

HYPOGLYCEMIC EFFECT AND TOXICITY OF *ELEUTHEROCOCCLUS SENTICOSUS* FOLLOWING ACUTE AND CHRONIC ADMINISTRATION IN MICE

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ABSTRACT Intragastric administrations of *E. senticosus* extract A (80-320 mg/kg/d × 5 d) in mice induced a hypoglycemic response by the 3rd or 4th d, without gross pharmacological effects. Acute ig LD₅₀ for extract A > 3 g/kg (25 g dried roots/kg). Acute ig LD₅₀ of extract B = 23 ml/kg, iv LD₅₀ = 8.6 ml/kg.

KEY WORDS *Eleutherococcus senticosus*; hypoglycemia; acute LD₅₀; mice

The Far Eastern plant *Eleutherococcus senticosus* (Rupr. + Maxim.) Maxim. (Family Araliaceae) (Ginseng family), formerly known as *Hedera senticosa* and *Acanthopanax senticosus*, is known commonly as "Siberian Ginseng", "Touch-me-not", "Devil's shrub", "Eleutherococc" and "Wild Pepper" (1). This plant is most abundant in the Khabarovsk and Primorsk Districts of the Soviet Union, but its distribution extends to the Middle Amur region in the North, Sakhalin Island and Japan in the East, and South Korea and the Chinese Provinces of Shansi and Hopei in the South (1,2). The plant has recently become an item for export from the People's Republic of China. *Eleutherococcus senticosus* has been used extensively in the Soviet Union as an adaptogen (3). An adaptogen may be defined as an innocuous (non-toxic) substance which has a "normalizing" action on a wide

range of physical, chemical and biochemical factors (4). Thus, *E. senticosus* is reported to have activity in alleviating numerous pathological changes when administered on a chronic basis. These adaptogenic effects of *E. senticosus*, as well as those of other natural products have been the subject of several recent reviews (2,6).

The oral administration of *E. senticosus* root extracts to small animals has been shown to have variable effects on blood glucose. It elicits either a slight hypoglycemic action in rabbits with epinephrine-induced hyperglycemia (6) or increases blood glucose following chronic administration (7). In addition, *E. senticosus* increases the resistance of rats to the toxic effects of alloxan (8), but has been reported to either prevent (9) or have no effect (8) on the development of alloxan-induced diabetes.

The effect of *E. senticosus* in humans has been more consistent. Extracts are reported to reduce postprandial blood glucose levels in healthy subjects, as well as blood glucose levels in patients with mild to moderate diabetes (8).

This study was undertaken to clarify the equivocal results in earlier investigations that *E. senticosus* elicits either a hypo- or hyperglycemia. In addition,

studies to evaluate the acute and chronic toxicity of the aqueous and commercial (ethanol) extracts of *E. senticosus* roots were performed.

Preparation of Extracts of Eleutherococcus senticosus

A sample of *E. senticosus* roots of Chinese origin was obtained from the Svenski Ortmedicinski Institute (Ulri-cehamn, Sweden) and was authenticated in our laboratory by microscopic and thin-layer chromatographic analysis. The sample used in this study was identical in all respects with a root sample taken from a reference herbarium specimen of the plant, kindly supplied by Professor Brekhman.

To every 100 g of powdered *E. senticosus*, 1000 ml of distilled water (60°C) was added, the mixture stirred for 10 min at 60°C, filtered twice and the filtrate frozen and lyophilized to obtain a dry powder weighing 1.6 g. Appropriate test solutions of this *E. senticosus* extract were made fresh daily with deionized distilled water, and are referred to as extract A.

Commercial liquid extracts of *Siberian Ginseng Liquid Extract* (Imedex) (33% ethanol) were used in this study. The liquid extract was used either undiluted, or diluted with deionized distilled water, and is referred to as extract B.

Experimental

Adult, male Swiss-Webster mice (25–30 g) (Scientific Small Animal Laboratory & Farm, Inc.) were used in all experiments. Mice were housed in plastic community cages (7 mice/cage). They were allowed free access to food and water. Before and between experiments, mice were housed in a room with the temperature held constant 20–30°C with alternating 12 h periods of darkness and light.

Mice were divided into appropriate groups for the administration of extract A (80, 160 or 320 mg/kg and distilled water

for control, by gastric intubation) each day for the number of days indicated. Food was removed 18 h prior to the collection of blood samples. On the morning of blood collection the mice received their last dose of the appropriate test solution or control. Two hours later all mice were decapitated and blood was collected in test tubes containing 143 USP units of heparin. Blood samples were centrifuged at 2500 rpm for 5 min (at 15°C), plasma was transferred to clean tubes, stoppered and frozen until assayed. All samples were assayed within 5 d of collection.

Acute toxicity effects of the two *E. senticosus* extracts (A and B) were also evaluated. Mice were divided into appropriate groups and administered either extract A (250–3000 mg/kg by gastric intubation) or extract B (16–64 ml/kg by gastric intubation or 2.5–12.5 ml/kg intravenously). Mice were fasted for 24 h prior to use in the experiments. Following administration of the extracts, all mice were observed for 24 h for deaths and/or gross pharmacological effects. The method of Litchfield and Wilcoxon (1949) was used for acute LD₅₀ determinations.

Blood Glucose Assay

Plasma glucose levels were determined by the colorimetric method of Carroll *et al* (1970). Measurements were made at 520 nm with a Beckman DU spectrophotometer. All samples were assayed in duplicate.

Table 1. Hypoglycemic effect of chronic oral administration of *Eleutherococcus senticosus* extract A in mice

<i>E. senticosus</i> (mg/kg × 5 d)	Blood glucose (mg% ± SD)	% of control
0	95 ± 24 (25)	100
80	57 ± 26* (24)	60
160	62 ± 27* (25)	65
320	37 ± 18* (25)	39

() Number of mice. * $P < 0.005$ from control

Results

The effects of *E. senticosus* extract A on blood glucose are shown in Table 1 and Fig 1. Chronic administration (5 d) to mice produced a dose-dependent decrease in blood glucose levels (Table 1). The time course of the development of this hypoglycemic response showed that *E. senticosus* extract A induced a hypoglycemic response by the 3rd or 4th d of drug administration (Fig 1).

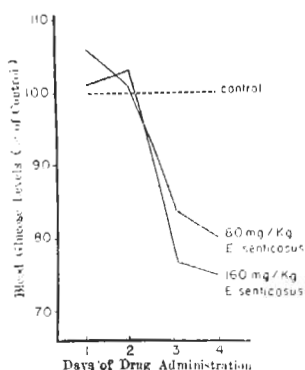


Fig 1. Hypoglycemic response after daily ig *Eleutherococcus senticosus* extract A in mice. Each point 7-8 mice. * $P < 0.025$, ** $P < 0.01$, *** $P < 0.005$ from control.

Acute administration of extract A produced no deaths or gross pharmacological effects in any of the mice (a total of 50 mice received the extract), up to 24 h following administration of the extract (Table 2). The LD_{50} for extract A was found to be greater than 3 g/kg. This would be roughly equivalent to an LD_{50} of more than 25 g/kg of dried roots of the plant. The acute po LD_{50} of extract B was calculated as 22.7 ml/kg, while the iv LD_{50} was calculated as 8.6 ml/kg.

In chronic experiments extract A produced no gross pharmacological effects when administered to mice for up to 5 d (20 to 320 mg/kg/d by gastric intubation). No fatalities were recorded and body weights of treated mice were not different from control mice. All mice continued to gain weight during the first 4 d, with a slight reduction of body weight recorded on the last day of pretreatment (during 13 h fast).

Discussion

Soviet reports on the effects of *E. senticosus* on blood glucose levels have been inconsistent. These have ranged from

Table 2. Acute toxicity of *Eleutherococcus senticosus* extracts A and B

A. Acute oral LD ₅₀ determination of extract A			LD ₅₀ >3 g/kg		
Group number	1	2	3	4	5
Dose(mg/kg)	250	500	1000	2000	3000
Mice died/Mice dosed	0/10	0/10	0/10	0/10	0/10
Percent mortality	0	0	0	0	0
B. Acute oral LD ₅₀ determination of extract B			LD ₅₀ = 23 ml/kg		
Group number	1	2	3	4	5
Dose(ml/kg)	16	20	32	40	64
Mice died/Mice dosed	0/10	3/10	10/10	10/10	10/10
Percent mortality	0	30	100	100	100
C. Acute intravenous LD ₅₀ determination of extract B			LD ₅₀ = 8.6 ml/kg		
Group number	1	2	3	4	5
Dose(ml/kg)	2.5	5.0	7.5	10.0	12.5
Mice died/Mice dosed	0/8	1/8	3/8	7/8	8/8
Percent mortality	0	13	38	88	100

a slight hypoglycemic action in rabbits with either epinephrine-(⁹) or 2,4-dinitrophenol-(¹⁰) induced hyperglycemia to hyperglycemia following chronic(30 d) administration(⁷). Bezdetko(⁸) has also reported a hypoglycemic action of *E. senticosus* in alloxan-induced diabetic rats. The interpretation of these experiments is difficult, since the Soviet studies were carried out with the 33% ethanol extracts, whereas our studies utilized aqueous extracts. *Eleutherococcus senticosus* has been reported to reduce postprandial blood glucose levels in humans with mild to moderate diabetes(²).

The administration of *E. senticosus* extract A to mice induced a dose-dependent hypoglycemia which was significantly different from controls following 3 d of daily administration. The group of mice receiving 80 mg/kg po of the aqueous extract showed a 40% decrease in blood glucose relative to controls; the 160 mg/kg po group showed a 35% decrease and the 320 mg/kg po group showed a decrease in blood glucose of 61% relative to controls. In separate experiments examining the temporal aspects of the hypoglycemic action, *E. senticosus* at 80 mg/kg po produced a statistically significant drop (16%) in blood glucose levels after 3 d of administration, while producing a 23% decrease relative to controls on the 4th d. At the 160 mg/kg po dose, 3 d of administration similarly induced a significant (22%) decrease in blood glucose levels, while inducing a 25% decrease in blood glucose levels on the 4th d.

The mechanism of this hypoglycemic action of *E. senticosus* remains unclear. Several purported adaptogens (*E. senticosus*, *Panax ginseng*, *Rhaponticum carthamoides* and *Rhodiola rosea*) have been reported to reduce blood glucose levels partially by enhanced resynthesis of glycogen and high energy phosphate

compounds(¹¹). Recently, *Panax ginseng* has also been shown to increase blood insulin levels possibly by enhancing the release of insulin from the pancreas.(¹²) This insulin-releasing action affords a partial explanation for the hypoglycemic action of *E. senticosus*. Dardymov and Khasina(¹³) have reported that *E. senticosus* glycosides prevent (an action similar to insulin) the inhibition of muscle hexokinase caused by stress, and also the formation in the plasma of a beta-lipoprotein inhibitor of hexokinase. *E. senticosus* is also reported to increase glucose consumption in rat diaphragm preparations; an effect similar to that seen with insulin.(¹⁴)

Eleutherococcus senticosus root aqueous extract A was found to have an acute oral LD₅₀ value of greater than 3 g/kg in adult ICR mice. Higher doses could not be employed due to the bulk of material required and the volume of solution that would have been required to administer the extract. Projecting this LD₅₀ to what might be anticipated for the toxicity of powdered root material (not extracted), the LD₅₀ value would be in excess of 25 g/kg. No unusual symptoms were noted in mice receiving extract A at any of the dose levels, when observed over a 24 h period.

The commercial *Siberian Ginseng Liquid Extract* (extract B), which contains 33% ethanol, was found to have an acute oral LD₅₀ in adult male ICR mice of 23 ml/kg. Gross symptoms in the treated mice were associated with severe depression, and deaths appeared to be due to respiratory depression. Since the extract contains 33% ethanol, and the acute oral LD₅₀ value in mice for ethanol is 9.5 g/kg,(¹⁵) it seems most likely that all deaths as well as the gross symptoms observed in mice receiving extract B may be attributed to the ethanol content of the preparation, rather than the extract itself.

Eleutherococcus senticosus (extract A)

has been shown to induce a dose-dependent decrease in blood glucose levels when administered on a chronic basis to mice. These results are consistent with the use of *E. senticosus* in the Soviet Union for the treatment of mild diabetes. Additional studies to elucidate the mechanism of this hypoglycemic action are needed. At the dosages employed in these experiments, *E. senticosus* extract A administration for up to 5 d produced no apparent toxicity or deaths. Gross pharmacologic symptoms associated with acute administration of *Siberian Ginseng Liquid Extract* (extract B) are apparently due to the ethanol content of the preparation.

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