SIBERIAN GINSENG

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.

Family

Araliaceae

This family includes some 84 genera of mostly woody vines (ivy), shrubs and trees.

The synonyms are *Acanthopanax senticosus* (Rupr. & Maxim.) Harms; *Acanthopanax asperatus* Franch. & Sav.; *Eleutherococcus asperatus* (Franch. & Sav.) Koidz.; and *Hedera senticosa* Rupr. & Maxim.[1]

Parts Used

Root.

Description

Siberian ginseng is a thorny, hardy shrub that can grow up to seven metres high but is usually around two metres high. It is native to the north-eastern region of China, Korea, Japan and the far-eastern region of Russia. It grows in mixed and coniferous mountain forests, forming low undergrowth, or is found in groups in thickets and edges.[2] It has erect, prickly stems, compound leaves and inconspicuous purple to yellow flowers produced in multi-flowered umbels.[3]

Traditional Use

Eleutherococcus is from the Greek eleutheros meaning free and kokkos meaning pip or seed. In Latin senticosus is an adjective meaning 'full of briars or thorns', referring to the plant's thorniness. This has led to the common Russian names of thorny eleutherococcus (eleutherokokk koljuchii), untouchable (nedotroga), devil's bush (dyavol'skii kust), wildpepper (dikii perets) or even thorny bearer of free berries (svobodnojagodnik koljuchii). The

far less common Russian name taiga root (tajozhnyi koren) derives from its association as an understory plant in the northern coniferous evergreen forests of the sub-arctic region (the so-called taiga bordered on the north by the treeless tundra and on the south by the steppe). One of the common names of Siberian ginseng in German is Taigawurzel (taiga root).[4]

In Russia, Siberian ginseng was originally used by people in the Siberian taiga region to increase performance and quality of life, and to decrease infections. In the late 1940s Russian scientists began to study compounds that brought about a state of 'non-specifically increased resistance' of an organism, which is a physiological condition that is linked with various disorders of the neuroendocrine–immune system, in experimental animals and humans. According to the late Professor Israel Itskovitch Brekhman, it was Dr Nikolai Vasilievich Lazarev, then the leading figure in Soviet pharmacology and toxicology and a developer of a number of new drugs, who first proposed to the scientific and medical community in the mid-1950s that substances which were able to bring about an increased non-specific resistance be called adaptogens. These various properties of an adaptogen were expanded upon and enumerated in outline form by Brekhman in 1968 and were published in his multidisciplinary publication on Siberian and Korean ginseng *(Panax ginseng)*. According to Brekhman: 1. The action of an adaptogen should be innocuous and cause minimal disturbance to the normal physiological functions of an organism. It must be absolutely harmless. 2. An adaptogenic agent should not be active only in a specific context or against a particular background. It must have a broad therapeutic spectrum of action. 3. The action of an adaptogen has to be non-specific, that is to say, resistance to a wide variety of action of harmful factors, whether of a physical, chemical or a biological nature, has to increase. In other words, the action of an adaptogen has to be more intense as unfavourable changes occur in an organism. 4. An adaptogen has to have a normalising or stabilising action independent of the direction of previous changes.[5]

This definition has been updated as 'a new class of metabolic regulators which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors'.[6] The term adaptogen was used as a functional claim for certain botanicals and herbal medicinal products in Europe and the USA and the adaptogen concept is now a generally accepted concept.[7]

Soviet scholars were the first to establish the fact that many plants belonging to the Araliaceae family are adaptogens. In the early 1950's, Soviet researchers pioneered the study of Korean ginseng, which was considered to be the primary adaptogen, and some other plants of the ginseng group. Because of its rarity, Korean ginseng was found to be impractical as a source of raw material for the mass production of medicines. Consequently, Soviet scholars shifted the focus of their research from studying Korean ginseng to other members of the ginseng group in order to find suitable substitutes. Four adaptogenic plants were identified, studied and finally introduced into therapeutic practice, between 1955 and 1964. Siberian ginseng was considered to be the most important of these substitutes.[8]

In that early period, a wide range of individuals appear to have taken up the use of Siberian ginseng, including elite athletes. Soviet-era coaches are reputed to have incorporated regular use of Siberian ginseng preparations into their athlete-training protocols because of its purported ergogenic (performance enhancing) activity. Familiarity with Siberian ginseng as an ergogenic aid and adaptogen entered Europe through encounters with Soviet-bloc trainers, coaches, athletes and sports physicians.[9] It was used by Russian athletes in the 1984 Moscow Olympics and has become a popular tonic in the former USSR.[10] In 1966 Siberian ginseng was recommended for use in the Soviet space program.[11]

Although not as popular as Korean ginseng, the medicinal use of Siberian ginseng dates back 2000 years according to Chinese medicine records (where it is known by its synonym Acanthopanax senticosus). Known as Ci Wu Jia in Chinese, Siberian ginseng is a widely used traditional Chinese herb that can invigorate qi (vital energy), strengthen the spleen and nourish the kidney in the theory of Traditional Chinese Medicine (TCM). In the Pharmacopoeia of the People's Republic of China it is known as efficient in invigorating the liver and kidney, replenishing the qi and strengthening bones, and can be used to relieve symptoms of transient cerebral ischemia attacks (mini stroke), cerebral arteriosclerosis, cerebral thrombosis and cerebral embolism caused by a deficiency in the liver and kidney. It is used to treat coronary heart disease, angina pectoris, a combination of neuroses and menopausal symptoms. It is well known to be highly effective in treating various conditions, including stress-induced pathophysiologic changes and inflammation.[12]

Siberian ginseng was first introduced into the American herb market in the late 1970s, as Wuchaseng and Wujiaseng, and it became commonly known as Eleuthero. It was previously marketed in the United States as Siberian ginseng because it has properties similar to those of Korean ginseng however it is only distantly related to the true ginseng species (*Panax ginseng* and *Panax quinquefolius*) and shows a marked difference from Korean ginseng in the main components. The active components of Siberian ginseng were considered to be lignans, while saponins were the most bioactive constituents in Korean ginseng. In May 2002, the United States Congressional amendment to the Federal Food, Drug and Cosmetic Act eliminated any confusion regarding what is true ginseng and, currently, only the genus Panax can be called ginseng on labelling or in advertising. Marketing Eleuthero as Siberian ginseng in the United States is illegal however it is still known as Siberian ginseng in Australia.[13]

Constituents

Although over 35 compounds have been identified from Siberian ginseng, the search for active substances is not finished yet. The observed activity of Siberian ginseng may be due to the combined effect of all its constituents, discovered or otherwise.[14] The exact mechanism of action of Siberian ginseng and the significance of each of its various constituents is not yet fully understood.[15] Phytochemical studies have revealed that there is no one constituent type that is characteristic of Siberian ginseng. The constituents responsible for the characteristic biological effects of Siberian ginseng appear to be a complex mixture of phenylpropane derivatives of diverse structure, and various sugar polymers. Studies have shown that components thought to represent the main active constituents ('eleutherosides') consist of a heterogeneous (varied) mixture of common plant constituents, including carbohydrates, coumarins, lignans, phenylpropanoids and triterpenoids.[16]

Carbohydrates: Polysaccharides (glycans); some have been referred to as eleutherans. Galactose, glucose, maltose, sucrose, methyl-alpha-D-galactose (eleutheroside C).

Phenylpropanoids: syringin and its monoglucoside (eleutheroside B), caffeic acid, sinapyl alcohol, coniferyl aldehyde.

Lignans: sesamin (eleutheroside B4), syringoresinol and its monoglucoside (eleutheroside E1) and diglucoside (eleutherosides D and E).

Triterpenoids: hederasaponin B, betasitosterol and its glucoside daucosterol (eleutheroside A), betulinic acid

Coumarins: isofraxidin and its monoglucoside (eleutheroside B1).

Vitamins: vitamin E, provitamin A (betacarotene).

Essential oil: 0.05% including isocaryophyllene and caryophyllene oxide.

Eleutheroside E has been found in all samples regardless of geographical origin, whereas eleutheroside B is present in all samples, except those from plants grown in the Democratic People's Republic of Korea.[17]

Eleutheroside B (syringin) and Eleutheroside E as main compounds might be responsible for stress protective, anti-inflammatory, hypoglycaemic and hepatoprotective effects, while polysaccharides are shown to have immunomodulating activity. However, the pharmacology of Siberian ginseng reflects the synergistic effects of its combined phytochemical constituents, especially those effects produced by the glycosides (eleutherosides) which are present.[18]

Actions

Adaptogen (modulates stress response), immunomodulator, antiviral, mild stimulant, tonic.

Stimulating action refers to the ability of medicinal substances to increase the work capacity of the organism after a single dose of the preparation. The tonic effect of a substance refers to the results obtained after prolonged doses. This effect is reported to be manifested by an increase in work capacity, not only during the time period that the substance is being used, but for a sustained period of time thereafter.[19]

Pharmacological Activity

Numerous clinical and pharmacological studies (animal and human) on Siberian ginseng have been conducted since the 1960s. Despite the high number of studies, Siberian ginseng preparations do not reach the level of well established use therefore the clinical data is still inconclusive, and does not prove the efficacy of Siberian ginseng in a well-defined clinical condition. In most of the studies, results were generally reported to be positive: e.g. blood pressure was normalised, serum prothrombin and cholesterol levels were reduced and overall wellbeing and physical work performance improved.[20] However these trials lacked good methodology (e.g. very few patients were involved, they lacked proper controls and randomisation, experiments were not double-blind etc.). The clinical data has a number of shortcomings such as deficiencies in the description of inclusion and exclusion criteria, description of the medication, diagnosis, study design, analysis etc. There is a wide range of clinical conditions that have been investigated and in some studies the number of patients was very small. The beneficial effects of Siberian ginseng (enhanced endurance capacity, elevated cardiovascular functions and altered metabolism for sparing glycogen) were found in a 2010 study after eight weeks treatment (see below in Adaptogenic activity).[21] However the small number of participants does not give evidence of clinical efficacy. A clinical study performed in 2013 showed that the addition of Siberian ginseng to stress management did not create any substantial effect.[22]

Efficacy of adaptogens has been reported by many groups of investigators. The extensive studies on Siberian ginseng have contributed much to the beginning of an understanding of the adaptogenic response. Modern clinical studies on adaptogens that were started only in recent years may provide a better insight in the future.[23]

The majority of the early literature on Siberian ginseng has been published in Russian and therefore difficulty is encountered in obtaining translations. These Soviet studies are summarised in English in the 1985 review article by Norman Farnsworth et al.[24] These clinical studies, involving more than 2100 normal and stressed human subjects, were conducted using an orally administered 33% ethanol root extract of Siberian ginseng. Doses ranging from two to 16mL were taken one to three times a day for up to 60 consecutive days (with a two-to-three-week resting interval between courses of administration). Up to five courses of administration have been given to male and female subjects, ranging from 19 to 72 years of age. The studies were performed to measure the adaptogenic response of humans to adverse conditions such as heat, noise, motion, work load increase, exercise, as well as to measure improvements in auditory disturbances, increased mental alertness, work output and the quality of work both under stress-inducing conditions and in athletic performance. Additional studies on its clinical effectiveness and side effects have been conducted involving over 2,200 human subjects suffering from a wide variety of ailments including neuroses, atherosclerosis, several forms of diabetes, hypertension, hypotension, chronic bronchitis, cancers, acute head trauma, rheumatic heart disease and other ailments. Dosage reported in these studies was less than for healthy subjects, ranging from 0.5mL to 6mL one to three times per day, with courses of administration lasting for a shorter overall duration of 35 days. Again, administration was interrupted for two to three weeks between treatments. These studies showed measurable improvements or, in some cases, normalisation with few side effects, though in no way can the results be interpreted as 'cures' for the ailments under investigation.[25]

Adaptogenic Activity

A number of clinical trials have clearly demonstrated that adaptogens exert an antifatigue effect that increases mental work capacity against a background of stress and fatigue, particularly in tolerance to mental exhaustion and enhanced attention. Studies on animals and isolated cells have revealed that adaptogens exhibit neuroprotective, antifatigue, antidepressive, anxiolytic, nootropic, and central nervous system stimulating and tonic effects. In contrast to conventional stimulants such as sympathomimetics (e.g., ephedrine, fenfluramine, phentermine, prolintane) and general tonics, adaptogens do not possess addiction, tolerance and abuse potentials, or impair mental function, or lead to psychotic symptoms with long term use. Recent pharmacological studies of a number of adaptogens have provided a rationale for these effects also at the molecular level.[26]

A 2013 American study has shown that the stress hormone neuropeptide Y (NPY) and heat shock protein Hsp70 can be used as molecular biomarkers for adaptogenic activity clarifying what the primary upstream targets are in response to stimulation by adaptogens.[27] Neuropeptide Y is widely distributed in the central and peripheral nervous system. The beneficial stress-protective effect of adaptogens is related to the regulation of homeostasis via mechanisms of action associated with the hypothalamic-pituitary-adrenal axis and the regulation of key mediators of the stress response, such as molecular chaperones (a group of proteins involved in cell homeostasis through protein folding and degradation), stress-activated c-Jun N-terminal protein kinase (a major cellular stress response protein induced by oxidative stress), forkhead box O transcription factor (an important family of proteins which are key regulators of cellular responses), cortisol (a hormone made by the adrenal glands) and nitric oxide (a free radical).[28]

In the first well conducted study of its kind, a small 2010 trial has shown that eight weeks of Siberian ginseng supplementation enhances endurance capacity, elevates cardiovascular functions and alters the metabolism for sparing glycogen in recreationally trained males. Nine recreationally trained males in college consumed 800mg/d of Siberian ginseng (equivalent to 3.2g/day of dried root and rhizome) or starch placebo for eight weeks according to a double-blind, randomised, placebo controlled and crossover design with a washout period of four weeks between the cycling trials. Subjects cycled at 75% peak oxygen uptake (VO2 peak) until exhaustion. The examined physiological variables included endurance time, maximal heart rate during exhaustion exercise, VO2, rating of perceived exertion and respiratory exchange ratio. The biochemical variables including the plasma free fatty acid (FFA) and glucose were measured at rest, 15 minutes, 30 minutes and exhaustion. The major finding of this study was the VO2 peak of the subjects elevated 12% ($p < 0.05$), endurance time improved 23% ($p < 0.05$) and the highest heart rate increased 4% ($p < 0.05$) significantly. The second finding was at 30 minutes of 75% VO2 peak cycling, the production of plasma FFA was increased and the glucose level was decreased both significantly ($p < 0.05$) over eight weeks of Siberian ginseng supplementation.[29]

The results of a 2008 study suggest that Siberian ginseng supplementation may have beneficial effects against oxidative stress and improve serum lipid profiles without subsequent side effects. The study examined the effects of Siberian ginseng supplementation on serum lipid profiles, biomarkers of oxidative stress and lymphocyte DNA damage in postmenopausal women. Forty postmenopausal women, aged 40 to 65, were randomly divided into two groups: (1) control group (calcium) and (2) treatment group (calcium plus Siberian ginseng). Both groups were treated for six months.[30]

A randomised, placebo-controlled trial on the effect of Siberian ginseng on psychological distress has confirmed that it is helpful for stress adaptation. The study found that Siberian ginseng is able to reduce cardiovascular responses to stress in healthy young volunteers, while placebo was ineffective. Forty-five paid, healthy volunteers (20 males, 25 females) were recruited.[31]

The influence of active components of Siberian ginseng were studied on cellular defence and physical fitness in humans. 50 healthy volunteers of both sexes were selected, and basic clinical examination and laboratory tests were performed in all subjects. All were randomly subdivided into two study groups: group A with 35 subjects receiving Siberian ginseng and group B with 15 subjects receiving Echinacea. 20 healthy males were randomly selected from both groups and underwent an ergospirometric study (a diagnostic procedure to continuously measure respiration and gas metabolism during ergometer exercise). The preparations were administered for 30 days as follows: Siberian ginseng 25 drops three times daily, Echinacea 40 drops three times daily. After one month blood was drawn for control tests. Changes in the following blood parameters were observed in comparison to initial values in group A: total and LDL cholesterol, triglycerides and glucose. No alterations were seen in group B. The ergospirometric test revealed a higher oxygen plateau in group A (Siberian ginseng). On the basis of the study the following conclusions were drawn: active components in Siberian ginseng affect cellular defence and physical fitness, as well as lipid metabolism.[32]

Siberian ginseng can increase stress resistance in several model systems and also increase the mean lifespan of the nematode C. elegans (roundworm) in a dose-dependent way suggesting a modulation of the ageing process.[33]

An *in vivo* study has found that Siberian ginseng reduces fatigue during exercise by the inhibition of exercise-induced serotonin (5-hydroxytryptamine-5-HT) synthesis and tryptophan hydroxylase (TPH) expression in the rodent dorsal raphe (located in the brainstem). Siberian ginseng increased the time to exhaustion by treadmill running and it suppressed the exercise-induced increase of 5-HT synthesis and TPH expression. It was as effective as caffeine for increasing the exhaustion time in treadmill running and for reducing the exercise-induced increase of 5-HT synthesis and TPH expression in the dorsal raphe.[34]

Immune Activity

Numerous *in vitro* and *in vivo* studies have examined the immunomodulatory effects of Siberian ginseng. The stimulating effect of Siberian ginseng is thought to involve the activation of T-lymphocytes by the eleutherosides. There may also be an indirect immune-enhancing effect mediated via the glycosides' more non-specific antistressor activity as stress may decrease the activity of the immune system, particularly that of natural killer T-cells.[35]

A placebo-controlled study of the effect of Siberian ginseng on the immune system was performed with 36 healthy volunteers. Volunteers in the verum (true) group received 10mL of an ethanolic (vincamine free) Siberian ginseng preparation, three times daily for four weeks. In the placebo, the Siberian ginseng was substituted by additional wine, resulting in identical final concentrations of ethanol in both preparations. The purpose of the double-blind study was the demonstration of possible effects on the cellular immune status, as determined by quantitative flow cytometry. The most salient feature in the verum group was a drastic increase in the absolute number of immunocompetent cells, with an especially pronounced effect on T-lymphocytes, predominantly of the helper/inducer type, but also on cytotoxic and natural killer cells. In addition, a general enhancement of the activation state of T-lymphocytes was observed. No side effects were observed during the trial or afterwards in the observation period of six months.[36]

An ethanol extract of Siberian ginseng inhibited the release of interleukin (IL)-4, IL-5 and IL-12 from human peripheral blood lymphocytes in *in vitro* experiments using human whole blood. The release of IL-6 was stimulated by higher concentrations of the Siberian ginseng preparation and inhibited with lower concentrations suggesting that Siberian ginseng has immunomodulatory rather than immunosuppressive or immunostimulant activity.[37]

Whole ethanolic fluid extract of Siberian ginseng was able to induce and enhance IL-1 and IL-6 but not IL-2 production *in vitro*.[38]

Evidence for the immune enhancing effects of Siberian ginseng is contradictory with other *in vitro* studies using mouse macrophages finding that an aqueous extract of ginseng root did not stimulate the expression of the range of cytokines investigated.[39]

Antiviral Activity

In vitro studies with an ethanolic extract of Siberian ginseng show strong antiviral activity against RNA (ribonucleic acid) -type viruses such as human rhinovirus, respiratory syncytial virus and influenza A virus.[40]

Antioxidant Activity

A 2014 study has shown Siberian ginseng possesses a very good ability to scavenge superoxide and hydroxyl radicals and showed no decomposition ability. The antioxidant defence system against the excessive production of radicals in mitochondria was sufficient.[41]

Siberian ginseng acted as a strong antioxidant in addition to exerting antiheat environmental stress effects in a recent animal study.[42]

Antiallergic Activity

A Japanese *in vivo* study found Siberian ginseng has antiallergic effects since it had inhibitory effects on histamine release from mast cells and seemed to have histamine and serotonin antagonistic activities at high doses.[43]

Siberian ginseng inhibits mast cell-mediated anaphylaxis in *in vivo* and *in vitro* rodent models. It can inhibit systemic anaphylaxis, passive cutaneous anaphylaxis reaction and histamine release from mast cells in a dose-dependent manner. Moreover, it had an inhibitory effect on antidinitrophenyl IgE-induced tumour necrosis factor-alpha (TNF-alpha) production from mast cells in a concentration-dependent manner.[44]

Anti-inflammatory Activity

A 2014 study has shown that Siberian ginseng has anti-inflammatory effects. The study examined the prophylactic and therapeutic effects of Siberian ginseng on rheumatoid arthritis using collagen-induced arthritis (CIA) mouse model. Siberian ginseng treatment delayed the onset and decreased the severity of CIA. *In vitro* examinations showed that Siberian ginseng is an antioxidant and that it suppresses tumour necrosis factor alpha (TNF-a) and interleukin-6 production in human peripheral blood mononuclear cells. The combination therapy with Siberian ginseng and anti-TNF-α antibody reduced the severity of arthritis compared with anti-TNF-α antibody alone.[45]

Excess production of nitric oxide (NO) is one of the characteristics of inflammation. Siberian ginseng significantly suppressed NO production and inducible nitric oxide synthase (iNOS) gene expression in a dose-dependent manner.[46]

In addition, excess production of reactive oxygen species by macrophages has been implicated in many inflammatory diseases. A Chinese study has shown that Siberian ginseng inhibited reactive oxygen species production by mouse peritoneal macrophages *in vitro* and *in vivo* and may be partly responsible for the anti-inflammatory function. Exposure of mouse peritoneal macrophages to Siberian ginseng significantly suppressed superoxide anion production induced by zymosan in a dose-dependent manner. Similarly, exposure of mouse peritoneal macrophages to Siberian ginseng significantly inhibited hydrogen peroxide production induced by phorbol 12-myristate 13-acetate (PMA) in a dose-dependent manner.[47]

Radioprotective Activity

Administration of Siberian ginseng given intraperitoneally 24 hours before a lethal dose of irradiation produced an 80% survival rate in mice and it was still effective when administered as late as 12 hours after irradiation with a survival rate of 30%.[48]

Mental and Behavioural Activity

A Russian study investigated the effect of Siberian ginseng on various psychophysiological parameters depending on their chronotype and time of day in healthy humans. It was reported that acute administration of liquid ethanolic extract (20 drops) significantly improves aural memory volume and decreases reactive anxiety. These effects were dependent on the time of day (morning versus evening) and the individual chronotype (circadian features) of each volunteer. Statistically significant effects were observed in mornings for evening people and in evenings for morning people.[49]

Siberian ginseng can improve the quality of life of the elderly a small study has found. The aim of the study was to test the mid-term effects of Siberian ginseng on health-related quality of life using a randomised, double-blind, placebo-controlled design. Twenty elderly (age ≥ 65 years) hypertensive patients, also prescribed digitalis, received either an extract of Siberian ginseng (300mg/day corresponding to around 2.5g of starting herb) or placebo for eight weeks. After four weeks of therapy patients receiving active treatment achieved significantly higher scores for social functioning (p = .017) and mental health (p = .02), compared to placebo. However, these differences were not as apparent after eight weeks. Significantly, no adverse events were observed and there was no adverse interaction with digitalis levels in the patients' blood samples, unlike a previous report.[50,51]

In a placebo-controlled 3-arm study, 80, 23 to 55-year-old subjects (38 men and 42 women) with a history of one to five years of neurosis were given Siberian ginseng 120mg twice a day (corresponding to 0.5mL liquid extract twice a day), 240mg twice a day (1mL of the liquid extract twice a day) or placebo for three to four weeks. Compared to placebo, both doses of herb significantly improved sleep, well-being, appetite, stamina, cognitive function and mood, without side effects. The lack of randomisation and unclear diagnostic grouping limit the quality of this early study.[52]

Patients diagnosed as having idiopathic chronic fatigue, who were treated for one month with Siberian ginseng extract 2g/day (about 9mg of eleutherosides), significantly improved on Rand Vitality Index scores compared with placebo. A longer period of treatment for two months was less effective for the whole group but still significantly effective in a subset of subjects with mild-to-moderate fatigue. These results indicate that in some patients with idiopathic chronic fatigue adaptogen effects may fade over time. In such cases, wash-out periods may be useful during long-term treatment.[53]

The effectiveness of Siberian ginseng (750mg three times a day) compared with fluoxetine (20mg am) as an adjunct to lithium (serum lithium levels 0.6 to 1.2mmol/L) in Chinese adolescents with bipolar disorder was evaluated in a six-week double-blind, randomised, controlled trial. Outcomes were defined as follows: Response was improvement of greater than 50% on HAMD-17; Remission was HAMD-17 less than 7; Switching to mania was a score greater than 16 on the Young Mania Rating Scale and meeting criteria for mania based on the Diagnostic and Statistical Manual of Mental Disorders. After six weeks of treatment, response and remission rates of the Siberian ginseng group and the fluoxetine group were similar (67.6% vs 71.8%, and 51.4% vs 48.7%, respectively). There was a significant time effect ($p < .01$) but not a significant group effect or group by duration of treatment interaction. In this study, Siberian ginseng as an adjunct to lithium in bipolar adolescents was as effective as fluoxetine. Both treatments were well tolerated, but Siberian ginseng had a better safety profile with fewer adverse events (10.8%) than fluoxetine (30.9%). Moreover, three subjects given fluoxetine switched to mania compared with no subject in the Siberian ginseng group. The use of Siberian ginseng as an adjunct to mood stabilisers in bipolar disorder warrants further study.[54]

Hepatoprotective Activity

An *in vivo* study showed that Siberian ginseng had a significantly decreasing effect of cadmium concentrations in the blood and liver of experiment mice. Moreover, it decreased the cadmium induced mitotic and apoptotic activity of liver cells.[55]

Anticancer and Antitumour Activity

A Korean study has found that the aqueous extract of Siberian ginseng is able to inhibit tumour metastasis prophylactically as well as therapeutically, and its antitumour effect is associated with activation of macrophages and natural killer cells.[56]

Skeletal System Activity

A prospective randomised study investigating the effects of Siberian ginseng on bone remodelling and bone mineral density in Korean postmenopausal women found it may have beneficial effects. The Siberian ginseng group showed a significant increase in serum osteocalcin levels compared to the control group. No significant adverse effects were observed. A total of 81 postmenopausal women with osteopenia or osteoporosis, and an age of less than 65 years, were enrolled in the study.[57]

Antidiabetic and Hypoglycaemic Activity

A 2013 German double blind, placebo-controlled trial has demonstrated that in contrast to *Panax quinquefolius* (American ginseng) and placebo, Siberian ginseng is able to lower elevated blood sugar levels in patients with type 2 diabetes, both at fasting states and after eating. It was also the first report demonstrating a favourable long-term effect on lipid metabolism and on peripheral neuropathy. In the trial, 75 patients were recruited and randomly allocated to receive either a purified solution of Siberian ginseng or a solution of American ginseng in addition to their regular oral antidiabetic medication for three months. All patients had a history of type 2 diabetes for at least seven years (oral medication 80%, insulin therapy 20%). In comparison a group of 25 patients were randomly allocated to receive a placebo preparation. The solution of Siberian ginseng consisted of a standardised dried extract of 9% Siberian ginseng diluted in 36.99% distilled water with 0.07% salt mixed together in 54% of a 70% sorbitol (sugar alcohol) solution. To this solution 0.27% of agar-agar was given. An additional 0.03% of an apple extract was added for taste purposes. Active ingredients eleutheroside E and B were found to be in a concentration of 1.12% in the Siberian ginseng preparation. Each day 30 minutes prior to breakfast, the subjects took a total of 450mg of the extract of Siberian ginseng orally. Similarly, a dried preparation of 450mg of American ginseng was diluted and given to the other group of patients with type 2 diabetes, while the control population took a solution which looked the same consisting only of a fibre mixture. Contrary to placebo and American ginseng, Siberian ginseng intake resulted in a highly significant decline ($p < .001$) of fasting blood sugar and postprandial (after eating a meal) blood sugar level at the end of the three-month period. Also, Siberian ginseng lowered significantly ($p < .001$) HbA1c (glycated haemoglobin), TC (total cholesterol) and TG (triglyceride) levels after the 12-week period. Patients taking Siberian ginseng demonstrated some recovery of sensitivity to an electrical stimulus. Since eleutherosides are only found in Siberian ginseng, the authors surmised that they contributed to the observed therapeutic effect, which may be due to their ability to blockade P-glycoprotein, an ATP-dependent drug efflux pump, which is responsible for an increase in insulin resistance. The doses taken at regular intervals were safe and effective, and they did not carry a significant risk of causing dangerously low blood sugar levels (hypoglycaemia) in diabetes patients, which otherwise took standard prescription drug medication. In addition, because of the lack of hypoglycaemia in any of the patients, Siberian ginseng can be considered an agent for assisting in the correction of an abnormal carbohydrate and lipid metabolism in people with type 2 diabetes. However, the authors stated that from the results of this study the conclusion cannot be drawn that Siberian ginseng is a substitute for any oral antidiabetic medication. It should be considered an adjunct to diabetic therapy and may act additively, or possibly synergistically, with standard oral antidiabetic agents. This was deemed a rational approach as a premix of insulin is advocated in patients who were otherwise failing to reach glycaemic targets on basal insulin. The authors concluded that because of the favourable results a follow-up study with Siberian ginseng should be undertaken where the preparation is given for a period of at least a year.[58]

The effects of an active principle of Siberian ginseng, syringin, on plasma glucose levels in streptozotocin-induced diabetic rats (STZ-diabetic rats) were investigated recently. The ability of syringin to enhance glucose utilisation and lower plasma glucose level in rats suffering from insulin deficiency suggest that this chemical may be useful in the treatment of human diabetes.[59]

Oral administration of the aqueous extract from Siberian ginseng has the ability to improve insulin sensitivity and delay the development of insulin resistance in rats and, thus, may be used as an adjuvant therapy for patients with insulin resistance a study has found.[60]

Indications

- As a tonic in cases of decreased performance such as chronic fatigue syndrome, fatigue, sensation of weakness, exhaustion, tiredness, irritability, insomnia, mild depression and loss of concentration.
- As a prophylactic and restorative tonic for enhancement of mental and physical wellbeing.
- Convalescence during recovery from acute or chronic disease, trauma, surgery and other stressful episodes.
- To increase the body's resistance to stressful exposures such as heat, cold, physical exhaustion, viruses, bacteria, chemicals, extreme working conditions, noise and pollution.
- Adjunctive cancer treatment to increase the tolerance of patients to the adverse effects of chemotherapy and radiation therapy.

Energetics

Warming.

Use in Pregnancy

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. It is not traditionally used in pregnancy.

Drug Interactions

Caution with alcohol, central nervous system depressants, digoxin, lithium and immunosuppressant drugs. Monitor with anticoagulant/antiplatelet and antidiabetic drugs. May be beneficial in chemotherapy – medical supervision recommended.

Contraindications

May cause insomnia in some people if taken too close to bedtime. People with hypertension should be monitored.[62]

Administration and Dosage

Liquid Extract:	1:1
Alcohol:	45%
Weekly Dosage:[63]	15 to 40mL

Some researchers recommend that Siberian ginseng should not to be taken for more than two months. For chronic conditions such as fatigue, preparations have been used for three months. Most researchers recommend that, if a course is repeated, the next course should start after a 10 to 14 days break.[64]

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