*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Panax Ginseng

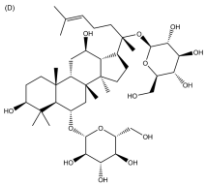
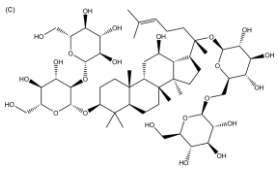
**Evidence Summary**

Some studies have shown that ginseng improves cognitive functions and decreases mortality and cancer risk in humans; safe when taken alone, but some drug interactions are known.

**Neuroprotective Benefit:** Numerous studies have reported cognitive benefit with ginseng in healthy people as well as in dementia patients, but the evidence remains inconclusive due to the lack of large, long-term well-designed trials.

**Aging and related health concerns:** Ginseng intake is associated with lower risks for mortality and cancers; also, some benefits seen in Asian people with ischemic heart disease, diabetes, hypertension, hypercholesteremia, and fatigue.

**Safety:** Numerous meta-analyses have reported that ginseng is generally safe when taken alone; however, ginseng interacts with several medications, and high doses may be associated with insomnia, tachyarrhythmias, hypertension, nervousness, and others.

| | | |
|---|---|---|
| **Availability**: OTC. In clinical trials, a standardized ginseng extract called G115 is often used. | **Dose**: 200-400 mg/day have been tested for cognitive benefit; higher doses for other indications | **Chemical formula:** e.g., $C_{42}H_{72}O_{14}$ (Ginsenoside Rg1); $C_{54}H_{92}O_{23}$ (Ginsenoside Rb1)<br><br>**MW**: e.g., 801.1 (Ginsenoside Rg1); 1109.3 (Ginsenoside Rb1) |
| **Half life**: 0.2-18 hours depending on the ginsenoside | **BBB**: some ginsenosides are penetrant | |
| **Clinical trials**: The largest meta-analysis included a total of 1,549 patients with ischemic heart disease across 18 RCTs. | **Observational studies**: The largest cohort study included 6,282 Korean subjects, of whom 3,680 subjects had used ginseng. |   <br>*Ginsenoside Rg1* *Ginsenoside Rb1* |

**What is it?** Ginseng (typically the root) is extensively used in traditional Chinese medicine to promote longevity, cognitive enhancement, and rejuvenation from stress, weakness, and fatigue, as well as treating illnesses including diabetes, cardiovascular disease, and inflammatory disorders [1]. Ginseng typically refers to plants of the genus *Panax*, which includes at least 11 species. The species most commonly used and studied in herbal medicine is *Panax ginseng*, also referred to as Korean or Asian ginseng. Many other species of *Panax* genus are also widely available, including *Panax quinquefolius* (American ginseng), *Panax japonicus* (Japanese ginseng), and *Panax notoginseng* (pseudoginseng).

Ginsenosides, which are triterpene saponins, are considered the main active compounds that contribute to the purported cognitive effects of ginseng [1]. There are well over 100 ginsenosides. Ginseng and ginsenosides have been reported to have anti-oxidative, anti-inflammatory, anti-neoplastic, and immunomodulatory effects [2].

**Neuroprotective Benefit:** Numerous studies have reported cognitive benefit with ginseng in healthy people as well as in dementia patients, but the evidence remains inconclusive due to the lack of large, long-term well-designed trials.

*Types of evidence:*

- 4 meta-analyses
- 13 clinical trials
- 2 observational studies
- Numerous laboratory studies

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?*

There have been numerous clinical trials and observational studies on ginseng supplementation. While some studies have shown benefit (described below), others have shown lack of benefit [3; 4; 5; 6; 7].

A 2010 Cochrane meta-analysis of 9 double-blind randomized controlled trials in healthy subjects and in those with cognitive impairment reported that ginseng treatment (*Panax genus* extract or ginseng compound HT008-1) for 8-12 weeks suggested improvement in some aspects of cognitive function, behavior, and quality of life [8]. Pooling the data was impossible due to heterogeneity in outcome measures, trial duration, and ginseng dosage. Individual studies within the meta-analysis have shown that ginseng (200 mg/day) treatment significantly improved working memory after 8 weeks and mental arithmetic after 12 weeks [9], while no benefits were seen for attention or concentration. However, in a different study, ginseng treatment (400 mg/day) for 2 days significantly improved speed of attention compared to placebo, while no benefits were seen in quality of memory, speed of memory, working memory, or secondary memory [10]. In an older study, ginseng (400 mg/day) for 8-9 weeks improved selective reminding but did not improve attention, concentration, or psychomotor performance compared to placebo [11].

In a double-blind randomized controlled trial of 30 healthy young adults, a single dose of *Panax ginseng* (G115, 200 mg) significantly improved Serial Sevens subtraction task performance and significantly reduced subjective mental fatigue [12]. This benefit was not observed when a higher dose (400 mg) was ingested. Overall, these data suggest that *Panax ginseng* can improve performance and subjective feelings of mental fatigue during sustained mental activity.

A review of 8 double-blind placebo-controlled studies in healthy subjects compared the cognitive effect sizes for *Panax ginseng*, *Bacopa monnieri*, and modafinil [13]. *Panax ginseng* studies used the standardized extract G115, which contains 4% ginsenosides. Seven of these studies were acute and one of the studies had a duration of 8 days. The highest effect sizes for cognitive outcomes were 0.77 for modafinil (visuospatial memory accuracy), 0.86 for ginseng (simple reaction time), and 0.95 for Bacopa (delayed word recall). Interestingly another measure, reaction time on the 3-back working memory task, showed a large positive effect size (d = 0.806) following acute ginseng administration and also had the largest impairment (d = -0.481) following dosing for 8 days. It is unclear why acute versus chronic ginseng treatment had opposing effects. Authors speculated that ginseng may improve cognitive functions by glucoregulation, modulation of acetylcholine and dopamine activity as well as increasing nitric oxide synthesis [13].

In a prospective cohort study of 6,422 community-dwelling elderly (from the Korean Longitudinal Study on Cognitive Aging and Dementia), those who had higher lifetime cumulative ginseng intake (over 5 years) showed higher cognitive scores (measured by CERAD total scores--Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet neuropsychological battery) compared to the no-use group after controlling for age, sex, education, socioeconomic status, smoking, alcohol intake, cardiovascular disease, and APOE genotype [14]. However, changes in cognitive function over 4 years of follow-up did not differ based on ginseng intake. Percentage of cognitive impairment (MCI or dementia) was significantly lower in the high-use group (24.7%) compared to the low-use group (27.1%), and both groups had lower incidence of cognitive impairment compared to the no-use group (32.6%). However, after controlling for potential covariates, low-use or high-use of ginseng intake was not associated with lower incidence of cognitive impairment. While this study suggests that cumulative ginseng use for longer than 5 years may be beneficial to cognitive function, there may be many confounding factors.

In a 2020 double-blind randomized controlled trial of 52 healthy individuals, Korean red ginseng treatment (1,000 mg/day) for 8 weeks significantly increased the gray matter volume of the left parahippocampal gyrus compared to the placebo group [15]. Also, the composite score of cognitive function significantly increased in the ginseng group by a greater magnitude compared to the placebo group. In terms of specific cognitive domains, the ginseng group showed significant increases (from baseline) in the scores for executive function ($p=0.02$), attention ($p=0.02$), and memory ($p<0.001$). In contrast, the placebo group did not show improvement in executive function ($p=0.12$), attention ($p=0.42$), or memory ($p=0.22$).

In a different 2020 double-blind randomized controlled trial of 50 healthy subjects with a high level of occupational stress, hydroponically cultivated red Panax ginseng was compared to traditionally harvested 6-year-old white Panax ginseng and placebo [16]. The hydroponically cultivated red Panax ginseng (HRG80, lot #PGS190114-001, Botalis SA, Ath, Belgium) came in 420 mg capsules, each containing 210 mg powdered herbal preparation of red ginseng root, consisting of 12%–15% total ginsenosides and 10%–12% rare ginsenosides. The comparator was a Panax ginseng Arkopharma product; each capsule contained 382 mg powdered Panax ginseng Meyer root corresponding to 9.8 mg of total ginsenosides Rg1, Re, Rf, Rh1, Rg2, Rb1, Rc, Rb2, Rd, Rg6, Rh4, Rg3, PPT, Rk1, C(K), Rh2, Rh3, and PPD; and 3.056 mg of rare ginsenosides Rh1, Rg2, Rg6, Rh4, Rg3, PPT, Rk1, C(K), Rh2, Rh3, and PPD. The placebo capsule contained 418 mg rice flour and brown sugar. A statistically significant time x treatment interaction ($p<0.0001$) was observed in the attention d2 test, indicating that the hydroponically cultivated ginseng treatment was more beneficial than the placebo. There was no significant difference between the effects of the traditional ginseng treatment compared to placebo. There was a significant difference between the effects of hydroponic ginseng and traditional ginseng ($p < 0.0001$) on mental performance, which was observed after single (Day 1) and repeated administrations on Days 5 and 12 of treatment. A statistically significant time x treatment interaction ($p<0.0001$) was observed for the memory test, indicating that the hydroponic ginseng treatment was more beneficial than the placebo on Days 5 and 12. The hydroponic ginseng also significantly decreased perceived stress scale ($p<0.0001$) after 5 days of treatment, whereas traditional ginseng decreased perceived stress only after 12 days of treatment. For perceived stress, a statistically significant time x treatment interaction ($p=0.0004$) was observed, indicating that the hydroponic ginseng treatment was more beneficial than the traditional ginseng.

In a 2019 double-blind randomized controlled trial of 55 people with high psychological stress levels (e.g., nurses and firefighters), treatment with Korean red ginseng (6-year-old red ginseng, LAX-101, containing 500 mg of ginseng powder per capsule, manufactured by Korea Ginseng Corporation) for 6 weeks significantly increased triglyceride levels but within the normal range, and decreased epinephrine levels [17]. The triglyceride increase was significantly correlated with epinephrine decrease, and given the role of epinephrine in stimulating triglyceride hydrolysis in adipocytes, Korean red ginseng may stabilize the sympathetic nervous system. In the cognitive function test, a trend for an interaction of group by time was detected between the two groups for correct response time although it did not reach statistical significance ($p=0.056$). The Korean red ginseng group had a shorter correct response time compared to the placebo group in the visually controlled continuous performance test after 6 weeks. No significant differences were observed for psychological measures, including perceived stress level, mood status, and cognitive complaints.

In a 2019 double-blind randomized controlled trial in 90 people with mild cognitive impairment, treatment with Panax ginseng (3 g/day, 4-year-old ginseng containing 53 mg/g ginsenoside, supplied by the Chungbuk Ginseng Cooperative Association) for 6 months did not result in significant benefits in cognitive functions (Korean MMSE, immediate recall, delayed recall) compared to placebo [18]. However, in a few individual cognitive tests, treatment effects were observed. In Rey's Complex Figure Test immediate recall (visual learning) and 20-minute delayed recall (visual memory), there were statistically significant differences between the ginseng group and placebo group ($p=0.0405$, $p=0.0396$, respectively). The authors speculated that the benefits might be partly driven by ginseng's ability to increase choline acetyltransferase levels (based on rodent studies), and increase synaptic plasticity as measured by long-term potentiation. Ginseng and its ginsenosides also exert neuroprotective properties in animal and in vitro studies. However, it is worth noting that the Seoul Neuropsychological Screening Battery included numerous cognitive tests for attention, language, visuospatial function, memory, and frontal executive function. There were no statistical corrections for multiple comparisons, and therefore the findings on Rey's Complex Figure test could be a product of type I error.

*Human research to suggest benefits to patients with dementia*:

In a 2020 systematic review of various randomized controlled trials in Alzheimer's patients, testing various supplements, the overarching conclusion was that benefits of most dietary interventions on cognition in Alzheimer's patients remain inconclusive [19]. This systematic review included 2 randomized controlled trials for ginseng and both trials showed that ginseng supplementation resulted in significant improvement in the cognitive outcomes evaluated [20; 21]. Patients with moderate to severe Alzheimer's disease (criteria: MMSE<20 and CDR score>1) treated with 4.5 g/day of Sun Ginseng (SG-135) showed significant improvement in cognitive functions (measured by ADAS-cog and MMSE) after 12 and 24 weeks of supplementation [20]. Similar results were found with the use of 4.5 and 9.0 g/day of Korean white ginseng in patients with mild to moderate Alzheimer's disease [21]. Compared to control, both doses resulted in improvement in the MMSE and ADAS-cog scores after 12 weeks of supplementation, while the effect disappeared 12 weeks after discontinuation of treatment. The authors of the systematic review noted that there were limitations in the methodological quality of the trials, which prevented them to draw conclusions about the cognitive benefits observed. Further studies with more optimal methodological quality are necessary to evaluate the use of ginseng supplementation in individuals with Alzheimer's disease.

In a 2016 meta-analysis of 4 randomized controlled trials in Alzheimer's patients, the effectiveness of ginseng combined with conventional treatment was inconsistent as measured by MMSE, ADAS-cog,

ADAS-noncog, and CDR [22]. This meta-analysis, the full text of which was unavailable, reported that benefits of ginseng on Alzheimer's patients were still inconclusive. The main limitations of the available studies were small sample sizes, poor methodological qualities and no placebo controls. Larger, well-designed studies are needed to test the effect of ginseng in Alzheimer's patients.

In contrast, an older 2009 systematic review of 2 randomized controlled trials in Alzheimer's patients suggested significant effect in favor of ginseng on the Mini-Mental Status Examination (weighted mean difference (WMD), 1.85; 95% CI, 0.88-2.82) and on the ADAS-cog (WMD, 3.09; 95% CI, 1.08-5.09) [23]. Details of the 2 trials are described below.

The first trial included 97 Alzheimer's patients; *Panax ginseng* treatment (powder, 4.5 g/day) for 12 weeks significantly improved cognitive scores as measured by ADAS-Cog and MMSE [21]. However, after discontinuing ginseng for 12 additional weeks, the improved ADAS and MMSE scores declined to scores comparable to the control group. Although these results suggest that *Panax ginseng* is clinically effective in improving cognitive functions in Alzheimer's patients, effects do not last after discontinuation of ginseng.

The second trial included 61 Alzheimer's patients; high dose *Panax ginseng* treatment (9.0 g/day) showed significant cognitive improvement (ADAS and CDR) after 12 weeks when compared with those in the control group [24]. The ginseng treatment was also associated with improvement from baseline MMSE when compared with the control (1.42 vs. -0.48), but this improvement was not statistically significant.

There has been one controlled trial in 40 moderately severe Alzheimer's patients. Patients who were in the high-dose ginseng group (4.5 g/day) showed improvements in ADAS-cog, ADAS-non-cog, and MMSE scores as early as after 12 weeks, and also at 24-weeks [20]. The results are not conclusive, however, because the control group had higher cognitive scores (ADAS-Cog, non-cog, and MMSE) at baseline. ADAS-Cog in the treatment group ranged from 40-48, while ADAS-Cog in the control group was 30.2.

The longest controlled trial in 61 Alzheimer's patients lasted 2 years. In the low-dose group (4.5 g/day of total powder capsule using a 6-year-old *Panax ginseng* root), the baseline MMSE was 22.0±4.0 and improved to 25.7±3.0 at 48 weeks, and 23.7±4.8 at 96 weeks [25]. In the high-dose group (9.0 g/day), the baseline MMSE was 21.4±6.6, improved to 22.0±5.7 at 48 weeks, and 24.0±3.7 at 96 weeks, showing slight improvement. There was no tendency to decline. ADAS-cog showed similar findings of improvement from 19.7±6.8 (baseline) to 9.5±6.3 (96 weeks) in the low-dose group, and from 23.0±8.7

(baseline) to 12.8±6.8 (96 weeks) in the high dose group. In this study, maximum improvement was observed around 24 weeks, then sustained for 2 years.

*Mechanisms of action for neuroprotection identified from laboratory and clinical research*:

An EEG study in healthy young volunteers reported that a single ingestion of *Panax ginseng* (200 mg, G115) led to a significant shortening of the latency of the P300 component of the evoked potential [26], suggesting that *Panax ginseng* can directly modulate brain electrical activity, and that these effects were more pronounced than those following *Ginkgo biloba*.

Numerous animal studies have shown that *Panax ginseng* (50-100 mg/kg extract or 250-1000 mg/kg crude) or ginsenoside (20 mg/kg) treatments ameliorate cognitive decline associated with diabetes [27], vascular dementia [28], and advanced glycation end (AGE) product [29]. These treatments improved cognitive functions by inhibiting oxidative/nitrosative damage [27], increasing antioxidant enzymes (GSH, SOD) [30], increasing acetylcholine levels (ChAT, VAChT expression) [30], decreasing inflammation (IL-1β, IL-6, TNF-α, NFκB) [27; 29], and decreasing apoptosis (upregulating Bcl-2, downregulating Bax) [28].

Ginsenosides, which are triterpene saponins, are considered the main active compounds that contribute to the purported cognitive effects of ginseng [1]. The half-life of many ginsenosides is short (range, 0.2-18 h) and bioavailability is low [1]. However, many ginsenosides have been reported to cross the blood-brain barrier, including Ginsenoside Rg1 [31; 32]. More details can be found in Cognitive Vitality Reports for Ginsenoside Rg1 and Ginsenoside Rg3.

In a 2020 review of the potential of Panax ginseng for Alzheimer's disease, authors discussed gintonin as a newly identified ginseng constituent that contains lysophosphatidic acids and attenuates Alzheimer's-related neuropathologies [33]. Gintonin inhibits Aβ-induced neurotoxicity and activates the nonamyloidogenic α-secretase activity through the lysophosphatidic acid receptor signaling pathway to reduce Aβ formation, while also increasing acetylcholine and choline acetyltransferase expression in the brain. *In vivo* studies have shown that oral administration of gintonin attenuates brain amyloid plaque deposits, boosts hippocampal cholinergic systems and neurogenesis, and ameliorates learning and memory impairments. Other mechanisms of neuroprotection by ginsenosides and gintonin include attenuation of mitochondrial oxidative stress and neuroinflammation, and enhancement of hippocampal neurotrophic factor expression, and neurogenesis [33].

*APOE4 interactions*: Unknown.

**Aging and related health concerns:** Ginseng intake is associated with lower risks for mortality and cancers; also, some benefits seen in Asian people with ischemic heart disease, diabetes, hypertension, hypercholesteremia, and fatigue.

*Types of evidence:*

- 8 meta-analyses or systematic reviews
- 2 randomized controlled clinical trials
- 3 observational studies
- Numerous laboratory studies

***Lifespan***: POTENTIAL BENEFIT. An observational study of 6,282 Korean people over the age of 55 reported that ginseng intake was significantly associated with decreased all-cause mortality in both men (HR 0.81; 95% CI, 0.74–0.89) and women (HR 0.89; 95% CI, 0.81–0.97) [34]. In this Korean cohort, 1,848 men and 1,832 women were infrequent or frequent ginseng users. After adjusting for age, education, occupation, drinking, smoking, self-reported chronic disease, body mass index, and blood pressure, all-cause mortality for male ginseng users remained significantly lower than that for male nonusers (HR = 0.90; 95% CI, 0.81-0.99). However, this association no longer remained significant in women (HR = 1.03; 95% CI, 0.94-1.13). Cancer-specific mortality was lower in female ginseng users than female nonusers after adjustment for covariates (HR = 0.80; 95% CI, 0.60-1.08). Compared to nonusers, the HR for cancer-specific mortality in women was 0.84 in infrequent users (95% CI, 0.62-1.15) and 0.61 in frequent users (95% CI, 0.32-1.14), though these findings were not statistically significant (p=0.09). Ginseng intake was not associated with cancer-specific mortality in men (HR = 0.95; 95% CI, 0.76-1.20). Mortality caused by cardiovascular diseases was not related to ginseng intake in men or women.

There is also preclinical evidence suggesting lifespan extension with ginseng. A study in *C. elegans* found that *Panax notoginseng* polysaccharides (albeit not from *Panax ginseng*) from the main root prolonged mean lifespan of wild type worms by 21% [35]. The authors attributed this lifespan extension to the elevation of antioxidant enzyme activities (e.g., SOD and catalase) and the reduction in oxidative stress (e.g., lipid peroxidation and malondialdehyde levels). They did not explore which bioactive compounds were responsible for this life-extending effects.

In a study in fruit flies, *Panax ginseng* (Korean red ginseng tonic) extended lifespan, increased resistance to starvation stress, and prevented weight gain [36]. The mean and median lifespans for flies reared on unsupplemented diet were 31.8 days and 33 days, respectively. For the flies given 1.2 µg/ml ginseng supplementation, the mean and median lifespans were 36.4 days and 38 days, respectively. For the flies given 12 µg/ml ginseng (highest dose tested), the mean and median lifespans were 36.1 days and 35 days, respectively. The highest ginseng dose (12 µg/ml) also significantly blocked weight gain while no effects were seen with the 2 lower doses (0.12 and 1.2 µg/ml).

In contrast to these findings, an old 1979 study in mice reported that ginseng treatment for 44 weeks (started at 8 weeks) did not significantly alter mean, median, or maximum lifespans [37]. The dose they used was 8 mg extract/kg/day, corresponding to 40 mg of whole root/kg/day, which the authors noted was roughly comparable to the recommended dose for humans.

***Diabetes***: BENEFIT. A meta-analysis of 8 randomized controlled trials in type 2 diabetes patients (total n=195) reported that ginseng supplementation improved fasting glucose, postprandial insulin, and HOMA-IR levels, though no differences in postprandial glucose or fasting insulin were observed [38]. Types of ginseng and doses used in these studies varied; *Panax ginseng* was used at 3-5 g/day, American ginseng was used at 3 g/day, fermented red ginseng was used at 2.7 g/day, and hydrolyzed ginseng extract was used at 0.96 g/day. Forest plots are shown below.

An older 2014 meta-analysis of 16 randomized controlled trials testing ginseng in people with and without diabetes reported similar findings [39]. Ginseng modestly (statistically significantly) improved fasting blood glucose (mean difference, -0.31 mmol/L, 95% CI,-0.59 to -0.03).

Two other double-blind randomized controlled trials in young healthy adults also reported that an acute treatment with *Panax ginseng* (G115; 200 or 400 mg) significantly lowers fasting blood glucose levels [12; 40].

***Neuropathy***: POTENTIAL BENEFIT. A double-blind randomized controlled study of 61 patients with type 2 diabetes reported that Korean ginseng tablets (500 mg of extract powder, equivalent to taking 3 g of Korean ginseng extract per day) for 24 weeks significantly improved diabetic neuropathy, as measured by the Current Perception Threshold of the lower extremities [41]. Current Perception Threshold levels were improved in those with a longer diabetes duration or those who already had neuropathy at the beginning of the study. Insulin resistance was improved in patients with a shorter diabetes duration. No treatment effects were seen in body mass index, blood pressure, HbA1c, fasting plasma glucose, HOMA-

IR, insulin levels, lipid profiles (total cholesterol, triglyceride, apolipoprotein A1, apolipoprotein B, HDL, and LDL-cholesterol), 8-epi-PGF2α, advanced glycation end product (AGE), or inflammatory markers (hsCRP, IL-6, and TNF-α).

***Obesity***: BENEFIT IN ANIMAL MODELS. A meta-analysis of 16 preclinical studies reported that treatment with *Panax ginseng* significantly reduced body weight than the control group (standardized mean difference, -1.50; 95% CI, -1.90 to -1.11) [42].

***Hypertension***: MIXED, POSSIBLY A SMALL BENEFIT. Several meta-analyses have examined the effects of ginseng on hypertension and blood pressure. A 2017 meta-analysis that included 9 double-blind randomized controlled trials in patients with pre-hypertension or hypertension reported that Korean red ginseng (*Panax ginseng*) treatment reduced blood pressure [43]. In 2 trials testing acute effects of *Panax ginseng*, reductions were seen in systolic blood pressure (mean difference, -6.52 mm Hg) and diastolic blood pressure (mean difference, -5.21 mm Hg). Two other trials failed to show changes in systolic or diastolic blood pressure with North American ginseng. Five RCTs assessed the long-term effects of ginseng, of which 2 studies showed positive effects of *Panax ginseng* on reducing systolic (mean difference, -2.92 mm Hg) and diastolic blood pressure (mean difference, -3.19 mm Hg) compared with placebo.

A 2016 meta-analysis of 17 randomized controlled trials including 1,381 subjects reported no significant effect of ginseng on systolic, diastolic, or mean arterial pressure, though in a stratified analysis, systolic blood pressure appeared to improve non-significantly in people with diabetes, metabolic syndrome, and obesity (mean difference, -2.76 mm Hg) [44].

In a 2020 randomized controlled trial of 80 patients with hypertension or type 2 diabetes, ginseng treatment (1.5 g/day ginsenoside Rg3-enriched Korean red ginseng and 0.75 g/day American ginseng co-administration, containing 75 mg of ginsenoside Rg3 and 375 mg of total ginsenosides) for 12 weeks decreased central systolic blood pressure (-4.69 ± 2.24 mmHg; p=0.04) compared to control and decreased end-systolic pressure (-6.60 ± 2.5 mmHg; p=0.01)[45]. However, there was no significant ginseng effects on reactive hyperemia index (0.09 ± 0.11; p=0.44), pulse-wave velocity (-0.40 ± 0.28 %; p=0.17), and other related pulse wave metrics. Thus, this ginseng combination treatment improved central systolic blood pressure and components of pulse waveform without directly affecting endothelial function. Other indicators of cardiac function, including heart rate, ejection duration, and central diastolic duration did not differ over the 12-week intervention. The ginsenoside Rg3 component has

been suggested to be the most potent ginsenoside to produce a vasodilatory response in animal and in vitro models.

***Cholesterol***: BENEFIT. A 2020 meta-analysis of 27 randomized controlled trials including a total of 1,245 participants (diverse study populations, including healthy people, people with type 2 diabetes, metabolic syndrome, obesity, hypertension, and others) reported that ginseng supplementation (0.3-20 g/day; most studies in the range of 1-3 g/day) did not significantly change the concentrations of total cholesterol, triglyceride, LDL, or HDL cholesterol [46]. However, subgroup analyses showed a significant effect of high dose ginseng supplementation (over 1.5 g/day) on lowering total cholesterol, LDL-cholesterol, and triglycerides. Also, the effects of ginseng on total cholesterol and triglycerides were significant in long-term interventions lasting over 12 weeks.

A 2019 meta-analysis of 18 randomized controlled trials (10 of which in people with metabolic syndrome, 3 in postmenopausal women, 2 in healthy volunteers, and 3 with other inclusion criteria) reported that Panax ginseng supplementation (0.2-20 g/day, median 3 g/day) for 2-12 weeks (median, 8 weeks) may induce a mean difference compared to placebo of -2.30 (95% CI, -3.79 to -0.80) and -1.47 (95% CI, -1.90 to -1.05) mg/dL per g/day of Panax ginseng in the levels of total and LDL-cholesterol, with no significant effects on HDL-cholesterol and triacylglycerides [47]. These findings are in line with some studies with Chinese, Korean, and Japanese traditional herbal formulas that include ginseng (e.g., Chai-Hun-Jia-Long-Gu-Muli-Tang), which have shown protective effects against atherosclerosis [48].

A meta-analysis of 8 randomized controlled trials in type 2 diabetes patients reported that ginseng supplementation (varied; Panax ginseng 3-5 g/day, American ginseng 3 g/day, fermented red ginseng, hydrolyzed ginseng extract, etc.) lowered levels of triglycerides, and total and LDL cholesterol, though no differences were seen in HDL levels [38].

A meta-analysis of 16 preclinical animal studies reported that treatment with *Panax ginseng* significantly increased serum HDL level and lowered serum LDL, triglyceride, and total cholesterol levels compared to the control group [42].

***Ischemic heart disease***: BENEFIT. Ginseng-based medicines and nitrates are commonly used in treating ischemic heart disease (angina pectoris) in China. In a meta-analysis of 18 randomized controlled trials including 1,549 patients with ischemic heart disease, ginseng-based medicines showed greater improvement in symptoms and ECG compared to nitrates [49]. Overall odds ratios (ginseng over nitrates) were 3.00 (95% CI, 2.27-3.96) in symptom improvement (n=18 RCTs) and 1.61 (95% CI, 1.20-

2.15) in ECG improvement (n=10 RCTs). These results suggest that ginseng is more effective than nitrates for treating angina pectoris. However, further randomized controlled trials of higher quality, larger sample size, and longer duration/follow-up are required to verify these results.

***Breast Cancer***: BENEFIT. In a cohort study of 6,282 middle-aged Korean people, cancer-specific mortality was lower in female ginseng users than female nonusers after adjustment of relevant covariates (HR = 0.80; 95% CI, 0.60-1.08) [34]. Compared to nonusers, the HR for cancer-specific mortality in women was 0.84 in infrequent ginseng users (95% CI, 0.62-1.15) and 0.61 in frequent ginseng users (95% CI, 0.32-1.14), though this effect did not reach statistical significance (p=0.09).

In a cohort of 1,455 breast cancer patients from the Shanghai Breast Cancer Study, compared with patients who never used ginseng, regular users had a significantly reduced risk of mortality [50]. Adjusted HRs associated with ginseng use were 0.71 (95% CI, 0.52-0.98) for total mortality and 0.70 (95% CI, 0.53-0.93) for disease-specific mortality or recurrence. Ginseng use after cancer diagnosis, particularly current use, was positively associated with QOL scores, with the strongest effect in the psychological and social well-being domains. Additionally, QOL improved as cumulative ginseng use increased. This study suggests that regular use of ginseng at a dose of 1.3 g per day may improve both overall and disease-free survival and enhance the QOL of Chinese breast cancer survivors.

Numerous preclinical studies have reported that ginseng may inhibit the growth of both estrogen-sensitive and estrogen-insensitive breast cancer cells, induce apoptosis of breast cancer cells, and exert synergistic benefits with chemotherapeutic agents [50].

***Colorectal Cancer***: BENEFIT. In a meta-analysis of 8 observational studies and 1 randomized clinical trial (a total of 7,436 cancer cases out of 334,544 subjects), ginseng intake was associated with reduced risk for colorectal cancer (summary RR=0.77) [51].

Several *in vitro* and *in vivo* studies have shown that ginseng not only reduces the incidence of colorectal cancer, but also improves patients' status by enhancing the effects of chemotherapy drugs [52]. Mechanisms are not entirely clear, but preclinical studies have shown antioxidant and anti-inflammatory effects as well as promotion/induction of apoptosis in cancer cells. For example, ginseng alters mitochondrial membrane permeability, increases cytochrome C release into the cytosol, and activates caspase 3 and 9 to promote cancer cell death. Ginsenosides have also been shown to increase death receptor DR4 expression and activate caspase 3 and 8 [53]. Ginsenosides Rh2, Rg3, and Rk1 inhibit the NF-kB pathway and cell proliferation while inducing apoptosis in cancer cells. Of the bioactive

compounds in ginseng, ginsenosides Rg3 and Rh2 appear to produce the most anticancer effects; however, there is a need for further studies to confirm these findings.

In a mouse model of colorectal cancer, Ginsenoside Rg3 (10 mg/kg/day, intragastric) significantly enhanced the efficacy of radiotherapy by improving the quality of life of mice and shrinking tumor volumes [54]. Rg3 enhanced the antitumor effects of radiotherapy by suppressing NF-κB and NF-κB-regulated gene products (cyclin D1, survivin, COX-2, and VEGF), leading to inhibition of tumors and extension of lifespan in mice with colorectal cancer. The Rg3+radiation combination treatment was also effective in suppressing angiogenesis, as indicated by lower CD31+ microvessel density compared with controls.

***Liver cancer***: POTENTIAL BENEFIT. In a 2020 meta-analysis of 9 studies including 13,866 subjects (of whom 9,235 consumed ginseng), ginseng consumption was associated with a significantly lower risk of developing liver cancer than those not consuming ginseng (OR=0.46; 95% CI, 0.40 to 0.52; p<0.001)[55]. Also, ginseng consumption as adjuvant-therapy was associated with better liver disease control rate (OR=4.47; 95% CI, 2.41 to 8.28; p<0.001), Karnofsky Performance Scale (OR=4.31; 95% CI, 1.80 to 10.36; p=0.001), response rate to chemotherapy (OR=1.79; 95% CI, 1.05 to 3.02; p=0.03), and decline in leukocyte count (OR=0.17; 95% CI, 0.07 to 0.42; p<0.001). However, there was no significant effect of ginseng consumption as adjuvant-therapy on 1-year survival rate (OR=1.48; 95% CI, 0.78 to 2.81; p=0.23), 2-year survival rate (OR=1.69; 95% CI, 0.87 to 3.25; p=0.12), gastrointestinal dysfunction (OR=0.55; 95% CI, 0.17 to 1.79; p=0.32), or hepatic dysfunction (OR=1.15; 95% CI, 0.59 to 2.22; p=0.68).

In contrast, in a 2020 meta-analysis of 14 randomized controlled trials (including a total of 992 subjects) on liver function, ginseng supplementation (0.75-6.0 g/day, most studies used 3 g/day) for 3-24 weeks did not result in any significant changes in alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and albumin levels, though it showed a minor significant increase in bilirubin levels [56]. These findings are in line with toxicological experiments showing that ginseng can weakly inhibit the enzymatic activity of cytochrome P450 (CYP) 2A6, which is responsible for the oxidation of bilirubin in human hepatocytes. Some studies have shown that mildly elevated serum bilirubin concentrations are associated with a lower prevalence of cardiovascular diseases, diabetes, arterial hypertension, and metabolic syndrome [57]. Subgroup analysis by dosage and baseline characteristics revealed a significant increase of bilirubin after ginseng supplementation at a dose equal to or higher than 3 g/day or in unhealthy individuals [56]. The authors noted that it is possible most studies that were included lacked sufficient power to detect statistically significant hepatoprotective effects of ginseng.

Some *in vitro* and *in vivo* studies have reported that ginseng benefits hepatocellular function through its anti-inflammatory (suppression of inflammatory cytokines/chemokines, NF-kB, and COX2), anti-oxidative (increased activities of multiple antioxidant enzymes, reduced oxidative damage biomarkers), and anti-apoptotic (inhibition of caspase-3) properties [56].

***Other Cancers***: BENEFIT. In a meta-analysis of 8 observational studies and 1 randomized clinical trial (a total of 7,436 cancer cases out of 334,544 subjects), ginseng intake was associated with reduced risk for lung cancer (summary RR=0.77), and gastric cancer (RR=0.83) [51]. Because there was only one study for each, meta-analysis data was not available for breast cancer (RR=0.71), hematologic malignancies (RR=0.75), and prostate cancer (RR=0.88).

In a cohort study of 42 patients with stage III gastric cancer, 5-year disease free survival and overall survival rate was significantly higher in patients taking red ginseng powder during postoperative chemotherapy versus control (68.2% versus 33.3%, 76.4% versus 38.5%, respectively, $p < 0.05$) [58]. Red ginseng powder may have some immunomodulatory properties associated with CD3 and CD4 activity in patients with advanced gastric cancer during postoperative chemotherapy. More specifically, flow cytometric analyses for peripheral T-lymphocyte subsets showed that the red ginseng powder restored CD4 levels to the initial preoperative values during postoperative chemotherapy. Depression of CD3 during postoperative chemotherapy was also inhibited by the red ginseng powder ingestion.

***Fatigue***: BENEFIT. A meta-analysis of 12 randomized controlled trials including 630 subjects reported that there was a statistically significant effect of ginseng supplements (9 *Panax ginseng*, 2 *Panax quinquefolius*, and 1 *Panax notoginseng*) on fatigue reduction (standardized mean difference = 0.34; 95% CI, 0.16 to 0.52). However, ginseng supplements were not associated with physical performance enhancement based on 8 trials (SMD = -0.01; 95% CI, -0.29 to 0.27).

In a double-blind randomized controlled trial of 409 patients with colorectal cancer who received modified FOLFOX-6 chemotherapy, Korean red ginseng treatment (2 g/day) for 16 weeks significantly improved cancer-related fatigue compared to the placebo group (p=0.019), particularly in mood and walking ability (p=0.038 and p=0.023, respectively)[59]. In subgroups of female patients over 60 years old, with high compliance (≥80%), or more baseline fatigue, the beneficial effects of Korean red ginseng were more pronounced than those of placebo. However, there were no significant changes in blood cytokines IL-1α, IL-1β, IL-6, or TNF-α in either group. This work was supported by Korea Ginseng Corporation, Republic of Korea.

In a double-blind randomized controlled trial of 47 chronic fatigue patients, Korean red ginseng treatment (3 g/day) for 6 weeks reduced fatigue (Visual Analog Scale; 33.375 ± 23.171), but not significantly more than the placebo group (26.826 ± 23.482)[60]. But a sub-group analysis indicated that patients with initial fatigue score (Visual Analog Scale) below 80 mm and older than 50 years had significantly greater reductions in the fatigue score if they were in the Korean red ginseng group compared to placebo. There were no significant treatment effects on secondary outcome measurements, including markers of antioxidants (d-ROMs, TBARS, BAP, and SOD) or cortisol levels.

In a double-blind randomized controlled trial of 174 people with asthenia (physical weakness or lack of energy), Korean red ginseng treatment (1.8 g/day or 3.6 g/day, with total saponins of 3.5-4.8 g/100g; capsules from Korea Ginseng Corporation) for 4 weeks significantly improved fatigue as assessed by the fatigue self-assessment scale and the traditional Chinese medicine syndrome questionnaire [61]. Notably, the results showed dose- and time-dependent improvements.

***Chronic obstructive pulmonary disease (COPD)*:** LACK OF BENEFIT. In a double-blind randomized controlled trial of 168 patients with COPD from Australia and China, ginseng treatment (100 mg twice daily) for 24 weeks failed to result in a treatment effect compared to placebo on health-related quality of life (St George's Respiratory Questionnaire, the COPD Assessment Test, and the Short Form Health Survey)[62].

**Safety:** Numerous meta-analyses have reported that ginseng is generally safe when taken alone; however, ginseng interacts with several medications, and high doses may be associated with insomnia, tachyarrhythmias, hypertension, nervousness, and others.

*Types of evidence:*

- 4 meta-analyses or systematic reviews
- 4 clinical trials
- Several laboratory studies

***Clinical data***: In a 2019 meta-analysis of 18 randomized controlled studies examining the effects of Panax ginseng (0.2-20 g/day) on lipid profiles, only 2 studies reported adverse events and insomnia was reported with a dose of 2 g/day in one subject, while flushing, gastrointestinal discomfort, and itching was reported in 5 subjects with a dose of 3 g/day [47]. But the incidence of treatment-related adverse events was generally not significantly different between ginseng and placebo groups [59; 63]. However,

high doses of Panax ginseng (more than 2.5 g/day) may cause adverse events such as insomnia, tachyarrhythmias, hypertension, headaches, gastrointestinal issues, and nervousness.

A 2010 Cochrane meta-analysis of 9 double-blind randomized controlled trials using ginseng extract reported no serious adverse events [8]. A newer 2013 systematic review of 30 randomized controlled trials testing any type of ginseng (Korean or American) reported that ginseng is generally safe and no serious adverse effects have been reported [64]. Two trials reported gastric upset and one reported constipation in the intervention group. The other trials reported various adverse effects that were not related to the intervention.

A 2002 systematic review of randomized controlled trials that included data on adverse effects and drugs interactions with *Panax ginseng* reported that the incidence of adverse events with ginseng monopreparations is comparable to that with placebo [63]. The most commonly experienced adverse events were headache, sleep, and gastrointestinal issues. The possibility of more serious adverse events is indicated in isolated case reports and data from spontaneous reports; however, causality is often difficult to determine from the evidence provided. In contrast, combination products containing ginseng as one of several constituents have been associated with serious adverse events and even fatalities. Interpretation of these cases is difficult as ingredients other than *Panax ginseng* may have caused the problems. Collectively, these data suggest that *Panax ginseng* monopreparations are rarely associated with adverse events.

In a meta-analysis of 18 randomized controlled trials in patients with ischemic heart disease, 4 studies reported adverse events, 2 studies reported no adverse events, and 1 study reported 3 subjects experienced a headache in the control group but no adverse events were seen in the ginseng group [49]. Another study reported that 8 participants suffered from headache in the control group and one participant got thirsty.

In a double-blind randomized controlled trial of 90 people with mild cognitive impairment, Panax ginseng treatment (3 g/day) for 6 months resulted in no serious adverse events, and none of the adverse events (which were mild or moderate and transient) were directly related to the ginseng product [18]. However, slight increases in systolic (+4.3 ± 15.3) and diastolic blood pressure (+5.4 ± 11.4) were observed, which were statistically significant compared to the placebo group (systolic, −2.5 ± 13.5; diastolic, 0.7 ± 8.3). No treatment effects were seen for laboratory test results or for pulse rate.

In a small trial in Alzheimer's patients, 2 years of Korean red ginseng (*Panax ginseng*) treatment (4.5 or 9.0 g/day) was not associated with a significant difference in adverse events compared to control groups [25]. Five patients in the low-dose ginseng group, 6 patients in the high-dose ginseng group, and 12 patients in the control group reported adverse effects and withdrew from the study during the first 24 weeks. Participants reported mild symptoms of heat sensation, nausea, diarrhea, and headache, and all subjects who reported adverse events withdrew from the study. However, the adverse events experienced by these patients were generally tolerable and subsided without specific treatment.

In a small trial in moderately severe Alzheimer's patients, there was no significant difference in adverse events between the 3 ginseng treatment groups and the control. At the 24-week follow-up, 4 patients in each group complained of adverse events, including urticaria, headache, palpitation, nausea, and irritability [20]. All patients who reported adverse events withdrew from the study. However, the adverse events experienced by these patients were usually tolerable and subsided without treatment.

***Drug interactions***: Ginseng affects blood sugar levels, and therefore may interact with anti-diabetics (WebMD.com). Ginseng also interacts with warfarin, aspirin, medications for depression, and immunosuppressants (e.g., azathioprine, basiliximab, cyclosporine, tacrolimus, sirolimus, prednisone, and other corticosteroids) (Drugs.com). Ginseng may intensify the effects of caffeine and other stimulants, leading to a rapid heartbeat, sweating, or insomnia. Additional interactions with ginseng have been reported with phenelzine and alcohol [63]. A list of 124 drugs that moderately interact with ginseng can be found at Drugs.com.

In an open-label, randomized clinical study, 15 healthy male volunteers received a single cocktail of CYP and OATP1B1 probe substrates (caffeine 100 mg, losartan 50 mg, omeprazole 20 mg, dextromethorphan 30 mg, midazolam 2 mg, and pitavastatin 2 mg) along with a single or multiple doses of red ginseng extract to examine the pharmacokinetic profiles and drug interactions of red ginseng [65]. The pharmacokinetic profiles after single- or multiple-dose administration of red ginseng extracts were comparable to the corresponding profiles of the control group. *In vitro* studies using human liver microsomes, cryopreserved human hepatocytes, and transporter-overexpressed cells also showed that the drug interaction potential of red ginseng extracts on drug-metabolizing enzymes and transporters were negative.

A rodent pharmacokinetic study reported that *Panax ginseng* (30-100 mg/kg) significantly increased expression of cytochrome p450 CYP3A11 protein in the liver and of organic anion transporter OAT1 in the kidney, and OAT1, OAT3, and multiple drug resistance receptor MDR1 in the liver [66]. Although

there were no significant changes in the metabolism of midazolam, ginseng significantly decreased the systemic exposure of fexofenadine in a dose-dependent manner. Only midazolam and fexofenadine were used as probe drugs; interactions with other drugs were not tested.

**Sources**: *Panax ginseng* and other ginsengs are available OTC as whole root, liquid extract, capsule, and powder forms. All ginseng produced in South Korea is *Panax ginseng*, while ginseng produced in China includes *Panax ginseng* and *Panax notoginseng*. Ginseng produced in the US and Canada is mostly American ginseng (*Panax quinquefolius*). *Panax ginseng* is the most widely studied in clinical studies and contains different types and proportions of ginsenosides compared to other species of ginseng.

Ginseng is a slow-growing perennial herb and the roots take 4-6 years to reach maturity. *Panax ginseng* often comes in either white or red ginseng. White ginseng is fresh ginseng that has been air-dried without being heated. Red ginseng is first steamed, then dried, and has a reddish color. Red ginseng has strong stimulating and restoring effects and is often used in short-term settings for restoring vitality and energy [50]. White ginseng, on the other hand, has a milder effect and is often used for a longer time to promote health and enhance disease resistance.

***G115***: In clinical trials, a standardized ginseng extract called G115 is often used [67]. The quality of G115 follows the US and European Pharmacopoeias. G115 is obtained by ethanol extraction (40% V/V) of the dried roots of Panax ginseng Meyer and standardized on the total content (4%) of major ginsenosides, with a drug extract ratio of 3-7:1. *In vivo* dose escalation or maximum tolerated dose studies with G115 have established an LD50 value higher than 5,000 mg/kg/day and 1,000 mg/kg when administered intraperitoneally for rats and mice, respectively. G115 given to rats at doses of 4,000 mg/kg/day for 20 days resulted in normal levels of hematological and histological biomarkers. G115 administered to beagle dogs in doses up to 15 mg/kg/day for 90 days did not cause subchronic toxicity. In male and female Sprague-Dawley rats, G115 was tested on growth, reproduction, lactation, and maturation, and at doses ranging from 1.5 to 15 mg/kg/day, G115 did not show adverse effects on the reproductive measures evaluated or treatment-related effects on animal behavior, physical appearance, or food consumption.

A significant number of double-blind placebo-controlled clinical trials have tested the efficacy of G115 [67]. Adverse events from G115 treatment are mild and mainly gastrointestinal or sleep-related, including stomach discomfort, nausea, vomiting, diarrhea, constipation, headache, and insomnia. Hypersensitivity reactions such as urticaria and itching as well as burning sensation in the eye have been reported, but these reactions were mild and transient. G115 has been used and marketed as a medical

product worldwide for decades, and the authors are not aware of any serious adverse events that have been reported.

**Doses**: Doses vary across studies and formulations. Ginseng is often taken in doses of 200-400 mg/day (Examine.com). It can also be consumed as soup (e.g., Samgye-tang, which is ginseng chicken soup), tea (Insam-cha, or ginseng tea), liquor (Insam-ju, or ginseng liquor), or in energy drinks.

**Research underway:** There are 44 ongoing clinical trials testing the effects of ginseng, though statuses of many of them are unknown (no updates in the last few years). A new randomized controlled trial just posted on July 6, 2018, will be investigating the acute and chronic effects of an American ginseng root extract on cognition and mood in young adults (age 18-30) (NCT03579095). They will be testing a supplement called Cereboost (200 mg/day) for 14 days versus placebo. This study is estimated to be completed in August 2018. This study was completed in 2019, but no results are posted.

A retrospective study in China is investigating the effectiveness of Chinese herbal medicine in Alzheimer's disease (NCT03221894). The herbal supplement GRAPE granules consist of ginseng, Rehmannia glutinosa, Acorus tatarinowii, Curcuma aromatica, and others. This study was scheduled to be completed in September 2017, but no results have been posted.

**Search terms:**
Pubmed, Google: ginseng

- + meta-analysis, + clinical trial, + cognitive, + memory, + blood-brain barrier, + APOE, + lifespan, + mortality, + cancer

Websites visited for ginseng or ginsenoside:

- Clinicaltrials.gov
- Examine.com
- Treato.com
- DrugAge (4)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Labdoor.com

- ConsumerLab.com
- Cafepharma.com (0)

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