

# *Panax ginseng*

## Introduction

*Panax ginseng*, used medicinally for thousands of years in China, Korea, and Japan,<sup>1</sup> is well known as an adaptogen and a restorative tonic that is widely used in traditional Chinese medicine (TCM) and Western herbal preparations.<sup>2,3</sup> Eclectic uses for *Panax ginseng* include fatigue, infertility, liver disease, amnesia, colds, menopause, and erectile dysfunction.<sup>2,4</sup> There are many species of *Panax*, which leads to some confusion in the literature. However, the two species that have been the most extensively researched and used are *Panax ginseng* and *Panax quinquefolius*. Another botanical species, although commonly called Siberian ginseng (*Eleutherococcus senticosus*), is not a true ginseng. This monograph reviews the constituents, mechanism of action, safety, and clinical efficacy of *Panax ginseng*.



## Description

*Panax ginseng* belongs to the Araliaceae family and is found throughout East Asia and Russia.<sup>5,6</sup> It grows natively in remote forests of Manchuria and North Korea, but has become over-harvested in other parts of Asia.<sup>4</sup> It is cultivated in Korea, China, and Japan for export and use as a medicinal herb.

*Panax ginseng* is a shade-loving, deciduous perennial with five-fingered leaves, tiny white flowers, red berries, and a yellowish-brown root.<sup>2,4</sup> The root is utilized medicinally, although active compounds are present in all other parts of the plant. The root of *Panax ginseng* is a thick structure that resembles a human-like form, which is responsible for its name in Chinese, jen shen, or “man-root.”<sup>2</sup> *Panax* is derived from the Latin word panacea, which refers to its historical usage for many conditions. There are two distinct forms of *Panax ginseng*, red and white ginseng. The difference is the method of processing that results in different pigment compositions; white ginseng is produced by harvesting the root and drying it in the sun,<sup>3</sup> while red ginseng is steamed after harvest and dried. The content of ginsenoside compounds differs slightly between the red and white forms. Growing time also impacts ginsenoside content, with roots from plants older than five years being more potent than roots from one- to two-year-old plants.<sup>3,4</sup>

## Active Constituents

*Panax ginseng* contains triterpene glycosides, or saponins, commonly referred to as ginsenosides. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides, and vitamins B<sub>1</sub> and B<sub>2</sub>.<sup>3</sup> Up to 40 distinct ginsenosides have been identified by thin layer chromatography (TLC) and methanol extraction experiments.<sup>3,7</sup> The nomenclature of ginsenosides is by the designation R<sub>x</sub>, where x represents the retention factor (Rf) value from the sequence of spots on TLC from bottom to top. The two major sub-types of ginsenosides,

protopanaxadiol and protopanaxatriol, are classified according to the arrangement and number of sugar residues – glucose, rhamnose, xylose, and arabinose – on the ginsenoside. Rb1, Rb2, Rc, and Rd are examples of protopanaxadiol ginsenosides. Re, Rf, Rg1, and Rg2 are examples of protopanaxatriols.<sup>2-4,6,7</sup> These ginsenosides have varying concentrations in red and white *Panax ginseng* extracts due to different processing methods that affect deacetylating enzymes within the raw plant material.<sup>8</sup>

### Pharmacokinetics

Recent research supports the hypothesis that ginsenosides are activated by intestinal bacteria through deglycosylation and esterification.<sup>9</sup> Protopanaxadiol and protopanaxatriol glycosides are absorbed into the blood or lymph and transported to target tissues for esterification with stearic, oleic, or palmitic fatty acids. The transformation into ginsenoside metabolites, M1 (20S-protopanaxadiol 20-O-B-D-glucopyranoside) and M4 (20S-protopanaxatriol) affect excretion and utilization of the metabolites.<sup>9</sup>

### Mechanism of Action

*Panax ginseng* is often referred to as an adaptogen, which suggests it has varied actions and effects on the body that support nonspecific resistance to biochemical and physical stressors, improve vitality and longevity, and enhance mental capacity.<sup>3,10,11</sup> Reviews suggest *Panax ginseng* has immuno-modulating activity by affecting the hypothalamic-pituitary-adrenal (HPA) axis.<sup>3,11</sup> *In vitro* experiments reveal enhanced natural killer (NK) cell activity and increased immune cell phagocytosis after ginsenoside exposure.<sup>3</sup> According to a 1999 World Health Organization review, ginseng saponins “are thought to decrease serum prolactin, thereby increasing libido” in male impotence.<sup>12</sup>

### Clinical Indications

*Panax ginseng* has been widely studied in double-blind, randomized, placebo-controlled trials (RCTs). Although ginseng has been used by Asian cultures for thousands of years for conditions such as fatigue, mental stress, blood sugar regulation, improving libido, and supporting longevity, modern clinical studies

have focused on the use of *Panax ginseng* in cancer prevention, blood sugar regulation, fatigue, and immunomodulation in human health and disease.

### Immune Modulation

A double-blind, placebo-controlled eight-week study examined the immune effects of 100 mg Ginsana® (G115), 100 mg liquid ginseng extract, or placebo twice daily in 60 healthy volunteers. Blood samples collected at baseline, week four, and week eight examined polymorphonuclear (PMN) cell chemotaxis, phagocytosis, total lymphocytes, T-helper and T-suppressor cells, and NK-cell activity. The groups receiving ginseng experienced consistent improvement in immune system activity at week four and statistically significant differences at week eight, evidenced by improvements in PMN cell chemotaxis, phagocytosis, and total number of T-helper and T-suppressor cells. The authors concluded ginseng extract stimulates the immune system and the standardized extract is more effective than the liquid ginseng extract.<sup>13</sup>

Some of the same researchers examined the effects of *Panax ginseng* extract on the immune response to vaccination. The multicenter, 12-week, double-blind RCT compared immune response in 227 participants, measured as NK-cell activity, at weeks eight and 12, post influenza vaccine given at week four. The treatment group received 100 mg G115 twice daily. NK-cell activity for the ginseng group was double that of the placebo group ( $p < 0.0001$ ) at weeks eight and 12. Serum antibody titers were 272 units in the ginseng group compared to 171 units in the placebo group. A significant decrease in the frequency of upper respiratory infections during weeks 4-12 was noted in the treatment group compared to placebo; 15 cases versus 42 cases, respectively. This study supports the role of ginseng in immune system modulation.<sup>14</sup>

An RCT compared the effects of red *Panax ginseng* on HIV-1 infected patients ( $n=61$ ).<sup>15</sup> The purpose of this study was to determine the effects of red *Panax ginseng* after accounting for HLA type (I or II and class A, B, and C), on CD4 counts, CD8 counts, and the trend toward decreased resistance to anti-retroviral drugs. HLA type can be associated with an improved prognosis in HIV patients, based on an algorithm that also predicts risk of disease progression.<sup>16</sup>

The treatment group received 5.4 g red *Panax ginseng* daily. Blood samples were taken from the control group (n=199) and HIV-1 infected patients every six months throughout the study. Data analysis revealed an inverse correlation between the HLA score and the decrease of CD4 T cells over time, a decrease in the decline of CD4 T cells associated with the intake of red *Panax ginseng*, and a significant ( $p<0.05$ ) decline of CD4 T cells, independent of the HLA class I effects on immune system cells. The authors concluded that red *Panax ginseng* and HLA type independently affect the slow depletion of CD4 T cells in HIV-infected patients.

## Diabetes

Eclectic medicine texts reference *Panax ginseng* for its beneficial use in blood sugar regulation.<sup>2,10</sup> In a double-blind RCT, Sotaniemi et al examined the efficacy of *Panax ginseng* in newly diagnosed type 2 diabetics.<sup>17</sup> Parameters measured included physical performance, mood, serum lipids, fasting blood glucose, hemoglobin A1c (HbA1c), aminoterminal propeptide (PIIINP) concentration, and body weight. PIIINP serum levels are associated with coronary artery disease and were used as a safety parameter in this study. The study participants (n=36) were given 100 mg ginseng extract, 200 mg ginseng extract, or placebo daily for eight weeks. Compared to the placebo group, the 200-mg ginseng group experienced elevated mood, improved physical performance, and reduced fasting blood glucose. The authors concluded ginseng warrants further study as an adjuvant to diabetes management.

A 2005 double-blind, crossover RCT examined the effects of *Panax ginseng* on blood glucose levels and cognitive performance during sustained mental activity.<sup>18</sup> Healthy young adults (n=30) took a 10-minute test battery for baseline results, then were given 200 mg G115, 400 mg G115, or placebo. One hour later the test battery was repeated six times in rapid succession. Blood sugar levels were assessed at baseline and twice during the testing procedure. The 200-mg and 400-mg G115 doses reduced blood glucose levels significantly ( $p<0.005$ ). Significant improvement was also noted in the ability to complete the serial sevens subtraction task after taking 200 mg G115 ( $p<0.05$ ). The authors concluded *Panax ginseng* improves mental performance, possibly by regulating glucose metabolism.

A double-blind, 12-week RCT examined the effect of red *Panax ginseng* on HbA1c levels in 19 subjects with well-controlled type 2 diabetes.<sup>19</sup> Study participants received 2 g ginseng or placebo three times daily before meals. Plasma glucose and insulin, insulin sensitivity, and oral glucose tolerance were secondary measures of efficacy, while blood pressure checks and liver and kidney function tests assessed safety. Although no change was seen in HbA1c levels with ginseng, the participants remained well controlled throughout the study without pharmaceutical intervention – with average levels of HbA1c of 6.5 percent. A significant 8- to 11-percent decrease in glucose on the oral glucose tolerance test and 33-percent decrease in plasma insulin ( $p<0.05$ ) was seen in the ginseng group compared to placebo. No change was reported in safety parameters throughout the study, which led the authors to conclude red *Panax ginseng* is safe to use in the treatment of type 2 diabetes.

## Cancer Prevention

Numerous *in vitro* and animal studies have examined the interaction of *Panax ginseng* with carcinogenesis, apoptosis, angiogenesis, and metastasis.<sup>7,20-23</sup> A recent paper proposed an anti-inflammatory role of *Panax ginseng* in the sequence of progression to promotion in a model of carcinogenesis.<sup>24</sup> *Panax ginseng* affects multiple points within the inflammatory cascade, including inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nuclear factor kappaB (NF-κB).<sup>25,26</sup>

In a review, Lee et al concluded *Panax ginseng* has a radioprotective effect associated with antioxidant and immune-modulation properties.<sup>8</sup>

An epidemiological study examined the protective effect of a variety of *Panax ginseng* products on 3,974 patients with different types of cancer compared to case-matched controls for 67 weeks.<sup>27</sup> Patients taking ginseng demonstrated a 50-percent lower risk of cancer recurrence compared to patients not taking ginseng. Red ginseng offered greater protection than white ginseng. Cancer incidence decreased by 36- and 69 percent in subjects taking ginseng for one year or five years, respectively. A greater protective effect was seen in cancers of the lip, esophagus, pharynx, lung, and liver.





## Monograph

A prospective study examined non-organ specific cancer prevention of *Panax ginseng*.<sup>28</sup> This cohort study used case-controlled matches (n=4,587) of Koreans over age 40. A questionnaire was used to determine pattern of ginseng intake, initial age of ginseng intake, frequency, duration, and form of ginseng (fresh, dried, etc.) used by study participants. Ginseng intake correlated with a 60-percent reduction in cancer incidence, with a direct dose-response relationship.

### Drug-Botanical Interactions

According to a review by Blumenthal et al, there are no known interactions between *Panax ginseng* and pharmaceuticals, as reported by the German Commission E.<sup>3,29</sup> Caution is advised with concomitant use with phenelzine, coumadin, oral hypoglycemics, insulin, and caffeine, based on preclinical studies and proposed mechanisms of action.<sup>11,30</sup> A recent review by Seely et al suggests cautious use of *Panax ginseng* in pregnancy and lactation, although no specific teratogenic or hormone-disrupting activity was noted.<sup>5</sup>

### Side Effects and Toxicity

*Panax ginseng* is associated with low toxicity; few adverse events have been reported with proper usage.<sup>3,29</sup> Adverse events have been associated with high doses and long-term usage, producing what has been cited in the literature as ginseng abuse syndrome,<sup>5,11</sup> although case studies associated with ginseng abuse syndrome have been discounted by several authors.<sup>3</sup> Side effects such as hypertension, nausea, diarrhea, headache, mastalgia, insomnia, and skin rash have been noted.<sup>2,5,11</sup>

### Dosage

Ginseng root can be chewed, or taken as a powder, liquid extract, decoction, or infusion. The level of ginsenosides can vary depending on steeping time and type of preparation. The ginsenoside concentration can vary from approximately 64-77 percent.

Crude preparations of 1-2 g dried root powder can be taken daily for up to three months, according to recommendations by the German Commission E.<sup>29</sup> A decoction can be prepared by simmering 3-9 g dried root in 720-960 mL (24-32 oz) water for 45 minutes. A fluid extract (1:2 concentration) prepared from crude

root can be dosed at 1-6 mL daily.<sup>31</sup> An infusion can be made by pouring 150-250 mL (5-8 oz) of boiling water over 1-2 g root, steeping for 10 minutes covered, and then straining before drinking.<sup>3</sup>

Dosage of *Panax ginseng* extract standardized to 4-percent ginsenosides is 200 mg per day, in divided doses, yielding 8 mg ginsenosides daily. Other reports suggest significantly higher doses of 80-240 mg ginsenosides daily might be warranted in some cases.<sup>3</sup>

### Warnings and Contraindications

The German Commission E and the World Health Organization report no known contraindications for *Panax ginseng*.<sup>3,12</sup> Caution is advised during pregnancy and lactation due to a lack of controlled human clinical studies.<sup>3,5</sup> Teratogenicity has been documented in an *in vitro* rat embryo model, but the implication for human health is questionable due to dosages used that exceed possible human consumption.<sup>32</sup> In Asian countries the use of *Panax ginseng* in TCM formulas is common throughout pregnancy and lactation.<sup>5</sup>

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