



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.

Gintonin

Evidence Summary

Preclinical studies show consistent neuroprotective benefits in many models of neurodegenerative diseases, but due to the limited human data to date for gintonin specifically, safety is not established.

Neuroprotective Benefit: Preclinical studies in many neurodegenerative disease models show consistent neuroprotective benefits through neurogenesis, anti-inflammatory/antioxidant effects, and autophagy. But only 1 small study in humans exists to date.

Aging and related health concerns: No studies have examined the effects of gintonin on age-related diseases in humans. Although preclinical evidence is very limited, gintonin may benefit metabolism, physical endurance, and cancer.

Safety: In contrast to the rich evidence for *Panax ginseng*, only one small open-labeled study has been carried out to date for gintonin. Optimal dosing and long-term safety of gintonin have not been established.

<p>Availability: not available, but methods for preparing gintonin-enriched fraction from ginseng have been published</p>	<p>Dose: not established; The only clinical study published to date used a dose of 300 mg per day.</p>	<p>Chemical formula: contains proteins, lipids, and carbohydrates; the 4 main bioactive components are lysophosphatidic acids, lysophosphatidylinositols, linoleic acid, and phosphatidic acid</p>
<p>Common/preferred brand: N/A</p>		
<p>Half life: not established</p>	<p>BBB: likely penetrant, via a paracellular pathway</p>	<p>MW: approximately 67 kDa</p>
<p>Clinical trials: One small open-label clinical study included 9 cognitively-impaired subjects.</p>	<p>Observational studies: There have been numerous observational studies on ginseng intake, but none specifically on gintonin.</p>	

What is it? Gintonin is a relatively recently identified glycoprotein found in the root of *Panax ginseng*. It contains carbohydrates, lipids, and proteins, such as ginseng major latex-like protein and ginseng ribonuclease-like storage proteins ([Im and Nah, 2013](#)). The 4 main bioactive components are lysophosphatidic acids (LPA, C18:2), lysophosphatidylinositol, linoleic acid, and phosphatidic acid. Gintonin has 3- to 130-fold greater affinity for LPA G protein-coupled receptors than free LPA, possibly because the protein components of gintonin may function as LPA carriers to LPA receptors while protecting LPA from breakdown. Gintonin linoleic acid and lysophosphatidylinositol interact with GPR40 and GPR55 and promote insulin secretion ([Choi et al., 2021](#)). Gintonin also activates endogenous G protein-coupled LPA receptor signaling pathways and induces transient elevation of intracellular Ca²⁺ levels via the activation of Gq/11 protein-coupled receptors ([Shin et al., 2012](#); [Rajabian et al., 2019](#)). Gintonin-mediated increases in intracellular calcium levels are thought to underlie gintonin's effects on neurotransmitter release, autophagic flux, and cognitive enhancement ([Choi et al., 2021](#)). Because of these mechanisms of action, gintonin has been extensively studied in preclinical models of neurodegenerative diseases ([Jakaria et al., 2020](#)).

Panax ginseng has many active components and the most studied have been the ginsenosides. It appears that gintonin has opposite effects from ginsenosides and may balance out the entire effect of ginseng ([Im and Nah, 2013](#)). For example, gintonin and LPA activate many cellular responses via G protein-coupled receptor activation while ginsenosides stabilize membrane potentials via modulation of ion channels. Also, gintonin induces a transient increase in Ca²⁺, while ginsenosides inhibit Ca²⁺ influx. As



research with gintonin is relatively recent, it is not clear yet how the actions of gintonin and ginsenosides interact.

Neuroprotective Benefit: Preclinical studies in many neurodegenerative disease models show consistent neuroprotective benefits through neurogenesis, anti-inflammatory/antioxidant effects, and autophagy. But only 1 small study in humans exists to date.

Types of evidence:

- 1 open-label clinical study
- Numerous laboratory studies

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

None available.

Human research to suggest benefits to patients with dementia:

In a small open-label clinical study of 9 subjects with cognitive impairment (early dementia or mild cognitive impairment), gintonin treatment (300 mg/day) for 12 weeks improved cognitive scores ([Moon et al., 2018](#)). The Korean Mini Mental State Examination score improved significantly on week 4 ($p=0.047$) and week 8 ($p=0.015$) compared with the baseline. The Korean AD assessment scale cognitive subscale (ADAS-Cog) score decreased significantly at week 4 ($p=0.028$) and continued to decrease at subsequent visits, although the differences were not statistically significant. The ADAS-noncognitive subscore also showed a significant improvement at week 4 ($p=0.006$). Overall, improvements were seen at early time points and not sustained at subsequent follow-up evaluations. The study was small and there was no placebo control, so it is not clear if the cognitive improvements were due to practice effects or occurred due to chance. A larger placebo-controlled trial is warranted.

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

Gintonin has been studied most extensively in aging-related neurodegenerative diseases, in preclinical models of Alzheimer's, Parkinson's, Huntington's, and others. The mechanisms of action of gintonin for neuroprotection include: 1) increased expression of neurotransmitter (acetylcholine and dopamine) synthesis enzymes; 2) increased hippocampal neurogenesis; 3) decreased oxidative stress leading to decreased neuronal apoptosis and neuroinflammation; 4) restoration of the blood-brain-barrier integrity; and 5) increased autophagy ([Choi et al., 2021](#)).



In vivo and *in vitro* studies in rodents have shown that gintonin enters the brain and binds to brain cells, including neurons, astrocytes, and oligodendrocytes ([Kim et al., 2018](#)). Gintonin also induces a rapid and transient opening of the blood-brain barrier and enhances the delivery of low and high molecular weight molecules to the brain via a paracellular pathway. Gintonin achieves these effects by causing morphological changes via the LPA receptor and ROCK pathway, increasing junctional spaces, and altering levels of junctional proteins (e.g., vascular endothelial-cadherin, occludin, zonula occludens 1, and claudin-5).

Cognitive impairment models: In a mouse model of cognitive impairment (D-galactose-induced hippocampal senescence mice), gintonin treatment (50 or 100 mg/kg/day, orally) for 4 weeks restored the D-galactose-induced memory deficits by enhancing hippocampal LPA1 receptor expression, synaptic plasticity (i.e., LTP), and neurogenesis ([Nam et al., 2018](#)). Gintonin treatment also increased expression of phosphorylated CREB (associated with learning and memory) in the hippocampal dentate gyrus of these mice. Gintonin treatment (25, 50, or 100 mg/kg) for 3 weeks also attenuated scopolamine-induced memory impairment ([Kim et al., 2015](#)).

Alzheimer's disease models: In a mouse model of Alzheimer's disease (APP^{swe}/PSEN-1 double transgenic mice), treatment with gintonin-enriched fraction (50 and 100 mg/kg, orally, 3 times a week) for 3 months increased the number of hippocampal neurons (as measured by BrdU incorporation) ([Kim et al., 2016](#)). In the same mouse model, treatment with gintonin-enriched fraction (25 or 50 mg/kg) for 3 months attenuated cholinergic dysfunctions (increased levels of acetylcholine and ChAT, decreased AChE), which was mediated by the activation of G protein-coupled LPA receptors ([Kim et al., 2015](#)). Another study using the same mouse model reported that gintonin treatment attenuated amyloid plaque deposition as well as short- and long-term memory impairment ([Hwang et al., 2012](#)). Gintonin promoted the release of soluble amyloid- β protein precursors (sA β PP α) produced via non-amyloidogenic pathways in a concentration- and time-dependent manner. Gintonin treatment also attenuated cytotoxicity and microglial activation, leading to decreased neuroinflammation. In summary, gintonin's neuroprotective effects in Alzheimer's models included 1) activation of non-amyloidogenic pathways, resulting in the formation of beneficial sA β PP α rather than the neurotoxic A β ; 2) restoration of the brain cholinergic system; and 3) stimulation of hippocampal neurogenesis ([Choi et al., 2021](#)).

Parkinson's disease models: In a mouse model of Parkinson's disease (MPTP-treated mice), gintonin pre-treatment (100 mg/kg, orally) for 12 days significantly ameliorated motor function (as measured by pole and rotarod tests) and significantly improved survival rate ([Choi et al., 2018](#)). These effects occurred concurrently with the increased preservation of dopaminergic neurons (tyrosine hydroxylase-



positive neurons), decreased microglial activation, decreased pro-inflammatory mediators (IL-6, TNF and COX-2), and maintenance of the blood-brain barrier integrity in the motor regions of the brain (substantia nigra pars compacta and/or striatum). Gintonin treatment also activated the antioxidative transcription factor Nrf2 and its pathways, while inhibiting the MAPK and NFkB signaling pathways that promote cytokine production. In this mouse model, gintonin inhibited the death of dopaminergic neurons from MPTP-induced neurotoxicity via anti-inflammatory and anti-oxidant mechanisms, through the regulation of LPA and LPA receptor-mediated signaling pathways. Gintonin also maintained blood-brain barrier integrity. In another mouse study (MPTP mice), gintonin treatment reduced α -synuclein accumulation in the substantia nigra and striatum ([Jo et al., 2019](#)). The neuroprotective effects of gintonin were mediated by the antioxidative Nrf2/HO-1 signaling pathway, which reduced proinflammatory cytokines, apoptotic markers, astrocytosis, and microgliosis.

Huntington's disease models: In two mouse models of Huntington's disease (3-NPA-induced striatal toxicity and N171-82Q-mutant HTT overexpression), treatment with gintonin-enriched fraction (25-100 mg/kg/day, orally) mitigated neurological impairment and reduced mortality ([Jang et al., 2019](#)). Gintonin pretreatment also attenuated mitochondrial dysfunction, reduced proinflammatory cytokines (i.e., IL-1 β , IL-6, TNF- α , COX-2, and iNOS), decreased microglial activation, and prevented primary and secondary cell death. In a cell culture model (STHdh cells), gintonin also reduced cell death and mutant huntingtin aggregates.

Wild-type mice: In mice, daily administration of gintonin for 1 week significantly improved fear memory in the contextual fear-conditioning test, while increasing the expression of phosphorylated CREB, associated with learning and memory, and the neurotrophic factor BDNF ([Kim et al., 2016](#)). Gintonin treatment also increased synaptic plasticity, as measured by long-term potentiation in the hippocampus.

In mice, treatment with gintonin-enriched fraction (50 and 100 mg/kg, orally, 3 times a week) for 3 months increased the number of hippocampal neurons (as measured by BrdU incorporation) ([Kim et al., 2016](#)). Treatment with gintonin-enriched fraction (50 or 100 mg/kg, oral) also changed mouse hippocampal gene expressions associated with memory, cognitive, anti-stress and anti-anxiety functions, and neurodegeneration, as indicated by the overexpression of choline acetyl transferase (critical for synthesis of the neurotransmitter acetylcholine), β 3-adrenergic receptor (increases serotonin synthesis), and corticotrophin-releasing hormone (regulates cortisol secretion), and decreased expression of tryptophan 2,3-dioxygenase (a protein increased in Alzheimer's patients) ([Lee et al., 2021](#)).



Cell culture: In cortical and hippocampal neurons, gintonin treatment activated LPA receptors, mobilized calcium levels, and enhanced both excitatory and inhibitory neurotransmission ([Park et al., 2015](#)). Gintonin-mediated LPA receptor activation resulted in synaptic enhancement and an increase in excitatory synaptic transmission in a phospholipase C-dependent manner. Gintonin also enhanced inhibitory neurotransmission but through a different mechanism.

In primary cortical astrocytes, gintonin administration induced autophagy by stimulating the AMPK-mTOR signaling pathway and elevating autophagic flux ([Rahman et al., 2020](#)). In cortical astrocytes, gintonin treatment dose- and time-dependently upregulated the lysosomal membrane protein, LAMP1 and the autophagy marker LC3.

Although neuroprotective activities of ginseng have been attributed in part to increased transcription of the neurotrophic factor BDNF, active components of ginseng such as ginsenoside and gintonin did not activate Bdnf transcription in neuronal cultures ([Fukuchi et al., 2019](#)).

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have examined the effects of gintonin on age-related diseases in humans. Although preclinical evidence is very limited, gintonin may benefit metabolism, physical endurance, and cancer.

Types of evidence:

- Several laboratory studies

Physical endurance: POTENTIAL BENEFIT IN MICE

In fasted mice, systemic administration of gintonin (30-100 mg/kg, i.p.), but not ginsenosides, increased blood glucose concentrations in a dose-dependent manner and enhanced performance on the rotarod test ([Lee et al., 2016](#)). Gintonin acted via the LPA-catecholamine-glycogenolysis axis, which in turn increased the supply of glucose to enhance physical performance and stamina on the rotarod test.

Metabolism: POTENTIAL BENEFIT IN MICE

No studies have examined the effects of gintonin on metabolism or obesity in humans. In mice and in adipocytes, treatment with gintonin-enriched fraction reduced lipid accumulation by reducing the expression of pro-adipogenic and lipogenic factors, and increased lipolysis and thermogenesis through activation of protein kinase A ([Lee et al., 2020](#)).



Cancer: POTENTIAL BENEFIT IN MICE

Autotaxin is a process responsible for metastasis, triggered by the overproduction of LPA in cancers. However, LPA, particularly LPA C18:2, is a strong negative feedback autotaxin inhibitor. In a mouse model of melanoma (melanoma cells injected into the tail vein), gintonin treatment at a daily dose of 25, 50, and 100 mg/kg (orally) for 3 weeks resulted in 24.8 ± 5.8 , 10.2 ± 3.4 and 1.8 ± 0.7 nodules, respectively, compared to 26.2 ± 3.2 nodules in the saline control group ([Hwang et al., 2013](#)). Gintonin treatment also inhibited lung metastasis in this mouse model. Additionally, gintonin treatment significantly suppressed the tumor growth induced by subcutaneous grafts of melanoma cells. Gintonin reduced tumor necrosis, the pleomorphism of tumor cells, tumor cell mitosis, and angiogenesis and these effects appeared to be mediated by the inhibition of autotaxin activity.

Inflammation: POTENTIAL BENEFIT BASED ON IN VITRO STUDIES

In cell culture (RAW 264.7 cells), gintonin potently suppressed nitric oxide production and levels of proinflammatory cytokines (iNOS, COX-2, IL-1 β , IL-6, and TNF- α), while increasing levels of mir-34a and mir-93 ([Saba et al., 2015](#)). Gintonin mediated its effects via canonical NF- κ B and MAPK pathways without affecting the levels of ERK.

Safety: In contrast to the rich evidence for *Panax ginseng*, only one small open-labeled study has been carried out to date for gintonin. Optimal dosing and long-term safety of gintonin have not been established.

Types of evidence:

- 1 open-label clinical study
- Several laboratory studies

In a small open-label clinical study of 9 subjects with cognitive impairment (early dementia or mild cognitive impairment), gintonin treatment (300 mg/day) for 12 weeks did not result in any adverse events throughout the study period ([Moon et al., 2018](#)). Adverse events that had previously been associated with *Panax ginseng*, such as facial flushing, headache, dizziness, and gastrointestinal disorders, were not observed in participants consuming gintonin daily. No laboratory abnormalities were found with gintonin treatment in any of the participants. However, the study was open-label and included only 9 subjects. The maximum tolerable dose and long-term safety of gintonin have not been established.

While gintonin is a large molecule with an apparent molecular weight of 67 kDa, studies using two model systems reported that gintonin could be absorbed in the intestine through transcellular and paracellular diffusion, and active transport ([Lee et al., 2018](#)). It is thought that the lipid component of gintonin may play a role in the intestinal absorption.

Drug interactions: Drug interactions have not been studied. Ginseng has been shown to be a mild inducer of CYP3A4 and decreases anticoagulant activity of warfarin, but it is not known if gintonin also has these actions ([Rajabian et al., 2019](#)).

Sources and dosing: Gintonin is not available commercially. Methods to prepare gintonin-enriched fractions from ginseng have been published. One method is brief and uses just ethanol and water ([Choi et al., 2015](#)). Ginseng is extracted with ethanol and the extract is fractionated with water to obtain water-soluble and water-insoluble fractions. The water-insoluble precipitate (but not the water-soluble supernatant) induced a large $[Ca^{2+}]_i$ transient in primary astrocytes and therefore deemed to be the gintonin-containing fraction. The yield of gintonin-enriched fraction using this method was 1.3%, but approximately 6-fold higher than that obtained by a previous method (0.2%). The yield of gintonin is about 0.2% in 4-year-old white ginseng and 6-year-old red ginseng, although the amount of gintonin is higher than individual ginsenosides ([Choi et al., 2021](#)). The small open-label clinical study of 9 subjects with cognitive impairment (early dementia or mild cognitive impairment) tested gintonin tablets (300 mg/day) that were manufactured following the above protocol ([Moon et al., 2018](#)).

Patents on gintonin: Several patents have been filed for gintonin ([Rajabian et al., 2019](#)). A Chinese patent, CN105477035 (A), reported that a composition containing gintonin was protective against memory and learning deficits in rats while attenuating amyloid plaque deposition and oxidative stress. In a Korean patent, KR20150041297 (A), the inventors introduced a composition comprising gintonin which promoted acetylcholine synthesis and choline acetyl transferase activity while improving learning and memory in mouse models of Alzheimer's disease (A β infusion and APP/PS1 transgenic mice). Another Korean patent KR20160062364 (A) provided a composition containing gintonin for improving synaptic transmission in the hippocampus and enhancing cognitive function. These neuroprotective benefits were seen through activation of LPA receptor that in turn increased phosphorylation of CREB and the expression of the neurotrophic factor BDNF.

Research underway: There are no clinical trials ongoing that are testing gintonin as an intervention, based on ClinicalTrials.gov. There are no NIH-funded programs that are specifically investigating gintonin.



Search terms:

Pubmed, Google:

- gintonin

Websites visited for gintonin:

- Clinicaltrials.gov (0)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- PubChem (0)
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