J Acupunct Meridian Stud 2011;4(2):85–97

REVIEW ARTICLE

ELSEVIER

Systematic Review of Randomized Controlled Trials Evaluating the Efficacy and Safety of Ginseng

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Received: Nov 9, 2010
Accepted: Feb 17, 2011

KEY WORDS:
efficacy;
ginseng;
randomized controlled trial;
safety;
systematic review

Abstract
This systematic review aims to evaluate the available evidence from randomized clinical trials of the clinical efficacy and safety of ginseng. Systematic literature searches were performed in 13 databases up to March 2009 without language restriction. All randomized clinical trials evaluating the clinical effects or safety of the use of ginseng monopreparations (*Panax ginseng* or *P. quinquefolium*) were considered for inclusion. A total of 411 potentially relevant studies were identified and 57 randomized clinical trials were included. The main indications included glucose metabolism, physical performance, psychomotor function, sexual function, cardiac function, pulmonary disease, and cerebrovascular disease. We found strong evidence of a positive effect of ginseng on glucose metabolism, psychomotor function, and pulmonary disease, whereas evidence suggests that ginseng is not effective at enhancing physical performance. However, ginseng generally has a good safety profile and the incidence of adverse effects seems to be low. In conclusion, our review compiles the evidence on the use of ginseng, finding a strong positive potential for glucose metabolism, psychomotor function, and pulmonary disease, but not for physical performance enhancement.

1. Introduction

In Asian countries, ginseng has been used by both patients and healthy individuals to restore and enhance vital energy [1]. Many *in vitro* and *in vivo* studies and clinical trials have investigated the pharmaceutical effects, efficacies, and active components of ginseng [2]. In addition, studies have proposed that ginseng reduces physical, chemical, and biological stress, while increasing general vitality and immune function, including physical and mental capacity [3,4]. The chemical constituents of ginseng have been identified, and approximately 40 active ingredients, including ginsenosides, polyacetylenes, sesquiterpenes, polysaccharides, and peptidoglycans, have been isolated [5,6].

The expanding consumption of ginseng for various health-related benefits raises critical concerns about its efficacy, safety, and drug interactions [7–10]. Although ginseng has long been broadly used

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in clinical settings in Asia, more rigorous scientific evaluation is required to establish appropriate clinical use. Recently, evidence-based medicine and evidence-based complementary and alternative medicine have become important in evaluating clinical trials [11,12]. For example, two recent clinical studies demonstrated that ginseng has no effect on exercise performance, contradicting other data in the medical literature and experimental research supporting the effect of ginseng on physical performance [13,14].

Relatively well designed randomized controlled trials (RCTs) are increasingly being conducted to determine the clinical efficacy and safety of ginseng for patients with specific diseases or conditions. These studies provide the best evidence in clinical medicine. The objective of this systematic review was to aid in the proper use of ginseng by critically evaluating the evidence from RCTs on its efficacy and safety.

2. Materials and Methods

2.1. Data sources and selection

Systematic literature searches were conducted using the electronic literature databases MEDLINE [15], CINAHL [16], EMBASE [17], five Korean medical databases (Korean Studies Information [18], DBPIA [19], Korea Institute of Science and Technology Information [20], Korea-Med [21], and Research Information for Health [22]), four Chinese medical databases (China Academic Journal [23], Century Journal Project [24], China Doctor/Master Dissertation Full-Text [25], and China Proceedings of Conference Full-Text [26]), and the Cochrane Library [27] from its inception to March 2009.

Studies in each language were screened using the following inclusion criteria: (1) human subjects, (2) use of a control procedure, (3) subjects randomized among treatment conditions, and (4) monopreparation tests of *Panax ginseng* or *P. quinquefolium*. An initial assessment using the inclusion criteria was made by reading abstracts. Articles that appeared to meet the criteria were then read in full by two authors, who then discussed the articles and made the decision to include or exclude them.

2.2. Data extraction and methodological quality assessment

Two authors extracted data from the articles using a standardized, predefined method that considered trial methods, study design, patient characteristics, type of ginseng, outcomes, and side effects. We used the Jadad scale to evaluate the quality of clinical trials [28]. Points were awarded depending on the description of randomization, double-blinding, and appropriate/inappropriate methods, including withdrawals and dropouts. On a five-point scale, trials with three or more points were considered high quality. Discrepancies were settled through discussions involving two authors.

2.3. Review process

The RCTs were heterogeneous with respect to ginseng species or variety, indications, dose, participant characteristics, and outcome measures. The outcomes of some studies, however, were poorly presented. Therefore, we decided not to pool the data statistically, but performed a qualitative review instead. We reviewed RCTs to formulate conclusions on the effectiveness of ginseng for the following indications: glucose metabolism, physical performance, sexual function, psychomotor function, cardiac function, pulmonary disease, and cerebrovascular function. This method consisted of four levels of evidence on the methodological quality and outcome of the studies [29,30] as follows: level 1, strong evidence, from generally consistent findings of multiple relevant, high-quality RCTs; level 2, moderate evidence, from generally consistent findings of one relevant, high-quality RCT and one or more relevant, low-quality RCTs; level 3, limited evidence, from generally consistent findings of multiple relevant, low-quality RCTs; and level 4, inconclusive evidence, from only one relevant, low-quality RCT, no relevant RCTs, or RCTs with conflicting results.

"Generally consistent" was defined as two-thirds or more of the studies having the same result (positive or negative), and "multiple" was defined as more than one.

3. Results

3.1. Final data analyzed

Our searches identified 411 potentially relevant studies, of which 57 trials met our inclusion criteria (Figure 1). The key data from all of the included RCTs are summarized in Tables 1–8 [13,14,31–85].

3.2. Description of studies and clinical questions

Of the 57 trials, 16 originated in Canada, 10 were in the United States, 13 were in Korea, 8 were in the United Kingdom, 4 were in China, and 1 each was in Australia, Brazil, Israel, Italy, Poland, and Thailand.

The clinical variables investigated were as follows: assessment of the effect of ginseng on glucose

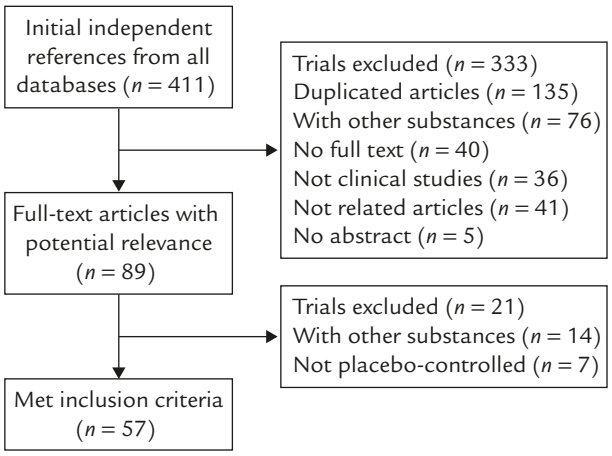

Figure 1 Scheme of the data selection process.

metabolism (12 trials), physical performance (9 trials), psychomotor function (8 trials), sexual function (7 trials), cardiac function (6 trials), and pulmonary disease (6 trials). The remaining nine RCTs addressed cerebrovascular function or miscellaneous issues.

3.3. Drug and participant characteristics

The 57 trials used two species of ginseng or a mixture of species as follows: *P. ginseng* (including red ginseng), 37 studies; *P. quinquefolium*, 15 studies; and multiple ginseng types, 5 studies. Trials included used either ginseng powder or ginseng extract (concentrated). The dosage was from 1 g to 9 g ginseng powder versus from 0.2 g to 1.125 g ginseng extract per day. Sixteen of the 57 trials were one time dosing trials. Seventeen of the 57 RCTs used commercially sold ginseng preparations, i.e., G115, Ginsana, COLD-fX, and CVT-E002, which were standardized and ginsenoside contents were verified. Other trials, however, supplied insufficient data about standardization.

The various trials included a total of 3471 participants. Healthy volunteers participated in 33 RCTs, patients with erectile dysfunction participated in 7 trials, patients with hypertension or heart disease participated in 5 trials, patients with respiratory disorders participated in 4 trials, patients with diabetes participated in 3 trials, and individuals who were senile participated in 2 trials. The other RCTs included patients with cerebrovascular disease, Alzheimer's disease, or chronic fatigue symptoms. The median number of participants was 30 (range: 8–481).

3.4. Methodological quality

Of the 57 RCTs, 40 trials were of high quality (≥3 Jadad score points), and 17 were low-quality trials (<3 Jadad score points).

3.5. Glucose metabolism

Twelve studies investigated the effects of ginseng on glucose metabolism [31–42]. The methodology of 11 of these studies was good, scoring three or more points on the Jadad scale. One study scored two points, indicating a low quality. Of the 11 high-quality trials, eight had positive results [31, 33–35,39–42], two had negative results [37,38] and one yielded variable results [36]. The result of one low-quality study was negative [32]. Therefore, there was strong evidence to suggest that ginseng shows pharmaceutical properties for glucose metabolism (level 1 of best-evidence synthesis). One study [36] showed different glucoregulatory effects by various ginsengs and it suggested that the ginsengs might have had dissimilar ginsenoside profiles.

3.6. Physical performance

The efficacy of ginseng on physical performance was evaluated in nine trials [13,14,43–49]. All nine trials used healthy volunteers, including athletes as well as sedentary men. The duration of ginseng use lasted from 1 to 8 weeks. Of the nine studies, eight scored more than three points on the Jadad scale, and one scored 2 points. All the eight high-quality studies yielded negative results [13,14,43,45–49]. Therefore, ginseng was not shown to enhance physical performance with strong evidence (level 1 of best-evidence synthesis).

3.7. Psychomotor function

Eight trials evaluated the efficacy of ginseng on psychomotor function using *P. ginseng* or red ginseng [50–57]. The methodology of five of the studies was good, with a Jadad score of more than three points; the other studies scored two points. These studies yielded six positive [50,51,53–55,57] and two negative findings [52,56], which indicated strong evidence (level 1) of efficacy.

3.8. Sexual function

Seven RCTs investigated the effects of ginseng on erectile dysfunction [58–64]. The methodology of six of these studies was poor, scoring less than three points on the Jadad scale. Only one study scored four points, indicating good quality. One high-quality trial revealed a negative result [62], and six low quality trials had positive results [58–61,63,64]. Therefore, there was moderate evidence that ginseng has pharmaceutical properties in erectile dysfunction (level 2 of best-evidence synthesis).

Table 1 Glucose metabolism studies [31–42]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Vuksan et al [31] 2008 Canada	Crossover 5 points	39 pts with type 2 diabetes Red ginseng 6 g (12 wk)	Q: Efficacy and safety of use for type 2 diabetes A: Improved plasma glucose and insulin regulation S: One case of hypoglycemia
Reay et al [32] 2006 UK	Crossover 2 points	57 healthy subjects *P. ginseng* ex. (G115) 0.2 or 0.4 g (1 time)	Q: Glucoregulatory effects of single ginseng dose A: Poor glucoregulation S: Not described
Sievenpiper et al [33] 2006 Canada	Crossover 4 points	19 healthy subjects Steamed *P. ginseng* 2 g, 4 g, or 6 g (1 time)	Q: Glucoregulatory effects: preparation and dose-finding study A: Good glucoregulation using 2 g rootlet S: None
Reay et al [34] 2006 UK	Crossover 4 points	27 healthy subjects *P. ginseng* ex. (G115) 0.2 g (1 time)	Q: Effects on blood glucose level and cognitive performance A: Improved glucose level and enhanced cognitive performance S: Not described
Reay et al [35] 2005 UK	Crossover 5 points	30 healthy subjects *P. ginseng* ex. (G115) 0.2 or 0.4 g (1 time)	Q: Glucoregulation and cognition improvement A: Good glucoregulation and cognitive function S: Not described
Sievenpiper et al [36] 2004 Canada	Crossover 3 points	12 healthy subjects 8 types of ginseng ex. 3 g (1 time)	Q: Glucoregulatory effects of multiple types of ginseng A: Variable effects according to ginsenoside profile S: Not described
Sievenpiper et al [37] 2003 Canada	Crossover 3 points	22 healthy subjects *P. ginseng* 1, 2, 3, 6, or 9 g (1 time)	Q: Glucoregulatory effects–acute dose escalation study A: Null and opposing effects S: Not described
Sievenpiper et al [38] 2003 Canada	Crossover 3 points	12 healthy subjects *P. quinquefolium* 6 g (1 time)	Q: Glucoregulatory effects of different batches A: Poor glucoregulation (probably due to depressed ginsenoside) S: Not described
Vuksan et al [39] 2001 Canada	Crossover 3 points	12 healthy subjects *P. quinquefolium* 1, 2, or 3 g (1 time)	Q: Timing and dosing effect on postprandial glycemia A: Good glucoregulation in a time-dependent manner S: None
Vuksan et al [40] 2000 Canada	Crossover 3 points	10 healthy subjects *P. quinquefolium* 3, 6, or 9 g (1 time)	Q: Glucoregulatory effects on healthy subjects A: Good glucoregulation (irrespective of time, dose) S: None
Vuksan et al [41] 2000 Canada	Crossover 3 points	10 pts with type-2 diabetes *P. quinquefolium* 3, 6, or 9 g (1 time)	Q: Glucoregulatory effects on pts with diabetes A: Good glucoregulation (irrespective of time or dose) S: None
Vuksan et al [42] 2000 Canada	Crossover 3 points	10 healthy/9 pts with diabetes *P. quinquefolium* 3 g (1 time)	Q: Glucoregulatory effects on different groups A: Good glucoregulation of both participant groups S: One case of mild insomnia

Pt=patient; ex=extract.

Table 2 Physical performance studies [13,14,43–49]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Yoon et al [43] 2008 Korea	Parallel (3) 3 points	30 healthy subjects Red ginseng 3 g (8 wk)	Q: Effect on aerobic, anaerobic performance, central and peripheral fatigue A: No significant effects S: Not described
Kulaputana et al [13] 2007 Thailand	Parallel (2) 4 points	60 healthy sailors *P. ginseng* 3 g (8 wk)	Q: Effects on exercise performance with lactate threshold A: No significant effect S: Not described
Hsu et al [44] 2005 China	Crossover 2 points	13 healthy men *P. quinquefolium* 1.6 g (4 wk)	Q: Effects on creatine kinase and lactate during endurance exercise A: Decreased creatine kinase, no change in other parameters S: Not described
Engels et al [14] 2003 USA	Parallel (2) 4 points	38 healthy subjects *P. ginseng* ex. (G115) 0.4 g (8 wk)	Q: Effects on heart rate recovery, secretory IgA after exercise A: No significant effect S: Not described
Engels et al [45] 2001 USA	Parallel (2) 4 points	24 healthy women *P. ginseng* ex. (G115) 0.4 g (8 wk)	Q: Effects on recovery from short, supramaximal exercise A: No significant effect S: One case of stomach discomfort
Allen et al [46] 1998 USA	Parallel (2) 4 points	28 healthy subjects *P. ginseng* ex. 0.2 g (3 wk)	Q: Effects on peak aerobic exercise performance A: No significant effect S: Two cases of mild diarrhea
Engels et al [47] 1997 USA	Parallel (3) 4 points	36 healthy men *P. ginseng* ex. (G115) 0.2 or 0.4 g (8 wk)	Q: Effects during graded maximal aerobic exercise A: No significant effect S: Three cases of diarrhea in high-dosage group
Morris et al [48] 1996 Canada	Parallel (3) 4 points	8 healthy subjects *P. quinquefolium* ex. 8 or 16 mg/kg (1 wk)	Q: Effects on physical response to intense exercise A: No significant effect S: Not described
Engels et al [49] 1996 USA	Parallel (2) 3 points	19 healthy female subjects *P. ginseng* ex. 0.2 g (8 wk)	Q: Effect on work performance and energy metabolism A: No significant effects S: Not described

Pt=patient; ex=extract.

3.9. Cardiac function

Six studies investigated the effects of ginseng on cardiac function or disease [65–70]. Three of the studies were of high quality, with a Jadad score of three or more points. Of the studies, four had positive results [67–70] and two had negative findings [65,66], indicating moderate evidence (level 2).

3.10. Pulmonary diseases

Six studies assessed the effects or safety of ginseng on pulmonary diseases [71–76]. Five studies were of high quality, scoring three or more points on the Jadad scale, and all five yielded positive findings [71–75]. Therefore, there is strong evidence (level 1) that ginseng is effective in pulmonary function.

3.11. Cerebrovascular function

Two studies investigated the effects of ginseng on cerebrovascular function [77,78]. One study [78] was of high quality, scoring four points, but the other was of low quality with a score of two points [77]. Both studies showed positive results indicating moderate evidence (level 2).

Table 3 Psychomotor function studies [50–57]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Lee et al [50] 2008 Korea	Parallel (2) 2 points	97 pts with AD *P. ginseng* 4.5 g (12 wk)	Q: Effects on cognitive performance of AD patients A: Significantly effective in the cognitive performance of AD patients S: Two cases of heat sense, one case of dizziness, nausea, anorexia, diarrhea, and headache
Heo et al [51] 2008 Korea	Parallel (3) 2 points	61 pts with AD Red ginseng 4.5 or 9 g (12 wk)	Q: Efficacy for the treatment of AD A: High dose group showed significant improvement in ADAS and CDR S: Two cases of fever (low dose), two cases of nausea (high dose)
Sunram-Lea et al [52] 2005 UK	Crossover 5 points	30 healthy subjects *P. ginseng* ex. (G115) 0.4 g (1 time)	Q: Effects on cognitive performance and mood A: No significant effect, except for "speed of attention" S: Not described
Scholey & Kennedy [53] 2002 UK	Crossover 4 points	20 healthy subjects *P. ginseng* ex. (G115) 0, 0.2, 0.4, or0.6 g (1 time)	Q: Dose-dependent effect on cognitive function A: Improved accuracy and time of responses S: Not described
Kennedy et al [54] 2002 UK	Crossover 4 points	20 healthy subjects *P. ginseng* ex. (G115) 0.4 g (1 time)	Q: Effects on modulation of cognition and mood A: Positively affected cognitive performance S: Not described
Kennedy et al [55] 2001 UK	Crossover 3 points	20 healthy subjects *P. ginseng* ex. (G115) 0.2, 0.4, or 0.6 g (1 time)	Q: Effects on cognitive performance A: Affected cognition in time-/dose-dependent manner S: Not described
Cardinal & Engels [56] 2001 USA	Parallel (3) 4 points	83 healthy subjects *P. ginseng* ex. (G115) 0.2 or 0.4 g (8 wk)	Q: Effects on mood A: No significant effect S: Not described
Ziemba et al [57] 1999 Poland	Parallel (2) 2 points	15 healthy subjects *P. ginseng* ex. 0.35 g (3 wk)	Q: Effects on psychomotor performance A: Improved psychomotor performance S: Not described

Pt=patient; ex=extract; AD=Alzheimer's disease; ADAS=Alzheimer's Disease Assessment Scale; CDR=Clinical Dementia Scale.

3.12. Miscellaneous

The following seven other RCTs were also evaluated: Studies on the biological response to physical exercise [79,80], investigations on the interaction of ginseng and warfarin [81,82], examining side effects of *P. ginseng* and *P. quinquefolium* [83], a study on the effect of ginseng on health-related quality of life (HRQOL) [84] and an examination of body temperature changes after taking ginseng [85].

The trials investigating the effects of ginseng on physical training showed no significant effects [79,80]. *P. quinquefolium* has been shown to reduce the anticoagulant effect of warfarin [82], whereas *P. ginseng* has no interaction with warfarin [81]. The other two trials showed no specific side effects of ginseng and no alteration of superficial body temperature by ginseng [83,85]. The HRQOL trial reported a positive effect of *P. ginseng* on the QOL [84].

3.13. Safety

Thirty of the 57 trials reported the presence or absence of adverse events: 16 reported some side effects, whereas 14 found no side effects during the trials. The 27 other trials did not address the topic. Some side effects were species-related. *P. ginseng* was associated with gastrointestinal problems ranging from stomach discomfort and nausea to vomiting and diarrhea [45–47,67], red ginseng was associated

Table 4 Sexual function studies [58–64]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
de Andrade et al [58] 2007 Brazil	Parallel (2) 2 points	60 subjects with ED Red ginseng 3 g (12 wk)	Q: Effects on ED A: Significantly improved IIEF-5 score S: None
Choi et al [59] 2003 Korea	Parallel (2) 2 points	30 pts with ED Red ginseng 1.8 g (4 wk)	Q: Effect on penile blood flow of patients with ED A: Significantly improved penile blood flow S: One case of gastric discomfort
Hong et al [60] 2002 Korea	Crossover 2 points	45 subjects with ED Red ginseng 2.7 g (8 wk)	Q: Effects on ED A: Significantly improved IIEF-5 score and penile tip rigidity S: Not described
Choi & Choi [61] 2001 Korea	Parallel (2) 1 points	50 pts with ED Red ginseng 1.8 g (8 wk)	Q: Effect on ED A: Significantly effective for ED S: One case of gastric discomfort
Kim & Paick [62] 1999 Korea	Parallel (2) 4 points	26 pts with mild impotence Red ginseng 2.7 g (12 wk)	Q: Effect on vasculogenic impotence A: No significant effect except for sexual satisfaction score S: Not described
Choi et al [63] 1999 Korea	Parallel (2) 2 points	50 pts with ED Red ginseng 1.8 g (12 wk)	Q: Effect on ED A: Significantly effective for ED S: Two cases of constipation, two cases of gastric upset
Choi & Seong [64] 1995 Korea	Parallel (3) 1 points	90 pts with ED Red ginseng 1.8 g (12 wk)	Q: Effect on ED A: Significantly effective for ED S: Not described

Pt=patient; ex=extract; ED=erectile dysfunction; IIEF-5=International Index of Erectile Function-5.

with gastric upset [59,61,63], with one case of hypoglycemia [31], and *P. quinquefolium* was associated with insomnia, headache, chest discomfort, and diarrhea [42,66,83], plus type 2 diabetes mellitus [73].

4. Discussion

As of March 2009, the electronic database MEDLINE contained more than 3400 papers on ginseng-related research. The majority of studies were conducted using animal and *in vitro* experiments. The first clinical trial with ginseng, in 1981, investigated general well-being, reaction time, lung function, and gonadal hormones [86]. Most RCTs studying ginseng have been performed since the late 1990s. Randomized controlled trials provide the best evidence of therapeutic efficacy, pharmaceutical effects, and the safety of drugs, including ginseng [87].

There are two major species of ginseng, i.e., *P. ginseng* (called Korean ginseng or Asian ginseng) and *P. quinquefolius* L. (called American ginseng) [88,89]. *P. ginseng* is found to have the main properties of a ginsenoside, polyacetylene, acid polysaccharide, anti-oxidative aromatic compound, and insulin-like acid peptides. The number of ginsenoside types of *P. ginseng* (38 ginsenosides) is substantially greater than those types present in *P. quinquefolium* (19 ginsenosides) [90]. Red ginseng refers to the steamed and dried form of *P. ginseng* [91]. In the course of the steaming process, ginseng starch is gelatinized, causing an increase in saponin content [9]. Results of clinical research studies have demonstrated that *P. ginseng* may improve psychological function, immune function, and conditions associated with diabetes [2]. The pharmacological effects of American ginseng have been observed in the central nervous, cardiovascular, endocrine, and immune systems [6,82,92]. Traditionally, red ginseng has been used to restore and enhance normal well-being, and is often referred to as an adaptogenic [9]. Accordingly, the RCTs that we reviewed posed various questions, including those

Table 5 Cardiac function studies [65–70]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Stavro et al [66] 2006 Canada	Crossover 3 points	52 hypertensive subjects *P. quinquefolium* 3 g (12 wk)	Q: Effect on hypertension A: No significant effect S: One case of diarrhea and one of headache
Stavro et al [65] 2005 Canada	Crossover 3 points	16 hypertensive subjects *P. quinquefolium* 3 g (12 wk)	Q: Effect on hypertension A: No significant effect S: None
Caron et al [67] 2002 USA	Parallel (2) 3 points	30 healthy subjects *P. ginseng* ex. (Ginsana) 0.2 g (4 wk)	Q: Effects on electrocardiograph A: Increased QTc interval, decreased diastolic BP S: One case of nausea and vomiting
Ding et al [68] 1995 China	Parallel (3) 2 points	45 pts with class IV cardiac function Red ginseng 6 g (15 d)	Q: Effect on congestive heart failure A: Showed significant effect as safe adjuvant S: None
Zhan et al [70] 1994 China	Parallel (3) 2 points	30 pts with mitral-valve disease *P. ginseng* saponins 0.6 or 1.2 mg/kg (10 d)	Q: Effect on myocardial IRI A: Showed protective effect against IRI S: Not described
Zhao [69] 1990 China	Parallel (2) 2 points	481 pts with CHD *P. ginseng* saponins 0.15 g (8 wk)	Q: Effect on aging and angina pectoris due to CHD A: Alleviated aging symptoms and angina pectoris S: None

Pt=patient; ex=extract; BP=blood pressure; IRI=ischemia reperfusion injury; CHD=coronary heart disease; QTc=heart rate-corrected QT.

pertaining to glucose metabolism, physical performance, sexual function, psychomotor function, cardiac function, pulmonary disease, and cerebrovascular function.

We found that ginseng has positive effects on all of these indications, except for physical performance. Strong evidence (level 1) indicates that ginseng improves glucose metabolism, psychomotor function, pulmonary disease, and cerebrovascular function. Notably, 8 of the 12 glucose metabolism RCTs showed positive results for healthy subjects or patients with diabetes mellitus. Numerous reports from both human and animal studies support our review-based results. For example, ginseng has been shown to increase insulin production and reduce cell death in pancreatic beta-cells [93–95]. To our knowledge, this study is the first systematic review of RCTs on the antidiabetic effects of ginseng varieties.

Many animal model-based studies have demonstrated the effects of ginseng, or its ginsenoside components, on anti-neurodegeneration [96], learning, and memory in aged and/or brain-damaged rodents [97,98]. All six psychomotor RCTs used only *P. ginseng*, whereas all of the ginseng varieties were used in the glucose metabolism RCTs.

Half of the pulmonary disease RCTs investigated the preventive effect of ginseng on respiratory illness, and all produced positive evidence [72–74]. This finding is in accordance with experiments using animal models [99,100].

Two RCTs found effects on central neuronal injury, cerebral blood flow, or vascular reactivity [77,78]. This is currently a major medical issue worldwide, because of the high incidence of cerebrovascular conditions and their impact on patient QOL. RTCs examining sexual function and cardiac function yielded moderate evidence (level 2) of ginseng efficacy. A recent systematic review article suggested that the results of seven RCTs investigating therapeutic efficacy in erectile dysfunction showed that red ginseng is effective in the treatment of erectile dysfunction [101]. Although experimental data suggest the potential use of ginseng for hypertension [102,103], two RCTs demonstrated no effect of ginseng on hypertension in our review [65,66].

Ginseng has long been believed to enhance well-being as a representative tonic [104]. However, contrary to our expectation, strong evidence (level 1) indicated that ginseng is no more effective than a placebo in enhancing physical performance.

Table 6 Pulmonary disease studies [71–76]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Vohra et al [71] 2008 Canada	Parallel (3) 5 points	75 children with URTI *P. quinquefolium* ex. 9–26 or 4.5–13 mg/kg (3 d)	Q: Safety and tolerability in the treatment of pediatric URTI (phase-2 study) A: Standard doses (9–26 mg/kg) are appropriate for phase 3 S: No serious adverse events
McElhaney et al [72] 2006 Canada	Parallel (2) 5 points	43 elderly subjects *P. quinquefolium* ex. (COLD-fX) 0.4 g (16 wk)	Q: Effects on prevention of ARI A: Significantly reduced the risk and duration of ARI S: Nonspecific adverse effects
Predy et al [73] 2005 Canada	Parallel (2) 5 points	323 subjects with history of colds *P. quinquefolium* ex. 0.4 g (16 wk)	Q: Effects on prevention of common colds A: Significantly reduced the risk of colds S: Two cases of type-2 diabetes mellitus
McElhaney et al [74] 2004 USA	Parallel (2) 4 points	198 elderly subjects *P. quinquefolium* ex. (CVT-E002) 0.4 g (8–12 wk)	Q: Effects on prevention of ARI A: Effective at preventing ARI S: None
Gross et al [75] 2002 Israel	Parallel (2) 4 points	100 subjects with COPD *P. ginseng* ex.(G115) 0.2 g (12 wk)	Q: Effect on pulmonary function in pts. with COPD A: Improved pulmonary function in pts. with COPD S: None
Scaglione et al [76] 2001 Italy	Parallel (2) 2 points	75 pt with chronic bronchitis *P. ginseng* ex.(G115) 0.2 g (9 d)	Q: Effects on chronic bronchitis A: Significantly effective in bacterial clearance S: Not described

Pt=patient; ex=extract; URTI=upper respiratory tract infection; ARI=acute respiratory illness; COPD=chronic obstructive pulmonary disease.

Table 7 Cerebrovascular function studies [77,78]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Jeong et al [77] 2006 Korea	Crossover 2 points	10 healthy men *P. ginseng*/red ginseng/ fermented red ginseng ex. 0.5 g (1 time)	Q: Effects on cerebral blood flow and cerebrovascular reactivity A: Enhanced cerebrovascular reactivity and increased cerebral blood flow S: None
Kennedy et al [78] 2003 UK	Crossover 4 points	15 healthy subjects *P. ginseng* ex. (G115) 0.2 g (1 time)	Q: Electroencephalograph effects of a single dose of ginseng A: Directly modulated cerebroelectrical activity S: Not described

Pt=patient; ex=extract.

However, all of the RCTs investigating physical performance used healthy volunteers or trained athletes, not patients. One review article, however, noted positive results from a trial using elderly subjects and a high ginseng dose [105].

Our review found that ginseng RCTs addressed heterogeneous questions, even when classified into eight broad categories, including miscellaneous. Therefore, some trials provided insufficient data, and statistical pooling was neither possible nor

Table 8 Miscellaneous [79–85]

Authors Year Country	Design (No. of arm) Jadad score	Pt characteristics Drug Dose (duration)	Questions (Q) Answers (A) Side effects (S)
Biondo et al [79] 2008 Canada	Crossover 2 points	14 healthy sedentary male *P. quinquefolium* ex. 1.125 g (5 wk)	Q: Effects on the immune response to moderate exercise A: No significant effect S: Two cases of mild insomnia and hot flashes
Gaffney et al [80] 2001 Australia	Parallel (3) 3 points	18 trained athletes *P. ginseng* 2 or 4 g (6 wk)	Q: Effects of *P. ginseng* on steroidal hormone indices and immune variables during exercise A: No significant effect S: Not described
Lee et al [81] 2008 Korea	Parallel (2) 3 points	34 pts with ischemic stroke *P. ginseng* 1.5 g (2 wk)	Q: Interaction between warfarin and *P. ginseng* in ischemic stroke patients A: *P. ginseng* does not affect the pharmacological action of warfarin S: No serious side effects
Yuan et al [82] 2004 USA	Parallel (2) 3 points	20 healthy subjects *P. quinquefolium* 2 g (3 d)	Q: Interactions between ginseng and warfarin A: Reduced anticoagulant effect of warfarin S: Not described
Seo et al [83] 2005 Korea	Parallel (5) 5 points	320 healthy men *P. ginseng*/ *P. quinquefolium* 3 g (4 wk)	Q: Side effects of *P. ginseng* and *P. quinquefolium* A: No specific adverse effects of either S: Two cases of chest discomfort in *P. quinquefolium* group
Ellis & Reddy [84] 2002 USA	Parallel (2) 5 points	30 young subjects *P. ginseng* ex. (Ginsana) 0.2 g (8 wk)	Q: Effects on HRQOL A: Improved mental health and social functioning S: One case of nausea and vomiting
Seo et al [85] 2003 Korea	Parallel (5) 5 points	320 healthy men *P. ginseng*/ *P. quinquefolium* 3 g (4 wk)	Q: Effect on superficial body temperature A: No significant effect S: Not described

Pt=patient; ex=*e*xtract; HRQOL=health-related quality of life.

informative. Because trials differed in ginseng variety, indications, dose, participant characteristics, and outcome measures, we performed a qualitative review and opted for a best-evidence synthesis. To maximize objectivity, we adopted the levels of evidence used in the systematic reviews of Cochrane [28]. In these analyses, sound evidence is deduced only from higher-quality studies, which are less likely to be biased. In our review, trials with three or more Jadad points were considered to be high-quality studies. Of the total 57 RCTs, 17 were rated as being of low quality based on the Jadad scale. Low-quality trials are more likely to overestimate efficacy [106]. In our review, low-quality trials tended to show positive results, with 88.2% (15/17) reporting positive findings compared with 45.0% (18/40) in high-quality trials. Therefore, we did not conduct a meta-analysis, which provides a strong analysis of methodologically sound RCT studies [107].

Our study is the largest systematic review of RCT-derived evidence on the clinical efficacies of ginseng. However, our results have some limitations. First, there are insufficient quantitative RCTs of ginseng to provide strong evidence for answering many clinical questions. Second, the RCTs were too heterogeneous in terms of design quality, sample size, species, dose, and duration to draw clear indications. Third, despite an extensive literature search, we may have missed trials and not all trials may have been identified. Moreover, review studies have a publication bias, as negative RCT results tend to have a lower chance of publication.

The safety profile of ginseng is generally good. The exact incidence of adverse effects is unknown, but it appears to be low. Side effects were not correlated with subject characteristics, ginseng species, dose, or duration. Unfortunately, 47.4% of the included RCTs did not investigate side effects.

As the use of herbal products is expanding worldwide, more concerns are being raised about interactions between herbs and conventional drugs, such as that of ginseng with phenelzine or warfarin [108–111]. Two RCTs in this review investigated interactions between ginseng and warfarin [81,82]. This result is important for both physicians and patients, as anticoagulant drugs and ginseng products are often used together.

In conclusion, ginseng is beneficial for glucose control, central nervous system function, prevention of acute pulmonary disease, and cerebrovascular function, but not for enhancing physical performance. This review provides a compact assessment of ginseng use for people interested in ginseng products, as well as physicians. Additional well-designed, large-scale RCTs should be conducted in the future.

Acknowledgments

This study was supported by a grant from the National Research Foundation as a Mid-career Researcher Program (R01-2007-000-11248-0) from the MEST, Republic of Korea.

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