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.

Ginsenoside Rg1

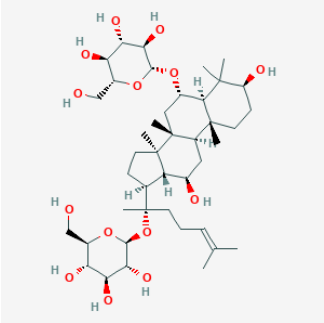
Evidence Summary

Promising for ameliorating cognitive decline, dementia, ischemic stroke, hypertension, diabetes, and arthritis, but no studies in humans exist; Rg1 may have antiplatelet effects and interacts with warfarin.

Neuroprotective Benefit: Numerous preclinical studies suggest that ginsenoside Rg1 promotes neuroprotection by ameliorating amyloid pathology, inhibiting oxidative stress, activating PKA/CREB, and inhibiting apoptosis, but no human studies exist.

Aging and related health concerns: Numerous preclinical studies suggest benefit in models of ischemic stroke, hypertension, diabetes, and arthritis, but no studies have tested ginsenoside Rg1 specifically in humans.

Safety: No studies have tested ginsenoside Rg1 specifically in humans; Rg1 may suppress platelet release reaction, leading to antiplatelet effects. Ginseng (and possibly some ginsenosides) interacts with warfarin, antidepressants, and other drugs.

Availability: research grade only; present in *Panax ginseng*	**Dose**: doses and routes varied widely; in old mice, 6 mg/kg every 3rd day, (orally) corresponded to 2-3 g of ginseng/day in a 60 kg adult human [1]	**Chemical formula:** $C_{42}H_{72}O_{14}$ **MW**: 801.1  Source: PubChem
Half life: 24 min for distribution half-life and 14 hr for elimination half-life, with oral bioavailability of 18.5% [2]	**BBB**: penetrant	
Clinical trials: none specifically testing ginsenoside Rg1	**Observational studies**: none specifically examining Rg1	

What is it? Ginsenoside Rg1 is most abundant in *Panax ginseng* [3](PubChem). There are well over 100 ginsenosides, but ginsenoside Rg1 has been studied extensively for its potential neuroprotective benefits and its ability to improve learning and memory. Ginsenoside Rg1 is thought to induce neuroprotection through ameliorating amyloid pathology, modulating APP, improving cognition, and activating PKA/CREB signaling [3].

Neuroprotective Benefit: Numerous preclinical studies suggest that ginsenoside Rg1 promotes neuroprotection by ameliorating amyloid pathology, inhibiting oxidative stress, activating PKA/CREB, and inhibiting apoptosis, but no clinical studies exist.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- 1 systematic review of preclinical studies
- Numerous laboratory studies

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

No studies have tested ginsenoside Rg1 alone for prevention of cognitive decline or dementia.

Human research to suggest benefits to patients with dementia:
No studies have tested ginsenoside Rg1 alone in patients with dementia.

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

Based on rodent studies, ginsenoside Rg1 does penetrate the blood-brain-barrier [4; 5]. Numerous preclinical studies suggest benefits of ginsenoside Rg1, with one exception. In a cell culture study using PC12 and SN-K-SH cells, ginsenoside Rg1 increased neurite outgrowth, but Aβ-induced cell death was *increased* [6]. Rg1 modestly enhanced the cytotoxicity of Aβ in these cell lines but was not itself cytotoxic. Mechanisms underlying the possible increased cell death are unknown.

Reviews: In a 2018 review of combination therapies for Alzheimer's, ginsenoside Rg1 was highlighted (among many other compounds like berberine, curcumin, etc.) as neuroprotective based on effects on tyrosine kinase receptors, serotonin receptors, glutamate NMDA receptors, and nicotinic acetylcholine receptors (nAChR) and prevention of oxidative damage by inhibiting ROS, lipid peroxidation, and NO production [3]. They concluded that ginsenoside Rg1 promotes cognitive functions by ameliorating amyloid pathology, modulating APP, and activating the PKA/CREB signaling.

In a 2015 systematic review of 12 preclinical studies, a stratified analysis revealed that of all ginsenosides, ginsenoside Rg1 had the greatest effect on acquisition and retention memory in Alzheimer's models [7]. The effect size was significantly higher for both acquisition and retention memory in studies that used female animals compared with male animals, but the reasons for this sex difference are unknown. Additional well-designed and well-reported animal studies are needed to inform further clinical investigations.

Cognitive deficit models: Numerous studies have shown benefits of ginsenoside Rg1 in models of cognitive deficits.

- In middle-aged mice, ginsenoside Rg1 treatment (0.1, 1, or 10 mg/kg, i.p.) for 30 days enhanced long-term memory while facilitating synaptic plasticity (LTP), and increasing dendritic spines in the hippocampus (CA1)[8]. In addition, ginsenoside Rg1 administration regulated the PI3K/AKT pathway (increased hippocampal p-AKT) and increased levels of the neurotrophic factor BDNF and a glutamate receptor subunit GluR1. In another mouse study where ginsenoside Rg1 treatment was started at 12 months of age (6 mg/kg, every 3rd day, orally) and continued until 24 months, spatial

memory was significantly improved while expression of synaptic plasticity-associated proteins (synaptophysin, NMDA receptor subunit 1, PSD-95, and CaMKII-α) in the hippocampus was upregulated [1]. Ginsenoside Rg1 appears to promote the rapamycin pathway.

- Ginsenoside Rg1 treatment (20 mg/kg/day, i.p.) for 28 days improved cognitive impairment induced by D-galactose in aged mice [9]. This treatment also decreased oxidative stress, increased antioxidants (SOD, glutathione peroxidase), and down-regulated the Akt/mTOR signaling pathway.

- In a mouse model of aging (SAMP8 mice), ginsenoside Rg1 (15 mg/kg/day, oral gavage) for 4 months significantly ameliorated memory deficit while regulating mRNA transcripts related to nervous system development and the MAP kinase signaling pathway [10]. In another study in SAMP8 mice, ginsenoside Rg1 treatment (2.5-10 mg/kg) for 3 months significantly and dose-dependently improved learning and memory, reduced soluble Aβ40 in the hippocampus, and dramatically increased phospho-CREB and the neurotrophic factor BDNF [11]. These data suggest that long-term consumption of ginsenoside Rg1 may delay cognitive decline, by affecting Aβ generation, PKA/CREB activity, as well as BDNF content in the brain.

- In a drug (LPS)-induced rat model of cognitive impairment, ginsenoside Rg1 (200 mg/kg/day) for 30 days alleviated cognitive decline as measured by working and spatial memory tests [12]. This treatment also restored levels of the neurotransmitter acetylcholine, its receptor (α7 nAChR), and changes in acetylcholinesterase activity.

- In rats with isoflurane anesthesia-induced cognitive impairment, ginsenoside Rg1 (20 mg/kg) for 7 days significantly prevented cognitive impairment via antioxidant, anti-inflammatory and anti-apoptotic effects (decreased caspase-3) mediated by the PI3K/AKT/GSK-3β pathway [13].

- In a mouse model of sepsis-associated encephalopathy, ginsenoside Rg1 treatment (40 or 200 mg/kg, i.p.) 1 hour before surgery (cecal ligation and puncture) improved survival rate and ameliorated cognitive impairments by decreasing cerebral inflammation (decreased Iba1 activation and inflammatory cytokines) and apoptosis (caspase 3 activation)[14].

Neural stem cell proliferation: Ginsenoside Rg1 appears to promote neural stem cell proliferation and neurogenesis.

- An *in vitro* study using embryonic rat cortical neural stem cells reported that ginsenoside Rg1 (at 0.32 μg/ml) promoted proliferation and glial-like-directed differentiation [15]. Mechanisms are unknown but ginsenoside Rg1 may act similarly to growth factors to promote the proliferation and differentiation of NSCs.

- In a rat model of aging (D-galactose-induced), ginsenoside Rg1 (20 mg/kg/day, i.p.) treatment for 28 days significantly attenuated changes in the hippocampus, including cognitive capacity, senescence-related markers, and hippocampal neurogenesis [16]. Ginsenoside Rg1 protected neural stem cells/progenitor cells by increasing levels of SOX-2 expression; reduced astrocytic activation (decreased Aeg-1 expression); increased hippocampal cell proliferation; enhanced antioxidant enzyme activity (glutathione peroxidase and SOD); decreased proinflammatory cytokines (IL-1β, IL-6 and TNF-α); increased the telomere lengths and telomerase activity; and down-regulated the mRNA expression of cellular senescence associated genes (p53, p21Cip1/Waf1 and p19Arf) in the hippocampus of aged rats.

Alzheimer's models: Numerous studies have shown benefits of ginsenoside Rg1 in models of Alzheimer's.

- In 3xTg-AD mice, ginsenoside Rg1 treatment (20 mg/kg, i.p.) for 6 weeks improved memory and ameliorated depression-like behaviors [17]. Proteomic results revealed a total of 28 differentially expressed hippocampal proteins between Rg1-treated and untreated 3xTg-AD mice. Among these proteins, complexin-2 (CPLX2), synapsin-2 (SYN2), and synaptosomal-associated protein 25 (SNP25) were significantly downregulated in the hippocampus of 3xTg-AD mice compared with the wild-type mice, while ginsenoside Rg1 treatment increased expression of CPLX2 and SNP25 in the hippocampus of 3xTg-AD mice to levels comparable to wild-type mice (and PSD95 and SNP25 were higher in treated mice compared to wild-type mice).

- In APP/PS1 mice, ginsenoside Rg1 treatment (10mg/kg, i.p.) for 30 days significantly ameliorated memory deficits and reduced the accumulations of Aβ42 and phosphorylated-tau [18]. Additionally, BDNF, p-TrkB, and synaptic plasticity-associated proteins were upregulated following ginsenoside Rg1 application. Correspondingly, synaptic plasticity (LTP) was restored following ginsenoside Rg1 application in the APP/PS1 mouse model. Taken together, ginsenoside Rg1 repaired hippocampal LTP and memory, likely through facilitating the clearance of Alzheimer's-associated proteins and through activation of the BDNF-TrkB pathway.

- In APP mice, ginsenoside Rg1 treatment (10 mg/kg/day, i.p.) for 3 months significantly reduced cerebral Aβ levels, reversed certain neuropathological changes, and preserved spatial learning and memory through activation of PKA/CREB signaling [19]. The beneficial effects were seen in aged APP mice even at 12-13 months of age with extensive amyloid pathology and severe neuropathological and cognitive malfunction.

- In primary cultured cortical neurons, ginsenoside Rg1 treatment rescued Aβ-mediated mitochondrial dysfunction as shown by increased mitochondrial membrane potential, ATP levels, activity of cytochrome c oxidase, and decreased cytochrome c release [20]. These findings suggest that ginsenoside Rg1 may attenuate Aβ-induced neuronal death through the suppression of intracellular mitochondrial oxidative stress.

A 2014 review of various medicinal herbs for Alzheimer's treatment has summarized many findings on ginsenoside Rg1 in Alzheimer's models [21]. Mechanisms of action included inhibition of β-secretase, oxidative damage (through inhibition of NO, ROS, and lipid peroxidation), calcium increase, apoptosis (increased Bcl-2, decreased Bax; decreased caspase-3), and pro-inflammatory cytokines (IL-1β, IL-8, TNF-α).

APOE4 interactions: Unknown.

Aging and related health concerns: Numerous preclinical studies suggest benefit in models of ischemic stroke, hypertension, diabetes, and arthritis, but no studies have tested ginsenoside Rg1 specifically in humans.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- Numerous laboratory studies, including one meta-analysis in experimental ischemic stroke

Lifespan: UNKNOWN. No studies have looked at ginsenoside Rg1 specifically for lifespan in humans, though an observational study has reported that *Panax 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) [22](see *Panax ginseng* report for details).

In a mouse model of sepsis (induced by cecal ligation and puncture), ginsenoside Rg1 (20 mg/kg, i.v., started 1 hour after cecal ligation) significantly improved survival (60% vs 30%)[23]. Ginsenoside Rg1 administration suppressed the inflammatory response (IL-10, IL-6, TNF-α) and enhanced bacterial clearance. The lung and liver showed only minor abnormalities in mice that received ginsenoside Rg1. In addition, Rg1 increased neutrophil counts in the peritoneal cavity and inhibited lymphocyte apoptosis in the thymus and spleen.

Cardiovascular: POTENTIAL BENEFIT IN PRECLINICAL MODELS. In mice fed a high fat diet, ginsenoside treatment (ranged, 10-500 mg/kg/d) for 4-8 weeks significantly decreased body weight, total cholesterol, total triglyceride levels, and fat accumulation [24; 25]. Mechanisms included regulation of transcription factors and lipid metabolism-related genes [25], increased phosphorylation of AMP kinase [24; 25], and inhibition of insulin resistance [24].

Also, in a rodent model of chronic thromboembolic pulmonary hypertension, ginsenoside Rg1 treatment for 1 month positively affected myocardial remodeling and pulmonary hemodynamics by upregulating MMP-2 and MMP-9 [26]. In another study in spontaneously hypertensive rats, ginsenoside Rg1 (5-20 mg/kg, i.p.) for 1 month improved the aortic outward remodeling by lowering the lumen diameter and reducing the media thickness [27]. Furthermore, ginsenoside Rg1 attenuated heart and kidney damage with improvement on cardiac and glomerular structure.

Cell culture studies have also reported that ginsenoside Rg1 inhibits vascular smooth muscle cell senescence (by inhibition of the p16INK4a/Rb and p53-p21Cip1/Waf1 signaling pathways)[28] and promotes endothelial progenitor cell proliferation and vasculogenesis while inhibiting cell senescence [29].

Ischemic stroke: POTENTIAL BENEFIT IN PRECLINICAL MODELS. In a meta-analysis of 11 preclinical studies in experimental ischemic stroke, all studies reported significant effects of ginseonside Rg1 for improving the neurologic function score when compared with the control group, and 4 studies reported significant effects of ginsenoside Rg1 for reducing infarct volume [30]. There were also studies reporting that ginsenoside Rg1 was more efficacious than the positive control drug nimodipine (0.7 or 1 mg/kg, intraperitoneal) according to the neurologic function score and infarct volume data. The results are positive, but effect sizes might be overestimated due to publication bias. Treatment paradigms ranged but most were started before the onset of ischemia and some included treatments both before and after ischemia. It is not clear whether ginsenoside Rg1 would be effective when given after the ischemic event.

Diabetes: POTENTIAL BENEFIT IN PRECLINICAL MODELS. Studies in a rat model of type 2 diabetes (streptozotocin-induced diabetes) reported that ginsenoside Rg1 treatment (10-50 mg/kg/d, i.p. or oral gavage) for 8-12 weeks improved blood glucose, insulin resistance [31], liver function [31], cardiac function (including myocardial lesions), and cardiomyopathy [32]. Ginsenoside Rg1 also reduced oxidative stress and attenuated myocardial apoptosis (by reducing caspase 3 and increasing Bcl-xL and levels of antioxidants such as SOD, catalase, and glutathione peroxidase)[32]. Other mechanisms of action included anti-apoptotic effects via inhibition of JNK activity, suppression of inflammation [31], and inhibition of ER stress-induced apoptosis [32].

Arthritis: POTENTIAL BENEFIT IN PRECLINICAL MODELS. Several preclinical studies have reported that ginsenoside Rg1 treatment may alleviate arthritis. In a rat model of adjuvant (LPS)-induced arthritis, ginsenoside Rg1 (5, 10, 20 mg/kg, i.p.) for 14 days significantly alleviated joint swelling while significantly reducing inflammation (decreased TNF-α and IL-6, increased PPAR-γ protein expression, inhibition of IκBα phosphorylation and NF-κB nuclear translocation) in the inflammatory joints [33].

In a different rat model of anterior cruciate ligament transection (model of osteoarthritis), ginsenoside Rg1 treatment (30 or 60 mg/kg, oral gavage) for 8 days (started 4 weeks after the transection) attenuated cartilage degeneration, and reduced type II collagen loss and MMP-13 levels [34]. Rg1 treatment inhibited IL-1β-induced chondrocyte gene and protein expressions of MMP-13, COX-2 and PGE2, and prevented type II collagen and aggrecan degradation. These effects were observed in a dose-dependent manner.

Safety: No studies have tested ginsenoside Rg1 specifically in humans; Rg1 may suppress platelet release reaction, leading to antiplatelet effects. Ginseng (and possibly some ginsenosides) interacts with warfarin, antidepressants, and other drugs.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- A few laboratory studies

Numerous meta-analyses and systematic reviews have reported that *Panax ginseng* is generally safe [35; 36; 37](see *Panax ginseng* report). However, no clinical studies have tested the safety or tolerability of ginsenoside Rg1 specifically. A review of potential combination therapies for Alzheimer's discussed a

study suggesting that ginsenosides interact with warfarin, resulting in decreased anticoagulant effects of warfarin in patients whose warfarin therapy had been stable previously [3]. The original article was not accessible, though based on the abstract, it was a single case study and not specific to ginsenoside Rg1 [38]. Still, because of the potential for platelet inhibition, ginseng supplements may not be recommended to use for at least one week before and after surgery.

Drug interactions: Ginseng interacts with warfarin, medications for depression, and immunosuppressants (e.g., azathioprine, basiliximab, cyclosporine, tacrolimus, sirolimus, prednisone, and other corticosteroids) (Drugs.com). Of compounds present in *Panax ginseng*, panaxynol is the most active antiplatelet component—it inhibits the aggregation, release reaction, and formation of thromboxane (induces platelet aggregation and arterial constriction) in rabbit platelets [39]. Ginsenosides Rg1 (and Ro and Rg2) suppressed the release reaction only.

Ginseng affects blood sugar levels, and therefore may interact with anti-diabetics (WebMD.com). It is not known which component of ginseng affects blood sugar levels. In addition, ginseng may intensify the effects of caffeine and other stimulants, leading to a rapid heartbeat, sweating, or insomnia.

Sources and dosing: Only research grade Ginsenoside Rg1 is available. In old mice (C57BL/6J mice), 6 mg/kg every 3rd day (orally) improved cognitive performance and increased synaptic proteins [1]. The authors noted that the dose corresponded to 2-3 g of ginseng/day in a 60 kg adult human.

Research underway: No clinical trials testing Ginsenoside Rg1 specifically are currently ongoing. There are also no grants funded through NIH that is testing Ginsenoside Rg1 specifically. There are 36 ongoing clinical trials testing the effects of ginseng, though statuses of many of them are unknown (no updates in the last few years).

Search terms:
Pubmed, Google:

- + meta-analysis, + clinical trial, + cognitive, + memory, + Alzheimer, + APOE, + lifespan, + mortality, + cancer, + arthritis, + cardiovascular, + atherosclerosis, + diabetes, + safety, + adverse

Websites visited for ginsenoside Rg1:

- Clinicaltrials.gov (0)
- Examine.com (ginseng)

- Treato.com (ginseng, ginsenoside Rg1 both unrated)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)
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