Ginseng, Eleutherococcus

Species (Family)

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae)

Synonym(s)

Acanthopanax senticosus, Devil's Shrub, Eleuthero, *Hedera senticosa*, Siberian Ginseng, Touch-Me-Not, Wild Pepper

Part(s) Used

Root

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]

Legal Category (Licensed Products)

Eleutherococcus ginseng is not included in the GSL.[G37]

Constituents[1,2,G6]

Eleutherosides A–M Heterogeneous group of compounds including sterol(A), phenylpropanoid(B), coumarin (B1, B3), monosaccharide(C), and lignan(B_4,D,E) structural types; many present as glycosides. Characterised eleutherosides include daucosterol(A), syringin(B), isofraxidin glucoside(B_1), (−)-sesamin(B_4), methyl-α-D-galactoside(C), (−)-syringaresinol glucoside(D), acanthoside D(E) and hedera-saponin B(M).

Carbohydrates Polysaccharides (glycans); some have been referred to as eleutherans.[3] Galactose, glucose, maltose, sucrose.

Some of the additional documented constituents represent aglycones of the eleutherosides, namely β-sitosterol, isofraxidin, (−)-syringaresinol and sinapyl alcohol.

Phenylpropanoids Caffeic acid and ester, coniferyl aldehyde.

Terpenoids Oleanolic acid.

Volatile oils 0.8%. Individual components not documented.

Food Use

Eleutherococcus ginseng is not used in foods.

Herbal Use

Eleutherococcus ginseng does not have a traditional herbal use in the UK, although it has been used for many years in the former Soviet Union. Like Panax ginseng, Eleutherococcus ginseng is claimed to be an adaptogen in that it increases the body's resistance to stress and builds up general vitality.[G6,G8,G49]

Dosage

Dry root 0.6–3 g daily for up to one month has been recommended.[G6,G49] Russian studies in healthy human subjects have involved the administration of an ethanolic extract in doses ranging from 2 to 16 mL one to three times daily, for up to 60 consecutive days.

Doses in non-healthy individuals ranged from 0.5 to 6.0 mL one to three times daily for up to 35 days. In both groups, multiple dosing regimens were separated by an extract-free period of two to three weeks.[1]

Pharmacological Actions

The adaptogenic properties of Eleutherococcus ginseng have been extensively investigated in the countries of the former USSR. Pharmacological studies on extracts of Eleutherococcus ginseng started in the 1950s and have been primarily reported by two groups of Russian scientists. In 1962, a 33% ethanolic extract of *Eleutherococcus senticosus* was approved for human use by the Pharmacological Committee of USSR Ministry of Health, and in 1976 it was estimated that some three million people were regularly using this extract.[1]

A review by Farnsworth *et al.*[1] describes the chemistry and toxicity of Eleutherococcus ginseng

and documents results of *in vitro*, *in vivo* and human studies involving the oral administration of an ethanolic extract.

The majority of literature on Eleutherococcus ginseng has been published in the Russian language and therefore great difficulty is encountered in obtaining translations.[1] This monograph will draw mainly on data included in the Farnsworth review as well as on more recent papers that have been published in English. When used in this monograph , 'ginseng' will refer to Eleutherococcus ginseng unless indicated otherwise.

In vitro and animal studies

Hypo/hyperglycaemic activity Hypo/hyperglycaemic activity has been documented in both normal animals and in those with induced hyperglycaemia (rabbit, mouse), but with little effect on alloxan-induced hyperglycaemia (rat).[1,4] Hypoglycaemic activity (mice, intraperitoneal injection) of an aqueous ginseng extract has been attributed to polysaccharide components termed eleutherans A–G.[5]

Central nervous system effects Sedative actions (rat, mouse), CNS-stimulant effects (intravenous/subcutaneous injection, rabbit), and a decrease/increase in barbiturate sleeping time has been reported.[1,6]

Immunostimulant, antitoxic actions Increased resistance to induced listeriosis infection (mouse, rabbit) with prophylactic ginseng administration and reduced resistance with simultaneous administration, stimulation of specific antiviral immunity (guinea-pig, mouse), regulation of complement titre and lysozyme activity post immunisation have been documented.[1] In addition, protection against cardiac glycoside (intravenous injection, frog), diethylglycolic acid (mouse) and alloxan (rat) toxicity has also been described.[1] Immune stimulant effects have been reported for polysaccharide components, together with an ability to lessen thioacetamide, phytohaemagglutinin and X-ray toxicity, and to exhibit antitumour effects.[5] Immunostimulant activity *in vitro* (using granulocyte, carbon clearance and lymphocyte-transformation tests) has been documented for high molecular weight polysaccharide components.[7,8]

Effects on overall performance A beneficial action on parameters indicative of stress (rat) and on overall work capacity (mouse) has been reported,[1] although a lack of adaptogenic response has also been reported in mice receiving various ginseng infusions (Siberian, Korean and American).[9,10] In one study, mice receiving a commercial concentrated extract of eleutherococcus ginseng were noted to exhibit significantly more aggressive behaviour.[9] Ginseng is claimed to result in a more economical utilisation of glycogen and high-energy phosphorus compounds, and in a more intense metabolism of lactic and pyruvic acids during stress.[1] It has been claimed that the adaptogenic effect of ginseng involves regulation of energy, nucleic acid, and protein metabolism in tissues.[1]

Steroidal activity Gonadotrophic activity in immature male mice (intraperitoneal injection), oestrogenic activity in immature female mice, and an anabolic effect in immature rats (intraperitoneal injection) has been reported.[1] *In vitro* studies have reported that ginseng extracts bind to progestin, mineralocorticoid, glucocorticoid and oestrogen receptors.[1]

Cardiovascular activity 3,4-Dihydroxybenzoic acid (DBA) has been identified as an anti-aggregatory component in eleutherococcus ginseng.[3] Compared with aspirin, activity of DBA was comparable versus collagen- and ADP-induced platelet aggregation, but less potent versus arachidonic acid-induced platelet aggregation.[3] Anti-oedema and anti-inflammatory actions (intravenous injection, mouse), have also been described.[1]

Effect on reproductive capacity Ginseng has been reported to improve the reproductive capacity of bulls and cows, and to have no adverse effects on the various blood parameters (haemoglobin, total plasma protein, albumin and globulin, protein coefficient) measured.[1]

Other actions documented for ginseng include the stimulation of liver regeneration in partially hepatectomised mice,[1] an increase in catecholamine concentrations in the brain, adrenal gland and urine,[1] a variable effect on induced hypothermia (rabbit, rat, mouse),[1] and *in vitro* inhibition (66%) of hexobarbitone metabolism.[6]

Clinical studies

In Russia, ginseng extract has been administered orally to more than 4300 human subjects in studies involving either healthy or non-healthy individuals.[1]

Administration to healthy subjects These studies were designed to investigate the adaptogenic effects of ginseng and measured parameters such as the ability of humans to withstand adverse conditions (heat, noise, motion, workload increase, exercise, decompression), improvement in auditory distur-

bances, quality of work under stress conditions and in athletic performance, and increase in mental alertness and work output.[1] The studies involved more than 2100 subjects and included both male and female subjects ranging in age from 19 to 72 years. Doses ranged from 2 to 16 mL of an ethanolic extract (33%), administered orally one to three times daily, for periods of up to 60 consecutive days. Multiple dosing regimens usually involved a two- to three-week interval between courses.[1] For many of the studies, it is unclear whether ginseng had a beneficial effect. However, ginseng was found to exert favourable effects in a number of situations including ability to perform physical labour, quality of proofreading, adaptation to a high-temperature environment, speed and quality of work by radiotelegraphers in noisy conditions, resistance to hypoxaemia and physical burdens in skiers, ability to withstand conditions designed to induce motion sickness, capillary resistance, haematological parameters in blood donors, and number of days lost to sickness amongst factory workers. Ginseng was also reported to increase excretion of vitamins B_1, B_2 and C given concurrently with ginseng. On its own, ginseng did not affect the excretion of water-soluble vitamins.

Administration to non-healthy subjects These studies involved more than 2200 subjects with various ailments and included both males and females ranging in age from 19 to 60 years. Ginseng doses ranging from 0.5 to 6 mL were administered orally between one to three times daily for up to 35 days, with as many as eight courses employed. Multiple dosing regimens involved a two- to three-week ginseng-free interval in between courses.[1] A favourable effect was noted in atherosclerosis (although treatment was stated to be less effective in patients with high blood pressure), acute pyelonephritis, various forms of diabetes mellitus (although no marked effect was noted in another study), hypertension and hypotension (tendency to normalisation), acute craniocerebral trauma, various types of neuroses, rheumatic heart disease (reduced blood coagulation properties), chronic bronchitis, and in children with abating forms of pulmonary tuberculosis.[1] An increase in the working capacity of six males, in a single blind crossover study using placebo and no treatment as comparators, has been reported for a 33% ethanolic ginseng extract.[11] The observed increase in working capacity was partially attributed to an improvement in bodily oxygen metabolism, reflected by the increase in all four measured parameters (oxygen uptake, oxygen pulse, total work and exhaustion time).[12]

Immunostimulant activity A strong immunomodulatory effect has been documented for an ethanolic extract of ginseng, in a placebo-controlled double-blind study using healthy volunteers.[13] A significant increase in the total lymphocyte count, especially in the T lymphocyte cells, was noted in the ginseng-treated group who received a daily dose of 30–40 mL extract (eleutheroside B 0.2% w/v). Specificity of action on the lymphocytes was confirmed by the fact that neither granulocyte or monocyte levels were significantly altered.[13]

Side-effects, Toxicity

No side-effects were documented from Russian studies involving more than 2100 healthy subjects.[1] Studies involving patients with various ailments have reported a few side-effects: insomnia, shifts in heart rhythm, tachycardia, extrasystole and hypertonia in some atherosclerotic patients; headaches, pericardial pain, palpitations, and elevated blood pressure in 2 of 55 patients (at high dose level) with rheumatic heart disease; insomnia, irritability, melancholy and anxiety in hypochondriac patients receiving higher doses of extract; hypersensitivity reaction (symptoms unspecified) in stressed individuals.[1] Hypertension and mastalgia have been documented as side-effects of ginseng (species unknown).[11]

Results of various animal toxicity studies have indicated ginseng to be non-toxic.[1] Many species have been exposed to extracts including mice, rats, rabbits, dogs, minks, deer, lambs, and piglets.[1] Documented acute oral LD_{50} values for various preparations include: 23 mL/kg and 14.5 g/kg (mice), and greater than 20 mL/kg (dogs) for a 33% ethanolic extract[1,4]; 31 g/kg (mice) for the powdered root; greater than 3 g/kg (mice) for an aqueous aqueous (equivalent to 25 g dried roots/kg).[4] No deaths occurred in mice administered single 3 g/kg doses of a freeze-dried aqueous extract.[12] Symptoms observed in dogs receiving 7.1 mL/kg doses of the ethanolic extract (sedation, ataxia, loss of righting reflex, hypopnoea, tremors, increased salivation and vomiting) were attributed to the ethanol content of the extract.[1] A chronic toxicity study reported no toxic manifestations or deaths in rats fed 5 mL/kg ethanolic extract for 320 days.[1]

Teratogenicity studies in male and female rats, pregnant minks, rabbits and lambs have reported no abnormalities in the offspring and no adverse

effects in the animals administered the extracts. Premature death in parent female rabbits fed 13.5 mL/kg ethanolic extract daily was attributed to ethanol intoxication.[1]

Mutagenicity studies using *Salmonella typhimurium* TA100 and TA98, and the micronucleus test in mice have reported no activity for ginseng.[14] Differences in various serum biochemical parameters have been reported between test (ginseng) and control groups.[14] Parameters affected included alkaline phosphatase and gamma-glutamyl transferase enzymes (increased), serum triglycerides (decreased), and creatinine and blood urea nitrogen (increased).[14] No pathological changes were found in rats receiving a ginseng extract.[14]

Contra-indications, Warnings

It has been stated 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.[11] In view of documented pharmacological actions, ginseng may interfere with a number of therapies including cardiac, anticoagulant, hypoglycaemic and hypo/hypertensive. Ginseng is stated to be unsuitable for individuals with high blood pressure (180/90 mmHg or greater)[1] and has been advised to be avoided by premenopausal women.[11]

Russian recommendations advise 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.[11] Individuals considered suitable to use ginseng are recommended to abstain from alcoholic beverages, sexual activity, bitter substances and spicy foods.[11]

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.[11] Human studies involving long-term administration of ginseng have involved ginseng-free periods of 2–3 weeks every 30–60 days.

Pregnancy and lactation Teratogenicity studies in various animal species have not reported any teratogenic effects for ginseng. However, in view of the many pharmacological actions documented for ginseng, and the general recommendation that it should not be used by premenopausal women, the use of ginseng during both pregnancy and lactation should be avoided. It is unknown whether the pharmacologically active constituents in ginseng are secreted in the breast milk.

Pharmaceutical Comment

Phytochemical studies have revealed that there is no one constituent type that is characteristic of Eleutherococcus ginseng. Studies have shown that components thought to represent the main active constituents ('eleutherosides') consist of a heterogeneous mixture of common plant constituents. Since the 1950s, many studies (animal and human) have been carried out in Russia, and more recently in Western countries, to investigate the reputed adaptogen properties of Eleutherococcus ginseng. An adaptogen is a substance that is defined as having three characteristics, namely lack of toxicity, non-specific action, and a normalising action.[1] Results of numerous studies in animals and humans seem to support these three criteria for Eleutherococcus ginseng, although pharmacological explanations for the observed actions are less well understood.[1] As with Panax ginseng, Eleutherococcus ginseng has been shown to possess a wide range of pharmacological activities. Consequently, it should be used with appropriate regard to traditional guidelines that have been drawn up in China and Russia.

References

See also General References G3, G5, G6, G8, G9, G15, G28, G31, G32, G36, G37, G43, G49, G50 and G56.

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