Eleutherococcus senticosus

Description

Eleutherococcus senticosus (also known as *Acanthopanax senticosus* or Ciwujia, and previously known as Siberian ginseng) is an approximately two-meter high, hardy shrub native to the far eastern areas of the Russian taiga and the northern regions of Korea, Japan, and China.[1]

Active Constituents

The active ingredients of this plant are typically concentrated in the root and mainly consist of chemically distinct glycosides called eleutherosides A-M.[2] Other phytochemicals found in the root structure include ciwujianosides (minor saponins), eleutherans (polysaccharides), beta sitosterol, isofraxidin (a coumarin derivative), syringin, chlorogenic acid,[3] sesamin[2] (lignans), and friedelin (triterpene).[2] Eleutherosides I, K, L, and M have also been identified and isolated from the leaf of the plant.[2]

Mechanisms of Action

Eleutherococcus is primarily known as an adaptogen. This term, coined by researcher I.I. Brekhman, suggests such a plant has four general properties: (1) it is harmless to the host; (2) it has a general, rather nonspecific, effect; (3) it increases the resistance of the recipient to a variety of physical, chemical, or biological stressors; and (4) for the user, it acts as a general stabilizer/normalizer.[4] Using animals to test this theory, researchers found Eleutherococcus decreases adrenal hypertrophy and the subsequent depletion of adrenal vitamin C levels in stressed rats.[5] Moreover, animals treated with an aqueous extract from the stem bark of this herb were able to increase their swimming time to exhaustion, confirming original research that mice exposed to Eleutherococcus have more stamina.[5,6]

In addition to its anti-fatigue and anti-stress effects, the plant also exhibits immunomodulatory effects. One study found intraperitoneal (i.p.) administration of an extract (primarily eleutherosides B and D) increased the cytostatic activity of natural killer cells by 200 percent after one week.[7] Another *in vitro* study confirmed a liquid extract of the root inhibits replication of RNA viruses (human rhinovirus, respiratory syncytial virus, and influenza A virus), but not cells infected with DNA viruses such as adenovirus or *Herpes simplex*, type 1.[8]

Eleutherococcus affects cytokine expression. A fluid extract, at doses of 0.1-1.0 mg/mL and 0.03-1.0 mg/mL, induced and enhanced the actions of IL-1 and IL-6, respectively, but not IL-2 *in vitro*.[9]

Studies using an animal model of cerebral ischemia demonstrated an anti-inflammatory and neuroprotective effect. Eleutherococcus markedly inhibited cyclooxygenase-2 (COX-2) expression and decreased cerebral ischemia in rats with induced cerebral artery occlusion.[10]

Other pharmacological actions associated with Eleutherococcus root include prevention of bone resorption during experimental, steroid-induced osteoporosis,[11] protection against experimentally-induced fulminant hepatic failure (possibly via apoptosis or antioxidant mechanisms),[12] radioprotection of the hematopoietic system in mice

exposed to lethal radiation,[13] inhibition of histamine release from rat peritoneal cells, and inhibition of systemic anaphylaxis in rats.[14] Other research has noted the stem bark not only increases the concentration of biogenic amines (noradrenalin and dopamine) in the rat brain,[15] but also prevents stress-induced gastric ulcerations in rats[16] and induces apoptosis in human stomach cancer KATO III cells.[17]

Clinical Indications

Athletic Performance

Eleutherococcus has been touted as the herb that builds Russian athletes. In his review of the Russian scientific literature, Farnsworth notes a single 4 mL dose of a 33-percent ethanolic liquid extract given to five male skiers 1-1.5 hours before a 20-50 kilometer race increased skier resistance to hypoxemia and enhanced their ability to adapt to increased exercise demands.[18] In another summary of the Russian studies, Halstead cites research on runners given either 2 mL (n=34) or 4 mL (n=33) of the extract 30 minutes before participating in a 10-kilometer race. The results were compared to 41 participants who did not take the herb (control). Those who took either 2 or 4 mL of the extract completed the race in an average time of 48.7 minutes and 45 minutes, respectively, compared to 52.6 minutes for the control group.[19]

After establishing baseline maximal work loads (control) using bicycle ergometry, six healthy male athletes (ages 21-22) were given 2 mL (150 mg of the dried material) of a 33-percent ethanol extract of Eleutherococcus or a comparable placebo in the morning and evening 30 minutes before meals for eight days. Compared to control, individuals who took the herb had significant increases in overall work performance, including maximal oxygen uptake ($p<0.01$), oxygen pulse ($p<0.025$), total work ($p<0.005$), and exhaustion time ($p<0.005$). The Eleutherococcus group experienced a 23.3-percent increase in total work and a 16.3-percent increase in time to exhaustion compared to only a 7.5-percent and 5.4-percent increase in respective placebo values ($p<0.05$).[20]

Other research, however, has not been able to reproduce the athletic-enhancing actions of Eleutherococcus. In a double-blind study involving nine endurance cyclists, 1,200 mg of a crude extract was taken daily for seven days prior to a simulated 10-kilometer time trial. Supplementation did not significantly alter the physiological responses of the athletes (e.g., oxygen consumption, respiratory exchange, heart rate, plasma lactate, plasma glucose, or perceived exertion) compared to placebo.[21]

Immune Deficiency

A few studies have examined the effects of *Eleutherococcus senticosus* on the immune response.

In a controlled trial, 36 subjects were randomized to receive 10 mL *Eleutherococcus senticosus* root extract or placebo three times daily after meals for one month. A flow cytometric evaluation of lymphocyte subpopulations was made before and after administration of the herb or placebo. After four weeks of therapy, those in the active group had a significant increase in total lymphocyte ($p<0.0001$), T-helper ($p<0.00001$), T-suppressor ($p<0.0001$), natural killer ($p<0.1$), and B-lymphocyte ($p<0.05$) cells compared to placebo.[22]

Russian research on Eleutherococcus confirms the herb's immunomodulatory effects in healthy controls. Compared to placebo, 838 children utilizing the fluid extract on a daily basis for two months had a 25-percent increase in T-lymphocytes, a 20-percent increase in B-lymphocytes, a 10-percent reduction in overall infections, and a 60-percent decrease in the incidence of pneumonia.[23] However, this improvement in lymphocyte subsets was not confirmed in a subsequent placebo-controlled study in athletes using 8 mL of a 35-percent ethanolic extract (equal to 4 g crude Eleutherococcus) daily before breakfast for six weeks.[24]

Chronic Stress

In a double-blind study, 45 healthy volunteers (20 men, 25 women; ages 18-30) were randomized to receive two vials of *Eleutherococcus senticosus* or placebo for 30 days. Patients were subject to the Stroop Colour-Word (Stroop CW) test in order to assess their stress response, along with heart rate, and systolic and diastolic blood pressure, before and after treatment. Unlike placebo, those employing the herb had a 40-percent reduction in heart rate response to the Stroop CW stressor. Moreover, in females but not

males, the use of Eleutherococcus accounted for a 60-percent reduction in systolic blood pressure response to the cognitive challenge test. These facts together suggest Eleutherococcus may be helpful for stress adaptation.[25]

Chronic Fatigue

A randomized, double-blind, controlled trial involving 96 patients with diagnosed idiopathic chronic fatigue evaluated the effectiveness of an Eleutherococcus extract compared to placebo. The extract was standardized to contain 2.24 mg eleutherosides per four 500-mg capsules (daily dose); 49 subjects received the herb and 47 received placebo. At the end of the two-month trial, 20 patients were lost to follow-up, leaving 76 evaluable subjects. After two months, a subset of subjects with mild-to-moderate fatigue demonstrated statistically significant improvement in Rand Vitality Index (RVI) scores compared to placebo. For the group as a whole, however, there was significant improvement in RVI scores at one month, but that improvement was not maintained for the duration of the study; after two months, RVI scores were not statistically different between treatment and placebo groups. These results might be expected, as adaptogens are not best suited to continual use but are typically more effective if given in a pulsed manner. Although this study used an imprecise, subjective measurement of fatigue, the results demonstrate a possible therapeutic benefit and additional studies are warranted.[26]

Upper Respiratory Tract Conditions

A few studies have found *Eleutherococcus senticosus* in conjunction with other botanicals is beneficial for treating upper respiratory tract infections (URTI).[27,28]

URTI/Sinusitis

The efficacy of a botanical combination product, Kan Jang, was evaluated in a double-blind, placebo-controlled, parallel-group, clinical trial involving 185 individuals (mean age 32) with acute URTI, with or without sinusitis. Kan Jang, a combination of 85 mg standardized extract of *Andrographis paniculata* and 10 mg *Eleutherococcus senticosus* extract, has been used in Scandinavia for over 20 years as a treatment for uncomplicated URTI. The duration of the trial was five days with 95 subjects randomized to the treatment group and 90 to the placebo group. Typical symptoms of URTI were scored and used as outcome measures. Compared to the placebo group, subjects in the treatment group demonstrated a highly significant improvement (up to 83%) in symptomology, including headache, nasal and throat symptoms, sinus symptoms, and general malaise.[27]

Acute Nonspecific Pneumonia

A botanical combination comprised of *Eleutherococcus senticosus* (24.4%), *Rhodiola rosea* (27.6%), and *Schisandra chinensis* (51%) was investigated for its therapeutic benefit as an adjuvant to standard treatment in acute, non-specific pneumonia. In a double-blind, placebo-controlled, randomized trial, 60 patients (ages 18-65 years) received standard treatment consisting of cefazolin (antibiotic), bromhexine (mucolytic agent), and theophylline (bronchodilator); 30 subjects also received the botanical combination and 30 received placebo. All medications were taken twice daily for 10-15 days and outcomes measured were duration of both antibiotic therapy and acute phase of disease, mental performance on a psychometric test, and self-evaluation for quality-of-life (QOL). Patients receiving the botanical combination required fewer days (5.67) of antibiotics than those in the placebo group (7.53 days), and also demonstrated a significantly higher level of performance on the psychometric tests. In addition, mean QOL scores in the treatment group were significantly higher than for those in the placebo group.[28]

Other Potential Clinical Indications

Animal studies demonstrating specific pharmacologic actions of *Eleutherococcus senticosus* indicate it may be of therapeutic benefit in prevention of bone resorption in steroid-induced osteoporosis.[11] Eleutherococcus also provides protection against fulminant hepatic failure.[12] Other *in vitro* research demonstrates Eleutherococcus possesses endothelium-dependent, nitric oxide-mediated vascular relaxation properties,[29] indicating a potential use in conditions characterized by endothelial dysfunction such as peripheral vascular disease, hypertension, coronary ischemia, and erectile dysfunction. A study in rats

indicates the anti-inflammatory and neuroprotective properties of *E. senticosus* may have therapeutic application in cases of cerebral artery occlusion and ischemia.[9]

Drug-Botanical Interactions

One case report indicated oral use of Eleutherococcus concomitantly with digoxin might result in dangerously high blood levels of digoxin.[30] However, it is likely the product used was adulterated with a botanical, often confused with Eleutherococcus (Ci-wuj-iia), called Wu jia (*Periploca sepium*),[31] a plant known to contain digitalis glycosides that could account for the adverse drug effects. A more recent study in mice demonstrated no digoxin-like immunoreactivity of *Eleutherococcus senticosus* when measured by five separate serum-digoxin assays.[32]

Eleutherococcus increases the action of hexobarbital given i.p. to rats and increases the efficacy of the antibiotic medications monomycin and kanamycin in humans treated for Shigella-positive dysentery and Proteus-induced enterocolitis.[33]

Diabetics should monitor blood glucose levels and adjust medication accordingly, due to the herb's reported hypoglycemic effects in animals.[34]

Research has demonstrated standardized extracts of *E. senticosus* at generally recommended dosages do not significantly alter the metabolism of medications dependent on the cytochrome hepato-detoxification pathways, CYP3A4 or CYP2D6.[35]

Side Effects and Toxicity

The oral LD_{50} of the 33-percent ethanolic extract is estimated to be 14.5 g/kg.[33] The extract is not considered to be teratogenic in mice at 10 mg/kg.[33] Safety in human pregnancy has not been established.

Dosage

In adults, dosage of the 33-percent ethanolic root extract is 10 mL three times per day.[21] Dosages of other extracts include the crude extract of the root at a dose of 2-3 g daily and extracts standardized to eleutheroside B and E at a dose of 300-400 mg daily. Any of these dosing regimens should be taken daily for 6-8 weeks, followed by a two-week pause before continuing.[36]

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