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Ginseng: Review of Recent Evidence

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Introduction

Ginseng is a herb traditionally valued as a tonic and panacea. Its first mention dates to 25 A.D. in the original manual of Chinese medicine, *Shen nung ben tsao jing*, where it is described as an "imperial herb" because of its nontoxic and rejuvenating properties¹. Today, 16-31% of Americans have consumed ginseng in the anticipation that it will enhance their general health and well-being^{2,3}. Ginseng grows primarily in temperate regions of Asia and North America, and belongs to the genus *Panax* (P.). This genus contains up to 14 species (Table 1), with *P. ginseng* and *P. quinquefolius*—sold as Chinese and American ginseng respectively—being the most popular. The root of the ginseng plant is the portion primarily valued for medicinal purposes, and after harvest it is dried under warm air and marketed whole or as a powder, water/alcohol extract, or a supplement¹.

Ginseng contains many medicinally active compounds, and its ginsenosides are the most thoroughly studied. These dammarane-type triterpene glycosides vary according to the positioning of hydroxyl groups and sugar residues, and by the type and number of sugar residues. Over 30 ginsenosides are identified, with the most common being Rb₁, Rb₂, Rc, Rg₃, Rd, Rg₁, Re, and Rf. Often, they are used in comparing ginseng species and assessing their quality. The profile of ginsenosides in ginseng depends on the species, location of growth, cultivation practices, and post-harvest processing¹. To date, a growing number of well designed RCTs have assessed ginseng's clinical efficacy and will be presented herein.

Ginseng: Clinical Research Summary

Well-designed clinical studies have tested ginseng's ability to modulate diabetes, cardiovascular disease, cognition, and physical performance.

Ginseng and Diabetes

Diabetes currently afflicts 9% of the American population, with over 90% of the cases being type 2. A recent systematic review of 42 RCTs on the efficacy of herbs, vitamins, and minerals for glycemic control in individuals with diabetes concluded that the best evidence for efficacy is available for *Coccinia indica* and *P. quinquefolius*⁵.

To date, five RCTs have investigated the effect of pure ground root of *P. quinquefolius* on acute changes in postprandial glycemia in individuals with or without type 2 diabetes^{6,7}. Studies including individuals with type 2 diabetes showed that intake of 3, 6, or 9 g of *P. quinquefolius* with or up to 120 min before a 25 g glucose meal lowered postprandial glucose equally well by 15-20% versus placebo. In healthy individuals, 1 to 9 g of *P. quinquefolius* similarly reduced postprandial glycemia compared to placebo, but only when it was administered between 40 and 120 min

before the glucose meal⁶. The ginsenosides in *P. quinquefolius* might mediate this effect. A study in 13 healthy individuals (age:31±3y) lends supporting evidence, it found that in comparison to placebo, *P. quinquefolius* with 3.2% total ginsenosides lowered postprandial glycemia whereas a batch with 1.7% total ginsenosides did not⁷.

Two long-term RCTs have determined the effect of ginseng on blood glycemia^{8,9}. An 8-week parallel-design study showed that 200 mg/d of an unspecified ginseng versus placebo significantly reduced hemoglobin A1c (HbA1c) in 36 individuals with type 2 diabetes (age: 58.7±7.3y; HbA1c: 6.2%). Unfortunately, body weight also decreased significantly, complicating interpretation of the finding⁸. The other study, which employed a crossover design, found that 8-week treatment with 3 g/d of *P. quinquefolius* versus placebo in 24 individuals with type 2 diabetes (age: 52±9y; HbA1c: 7.2%) significantly reduced HbA1c and fasting blood glucose⁹. Overall, sufficient evidence indicates that *P. quinquefolius* can reduce blood glucose in individuals with and without type 2 diabetes.

Ginseng and Cardiovascular Disease

Ginseng and human cardiovascular research is primarily focused on blood pressure (BP) regulation. Currently, concern exists that ginseng might elevate BP^{10,11}. Such a notion stems from an early prospective study of 133 regular ginseng users. Two-year follow-up revealed that 14 participants taking *P. ginseng* together with caffeinated beverages periodically presented with hypertension, nervousness, nausea, and insomnia. Their average intake of *P. ginseng* equaled 3 g/d, but for some it reached as high as 15 g/d^{10,11}. Importantly, certain caveats of the study precluded the conclusion that ginseng elevates BP. First, the study lacked a placebo group for proper comparison. Second, it failed to assess ginseng authenticity and quality. Also, five of the participants developed hypotension. Since publication of this study, three clinical trials—two RCTs and one non-randomized—found ginseng to be safe for BP regulation¹²⁻¹⁴.

The most recent RCT showed that 4-week parallel-treatment with 200 mg/d of a *P. ginseng* extract versus placebo failed to affect long-term BP control in 29 healthy individuals (age: 22±3y). However, *P. ginseng* did significantly reduce diastolic BP from 75±5 mm Hg to 70±6 mm Hg 120 min after intake on the first day. Also, the QTc interval significantly increased by 0.015 seconds at this same time point in comparison with placebo¹².

A second RCT employing a crossover design found that 8-week *P. quinquefolius* treatment at a dose of 3 g/d significantly lowered systolic/diastolic BP from 137±19/83±9 mm Hg

to 126±18/78±10 mm Hg in 24 individuals with type 2 diabetes (age: 52±9 years; HbA1c: 7.2%). This reduction achieved significance versus placebo¹³.

A non-randomized study investigated the effect of Korean red ginseng (KRG) on BP in 26 individuals with hypertension (age: 59±9y). At baseline, twenty-four hour ambulatory BP equaled 147.9±14.2 mm Hg, after 4-week treatment with 4.5 g/d of placebo it rose non-significantly to 149.3±12.1 mm Hg, then after 8-week treatment with 4.5 g/d of KRG it decreased significantly to 143.6±10.3 mm Hg. Although this study was non-randomized and had treatment phases of unequal length, its findings suggest that KRG might possess BP-lowering activity¹⁴.

Overall, *P. ginseng*, *P. quinquefolius*, and KRG appear to be safe for individuals with hypertension. Also, further testing might reveal ginseng to be an adjunct in BP management.

Ginseng and Cognition

Cognition is a broad term encompassing the processes of memory, perception, and judgment. To date, two long-term and three short-term RCTs have determined how cognitive performance changes following ginseng consumption. An initial long-term study showed that 12-week consumption of a *P. ginseng* extract versus placebo at 200 mg/d significantly improved mental arithmetic testing in 32 healthy individuals (age: 20-24y). The other long-term study, conducted in 112 healthy individuals (age: 40-70 y), demonstrated that 8-9 week treatment with 400 mg/d of a *P. ginseng* extract versus placebo significantly improved reaction time and the Wisconsin Card Sort Test, a putative test of executive function. These findings suggest that chronic *P. ginseng* intake could improve cognition¹⁵.

The first short-term study, conducted in 20 healthy individuals (age: 21±3y), showed that 200, 400, and 600 mg doses of a *P. ginseng* extract significantly improved secondary memory as compared with placebo. The 400 mg dose best exerted this effect; however, the 200 and 600 mg doses actually reduced speed of attention¹⁶. A similarly designed study in 20 healthy individuals (age: 21.2±4y) confirmed that 400 mg of the identical *P. ginseng* extract versus placebo significantly improved secondary memory and accuracy of attention¹⁷. An additional study in 20 healthy individuals (age: 21±3y) employed a more demanding test of cognition—the Serial 7s subtraction task—and found that the 400 mg dose significantly improved accuracy whereas the 200 mg dose significantly reduced performance but also improved accuracy¹⁸. Overall, the effect of *P. ginseng* on acute changes in cognitive performance is dependent on the dose that is used.

Ginseng in Physical Performance and Fatigue

Numerous clinical investigations have examined the ability of ginseng to enhance physical performance and modify fatigued states. Two review articles summarized the evidence on this topic until 2000^{19,20}. Together, they described 13 RCTs that tested the effect of *P. ginseng*, *P. quinquefolius*, and *E. senticosus* on maximal aerobic power, maximal anaerobic power, and physical work capacity in humans of various ages. Of these studies, 12 showed no effect of ginseng on physical performance and modification of fatigue. One study demonstrated in 30 individuals that *P. ginseng* versus placebo at a dose of 1 g/d for 6 weeks improved maximal oxygen uptake, postexercise recovery, pectoral strength, and quadriceps strength. Since these reviews, only one RCT showed improved exercise capacity with *P. ginseng* supplementation. In this study, *P. ginseng* extract G115 at a dose of 200 mg/d for 12 weeks in 49 patients with chronic obstructive pulmonary disease improved maximal oxygen consumption by 37% in comparison with placebo²¹. Overall, ginseng shows little ability to improve physical performance and modify fatigued states in humans.

Ginseng and Adverse Effects and Drug Interactions

Studies have assessed ginseng's potential to cause adverse events and to interact with drugs. A systematic review of 82 clinical trials, representing an exposure population of over 3500 individuals, concluded that the incidence of adverse events associated with *P. ginseng* is equal to that observed with placebo²². In addition, three clinical studies show a low risk for ginseng-drug interaction²³⁻²⁵.

The interaction of *P. ginseng* with a 25 mg dose of warfarin was tested in 12 healthy males (age: 20-40y) through a randomized, crossover trial. Seven-day pretreatment with a *P. ginseng* extract (equivalent to 3g/d *P. ginseng* root) failed to influence the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin. While *P. ginseng* did increase the urinary excretion rate for S-7-hydroxy-warfarin, it did not influence the international normalized ratio and platelet aggregation. *P. ginseng* is ineffective at influencing the activities of cytochrome P450 (CYP) 1A2, CYP3A4, and CYP2C9, the enzymes responsible for warfarin metabolism.

In another study, 14 day treatment with 200 mg/d of a *P. ginseng* extract in 20 healthy individuals

(age: 32±11y) showed no effect on CYP3A activity. As well, after supplementation with 1.5 g/d of *P. ginseng* for 28 days in 12 healthy individuals (age: 25±4y) the activity of CYP3A4, CYP1A2, CYP2E1, and CYP2D6 remained unchanged. Accordingly, *P. ginseng* shows no effect on the general disposition of co-administered medications dependent on the enzyme pathways for elimination described above.

Ginseng in Combination with Multivitamins

Four RCTs have investigated the effect of ginseng with multivitamin/mineral (MVM) complexes on various clinical parameters. A 12-week trial in 501 men and women found that daily consumption of an MVM-*P. ginseng* capsule versus an MVM capsule alone significantly improved quality of life²⁶. Two studies in the same group of 15 smokers (age: 24±3y) showed that daily supplementation of a vitamin E/β-carotene/vitamin C/red ginseng versus placebo for 4-weeks significantly increased plasma antioxidant status^{27,28} and decreased plasma lipid peroxidation²⁷ and oxidative DNA/protein damage²⁸.

In another study, 34 women (age: 45±12y) who consumed ArginMax (ginseng/ginkgo/damiana/L-arginine/MVM) daily for 4-weeks reported a significant improvement in their overall sex life as compared with 43 women (age: 41±12y) taking placebo²⁹. Overall, these studies show that ginseng taken in combination with MVM complexes can cause improvements in the clinical parameters described above.

Conclusion

The best evidence for ginseng's potential to improve clinical conditions is for diabetes and cognition. While ginseng might reduce BP, additional long-term RCTs with different ginsengs are necessary to confirm this. As for physical performance, little evidence demonstrates that ginseng can improve it. Overall, since ginseng's adverse event profile is similar to placebo and its potential to interact with drugs is low, ginseng can be considered safe for general use.

Table 1. The six most common ginseng species.

Latin Name	Region of Cultivation	Marketing Name
Panax ginseng	China and Korea	Chinese white ginseng* Korean red ginseng**
Panax quinquefolius	Canada and United States	American ginseng, Canadian ginseng, or North American ginseng
Panax notoginseng	China	Sanchi ginseng
Panax japonicus	Japan	Japanese ginseng
Panax vietnamensis	Vietnam	Vietnamese ginseng
E. senticosus	Russia	Siberian ginseng

* Panax ginseng that is air-dried after harvest

** Panax ginseng that is high-temperature steamed and then air-dried after harvest

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