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 Rg3

Evidence Summary

Numerous preclinical studies have shown potential benefit for neuroprotection, anti-inflammatory effects, and anti-tumor properties, but clinical evidence is limited to a few studies in cancer patients.

Neuroprotective Benefit: Preclinical studies suggest that it crosses the blood-brain barrier and decreases inflammation and oxidative stress, though no studies have examined potential neuroprotective benefits in people.

Aging and related health concerns: Ginsenoside Rg3 when combined with chemotherapy appears to improve survival and alleviate chemotherapy-related adverse events in some cancer patients, but full texts were inaccessible or in Chinese.

Safety: Based on 2 clinical studies to date, ginsenoside Rg3 may increase constipation and nosebleeds, but it may alleviate many chemotherapy-related adverse events, such as anemia, leukopenia, thrombocytopenia, fatigue, and anorexia.

Availability: for research use only; Shenyi capsule, a pure form of ginsenoside Rg3, is in development by Yatai Pharme	**Dose**: 20 mg, twice daily, in a clinical trial in people with liver cancer	**Chemical formula:** $C_{42}H_{72}O_{13}$ **MW**: 785.01
Half life: 32-54 hr with 10-60 mg, i.m. injection	**BBB**: penetrant based on preclinical studies	
Clinical trials: largest randomized controlled trial included 228 patients with advanced liver cancer	**Observational studies**: none specific to ginsenoside Rg3	

What is it? Ginsenoside Rg3 is a type of triterpenoid saponin, rich in *Panax ginseng*, which is used extensively in traditional Chinese medicine as well as in Korea and Japan. The major ginsenosides, such as Rb1, Rb2, and Rd can be readily converted into ginsenoside Rg3 [1]. There are 2 enantiomers, 20(R)- and 20(S)-isomers. There are well over 100 ginsenosides, but ginsenoside Rg3 has been one of the most studied ginsenoside. It is thought to have significant biological activities, including hepatoprotection, neuroprotection, promotion of immune functions, as well as anti-fatigue, antioxidant, anti-inflammatory, and anti-tumor effects.

Neuroprotective Benefit: Preclinical studies suggest that it crosses the blood-brain barrier and decreases inflammation and oxidative stress, though no studies have examined potential neuroprotective benefits in people.

Types of evidence:

- 0 meta-analyses
- 0 clinical trials
- A few laboratory studies

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

No studies have tested ginsenoside Rg3 alone for prevention of cognitive decline or dementia.

Human research to suggest benefits to patients with dementia:
No studies have tested ginsenoside Rg3 alone in patients with dementia.

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

In a rat model of cognitive impairment (induced by LPS), ginsenoside Rg3 (10, 20, and 50 mg/kg, i.p.) for 21 days markedly improved learning and memory deficits, as measured by the step-through passive avoidance test and the Morris water maze test [2]. Ginsenoside Rg3 administration appeared to improve cognitive functions by significantly decreasing expression of pro-inflammatory mediators such as TNF-α, IL-1β, and COX-2 in the hippocampus.

A study testing a nanoparticle formulation of ginsenoside Rg3 with biodegradable poly(lactic-co-glycolic acid) reported that they crossed an *in vitro* model of the blood-brain barrier and decreased oxidative stress (ROS/RNS activity) in cell culture [3].

APOE4 interactions: Unknown.

Aging and related health concerns: Ginsenoside Rg3 when combined with chemotherapy appears to improve survival and alleviate chemotherapy-related adverse events in some cancer patients, but full texts were inaccessible or in Chinese.

Types of evidence:

- 1 meta-analysis in breast cancer patients
- 3 clinical trials
- Numerous laboratory studies

Lifespan: POTENTIAL BENEFIT IN PRECLINICAL MODEL. Based on deep learning analysis of thousands of compounds and combinations, Ginsenoside (Rg3) along with withaferin A and gamma linolenic acid were identified by Insilico (Longevity AI) to maximally activate anti-aging pathways (EurekAlert article) [4]. They applied several bioinformatic approaches and deep learning methods to the Library of Integrated Network-based Cellular Signatures (LINCS) dataset to find metformin and rapamycin mimetics. Ginsenoside was found to be a metformin mimetic, and withaferin A was found to be both a metformin- and rapamycin-mimetic. Although LifeExtension now sells a supplement containing these 3 compounds, it is currently unknown whether this combination enhances lifespan in humans.

Breast Cancer: MIXED. A meta-analysis involving 274 female breast cancer patients in China reported that ginsenoside Rg3 (Shenyi capsule) in combination with chemotherapy exhibited significantly attenuated leukopenia. However, there were no significant differences in the total response rate compared with the chemotherapy alone group (discussed in [1]; original paper in Chinese).

Colorectal Cancer: POTENTIAL BENEFIT IN PRECLINICAL MODEL. 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 or preventing the growth of tumors [5]. 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 colorectal cancer mice. 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. No studies have examined whether ginsenoside Rg3 may prevent liver cancer. In an open-label prospective randomized controlled trial of 228 people with advanced hepatocellular carcinoma, ginsenoside Rg3 (20 mg, twice daily) combined with transcatheter arterial chemoembolization (TACE) significantly increased median overall survival by 3 months compared to TACE treatment alone (13.2 months vs 10.1 months) [6]. Median time to progression (4.3 vs 3.2 months, respectively) and median time to untreatable progression (8.3 vs 7.3 months, respectively) were not significantly different. Disease control rate was 69.7% in the TACE with Rg3 group versus 51.3% in the control group (p=0.012). In patients with advanced hepatocellular carcinoma and adequate liver function, the combination of TACE and ginsenoside Rg3 may prolong overall survival when compared with TACE alone.

Lung Cancer: POTENTIAL BENEFIT. A prospective randomized controlled study of 133 patients with non-small cell lung cancer reported that ginsenoside Rg3 treatment (Shenyi capsule) in combination with chemotherapy improved the post-operative lifespan of patients, though differences between groups (Shenyi alone, chemo alone, and combo) were not statistically significant [7]. The one-year survival rates in the Shenyi group, the combined group, and the chemotherapy group were 76.7% (33/43), 82.6% (38/46), and 79.5% (35/44), respectively; the two-year survival rates were 67.4% (29/43), 71.7% (33/46), and 70.5% (31/44), respectively; and the three-year survival rates were 46.5% (20/43), 54.3% (25/46), and 47.7% (21/44), respectively. Authors speculated that the mechanism of action involves improvement in immune function. They also examined levels of VEGF and others, but the full text was unavailable and therefore I could not evaluate the data.

Esophageal Cancer: POTENTIAL BENEFIT. In a randomized controlled trial of 60 patients with advanced esophageal cancer, the combination of chemotherapy (gemcitabine plus cisplatin) with ginsenoside Rg3 (Shenyi Capsule) significantly improved one-year survival rate and quality of life of patients compared to chemotherapy alone [8]. Declines in white blood cell and blood platelet, and incidences of nausea and vomiting in the combination group were significantly lower than those in the control group. The combination treatment appeared to be effective in inhibiting new angiogenesis of esophageal cancer. Magnitudes of effects could not be assessed because the article was in Chinese (the abstract was in English).

Other cancers: POTENTIAL BENEFIT. In general, published clinical studies suggest that Rg3 is a good antitumor agent by improving immune function and quality of life of cancer patients [1].

Numerous preclinical studies have shown anticancer activities of ginsenoside Rg3 and their proposed mechanisms of action. The suggested mechanisms include the induction of apoptosis, and inhibition of proliferation, metastasis, and angiogenesis, as well as the promotion of immune function. In addition, ginsenoside Rg3 can be used as an adjuvant to conventional cancer therapies, improving the efficacy and/or reducing adverse effects via synergistic activities.

Safety: Based on 2 clinical studies to date, ginsenoside Rg3 may increase constipation and nosebleeds, but it may alleviate many chemotherapy-related adverse events, such as anemia, leukopenia, thrombocytopenia, fatigue, and anorexia.

Types of evidence:

- 1 clinical trial
- 1 PK study in healthy volunteers
- Numerous laboratory studies

Clinical: In an open-label prospective randomized controlled trial of 228 people with advanced hepatocellular carcinoma, treatment with ginsenoside Rg3 (20 mg, twice daily) combined with transcatheter arterial chemoembolization (TACE) significantly increased the incidence of constipation and nosebleeds [6]. However, the combination with ginsenoside Rg3 alleviated some TACE-related adverse syndromes and blood anomalies, such as ascites (23.7% for the TACE with Rg3 group vs 48.7% for the TACE group), anorexia (12.5% for the combo group vs 44.7% for the TACE alone), and fatigue (9.9% for the combo group vs 50.0% for the TACE alone). Additionally, Rg3 helped repair blood disorders

such as anemia (36.8% for the combo group vs 51.3% for the TACE alone), leukopenia (46.7% vs 76.3%), thrombocytopenia (32.9% vs 50.0%), and hyperbilirubinemia (17.8% vs 34.2%).

A clinical pharmacokinetic study in 33 healthy volunteers reported that ginsenoside Rg3 (10-60 mg, i.m. injection; Beijing Xinliheng Pharmaceutical Technology Development Co., Ltd) for up to 15 days was generally well-tolerated [9]. 20(S)-ginsenoside Rg3 was rapidly absorbed, with a time to reach maximum plasma concentration (T max) of 4 hours. After single-dose administration of 10, 30 and 60 mg 20(S)-ginsenoside Rg3, elimination half-life t ½ was 32.0 ± 26.7, 51.7 ± 15.4, and 53.9 ± 25.7 hours; maximum plasma concentration (C max) was 135.4 ± 35.3, 162.1 ± 47.2 and 399.8 ± 217.0 ng/mL; clearance CL/F was 3.2 ± 0.9, 3.8 ± 0.7 and 2.7 ± 1.3 L/h; respectively. In these studies, 20(S)-ginsenoside Rg3 exhibited a pharmacokinetic profile suitable for once-every-2-days dosing. There were no serious adverse events or adverse events leading to premature study discontinuation. In the single ascending dose paradigm, no treatment-emergent adverse events or changes in laboratory measurements, vital signs, or ECG parameters were reported. For the multiple dose paradigm, 9 laboratory adverse events were reported, and the most frequently reported treatment-emergent adverse event was increase of creatine kinase (66.7 %). Six subjects (5 males and 1 female) had elevation of creatine kinase. The max value generally occurred on day 5 and the average max value of creatine kinase was 988.0 ± 692.9 unit L^{-1} (the normal range was 18–189 unit L^{-1}). The duration of creatine kinase increase was 14.3 ± 9.9 days. Based on isoenzyme electrophoresis, skeletal muscle type creatine kinase was elevated, but the cerebral or myocardial type creatine kinases were unchanged. The elevation of creatine kinase was therefore attributed to muscular injury in the injection site. This adverse event was considered treatment related, mild or moderate in severity, transient, and resolved without treatment. Creatine kinase is not thought to increase with oral formulations ginsenoside Rg3, though this has not been tested.

Preclinical: A preclinical study testing a nanoparticle formulation of ginsenoside Rg3 with biodegradable poly(lactic-co-glycolic acid) reported that nanoparticles were taken up by rat glial cells and no visible toxicity was observed at 96 hours post-treatment [3].

Drug interactions: Drug interactions for ginsenoside Rg3 has not been well-studied. However, ginseng affects blood sugar levels, and therefore ginsenoside Rg3 may also interact with anti-diabetics (WebMD.com). Ginseng (and possibly ginsenoside Rg3) also interacts with warfarin, medications for depression, and immunosuppressants (e.g., azathioprine, basiliximab, cyclosporine, tacrolimus, sirolimus, prednisone, and other corticosteroids) (Drugs.com). Ginseng (and possibly Rg3) may intensify the effects of caffeine and other stimulants, leading to a rapid heartbeat, sweating, or insomnia.

Sources: Ginsenoside Rg3 is present in *Panax ginseng*, which is available OTC as whole root, liquid extract, capsule, and powder forms.

A pure form of ginsenoside Rg3, referred to as Shenyi Capsule, is in development by Yatai Pharme in China (Yatai Pharme). Based on the company website, it went on sale in 2000 "upon the acquisition of SZH New Drug Certificate of Traditional Chinese Medicine and documents of approval for production issued by the State Drug Administration". They noted that "Shenyi Capsule is the first new drug of Class I monome of Chinese herb subject to independent development and intellectual property rights" and is "likely to step into the international market". However, it has been 18 years since this announcement and the product does not appear to be in the international market.

Research underway: Two entries were found for ginsenoside Rg3 in ClinicalTrials.gov. One study tested Rg3 for prevention of postoperative recurrence of hepatocellular carcinoma in stage I and II patients (NCT01717066). This study has been completed, though no results are posted or published. The other study is testing the safety and efficacy of ginsenoside Rg3 in combination with first-line chemotherapy in advanced gastric cancer (NCT01757366). The trial was registered in December 2012, but the status of this trial is unknown.

Search terms:
Pubmed, Google:

- + clinical trial, + cognitive, + memory, + blood-brain barrier, + APOE, + lifespan, + cancer, + diabetes, + cholesterol, + hypertension

Websites visited for ginseng or ginsenoside:

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

- Cafepharma.com (0)

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