. ABC of chronic obstructive pulmonary disease.Non-pharmacological management. Br Med J. 2006;332(7554):1379-81. PubMed PMID: 16763252. Pubmed Central PMCID: 1476732. Epub 2006/06/10. eng.
61. Suzuki M, Muro S, Ando Y, Omori T, Shiota T, Endo K, et al. A randomized, placebo-controlled trial of acupuncture in patients with Chronic Obstructive Pulmonary Disease (COPD) the COPD-acupuncture trial (CAT). Arch Intern Med. 2012;172(11):878-86.
62. Yin HH, Shuai HC. Fundamentals of traditional Chinese medicine. Beijing, China: Foreign Languages Press; 1992.
63. Maciocia G. The Foundations of Chinese Medicine. Hong Kong: Churchill Livingstone; 1998.

64. Criteria of diagnosis and therapeutic effect of disease and syndromes in traditional Chinese medicine: State Administration of Traditional Chinese Medicine; China; 1995.
65. Lee DCW, Lau ASY. Effects of Panax ginseng on tumor necrosis factor-α-mediated inflammation: A mini-review. Molecules. 2011;16(4):2802-16.
66. An X, Zhang AL, Yang AW, Lin L, Wu D, Guo X, et al. Oral ginseng formulae for stable chronic obstructive pulmonary disease: A systematic review. Respir Med. 2011;105(2):165-76.
67. Jobst KA. A critical analysis of acupuncture in pulmonary disease: efficacy and safety of the acupuncture needle. J Altern Complement Med. 1995;1(1):57-85. PubMed PMID: 9395603. Epub 1995/01/01. eng.
68. Chan AWK, Lee A, Suen LKP, Tam WWS. Tai chi Qigong improves lung functions and activity tolerance in COPD clients: A single blind, randomized controlled trial. Complement Ther Med. 2011;19(1):3-11.
69. Jung SH, Woo MS, Kim SY, Kim WK, Hyun JW, Kim EJ, et al. Ginseng saponin metabolite suppresses phorbol ester-induced matrix metalloproteinase-9 expression through inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathways in human astroglioma cells. Int J Cancer. 2006;118(2):490-7.
70. Park MT, Cha HJ, Jeong JW, Kim SI, Chung HY, Kim ND, et al. Glucocorticoid receptor-induced down-regulation of MMP-9 by ginseng components, PD and PT contributes to inhibition of the invasive capacity of HT1080 human fibrosarcoma cells. Mol Cells. 1999;9(5):476-83.
71. Swanson SM, Jiang JX, Chang YS, De Souza NJ, Pezzuto JM. A rapid and sensitive bioassay involving cultured rat glioma cells to screen for substances capable of elevating intracellular cyclic AMP concentration. J Nat Prod. 1988;51(5):929-36.
72. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Adv Data. 2004 (343):1-19.
73. Zhang AL, Story DF, Lin V, Vitetta L, Xue CC. A population survey on the use of 24 common medicinal herbs in Australia. Pharmacoepidemiol Drug Saf. 2008;17(10):1006-13.
74. The International Plant Names Index [Internet] 2012 [cited 2012 December 05]. Available from: http://www.ipni.org/.
75. Collins RA. A ten-year audit of traditional Chinese medicine and other natural product research published in the Chinese Medical Journal (2000 - 2009). Chin Med J (Engl). 2011;124(9):1401-8. PubMed PMID: 21740755. eng.
76. Mar C, Bent S. An evidence-based review of the 10 most commonly used herbs. West J Med. 1999;171(3):168-71.
77. Zhu S, Zou K, Fushimi H, Cai S, Komatsu K. Comparative study on triterpene saponins of Ginseng drugs. Planta Med. 2004 Jul;70(7):666-77. PubMed PMID: 15303259. Epub 2004/08/12. eng.
78. Panax ginseng. Altern Med Rev. 2009;14(2):172-6.
79. Yang SZ. Divine Farmer's Material Medica: A Translation of the Shen Nong Ben Cao Jing. USA: Blue Poppy Press; 1998.
80. Ben Cao Tu Jing (Atlas of Materia Medica), collected and edited by Zhijun Shang and published by Anhui: Anhui Science and Technology Press (In Chinese) [Internet]: The James Lind Library 1994 [cited 2012 July 02]. Available from: www.jameslindlibrary.org/trial_records/11th_Century/ben_cao_tu_jing/ben_cao_tu_jing_trans.html.

81. Bensky D, Clavey S, Stoger E. Chinese herbal medicine: Materia medica, 3rd edition. Seattle: Eastland Press; 2004.
82. Christensen LP. Ginsenosides chemistry, biosynthesis, analysis, and potential health effects. Adv Food Nutr Res. 2009;55:1-99. PubMed PMID: 18772102. Epub 2008/09/06. eng.
83. World Health Organisation. Monographs on selected medicinal plants: Volume 1. Geneva, Switzerland: World Health Organization; 1999.
84. Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in commercial ginseng products: An analysis of 25 preparations. Am J Clin Nutr. 2001;73(6):1101-6.
85. Qi LW, Wang CZ, Du GJ, Zhang ZY, Calway T, Yuan CS. Metabolism of ginseng and its interactions with drugs. Curr Drug Metab. 2011 Nov;12(9):818-22. PubMed PMID: 21619519. Pubmed Central PMCID: 3291795. Epub 2011/05/31. eng.
86. Han M, Sha X, Wu Y, Fang X. Oral absorption of ginsenoside Rb1 using in vitro and in vivo models. Planta Med. 2006;72(5):398-404.
87. Xu QF, Fang XL, Chen DF. Pharmacokinetics and bioavailability of ginsenoside Rb1 and Rg1 from Panax notoginseng in rats. J Ethnopharmacol. 2003;84(2-3):187-92.
88. Hasegawa H. Proof of the mysterious efficacy of ginseng: Basic and clinical trials: Metabolic activation of ginsenoside: Deglycosylation by intestinal bacteria and esterification with fatty acid. J Pharmacol Sci. 2004;95(2):153-7.
89. Zangara A. Ginsana Clinical Review [Internet]: Flordis Pty Ltd; 2011 [cited 2012 November 25]. Available from: http://www.flordis.com.au/sites/default/files/pro-resources/Ginsana%20Clinical%20Review.pdf.
90. Scaglione F, Pannacci M, Petrini O. The standardised G115® *Panax ginseng* C.A. Meyer extract: A review of its properties and usage. Evidence-Based Integrative Medicine. 2005;2(4):195-206.
91. Blumenthal M, Lindstrom A, Lynch ME, Rea P. Herb Sales Continue Growth – Up 3.3% in 2010. HerbalGram: The Journal of the American Botanical Council. 2010 (90):64-7.
92. Cui J, Garle M, Eneroth P, Bjorkhem I. What do commercial ginseng preparations contain? Lancet. 1994;344(8915):134.
93. Pharmacopoeia of the People's Republic of China (English ed.). Vol. 1. Guangzhou, Guangdong Science and Technology Press. 2000; 172-3.
94. The European Scientific Cooperative on Phytotherapy (ESCOP) Monographs, Second Edition. The European Scientific Cooperative on Phytotherapy. 1996:211-22.
95. Coon JT, Ernst E. Panax ginseng: A systematic review of adverse effects and drug interactions. Drug Saf. 2002;25(5):323-44.
96. Seely D, Dugoua JJ, Perri D, Mills E, Koren G. Safety and efficacy of Panax ginseng during pregnancy and lactation. Canadian Journal of Clinical Pharmacology. 2008;15(1):e87-e94. PubMed PMID: 2008048806.
97. DerMarderosian A, Beutler JA. The review of natural products : the most complete source of natural product information. 5th ed. USA: Wolters Kluwer Health; 2010.
98. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. J Clin Psychopharmacol. 1987;7(3):201-2.
99. Shader RI, Greenblatt DJ. Bees, ginseng and MAOIs revisited. J Clin Psychopharmacol. 1988;8(4):235.

100. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm. 1997;54(6):692-3.
101. Chung E, Lee KY, Lee YJ, Lee YH, Lee SK. Ginsenoside Rg1 down-regulates glucocorticoid receptor and displays synergistic effects with cAMP. Steroids. 1998;63(7-8):421-4. PubMed PMID: 9654649. Epub 1998/07/09. eng.
102. Tamaoki J, Nakata J, Kawatani K, Tagaya E, Nagai A. Ginsenoside-induced relaxation of human bronchial smooth muscle via release of nitric oxide. Br J Pharmacol. 2000;130(8):1859-64. PubMed PMID: 10952675. Pubmed Central PMCID: 1572269. Epub 2000/08/22. eng.
103. Kim JY, Germolec DR, Luster MI. *Panax ginseng* as a potential immunomodulator: studies in mice. Immunopharmacol Immunotoxicol. 1990;12(2):257-76. PubMed PMID: 2229924. Epub 1990/01/01. eng.
104. Kim SJ, Jeong HJ, Yi BJ, Kang TH, An NH, Lee EH, et al. Transgenic Panax ginseng inhibits the production of TNF-α, IL-6, and IL-8 as well as COX-2 expression in human mast cells. Am J Chin Med. 2007;35(2):329-39.
105. Kenarova B, Neychev H, Hadjiivanova C, Petkov VD. Immunomodulating activity of ginsenoside Rg1 from Panax ginseng. Jpn J Pharmacol. 1990;54(4):447-54.
106. Lopez MV, Cuadrado MP, Ruiz-Poveda OM, Del Fresno AM, Accame ME. Neuroprotective effect of individual ginsenosides on astrocytes primary culture. Biochim Biophys Acta. 2007 Sep;1770(9):1308-16. PubMed PMID: 17659841. Epub 2007/07/31. eng.
107. Kim H, Chen X, Gillis CN. Ginsenosides protect pulmonary vascular endothelium against free radical-induced injury. Biochem Biophys Res Commun. 1992;189(2):670-6. PubMed PMID: 1472038. Epub 1992/12/15. eng.
108. Zhang D, Yasuda T, Yu Y, Zheng P, Kawabata T, Ma Y, et al. Ginseng extract scavenges hydroxyl radical and protects unsaturated fatty acids from decomposition caused by iron-mediated lipid peroxidation. Free Radic Biol Med. 1996;20(1):145-50.
109. Hiai S, Yokoyama H, Oura H, Yano S. Stimulation of pituitary-adrenocortical system by ginseng saponin. Endocrinol Jpn. 1979 Dec;26(6):661-5. PubMed PMID: 232038. Epub 1979/12/01. eng.
110. Churg A, Wang RD, Tai H, Wang X, Xie C, Wright JL. Tumor necrosis factor-α drives 70% of cigarette smoke-induced emphysema in the mouse. Am J Respir Crit Care Med. 2004;170(5):492-8.
111. Suh SO, Kroh M, Kim NR, Job YG, Cho MY. Effects of red ginseng upon postoperative immunity and survival in patients with stage III gastric cancer. Am J Chin Med. 2002;30(4):483-94.
112. Yun T, Zheng S, Choi S, Cai SR, Lee Y, Liu XY, et al. Non-organ-specific preventive effect of long-term administration of Korean red ginseng extract on incidence of human cancers. J Med Food. 2010;13(3):489-94. PubMed PMID: 2010690819. Language: English. Entry Date: 20100806. Revision Date: 20100806. Publication Type: journal article.
113. Xie JT, McHendale S, Yuan CS. Ginseng and diabetes. Am J Chin Med. 2005;33(3):397-404. PubMed PMID: 16047557. eng.
114. Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, et al. Antidiabetic effects of *Panax ginseng* berry extract and the identification of an effective component. Diabetes. 2002;51(6):1851-8.

115. Avakian EV, Sugimoto RB, Taguchi S, Horvath SM. Effect of Panax ginseng extract on energy metabolism during exercise in rats. Planta Med. 1984;50(2):151-4. PubMed PMID: 6473548. eng.
116. Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. Medical Science Monitor. 2004;10(8):RA187-RA92.
117. Gillis CN. Panax ginseng pharmacology: A nitric oxide link? Biochem Pharmacol. 1997;54(1):1-8.
118. Kim TH, Lee SM. The effects of ginseng total saponin, panaxadiol and panaxatriol on ischemia/reperfusion injury in isolated rat heart. Food Chem Toxicol. 2010;48(6):1516-20. PubMed PMID: 20353807. eng.
119. Joo SS, Yoo YM, Ahn BW, Nam SY, Kim YB, Hwang KW, et al. Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation. Biol Pharm Bull. 2008;31(7):1392-6. PubMed PMID: 2008319856.
120. Radad K, Gille G, Liu L, Rausch WD. Use of ginseng in medicine with emphasis on neurodegenerative disorders. J Pharmacol Sci. 2006;100(3):175-86.
121. Benishin CG, Lee R, Wang LCH, Liu HJ. Effects of ginsenoside Rb 1 on central cholinergic metabolism. Pharmacology. 1991;42(4):223-9.
122. Geng J, Dong J, Ni H, Lee MS, Wu T, Jiang K, et al. Ginseng for cognition. Cochrane database of systematic reviews [Internet] 2010 [cited 2012 August 26]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007769.pub2/abstract.
123. Unschuld P. Huang di nei jing su wen: Nature, knowledge, imagery in an ancient Chinese medical text. Berkeley: University of California Press; 2003.
124. Zhen ZY. Zhong Guo Yi Xue Shi [Chinese Medical History]. Taipei: Zhiyin Publishing Company; 1994.
125. May BH, Lu C, Bennett L, Hügel HM, Xue CCL. Evaluating the traditional Chinese literature for herbal formulae and individual herbs used for age-related dementia and memory impairment. Biogerontology. 2012;13(3):1-14.
126. Kong DX, Li XJ, Tang GY, Zhang HY. How many traditional Chinese medicine components have been recognized by modern western medicine? A chemoinformatic analysis and implications for finding multicomponent drugs. Chemmedchem. 2008;3(2):233-6.
127. Kong DX, Li XJ, Zhang HY. Where is the hope for drug discovery? Let history tell the future. Drug Discov Today. 2009;14(3-4):115-9.
128. Wright CW. Traditional antimalarials and the development of novel antimalarial drugs. J Ethnopharmacol. 2005;100(1-2):67-71.
129. Liu Ws, Lin L. The Clinical Practice of Chinese Medicine: COPD and Asthma. Beijing: People's Medical Publishing House; 2007.
130. Jiangsu New Medical Academy editors. Zhong yao da ci dian [Great Compendium of Chinese Medicines]. Shanghai: Shanghai Scientific and Technical Publishers; 1986.
131. Peng HR, ed. Zhong Yi Fang Ji Da Ci Dian [Great Compendium of Chinese Medicinal Formulae]. Beijing: People's Medical Publishing House; 1993.
132. Lin ZG, ed. Zhong xi yi bing ming dui zhao da ci dian. Beijing: Ren min wei sheng chu ban sha; 2002.
133. Yu YA, Fu JH. Zhong Yi Gu Ji Zhen Ben Ti Yao [Outlines of Major Classical Texts of Chinese Medicine]: Beijing, China: Zhong yi gu ji chu ban she; 1992.

134. Porter RS, Kaplan JL. The Merck Manual of Diagnosis and Therapy 19th Edition. USA: Merck Sharp and Dohme Corp; 2011.
135. Goldschmidt A. The evolution of Chinese medicine: Song Dynasty, 960-1200. London: Routledge; 2009.
136. Scheid V, Bensky D, Ellis A, Barolet R. Chinese Herbal Medicine: Formulas & Strategies 2nd Edition. Seattle: Eastland Press; 2009.
137. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7).
138. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7.
139. Shea BJ, Dube C, Moher D. Assessing the quality of reports of systematic reviews: the QUOROM statement compared to other tools. Systematic review in health care meta-analysis in context. London: BMJ Books, 2001; (7): 122-39.
140. Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kaptchuk TJ. Systematic review of the effects of ginseng on cardiovascular risk factors. Ann Pharmacother. 2006;40(1):83-95.
141. Coleman CI, Hebert JH, Reddy P. The effects of *Panax ginseng* on quality of life. J Clin Pharm Ther. 2003;28(1):5-15.
142. Hur MH, Lee MS, Yang HJ, Kim C, Bae IL, Ernst E. Ginseng for reducing the blood pressure in patients with hypertension: A systematic review and meta-analysis. J Ginseng Res. 2010;34(4):342-7.
143. Jia Y, Zhang S, Huang F, Leung SW. Could ginseng-based medicines be better than nitrates in treating ischemic heart disease? A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2012;20(3):155-66. PubMed PMID: 22500665. Epub 2012/04/17. eng.
144. Jang DJ, Lee MS, Shin BC, Lee YC, Ernst E. Red ginseng for treating erectile dysfunction: A systematic review. Br J Clin Pharmacol. 2008;66(4):444-50.
145. Kim S, Shin BC, Lee MS, Lee H, Ernst E. Red ginseng for type 2 diabetes mellitus: A systematic review of randomized controlled trials. Chin J Integr Med. 2011(c);17(12):937-44. PubMed PMID: 22139546. eng.
146. Lee MS, Yang EJ, Kim JI, Ernst E. Ginseng for cognitive function in alzheimer's disease: A systematic review. J Alzheimers Dis. 2009;18(2):339-44.
147. Lee N-H, Son C-G. Systematic Review of Randomized Controlled Trials Evaluating the Efficacy and Safety of Ginseng. J Acupunct Meridian Stud. 2011;4(2):85-97.
148. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol. 1999;55(8):567-75.
149. Jung JW, Kang HR, Ji GE, Park MS, Song WJ, Kim MH, et al. Therapeutic effects of fermented red ginseng in allergic rhinitis: a randomized, double-blind, placebo-controlled study. Allergy Asthma Immunological Research. 2011(b);3(2):103-10. PubMed PMID: CN-00784505.
150. Kennedy DO, Reay JL, Scholey AB. Effects of 8 weeks administration of Korean Panax ginseng extract on the mood and cognitive performance of healthy individuals. J Ginseng Res. 2007;31(1):34-43.
151. Reay JL, Kennedy DO, Scholey AB. The behavioural and mood effects of Panax ginseng (G115): A 20 week chronic trial. Appetite. 2008;50(2-3):564.

152. Gagnier JJ, DeMelo J, Boon H, Rochon P, Bombardier C. Quality of Reporting of Randomized Controlled Trials of Herbal Medicine Interventions. Am J Med. 2006(c);119(9):800.e1-.e11.
153. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.
154. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: The CONSORT statement. JAMA. 1996;276(8):637-9.
155. Moher D, Schulz KF, Altman DG, Lepage L. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. Ann Intern Med. 2001;134(8):657-62.
156. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: An elaborated CONSORT statement. Ann Intern Med. 2006(b);144(5):364-7.
157. Cho YK, Sung H, Lee HJ, Joo CH, Cho GJ. Long-term intake of Korean red ginseng in HIV-1-infected patients: development of resistance mutation to zidovudine is delayed. Int Immunopharmacol. 2001 Jul;1(7):1295-305. PubMed PMID: 11460310. Epub 2001/07/20. eng.
158. Hallstrom C, Fulder S, Carruthers M. Effects of Ginseng on the Performance of Nurses on Night Duty. Comp Med East West. 1982;6(4):277-82.
159. Han KH. Effect of Red Ginseng on Blood Pressure in Patients with Essential Hypertension and White Coat Hypertension. Am J Chin Med. 1998;26(2):199-209.
160. Reay JL, Scholey AB, Milne A, Fenwick J, Kennedy DO. Panax ginseng has no effect on indices of glucose regulation following acute or chronic ingestion in healthy volunteers. The British journal of nutrition. 2009;101(11):1673-8. PubMed PMID: CN-00697924.
161. Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of *Panax ginseng* C.A. Meyer. Drugs Exp Clin Res. 1990 (10):537-42. PubMed PMID: CN-00076943.
162. D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E, Lecchini S, et al. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. J Ethnopharmacol. 1986;16(1):15-22. PubMed PMID: CN-00044324.
163. Fulder S, Kataria M, Gethyn-Smith B. A double-blind clinical trial of Panax ginseng in aged subjects (abstr). 4th International Ginseng Symposium; Sept 18-20; Daejeon, Korea: Korea Ginseng & Tobacco Research Institute; 1984.
164. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY, et al. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. Eur J Neurol. 2008;15(8):865-8.
165. Kennedy DO, Scholey AB, Wesnes KA. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. Nutr Neurosci. 2001;4(4):295-310.
166. Kennedy DO, Scholey AB, Wesnes KA. Modulation of cognition and mood following administration of single doses of Ginkgo biloba, ginseng, and a ginkgo/ginseng combination to healthy young adults. Physiol Behav. 2002;75(5):739-51.

167. Kennedy DO, Scholey AB, Drewery L, Marsh VR, Moore B, Ashton H. Electroencephalograph effects of single doses of Ginkgo biloba and Panax ginseng in healthy young volunteers. Pharmacol Biochem Behav. 2003;75(3):701-9.
168. Lee S, Chu K, Sim J, Heo J, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord. 2008(b);22(3):222-6.
169. Reay JL, Kennedy DO, Scholey AB. Single doses of Panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J Psychopharmacol (Oxf). 2005;19(4):357-65.
170. Reay JL, Kennedy DO, Scholey AB. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol (Oxf). 2006; (6):771-81. PubMed PMID: CN-00570118.
171. Reay JL, Scholey AB, Kennedy DO. Panax ginseng (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults. Human Psychopharmacology: Clinical and Experimental. 2010;25(6):462-741.
172. Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand. Hum Psychopharmacol. 2002;17(1):35-44. PubMed PMID: CN-00410927.
173. Sorensen H, Sonne J. A double-masked study of the effects of ginseng on cognitive functions. Curr Ther Res Clin Exp. 1996;(12):959-968. PubMed PMID: CN-00173507.
174. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. Effects of psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminalpropeptide concentration, and body weight. Diabetes Care. 1995;(10):1373-75. PubMed PMID: CN-00187739.
175. Sunram-Lea SI, Birchall RJ, Wesnes KA, Petrini O. The effect of acute administration of 400mg of Panax ginseng on cognitive performance and mood in healthy young volunteers. Curr Top Nutraceutical Res. 2005;(1):65-74. PubMed PMID: CN-00575480.
176. Ziemba AW, Chmura J, Kaciuba-Uscilko H, Nazar K, Wisnik P, Gawronski W. Ginseng treatment improves psychomotor performance at rest and during graded exercise in young athletes. Int J Sport Nutr. 1999;(4):371-7. PubMed PMID: CN-00274944.
177. Allen JD, McLung J, Nelson AG, Welsch M. Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. J Am Coll Nutr. 1998;17(5):462-6. PubMed PMID: 9791844. eng.
178. Cherdrungsi P, Rungroeng K. Effects of standardized ginseng extract and exercise training on aerobic and anaerobic exercise capacities in humans. Korean Journal of Ginseng Science. 1995;19:93-100.
179. Engels HJ, Said JM, Wirth JC. Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. Nutrition Research. 1996;(8):1295-1305. PubMed PMID: CN-00170036.
180. Engels H, Wirth JC. No ergogenic effects of ginseng (Panax ginseng CA Meyer) during graded maximal aerobic exercise. J Am Diet Assoc. 1997;97(10):1110-5. PubMed PMID: 1998003316. Language: English. Entry Date: 19980101. Revision Date: 20091218. Publication Type: journal article.

181. Engels H, Kolokouri I, Cieslak TJ, II, Wirth JC. Effects of ginseng supplementation on supramaximal exercise performance and short-term recovery. J Strength Cond Res. 2001;15(3):290-5. PubMed PMID: 2002023932. Language: English. Entry Date: 20020208. Revision Date: 20100709. Publication Type: journal article.
182. Engels HJ, Fahlman MM, Wirth JC. Effects of ginseng on secretory IgA, performance, and recovery from interval exercise. Med Sci Sports Exerc. 2003;(4):690-6. PubMed PMID: CN-00472916.
183. Knapik J, Wright J, Welch M. The influence of Panax ginseng on indices of substrate utilization during repeated, exhaustive exercise in man (abstr). Fed Proc. 1983;42(336).
184. Kulaputana O, Thanakomsirichot S, Anomasiri W. Ginseng supplementation does not change lactate threshold and physical performances in physically active Thai men. J Med Assoc Thai. 2007;(6):1172-9. PubMed PMID: CN-00700725.
185. Ping FW, Keong CC, Bandyopadhyay A. Effects of acute supplementation of Panax ginseng on endurance running in a hot & humid environment. Indian J Med Res. 2011;133(1):96-102. PubMed PMID: CN-00778948.
186. Teves MA, Wright JE, Welch MJ, Patton JF, Mello RP, Rock PB, et al. Effects of Ginseng on Repeated Bouts of Exhaustive Exercise (abstr). Med Sci Sports Exerc. 1983;15(2):162.
187. Ahn CM, Hong SJ, Choi SC, Park JH, Kim JS, Lim DS. Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with first ST-segment elevation acute myocardial infarction. Phytother Res. 2011;25(2):239-49.
188. Caron MF, Hotsko AL, Robertson S, Mandybur L, Kluger J, White CM. Electrocardiographic and hemodynamic effects of Panax ginseng. Ann Pharmacother. 2002;36(5):758-63.
189. Chen Y. A clinical study of Ginseng in treating Silent Myocardial Ischemia (SMI). Journal of Practical Traditional Chinese Internal Medicine. 1993;7(3):5-6.
190. Jovanovski E, Jenkins A, Dias AG, Peeva V, Sievenpiper J, Arnason JT, et al. Effects of Korean red ginseng (Panax ginseng C.A. Mayer) and its isolated ginsenosides and polysaccharides on arterial stiffness in healthy individuals. Am J Hypertens. 2010;23(5):469-72. PubMed PMID: 20134405. eng.
191. Kim NR, Kim JH, Kim CY. Efect of Korean red ginseng supplementation on ocular blood flow in patients with glaucoma. J Ginseng Res. 2010;34(3):237-45.
192. Lee SH, Ahn YM, Ahn SY, Doo HK, Lee BC. Interaction between warfarin and Panax ginseng in ischemic stroke patients. J Altern Complement Med. 2008(a);6:715-21. PubMed PMID: CN-00667328.
193. Lee YH, Lee BK, Choi YJ, Yoon IK, Chang BC, Gwak HS. Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. Int J Cardiol. 2010;145(2):275-6. PubMed PMID: 19913311. eng.
194. Rhee MY, Kim YS, Bae JH, Nah DY, Kim YK, Lee MM, et al. Effect of Korean red ginseng on arterial stiffness in subjects with hypertension. J Altern Complement Med. 2011;(1):45-9. PubMed PMID: CN-00785241.
195. Sung J, Han KH, Zo JH, Park HJ, Kim CH, Oh BH. Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. Am J Chin Med. 2000;28(2):205-16. PubMed PMID: 10999439. eng.

196. De Souza LR, Jenkins AL, Sievenpiper JL, Jovanovski E, Rahelić D, Vuksan V. Korean red ginseng (Panax ginseng C.A. Meyer) root fractions: Differential effects on postprandial glycemia in healthy individuals. J Ethnopharmacol. 2011;137(1):245-50.
197. Ma SW, Benzie IFF, Chu TTW, Fok BSP, Tomlinson B, Critchley LAH. Effect of Panax ginseng supplementation on biomarkers of glucose tolerance, antioxidant status and oxidative stress in type 2 diabetic subjects: Results of a placebo-controlled human intervention trial. Diabetes Obes Metab. 2008;10(11):1125-7.
198. Sievenpiper JL, Arnason JT, Leiter LA, Vuksan V. Null and Opposing Effects of Asian Ginseng (Panax ginseng C.A. Meyer) on Acute Glycemia: Results of Two Acute Dose Escalation Studies. J Am Coll Nutr. 2003;22(6):524-32.
199. Sievenpiper JL, Sung MK, Di Buono M, Seung-Lee K, Nam KY, Arnason JT, et al. Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation- and dose-finding studies. J Am Coll Nutr. 2006;25(2):100-7. PubMed PMID: 16582025. eng.
200. Vuksan V, Sung MK, Sievenpiper JL, Stavro PM, Jenkins AL, Di Buono M, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metab Cardiovasc Dis. 2008;18(1):46-56. PubMed PMID: CN-00617420.
201. Scaglione F, Cogo R, Cocuzza C, Arcidiacono M, Beretta A. Immunomodulatory effects of Panax ginseng C.A. Meyer (G115) on alveolar macrophages from patients suffering with chronic bronchitis. Int J Immunother. 1994;10(1):21-4.
202. Scaglione F, Cattaneo G, Alessandria M, Cogo R. Efficacy and safety of the standardized ginseng extract G115 for potentiating vaccination against common cold and/or influenza syndrome. Drugs Under Experimental and Clinical Research. 1996;(2):65-72. PubMed PMID: CN-00173192.
203. Scaglione F, Weiser K, Alessandria M. Effects of the standardised ginseng extract G115(TM) in patients with chronic bronchitis: A nonblinded, randomised, comparative pilot study. Clin Drug Investig. 2001 (1):41-5. PubMed PMID: CN-00341018.
204. Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. Int J Impot Res. 1995;(3):181-6. PubMed PMID: CN-00128843.
205. de Andrade E, de Mesquita AA, Claro Jde A, de Andrade PM, Ortiz V, Paranhos M, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. Asian J Androl. 2007;(2):241-4. PubMed PMID: CN-00576270.
206. Hong B, Ji YH, Hong JH, Nam KIY, Ahn TY. A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: A preliminary report. J Urol. 2002;168(5):2070-3.
207. Kim TH, Jeon SH, Hahn EJ, Paek KY, Park JK, Youn NY, et al. Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction. Asian J Androl. 2009;11(3):356-61.
208. Gaffney BT, Hügel HM, Rich PA. The effects of Eleutherococcus senticosus and Panax ginseng on steroidal hormone indices of stress and lymphocyte subset numbers in endurance athletes. Life Sci. 2001;70(4):431-42.
209. Jung HL, Kwak HE, Kim SS, Kim YC, Lee CD, Byurn HK, et al. Effects of Panax ginseng Supplementation on Muscle Damage and Inflammation after Uphill Treadmill Running in Humans. Am J Chin Med. 2011(a);39(3):441-50. PubMed PMID:

2011059348. Language: English. Entry Date: 20110722. Revision Date: 20110812. Publication Type: journal article.
210. Srisurapanon S, Rungroeng K, Apibal S, Cherdrugsi P, Siripol R, Vanich-Angkul V, et al. The effect of standardized ginseng extract on peripheral blood leukocytes and lymphocyte subsets: a preliminary study in young health adults. J Med Assoc Thai. 1997;S81-5. PubMed PMID: CN-00255269.
211. Cardinal BJ, Engels HJ. Ginseng does not enhance psychological well-being in healthy, young adults: results of a double-blind, placebo-controlled, randomized clinical trial. J Am Diet Assoc. 2001;101(6):655-60. PubMed PMID: 2002010220. Language: English. Entry Date: 20020104. Revision Date: 20091218. Publication Type: journal article.
212. Ellis JM, Reddy P. Effects of Panax ginseng on quality of life. Ann Pharmacother. 2002;36(3):375-9.
213. Kim JH, Chan YP, Lee SJ. Effects of sun ginseng on subjective quality of life in cancer patients: A double-blind, placebo-controlled pilot trial. J Clin Pharm Ther. 2006;31(4):331-4.
214. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Int J Clin Pharmacol Res. 1999;(3):89-99. PubMed PMID: CN-00277176.
215. Kim HS, Lee BM. Protective effects of antioxidant supplementation on plasma lipid peroxidation in smokers. J Toxicol Environ Health A. 2001;63(8):583-98. PubMed PMID: 11549118. eng.
216. Kim HG, Yoo SR, Park HJ, Lee NH, Shin JW, Sathyanath R, et al. Antioxidant effects of Panax ginseng C.A. Meyer in healthy subjects: a randomized, placebo-controlled clinical trial. Food Chem Toxicol. 2011(a);49(9):2229-35. PubMed PMID: 21699953. eng.
217. Kim SY, Seo SK, Choi YM, Jeon YE, Lim KJ, Cho S, et al. Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial (abstr). Menopause. 2011(b);19(4):461-6. PubMed PMID: 22027944. Eng.
218. Oh KJ, Chae MJ, Lee H-S, Hong HD, Park K. Effects of Korean red ginseng on sexual arousal in menopausal women: Placebo-controlled, double-blind crossover clinical study. J Sex Med. 2010;7(4, Pt 1):1469-77.
219. Park JW, Lee BJ, Bu Y, Yeo I, Kim J, Ryu B. Effects of Korean red ginseng on dry mouth: A randomized, double-blind, placebo-controlled trial. J Ginseng Res. 2010;34(3):183-91.
220. Lu AP, Chen QR, Ji B. Ginseng combined withTotal Parenteral Nutrition (TPN) treatment for 30 cases of severe ulcerative colitis. Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care. 2009;16(5):284-6.
221. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol. 2004;26(8):1044-80.
222. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. Control Clin Trials. 1995;16(1):62-73.

223. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
224. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. JAMA. 2009;302(9):977-84.
225. Wu TX, Li YP, Bian ZX, Li TQ, Li J, Dagenais S, et al. Consolidated standards for reporting trials of traditional Chinese medicine (CONSORT for TCM) (for solicitation of comments). Chinese Journal of Evidence-Based Medicine. 2007;7(9):625-30.
226. Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet. 2005;365(9465):1159-62.
227. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration. J Clin Epidemiol. 2006;59(11):1134-49.
228. Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Randomized controlled trials of herbal interventions underreport important details of the intervention. J Clin Epidemiol. 2011;64(7):760-9.
229. Wolsko PM, Solondz DK, Phillips RS, Schachter SC, Eisenberg DM. Lack of herbal supplement characterization in published randomized controlled trials. Am J Med. 2005;118(10):1087-93.
230. Chai H, Wang Q, Huang L, Xie T, Fu Y. Ginsenoside Rb1 inhibits tumor necrosis factor-α-induced vascular cell adhesion molecule-1 expression in human endothelial cells. Biol Pharm Bull. 2008;31(11):2050-6.
231. Chan LY, Kwok HH, Chan RW, Peiris MJ, Mak NK, Wong RN, et al. Dual functions of ginsenosides in protecting human endothelial cells against influenza H9N2-induced inflammation and apoptosis. J Ethnopharmacol. 2011;137(3):1542-6. PubMed PMID: 21872652. Epub 2011/08/30. eng.
232. Chen XC, Fang F, Zhu YG, Chen LM, Zhou YC, Chen Y. Protective effect of ginsenoside Rg1 on MPP+-induced apoptosis in SHSY5Y cells. J Neural Transm. 2003;110(8):835-45. PubMed PMID: 12898340. Epub 2003/08/05. eng.
233. Cho JY, Yoo ES, Baik KU, Park MH, Han BH. In vitro inhibitory effect of protopanaxadiol ginsenosides on tumor necrosis factor (TNF)-α production and its modulation by known TNF-α antagonists. Planta Med. 2001;67(3):213-8.
234. Choi IY, Kim SJ, Kim MC, Kim HL, Shin HJ, Kang TH, et al. Inhibitory effects of the transgenic Panax ginsengs on phorbol ester plus A23187-induced IL-6 production and cyclooxygenase-2 via suppression of NF-B and MAPKs in HMC-1. Immunopharmacol Immunotoxicol. 2011a;33(1):205-10. PubMed PMID: 2011072940.
235. Choi Y, Yoon J, Cha S, Lee S. Ginsenoside Rh1 inhibits the invasion and migration of THP-1 acute monocytic leukemia cells via inactivation of the MAPK signaling pathway. Fitoterapia. 2011b;82(6):911-9. PubMed PMID: 2011204239.
236. He F, Guo R, Wu SL, Sun M, Li M. Protective effects of ginsenoside Rb1 on human umbilical vein endothelial cells in vitro. J Cardiovasc Pharmacol. 2007;50(3):314-20. PubMed PMID: 17878761. Epub 2007/09/20. eng.
237. Kwok HH, Ng WY, Yang MS, Mak NK, Wong RN, Yue PY. The ginsenoside protopanaxatriol protects endothelial cells from hydrogen peroxide-induced cell injury and cell death by modulating intracellular redox status. Free Radic Biol Med. 2010;48(3):437-45. PubMed PMID: 19932166. Epub 2009/11/26. eng.

238. Lee DCW, Yang CLH, Chik SCC, Li JCB, Lau ASY. Bioactivity-guided identification and cell signaling analysis to investigate the immunomodulatory effects of ginseng on U937 cells. Cytokine. 2009;48 (1-2):101. PubMed PMID: 70166626.
239. Lee HC, Vinodhkumar R, Yoon JW, Park SK, Lee CW, Kim HY. Enhanced inhibitory effect of ultra-fine granules of red ginseng on LPS-induced cytokine expression in the monocyte-derived macrophage THP-1 cells. Int J Mol Sci. 2008;9(8):1379-92. PubMed PMID: 19325809. Pubmed Central PMCID: 2635732. Epub 2009/03/28. eng.
240. Nikaido T, Ohmoto T, Sankawa T, Tanaka O, Kasai R, Shoji J, et al. Inhibitors of Cyclic AMP Phosphodiesterase in *Panax ginseng* C. A. Meyer and *Panax japonicus* C. A. Meyer. Chem Pharm Bull (Tokyo). 1984;32(4):1477-83.
241. Ohashi R, Yan S, Mu H, Chai H, Yao Q, Lin PH, et al. Effects of homocysteine and ginsenoside Rb1 on endothelial proliferation and superoxide anion production. J Surg Res. 2006;133(2):89-94. PubMed PMID: 16271366. Epub 2005/11/08. eng.
242. Zhou BR, Xu Y, Wu D, Permatasari F, Gao YY, Luo D. Ginsenoside Rg1 protects human fibroblasts against psoralen- and UVA-induced premature senescence through a telomeric mechanism. Archives of Dermatological Research Journal. 2012;304(3):223-8. PubMed PMID: 22350182. eng.
243. Cho WC, Chung WS, Lee SK, Leung AW, Cheng CH, Yue KK. Ginsenoside Re of Panax ginseng possesses significant antioxidant and antihyperlipidemic efficacies in streptozotocin-induced diabetic rats. Eur J Pharmacol. 2006 Nov 21;550(1-3):173-9. PubMed PMID: 17027742. Epub 2006/10/10. eng.
244. Jie YH, Cammisuli S, Baggiolini M. Immunomodulatory effects of Panax Ginseng C.A. Meyer in the mouse. Agents Actions. 1984;15(3-4):386-91. PubMed PMID: 6084415. Epub 1984/10/01. eng.
245. Joh EH, Lee IA, Jung IH, Kim DH. Ginsenoside Rb1 and its metabolite compound K inhibit IRAK-1 activation - The key step of inflammation. Biochem Pharmacol. 2011;82(3):278-86. PubMed PMID: 2011346932.
246. Kim JY, Germolec DR, Luster MI. Panax ginseng as a potential immunomodulator: Studies in mice. Immunopharmacol Immunotoxicol. 1990;12(2):257-76.
247. Kim TW, Joh EH, Kim B, Kim DH. Ginsenoside Rg5 ameliorates lung inflammation in mice by inhibiting the binding of LPS to toll-like receptor-4 on macrophages. Int Immunopharmacol. 2012;12(1):110-6.
248. Liou CJ, Huang WC, Tseng J. Short-term oral administration of ginseng extract induces type-1 cytokine production. Immunopharmacol Immunotoxicol. 2006;28(2):227-40. PubMed PMID: 16873092. Epub 2006/07/29. eng.
249. Liou CJ, Li ML, Tseng J. Intraperitoneal injection of ginseng extract enhances both immunoglobulin and cytokine production in mice. Am J Chin Med. 2004;32(1):75-88. PubMed PMID: 15154287. Epub 2004/05/25. eng.
250. Quan FS, Compans RW, Cho YK, Kang SM. Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine. 2007;25(2):272-82. PubMed PMID: 16945454. Epub 2006/09/02. eng.
251. Song Z, Johansen HK, Faber V, Moser C, Kharazmi A, Rygaard J, et al. Ginseng treatment reduces bacterial load and lung pathology in chronic Pseudomonas aeruginosa pneumonia in rats. Antimicrob Agents Chemother. 1997;41(5):961-4. PubMed PMID: 9145852. Pubmed Central PMCID: 163833. Epub 1997/05/01. eng.

252. Song Z, Moser C, Wu H, Faber V, Kharazmi A, Hoiby N. Cytokine modulating effect of ginseng treatment in a mouse model of Pseudomonas aeruginosa lung infection. J Cyst Fibros. 2003;2(3):112-9. PubMed PMID: 15463859. Epub 2004/10/07. eng.
253. Berger A. Science commentary: Th1 and Th2 responses: What are they? Br Med J. 2000;321(7258):424.
254. Boswell-Smith V, Spina D, Page CP. Phosphodiesterase inhibitors. Br J Pharmacol. 2006 Jan;147 Suppl 1:S252-7. PubMed PMID: 16402111. Pubmed Central PMCID: 1760738. Epub 2006/01/13. eng.
255. Stuhlinger MC, Tsao PS, Her JH, Kimoto M, Balint RF, Cooke JP. Homocysteine impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine. Circulation. 2001;104(21):2569-75. PubMed PMID: 11714652. eng.
256. Oikawa S, Kawanishi S. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. FEBS Lett. 1999;453(3):365-8. PubMed PMID: 10405177. eng.
257. Nielsen F, Mikkelsen BB, Nielsen JB, Andersen HR, Grandjean P. Plasma malondialdehyde as biomarker for oxidative stress: reference interval and effects of life-style factors. Clin Chem. 1997;43(7):1209-14. PubMed PMID: 9216458. eng.
258. Barnes PJ. The cytokine network in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2009;41(6):631-8.
259. Liu ZG. Molecular mechanism of TNF signaling and beyond. Cell Res. 2005;15(1):24-7. PubMed PMID: 15686622. Epub 2005/02/03. eng.
260. Rahman I. Oxidative stress, chromatin remodeling and gene transcription in inflammation and chronic lung diseases. Int J Biochem Mol Biol. 2003 Jan 31;36(1):95-109. PubMed PMID: 12542980. Epub 2003/01/25. eng.
261. Sandborn WJ. Strategies for targeting tumour necrosis factor in IBD. Best Pract Res Clin Gastroenterol. 2003;17(1):105-17. PubMed PMID: 12617886. Epub 2003/03/06. eng.
262. Paredi P, Kharitonov SA, Leak D, Ward S, Cramer D, Barnes PJ. Exhaled ethane, a marker of lipid peroxidation, is elevated chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(2 Pt 1):369-73.
263. State Government of Victoria, Australia. Department of Health. Streamlining ethical review [Internet] 2012 [cited 2012 November 25]. Available from: http://www.health.vic.gov.au/clinicaltrials/streamlining.htm.
264. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Adopted Helsinki, 1964 amended 2000 [Internet]: Ferney-Voltaire, France; 1964 [cited 2012 June 14]. Available from: www.wma.net.
265. International Conference on Harmonisation. Guideline for Good Clinical Practice [Internet] 1996 [cited 2012 December 06]. Available from: http://www.ich.org/.
266. Theraputic Goods Administration. Note for guidence on good clinical practice (CPMP/ICH/135/95): Annotated with TGA comments [Internet]: Australia; 2000 [cited 2012 December 06]. Available from: http://www.tga.gov.au/pdf/euguide/ich13595.pdf.
267. Ginsana® Vitalise [Internet] 2012 [cited 2012 September 06]. Available from: http://www.ginsanaproducts.com/our-products/ginsana.html.
268. Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with COPD [Internet]: The European Agency for the Evaluation of

Medicinal Products; 1999 [cited 2010 March 05]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003557.pdf.
269. CareFusion. SpiroUSB™ fully featured PC Spirometry in 3 easy steps [Internet] 2010 [cited 2012 August 30]. Available from: http://www.carefusion.com.
270. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. Population. Am J Respir Crit Care Med. 1999;159(1):179-87.
271. National Health and Nutrition Examination Survey (NHANES): Respiratory Health Spirometry Procedures Manual [internet]: Centres of Disease Control; 2008 [cited 2012 August 30]. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/spirometry.pdf.
272. Anthonisen NR, Manfreda J, Warren CPW. Antiobiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106(2):196-204.
273. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med. 1997;155(4):1283-9.
274. Ludbrook J. Multiple comparison procedures updated. Clin Exp Pharmacol Physiol. 1998;25(12):1032-7.
275. Ludbrook J. Multiple inferences using confidence intervals. Clin Exp Pharmacol Physiol. 2000;27(3):212-5.
276. Shergis JL, Parker S, Coyle ME, Zhang AL, Xue CC. Key considerations for conducting Chinese medicine clinical trials in hospitals. Chin Med. 2013;8(1):3. PubMed PMID: 23414529. Pubmed Central PMCID: 3577434. Epub 2013/02/19. eng.
277. The European Agency for the Evaluation of Medicinal Products. Points to consider on multiplicity issues in clinical trials [Internet]. 2002 [cited 2012 March 10]. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003640.pdf.
278. Shergis JL, Zhang AL, Zhou W, Xue CC. The methodological quality and risk of bias of Panax ginseng randomized controlled trials: a review. Am J Chin Med. 2013;41(2).
279. Xue CC, Shergis JL, Zhang AL, Worsnop C, Fong H, Story D, et al. Panax ginseng C.A Meyer root extract for moderate Chronic Obstructive Pulmonary Disease (COPD): Study protocol for a randomised controlled trial. Trials. 2011;12.
280. Minghang W, Jiansheng L, Suyun L, Haifeng W, Xueqing Y, Hailong Z. Effect of traditional Chinese medicine on outcomes in patients with mild/moderate chronic obstructive pulmonary disease: study protocol for a randomized placebo-controlled trial. Trials. 2012;13:109. PubMed PMID: 22799753. Pubmed Central PMCID: 3475096. Epub 2012/07/18. eng.

Appendices

Appendix 1: Data extraction form for the systematic review

Part A: Demographic characteristics of studies	
Item	**Details**
First author	
Year of publication	
Country where study was conducted	
Title	
Source of participants	
Trial design	
Condition treated	
Total number of participants	
Number of participants - Treatment group (Randomised/Analysed)	
Number of participants – Control group (Randomised/Analysed)	
Number of Male / Number of Female	
Age range and/or mean ± SD (years)	
Part B: Intervention and outcome characteristics of studies	
Study intervention	
Control intervention	
Administration type (e.g., capsules, power)	
Dosage	
Treatment duration and follow-up	
Outcomes	
Results, mean and standard deviation or number of events	
Adverse events	
Authors' conclusions	

Appendix 2: Chinese medicine syndrome differential diagnosis form

Key: 0= None (does not have this symptom)
1= Mild (symptom present once in a while but does not effect daily life)
2= Moderate (symptom can cause an inconvenience to daily life)
3= Severe (symptom effects the performance of daily duties)

In the last one year;		**Severity** (Trial coordinator to complete)				**Differentiation** (Chinese medicine practitioner to complete)
		0	**1**	**2**	**3**	
1.	Have you had a cough?					Lung Qi deficiency? (tick ✓) **( ) Yes** **( ) No**
2.	Have you had wheezing?					
3.	Have you had shortness of breath at any time?					
4.	Have you had clear sputum?					
5.	Have you had white sputum?					
6.	Did you catch a cold and/or was it difficult to recover from a cold?					
7.	Have you found that you sweat easily, even when you are not doing exercise?					
8.	Have you had headache or felt a heavy headed?					Spleen Qi deficiency? (tick ✓) **( ) Yes** **( ) No**
9.	Have you felt tired or exhausted?					
10.	Have your limbs felt heavy?					
11.	Have you had a poor appetite?					
12.	Have you had loose bowel motions?					
13.	Have you felt full in the stomach even when you hadn't just eaten?					
14.	Have you felt aversion to the cold?					Kidney Qi deficiency? (tick ✓) **( ) Yes** **( ) No**
15.	Have your limbs felt cold?					
16.	Have you felt weak, especially in the lower back area, or the knees?					
17.	Have you frequently (>2 times) woken in the night to go to the toilet?					
18.	Have you felt short of breath after slight exercise?					
Tongue	Provide details if the subject has taken food/drink within 2 hours prior to examination: (Trial coordinator to complete)_____ Tongue observation: (Chinese medicine practitioner to complete). Colour:_____Coating:_____Shape:_____Texture:_____Other:_____					

Chinese Medicine Syndrome Differentiation: Tick (✓)	
(1) ☐ Lung Qi Deficiency	**(2) ☐ Lung & Spleen Qi Deficiency**
(3) ☐ Other (specify)_____	
Diagnosis completed By: _____	
Signature: _____	
Date: _____	

Appendix 3: Media promotion and advertising for the GEARS clinical trial

Appendix 3.1: 'The Senior' Newspaper

Ginseng may help with lungs

THE ancient Chinese herbal medicine ginseng is being researched as a treatment for chronic obstructive pulmonary disease.

Almost 20 per cent of adults suffer emphysema and chronic bronchitis – known as COPD.

"It is critical to provide effective symptomatic relief and to improve quality of life for COPD sufferers," said Professor Frank Thien, director of respiratory medicine at Box Hill Hospital.

"Some current medications cause side-effects, so other and safer treatments need to be investigated."

There is no cure and current treatments only offer limited relief but there may be some hope with ginseng.

"There has been increasing interest in complementary and alternative medicine for the management of COPD," said Professor Charlie Xue, director of the WHO Collaborating Centre for Traditional Medicine at RMIT University.

"In Chinese herbal medicine, ginseng has been used for thousands of years to treat breathlessness and fatigue as well as debilitation and reduced mental and physical capacities due to chronic illness."

RMIT University, the Box Hill Hospital and Austin Health in Melbourne are investigating the use of ginseng in patients with COPD.

■ To find out more or to participate in the research phone 9925-6527 or email gears@rmit.edu.au

Appendix 3.2: 'Nova Holistic' Magazine

Chinese medicine looks to local research

China's largest Chinese Medicine hospital is backing Australian researchers to help provide better health outcomes for sufferers of emphysema and chronic bronchitis.

Chronic Obstructive Pulmonary Disease (COPD) is a growing international health problem, particularly in China, affecting millions of smokers, and is a focus of a new research agreement with RMIT University.

Guangdong Provincial Hospital of Chinese Medicine and Guangdong Provincial Academy of Chinese Medical Sciences Research has signed a $2 million deal with RMIT's School of Health Sciences and Health Innovations Research Institute.

Professor Yu Bo Lu, President of the Guangdong Provincial Hospital of Chinese Medicine said RMIT was well recognised in China and also internationally for its excellence in Chinese Medicine research and education.

"The principal aims of our research collaboration are to develop the evidence base in order to inform clinical practice and provide better health outcomes for people throughout the world," he said.

Professor Charlie Xue, Head of School of Health Sciences and Director of the Traditional and Complementary Medicine Research Program, said RMIT had been the largest provider of Traditional Chinese Medicine (TCM) studies in Australia since 1993 and was committed to an evidence-based approach.

"TCM is a complete healthcare system with a 2,500-year history," he said. "Unlike Western medicine, which focuses on identifying and treating conditions affecting individual body systems and organs, TCM looks at the overall relationships between body systems and organs."

From July 2012, national registration of Chinese Medicine as a primary health care profession will start under the National Registration and Accreditation Scheme. ●

Appendix 3.3: 'Diamond Valley and Heidelberg Leader' Newspaper

Herb trial offers hope

Health | Shaun Campbell

A CHINESE herb could change the lives of people like Diamond Creek's Bill Niam.

The 71-year-old, who has chronic lung disease, is part of a ground-breaking trial led by respiratory researchers at the Austin hospital.

The trial — the first of its kind — will investigate whether ginseng can improve the lung function and quality of life for people with chronic obstructive pulmonary disease.

Mr Niam, an ex-smoker who was diagnosed with COPD in 2009, volunteered for the trial a year ago. "If I can improve my health I will do it, and it can help other people," he said.

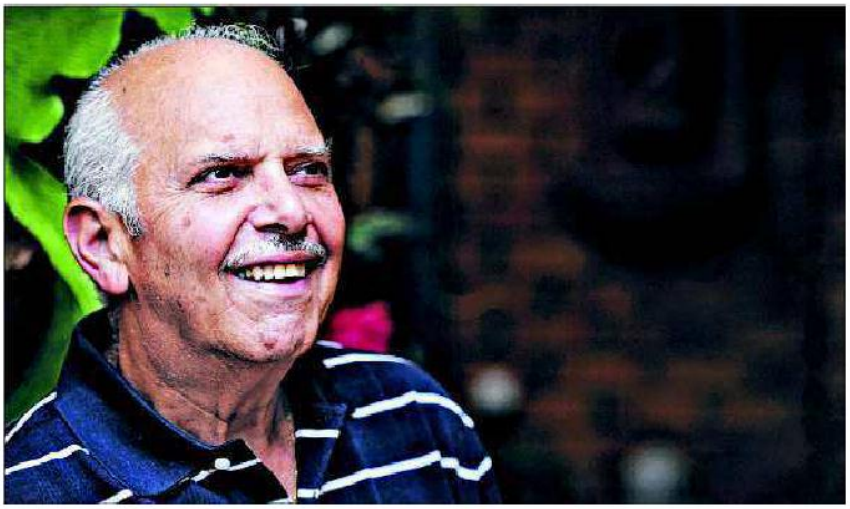
More than 1 million Australians have the disease, which damages the lungs, making it difficult to breathe.

Hospital respiratory specialist Christopher Worsnop said the project could help more than 10 per cent of the adult population suffering from the disease. Ginseng had been used for centuries to relieve symptoms of lung disease, but no rigorous clinical trials had been done, he said.

Mr Niam said he was treated for 24 weeks and continued to be monitored.

The trial needs volunteers who are ex-smokers with COPD.

For details, contact 9925 6527 or gears@rmit.edu.au.

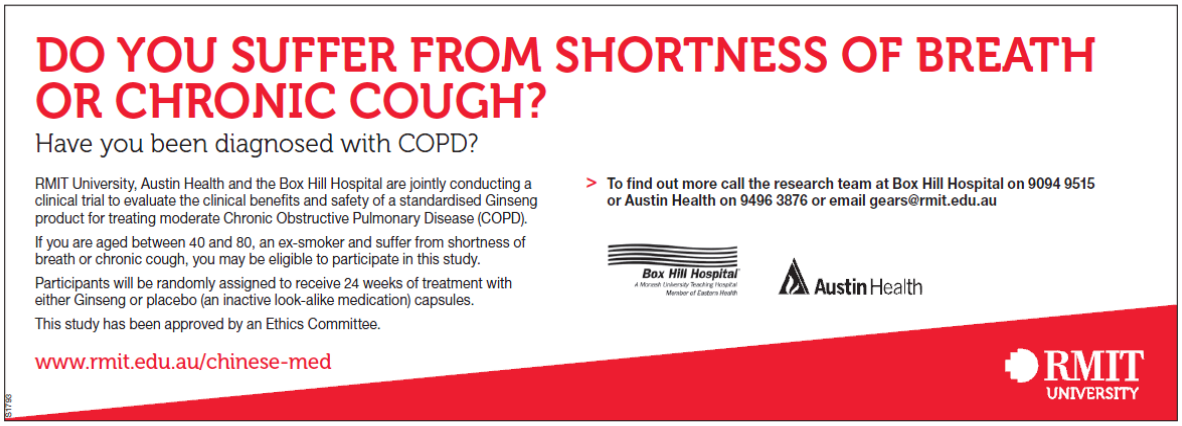


Bill Niam has lung disease and is volunteering for a research project at Austin Hospital that is investigating the use of the Chinese herb ginseng to improve the ailment. N34dv709

Appendix 3.4: 'Channel 7 News'

Appendix 3.5: 'The Age' Newspaper Advertising

Appendix 3.6: 'Whittlesea Leader' Newspaper Advertising



Appendix 4: Participant information and consent form

PARTICIPANT INFORMATION AND CONSENT FORM (PICF)

Version: 6.0 dated 29.09.2010

Participant number:_____

Short Title (Acronym): Ginseng Extract And Respiratory Symptoms (GEARS)

PROJECT TITLE: The effect of a standardised ginseng extract in patients with moderate chronic obstructive pulmonary disease (COPD): a randomised, double blind, placebo controlled trial

PRINCIPAL INVESTIGATORS:
Dr. Christopher Worsnop (Respiratory and Sleep Physician, Austin Health)
A/Prof. Frank Thien (Head, Respiratory Medicine, Box Hill Hospital)
A/Prof. David Langton (Director, Thoracic and Sleep Medicine, Frankston Hospital)

OTHER PROJECT CHIEF INVESTIGATORS:
Professor Charlie Xue (Director, TCM Research Program, RMIT University)
Dr Tony Zhang (Research Fellow, TCM Research Program, RMIT University)

This Participant Information and Consent Form is 11 pages long. Please make sure you have all the pages.

1. Introduction

You are invited to take part in this research project. This is because you have Chronic Obstructive Pulmonary Disease, including Chronic Bronchitis and Emphysema. The research project is testing a new compound for Chronic Obstructive Pulmonary Disease. The new compound is a standardised Ginseng extract, called Ginseng G115 and comparing it to a placebo (a look alike inactive medication).

This Participant Information and Consent Form (PICF) tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research. Please read this information carefully. Before deciding whether or not to take part, you might want to talk about it with a relative or friend. If you have questions about anything that you don't understand or want to know more about, please ask the study doctor or research staff. Participation in this research is voluntary. If you don't wish to take part, you don't have to. You are also free to leave the study at any time. If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to have the tests and treatments that are described; and
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research?

The aim of this project is to investigate the effectiveness and safety of a standardised Ginseng extract, with the focus being on quality of life improvements in adults with moderate Chronic Obstructive Pulmonary Disease.

There are an increasing number of Chronic Obstructive Pulmonary Disease sufferers in Australia. Current treatments aim to relieve and control symptoms and to reduce complications. However, many people still have reduced quality of life. There has been a lot of interest in complementary / alternative medicine (CAM) especially herbal medicine for managing Chronic Obstructive Pulmonary Disease. Despite a long history of use and much research into herbal medicines, there is not much research into how effective they are in many conditions, including the use of Ginseng for people with Chronic Obstructive Pulmonary Disease. This research will test whether the standardised Ginseng extract compared to a placebo improves lung function, reduces the use of usual medications, as well as improves the quality of life in people with moderate Chronic Obstructive Pulmonary Disease. Many clinical studies looking at the safety of Ginseng have shown that, if taken at the recommended dosage, Ginseng is safe and does not have any significant side effects. Ginseng has been listed with the Therapeutic Goods Administration (TGA) for public use in Australia since 2002 as a medicine/herbal product (Aust L14987), for maintaining stamina and endurance by improving the recovery rate after intense physical effort. It helps to relieve nervous fatigue, tension, anxiety, stress and can increase the oxygen uptake capacity. It also improves vitality and general quality of life. However, it is considered an experimental treatment, and it is not an approved treatment for Chronic Obstructive Pulmonary Disease.

If you take part in this research you will be one of the 168 participants. 84 people are expected to participate at Austin Health and 84 people are expected to participate at the Box Hill Hospital. You will have a 50/50 chance of being randomly assigned to either the active Ginseng group or the placebo (non-active study medication) group. This design allows us to compare the therapeutic effects of the active treatment with the placebo treatment and make sure changes are not just happening by chance. If the results of this study show that Ginseng is effective in the treatment of moderate Chronic Obstructive Pulmonary Disease, then we will be happy to provide the same dose and duration of real treatment (24 weeks) free of charge to those in the placebo group, at the completion of the study including data analysis for all participants (i.e., from the beginning of 2013 based on current study plan).

During the 24-week treatment phase of your participation in the study, you will either receive Ginseng 100mg capsule or identical placebo capsule, twice daily for 24 weeks, followed by 24 weeks of follow-up, without study medication.

This study is being conducted by the Traditional & Complementary Medicine Research Program at RMIT University's Health Innovations Research Institute, the Respiratory and Sleep Medicine Department of Austin Health and the Respiratory Medicine Department of the Box Hill Hospital. This research is funded by a Project Grant from the Australian Government's National Health and Medical Research Council (NHMRC) and a Development Grant from the Australian *National Institute of Complementary Medicine* (*NICM*). The results of this research will be used by the student researcher Johannah Shergis for her Doctor of Philosophy (PhD) degree. No member of the research team will obtain any financial benefit from their involvement in this project (other than their ordinary wages).

3. What does participation in this research involve?

If the study is suitable for you, you will be asked to attend one of the two study sites/hospitals, 6 times in total over 52 weeks.

Visit 1-Initial assessment: (this will take approximately 1.5 hours) It will involve discussion about the study and signing of the consent form. You will be asked to complete a screening questionnaire and a respiratory doctor will carry out a medical assessment, and if needed your

current Chronic Obstructive Pulmonary Disease medicines. You may need to withdraw from medications for Chronic Obstructive Pulmonary Disease. This is to avoid a mix-up of effects/results between the old medicine and the study medicine. You will also take a lung function test. This is to measure your lung function before participation and help to differentiate between various disease processes. It requires you to be in a seated position, and you blow into a tube as instructed by an experienced researcher. This will occur before and then 10 minutes after inhalation of Ventolin®. We will also collect 10mL (about a teaspoon) of blood from a vein in your arm.

Consenting participants will complete 3 questionnaires (this will take approximately 20-30 minutes in total) as the baseline data before completion of the visit. These are:

- SGRQ: St Georges Respiratory Questionnaire
- SF-36: Quality of Life Questionnaire
- CAT: Chronic Obstructive Pulmonary Disease Assessment Test

The trial coordinator will complete a Chinese Medicine Syndrome Differential Diagnosis Form with you (this will take approximately 5 minutes). They will also take a digital photo of your tongue. In Chinese medicine, important health information can be obtained from reviewing the tongue including colour, coating, shape and texture by an experienced practitioner to confirm the diagnosis. To ensure your privacy, the photo will be restricted to the tongue only and no other part of your face or body will be included in this image. A representative from the research team will be available to answer any questions.

Between Visits 1 and 2, a four-week run-in period will occur, you only have to complete the participant diary. You will not commence the Ginseng or placebo treatment until visit number 2. You will be contacted by the research team in this time to confirm eligibility after reviewing your blood test results and schedule your second visit.
During the study, you will be given Ventolin® Inhaler, to use as "relief medication", when needed. This is a short acting bronchodilator to rapidly open up the airways for the relief of breathlessness.

You will also be given a participant diary to note down daily relief medication usage during the next four weeks. A member from the research team will explain the questionnaires and participant diary fully.

Visit 2 - <u>Randomisation</u>: this visit will be scheduled 4 weeks after the first visit and will take approximately 1.5 hours. Participants are to return the participant diary for relief medication use and discussion will occur as to any questions or concerns prior to treatment allocation. You will be again asked to perform a lung function test (by blowing into a tube). You will be randomly allocated to receive either the active Ginseng treatment or the placebo treatment, which is an inactive look alike medication. You have a 50 / 50 chance of being entered into the active Ginseng group. Once randomisation occurs, you will need to complete 3 questionnaires (SGRQ, SF-36, CAT) this will take approximately 20-30 minutes in total, during the visit. A participant diary will be given to you to take home for completion. The first pack of trial medication (12 weeks) will be supplied. You will be asked to take one capsule (100mg) each time, twice a day (after meal in the morning and evening OR with 4 hours between the two daily dosages) for 12 weeks. You should not take more than two capsules each day. In a situation that you forgot to take it in the morning, mid-day is alright as long as you have 4 hours between the two doses. Please record your medication usage in the participant diary.

Visits 3 & 4 - <u>Treatment Period</u>: during the 24-week treatment period, you will be asked to attend 2 visits, at week 16 and week 28. They will last approximately 1.5 hours and involve symptom assessment, completion of questionnaires (this will take approximately 20-30 minutes in total), collection and distribution of the participant diary as well as lung function tests. You will receive your next pack of trial medication. At the end of the treatment phase (Visit 4), another 10mL (about a teaspoonful) of blood will be taken from your arm.

Visits 5 & 6 - <u>Follow-Up Period</u>: during the 24-week follow-up period, you will be asked to attend 2 visits, at week 40 and week 52. They will last approximately 1.5 hours and involve symptom assessment, completion of questionnaires (this will take approximately 20-30 minutes in total), collection and distribution of participant diary as well as lung function tests. Visit 6 will mark your completion of the trial.
At your final visit, the study doctor will discuss your current condition. They will then provide you with details about the treatment options and refer any comments/concerns onto your local doctor.

You will not have to pay for any aspect of this research including consultation, tests and medication. The study medication, visits, and procedures will all be covered by the research grants that we received. Other health care not related to this Chronic Obstructive Pulmonary Disease study will be your own responsibility and/or that of your insurance company.

You will not be paid for your participation in this research. You will be reimbursed for parking and/or public transport costs you incur from attending study visits (on production of a receipt).

4. What will happen to my test samples?

Blood samples will be taken on two occasions, at the first visit (initial visit) and visit 4. These samples will be assessed for α1-antitrypsin level (an enzyme deficiency that causes emphysema, at the initial assessment), full blood count and blood biochemistry for liver and kidney function (at the initial assessment and week 28). The samples will be labelled with your trial participant ID and date of collection, there will be no other identifiable information. The samples will be safely stored at the pathology laboratories at the two hospitals, and used only for this trial. These samples are taken so we are able to monitor any changes in blood counts and chemistry throughout the treatment phase. This will contribute to assessing any inflammation and safety of the trial medication. Once the research is completed the samples will be destroyed.

5. What are the possible benefits?

We cannot guarantee or promise that you will receive any benefits from this research. Results arising from the current study may help other people with moderate Chronic Obstructive Pulmonary Disease in the future.

6. What are the possible risks?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your doctor. Your doctor will also be looking out for side effects.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be severe, long lasting or permanent. If a severe side effect or reaction occurs, your doctor may need to stop your treatment with the study medication. Tell your doctor if you have any problems. Your doctor will discuss the best way of managing any side effects with you. There may be unknown or unforseen side effects from this study medication.

<u>In a medical emergency, call 000, or go to the emergency department</u>

Description of known possible side effects are listed below

Study Medication
Ginseng G115
Rarely some people are allergic to Ginseng, if you experience hives, difficulty breathing, itching, and/or swollen face/tongue call for medical assistance immediately. There are no

specific warnings for Ginseng G115, however rare occurrences of minor gastrointestinal discomfort such as diarrhoea may occur.

Study Relief medication
Ventolin®
Ventolin® is available by prescription and over the counter, it will be given to you to use when needed.
It can produce some side effects:
COMMON
- Headache
- Shaky or tense feeling
- Tachycardia – fast heart beat

UNCOMMON
- Mouth or throat irritation
- Muscle cramps
- 'Warm' feeling
- Decrease in potassium in the blood

What other possible risks are there?

Lung Function Test
During the lung function tests (by blowing into a tube), you may feel some shortness of breath, chest tightness, coughing and/or faintness. If any of these symptoms occur you will receive medical treatment immediately.

Blood Sample Taking
Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can easily be treated.

Conception, Pregnancy and Breast-feeding
The effects of Ginseng G115 on the unborn child and on the newborn baby are not known. Because of this, it is important that the study participants are not pregnant or breastfeeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding.

Both male and female participants are strongly advised to use effective contraception during the course of the research. You should discuss methods of effective contraception with your doctor.

For female participants: If you do become pregnant whilst participating in the study, you should advise your treating doctor immediately. Your doctor will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

For male participants: You should advise your treating doctor if you father a child while participating in the research project. Your doctor will advise on medical attention for your partner should this be necessary.

Could my Chronic Obstructive Pulmonary Disease get worse during the study?
You will be asked to stop taking your relief medication (ventolin/salbutamol) for a certain period of time prior to a breathing test. In addition, there are certain medications that you will not be able to use throughout the study. Talk to your study doctor about these medications. If you stop your regular medication to be in the study, your Chronic Obstructive Pulmonary Disease symptoms might come back or get worse. Notify the study doctor or staff if this occurs.

During the study, your Chronic Obstructive Pulmonary Disease symptoms may get worse, stay the same, or get better. If you feel that your Chronic Obstructive Pulmonary Disease is getting

worse, use the relief medication given to you. If your Chronic Obstructive Pulmonary Disease does not get better after using the relief medication, call the study doctor at the phone number listed on this form. Please follow your study doctor's instructions.

If you become upset or distressed as a result of your participation in this research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your doctor immediately about any new or unusual symptoms that you get.

7. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and your doctor will discuss whether this new information affects you.

8. Can I have other treatments during this research project?

While you are participating in this research project, you may not be able to take some or all of the medications or treatments that you have been taking for your Chronic Obstructive Pulmonary Disease or for other reasons. It is important to tell your doctor and the research staff about any treatments or medications you may be receiving, including over the counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your doctor and the research staff about any changes to these during your participation in the research. Also ask your doctor to explain to you which treatments or medications may need to be stopped for the time that you are in the trial.
If your Chronic Obstructive Pulmonary Disease symptoms get worse during the trial you may have to take new medications prescribed by your local doctor, if this happens you may have to be withdrawn from the study.

9. Are there alternatives to participation?

Participation in this research is not your only option. Your other options may include continuation of previous care, speaking with your doctor about new and/or different treatments or seeking out other clinical trials for Chronic Obstructive Pulmonary Disease. Discuss these options with your doctor before deciding whether or not to take part in this research project.

10. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health or Box Hill Hospital or Northern Hospital or Frankston Hospital and/or RMIT University.

11. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow the research team to further discuss any health risks or special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that have been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you join the research project.

12. Could this research project be stopped unexpectedly?

This research project may be stopped for a variety of reasons. These may include reasons such as:

- Unacceptable side effects;
- The study medication being shown not to be effective;
- The study medication being shown to work and not need further testing.

The research team and study doctor may remove you from further participation in this study if:

- Staying in the study would be unsafe or harmful;
- You need treatment not allowed in this study;
- You fail to follow instructions;
- You resume smoking;
- You become pregnant.

13. What will happen when my participation in this research project ends?

After the research project ends including both the treatment and follow-up period (in total 52-weeks) as well as the time required for data analysis, those individuals who received the placebo treatment will be offered the real Ginseng treatment free of charge for a period of 24 weeks (equivalent to that in the trial). You are advised to inform your medical doctor about Ginseng usage after your participation in this study. You should also seek advice from your medical doctor about the use of other medications including *Ventolin*®.

The Ginseng study medication is currently listed in the Australian Register of Therapeutic Goods and it is a practitioner only product. There are other Ginseng products available in Australia, but we are not sure about their equivalence.

14. How will I be informed of the results of the research project?

After completion of the trial by all participants, the results will be compiled and a detailed research report will then be prepared. These results will be published in Australian and/or international peer-reviewed medical journals. A summary report of the study will also be provided to you.

15. What else do I need to know?

What will happen to information about me?

- All case record forms (CRF) and participant diaries will be stored at RMIT University, Bundoora Victoria, for 15 years after completion of the trial. This is in line with Australian Government's Therapeutic Goods Administration (TGA) guidelines.
- Data will be stored in locked cabinets and all electronic files will be stored in a password-protected computer. Access will only be authorised personnel involved in the research.
- This data will not be reused or extended for use in any other research projects.

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.
Your health records and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, or as required by law. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified. Data will be presented as group data and aggregates, not data relating to specific individuals.

It is desirable that your local doctor be advised of your decision to participate in this research project. By signing the consent section, you agree to your local doctor being notified of your decision to participate in this research project. Information about your participation in this research may be recorded in your health records.

How can I access my information?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

What happens if I am injured as a result of participating in this research project?

If you suffer an injury as a result of participation in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committees of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Is this treatment the same or similar to the standard treatment for moderate Chronic Obstructive Pulmonary Disease?

This study uses a new medication for moderate Chronic Obstructive Pulmonary Disease. Standard treatment may involve several different and/or a combination of medications depending on what works best for each individual. Relief medication Ventolin® will be provided to all participants for use when needed, this is in line with current standard treatment.

Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information and appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the Trial Doctor at Austin Health, Northern Hospital, Dr Christopher Worsnop or at Box Hill Hospital, Prof. Frank Thien or at Frankston Hospital, Prof. David Langton.
If you need urgent medical treatment, please contact your GP or dial 000 as appropriate.

For complaints:

If you wish to contact someone, independent of the study, about ethical issues or your rights or to make a complaint, you may contact (Name of site representative, Position, Contact Number).

Thank you, we appreciate you taking the time to read this information.

CONSENT FORM

PROJECT TITLE: The effect of a standardised ginseng extract in patients with Moderate Chronic Obstructive Pulmonary Disease: a randomised, double blind, placebo controlled trial

I have read, or have had read to me in a language that I understand, participant information version 6.0 dated 29.09.2010 and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to RMIT University concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I understand that relevant sections of any of my medical records and data collected during the study may be looked at by responsible individuals from the Traditional & Complementary Medicine Research Program at RMIT University, Austin Health or Box Hill Hospital or Northern Hospital or Frankston Hospital, from regulatory authorities or from the approving Ethics Committee. I give permission for these individuals to have access to my records.
I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I consent to the storage and use of blood samples taken from me for use in this specific research project, as described in Section 4 of this document.

I agree to my GP being informed of my participation in the study.

I understand that I will be given a signed copy of this document to keep.

Participants name (printed)…….

Signature_____ Date____/____/____

Name of witness to participants signature (printed)…….

Signature_____ Date____/____/____

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood the explanation.

Researcher's name (printed)……..…….

Signature_____ Date____/____/____

*A member of the research team must provide the explanation and provision of information concerning the research project.
Note: All parties signing the Consent Form must date their own signature.

Appendix 5: Case Record Form

Visit 1 (Week 0): Initial Assessment

Date of visit: _ _ / _ _ / _ _ _ _

INFORMED CONSENT

Has the patient freely given written informed consent? Yes☐ No☐

Date of Consent: _ _ / _ _ / _ _ _ _ Time of Consent: _____

Has the participant completed the General Information Questionnaire?	Yes☐ No☐
Has the participant completed the Screening Questionnaire?	Yes☐ No☐

DEMOGRAPHICS

Date of Birth: _ _ / _ _ / _ _ _ _ Age (yrs): ☐☐ Gender: Female ☐ Male ☐

SMOKING STATUS

Is the participant an ex-smoker? Yes☐ No☐ Last day of smoking: _ _ / _ _ / _ _ _ _

Number of years smoking;……..years, cigarettes/ day_____

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

BLOOD COLLECTION

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**?	Yes☐ No☐
Has the participant completed the **SF-36**?	Yes☐ No☐
Has the participant completed the **CAT**?	Yes☐ No☐
Have you completed the Chinese medicine differential diagnosis form with the participant?	Yes☐ No☐
Have you taken a digital photo of their tongue?	Yes☐ No☐

VITAL SIGNS
Pulse Rate: ☐☐☐ Blood Pressure (seated): ☐☐☐ / ☐☐☐ mmHg Bpm
Height (cm): ☐☐☐.☐ Weight (Kg): ☐☐☐.☐

MEDICAL HISTORY ***(to be completed by the trial doctor)***			
Medical Condition	**Current (Yes / No)**	**Year of Onset**	**Treatment/ Outcome/ Comment**
Medical History taken by: _____ Signature: _____ Date: _ _ / _ _ / _ _ _ _			

MEDICATION USAGE

Is the participant currently on any medications? Yes* ☐ No ☐ *** If yes, what are these medications?**

Please also record any <u>continuing</u> medications on the 'Concomitant Medication Form'

1._____ 6. _____

2. _____ 7. _____

3. _____ 8. _____

4. _____ 9. _____

5. _____ 10. _____

Are any of these medications 'NOT TO BE USED throughout the trial? Yes* ☐ No ☐

(As per section 6.6 the study protocol – See below)

Treatments for COPD not to be used throughout the trial:

- Short acting anticholinergics
- Combinations of β2-agonists and inhaled corticosteroids
- Long-acting β2-agonists as monotherapy
- Short acting β2-agonists (other than Ventolin®)
- Theophylline (any formulation)

Treatments for other conditions not to be used throughout the trial:

- Corticosteroids
- Immunotherapy
- Monoamine Oxidase Inhibitor anti-depressants
- Anti-coagulants
- Anti-hyperglycaemics

If yes, does the participant agree to discontinue these medications throughout the trial? Yes ☐ No ☐

If yes, what medication were stopped and what was the stop date

_____

* If no, please provide a reason

_____

Medication review conducted by: _____

Signature: _____ Date: _ _ / _ _ / _ _ _ _

INCLUSION CRITERIA		**Yes** (tick ✓)	**No***
1	Has the participant willingly given written informed consent?	☐	☐
2	Is the participant between 40 to 80 years inclusive?	☐	☐
3	Is the participant an ex smoker, ceased smoking at least 3 months ago and agree to refrain from smoking throughout the trial?	☐	☐
4	Are the participant's spirometry values within moderate (stage II) range? That is; FEV1/FVC ratio < 0.7 (post-broncho) and FEV1 between 50% to 80% (post-broncho) **FEV1/FVC: _____ FEV1: _____**	☐	☐
5	Is the participant clinically stable? Did not experience an acute infective exacerbation of COPD from at least 4 week prior to trial entry.	☐	☐
6	Meet the Chinese medicine diagnostic criteria for Lung Qi deficiency or Lung and Spleen Qi deficiency?	☐	☐
*If any inclusion criteria are ticked NO then the participant is not eligible for the study.			
EXCLUSION CRITERIA		**Yes*** (tick ✓)	**No**
1	Does the participant have a history of asthma or chronic systematic infections or inflammatory conditions in the last 3 months?	☐	☐
2	Is the participant pregnant, breast-feeding or intending to become pregnant during the course of the study?	☐	☐
3	Does the participant have a serious illness such as e.g. severe heart disease, liver or kidney disease?	☐	☐
4	Is the participant unable to perform spirometry?	☐	☐
5	Is the participant taking long-term immunosuppressive agents or immuno- stimulants?	☐	☐
6	Has the participant used ginseng-containing products in the last 3 months?	☐	☐
7	Does the participant have an allergic history to ginseng products?	☐	☐
8	Is the participant currently using monoamine oxidase inhibitor antidepressants, anticoagulants and/or anti-hyperglycemic medications?	☐	☐
9	Is the participant a Current smoker?	☐	☐
10	Has the participant undertaken pulmonary rehabilitation within the last 3 months, or intend to enter pulmonary rehabilitation during the study?	☐	☐
* If any exclusion criteria are ticked YES then the participant is not eligible for the study.			

MEDICATIONS

Have you dispensed relief medication, Ventolin? Yes☐ No☐
(If yes, Please complete Medication Accountability Form)

PARTICIPANT DIARY

Have you issued a participant diary? Yes☐ No☐

POST VISIT FOLLOW UP

BIOCHEMISTRY/ HAEMATOLOGY

Have the biochemistry/ haematology reports been reviewed? Yes ☐ No☐

Are any of the findings clinically significant? Yes* ☐ No☐

* If yes please comment

_____

Name of reviewer: _____

Signature: _____ Date: _ _ / _ _ / _ _ _ _

LOCAL DOCTOR FOLLOW UP

Have you contacted the participants 'usual' treating doctor to inform them of their patients interest in participating in the study? Yes ☐ No☐

CHINESE MEDCINE DIAGNOSIS

Have you emailed the Chinese medicine syndrome differential diagnosis form and digital tongue photo to the Chinese medicine practitioner? Yes ☐ No☐

Clinical trial coordinator signature: _____ Date: __ __/__ __ /__ __

Visit 2 (Week 4): Randomisation/ Start of Treatment

Date of visit: _ _ / _ _ / _ _ _ _

PLEASE CONDUCT SPIROMETRY AND COMPLETE SGRQ TO DETERMINE ELIGIBILITY PRIOR TO RANDOMISATION

EXCLUSION CRITERIA		**Yes*** (tick ✓)	**No**
1	Was there deterioration in the participant's spirometry values and they are no longer within the moderate (stage II) range? That is; FEV1/FVC ratio < 0.7 (post-broncho) and FEV1 between 50% to 80% (post-broncho)	☐	☐
2	Has the participant been diagnosed as Alpha1-antitrypsin deficient?	☐	☐
3	Did the participant experience an acute infective exacerbation of COPD since baseline, visit 1?	☐	☐
* If any of the exclusion criteria are ticked YES then the participant is not eligible for randomisation.			

RANDOMISATION

Does the participant continue to meet the eligibly criteria? Yes ☐ No ☐

If Yes, select **randomisation envelope**. If No, participant should be withdrawn from the study.

Randomisation Number:

ttach randomisation sticker here

SMOKING STATUS

Has the participant smoked since the last visit?
Note: As per section 8 of the study protocol, subjects who resume smoking during the trial period need to be reviewed by the Principal Investigator to determine ongoing eligibility. Yes ☐ No ☐

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**? Yes ☐ No ☐

Has the participant completed the **SF-36**? Yes ☐ No ☐

Has the participant completed the **CAT**? Yes ☐ No ☐

PARTICIPANT DIARY	
Have you collected the participant diary?	Yes ☐ No ☐
Have you issued a participant diary?	Yes ☐ No ☐

DATA COLLECTION	
Have any adverse events occurred since the last visit? (If yes, please record on Adverse Event Record Form)	Yes ☐ No ☐
Have any exacerbations occurred since the last visit? (If yes, please record on Exacerbations Form)	Yes ☐ No ☐
Have any other medical services relating to COPD been accessed since the last visit? (If yes, please record on Medical Service Utilisation Form)	Yes ☐ No ☐
Have any concomitant medications (other than Ventolin) been taken since the last visit? (If yes, please record on Concomitant Medication Form)	Yes ☐ No ☐
MEDICATIONS	
Have you dispensed the trial medication? (If yes, Please complete Medication Accountability Form)	Yes ☐ No ☐
Have you dispensed relief medication, Ventolin? (If yes, Please complete Medication Accountability Form)	Yes ☐ No ☐
LOCAL DOCTOR FOLLOW UP	
Have you contacted the participants 'usual' treating doctor to collect data on number of consultations?	Yes ☐ No ☐

Clinical trial coordinator signature: _____ Date: __ __/__ __ /__ __

Visit 3 (Week 16): Mid Treatment

Date of visit: _ _ / _ _ / _ _ _ _

SMOKING STATUS

Has the participant smoked since the last visit?
Note: As per section 8 of the study protocol, subjects who resume smoking during the trial period need to be reviewed by the Principal Investigator to determine ongoing eligibility. Yes ☐ No ☐

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**? Yes ☐ No ☐

Has the participant completed the **SF-36**? Yes ☐ No ☐

Has the participant completed the **CAT**? Yes ☐ No ☐

PARTICIPANT DIARY

Have you collected the participant diary? Yes ☐ No ☐

Have you issued a participant diary? Yes ☐ No ☐

DATA COLLECTION

Have any adverse events occurred since the last visit?
(If yes, please record on Adverse Event Record Form) Yes ☐ No ☐

Have any exacerbations occurred since the last visit?
(If yes, please record on Exacerbations Form) Yes ☐ No ☐

Have any other medical services relating to COPD been accessed since the last visit?
(If yes, please record on Medical Service Utilisation Form) Yes ☐ No ☐

Have any concomitant medications (other than Ventolin) been taken since the last visit?
(If yes, please record on Concomitant Medication Form) Yes ☐ No ☐

MEDICATIONS

Have you dispensed the trial medication?
(If Yes, Please complete Medication Accountability Form) Yes ☐ No ☐

Have you dispensed relief medication, Ventolin?
(If yes, Please complete Medication Accountability Form) Yes ☐ No ☐

LOCAL DOCTOR FOLLOW UP

Have you contacted the participants 'usual' treating doctor to collect data on number of consultations? Yes ☐ No ☐

Visit 4 (Week 28): End of Treatment

Date of visit: _ _ / _ _ / _ _ _ _

SMOKING STATUS

Has the participant smoked since the last visit? Yes ☐ No ☐
Note: As per section 8 of the study protocol, subjects who resume smoking during the trial period need to be reviewed by the Principal Investigator to determine ongoing eligibility.

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

BLOOD COLLECTION

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**? Yes ☐ No ☐

Has the participant completed the **SF-36**? Yes ☐ No ☐

Has the participant completed the **CAT**? Yes ☐ No ☐

PARTICIPANT DIARY

Have you collected the participant diary? Yes ☐ No ☐

Have you issued a participant diary? Yes ☐ No ☐

DATA COLLECTION

Have any adverse events occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Adverse Event Record Form)

Have any exacerbations occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Exacerbations Form)

Have any other medical services relating to COPD been accessed since the last visit? Yes ☐ No ☐
(If yes, please record on Medical Service Utilisation Form)

Have any concomitant medications (other than Ventolin) been taken since the last visit? Yes ☐ No ☐
(If yes, please record on Concomitant Medication Form)

MEDICATIONS

Have you dispensed relief medication, Ventolin? Yes ☐ No ☐
(If yes, Please complete Medication Accountability Form)

POST VISIT FOLLOW UP

BIOCHEMISTRY/ HAEMATOLOGY

Have the biochemistry/ haematology reports been reviewed? Yes ☐ No ☐

Are any of the findings clinically significant? Yes* ☐ No ☐
(If yes, Please complete Adverse Event Record Form)

Name of reviewer: _____

Signature: _____ Date: _ _ / _ _ / _ _ _ _

LOCAL DOCTOR FOLLOW UP

Have you contacted the participants 'usual' treating doctor to collect data on number of consultations? Yes ☐ No ☐

Clinical trial coordinator signature: _____ Date: __ __/__ __ /__ __

Visit 5 (Week 40): Mid Follow Up

Date of visit: _ _ / _ _ / _ _ _ _

SMOKING STATUS

Has the participant smoked since the last visit? Yes ☐ No ☐
Note: As per section 8 of the study protocol, subjects who resume smoking during the trial period need to be reviewed by the Principal Investigator to determine ongoing eligibility.

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**? Yes ☐ No ☐

Has the participant completed the **SF-36**? Yes ☐ No ☐

Has the participant completed the **CAT**? Yes ☐ No ☐

PARTICIPANT DIARY

Have you collected the participant diary? Yes ☐ No ☐

Have you issued a participant diary? Yes ☐ No ☐

DATA COLLECTION

Have any adverse events occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Adverse Event Record Form)

Have any exacerbations occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Exacerbations Form)

Have any other medical services relating to COPD been accessed since the last visit? Yes ☐ No ☐
(If yes, please record on Medical Service Utilisation Form)

Have any concomitant medications (other than Ventolin) been taken since the last visit? Yes ☐ No ☐
(If yes, please record on Concomitant Medication Form)

MEDICATIONS

Have you dispensed relief medication, Ventolin? Yes ☐ No ☐
(If yes, Please complete Medication Accountability Form)

LOCAL DOCTOR FOLLOW UP

Have you contacted the participants 'usual' treating doctor to collect data on number of consultations? Yes ☐ No ☐

Visit 6 (Week 52): Completion of Trial

Date of visit: _ _ / _ _ / _ _ _ _

SMOKING STATUS

Has the participant smoked since the last visit? Yes ☐ No ☐
Note: As per section 8 of the study protocol, subjects who resume smoking during the trial period need to be reviewed by the Principal Investigator to determine ongoing eligibility.

SPIROMETRY

Taken By: _____

Please attach a printed copy of all results to the CRF.

QUESTIONNAIRES

Has the participant completed the **SGRQ**? Yes ☐ No ☐

Has the participant completed the **SF-36**? Yes ☐ No ☐

Has the participant completed the **CAT**? Yes ☐ No ☐

Has the participant completed the **Opinion of Chinese Medicine Questionnaire**? Yes ☐ No ☐

PARTICIPANT DIARY

Have you collected the participant diary? Yes ☐ No ☐

DATA COLLECTION

Have any adverse events occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Adverse Event Record Form)

Have any exacerbations occurred since the last visit? Yes ☐ No ☐
(If yes, please record on Exacerbations Form)

Have any other medical services relating to COPD been accessed since the last visit? Yes ☐ No ☐
(If yes, please record on Medical Service Utilisation Form)

Have any concomitant medications (other than Ventolin) been taken since the last visit? Yes ☐ No ☐
(If yes, please record on Concomitant Medication Form)

LOCAL DOCTOR FOLLOW UP

Have you contacted the participants 'usual' treating doctor to collect data on number of consultations? Yes ☐ No ☐

Have you informed the participants 'usual' treating doctor of their completion of participation in the trial? Yes ☐ No ☐

MEDICATION ACCOUNTABILITY

Trial Medication Ginseng/Placebo 100mg capsules							
Date of Dispensing	Randomisation & Bottle Number	No. of capsules dispensed	Dispenser's initials	Date Returned	No. of capsules returned	Receiver's initials	Comment

Relief Medication Ventolin 100mcg MDI							
Date of Dispensing	Visit Number	No. of inhalers dispensed	Dispenser's initials	Date Returned	No. of inhalers returned	Receiver's initials	Comment

ADVERSE EVENTS RECORD FORM

Event	**Start (Date/Time)**	**Stop (Date/Time)**	**Intensity (1-3)**	**Relationship to treatment (1,2,3 or 4)**	**Serious adverse event* Yes/No**

Intensity:
1 = mild (easily tolerated by patient, causing minimal discomfort)
2 = moderate (discomfort significant enough to interfere with daily activities)
3 = severe (incapacitating and/or requiring therapeutic intervention)

Relationship to treatment:
1 = unrelated 2 = possibly 3 = probably 4 = definitely

* Serious adverse event (SAE): defined as potential to be fatal, life threatening, permanent incapacitating or resulting in hospitalisation.

RECORD OF MEDICAL SERVICE UTILISATION RELATING TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Actions	Date	Out of pocket expenses ($)	Remarks
Visits to Medical Doctor and/or Specialists			
Hospitalisation			
Emergency Department Presentations			
Medications / Other (please specify)			

EXACERBATIONS FORM

Event	Start (Date/Time)	Stop (Date/Time)	Intensity (1-3)	Medication use (Specify)	Remarks

CONCOMITANT MEDICATION FORM

Name of Medication	Start (Date)	Stop (Date)	Dose	Frequency	Remarks / Continuing

COMPLETION/TERMINATION FORM

Completion of Study: Please mark the primary reason why the participant has finished with their participation in the study. Reasons '**other than'** Completed Study require explanation next to the response.

☐ **COMPLETED STUDY** (52 weeks)
☐ AE/SAE **(complete AE & SAE form, if applicable)**
☐ Lost to follow-up
☐ Non-compliant participant
☐ Concomitant medication
☐ Medical contraindication
☐ Withdrawal of consent
☐ Death **(complete SAE form)**
☐ Other

Appendix 6: Screening questionnaire

1. What is your smoking status?

☐ Current ☐ Former ☐ Never

If current smoker, how many cigarettes per day? _____/day, and for how many years? _____years

If former smoker, when did you stop smoking? Approximate date_____/_____/_____

How many cigarettes per day and for how many years did you smoke? ____per day for ___years

***2.One of the conditions to participate in the current trial is agree to refrain from smoking throughout the trial. Please confirm you agree to do so for the whole duration of the trial (52 weeks**)?*

☐ No ☐ Yes

3. Your participation is voluntary and you are free to withdraw from the study at any time. However, to get meaningful results from this study, it is desirable that you stay in the trial until it is fully completed, except for situations that you are advised by the research team and/or your medical doctor to discontinue participation. Do you agree with this statement?

☐ No ☐ Yes

4. Have you been diagnosed with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema, by a medical practitioner?

☐ No ☐ Not sure ☐Yes, and the year of diagnosis was _____

5. Do you or any of your family members suffer from Chronic Obstructive Pulmonary Disease (COPD) or other respiratory disease?

☐ No ☐ Not sure ☐ Yes

If yes, please tick (✓) relevant box(es)

Family Member	**Chronic Obstructive Pulmonary Disease** Including: Chronic Bronchitis & /or Emphysema	**Asthma**	**Bronchiectasis**	**Alpha-1 antitrypsin deficiency**	**Other respiratory disease**
Yourself					
Father					
Mother					
Brother					
Sister					
Other:					

6. Do you have any of the following symptoms? If yes, please also indicate the severity of the symptoms. (Please tick ✓)

Symptoms	**Severity** **0= no symptoms 1= mild 2= moderate 3= severe**			
	0	1	2	3
Breathlessness				
Cough				
Sputum / Phlegm				
Chest Tightness				
Wheezing				
Rapid or laboured Respiration				

7. Do the symptoms above interfere with your daily life?

☐ Never ☐ Rarely (1-2 day per week) ☐ Sometimes (3-4 days per week)

☐ Often (5-7 days per week) ☐ Always (Everyday)

8. Have you had a surgical treatment for Chronic Obstructive Pulmonary Disease (COPD)?

☐ No ☐ Yes, Please specify
_____

9. Have you been hospitalised due to an exacerbation of Chronic Obstructive Pulmonary Disease (COPD), in the last 3 months?

☐ No ☐ Yes, Please specify when and for how long_____

10. Have you used antibiotics for a Chronic Obstructive Pulmonary Disease (COPD) exacerbation, in the last 3 months?

☐ No ☐ Yes, Please specify when and name
_____

11. Have you been taking long acting β2-agonists (eg. Seretide/Serevent/Foradile/Oxis/Symbicort) and/or Anticholinergics (eg. Atrovent/Spiriva) and /or Methylxanthines (eg.Nuelin) within the last 3 months?

☐ No ☐ Yes, Please specify when and name
_____

12. Have you been treated with inhaled corticosteroids (eg. Qvar(beclomethasone)/ Pulmicort/ Symbicort(budesonide)/Flixotide/Seretide(fluticasone)/Alvesco(ciclesonide)) / oral corticosteroids (eg. Panafocortelone/Prednisolone/Solone(prednisolone)) / cortisone injections for Chronic Obstructive Pulmonary Disease (COPD) or other conditions within the last 3 months?

☐ No ☐ Yes, Please specify_____

13. Have you used long-term oxygen therapy for your Chronic Obstructive Pulmonary Disease (COPD)?

☐ No ☐ Yes, Please specify _____

14. Have you used a non-invasive ventilator (CPAP/BiPAP) for supporting your breathing in the past one year?

☐ No ☐ Yes, Please specify_____

15. Do you have any other diseases including infectious disease (eg. HIV, Hep B, Hep C)?

☐ No ☐ Yes, Please specify_____

16. Are you currently taking any of the following medications?

a) Anti-depressant (e.g.Aropax, Aurorix, Avanza, Cipramil, Deptran, Endep, Lexapro, Lovan, Luvox, Pristiq, Prozac, Sinequan, Tofranil, Tolvon, Zoloft) ☐ No ☐ Yes, Please specify_____

b) Anti-coagulant (stops blood clotting) (e.g. Warfarin, Coumadin, Dindevan) ☐ No ☐ Yes, Please specify_____

c) Anti-hyperglycaemic (lowers blood sugar) (e.g. Actos, Amaryl, Avandia, Daonil, Diabex, Diaformin, Diamicron, Glimel, Glucophage, Minidiab) ☐ No ☐ Yes, Please specify_____

17. Have you been treated with Chinese Herbal Medicine in the last year?
If so, for what condition?

☐ No ☐ Yes, Please specify_____

18. Have you used any ginseng containing product in the last 3 months?

☐ No ☐ Yes, Please specify_____

19. Do you have any allergies (including allergy to ginseng products)?

☐ No ☐ Yes, Please specify_____

20. If you are female, please answer the following questions:

a. Are you currently pregnant or planning to get pregnant in the next 12 months? ☐ No ☐ Yes

b. Are you currently breast-feeding? ☐ No ☐ Yes

21. Please list any regular medicines you use for Chronic Obstructive Pulmonary Disease (COPD) and/or any medicines you use for other diseases/symptoms.

Name of Medication	Medical condition	Dosage	Frequency (times/day or week)	How long have you been taking it?

Appendix 7: St. George's Respiratory Questionnaire

Before completing the rest of the questionnaire:

Please tick one box which best describes your present health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

PART 1

These questions are about how much chest trouble you have had over the last 4 weeks.

Please tick (✓) *one box for each questio*n:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
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 □

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.
Please tick (✓) *one*:

- 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 <u>these days</u>.

For each activity, please tick (✓)
one box as it applies to you ***these days***:

	True	False
Sitting or lying still	□	□
Getting washed or dressed	□	□
Walking around the home	□	□
Walking outside on level ground	□	□
Walking up one flight of stairs	□	□
Walking up hills	□	□
Playing sports or active games	□	□

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

For each situation, please tick (✓)
one box as it applies to you ***these days***:

	True	False
My cough hurts	□	□
My cough makes me tired	□	□
I am breathless when I talk	□	□
I am breathless when I bend over	□	□
My cough or breathing disturbs my sleep	□	□
I get exhausted easily	□	□

Section 4

These are questions about other effects that your chest trouble may have on you <u>these days</u>.

For each situation, please tick (✓)
one box as it applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	□	□
My chest trouble is a bother to my family, friends or neighbours	□	□
I get afraid or panic when I cannot get my breath	□	□
I feel that I am not in control of my chest problem	□	□
I do not expect my chest to get any better	□	□
I have become frail or an invalid because of my chest	□	□
Exercise is not safe for me	□	□
Everything seems too much of an effort	□	□

Section 5

These are questions about your medication. If you are receiving no medication go straight to Section 6.

For each situation please tick (✓)
one box as it applies to you ***these days***:

	True	False
My medication does not help me very much	□	□
I get embarrassed using my medication in public	□	□
I have unpleasant side effects from my medication	□	□
My medication interferes with my life a lot	□	□

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***:

	True	False
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 <u>usually</u> affects your daily life.

For each situation, please tick (✓) the ***correct box*** that applies to you ***because of your chest trouble***:

	True	False
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 8: Short Form Health Survey (SF-36)

In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3 The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a kilometre	☐ 1	☐ 2	☐ 3
h	Walking several hundred metres	☐ 1	☐ 2	☐ 3
i	Walking one hundred metres	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	☐	☐	☐	☐	☐
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	☐	☐	☐	☐	☐
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	☐	☐	☐	☐	☐
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

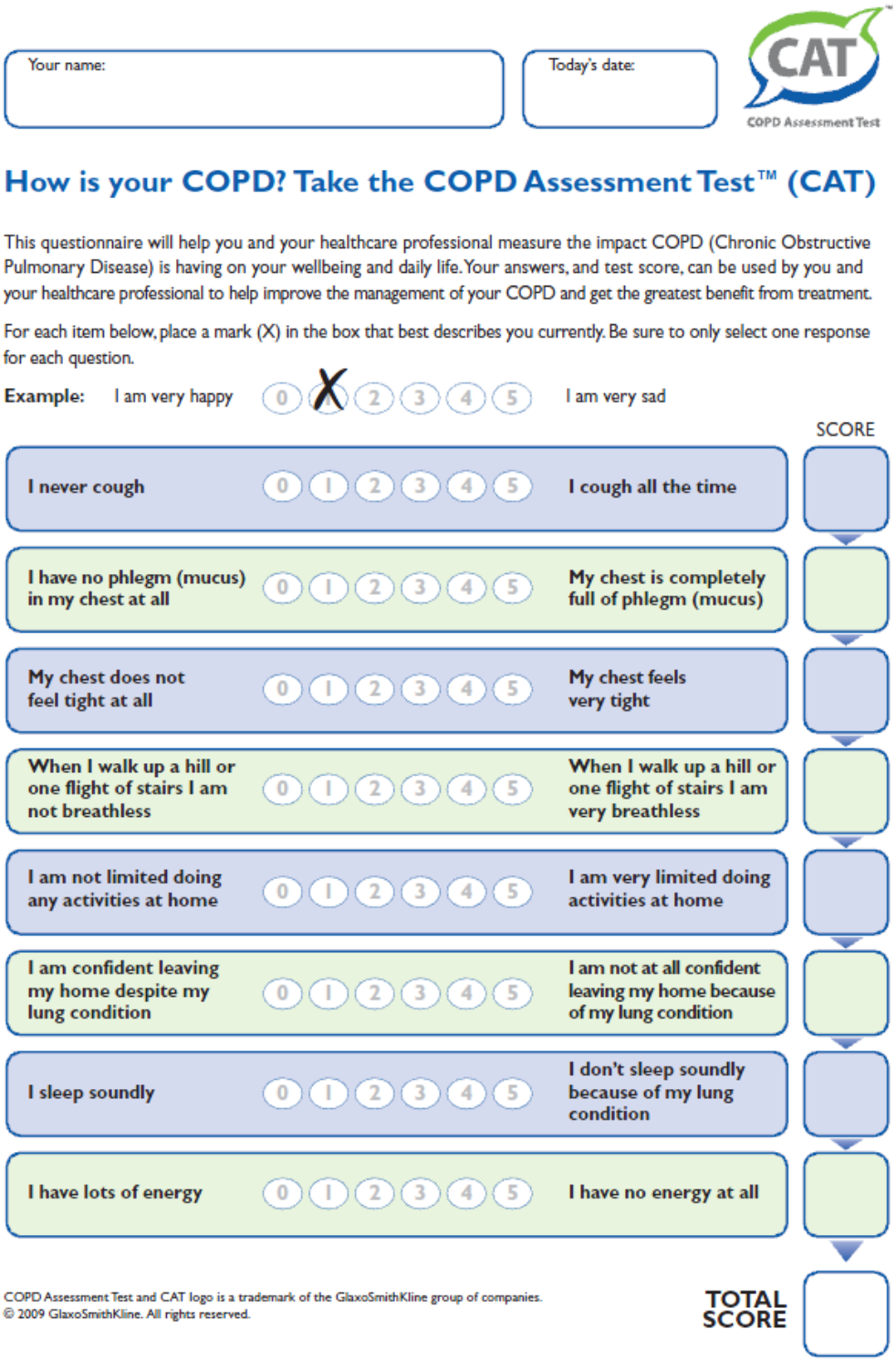
10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	☐	☐	☐	☐	☐
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 9: COPD Assessment Test



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Appendix 10: Participant dairy

Trial Medication

(Please indicate with a tick (✓), every time you take this medication).

Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
/ /		/ /		/ /		/ /		/ /		/ /		/ /	
AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM

Relief Medication - Ventolin®

(Please indicate the NUMBER OF PUFFS of the relief medication you used during the past 24 hours).

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
/ /	/ /	/ /	/ /	/ /	/ /	/ /

Other Medications

NOTE: You are required to cease any existing COPD medication prior to the commencement of the trial, standardised relief medication will be provided to you (Ventolin®).

If you use any medications other than those provided by the research team, please fill in the details below:

Medication Name:							
Date Taken:	/ /	/ /	/ /	/ /	/ /	/ /	/ /
Dose:							
Frequency:							

Appendix 11: Participant opinion of Chinese medicine questionnaire

1. At this point, how logical does the treatment offered to you seem?

1	2	3	4	5	6	7	8	9
Not at all				Somewhat logical				Very logical

2. At this point, how useful do you ***think*** the treatment will be in reducing your Chronic Obstructive Pulmonary Disease symptoms?

1	2	3	4	5	6	7	8	9
Not useful				Somewhat useful				Very useful

3. How confident would you be in recommending this treatment to a friend who experiences similar problems?

1	2	3	4	5	6	7	8	9
Not at all confident				Somewhat confident				Very much confident

4. By the end of the treatment period, how much improvement in your Chronic Obstructive Pulmonary Disease symptoms do you ***think*** will occur?

1	2	3	4	5	6	7	8	9
None at all				Some				Total Improvement

5. At this point, how much do you really ***feel*** that treatment will help you to reduce your Chronic Obstructive Pulmonary Disease symptoms?

1	2	3	4	5	6	7	8	9
Not at all useful				Somewhat useful				Very useful

6. By the end of the treatment period, how much improvement in your Chronic Obstructive Pulmonary Disease symptoms do you really ***feel*** will occur?

1	2	3	4	5	6	7	8	9
Not at all				Somewhat				Very much

Reference
G.J. Devilly, T.D. Borkovec. Psychometric properties of the credibility/expectancy questionnaire. *J. Behav. Ther. & Exp. Psychiat.* 31 (2000) 73-86.

Additional Question:

For assessing the effectiveness of the blinding process in this study, please indicate the treatment that you believe you have received (please✓):

□ Real treatment

□ Placebo treatment

□ Not sure

Appendix 12: Analytical reports

Appendix 12.1: Analytical report of G115

Analytical report / **Certificado de análisis**
Analysen-Attest / **Certificat d'analyse No.** 0617710100

ginsana

Product/Producto/Produkt/Produit:	Batch/Lote/Charge/Lot:	
GINSANA CAPSULES G115	0617710100	VERUM

TESTS	REQUIREMENTS	RESULTS
Galenic form	soft gelatin capsule 6 minims oblong	conform
Appearance	regular shiny not oily	conform
Color	brown-opaque	conform
Odor of content	faintly present, characteristic	conform
Appearance of the content	caramel homogeneous paste	conform
Average weight of the content	380.0 - 420.0 mg (400.0 mg +/-5%)	402.0 mg
Uniformity of mass of capsule content Uniformity of mass of capsule content	average mass +/- 7.5% (>18/20) average mass +/- 15% (20/20)	conform conform
Disintegration time	max. 30 minutes	conform
Identification of the coloring agent iron oxides (E172)	positive	positive
Microbiological purity	conform to Ph.Eur. current edition	conform
Active ingredient:		
Identification of the standardized Panax ginseng extract G115	positive	positive
Quantitative determination of the standardized Panax ginseng extract G115	100.0 mg (90.0 - 110.0 mg)	98.85 mg

Data/Fecha/Datum/Date:	Conform and released: / Konform und freigegeben: / Conforme y liberado: / Conforme et libéré:
01.03.2010	Dr.pharm.Pier Francesco Campanini, Manager Quality Assurance

Appendix 12.2: Analytical report of placebo

Analytical report **Certificado de análisis**
Analysen-Attest **Certificat d'analyse No.** 0002980200

ginsana

Product/Producto/Produkt/Produit:	Batch/Lote/Charge/Lot:
GINSANA capsules	0002980200 PLACEBO

TESTS	RESULTS
Avarage weight of the content	364.2 mg
Microbiological purity	conform
Quantitative determination of Standardized Panax ginseng extract G115	absent

Data/Fecha/Datum/Date:	Conform and released: / Konform und freigegeben: / Conforme y liberado: / Conforme et libéré:
01.03.2010	Dr.pharm.Pier Francesco Campanini, Manager Quality Assurance

Appendix 13: Trail medication frequently asked questions

For how many weeks will I have to take the trial medication?
You will be asked to take the trial medication for 24 weeks in total, between your 2nd and 7th months of participation.

Does the trial medication need to be taken every day?
Yes, twice a day.

How many capsules per day?
2, one each time.

Does the trial medication have to be taken at a particular time?
Preferably the capsules should be taken in the morning with breakfast and in the evening with dinner.

Can I take 2 capsules at once as I am very forgetful in the afternoons?
No, you need to wait at least 4 hours between each capsule.

Should I take the trial medication before or after a meal?
There is no specific rule as long as you take 2 capsules per day.

What happens if I forget to take a capsule at breakfast?
This is not a problem. The capsules can be taken anytime throughout the day as long a minimum of 4 hours is left between doses. For example you could take a capsule at lunchtime and then at dinner.

What happens if I only take one capsule for the day? Should I take a double dose the next day?
No, you should not take a double dosage. The next day just take 2 capsules as you normally would.

Should I chew the capsules or just swallow them?
You should not chew the capsules. They should be swallowed with a small amount of liquid (non alcoholic).

Will all the trial medications be given to me at the first visit?
No, you will be given the medications in 2 lots. The first lot will be given at visit 2 and the second at visit 3.

Will the trial medications be in one bottle?
No, you will be given 3 bottles of trial medication each time. There are 60 capsules per bottle and one bottle will last 4 weeks.

Sometimes I am forgetful and need to keep my medications in the kitchen for my morning dose and in the bedroom for my night time dose, can I open two bottles and leave them in different locations?
Yes, as long as it helps you to remember to take your medications.

I have other medications that I take, is it ok to take the trial medications at the same time?
Yes, you can take the trial medication with other medications. However if you start any **new** medication/s you must seek advice from the research team as soon as possible.

Should I keep the trial medications in the fridge?
It is not necessary to keep them in the fridge. They should be kept at room temperature, with the lid on.

What happens if the trial medications make me feel sick?
If you feel unwell, you should contact your local doctor and notify the research team.

What happens if I misplace my trial medications?
Contact the research team immediately.