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## PHYTONEWS

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### American Ginseng (*Panax quinquefolium*) – a Brief Review

Ginseng root (*Panax ginseng*) has long been the most highly regarded and widely consumed medicinal plant in China and Korea, mainly as an anti-fatigue agent and to help promote longevity. Over the years it has become increasingly recognised as an agent which can help combat stress, enhance the central nervous system, and contribute towards maintaining optimal oxidative status against certain chronic disease states and aging.

Less well known amongst white American residents and western phytotherapy practitioners is the closely related American ginseng (*Panax quinquefolium*), which has a history of remarkably similar medicinal and folkloric applications developed independently by various North American Indian tribes<sup>(1)</sup>. These similarities were recognised early on by the Chinese, and for many years American ginseng has been highly sought after in China as a substitute for Asian ginseng. Chinese or Korean (Asian) ginseng (*Panax ginseng*) is now rarely found in stores, and most Chinese herbalists appear to be using American ginseng (*Panax quinquefolium*) as a substitute for the Asian species.

#### Distribution

Ginseng is a native of most of the middle and northern states of the U.S.A. and parts of Canada, and extends to the mountains far south, growing in rich soil and shaded situations. Due to the gathering and export of large quantities to China since the 19<sup>th</sup> century, wild sources have subsequently become rare, and American ginseng is now regarded as being at risk of extinction in the wild<sup>(2)</sup>.

#### Main Constituents

Like *Panax ginseng*, a complex mixture of triterpenoid dammarane saponins termed ginsenosides or quinquenosides, are generally regarded as the most significant constituents. Although many saponins similar to those found in *Panax ginseng* occur, the overall components in American ginseng are quite different<sup>(3)</sup>. An important parameter for differentiating *P. ginseng* and *P. quinquefolium* is the presence of 24-R-pseudoginsenoside

F11 in American but not *Panax ginseng*<sup>(4)</sup>. Polysaccharides, volatile oil, resin and polyacetylenes are also present.

Different ginsenoside profiles of different ginseng preparations, appear to relate to variable effects in a range of pharmacological tests<sup>(5,6)</sup>.

## **Pharmacology**

### Adaptogenic activity

Adaptogens are defined as agents which have various effects on living organisms to help protect against unfavourable stress conditions, be they physical, biological or mental<sup>(7)</sup>. *Panax ginseng* is the best known plant adaptogen, showing evidence of such activity in a wide range of experimental models<sup>(8,9,10)</sup>.

Like its Asian counterpart, American ginseng is regarded as a mild tonic and stimulant, useful in loss of appetite, slight nervous debility, and a weak stomach. It was traditionally considered an important remedy in nervous dyspepsia, and in mental exhaustion from overwork<sup>(11)</sup>.

Both *Panax ginseng* and American ginseng have strong reputations to help reduce fatigue, and mixed but generally positive results from human clinical trials have now been documented for *Panax ginseng*<sup>(12,13,14)</sup>. American ginseng however, has to date not been subject to the same amount of evaluation in this regard. Enhanced exercise endurance in rats has however been found following four days administration of ginseng saponins, with Rb1 and Rg1 being required for activity<sup>(8)</sup>.

Mechanisms of adaptogenic activity are probably multiple, but various influences by ginsenosides on the hypothalamo-pituitary-adrenal (HPA) response are likely to be contributory<sup>(15,16,17)</sup>. Widespread enhancement of antioxidant processes<sup>(18,19,20)</sup> including stimulation of nitric oxide production<sup>(21,22,23)</sup>, and modulation of adrenal catecholamine secretion<sup>(24,25)</sup>, are also probably relevant.

### Effects on Cognitive function

Possible beneficial effects on age-related cognitive impairments are strongly supported by the *in vitro* pharmacology of ginsenoside constituents, traditional usage particularly of the closely related *Panax ginseng*, and results from animal studies.

Ginsenoside constituents of American ginseng have neuroprotective effects during ischaemia<sup>(26,27)</sup>, and protective effects against neurotoxin-induced neurodegeneration, in animal studies<sup>(27,28,29,30)</sup>. The potentially adverse effects of drugs such as methamphetamine and cocaine on dopamine receptor neurochemistry are inhibited by ginsenosides<sup>(31,32,33)</sup>, and neurite outgrowth enhanced *in vitro*<sup>(34)</sup>.

A reduction in amnesia induced by the drug scopolamine, has also been shown for both ginsenoside Rb1<sup>(35,36)</sup> and an extract of American ginseng<sup>(37)</sup>, in rats. Increased acetylcholine release and choline uptake by nerve terminals<sup>(36,38,39)</sup>, have been related to these anti-amnesic effects.

Preliminary results from a recent clinical trial using a preparation of *Panax ginseng* and *Panax notoginseng* found improved memory in a group of patients with mild to moderate vascular dementia as a result of multiple small strokes<sup>(40)</sup>.

Interactions with GABA(A) receptors, modulation of the brainstem GABAergic mechanism<sup>(41)</sup>, and a concentration-dependent inhibition of neuronal discharge frequency in brainstem unitary activity<sup>(42)</sup> have been shown for American ginseng in an *in vitro* neonatal rat brainstem-gastric preparation. These studies indicate further possible modulatory effects on brain function.

A preliminary open study involving treatment of 36 children ranging in age from three to 17 years with a combination of American ginseng and Ginkgo biloba, suggested possible improvement in symptoms of attention-deficit hyperactivity disorder (ADHD) after two weeks treatment. Further improvements were apparent after four weeks treatment<sup>(43)</sup>.

Several studies have demonstrated that behavioural activation induced by psychostimulants is prevented by ginseng saponins<sup>(44)</sup>. Animal studies have also provided evidence of significant aggression-inhibiting effects<sup>(45)</sup>, as well as possible anxiolytic activity<sup>(46)</sup>.

#### Anti-cancer activity

A large and growing body of evidence exists for wide-ranging cancer-preventive effects for *Panax ginseng*, both in experimental models and in epidemiological studies<sup>(47,48,49,50)</sup>. Various ginsenoside constituents, including several found also in American ginseng, appear to be largely contributory to such effects<sup>(51,52,53)</sup>. Anti-proliferative effects are produced in human renal, breast and prostate cancer cell lines<sup>(52,54,55)</sup>, as well as protection against radiation-induced DNA damage<sup>(57,58)</sup>. A decreased incidence of carcinogen (7,12-dimethylbenz(a)anthracene)-initiated tumorigenesis in mice has been reported, and this has been related to inhibition of carcinogen-induced activation of cytochrome P450 enzymes<sup>(57)</sup>.

Apart from direct anti-cancer effects, use of *Panax ginseng*, *Panax notoginseng* or their total saponins has been shown to potentiate the activity of various cytotoxic drugs<sup>(58,59)</sup> as well as ionising radiation<sup>(60)</sup>, on tumour cells both *in vitro* and in mice.

American ginseng has been shown to cause a dose-dependent decrease in proliferation of breast cancer cells *in vitro*, and potentiation of the suppressive effects of various anti-cancer drugs on breast cancer cell growth<sup>(61)</sup>. Induction of a universal cell cycle inhibitor p21 protein by activation of the p21 gene in both hormone sensitive and insensitive breast cancer cell lines, may be involved in this activity<sup>(62)</sup>.

#### Aphrodisiacal properties

In Asia, ginseng is commonly recommended for the treatment of sexual dysfunction, and oral administration of American ginseng has been shown to produce a dose-related enhancement in copulatory behaviour in male rats<sup>(63)</sup>. Effects included a decrease in mounting, intromission and ejaculation latencies compared to vehicle controls. No effects on plasma luteinising hormone or testosterone levels were measured between ginseng and vehicle-treated control animals, but plasma prolactin levels were reduced by all doses of ginseng treated.

This suggests that ginseng-induced alterations in dopaminergic neurotransmission may contribute to its enhancement of libido and copulatory performance. Ginsenoside-mediated vasodilatation and relaxation of penile corpus cavernosum, as well as influences on the anterior pituitary, possibly through a nitric oxide-mediated action, may be relevant<sup>(64,65)</sup>.

#### Antioxidant, cardioprotective and hepatoprotective effects

Saponins from American ginseng have shown antioxidant properties in cultured rat cardiac myocytes, and protect human low density lipoprotein (LDL) against oxidation<sup>(66)</sup>, this activity being potentiated by vitamin C *in vitro*<sup>(67)</sup>. Antioxidant activity by American ginseng extracts is evident in both lipid and aqueous mediums, and has been related to both chelation of metal ions and scavenging of free radicals<sup>(68)</sup>.

Several studies have found potentially beneficial actions of American ginseng ginsenosides in animal and cell culture models of hypoxia and ischaemia<sup>(67,70,71)</sup>, as well as in acute myocardial infarction in dogs<sup>(72)</sup>. Antioxidant activities including enhanced release of nitric oxide, are likely to contribute to these protective effects<sup>(69,73)</sup>.

An open Chinese study involving patients with advanced congestive heart failure, found improvement in haemodynamic and biochemical indices following treatment with ginseng alone or combined with digoxin<sup>(74)</sup>.

A possible role of ginsenoside Rb1 in the regulation of rat liver triglycerides has been proposed<sup>(75)</sup>, and oral administration of *Panax ginseng* reduces serum cholesterol and triglyceride levels, and platelet adhesiveness in partially hepatectomised rats<sup>(76)</sup>. This suggests a possible protective effect against a fatty liver, and other researchers have reported protective effects against liver injury in rodents<sup>(77)</sup>.

#### Immunomodulatory actions

Aqueous extracts of American ginseng containing mainly oligosaccharides and polysaccharides have exhibited *in vitro* immunomodulatory activities in murine spleen cells, peritoneal and alveolar macrophages, including enhanced production of interleukin-1, interleukin-6, TNF-alpha, and nitric oxide<sup>(78,79)</sup>.

While these studies and others involving *Panax ginseng* indicate polysaccharide-related immunostimulant and immunomodulatory effects *in vitro* for both species, it remains to be established whether such effects are produced also following oral administration of ginseng preparations due to the poor bioavailability of these large molecules.

#### Other possible activities

Experiments involving American ginseng in an *in vitro* neonatal rat brainstem-gastric preparation, resulted in a concentration-related inhibition in neuronal discharge frequency in the brainstem unitary activity. This suggests a possible regulatory role on the digestive system, mediated through modulation of brain function<sup>(80)</sup>. Improvements in hyperperistalsis of the small intestine have been shown for *Panax ginseng* as well as ginsenoside Rb1<sup>(81)</sup>. American Indians considered American ginseng to be particularly useful in nervous dyspepsia, as well as loss of appetite and a weak stomach<sup>(11)</sup>.

Canadian researchers have shown an improvement in glucose tolerance and a reduction in postprandial glycaemia in non-diabetic human volunteers, when American ginseng is taken in dosages ranging from 1 to 9g, 40 minutes before a glucose challenge test<sup>(6,82,83)</sup>. These studies suggest potential benefits to help improve control of diabetes, possibly by enhancing insulin secretion<sup>(84)</sup>. A reduction in associated risk factors such as hyperlipidaemia and hypertension, may also be additional positive influences of American ginseng in diabetic patients.

*Panax ginseng* is sometimes recommended to help alleviate menopausal symptoms, and ginsenoside Rb1 acts as a weak phytoestrogen in breast cancer cell lines<sup>(85)</sup>.

Ginseng is a popular constituent of various anti-asthmatic Chinese traditional medicines, and ginsenoside-induced relaxation of human bronchial smooth muscle has been shown<sup>(86)</sup>.

Possible analgesic activity has also been suggested in a chronic pain model involving mice<sup>(87)</sup>.

A novel protein designated quinqueginsin which has been isolated from American ginseng roots, has *in vitro* activity against the human immunodeficiency virus and antifungal activity against *Fusarium oxysporum*, *Rhizoctonia solani*, and *Coprinus comatus*<sup>(88)</sup>.

Various effects on cellular function and metabolism have been shown for *Panax ginseng*, including stimulation of DNA and protein synthesis in testes<sup>(89)</sup> and bone marrow<sup>(90)</sup> of rats. Cell culture studies in recent years have also produced evidence of enhancement of cell growth by ginseng fractions<sup>(91,92,93)</sup>, including haematopoietic progenitor cells taken from patients with aplastic anaemia<sup>(94)</sup>.

#### **Adverse effects and Contraindications**

No significant adverse effects have been documented for American ginseng to date, although like *Panax ginseng* high doses can in some cases induce an excessive stimulant effect and insomnia<sup>(95)</sup>. Ginseng is generally regarded as contraindicated in those who drink moderate to large amounts of coffee or other caffeinated beverages, and where sleep disturbance is predominant.

Adverse effects such as hypertension, nervousness, diarrhoea, euphoria<sup>(96)</sup> and inappropriate menstrual bleeding<sup>(97,98)</sup> have been reported for *Panax ginseng*, although these appear to be rare.

Like most adaptogens, American ginseng is said to be contraindicated during acute infections. It is also traditionally avoided where there are signs of heat, hypertension, excessive menstruation or bleeding disorders.

### Interactions and contraindications

While one study documented *in vitro* inhibition of liver cytochrome P450 activity by *Panax ginseng*<sup>(99)</sup>, subsequent research found no influence by various ginsenosides on cP450 isoforms<sup>(100)</sup>.

Several potentially beneficial interactions between ginseng saponins and various treatments for cancer have been suggested from *in vitro* studies in recent years. These include a reduction in testicular toxicity associated with use of the cytotoxic drug doxorubicin<sup>(101)</sup>, sensitisation of leukaemic cells to cytotoxic drugs<sup>(59)</sup>, and sensitisation of tumour cells to the cytotoxic effects of radiation<sup>(60)</sup>. Possible reversal of multidrug resistance mediated by the cellular efflux protein P-glycoprotein, may contribute to these effects<sup>(102)</sup>.

### Dosage

In traditional Chinese medicine, doses of 2 to 10g per day of a dried root decoction are normally taken, in one or two divided doses per day. While somewhat contentious, it is generally recommended that a break from treatment is taken after 2 or 3 months. Lower doses are generally used in older people, in whom the need for a break in treatment is not regarded as necessary.

In modern phytotherapy, a dose range of 0.5-3g, (1-6ml of a 1:2 liquid extract) per day, is normally recommended.

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