ORIGINAL ARTICLE

12-month randomised controlled trial of ginseng extract for moderate COPD

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ABSTRACT

Background *Panax ginseng* (ginseng) is a therapeutic herb which might be beneficial in COPD. The study investigated if ginseng, compared with placebo, is effective and safe for people with moderate COPD.

Methods This multicentre, randomised, double-blind, placebo-controlled trial compared 24 weeks of ginseng capsules (100 mg twice daily) with placebo. Participants were followed up for a further 24 weeks. Participants were aged 40 years and over and had airflow limitation in the moderate (Global Initiative for Chronic Obstructive Lung Disease 2) COPD range. The coprimary endpoints were the St George's Respiratory Questionnaire, the COPD Assessment Test and the Short Form Health Survey. Secondary outcomes included lung function, exacerbation rate and use of relief medication.

Findings 168 participants were randomised 1:1 from five centres in Australia and China. Baseline characteristics were balanced between groups. There were no significant differences between ginseng and placebo, with overall results improving in both groups. Ginseng seemed safe for, and well tolerated by, people with COPD.

Interpretation There was no significant difference in improvement in health-related quality of life (primary outcome) between the ginseng and placebo groups.

Trial registration number ACTRN12610000768099.

Key messages

What is the key question?
- Can *Panax ginseng* improve health-related quality of life in people with COPD?

What is the bottom line?
- Ginseng and placebo demonstrated similar benefits in health-related quality of life at the end of treatment.
- Ginseng was safe for people with COPD, including people taking standard inhaled therapies for COPD.

Why read on?
- This is the first international, multicentre, randomised controlled trial of ginseng for COPD, and the study design could be used as an example for future studies.

INTRODUCTION

Conventional COPD treatments include bronchodilators and corticosteroids (alone or in combination), which help to control and alleviate symptoms and reduce exacerbations.[1] However, these treatments have limited benefit for people with mild-to-moderate COPD and are associated with a range of adverse effects.[2 3] Some novel approaches to treatment, such as phosphodiesterase-4 inhibitors, have been investigated. However, the clinical usefulness of the drugs developed so far has been limited by adverse effects.[4] Such adverse effects are one reason that up to 40% of people with COPD use herbs to help manage their symptoms.[5 6]

Herbal treatments that reduce the impact of COPD and have a greater benefit to risk ratio are needed to improve health outcomes for people with COPD. This is especially the case for Asian populations, where the prevalence of COPD and smoking are higher than other regions.[7] Ginseng is one of the most promising herbs for treating COPD.[8] It may improve lung function and quality of life and has an excellent safety profile.[9 10]

Panax ginseng CA Meyer (from the Araliaceae family; commonly known as 'ginseng') has long been used to treat a range of respiratory conditions, including COPD, in China and other East Asian countries. Clinical studies show people tolerate ginseng well, with infrequent occurrences of minor discomfort, such as diarrhoea, palpitations and headache.[11] A systematic review also concluded that it was rarely associated with adverse events or drug interactions.[12] Scaglione and colleagues[13] reviewed the safety of a standardised ginseng extract, and like other studies their conclusions support the overall safety of ginseng.

If there are any beneficial effects of ginseng on COPD, the mechanism may involve its active constituents, the ginsenosides. Several studies have investigated ginseng's pharmacological actions and therapeutic potential. Its key actions relevant to COPD include anti-inflammatory effects, such as inhibiting kinase phosphorylation, nuclear factor kappa-light-chain-enhancer of activated B cells(NF-κB) transcription factor induction/translocation and DNA binding. Ginseng also inhibits proinflammatory mediators (tumour necrosis factor-α, interleukin [IL]-6, IL-8, reactive oxygen species and proteases) and protects against oxidative stress by increasing antioxidative enzymes and reducing the production of oxidants.[8] This suggests

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ginseng inhibits the processes that contribute to COPD pathogenesis, providing plausible explanations for its clinical effects.

We evaluated ginseng in people with stable symptomatic COPD, with infrequent exacerbations, taking standard inhaled therapy. This is the first high-quality, multicentre, randomised study focusing on ginseng's therapeutic value and safety profile in patients with moderate (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2) COPD. The study integrates rigorous, contemporary clinical research methodology with the theory that guides appropriate use of Chinese medicine in clinical practice.

METHODS

Study design

This study was a randomised, double-blind, parallel-group, placebo-controlled and multicentre clinical trial. Participants were recruited from five hospitals across Melbourne, Australia and Guangzhou, China. We randomised 168 participants at a 1:1 ratio to ginseng or matching placebo, using a computer-generated randomisation code with block sizes of four and six. Treatment allocation was concealed in opaque envelopes, and medications were packaged to mask the randomisation code and dispensed by hospital pharmacists who were blind to allocation. Study participants, research personnel and outcome assessors were blind to randomisation sequence and group allocation. Participants were diagnosed with moderate COPD and received 24 weeks of ginseng (100 mg twice daily) or placebo. The total study duration was 52 weeks, with 4 weeks run-in to ensure participants did not have an acute COPD exacerbation, followed by 24 weeks of treatment and 24 weeks of follow-up to evaluate any lasting effects of the ginseng.

The study was registered and a published protocol is available.[14] A Data Safety Monitoring Board oversaw the study.

Participants

Eligible participants, aged 40 years and over, had a diagnosis of moderate COPD defined by GOLD[1] as FEV_1/FVC less than 0.7 and FEV_1 greater than 50% and less than 80% predicted, confirmed by spirometry. When the study was implemented in 2010, spirometry assessment was the primary COPD classification. The "ABCD" assessment tool currently recommended in the GOLD guidelines was not applied in this study.[1]

Participants met the Chinese medicine syndrome classification of *lung qi deficiency* with or without *spleen and kidney qi deficiency*, diagnosed by a registered Chinese medicine practitioner. A review of participant enrolment after the first year of recruitment indicated that the protocol was restrictive, and several potential participants were excluded due to age and smoking status especially in China. Initially, the study only included ex-smokers and people aged between 40 and 80 years. Therefore, after consulting several experts, including respiratory physicians and clinical trial investigators, a protocol amendment was made to include current smokers and non-smokers and removal of the restriction to the upper age limit.

Key exclusion criteria were a current diagnosis of asthma, alpha-1 antitrypsin deficiency, a coexisting illness or medications that may interfere with the study results, had undertaken pulmonary rehabilitation within 3 months of commencement of the study, or intended to enter pulmonary rehabilitation during the study. Participants were also excluded if they were taking ginseng-containing products or had taken them within 3 months of the study's commencement or had an allergic history to ginseng products.

Interventions

The study intervention was *P. ginseng* CA Meyer standardised root extract. The ginseng and matching lactose-based placebo were administered as 100 mg gel-filled capsules for oral intake in the morning and at night (total 200 mg per day). Ginsana SA, Switzerland manufactured the ginseng (G115) and placebo following Good Manufacturing Practice. The raw material was sourced from China and inspected by qualified experts at Ginsana for botanical and physical characteristics, in addition to chemical fingerprinting at the Ginsana laboratory. A retention sample is stored at Ginsana, with reference number 9 16 708. Raw ginseng roots were processed and extracted using 96% ethanol, water (40:60 v/v), producing a ratio of 5:1 herbal drug to extract ratio. The content of the final product includes 30%–55% ginseng native extract, 2% silica colloidal anhydrous (European Pharmacopoeia, Ph Eur) and 43%–68% lactose monohydrate (Ph Eur). One capsule contains 100 mg of G115, including 4 mg of ginsenosides, the active/marker constituents. The ginseng was tested for aflatoxins, heavy metals and pesticide residue. G115 is the highest quality, standardised ginseng product available, and has been evaluated in several laboratory studies and clinical trials.[13] G115 is listed on the Australian Register of Therapeutic Goods (ARTG ID 199134). The dose was determined by reviewing previous clinical trials[9 11 15] and manufacturer recommendations.

Participants were given symptomatic relief medication to be used as needed and could continue their usual COPD medications according to COPD guidelines at the time of the study. These medications included short-acting bronchodilator relievers (eg, albuterol) and long-acting anticholinergics (eg, tiotropium). Participants taking COPD medications not recommended for moderate COPD, such as theophylline, corticosteroids and combination bronchodilator/inhaled corticosteroids, were asked to discontinue the medication during the run-in period. If it was unsafe to discontinue or they refused, they were not eligible for randomisation. Participants recorded their study medication and other medication in a take-home diary. They were also asked to return their unused medication to be checked against their diary.

Outcome measures

The coprimary endpoints were health-related quality of life improvements assessed by change from baseline in St George's Respiratory Questionnaire (SGRQ), the COPD Assessment Test (CAT) and the Short Form Health Survey (SF-36). Secondary endpoints included change from baseline in FEV_1 and FVC, use of relief medication (albuterol), and number of COPD exacerbations. Safety endpoints included adverse events and blood parameters, including full blood count and blood biochemistry for liver and renal function.

Assessment of COPD-related use of medical resources, such as visits to emergency departments and medical practitioners, was planned but not analysed due to low rates of occurrence. Efficacy was analysed until the end of treatment (week 24) in an intention-to-treat population, and until the end of follow-up (week 52) in an available case population.

Efficacy and safety assessments

Questionnaires were administered, and spirometry was performed at baseline, beginning of treatment, mid-treatment, end of treatment, mid-follow-up and end of follow-up. COPD exacerbations were defined as a worsening in two or more symptoms, such as worsening dyspnoea and an increase in sputum purulence or volume or both, or a single major symptom and more than one minor symptom, such as upper airway infection,

unexpected fever or increased wheezing that lasted 2 or more days.[16] Exacerbations were not considered adverse events unless they were serious and required hospitalisation. Exacerbations were managed by participants' usual treating doctor and details were recorded in the case record form.

At each site, the same person performed all assessments. Site coordinators were experienced and trained in study implementation using standard procedures. Quality of life questionnaires were available in English and Mandarin, and data from the sites were merged for analysis. At each site, spirometry was conducted using SpiroUSB (CareFusion) and Spide5 software. Spirometry was measured prebronchodilator and postbronchodilator, after 400 μg of inhaled albuterol.

Statistical analysis

An independent statistician blinded to participant allocation used SPSS V.24 to analyse data. The sample size of 168 was based on the primary outcome of SGRQ from a salmeterol study.[17] In the study, the mean score change on the SGRQ was significantly higher in the treatment group (–6.8±13.2) than in the placebo group (–1.4±11.7). To achieve a similar difference between the ginseng extract and placebo with an 80% power to detect a group difference corresponding to an effect size estimate of 0.43 and a two-tailed significance level of 5%, 84 participants per group were required, that is, 168 in total.

Within-group changes from baseline to end of treatment, and from baseline to end of follow-up, were assessed for all outcomes using paired t-tests.[18] Two-sample t-tests were used for assessing the difference in mean change scores between groups. Group differences on exacerbations of COPD and use of relief medication at the end of treatment and end of follow-up were assessed using two-sample t-tests. Intention-to-treat analysis was performed with the last observation carried forward up to and until the end of treatment. Due to the long period (24 weeks) between end of treatment and end of follow-up, and the unknown changes in patient symptoms, the last observation carried forward was dispensed with during the follow-up period by only analysing data on available cases.

Data analyses are presented as changes from baseline via mean, SD and 95% CI, except for exacerbations and use of relief medication data which are presented as between-group differences at the end of treatment and end of follow-up using t-tests (paired t-tests) and χ^2 tests. Subgroup analyses involving location, smoking status, gender and age were performed on all outcome variables.

RESULTS

Participants

Between May 2010 and May 2016, 168 participants were randomised, 82 to ginseng and 86 to placebo. Most of the participants were enrolled at the Guangdong Provincial Hospital of Chinese Medicine in China (n=110). The remaining 58 participants were enrolled at four hospitals in Melbourne, Australia. By week 52, 24 participants had dropped out, 12 in each group. The reasons for dropping out are presented in figure 1, with most dropouts due to the patient's decision (87.5%) or adverse events (12.5%). Participant demographics and clinical characteristics were well matched across the groups at baseline (table 1). The mean age was 67.8 years with an SD of 8.54 years. Most participants were men (135, 80%) and 26.8% were smokers.

Health-related quality of life

St George's Respiratory Questionnaire

After treatment, the SGRQ total score improved (was lower) in both groups, indicating improved quality of life (table 2). The

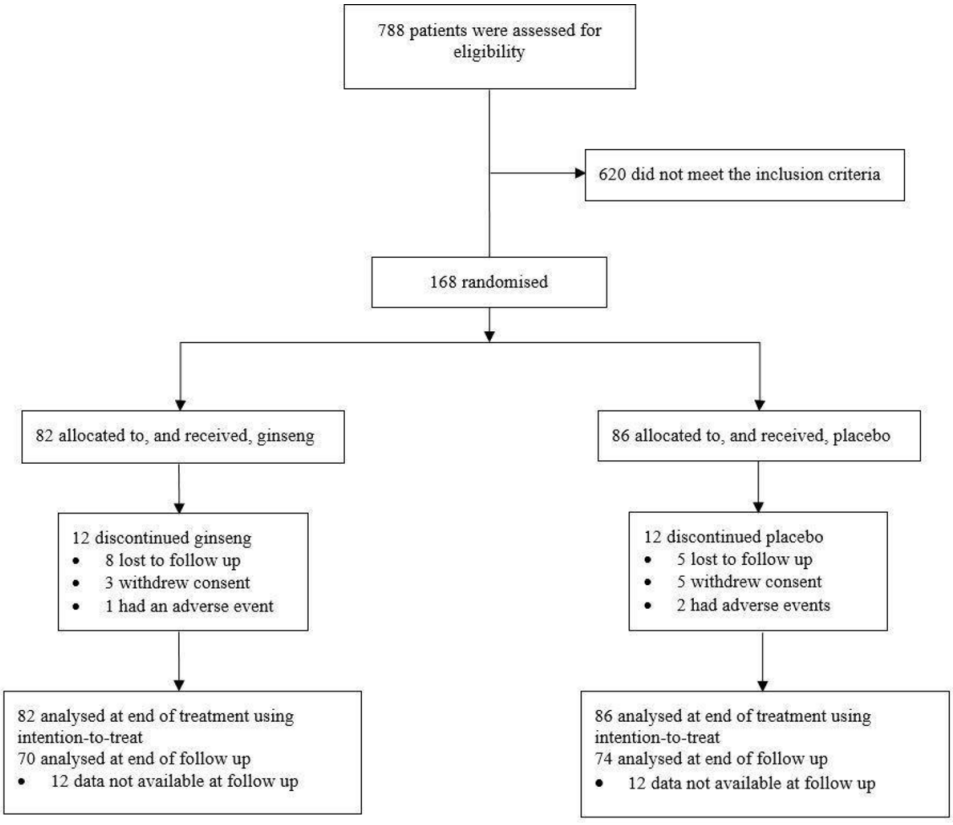

Figure 1 Study enrolment.

Table 1 Baseline demographics and clinical characteristics

Characteristics	Ginseng	Placebo
Number of participants	82	86
Location		
► Guangzhou, China	55	55
► Melbourne, Australia	27	31
Age, years, mean (SD)	68.05 (9.03)	67.55 (8.10)
Male, n (%)	65 (79.3)	70 (81.4)
Smoking status, n (%)		
► Current	18 (22.0)	27 (31.4)
► Former	50 (61.0)	50 (58.1)
► Never	14 (17.0)	9 (10.5)
Body mass index, mean (SD)	25.0 (5.89)	24.45 (4.64)
FEV_1, L, mean (SD)	1.65 (0.44)	1.72 (0.45)
SGRQ total score, mean (SD)	28.57 (12.54)	29.0 (14.66)
Duration of COPD, years, mean (SD)	5.18 (5.50)	4.05 (3.32)
COPD medication, n (%)		
► Long-acting bronchodilators (muscarinic antagonists or beta-agonists)	11 (13.4)	19 (22.1)
► Inhaled corticosteroids plus long-acting beta-agonists	14 (17.1)	16 (18.6)
Chinese medicine diagnosis, n (%)		
► Lung qi deficiency	9 (11.0)	10 (11.6)
► Lung and spleen qi deficiency	22 (26.8)	28 (32.6)
► Lung, spleen and kidney qi deficiency	24 (29.3)	21 (24.4)
► Lung and kidney deficiency	27 (32.9)	27 (31.4)

SGRQ, St George's Respiratory Questionnaire.

difference between groups, in terms of change over time, was similar but not statistically significant after treatment. However, after follow-up there was a statistically significant difference in favour of ginseng, with a mean difference (MD) between groups of –2.76 points (95% CI –5.31 to –0.21; t=–2.14, df=166, p=0.034) (table 3). Further analysis involving subgroups showed that ginseng performed no better or worse than placebo, reflecting similar results to that obtained with the overall pool of participants. Subgroups included location, smoking status, gender, medications at baseline, body mass index and age (40–59, 60–69, 70–79 and 80+ years old). The number of participants in each treatment group who achieved a clinically meaningful improvement of four or more points on the SGRQ was similar after treatment (ginseng n=27, 32.5% and placebo n=33, 38.4%; p=0.46) and after follow-up (ginseng n=22, 26.8% and placebo n=19, 22.1%; p=0.48).

After 24 weeks of treatment, the mean changes in CAT total scores from baseline were not significantly different between treatment groups. However, the mean change in CAT total scores from baseline to end of follow-up was significantly lower in the ginseng group (MD=1.54, 95% CI 0.60 to 2.48; t=3.25, df=81, p=0.002) but not in the placebo group (MD=0.33, 95% CI –0.90 to 1.55; t=0.53, df=85, p=0.60) (table 2). Subgroup analysis by location revealed that participants in China who were given ginseng had significantly better (lower) mean change CAT total scores from baseline to end of follow-up than those on placebo (MD=–1.58, 95% CI –3.11 to –0.06; t=–2.01, df=108, p=0.042, n=110), but this was not the case for Australian participants (MD=–0.29, 95% CI –3.65 to 3.07; t=–0.17, df=56, p=0.86, n=58). However, this result did not meet the minimum clinically important difference of two points.[19]

After 24 weeks treatment, a similar number of participants in the ginseng and placebo groups improved by two or more points on the CAT (ginseng n=37, 45.1% and placebo n=38, 44.2%; p=0.90). However, after follow-up, more participants taking ginseng improved by two or more points than those taking placebo, but this result was not statistically significant (ginseng n=33, 40.2% and placebo n=24, 27.9%; p=0.09).

Short Form Health Survey

Changes between baseline and end of treatment in the SF-36 mental and physical scores were similar across the ginseng and placebo groups (table 2). However, ginseng produced significantly better outcomes than placebo in terms of the SF-36 physical change score between the end of treatment and the end of follow-up (MD=1.29, 95% CI 0.01 to 2.59; t=1.98, df=166, p=0.048) (table 3). Subgroup analysis by location after follow-up revealed that participants in China taking ginseng had significantly better SF-36 mental scores than those on placebo (MD=2.11, 95% CI 0.57 to 3.67; t=2.71, df=108, p=0.008), but the mean change in physical scores was similar between groups.

Lung function

Mean changes in FEV_1 from baseline to end of treatment were not significant in the ginseng or placebo groups (MD=30 mL, 95% CI –4 mL to 60 mL; t=1.70, df=81, p=0.09 and MD=20 mL, 95% CI –10 mL to 50 mL; t=1.13, df=85, p=0.26, respectively). However, participants taking ginseng rather than placebo had a small, short-term improvement in their FVC % after 3 months of treatment (MD=4.64%, 95% CI 0.53% to 8.7%; t=0.38, df=166, p=0.02). However, the improvement was not sustained at 6 months. Subgroup analysis involving gender showed that women who took ginseng had better FEV_1 after treatment than women in the placebo group (MD=63 mL, 95% CI 10 mL to 110 mL; t=2.59, df=16, p=0.020 and MD=2.71%, 95% CI 0.12% to 5.29%; t=2.2, df=16, p=0.042, n=17). Subgroup analyses based on other variables such as location, smoking status and age groups revealed no statistically significant differences in change between baseline and end of treatment after taking ginseng or placebo.

Relief medication

In both groups, the use of relief medication (albuterol) was reduced. However, the difference between groups was not significant. In the ginseng group, the mean number of puffs during the treatment phase was 126.98 (approximately 5.29 puffs per week) and 92.40 during the follow-up phase (approximately 3.85 puffs per week). In the placebo group, the mean number of puffs was 77.36 (approximately 3.22 puffs per week) during treatment and 58.33 (approximately 2.43 puffs per week) during follow-up. After treatment, the difference in mean number of puffs between groups was not significant (MD=–49.61 puffs, 95% CI –114.24 to 15.01; t=–1.52, df=165, p=0.13).

Exacerbations

Sixty-eight participants (40%) experienced an acute exacerbation of COPD during the study. Of these 68 participants, 39 had one exacerbation, 15 had two exacerbations, 13 had three exacerbations and 1 had four exacerbations. There was no significant difference in mean number of exacerbations between groups

Table 2 Results of primary outcomes: quality of life

Group	Baseline (B) (start of treatment)	Mid-treatment	End of treatment (EoT)	Mid-follow-up	End of follow-up (EoFu)
St George's Respiratory Questionnaire total score					
Ginseng, mean (SD)	28.57 (12.54)	27.81 (13.61)	27.41 (13.88)	28.48 (14.27)	27.16 (14.57)
Placebo, mean (SD)	29.19 (14.46)	26.46 (13.95)	26.60 (16.0)	27.55 (15.83)	29.11 (15.73)
Ginseng change, mean (95% CI)	B–EoT: 1.17 (–0.85 to 3.19), p=0.25 B–EoFu: 1.41 (–0.78 to 3.61), p=0.20			EoT–EoFu: 0.25 (–1.32 to 1.81), p=0.75	
Placebo change, mean (95% CI)	B–EoT: 2.59 (0.81 to 4.38*), p=0.005 B–EoFu: 0.08 (–2.33 to 2.49), p=0.95			EoT–EoFu: –2.52 (–4.53 to –0.50*), p=0.02	
Between-group difference, mean (95% CI)	0.62 (–3.51 to 4.75)	–1.35 (–5.55 to 2.85)	–0.81 (–5.38 to 3.76)	–0.94 (–5.53 to 3.66)	1.95 (–2.67 to 6.58)
COPD Assessment Test					
Ginseng, mean (SD)	13.57 (5.36)	13.18 (5.64)	12.72 (5.65)	13.13 (5.78)	12.04 (5.89)
Placebo, mean (SD)	13.43 (5.49)	13.05 (5.83)	12.71 (6.40)	12.74 (6.51)	13.10 (6.77)
Ginseng change, mean (95% CI)	B–EoT: 0.85 (–0.20 to 1.91), p=0.11 B–EoFu: 1.54 (0.60 to 2.48*), p=0.002			EoT–EoFu: 0.68 (–0.11 to 1.47), p=0.09	
Placebo change, mean (95% CI)	B–EoT: 0.72 (–0.12 to 1.57), p=0.09 B–EoFu: 0.33 (–0.90 to 1.55), p=0.60			EoT–EoFu: –4.0 (–1.46 to 0.67), p=0.46	
Between-group difference, mean (95% CI)	–0.14 (–1.80 to 1.51)	–0.14 (–1.89 to 1.61)	–0.01 (–1.85 to 1.83)	–0.39 (–2.27 to 1.49)	1.07 (–0.87 to 3.01)
Short Form Health Survey: mental score					
Ginseng, mean (SD)	51.20 (7.88)	NC	52.26 (6.86)	NC	52.50 (7.12)
Placebo, mean (SD)	51.86 (7.80)	NC	52.22 (8.74)	NC	51.39 (8.55)
Ginseng change, mean (95% CI)	B–EoT: –1.06 (–2.41 to 0.29), p=0.12			EoT–EoFu: –0.24 (–1.17 to 0.69), p=0.61	
Placebo change, mean (95% CI)	B–EoT: –0.36 (–1.68 to 0.97), p=0.59			EoT–EoFu: 0.84 (–0.58 to 2.26), p=0.25	
Between-group difference, mean (95% CI)	0.66 (–1.73 to 3.05)	NC	–0.04 (–2.44 to 2.36)	NC	–1.12 (–3.52 to 1.29)
Short Form Health Survey: physical score					
Ginseng mean (SD)	47.19 (6.14)	NC	47.00 (6.46)	NC	47.28 (5.61)
Placebo, mean (SD)	45.82 (7.31)	NC	46.69 (7.08)	NC	45.67 (7.37)
Ginseng change, mean (95% CI)	B–EoT: 0.18 (–0.83 to 1.96)			EoT–EoFu: –0.27 (–1.12 to 0.57)	
Placebo change, mean (95% CI)	B–EoT: –0.87 (–1.89 to 0.14)			EoT–EoFu: 1.02 (0.04 to 2.0)	
Between-group difference, mean (95% CI)	–1.37 (–3.43 to 0.69)	NC	–0.31 (–2.38 to 1.75)	NC	–0.61 (–3.61 to 0.39)

Results are presented using intention-to-treat between baseline and end of treatment; intention-to-treat was dispensed with at mid-follow-up and end of follow-up.
*Statistically significant at 5% level of significance. Paired t-tests were used for testing within-group difference, and two-sample t-tests were used for testing between group mean change difference.
NC, not calculated.

after 52 weeks (MD=0.11, 95% CI –0.31 to 0.52; t=0.51, df=66, p=0.61).

Adverse events

In the ginseng group, 35 participants reported 75 adverse events. The most common events were upper respiratory tract infection (19 cases), headache (7 cases) and back pain (6 cases). All events were mild or moderate, except for four events that were classified as serious adverse events (SAEs). The SAEs included pneumonia, exacerbation of COPD, pancreatitis, perforated bowel caused by the participant's superpubic catheter and Creutzfeldt-Jakob disease. All patients were admitted to the hospital, and all events, except for the participant with Creutzfeldt-Jakob disease, were resolved. The participant with Creutzfeldt-Jakob disease passed away. Exacerbations of COPD were not classified as adverse events unless they required hospitalisation.

In the placebo group, 30 participants reported 70 adverse events. The most common events were upper respiratory tract infection (12 cases), headache (9 cases) and cough (8 cases). All events were of mild or moderate intensity, except for six events that were classified as SAEs. The SAE events included adenocarcinoma of the lung, acute myocardial infarction in addition to an acute worsening of their Crohn's disease, stroke, deep vein thrombosis, dyspnoea, left-sided chest pain and hospitalisation due to an exacerbation of COPD. All six participants who experienced an SAE were admitted to the hospital and the events resolved.

Table 3 Between-group mean change difference in various outcome measures from baseline to end of treatment, and from end of treatment to end of follow-up

Outcome measures	Change difference from baseline to end of treatment between treatment groups Mean (95% CI)	P value assessing significance of mean change difference between treatment groups
SGRQ total score	1.43, to −1.24 to 4.10	0.293
CAT total score	−0.13, to −1.47 to 1.21	0.845
SF-36 (mental score)	0.70, to −1.18 to 2.58	0.462
SF-36 (physical score)	−1.05, to −2.48 to 0.37	0.145
FEV_1, L	−0.01, to −0.06 to 0.04	0.689
FEV_1, %	−0.50, to −2.31 to 1.31	0.584
FVC, L	−0.02, to −0.11 to 0.07	0.663
FVC, %	−0.96, to −3.83 to 1.91	0.509
Outcome measures	Change difference from end of treatment to end of follow-up between treatment groups Mean (95% CI)	P value assessing significance of mean change difference between treatment groups
SGRQ total score	−2.76, to −5.30 to −0.23	0.0334*
CAT total score	−1.08, to −2.39 to 0.24	0.109
SF-36 (mental score)	1.07, to −0.61 to 2.76	0.211
SF-36 (physical score)	1.29, to 0.01 to 2.59	0.048*
FEV_1, L	0.001, to −0.04 to 0.04	0.979
FEV_1, %	0.43, to −1.09 to 1.95	0.575
FVC, L	−0.01, to −0.10 to 0.08	0.836
FVC, %	0.04, to −2.66 to 2.74	0.979

Means are calculated from data using baseline minus end of treatment or end-of-follow-up score for each treatment group.
Lung function values are postbronchodilator.
*Statistically significant at 5% level of significance. Two-sample t-tests were used for assessing mean change difference between treatment groups.
CAT, COPD Assessment Test; SF-36, Short Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

All adverse events were not considered to be related to the ginseng intervention or placebo. The adverse event profiles were similar between groups. Table 4 includes a list of adverse events occurring in two or more participants in the ginseng and placebo groups.

Table 4 Adverse events in the ginseng and placebo groups

Adverse events occurring in ≥2 participants	Ginseng (n=82) n (%)	Placebo (n=86) n (%)
Upper respiratory tract infection	19 (23.2)	12 (14)
Headache	7 (8.5)	9 (10.5)
Back pain	6 (7.3)	0
Cystitis	3 (3.7)	0
Loss of balance	2 (2.4)	0
Ear infection	2 (2.4)	0
Sinusitis	2 (2.4)	0
Anxiety	2 (2.4)	0
Cough	0	8 (9.3)
Epistaxis	0	5 (5.8)
Insomnia	0	3 (3.5)
Hearing loss	0	2 (2.3)
Leg cramps	0	2 (2.3)
Conjunctivitis	0	2 (2.3)

Blood parameters, including full blood count and blood biochemistry for liver and renal function, were taken before and after treatment. At baseline, most results were within normal parameters, except for six participants with mild anaemia (three ginseng; three placebo) and seven with leucocytosis (four ginseng, three placebo). These results were consistent with the patients' medical history. The liver and kidney function tests were not clinically significant before or after treatment, except for one patient in the ginseng group who showed increased urea and creatinine. The result was not considered to be causally related to the ginseng treatment because of the patient's medical history.

DISCUSSION

This is the first high-quality, international, multicentre, randomised controlled trial evaluating the efficacy and safety of ginseng for moderate COPD. After treatment, participants given ginseng and participants given placebo had similar improvements in quality of life outcomes (SGRQ, CAT, SF-36). After follow-up, significant improvements were seen in the SGRQ and CAT total scores of participants in the ginseng group, but not in the placebo group. However, the statistically significant differences were not clinically relevant, and the mean improvements in the SGRQ and CAT did not meet the minimum clinically important difference of four or two points, respectively.[19 20] Included participants were at the lower end of COPD severity, and their SGRQ and CAT total scores (at baseline) were towards the lower limit of symptomatic morbidity. Therefore, the room for improvement was small. In addition, ginseng is readily available over the counter and from herbal medicine practitioners, and it is possible that participants in the placebo group were also exposed.

In terms of change in lung function, FEV_1 and FVC, both ginseng and placebo groups showed improvement, but differences in change between groups were not statistically significant. In the short-term (mid-treatment, 3 months), ginseng produced better FVC results than placebo, but these results were not statistically significant at 6 months (end of treatment). Women had the largest positive results from treatment, but this finding is inconclusive due to the small number of female participants.

Use of relief medication and COPD exacerbations were similar between groups, and not statistically significant, possibly due to the infrequent use of relief medication and the small number of patients with exacerbations.

When interpreting the results of this study, some cautions due to limitations should be considered. During screening, 620 (79%) of the screened participants were not included because their airflow limitation was outside the moderate (GOLD 2) COPD range (either too good or too poor). We believe that people were enthusiastic to participate in this ginseng study; however, they did not know their level of lung function. Future studies could include participants with more severe COPD to improve recruitment and the generalisability of results. The end of study follow-up sample size was reduced and only 144 (86%) participants completed the study, possibly affecting the analysis.

Overall the magnitude of ginseng's benefit was small, but in keeping with other studies that have assessed moderate (GOLD 2) COPD, showing that improvement or deterioration occurs at similar rates in treatment and placebo groups.[21 22] Adverse events were reported in the ginseng and placebo groups. However, they had minor health impacts and not causally related to ginseng. There were no incidences of herb–drug interactions, and blood

biochemistry results for liver and kidney function did not show any notable results.

A common challenge for herbal medicine clinical studies is the ability to generalise and translate results to clinical practice. Participants selected for this study had moderate COPD and a Chinese medicine diagnosis of *lung qi deficiency* with or without *spleen and kidney qi deficiency*. Therefore, we adhered to the Chinese medicine principle that therapies must match the Chinese medicine syndrome. This ensured the results could be translated into Chinese medicine clinical practice and conventional medicine clinical practice.

An issue with herbal medicine studies is the authenticity and quality of the medicinal herbs. To address this issue, we chose an internationally recognised standardised extract of ginseng, which was manufactured and certified under strict quality control procedures. In addition, patients remained on their usual medications for moderate COPD, meaning that the study population better reflected the real-world population of patients with moderate COPD.

CONCLUSIONS

This study examined ginseng's efficacy and safety for treating moderate COPD. It used rigorous methodology and randomised participants from five hospitals in Australia and China. We found no significant differences after treatment between ginseng and placebo. Ginseng was safe for this group of participants.

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