ORIGINAL ARTICLE

Panax Ginseng for Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

INTRODUCTION: Panax ginseng is a traditional Chinese medicine used for chronic obstructive pulmonary disease (COPD). The study assessed Panax ginseng's advantages for patients with COPD. **MATERIAL AND METHOD:** PRISMA guidelines were used based on the PICOS model. A systematic search of PubMed/Medline and the Cochrane Library was conducted till March 2022. I2 statistic and random effects model was employed to assess heterogeneity, and GRADE assessment was used to evaluate the quality of outcomes. **RESULTS:** Four trials involving 469 participants were included. Panax ginseng had no significant effects in reducing the frequency of COPD exacerbations (p=0.08) or improve FEV1 (p=0.22), FEV1 (p=0.28), FVC (p=0.20), FVC (p=0.79), and FEV1/FVC ratio (p=0.06) as compared to the placebo. No effects on the mental health-related quality of life (p=0.94), physical health-related quality of life (p=0.92), and respiratory health-related quality of life (p=0.29) were observed. The severity of COPD (p=0.64) was also not affected. Adverse effects documented by Panax ginseng, including insomnia (p=0.15), epistaxis (p=0.69), respiratory tract infection (p=0.83), and white blood cells (p=0.33), were insignificant compared with placebo. **CONCLUSIONS:** There is low to moderate certainty of evidence that Panax ginseng improves exacerbation or lung functions in COPD patients. Thus, more high-quality double-blind RCTs are required to establish its clinical effectiveness, and at present, Panax ginseng should not be considered a substitute for conventional COPD treatment.

Keywords
Panax ginseng; COPD; traditional medicine

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Received: 13th February 2024; Accepted: 25th February 2025

Doi: https://doi.org/10.31436/imjm.v24i02.2391

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable lung condition that affects millions worldwide and is currently the third leading cause of death, responsible for over 3 million deaths annually.[1] People have been affected by this disease all around the world, and most countries have experienced major social and economic hardships as a result.[2] Currently, due to the growing number of senior citizens, the number of COPD patients is anticipated to be higher.[3]

Respiratory symptoms in COPD patients are breathlessness and chronic cough with or without sputum production.[2] In stable COPD patients, medications are prescribed depending on the stage of the disease and limitation of airflow based on spirometry. Medications such as long-acting beta-2 adrenoceptor agonists (LABA) and long-acting muscarinic receptor antagonists (LAMA) can be administered individually or in combination (LAMA). Inhaled corticosteroids (ICS) are also given with LABAs/LAMAs, usually at a later stage.[4] Despite the availability of treatments like LABAs and LAMAs, many COPD patients seek complementary therapies such as Panax ginseng. However, the evidence regarding its efficacy for COPD remains unclear, prompting this systematic review.

Panax ginseng, commonly used in traditional Chinese and Korean medicine, has shown promise due to its anti-inflammatory and antioxidant properties, which could theoretically benefit COPD patients.[5] Since "Panax" means "cure all" in Greek, there are numerous ways to use ginseng to treat and cure various medical issues. It is also famous in Western countries as part of

complementary medicine and alternative therapies.[5] Panax ginseng is known as Korean ginseng or renshen.[6] Panax ginseng can be consumed in various forms, including capsules, tablets, extracts, and teas.[5]

The Panax ginseng used in our study contained ginseng extract capsule, G115. G115 was the first ginseng extract to be registered on the European market and to be standardised on a specified amount of ginsenosides.[7] Ginsenosides are the primary bioactive constituents of Panax ginseng.[8] In all four trials in this study, the G115 capsule was produced by the same supplier – Ginsana SA, Switzerland.[9–12] However, only two trials mentioned that one capsule of 100 mg of ginseng (G115) containing 4 mg ginsenosides.[9,10] One study mentioned that Panax ginseng used contained 4% ginsenosides.[11] One study did not mention the content of ginsenosides in the Ginseng capsule.[12] Although all four trials used G115 capsules, only two reported the standard ginsenoside content, highlighting a need for more consistent reporting in future studies. This systematic review aims to evaluate whether Panax ginseng G115 can effectively reduce COPD exacerbations and improve lung function, potentially offering a complementary approach to existing pharmacological treatments.

The mechanism underlying the effects of ginseng in treating COPD are thought to be related to multiple pathways. Panax ginseng's primary bioactive compounds, ginsenosides, are known to reduce oxidative stress and inflammation, both key contributors to COPD pathogenesis.[4,13] Glutathione and superoxide dismutase are two examples of anti-oxidative enzymes and antioxidants that are increased in response to Panax ginseng and ginsenosides.[13] By increasing antioxidants like glutathione and inhibiting inflammatory cytokine production, ginsenosides may improve lung function and reduce exacerbations.

Second, ginseng has the potential benefit of reducing inflammation, an important factor in COPD which are regarded to be important component in COPD. Ginseng's effect might be related to, which is involved in various inflammation and immune regulation. Ginsenoside inhibits the pathway that related to lung inflammation and reduction of cytokine production leading to the inflammatory response. Thus, the inhibitory potential of ginsenosides can contribute to their in vivo lung anti-inflammatory action which can be effective against lung inflammatory diseases such as bronchitis and COPD.[14] Apart from anti-inflammatory effects, ginsenosides also provide a range of health benefits, including antiallergy and anticancer properties.[15] It also has been shown to benefit several numbers of health conditions, as evidenced by a systemic review such as erectile dysfunction,[16] diabetes,[17] and fatigue.[18]

This review focuses on the studies of Panax ginseng G115 on the COPD patient. Given the limitations and side effects associated with standard COPD medications, Panax ginseng offers an attractive alternative or adjunctive treatment, particularly for those seeking natural or complementary therapies.

MATERIALS AND METHODS

Our protocol was registered in PROSPERO (CRD42022308128) to ensure transparency and minimize bias in the systematic review and meta-analysis process. A systematic review and meta-analysis were chosen to consolidate existing evidence and quantitatively assess the effectiveness of Panax ginseng in COPD, providing a robust conclusion based on aggregated RCT data. In this paper, a systemic review and meta-analysis of RCTs comparing Panax ginseng preparations as an intervention with a placebo toward patients with COPD are conducted. The research was conducted based on the standards provided by PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) guidelines.

Literature Searching Strategies

MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Epistemonikos were used to search for RCTs and controlled clinical trials involving these patients. The search included the terms 'Panax ginseng,' 'COPD,' and 'COAD' combined with Boolean operators such as 'AND' and 'OR' to refine the search results. The reference lists of RCTs that had been identified were checked to locate unpublished trials or

trials that were not found via electronic searches. In addition, the reference lists of the included RCTs were checked to locate any unpublished trials or studies that might not have been indexed in the electronic databases, ensuring a comprehensive literature search. The ongoing trials were searched through the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/ and www.clinicaltrials.gov).

Inclusion and Exclusion Criteria

The study population comprised adults who were diagnosed with COPD. In contrast to a placebo, Panax ginseng was included in any dosage and duration to capture the broad scope of its use in COPD management, though this may introduce heterogeneity, which was accounted for in subgroup analyses.

The primary outcomes were frequency of COPD exacerbations, duration of COPD exacerbations, and lung function test, whereas the secondary outcomes were quality of life; severity of COPD; the number of use relief medication; adverse events such as insomnia, dizziness, and epistaxis; and blood parameters such as white blood cells; and renal and liver functions. Quality of life was assessed using validated instruments such as the St. George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT). Both blinded and open-label studies were included.

Quality assessment

The titles and abstracts from the searches were scanned, and full-text articles were obtained. The reviewers assessed the eligibility criteria of the RCTs to be included in this study. The justifications for exclusion were stated, and assessments were done independently. For example, studies were excluded if they lacked a placebo-controlled comparison or if the intervention did not solely include Panax ginseng. If clarification was necessary, the authors were contacted.

The data were extracted independently, which included characteristics of the trials (study setting), the participant's characteristics (age, sex, and ethnicity), the method used for the trials (number of participants randomized and analysed and the duration of follow-up), description of the intervention, and the study outcomes. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selectivity of outcome reporting, and other bias.[19]

Any disagreements between reviewers were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted to ensure unbiased selection. Using a GRADE approach, the researchers assessed the quality of the evidence in the systemic reviews and the strength of the recommendations. Based on the GRADE methodology,[20] we assessed the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias for both the primary and secondary outcomes, which were rated as very low, low, moderate, or high.

Statistical Analyses

Review Manager 5.4 was used due to its comprehensive tools for conducting meta-analyses of clinical trials and generating forest plots to visualize treatment effects.

The level of heterogeneity was evaluated. The obvious heterogeneity at face value by comparing populations, settings, interventions, and outcomes was assessed. Next, we used the I2 statistic to evaluate statistical heterogeneity.[19] Thresholds for interpreting the I2 statistic might be deceptive because the importance of inconsistency varies on a range of factors. The heterogeneity can be classified as follows: 0%–40% represented not important; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity.[19] High heterogeneity (e.g., I2 >75%) indicates substantial differences across studies, which may limit the reliability of pooled estimates and necessitates cautious interpretation of overall results.

We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by

comparing populations, settings, interventions, and outcomes. Second, we evaluated statistical heterogeneity using the I^2 statistic.[19] Risk ratios and absolute risk reduction are used to calculate the treatment effect for dichotomous outcomes. Meanwhile, mean differences (MDs) with 95% confidence intervals (CIs) were used for continuous outcomes. In this study, subgroup analyses by dosage and duration were conducted to identify specific contexts in which Panax ginseng might be more effective. These analyses help to account for heterogeneity and reveal dosage-specific effects.

We checked included trials for a unit of analysis errors. Unit of analysis errors can lead to inflated significance levels. Unit of analysis errors can occur when trials randomized participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. Adjustments were made to ensure the integrity of statistical outcomes, using the mean cluster size and intracluster correlation coefficient.[19] We contacted the original trial authors to request missing or inadequately reported data. We performed analyses on the available data in case missing data are not available. To investigate the impact of risk of bias for sequence generation and allocation concealment of included studies, we performed a sensitivity analysis. Funnel plots were to be assessed for asymmetry as an indicator of possible publication bias, with significant asymmetry suggesting the likelihood of underreported or overrepresented results.

RESULTS

Results of the Search

A total of 178 records were identified through database and other searches, and after duplicate removal, 140 unique records were screened. Figure 1 outlines the selection process for the included studies, including reasons for exclusion at each stage, leading to the final inclusion of four trials.

Trials were excluded because it was a protocol [21] and did not have the outcome of interest.[22] Consequently, four trials are included, and two trials are disregarded from the review.

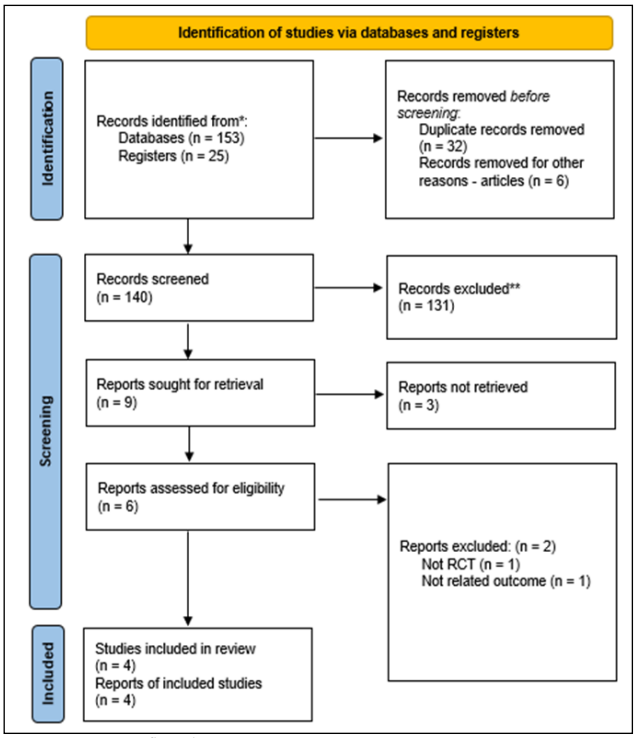

Figure 1: PRISMA flow chart.

Table I: Characteristics of included studies.

Reference	Country	Participants	COPD severity	Duration of intervention	Intervention /Dosage	Control
[10]	China	Intervention: 100 Control: 100	Moderate to very severe using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 less than 80% predicted, confirmed by spirometry	24 weeks	anax ginseng capsule (G115®)/ 200mg twice daily	Placebo (lactose-based)
[9]	China Austral-ia	Intervention: 82 Control: 86	Moderate using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 greater than 50% and less than 80% predicted, confirmed by spirometry	24 weeks	Panax ginseng capsule (G115®)/ 100mg twice daily	Placebo (lactose-based)
[11]	China	Intervention: 4 Control: 5	Moderate to very severe using GOLD Guidelines as FEV_1/ FVC less than 0.7 and FEV_1 between 20% and 79%	4 weeks	Panax ginseng extract capsule (G115®)/ 200mg twice daily	Placebo (lactose-based)
[12]	Israel	Intervention: 51 Control: 41	Moderate as FEV_1 50 to 65% of predicted	12 weeks	Panax ginseng extract capsule/ 100mg twice daily	Placebo

Four trials, including 469 participants, assessed FEV_1 (Litres) and FVC (Litres), with treatment durations ranging from 4 to 24 weeks.[9–12] All trials declared funding from ginseng manufacturers.[9–12] Two trials were conducted in multicentre hospitals.[9,10] Two trials recruited participants from hospitals in China.[10,11] One trial recruited participants from hospitals in Australia and China [9] and one trial recruited participants from Israel.[12] One trial did not mention the setting from which the participants were recruited.[12] Two trials chose participants with moderate severity of COPD [10,11] and another two trials chose moderate to very severe severity of COPD for the participants.[9,12] Four trials included participants that were aged 40 years and above.[9–12]

Trial subjects were randomly divided into intervention and control groups. For two trials, the intervention was Panax ginseng total daily dose of 200 mg,[9,12] whereas the other two trials were using Panax ginseng total daily dose of 400mg.[10,11] The ginseng was administered orally in four trials.[9–12] The duration of the treatment was 24 weeks,[9,10] 12 weeks,[12] and four weeks.[11] Participants in the control groups were given a placebo. Three trials mentioned the lactose-based content of the placebo.[9–11] One trial did not mention the content of the placebo. [12] The participants in three trials were given symptomatic relief to be used when needed.[9,10] Two trials mentioned that participants could continue their usual COPD drugs according to COPD guidelines.[9,10]

One trial stated that respiratory drugs including long-acting anticholinergic or long-acting β2 agonists alone or in combination with glucocorticoids could be used throughout the study under the advice of the participants' respiratory physician.[11] One trial did not mention whether the standard treatment was given or not.[12] Almost all the outcomes in one trial were reported in mean change such as FEV_1, FEV_1%, FVC, FVC%, mental-related quality of life, physical-related quality of life, respiratory-related quality of life, the severity of COPD, and use of relief medication.[10] Considering that it was reported in one trial that it has no change in the baseline results of the post-intervention; therefore, the baseline results are used for the control group.[12] Table 1 summarizes the characteristics of the four trials.

PRIMARY OUTCOMES

The primary outcomes reported about frequency, duration of exacerbation of COPD, and lung function test. Three trials reported the frequency of COPD exacerbation.[9,10] One trial reported the duration of exacerbations.[10] Four trials reported FEV1 (Litres) and FVC (Litres).[9–12] Two trials reported outcomes about FEV_1% and FVC%.[9,10] Two trials reported FEV1/FVC.[11,12] Secondary outcomes were reported in four trials.[9–12] The mental-related quality of life was measured using a short-form health survey (SF-36) questionnaire in three trials.[9–11] The physical-related quality of life was measured using an SF-36 questionnaire in two trials [9,10] and 6-minute walking test in two trials.[10,11] Three trials measured outcomes using respiratory-related quality of life.[9–11] Respiratory-related quality of life was assessed using the St. Georges Respiratory Questionnaire. Three trials reported the severity of COPD[9–11] using the COPD Assessment Test (CAT).

Three trials reported the use of relief medication as an outcome.[9–11] Regarding adverse effects, two trials reported insomnia and epistaxis.[9,10] Three trials reported respiratory tract infection.[9–11]

Figure 2 summarizes bias indicators across studies, highlighting domains like allocation concealment and blinding, while Figure 3 details the risk of bias for individual studies. The details of these trials are found in the table of characteristics of included studies.

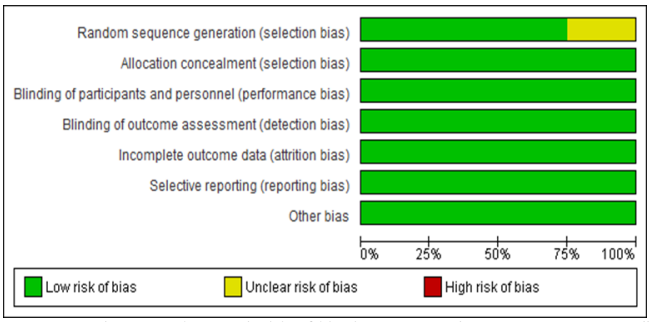

Figure 2: Judgements about each risk of bias item presented as percentages across all included studies.

Random sequence generation was low risk in three trials.[9–11] The trials randomized the participants using a computer-generated randomization code 1:1 ratio,[9,10] SPSS statistical software.[11] We judged random sequence generation as an unclear risk of bias when the method of

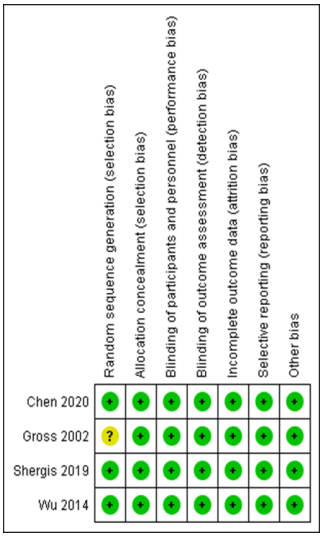

Figure 3: Judgments about each risk of bias item for each included study.

randomization was not reported.[12] Allocation concealment was low risk in four trials.[9–12] The trials concealed the randomization numbers in opaque envelopes. Blinding was low risk in the four trials.[9–12] The trials blinded the participants, personnel, and outcome assessment to group allocation. Incomplete outcome data was low risk in four trials.[9–12] Based on the data given in three trials, the missing data were balanced across the intervention and control groups.[9–11] One trial did not mention whether the missing data was balanced or not.[12] Three trials mentioned that the dropouts were due to participants who no longer wanted to participate.[9,10,12] Two trials stated missing data due to adverse effects.[9,10] Three trials mentioned missing data were due to loss of follow-up.[9–11] In three trials, missing data were balanced between intervention and control groups, accounting for approximately 5-10% of total participants. Sensitivity analyses indicated that excluding these data did not significantly affect the primary outcome measures. The use of intention-to-treat analysis minimizes potential biases from participant dropouts, thereby providing a more conservative estimate of treatment effects. Two trials carried out an intention-to -treat analysis in which the participants were analysed according to the groups that they were initially assigned.[9,10] Two trials analysed the participants by per-protocol analysis.[11,12] Four trials reported a low risk of bias for selective reporting.[9–12] The assessment indicated a low risk of bias across key domains, which supports the reliability of the findings, although inconsistency due to sample size variability and reporting issues remains a concern. All trials reported the outcomes as specified in their methods. We detected no other potential sources of bias.

As depicted in Figure 4, the confidence interval (MD-0.20, 95% CI -0.43 to 0.02) crosses zero, indicating that there is no significant difference between Panax ginseng and placebo in reducing COPD exacerbations. One trial had none of the participants experience an exacerbation during the study duration.[11]

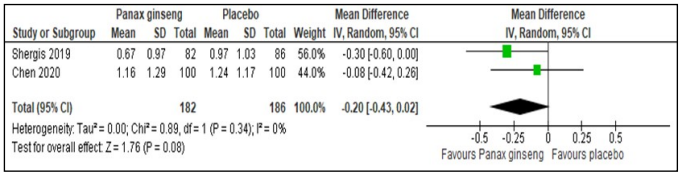

Figure 4: Forest plot for the outcome frequency of COPD exacerbations.[9,10]

Only one trial measured the duration of COPD exacerbations (MD -1.04 95% CI -1.89 to -0.19; one trial, 200 participants, low–quality evidence).[10] Panax ginseng showed no difference in FEV_1 compared to placebo (MD 0.11, 95% CI -0.06 to 0.27; I^2 statistic=74%; P=0.22; four trials, 469 participants, moderate–quality evidence)[9–12] (Table 2).

Subgroup analysis for FEV_1 by dosage was performed. Panax ginseng of 200 mg daily (MD 0.14, 95% CI -0.31 to 0.60; I^2 statistic=87%; P=0.54; two trials, 260 participants, low–quality evidence)[9,12] and 400 mg daily (MD 0.24, 95% CI -0.29 to 0.76; I^2 statistic=71%; P=0.37; two trials, 209 participants, low–quality evidence) [10,11] showed no difference compared to placebo. The subgroup analysis for FEV_1 by dosage revealed substantial heterogeneity (I^2=87%), suggesting that differences in study populations or intervention characteristics likely influenced these results. This limits the generalizability of the findings.

Panax ginseng showed no difference in FEV_1 compared to placebo (MD -2.21, 95% CI -6.24 to 1.81; I^2 statistic=82%; P=0.28; two trials, 368 participants, low–quality evidence).[9,10] Panax ginseng showed no difference in FVC compared to placebo (MD 0.20, 95% CI -0.11 to 0.51; I^2 statistic=83%; P=0.20; four trials, 469 participants, moderate – quality evidence)[9–12] (Table 2).

Table II: Summary of the findings, including GRADE quality assessment for comparison between Panax ginseng and placebo.

Panax ginseng compared to placebo for COPD COPD patient Intervention: Panax ginseng Comparison: placebo								
Outcome	**Anticipated Absolute Effects *(95% CI)**		**Study event rates (%)**		**Relative effect (95% CI)**	**No of Participants (Studies)**	**Certainty of the Evidence (Grade)**	**Comments**
	Risk with placebo	Risk with Panax ginseng	With placebo	With Panax ginseng				
Frequency of COPD exacer-bations	The mean of frequency of COPD exacerbations was 0	MD 0.2 lower (0.43 lower to 0.02 higher)	186	182	-	368 (2 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
FEV_1 (Litres)	The mean of FEV_1 (Litres) was 0	MD 0.11 higher (0.06 lower to 0.27 higher)	232	237	-	469 (4 RCTs)	⨁⨁⨁◯† Moderate	Risk of bias: not serious Inconsistency: serious Indirectness: not serious Imprecision: not serious
FVC (Litres)	The mean FVC (Litres) was 0	MD 0.2 higher (0.11 lower to 0.51 higher)	232	237	-	469 (4 RCTs)	⨁⨁⨁◯† Moderate	Risk of bias: not serious Inconsistency: serious Indirectness: not serious Imprecision: not serious
FEV_1/FVC (percentage)	The mean FEV_1/FVC (percentage) was 0	MD 0.07 higher (0 to 0.15 higher)	46	55	-	101 (2 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
Mental health related quality of life	The mean mental health related quality of life was 0	MD 0.04 higher (1.09 lower to 1.17 higher)	191	186	-	377 (3 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious
Physical health related quality of life	The mean physical health related quality of life was 0	SMD 0.01 higher (0.22 lower to 0.25 higher)	291	286	-	577 (3 RCTs)	⨁⨁⨁⨁ High	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious
Severity of COPD	The mean severity of COPD was 0	MD 0.24 higher (0.78 lower to 1.27 higher)	191	186	-	377 (3 RCTs)	⨁⨁⨁◯‡ Moderate	Risk of bias: not serious Inconsistency: not serious Indirectness: not serious Imprecision: serious

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; SMD: Standard mean difference
GRADE Working Group grades of evidence:
High certainty indicates we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty indicates we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty indicates our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty indicates we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect. ⨁⨁⨁ ◯ refers to Quality of the evidence (GRADE). †There is a presence of statistical inconsistency.
‡Downgraded due to large CIs from small sample size.

Subgroup analysis for FVC by dosage was performed. Panax ginseng 200 mg daily (MD 0.22, 95% CI -0.56 to 0.99; I^2 statistic=93%, P=0.58; two trials, 260 participants, low – quality evidence)[9,12] and 400 mg daily (MD 0.23, 95% CI -0.29 to 0.75; I^2 statistic=66%, P=0.39; two trials, 209 participants, low–quality evidence)[10,11] showed no difference compared to placebo. Panax ginseng showed no difference in FVC compared to placebo (MD 0.31, 95% CI -1.97 to 2.60; I^2 statistic=0%; P=0.79; two trials, 368 participants, moderate – quality evidence).[9,10]

Panax ginseng showed no difference in FEV1/FVC compared to placebo (MD 0.07, 95% CI -0.00 to 0.15; I^2 statistic=0%; P=0.06; two trials, 101 participants, moderate–quality evidence).[11,12] The lack of significant improvement in COPD outcomes suggests that Panax ginseng, as studied, may not effectively modulate key pathophysiological processes in COPD, such as airflow limitation or chronic inflammation, at the studied dosages and durations.

SECONDARY OUTCOMES

Panax ginseng showed no difference in the mental-related quality of life (MD 0.04, 95% CI -1.09 to 1.17; I^2 statistic=0%; P=0.94; three trials, 377 participants, moderate-quality evidence),[9–11] compared to placebo. Panax ginseng group showed no difference in the physical -related quality of life compared to the placebo (MD 0.01, 95% CI -0.22 to 0.25; I^2 statistic=41 %; P=0.92; three trials, 577 participants, high–quality evidence).[9–11] Panax ginseng group showed no difference in the respiratory-related quality of life compared to the placebo (MD -2.54, 95% CI -7.23 to 2.16; I^2 statistic=62%; P=0.29; three trials, 377 participants, low–quality evidence).[9–11] Panax ginseng group showed no difference in the severity of COPD compared to placebo (MD 0.24 95% CI -0.78 to 1.27; I^2 statistic=0%; P=0.64; three trials, 377 participants, moderate-quality evidence).[9–11] Panax ginseng showed no difference in the scoring as compared to placebo (MD 43.75, 95% CI -44.62 to 132.11; I^2 statistic=96%; P=0.33; three trials, 377 participants, low–quality evidence).[9,10] There was no difference in the number of participants with insomnia in the Panax ginseng group and placebo (MD 0.22, 95% CI 0.02 to 1.89; I^2 statistic=0%; P=0.15; two trials, 368 participants, moderate-quality evidence).[9,10] There was no difference in the number of participants with epistaxis in the Panax ginseng group and placebo. (MD 0.50, 95% CI 0.02 to 15.24; I^2 statistic = 61%; P = 0.69; two trials, 368 participants, low–quality evidence)[9,10] (Figure 18). There was no difference in the number of participants with respiratory tract infection in the Panax ginseng group and placebo (MD 1.11, 95% CI 0.43 to 2.91; I^2 statistic=57%; P=0.83; three trials, 377 participants, low–quality evidence).[9,10] Two trials were reported regarding leukocytosis. There was no significance difference in Panax ginseng and placebo (MD 1.92, 95% CI 0.52 to 7.15; I^2 statistic=0%; P=0.33; two trials, 368 participants, moderate–quality evidence).[9,10] Certainty was downgraded to moderate due to imprecision resulting from small sample sizes and wide confidence intervals, particularly affecting the mental and respiratory quality of life outcomes.

DISCUSSION

This review was designed to include all RCTs addressing the effectiveness of Panax ginseng for patients with COPD. The four identified trials formed a heterogeneous group addressing several comparisons and a variety of outcomes. This study shows that Panax ginseng use does not significantly reduce the frequency and duration of COPD exacerbations in patients with COPD. The values of lung function tests were not much improved by using Panax ginseng. There were no significant changes in quality of life, the severity of COPD, and the use of relief medication with the usage of Panax ginseng. Reporting of the adverse effects was limited to minor side effects, which included insomnia, dizziness, upper respiratory tract infections, epistaxis, and leucocytosis, which not significantly occur in Panax ginseng usage.

We performed a comprehensive and extensive literature review for assessing the effectiveness of Panax ginseng for patients with COPD. Our review evaluated the mono-preparation of Panax ginseng, with a different total dosage of the Panax ginseng, but was not able to show whether different dosages made difference in the outcomes. The control group is a placebo. The duration and doses of the

Panax ginseng were different in each trial, thereby limiting the applicability of the findings in this review. The adverse effects of the Panax ginseng have no difference as compared to the placebo in our review. A further consequence of the lack of a sufficient number of studies was that we could not conduct any of our pre-planned subgroups. These analyses, as well as potentially additional interesting subgroup analyses (e.g., according to the duration of Panax ginseng), can hopefully be considered in future updates of this review.

Generally, there was a low risk of bias in most of our included studies in the domains. There was an unclear risk of bias in assessment in random sequence generation in one trial because the method of randomization was not reported. This meta-analysis found that there was no evidence of selective reporting bias in all included studies, as all the trials reported the outcomes as specified in their methods. Otherwise, the attrition bias and performance bias were at low risk of bias in all the trials. For the GRADE criterion "imprecision," we had to downgrade the ratings in several cases if the optimal information criterion size was not met. We encountered high heterogeneity in the trials reporting FEV_1 and FVC; nevertheless, it cannot be explained by the different dosages. Using the GRADE approach, we, therefore, assessed the overall level of evidence contributing to this review as low to high quality.

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases. Despite the vigorous search of journal databases, we cannot be sure that we have extracted all trials relevant to our review. We were not able to construct a funnel plot for detecting bias due to insufficient trials.

Although Panax ginseng has demonstrated efficacy in conditions such as glucose control[23] and erectile dysfunction[16], its inability to significantly affect COPD outcomes may be attributed to the distinct pathophysiological mechanisms underlying COPD, which may not be as susceptible to ginseng's anti-inflammatory and antioxidant properties.[23]

Panax ginseng had no difference in causing adverse events which were also observed in the placebo group. General symptoms for adverse events such as insomnia, epistaxis, dizziness, dyspepsia, skin disorders, dried mouth, diarrhoea, headaches, hot flushes, chest discomfort, constipation, tachycardia, and anorexia were reported in both ginseng and placebo groups.[24] However, these were limited to systematic reviews without meta-analyses.

Implications for Clinical Practice

Nowadays, individuals with COPD around the world are turning to traditional Chinese medicine (TCM) as a supplemental or dietary supplement. According to a review, TCM benefits people with COPD by lowering their risk of exacerbations, improving lung function, their quality of life, and their ability to exercise.[25] Previous studies suggest that TCM combinations, rather than mono -preparations like Panax ginseng, may be more effective in improving COPD symptoms. According to this review, there was no difference between Panax ginseng and placebo for patients with COPD, but it is safe to take Panax ginseng as a medication. Future research should consider the role of Panax ginseng as part of multi-herb formulations, potentially enhancing its therapeutic effects.

CONCLUSION

In conclusion, safety profile of Panax ginseng has been demonstrated in this systematic review, concluding that Panax ginseng mono-preparations are rarely associated with adverse events. While Panax ginseng has shown no significant adverse events, it should be recommended only as an adjunctive treatment for COPD, particularly for patients interested in complementary medicine, and not as a replacement for standard therapies such as LABAs and LAMAs

However, the use of Panax ginseng in COPD patients did not give significant effects in improving exacerbation or improving the lung functions based on the evidence and the analysis in this review. Nevertheless, further high quality double blind RCT are required to establish the clinical effectiveness of Panax ginseng in treating COPD. Drawbacks of this review are that there is a lack of a sufficient number of studies to proceed with subgroups

analysis. Potentially additional interesting subgroup analyses (e.g., according to the duration of Panax ginseng), can hopefully be considered in future updates of this review. Future RCTs should standardize the dosage of Panax ginseng (e.g., 400 mg per day), extend treatment durations (e.g., 12-24 weeks), and focus on homogeneous COPD populations to reduce variability and increase the reliability of results.

Although Panax ginseng is rarely associated with adverse events, this review indicates that it does not significantly improve exacerbation rates or lung function in COPD patients, pointing to the need for more rigorous and larger trials before it can be recommended clinically.

FUNDING

This research received no external funding

CONFLICT OF INTEREST

The authors declared no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The study did not require ethical approval.

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