

Ginseng, Panax

Species (Family)

Various *Panax* species (Araliaceae) including:

- (i) *Panax ginseng* Meyer
- (ii) *Panax quinquefolius* L.
- (iii) *Panax notoginseng* (Burkh.) Hoo & Tseng

Synonym(s)

- (i) Asiatic Ginseng, Chinese Ginseng, Japanese Ginseng, Jintsam, Korean Ginseng, Ninjin, Oriental Ginseng, *Panax pseudoginseng* Wall., *Panax schin-seng* Nees, Schinsent
- (ii) American Ginseng, Sanchi Ginseng and Tienchi Ginseng
- (iii) American Ginseng, Five-Fingers, Sang and Western Ginseng

Part(s) Used

Root. White ginseng represents the peeled and sun-dried root whilst red ginseng is unpeeled, steamed and dried.

Pharmacopoeial and Other Monographs

BHC 1992^(G6)
BHP 1996^(G9)
BP 2001^(G15)
Complete German Commission E^(G3)
Martindale 32nd edition^(G43)
Mills and Bone^(G50)
PDR for Herbal Medicines 2nd edition^(G36)
Ph Eur 2002^(G28)
USP24/NF19^(G61)

Legal Category (Licensed Products)

GSL^(G37)

Constituents^(G2,G6,G41,G64)

Terpenoids Complex mixture of compounds (ginsenosides) involves three aglycone structural types – two tetracyclic dammarane-type saponogenins (protopanaxadiol and protopanaxatriol) and a pentacyclic triterpene oleanolic acid-type. Different naming conventions have been used for these compounds. In Japan, they are known as ginsenosides and are represented by R_x where 'x'

indicates a particular saponin. For example, R_a, R_{b-1}, R_c, R_d, R_{g-1}. In Russia, the saponins are referred to as panaxosides and are represented as panaxoside X where 'X' can be A–F. The suffixes in the two systems are not equivalent and thus panaxoside A does not equal R_a but R_{g-1}.⁽¹⁾

The saponin content varies between different *Panax* species. For example, in *P. ginseng* the major ginsenosides are R_{b-1}, R_c and R_{g-1} whereas in *P. quinquefolis* R_{b-1} is the only major ginsenoside.⁽¹⁾

Other constituents Volatile oil (trace) mainly consisting of sesquiterpenes including panacene, limonene, terpineol, eucalyptol, α -phellandrene and citral,⁽²⁾ sesquiterpene alcohols including the pansinsanols A and B, and ginsenol,^(3,4) polyacetylenes,^(5,6) sterols, polysaccharides (mainly pectins and glucans),⁽⁷⁾ starch (8–32%), β -amylase,⁽⁸⁾ free sugars, vitamins (B₁, B₂, B₁₂, panthotenic acid, biotin), choline (0.1–0.2%), fats, minerals.

The sesquiterpene alcohols are stated to be characteristic components of *Panax ginseng* in that they are absent from the volatile oils of other *Panax* species.⁽⁴⁾

Food Use

Ginseng is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that ginseng can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product.^(G16)

Herbal Use

Ginseng is stated to possess thymoleptic, sedative, demulcent and stomachic properties, and is reputed to be an aphrodisiac. Traditionally, it has been used for neurasthenia, neuralgia, insomnia, hypotonia, and specifically for depressive states associated with sexual inadequacy.^(G2,G6,G8,G64)

Ginseng has been used traditionally in Chinese medicine for many thousands of years as a stimulant, tonic, diuretic and stomachic.⁽⁹⁾ Traditionally, ginseng use has been divided into two categories: short-term – to improve stamina, concentration, healing process, stress resistance, vigilance and work efficiency in healthy individuals, and long-term – to

improve well-being in debilitated and degenerative conditions especially those associated with old age.

Dosage

Traditionally, dosage recommendations differ between the short-term use in healthy individuals and the long-term use in elderly or debilitated persons.

Short-term (for the young and healthy) 0.5–1.0 g root daily, as two divided doses, for a course generally lasting 15–20 days and with a root-free period of approximately two weeks between consecutive courses. Doses are recommended to be taken in the morning, 2 hours before a meal, and in the evening, not less than 2 hours after a meal.⁽⁹⁾

Long-term (for the old and sick) 0.4–0.8 g root daily. Doses may be taken continuously.⁽¹⁾

Pharmacological Actions

In the 1950s, early studies on ginseng reported its ability to improve both physical endurance and mental ability in animals and humans.⁽¹⁰⁾ In addition, the 'tonic' properties of ginseng were confirmed by the observation that doses taken for a prolonged period of time increased the overall well-being of an individual, measured by various parameters such as appetite, sleep and absence of moodiness, resulting in an increased work efficiency. Furthermore, these effects were felt for some time after cessation of ginseng treatment.⁽¹⁰⁾ In addition, gonadotrophic activity, slight anti-inflammatory activity and an effect on carbohydrate metabolism were noted.⁽¹⁰⁾ Since then, numerous studies have investigated the complex pharmacology of ginseng in both animals and humans. The saponin glycosides (ginsenosides/panaxosides) are generally recognised as the main active constituents in ginseng, although pharmacological activities have also been associated with non-saponin components.

The following sections on animal and human studies are intended to give an indication of the type of research that has been published for ginseng rather than to provide a comprehensive bibliography of ginseng research papers.

In vitro and animal studies

Corticosteroid-like activity Many of the activities exhibited by Panax ginseng have been compared to corticosteroid-like actions and results of endocrinological studies have suggested that the ginsenosides may primarily augment adrenal steroidogenesis via

an indirect action on the pituitary gland.⁽¹¹⁾ Ginsenosides have increased adrenal cAMP in intact but not in hypophysectomised rats and dexamethasone, a synthetic glucocorticoid that provides positive feedback at the level of the pituitary gland, has blocked the effect of ginsenosides on pituitary corticotrophin and adrenal corticosterone secretion.⁽¹¹⁾ Hormones produced by the pituitary and adrenal glands are known to play a significant role in the adaptation capabilities of the body.⁽¹²⁾ Working capacity is one of the indices used to measure adaptation ability and ginseng has been shown to increase the working capacity of rats following single (132%) and seven-day (179%) administration (intraperitoneal). Furthermore, seven-day administration of ginseng decreased the reduction seen in working capacity when the pituitary–adrenocortical system is blocked by prior administration of hydrocortisone.⁽¹²⁾

Hypoglycaemic activity Hypoglycaemic activity has been documented for ginseng and attributed to both saponin and polysaccharide constituents. *In vitro* studies using isolated rat pancreatic islets have shown that ginsenosides promote an insulin release which is independent of extracellular calcium and which utilises a different mechanism to that of glucose.⁽¹³⁾ In addition, *in vivo* studies in rats have reported that a ginseng extract increases the number of insulin receptors in bone marrow and reduces the number of glucocorticoid receptors in rat brain homogenate.⁽¹⁴⁾ Both of these actions are thought to contribute to the antidiabetic action of ginseng, in view of the known diabetogenic action of adrenal corticoids and the knowledge that the number of insulin receptors generally decreases with ageing.⁽¹⁴⁾

Hypoglycaemic activity observed in both normal and alloxan-induced hyperglycaemic mice administered ginseng (intraperitoneal) has also been attributed to non-saponin but uncharacterised principles^(15–18) and to glycan (polysaccharide) components, Panaxans A–E and Q–U.^(19–23) Glycans isolated from Korean ginseng or Chinese ginseng (A–E) were found to possess stronger hypoglycaemic activity than those isolated from Japanese ginseng (Q–U).⁽²³⁾ Proposed mechanisms of action have included elevated plasma insulin concentration due to an increase of insulin secretion from pancreatic islets, and enhancement of insulin sensitivity.⁽²¹⁾ However, these mechanisms do not explain the total hypoglycaemic activity that has been exhibited by the polysaccharides and further mechanisms are under investigation.⁽²¹⁾

The effect of panaxans A and B on the activities of key enzymes participating in carbohydrate metabolism has been studied.⁽¹⁸⁾ DPG-3-2, a non-saponin

component isolated from ginseng, has been shown to stimulate insulin biosynthesis in pancreatic preparations from various hyperglycaemic (but not normoglycaemic) animals; ginsenosides R_{b1} and R_{g1} were found to decrease islet insulin concentrations to an undetectable level.⁽¹⁶⁾

Cardiovascular activity Individual saponins have been reported to have different actions on cardiac haemodynamics.⁽²⁴⁾ For instance R_g, R_{g-1} and total flower saponins have increased cardiac performance whilst R_b and total leaf saponins have decreased it; calcium antagonist activity has been reported for R_b but not for R_g; R_b but not R_g has produced a protective effect on experimental myocardial infarction in rabbits.⁽²⁴⁾ Negative chronotropic and inotropic effects *in vitro* have been observed for ginseng saponins and a mechanism of action similar to that of verapamil has been suggested.⁽²⁵⁾ *In vitro* studies on the isolated rabbit heart have reported an increase in coronary blood flow together with a positive inotropic effect.⁽²⁶⁾ Anti-arrhythmic action on aconitine and barium chloride (rat) and adrenaline (rabbit)-induced arrhythmias, and prolongation of RR, PR and QT_c intervals (rat), have been documented for saponins R_{c-1} and R_{d-1}. The mode of action was thought to be similar to that of amiodarone.⁽²⁷⁾ Ginsenosides (i.p.) have been reported to protect mice against metabolic disturbances and myocardial damage associated with conditions of severe anoxia.⁽²⁸⁾

Ginseng has produced a marked hypotensive response together with bradycardia following intravenous administration to rats. The dose-related effect was blocked by many antagonists suggesting multi-site activity.⁽²⁶⁾ Higher doses of ginseng were found to cause vasoconstriction rather than vasodilation in renal, mesenteric and femoral arteries.⁽²⁶⁾

The total ginseng saponin fraction has been reported to be devoid of haemolytic activity. However, individual ginsenosides have been found to exhibit either haemolytic or protective activities. Protective ginsenosides include R_c, R_{b-2} and R_e, whereas haemolytic saponins have included R_g, R_h and R_f.⁽²⁹⁾ The number and position of sugars attached to the sapogenin moiety was thought to determine activity.⁽²⁹⁾ Haemostatic activity has also been documented for ginseng.⁽³⁰⁾

Oral administration of ginseng to rats fed a high cholesterol diet reduced serum cholesterol and triglycerides, increased high-density lipoprotein (HDL) cholesterol, decreased platelet adhesiveness, and decreased fatty changes to the liver.⁽³¹⁾ Ginseng has also been reported to reduce blood coagulation and enhance fibrinolysis.⁽³²⁾ Panaxynol and the ginseno-

sides R_o, R_{g-1} and R_{g-2} have been documented as the main antiplatelet components in ginseng inhibiting aggregation, release reaction and thromboxane formation *in vitro*.⁽³²⁾ Anti-inflammatory activity and inhibition of thromboxane B₂ have previously been described for panaxynol.⁽³²⁾ Anticomplementary activity *in vitro* (human serum) has been documented for ginseng polysaccharides with highest activity observed in strongly acidic polysaccharide fractions.⁽⁷⁾

Effects on neurotransmitters Studies in rats have shown that a standardised ginseng extract (G115) inhibits the development of morphine tolerance and physical dependence, of a decrease in hepatic glutathione concentrations, and of dopamine receptor sensitivity without antagonising morphine analgesia, as previously documented for the individual saponins.⁽³³⁾ The inhibition of tolerance was thought to be associated with a reduction in morphinone production, a toxic metabolite which irreversibly blocks the opiate receptor sites, and with the activation of morphinone-glutathione conjugation, a detoxication process. The mechanism of inhibition of physical dependence was unclear but thought to be associated with changed ratios of adrenaline, noradrenaline, dopamine and serotonin in the brain.⁽³³⁾

A total ginsenoside fraction has been reported to inhibit the uptake of various neurotransmitters into rat brain synaptosomes in descending order of gamma-aminobutyrate and noradrenaline, dopamine, glutamate and serotonin.⁽³⁴⁻³⁶⁾ The fraction containing ginsenoside R_d was most effective. Uptake of metabolic substrates 2-deoxy-D-glucose and leucine was only slightly affected and therefore it was proposed that the ginseng extracts were acting centrally rather than locally as surface active agents.

Studies in rats have indicated that the increase in dopaminergic receptors in the brain observed under conditions of stress is prevented by pretreatment with ginseng.⁽³⁷⁾

Hepatoprotective activity Antioxidant and detoxifying activities have been documented for ginseng.⁽³⁸⁾ Protection against carbon tetrachloride- and galactosamine-induced hepatotoxicity has been observed in cultured rat hepatocytes for specific ginsenosides (oleanolic acid and dammarane series).^(38,39) However, at higher doses certain ginsenosides from both series were found to exhibit simultaneous cytotoxic activity.⁽³⁶⁾

Cytotoxic and antitumour activity Cytotoxic activity (ED₅₀ 0.5 µg/mL) versus L1210 has been documented for polyacetylenes isolated from the root.^(5,6,40) The

antitumour effect of ginseng polysaccharides in tumour-bearing mice has been associated with an immunological mechanism of action.⁽⁴¹⁾ Ginseng polysaccharides have been reported to increase the lifespan of tumour-bearing mice and to inhibit the growth of tumour cells *in vivo*, although cytotoxic action was not seen *in vitro*.⁽⁴¹⁾ Antitumour activity *in vitro* versus several tumour cell lines has been documented for a polyacetylene, panaxytriol.^(42,)

Antiviral activity Antiviral activity (versus Semliki forest virus; 34–40% protection) has been documented for ginseng extract (G115, Pharmaton) administered orally to rats.⁽³⁷⁾ The ginseng extract also enhanced the level of protection afforded by 6-MFA, an interferon-inducing agent of fungal origin.⁽⁴³⁾ Ginseng has been found to induce *in vitro* and *in vivo* production of interferon and to augment the natural killer and antibody dependent cytotoxic activities in human peripheral lymphocytes.^(43,44) In addition, ginseng enhances the antibody-forming cell response to sheep red blood cells in mice and stimulates cell mediated immunity both *in vitro* and *in vivo*.^(43,44) In view of these observations, it has been proposed that the antiviral activity of ginseng may be immunologically mediated.^(43,44)

Clinical studies

Improvements in serum total cholesterol, HDL cholesterol, triglycerides, non-essential fatty acids and lipoperoxides have been observed in 67 hyperlipidaemic patients administered 2.7 g/day red ginseng.⁽²⁷⁾ The addition of ginseng (3 g/65 kg body weight) to alcohol consumption (72 g/65 kg body weight of 25% ethanol) has been reported to enhance blood alcohol clearance by 32–51%.⁽⁴⁵⁾

A preparation containing ginseng extract with multivitamins and trace elements has been shown to modify some indices of metabolic and liver function in elderly patients with chronic hepatotoxicity induced by alcohol and drugs.⁽⁴⁶⁾ Patients who received ginseng exhibited an increase in bromosulphthalein excretion (which is related to hepatic detoxification) and improved serum zinc concentrations.⁽⁴⁶⁾

A favourable effect on various tests of psychomotor performance (attention, processing, integrated sensory motor function and auditory reaction time) in healthy individuals receiving a ginseng extract (200 mg daily for 12 weeks) has been documented in a double-blind placebo-controlled study.⁽⁴⁷⁾ No difference was observed between ginseng and placebo groups in tests of pure motor function, recognition and visual reaction time.⁽⁴⁷⁾

Ginseng has been reported to improve the overall control of status asthmaticus when added to conventional steroid, bronchodilator and antibiotic therapies.⁽⁴⁸⁾

Ginseng has been shown to reduce blood sugar concentrations in both diabetics and non-diabetics,⁽¹⁾ such that in one study insulin therapy was no longer required in a proportion of the patients investigated.⁽¹⁾

Ginseng has also been reported to normalise both high and low blood pressure states.⁽¹⁾

Ginseng has been found to affect concentrations of corticosteroids such as adrenocorticotrophic hormone (ACTH) and cortisol and noradrenaline.⁽¹⁾

Ginseng has been reported to successfully treat cases of diabetic polyneuropathy, reactive depression, psychogenic impotence, enuresis and various child psychiatric disorders.⁽⁴⁹⁾

Side-effects, Toxicity

In Japan, ginseng (panax) has been given to more than 500 individuals over the course of two studies with no side-effects experienced.⁽¹⁾ However, suspected adverse events associated with ginseng treatment have been documented although it is often difficult to assess individual cases due to a lack of information concerning dose, duration of treatment, species of ginseng used, and concurrent medication.⁽¹⁾ Nevertheless, symptoms documented include hypertension⁽¹⁾ (ginseng species unspecified), diarrhoea,⁽¹⁾ insomnia⁽¹⁾ (as a result of over stimulation), mastalgia,⁽¹⁾ skin eruptions⁽¹⁾ and vaginal bleeding⁽¹⁾. A case of vaginal bleeding in a postmenopausal woman has been associated with the use of a ginseng face cream.⁽⁵⁰⁾ In 1979, two studies referred to a ginseng abuse syndrome (GAS) which emphasised that most side-effects documented for ginseng were associated with the ingestion of large doses of ginseng together with other psychomotor stimulants, including tea and coffee.⁽¹⁾ GAS was defined as diarrhoea, hypertension, nervousness, skin eruptions and sleeplessness. Other symptoms occasionally observed included amenorrhoea, decreased appetite, depression, euphoria, hypotension and oedema. However, these two studies have been widely criticised over the variety of ginseng and other preparations used, and over the lack of authentication of the ginseng species ingested.⁽¹⁾ Elsewhere, symptoms of overdose have been described as those exhibited by individuals allergic to ginseng, namely palpitations, insomnia and pruritus, together with heart pain, decrease in sexual potency, vomiting, haemorrhagic diathesis, headache and epistaxis; ingestion of very large doses have even been reported to be fatal.⁽⁹⁾

Two cases of a suspected interaction between ginseng and phenelzine have been documented.⁽⁵¹⁾ Symptoms of headache and tremulousness in one 64-year-old woman and of manic-like symptoms in a 42-year-old woman were described.⁽⁵¹⁾

Results documented for toxicity studies carried out in a number of animal species using standardised extracts (SE) indicate ginseng to be of low toxicity.⁽⁵²⁻⁵⁶⁾

Acute toxicity Single doses of up to 2 g SE have been administered to mice and rats with no toxic effects observed.⁽⁵⁵⁾ LD₅₀ values (p.o.) in mice and rats have been estimated at 2 g/kg and greater than 5 g/kg.⁽⁵²⁾ In addition, LD₅₀ values (i.p., mice) have been estimated for individual ginsenosides as 305 mg/kg (R_{b-2}), 324 mg/kg (R_d), 405 mg/kg (R_c), 410 mg/kg (R_c), 1110 mg/kg (R_{b-1}), 1250 mg/kg (R_{g-1}), and 1340 mg/kg (R_f); an LD₅₀ (i.v., mice) of 3806 mg/kg has been estimated for the saponins R_{c-1} and R_{d-1}.⁽⁵²⁾

Subacute toxicity Doses of approximately 720 mg of a ginseng extract (G115) have been administered orally to rats for 20 days with no side-effects documented.⁽⁵⁶⁾

Chronic toxicity Daily doses of up to 15 mg G115/kg body weight have been administered orally to dogs for 90 days with no toxic effects documented. An initial increase in excitability which disappeared after two to three weeks was the only observation reported in rats fed 200 mg G115/kg body weight for 25 weeks.⁽⁵⁵⁾

P. quinquefolis has been reported to be devoid of mutagenic potential when investigated versus *Salmonella typhimurium* strain TM677.⁽⁵⁷⁾

Contra-indications, Warnings

Ginseng may potentiate the action of monoamine oxidase inhibitors (MAOIs) (inhibits uptake of various neurotransmitter substances)⁽³⁴⁾ and two cases of suspected ginseng interaction with phenelzine have been documented.⁽³¹⁾ The use of ginseng has been contraindicated during acute illness, any form of haemorrhage and during the acute period of coronary thrombosis⁽¹⁾. It has been recommended that ginseng should be avoided by individuals who are highly energetic, nervous, tense, hysteric, manic or schizophrenic, and that it should not be taken with stimulants, including coffee, antipsychotic drugs or during treatment with hormones.^(1, G49)

In view of documented pharmacological actions and side-effects, ginseng should also be used with caution in the following circumstances: cardiac dis-

orders, diabetes, hyper- and hypotensive disorders, and with all steroid therapy. Women may experience oestrogenic side-effects.

In Russia, it is recommended that healthy people under the age of 40 should not use ginseng and that middle-aged people can be treated with small doses of ginseng on a daily basis. In general, long-term use of ginseng is not recommended and one author has documented that the main side-effect of prolonged use manifests as an inflamed nerve, frequently the sciatic, which then causes muscle spasm in the affected area.⁽¹⁾ In Russia, those individuals considered suitable to use ginseng are recommended to abstain from alcoholic beverages, sexual activity, bitter substances and spicy foods.⁽⁹⁾ Patients allergic to ginseng may exhibit symptoms of palpitation, insomnia, and pruritus.⁽⁹⁾

Pregnancy and lactation No fetal abnormalities have been observed in rats and rabbits administered a standardised extract (40 mg/kg, p.o.) from day 1 to day 15 of pregnancy.⁽⁵⁵⁾ Ginseng has also been fed to two successive generations of rats in doses of up to 15 mg G115/kg body weight/day (equivalent to approximately 2700 mg ginseng extract) with no teratogenic effects observed.⁽⁵²⁾ However, the safety of ginseng during pregnancy has not been established in humans and therefore its use should be avoided. Similarly, there are no published data concerning the secretion of pharmacologically active constituents from ginseng into the breast milk and use of ginseng during lactation is therefore best avoided.

Pharmaceutical Comment

Phytochemical studies on panax ginseng are well documented and have initially concentrated on the saponin components (ginsenosides) which are generally considered to be the main active constituents. More recently, pharmacological actions documented for the non-saponin components, principally polysaccharides, have stimulated research into identifying non-saponin active constituents. Many of the pharmacological actions documented for ginseng directly oppose one another and this has been attributed to the actions of the individual ginsenosides. For example, ginsenoside R_{b1} exhibits CNS-depressant, hypotensive and tranquillising actions whilst ginsenoside R_{g1} exhibits CNS-stimulant, hypertensive and anti-fatigue actions. These opposing actions are thought to explain the 'adaptogenic' reputation of ginseng, that is the ability to increase the overall resistance of the body to stress and to balance bodily functions.

In summary, ginseng has been shown to possess a wide range of pharmacological activities

and it should consequently be used with appropriate regard to the traditional guidelines drawn up in China, Japan and Russia, to the health of the individual and to any concomitant therapies. When used appropriately, ginseng appears to be relatively non-toxic and most documented side-effects are associated with inappropriate use when compared with traditional warnings and guidelines.

References

See also General References G2, G3, G5, G6, G8, G9, G16, G18, G28, G29, G31, G32, G36, G37, G41, G43, G46, G49, G50, G56, G61 and G64.

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