Global Science Research Journals

ISSN: 2505-001X Vol. 4(8), pp. 247-253, August, 2016.

http://www.globalscienceresearchjournals.org/

Global Journal of Biological and Biomedical Research

Review

Potentials on the pharmacological and therapeutic effects of *Eleutherococcus senticosus* (ES)

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Accepted 28 July, 2016

Eleutherococcus senticosus **(Rupr. et Maxim.) Harms (*Acanthopanax senticosus*, Araliaceae, ES, thereafter), also called Siberian ginseng, Ciwujia in Chinese, and Gasiogalpi in Korea, is distributed in the southeastern Russia, northeast China, Korea, and Japan. The woody medicinal plant has been known since ancient times for its curative properties, and particularly the cortical roots and stem tissues of ES have been utilized for the treatment of various ailments such as cancer, diabetes, cardiovascular diseases, hepatitis, spleen and liver complaints. Due to its giant therapeutic efficacy, more and more investigations have been carried out on the isolation and analysis of active compounds of ES, and their *in vitro* and *in vivo* pharmacological activities and even clinical effects in humans. This review, therefore, provides a comprehensive review of the pharmacologically relevant compounds of ES characterized so far and of the studies supporting its use as a medicinal plant. Particular attention has been given to anti-inflammatory, anti-oxidative, anti-carcinogenic, anti-fatigue, anti-diabetes, hypolipide, immunoprotection and immunoregulation, and antimicrobial and antiviral activities. This work presented here would help more detailed pharmacological cognition and further understanding of natural components of this medicinal plant species.**

Key words: *Eleutherococcus senticosus*, *Acanthopanax senticosus*, pharmacology, biological activity, medicinal plant, adaptogen.

INTRODUCTION

As the standard of living is increasingly advancing, the demands of people on functional foods or nature products to pursue healthy aging are as well as expanding. Particularly, natural, crude products as green medicines are considered healthier and more harmless or safer than synthetic ones (Parvath and Brindha, 2003). To date, more and more traditional herbal medicines have been used for the management and treatment of various chronic human pathological conditions (Guo et al., 2008). Due to their inability to cause side effects and combat antibiotic resistant microorganisms, the medicinal plants are being paid more and more attentions (Rawat and Uniyal, 2003). *Eleutherococcus senticosus* (Rupr. et Maxim.) Harms (=*Acanthopanax senticosus*, Araliaceae, ES, thereafter), a woody medicinal plant popularly known as Siberian ginseng, and also named Ciwujia in Chinese and Gasiogalpi in Korea, is distributed in southeast Russia, northeast China, Korea, and Japan (Lee, 1979;

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Abbreviation: **ES**, *Eleutherococcus senticosus*; **LC**, liquid-chromatography; **ES-ITMS**, electrosparay-ion trpa mass spectrometry; **HPLC-ESI/TOF/MS**, high-performance liquid chromatography-electrospray time-of-flight mass spectrometry; **GC**, gas chromatography; **DPPH**, 1,1-diphenyl-2-picrylhydrazyl; IC_{50}, inhibitor concentration yielding 50% inhibition; GI_{50}, 50% growth inhibition; **CK**, creatine kinase; **LDH**, lactate dehydrogenase; **LAD**, left anterior descending artery; **LPS**, lipopolysaccharides; i**NOS**, inducible nitric-oxide synthase; COX-2, cyclooxygenase-2; **DSHEA**, dietary supplement health and education act.

Hahn et al., 1985; Shao et al., 1988). In the theory of Traditional Chinese Medicine, it has been known as an adaptogen and recorded to strengthen spleen and nourish kidney (Huang et al., 2011a). Many active compounds have been isolated and identified from different parts of ES. The major active compounds include acanthoside, eleutheroside, chiisanoside, senticoside, triterpenic saponin, syringin, flavones, vitamin, minerals, *β*-sitosterol, sesamine and savinine (Davydov and Krikorian, 2000; Lee et al., 2004; Li et al., 2006). The first evidence for its pharmacological effects of ES was mentioned in the late 1950s and 1960s (Brekhman, 1968, 1976). Through nearly fifty years' investigations, ES has been shown to possess abilities to treat stress-induced physiological changes, inflammation, cancer, hypoglycemia, and choleretic action on cultured cell lines, small laboratory animals, and human subjects (Fujikawa et al., 1996; Yi et al., 2002; Jung et al., 2003; Hibasami et al., 2000). Until recently, many investigations have been undertaken to shown the chemical constituents, pharmacology and clinical effects of ES, but there is a lack of a review paper. Therefore, in the following an overview of the literatures covering the occurrence of biologically and pharmacologically relevant compounds in ES, as well as of the studies supporting its use as medicinal plant will be given. This work presented here would help encourage the potentials on the pharmacological effects and further understand the abilities of therapeutic effects of ES.

ACTIVE COMPOUNDS OF ES

With the advancement of different analytical techniques, more and more active compounds of ES are being isolated and identified (Deyama et al., 2001; Tolonen et al., 2002; Yang et al., 2004; Apers et al., 2005). Until now, lignans (sesamine, eleutheroside D), glycans (eleutherans A, B, C, D, E, F, and G, eleutheroside C), triterpene saponins (eleutheroside I, K, L, and M), steroid glycosides (eleutheroside A), hydroxycoumarins (isofraxidin), phenylacrylic acid derivatives (eleutheroside B), and flavones have been found in ES. In the late 1950s and 1960s, the chemical investigations on pharmacological effects were firstly performed and reported in active compounds of ES (Brekhman, 1968, 1976). Later, many investigations on the isolation and identification of components were in succession reported in ES. For instance, eleutherans A, B, C, D, E, F, and G were isolated from ES roots (Hikino et al., 1986). Sinapaldehyde glucoside, coniferaldehyde glucoside, coniferin and 1,5-di-*O*-caffeoylquinic acid were firstly isolated and identified from ES by centrifugal partition chromatography (Slacanin et al., 1991). Li et al. (2001) reported the isolation of a new lignin glycoside, eleutheroside E2, interpretated as episyringaresinol 4-*O*-β-D-glucopyranoside with different structure of eleutheroside E1. Simultaneously, isomaltol 3-*O*-α-D-glucopyranoside was isolated and reported for the first time as a naturally occurring compound, eleutheroside B, E and E1, and thymidine were as well as isolated and reported in this investigation (Li et al., 2001). Until 2002, liquid-chromatography (LC) coupled with electrosparay-ion trpa mass spectometry (ES-ITMS) was applied to the quantification of eleutherosides B and E of ES, and this finding achieved more rapid and simpler gradient separation of both underivatized eleutherosides without pre-purification at very low concentration (Choi and Kim, 2002). Somewhat later, a novel NMR technique combined with high-performance liquid chromatography-electrospray time-of-flight mass spectrometry (HPLC-ESI/TOF/MS) was applied to the identification of the phenolic constituents of ES (Tolonen et al., 2002). In this investigation, 3',5'-*O*-dicaffeoylquinic acid and 4',5'-*O*-dicaffeoylquinic acid were firstly isolated from this species (Tolonen et al., 2002). Moreover, another derivative, 1,4-di-*O*-caffeoylquinic acid was firstly isolated and identified from ES (Kim et al., 2005). To understand the composition of the volatile constituents of ES, gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) spectrometric techniques were applied on this species and identified several volatile compounds including α-bergamotnen, δ-elemene, β-elemene, and γ-cadinene, α-pinene, bicycloheptane derivative and (+)-aromadendrene (Lim et al., 2007).

BIOLOGICAL AND PHARMACOLOGICAL EFFECTS

The extracts from different parts of Siberian ginseng have long been considered to be good for health (Han et al., 2006). As an adaptogen, ES not only supplies some nutritional compositions, but helps enhance the body's immune system and improve rehabilitation of any physiological, biochemical or immunological defects (Winston and Maines, 2007). Biological and pharmacological effects of ES include antioxidant, antidiabetes, anticancer, anti-inflammatory, immunoregulatory and immunomodulating, antimicrobial and antiviral activities.

Antioxidant effects

High antioxidant activities evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and antilipid peroxidation were determined in rat liver microsomes with the treatment of ES root extracts (Yu et al., 2003). Particularly, the ethyl acetate and n-butanol fractionations revealed stronger antioxidant against scavenging on DPPH free radical and also ethyl acetate fraction exhibited high antilipid peroxidative activities (Yu et al., 2003). The fruit extracts from ES also showed strong DPPH radical scavenging activity, with the strongest one of 57.3 µg/ml at inhibitor concentration yielding 50%

inhibition (IC_{50}) in water extract (Kim et al., 2006). Ethanol, methanol, butanol, and water extracts of ES all were reported to have high antioxidant activities (Kim et al., 2002). Moreover, the active components isolated from ES plantlets such as chlorogenic acid and 1,4-di-*O*-caffeoylquinic acid were also found to have high DPPH free radical scavenging activities (Kim et al., 2005).

As known, antioxidant activities are generally associated with other protective effects, antimicrobial activities against gram negative bacteria and gram positive bacteria were found in ES fruit extracts (Kim et al., 2006). Strong inhibitive effect on cancer cell growth was evaluated in various-solvent extracts of ES (Kim et al., 2002). Similar results were investigated in seven human cancer cell lines that the values of 50% growth inhibition (GI_{50}) evaluated by the cytotoxic sulforhodamine B assay showed below 30 µg/ml for crude extracts to be considered as significantly active (Yu et al. 2003). The ethanol extracts from ES root barks could not only reduce growth of liver cancer cell (Hep3B) by 94% and lung cancer cell (A549) by 90%, but enhance glutathione *S* transferase activity by 241%. More importantly, the growth of T-cell and viability were not inhibited, contrarily activated by 275% (Hibasami et al., 2000).

Antimicrobial and antiviral effects

The antiviral activities of ES have been early known and used for prophylaxis of infectious diseases (Eilmes, 1978; Protasova and Zykov, 1984). Particularly, in this decade, ES root extracts were found to possess the ability to inhibit the replication of human rhinovirus, respiratory syncytial virus and influenza A virus (Glatthaar-Saalmüller et al., 2001). Their reducing effects on the cell population of *Lactobacillus acidophilus*, *Lactobacillus bularicus*, and *Lactobacillus paracasei*, particularly for *L. acidophilus* showed a positive activity in cell damage during freeze dry (Choi et al., 2004).

Antidiabetic effect

Triterpene saponins are one kind of the important active compounds in ES, of which the noroleanane-type and oleanane-type triterpene saponins have been denoted as ciwujianosides (Shao et al., 1988). Inhibitory effect on asthmatics and histamine release functioned by ciwujianosides D1 have been reported in the investigation of Orr and Cox (1969). In this work, they compared the effects of ciwujianosides D1 with those of disodium cromoglycate, an effective inhibitor of experimental allergen-induced bronchoconstriction, and suggested the more significantly inhibition. Somewhat later, ciwujianosides D1 and C1 extracted from ES were investigated to able to strongly inhibit histamine release in a concentration-dependent manner in rat peritoneal mast cells (Umeyama et al., 1992). Expect of the effect of histamine release, saponin was reported to be able to decrease various cases of experimental hyperglycemias induced by injection of adrenaline, glucose and alloxan, without affecting the levels of blood sugar in normal mice (Sui et al., 1994a). Saponin was also investigated to significantly reduce the sizes of acute myocardical infarcts and decline the serum creatine kinase (CK) and lactate dehydrogenase (LDH) activity after ligation of the left anterior descending artery (LAD) (Sui et al., 1994b).

As the healthy food accession, the effects on reducing serum lipid have been found in rats, with syringin as the active principle in ES extracts (Niu et al., 2008a, b). Syringin injection resulted in plasma glucose utilization accompanying with the increase of plasma insulin and C-peptide in anesthetized Wistar rats (Niu et al., 2008a). This result suffering from insulin deficiency makes syringin be useful in the treatment of human diabetes (Niu et al., 2008b). Further investigation talked the effect of syringin on plasma glucose and the possible mechanisms (Liu et al., 2008), suggesting that syringin has an ability to raise the release of acetylcholine from nerve terminals, stimulate mascarinic M3 receptors in pancreatic cells and augment the insulin release.

In addition, the hypoglycemic activities of ES extracts were continuously studied by scientists (Choi et al., 2008). Someone reported the effect was mainly functioned by eleutherans A, B, C, D, E, F, and G (Hikino et al., 1986). Someone compared hypolipidemic activities of ES extracts with taurine, carnitine and several oriental medicinal herb extracts, and suggested ES extracts showed higher activities (Song et al., 2002; Choi et al., 2008). The hypolipidemic effects of ES extracts were also evaluated on significantly reduced weight gain of experimental rats and serum cholesterol levels (Rhie and Won, 2004).

Anti-fatigue effects

Extracts from different parts of ES have been showed to possess the potent abilities to alleviate fatigue and protect from both stress-induced physical and mental changes (Takasugi et al., 1985; Nishiyama et al., 1985), e.g. improving endurance exercise in rats (Nishibe et al., 1990; Song et al., 2002). There was investigation demonstrated that the ES extract of the stem bark or its components such as chlorogenic acid and syringaresinol di-o-*β*-D-glucoside markedly inhibited the occurrence of gastric ulcer in rats exposed to restraint stress in water (Fujikawa et al., 1996). However, the anti-fatigue and anti-stress effects were mainly owed to the contribution of eleutheroside E, one of main active compounds in ES extracts (Kimura and Sumiyoshi, 2004; Huang et al., 2011b). Kimura and Sumiyoshi (2004) evaluated the anti-fatigue action of eleutheroside E isolated from ES

extracts and its coordinated responses in swimming-stressed rats, showing that the reduction of natural killer activity could be recovered and corticosterone levels were enhanced. Huang et al. (2011a) found eleutheroside E played roles in reducing the level of plasma triglyceride, increasing fat utilization, delaying the accumulation of blood urea nitrogen, and increasing the lactate dehydrogenase to reduce the accumulation of lactic acid in muscle and then protect the muscle tissue. For the action mechanisms of anti-stress effect, Gaffney et al. (2001a, b) carried out their particular opinions that ES increased the occupancy of stress hormone receptors which function to redistribute the body's energy reserves from regeneration to activity, by inhibiting catechol-*O*-methyl transferase activity that reside in close proximity to stress hormone receptors.

To date, the anti-fatigue and anti-stress effects of ES extracts have been largely investigated in many series of experimental samples and even humans, e.g. improving stress resistance in competition horses (Colas et al., 2008), increasing stress resistance and a longer lifespan of *Caenorhabditis elegans* (Wiegant et al., 2009), improving endurance in competitive club-level endurance athletes engaged in their normal in-season training (Gaffney et al., 2001a), and improving some aspects of mental health and social functioning in elderly hypertensive and digitalized volunteers (Cicero et al., 2004).

Immunoprotective and immunomodulating effects

As known, some physical and mental stresses suppress the ability of the immune system, although there is difference between acute (short-lived) stress and chronic (ongoing) stress. Short-lived stress can usually be dealt with the neuroendocrine system, but do not affect the immune system (Winston and Maines, 2007). Adaptogens have been attracted to have effects on immunity and the immune system. They help to counter chronic immune cell depletion, and they improve the body's defenses by increasing the production of specialized cells. They also help produce an increased secretion of cortisol in response to injury or infection, and they have a direct effect on the nervous system, allowing for an improved mind-body connection. This effect is commonly called immunomodulating or immunostimulating effect. ES, as an adaptogen, has long been recommended for use a complex treatment of nervous and cardiovascular disease, and also as generally restorative and tonic agent due to the immune-modulatory potency, rather than immune-suppressive or -stimulating function (Zamotaev, 1990; Schmolz et al., 2001). Steinmann et al. (2001) have investigated immunopharmacological effects on major histocompatibility complex class I and II molecules, human lymphocyte marker flow cytometry, and *in vitro* testing of human lymphocyte functions, with enhanced Interleukin-1 and interleukin-6 levels. ES extract was found to increase the immunoglobulin levels in mice blood serum, stimulate humoral immunological system (Drozd et al., 2002), and also attenuate lipopolysaccharides (LPS)-induced inducible nitric-oxide synthase (iNOS) expression but not cyclooxygenase-2 (COX-2) expression (Jung et al., 2007).

The Dietary supplement health and education act of 1994 (DSHEA) permits the direct marketing of ES as dietary supplements to consumers in the United States without food and drug administration regulation. The safety and efficacy of ES supplement have been assessed on the activities of cytochrome P450 CYP2D6 (dextromethorphan as a probe) and CYP3A4 (alprazolam as a probe), two predominant isoforms (Brosen, 1996), suggested that ES extract with normally recommended dose supplement, do not affect the metabolism of CYP2D6 or CYP3A4 pathways at least (Donovan et al., 2003). Based on the permit of ES as a dietary supplement, many products with ES extract accession were coming forth in the market, and the relevant immunomodulating effects were also received much attentions. The Taiga Wurzel preparation containing ES extract affected cellular defence and improved physical fitness in man (Szolomicki et al., 2000). A fixed combination (KanJang®) with ES accession showed effects on proliferation of human lymphocytes, production of cytokines and immune activation markers in the whole blood cell culture (Panossian et al., 2002), and clinical treatment of acute respiratory infection (Narimanian et al., 2005). Another fixed combination (ImmunoGuard®) with ES accession showed strong clinical efficacy in the treatment of familial Mediterranean fever (Amaryan et al., 2003). The other combination with ES accession was reported to boost the suppressed immunity in ovarian cancer patients who are subject to chemotherapy (Kormosh et al., 2006).

In addition, the crude polysaccharides fraction from ES, named EN-3, was showed to possess activities to potentially enhance humoral and cellular immune responses against bovine serum albumin or ovalbumin (Hwang et al., 2003). In another study, the administration of EN-3 (0.5, 5, and 50 µg/mouse) showed inhibiting effects on the murine tumor metastasis and growth model compared with control in 33.6, 66.8, and 81.8%, respectively and 66.1% therapeutic effect on lung tumor metastasis at 50 µg/mouse of EN-3 administration (Ha et al., 2003). Oral administration of EN-3 also induced antigen-specific immune response in mice when inhibiting tumor metastasis (Sung et al., 2006). These results indicated that EN-3 could stimulate immune system non-specifically and apply to the biological response modifiers in chemo-immunotherapy for tumor prevention. Similar anti-carcinogenic effects of the root extracts of ES have also been reported on the models of carcinogenesis of the nervous system and kidneys in rats (Bespalov et al.,

1993).

Other pharmacological effects

Except of the foregoing multitudinous uses of ES extracts, other pharmacological activities have been investigated. Particularly for Parkinson's disease caused by neurodegenerative disorders, ES extract showed a regulative effect of noradrenaline and dopamine levels in specific brain regions (Fujikawa et al., 2002), prevention of the parkinsonian bradykinesia and depressive behavior to suppress depletion in rotenone-induced parkinsonian rats (Fujikawa et al., 2005). Neurons with atrophic neuritis could remain alive and thus have the potential to regenerate even when neuronal death has occurred in some parts of the brain. ES was found to possess abilities to protect brain neurons from various injuries (Bocharov et al., 2008), and neuritic atrophy and cell death under amyloid β treatment (Tohda et al., 2008).

For the treatment of osteoporosis, ES extracts that were considered to be involved in bone tissue metabolism (Kim et al., 2007a), showed a positive function. And the ES extract combined with a novel formulation of low-dose calcium and vitamin D3 was then used for therapeutic purpose for reducing rapidly decreasing bone mineral density in postmenopausal women (Oh et al., 2007). It was suggested that ES extracts could enhance the longitudinal bone growth with over-expression of IGF-1 gene, a major bone growth factor (Yang et al., 2003), and prevent the development of bone loss in ovariectomy-induced rats (Kim et al., 2007b).

The antimutagenic effects of methanol extract from ES were reported on the mutagenicty induced by direct mutagens 2-AF, and Trp-P-1 (Park et al., 2002) and 1-NP (Park et al., 2003). The extracts from root, stem, and leaf of ES showed inhibitory effects of 72.8, 70.0, and 78.7% on 2-AF-induced mutagenicity, and 69.2, 64.9, and 59.4% by Trp-P-1, respectively (Park et al., 2002). Water-soluble polysaccharides from ES stem extracts were investigated to attenuate fulminant hepatic failure induced by D-galactosamine/LPS in mice (Park et al., 2004), with deduced alanine aminotransferase, aspartate aminotransferase and tumour necrosis factor-α levels in serum, and decreased apoptotic cells in liver. ES combined with $CdCl_2$, an important industrial pollutant and toxic, leads to a significant decrease of cadmium concentration in the blood and liver of experimental mice (Smalinskiene et al., 2009). ES extracts were also used to reduce cardiovascular responses in healthy young volunteers (Facchinetti et al., 2002), and enhance vascular relaxation with endothelium-dependence depending on the vessel size (Kwan et al., 2004).

CONCLUSIONS

According to the report of the World Health Organization, 80% of the world population continues to rely mainly on traditional medicines for their health care. ES, as an adaptogenic medicine and crude drug, will indisputably receive increasing attentions. Many active ingredients isolated from different parts, have been suggested to possess many therapeutic effects for the treatment of various diseases in ES. Multiple reports in the literature have demonstrated a wide range of possible therapeutic and clinical uses of this plant species, because of its anti-inflammatory, anti-tumor, anti-diabetic, anti-microbial and anti-viral effects. However, the diverse pharmacological activities of ES have mostly been assayed in *in vitro* or *in vivo* tests using laboratory animals, and the results may not necessarily be portable to the situation in humans. It is expected that further investigations are required to lead to a better understanding of existing roles and other roles that ES plays in preventing and treating of human diseases. This work could provide more information on the beneficial effect of ES. In view of the multitude of promising findings and fact described previously, they justifiably believe that further research on ES would not only be a scientific challenge, but also an interesting economic perspective.

ACKNOWLEDGEMENT

This work was supported by Nutraceutical Bio Brain Korea 21 Project Group.

REFERENCES

Amaryan G, Astvatsatryan V, Gabrielyan E, Panossian A, Panosyan V, Wikman G (2003). Double-blind, placebo-controlled, randomized, pilot clinical trial of ImmunoGuard®-a standardized fixed combination of *Andrographis paniculata* Nees, with *Eleutherococcus senticosus* Maxim, *Schizandra chinensis* Bail. and *Glycyrrhiza glabra* L. extracts in patients with familial Mediterranean fever. Phytomedicine, 10: 271-285.

Apers S, Naessens T, Van MS, Pieters L, Vlietinck A (2005). Quality control of roots of *Eleutherococcus senticosus* by HPLC. Phytochem. Anal., 16: 55-60. doi:10.1002.pca.811.

Bespalov VG, Aleksandrov VA, Yaremenko KV, Limarenko AY, Petrov AS, Troyan DN (1993). Inhibiting effect of the extract of *Eleutherococcus senticosus* Rupr. et Maxim. on the development of experimentally induced tumors of nervous system, cervix uteri and vagina. Pharm. Chem. J., 27: 358-361. doi:10.1007/BF00819969.

Bocharov EV, Kucherianu VG, Bocharova OA, Karpova RV (2008). Neuroprotective features of phytoadaptogens. Vestn. Ross. Akad. Med. Nauk., 4: 47-50.

Brekhman II (1968). Eleutherokokk (*Eleutherococcus*). Nauka Publishing House, Leningrad, USSR (in Russian).

Brekhman II (1976). Chelovek I biologicheski aktivnye vezshestva (Man and Biologically Active Substances). Nauka Publishing House, Leningrad, USSR (in Russian).

Brøsen K (1996). Drug-metabolizing enzymes and therapeutic drug monitoring in psychiatry. Ther. Drug Monit., 18: 393-396.

Choi HS, Kim YH, Han JH, Park SH (2008). Effects of *Eleutherococcus senticosus* and several oriental medicinal herbs extracts on serum lipid concentrations. Korean J. Food Nutr., 21: 210-217.

Choi JB, Shin YW, Paek NS, Kim YM (2004). Enfluence of herbal extract on lactic acid bacteria growth and cryoprotectants. Korean J. Food Nutr., 17: 286-293.

Choi YH, Kim JW (2002). Quantitative analysis of eleutherosides B and using HPLC-ESI/MS. Korean J. Pharmacogn., 33: 88-91.

Cicero AFG, Derosa G, Brillante R, Bernardi R, Nascetti S, Gaddi A (2004). Effects of Siberian ginseng (*Eleutherococcus senticosus* Maxim.) on elderly quality of life: a randomized clinical trial. Arch. Gerontol. Geriatr. Suppl., 9: 69-73.

Colas C, Popot MA, Garcia P, Bonnaire Y, Bouchonnet S (2008). Analysis of iridoids from *Harpagophytum* and eleutherosides from *Eleutherococcus senticosus* in horse urine. Biomed. Chromatogr., 22: 912-917. doi:10.1002/bmc.1030.

Davydov M, Krikorian AD (2000). *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. J. Ethnopharmacol., 72: 345-393.

Deyama T, Nishibe S, Nakazawa Y (2001). Constituents and pharmacological effects of *Eucommia* and Siberian ginseng. Acta Phamatcol. Sin., 22: 1057-1070.

Donovan JL, DeVane CL, Chavin KD, Taylor RM, Markowitz JS (2003). Siberian ginseng (*Eleutherococcus senticosus*) effects on CYP2D6 and CYP3A4 activity in normal volunteers. Drug Metab. Dispos., 31: 519-522. doi:10.1124/dmd.31.5.519.

Drozd J, Sawicka T, Prosinska J (2002). Estimation of humoral activity of *Eleutherococcus senticosus*. Acta Pol. Pharm. Drug Res., 59: 395-401.

Facchinetti F, Neri I, Tarabusi M (2002). *Eleutherococcus senticosus* reduces cardiovascular stress response in healthy subjects: a randomized, placebo-controlled trial. Stress Health, 18: 11-17. doi:10.1002/smi.914.

Fujikawa T, Kanada N, Shimada A, Ogata M, Suzuki I, Hayashi I, Nakashima K (2005). Effect of sesamin in *Acanthopanax senticosus* HARMS on behavioral dysfunction in rotenone-induced parkinsonian rats. Biol. Pharm. Bull., 28: 169-172.

Fujikawa T, Soya H, Hibasami H, Kawashima H, Takeda H, Nishibe S, Nakashima K (2002). Effect of *Acanthopanax senticosus* Harms on biogenic monoamine levels in the rat brain. Phytother. Res., 16: 474-478. doi:10.1002/ptr.1024.

Fujikawa T, Yamaguchi A, Morita I, Takeda H, Nishibe S (1996). Protective effects of *Acanthopanax senticosus* Harms from Hokkaido and its components on gastric ulcer in restrained cold water stressed rats. Biol. Pharm. Bull., 19: 1227-1230.

Gaffney BT, Hügel HM, Rich PA (2001a). The effects of *Eleutherococcus senticosus* and *Panax ginseng* on steroidal hormone indices of stress and lymphocyte subset numbers in endurance athletes. Life Sci., 70: 431-442.

Gaffney BT, Hügel HM, Rich PA (2001b). *Panax ginseng* and *Eleutherococcus senticosus* may exaggerate an already existing biphasic response to stress *via* inhibition of enzymes which limit the binding of stress hormones to their receptors. Med. Hypotheses, 56: 567-572. doi:10.1054/mehy.2000.1163.

Glatthaar-Saalmüller B, Sacher F, Esperester A (2001). Antiviral activity of an extract derived from roots of *Eleutherococcus senticosus*. Antiviral Res., 50: 223-228. doi:10.1016/S0166-3542(01)00143-7

Guo JF, Zhou JM, Zhang Y, Deng R, Liu JN, Feng GK, Liu ZC, Xiao DJ, Deng SZ, Zhu XF (2008). Rhabdastrellic acid-A inhibited P13K/Akt pathway and induced apoptosis in human leukemia HL-60 cells. Cell Biol. Int., 32: 48-54. doi:10.1016/j.cellbi.2007.08.009.

Ha ES, Hwang SH, Yu KW, Shin KS, Cho HM, Kim CH, Park WM, Yoon TJ (2003). Immunostimulation activity of the crude polysaccharides fractionated from *Eleutherococcus senticosus*, and its application toprevent of tumors by combination therapy with cisplatin. Yakhak Hoeji, 47: 159-166.

Hahn DR, Kim CJ, Kim JH (1985). A study on chemical constituents of *Acanthopanax koreanum* Nakai and its pharmaco-biological activities. Yakhak Hoeji, 29: 357-361.

Han JH, Jung IC, Cho HE, Park SH (2006). Total polyphenol, water soluble antioxidants contents and antioxidative activity from a composite with *Eleutherococcus senticosus* and several oriental medicinal herbs. Korean J. Ori. Physiol. Pathol., 20: 1275-1281.

Hibasami H, Fujikawa T, Takeda H, Nishibe S, Satoh T, Fujisawa T, Nakashima K (2000). Induction of apoptosis by *Acanthopanax senticosus* HARMS and its component, sesamin in human stomach cancer KATO III cells. Oncol. Rep., 4: 1213-1216.

Hikino H, Takahashi M, Otake K, Konno C (1986). Isolation and hypoglycemic activity of eleutherans A, B, C, D, E, F, and G: glycans of *Eleutherococcus senticosus* roots. J. Nat. Prod., 49: 293-297.

Huang LZ, Huang BK, Ye Q, Qin LP (2011b). Bioactivity-guide fractionation for anti-fatigue property of *Acanthopanax senticosus*. J. Ethnopharmacol., 133: 213-219. doi:10.1013/j.jep.2010.09.032.

Huang LZ, Zhao HF, Huang BK, Zheng CJ, Peng W, Qin LP (2011a). *Acanthopanax senticosus*: review of botany, chemistry and pharmacology. Pharmazie, 66: 83-97. doi:10.1691/ph.2011.0744.

Hwang SH, Ha ES, Yu KW, Shin KS, Lee SH, Lee JK, Lee KH (2003). Effect of the crude polysaccharides fraction from *Eleutherococcus senicosus* as a immunoadjuvant to soluble antigens (BSA and OVA). Yakhak Hoeji, 47: 167-175.

Jung CH, Jung H, Shin YC, Park JH, Jun CY, Kim HM, Yim HS, Shin MG, Bae HS, Kim SH, Ko SG (2007). *Eleutherococcus senticosus* extract attenuates LPS-induced iNOS expression through the inhibition of Akt and JNK pathways in murine macrophage. J. Ethnopharmacol., 113: 183-187. doi:10.1016/j.jep.2007.05.023.

Jung HJ, Park HJ, Kim RG, Shin KM, Ha J, Choi JW, Kim HJ, Lee YS, Lee KT (2003). *In vivo* anti-inflammatory and antinociceptive effects of liriodendrin isolated from the stem bark of *Acanthopanax senticosus*. Planta Med., 69: 610-616.

Kim JK, Kim SW, Kim HY, Lee BE, Ko SY (2007b). OPB, a water extract from *Rehmannia glutinosa* Libosch and *Eleutherococcus senticosus* Max, inhibits osteoclast differentiation and function. Int. J. Oral Biol., 32: 23-34.

Kim JK, Kim SW, Ko SY, Kim SN, Kwon JS, Hwang HH (2007a). The effect of combined *Rehmannia glutinosa* Libosch and *Eleutherococcus senticosus* Max (OPB) extracts on bone mineral density in ovariectomized rats. Int. J. Oral Biol., 32: 143-151.

Kim MJ, Kim NY, Kang WH, Choi WC, Yu CY (2002). *In vitro* antioxidant activity and anticancer effects of the extracts from *Eleutherococcus senticosus* Max. Korean J. Med. Crop Sci., 10: 269-272.

Kim MJ, Kwon YS, Yu CY (2005). Antioxidative compounds in extracts of *Eleutherococcus senticosus* Max. plantlets. Korean J. Med. Crop Sci., 13: 194-198.

Kim MK, Jin YS, Heo SI, Shim TH, Sa JH, Wang MH (2006). Studies for component analysis and antioxidant effect, antimicrobial activity in *Acanthopanax senticosus* HARMS. Korean J. Pharmacogn., 37: 151-156.

Kimura Y, Sumiyoshi M (2004). Effects of various *Eleutherococcus senticosus* cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice. J. Ethnopharmacol., 95: 447-453. doi:10.1016/j.jep.2004.08.027.

Kormosh N, Laktionov K, Antoshechkina M (2006). Effect of a combination of extract from several plants on cell-mediated and humoral immunity of patients with advanced ovarian cancer. Phytother. Res., 20: 424-425. doi:10.1002/ptr.1889.

Kwan CY, Zhang WB, Sim SM, Deyama T, Nishibe S (2004). Vascular effects of Siberian ginseng (*Eleutherococcus senticosus*): endothelium-dependent NO- and EDHF-mediated relaxation depending on vessel size. Naunyn-Schmiedeberg's Arch. Pharmacol., 369: 473-480. doi: 10.1007/s00210-004-0927-4.

Lee S, Son D, Ryu J, Lee YS, Jung SH, Kang J, Lee SY, Kim HS, Shin KH (2004). Antioxidant activities of *Acanthopanax senticosus* stems and their lignin components. Arch. Pharm. Res., 27: 106-110.

Lee WT (1979). Distribution of *Acanthopanax* plants in Korea. Korean J. Pharmacol., 10: 103-107.

Li Q, Jia Y, Xu L, Wang XH, Shen ZD, Liu YL, Bi KS (2006). Simultaneous determination of protocatechuic acid, syringin, chlorogenic acid, caffeic acid, liriodendrin and isofraxidin in *Acanthopanax senticosus* HARMS by HPLC-DAD. Biol. Pharm. Bull., 29: 532-534.

Li XC, Barnes DL, Khan IA (2001). A new lignin glycoside from *Eleutherococcus senticosus*. Planta Med., 67: 776-778. doi:10.1055/s-2001-18352.

Lim SS, Lee JM, Park HS, Cho SH, Shin KH, Lee SH (2007). GC/MS analysis of volatile constituents from *Acanthopanax senticosus*. Korean J. Pharmacogn., 38: 327-333.

Liu KY, Wu YC, Liu IM, Yu WC, Cheng JT (2008). Release of acetylcholine by syringin, an active principle of *Eleutherococcus senticosus*, to raise insulin secretion in Wistar rats. Neurosci. Lett., 434: 195-199. doi:10.1013/j.neulet.2008.01.054.

Narimanian M, Badalyan M, Panosyan V, Gabrielyan E, Panossian A, Wikman G, Wagner H (2005). Randomized trial of a fixed combination (KanJang®) of herbal extracts containing *Adhatoda vasica*, *Echinacea purpurea* and *Eleutherococcus senticosus* in patients with upper respiratory tract infections. Phytomedicine, 12: 539-547. doi:10.1016/j.phymed.2004.10.001.

Nishibe S, Kinoshita H, Takeda H, Okano G (1990). Phenolic compounds from stem bark of *Acanthopanax senticosus* and their pharmacological effect in chronic swimming stressed rats. Chem. Pharm. Bull., 38: 1763-1765.

Nishiyama N, Kamegawa T, Iwai A, Saito H, Sanada S, Ida Y, Shoji J (1985). Effect of *Eleutherococcus senticosus* and its components on sex and learning-behaviors and tyrosine hydroxylase activity of adrenal gland and hypothalamic region in chronic stressed mice. Shoyakugaku Zasshi, 39: 238-242.

Niu HS, Hsu FL, Liu IM (2008a). Role of sympathetic tone in the loss of syringin-induced plasma glucose lowering action in conscious Wistar rats. Neurosci. Lett., 445: 113-116. doi:10.1016/j.neulet.2008.08.066.

Niu HS, Liu IM, Cheng JT, Lin CL, Hsu FL (2008b). Hypoglycemic effect of syringin from *Eleutherococcus senticosus* in streptozotocin-induced diabetic rats. Planta Med., 74: 109-113. doi:10.1055/s-2008-1034275.

Oh SY, Aryl DK, Kim YG, Kim HG (2007). Effects of *R. glutinosa* and *E. senticosus* on postmenopausal osteoporosis. Korean J. Physiol. Pharmacol., 11: 121-127.

Orr TSC, Cox JSG (1969). Disodium cromoglycate, an inhibitor of mast cell degranulation and histamine release induced by phospholipase A. Nature, 223: 197-198. doi:10.1038/223197b0.

Panossian A, Davtyan T, Gukassyan N, Gukasova G, Mamikonyan G, Gabrielian E, Wikman G (2002). Effect of andrographolide and Kan Jang-fixed combination of extract SHA-10 and extract SHE-3-on proliferation of human lymphocytes, production of cytokines and immune activation markers in the whole blood cells culture. Phytomedicine, 9: 598-605.

Park EJ, Nan JX, Zhao YZ, Lee SH, Kim YH, Nam JB, Lee JJ, Sohn DH (2004). Water-soluble polysaccharide from *Eleutherococcus senticosus* stems attenuates fulminant hepatic failure induced by D-galactosamine and lipopolysaccharide in mice. Basic Clin. Pharmacol. Toxicol., 94: 298-304. doi:10.1111/j/1742-7843.2004.pto970607.x.

Park JS, Ahn BY, Koh HY, Choi DS (2003). Inhibitory effect of methanol extract of *Eleutherococcus senticosus* Maxim. on the direct mutagen mutagenicity. Korean J. Biotechnol. Bioeng., 18: 217-221.

Park JS, Oh CH, Koh HY, Choi DS (2002). Antimutagenic effect of extract of *Eleutherococcus senticosus* Maxim. Korean J. Food Sci. Technol., 34: 1110-1114.

Parvath S, Brindha R (2003). Ethnobotanical medicines of Animalai union. Ancient Sci. Life, 22: 14.

Protasova SF, Zykov MB (1984). Antiviral effect of *Eleutherococcus* in experimental influenza infection. Proceedings of the Second International Symposium on *Eleutherococcus*, Part II, Academy of Science or the USSR Far East Science Centre, Vladivostok, USSR, pp. 170-174.

Rawat RBS, Uniyal RC (2003). National medicinal plant board committed for overall development of the sector. Agro. Bios. Med. Plant, 1: 12-16.

Rhie SG, Won HR (2004). Effect of hot water soluble extract from *Eleutherococcus senticosus* and dietary carnitine on the lipid metabolism and antioxidant defense system of rats on hypercholesterol diet. Korean J. Comm. Living Sci., 15: 105-113.

Schmolz MW, Sacher F, Aicher B (2001). The synthesis of rantes, G-CSF, IL-4, IL-5, IL-6, IL-12 and IL-13 in human whole-blood cultures in modulated by an extract from *Eleutherococcus senticosus* L. roots. Phytother. Res., 15: 268-270. doi:10.1002/ptr.746.

Shao CJ, Kasai R, Xu JD, Tanaka O (1988). Saponins from leaves of *Acanthopanax senticosus* HARMS. Ciwujia: structure of ciwujianosides B, C1, C2, C3, C4, D1, D2, E. Chem. Pharm. Bull., 36: 601-608.

Slacanin I, Marston A, Hostettmann K, Guédon D, Abbe P (1991). The isolation of *Eleutherococcus senticosus* constituents by centrifugal partition chromatography and their quantitative determination by high performance liquid chromatography. Phytochem. Anal., 2: 137-142. doi:10.1002/pca.2800020310.

Smalinskiene A, Lesauskaite V, Zitkevicius V, Savickiene N, Savickas A, Ryselis S, Sadauskiene I, Ivanov L (2009). Estimation of the

combined effect of *Eleutherococcus senticosus* extract and cadmium on liver cells. Natural compounds and their role in apoptotic cell signaling pathways: Ann. N. Y. Acad. Sci., 1171: 314-320. doi:10.1111/j.1749-6632.2009.04678.x.

Song YJ, Han DS, Oh SW, Paik IY, Park TS (2002). Effect of dietary supplementation of *Eleutherococcus senticosus*, taurine and carnitine on endurance exercise performance in rats. Korean J. Nutr., 35: 825-833.

Steinmann GG, Esperester A, Joller P (2001). Immunopharmacological *in vitro* effects of *Eleutherococcus senticosus* extracts. Drug Res., 51: 76-83.

Sui DY, Lu ZZ, Li SH, Cai Y (1994a). Hypoglycemic effect of saponin isolated from leaves of *Acanthoganax senticosus* (Rupr. et Maxin.) Harms. Zhongguo Zhong Yao Za Zhi, 19: 683-685, 703.

Sui DY, Lu ZZ, Ma LN, Fan ZG (1994b). Effects of the leaves of *Acanthopanax senticosus* (Rupr. et Maxim.) Harms. on myocardial infarct size in acute ischemic dogs. Zhongguo Zhong Yao Za Zhi, 19: 746-747, 764.

Sung JY, Yoon TJ, Yu KW, Lee KH, Lee H (2006). Enhancement of immunological activities in mice by oral administration of pectic polysaccharides from *Eleutherococcus senticosus*. Food Sci. Biotechnol., 15: 117-121.

Szolomicki S, Samochowiec L, Wójcicki J, Drozdzik M (2000). The influence of active components of *Eleutherococcus senticosus* on cellular defence and physical fitness in man. Phytother. Res., 14: 30-35.

Takasugi N, Moriguchi T, Fuwa T, Sanada S, Ida Y, Shoji J (1985). Effect of *Eleutherococcus senticosus* and its components on rectal temperature, body and grip tones, motorcoordination, and exploratory and spontaneous movements in acute stressed mice. Shoyakugaku Zasshi, 39: 232-237.

Tohda C, Ichimura M, Bai YJ, Tanaka K, Zhu S, Komatsu K (2008). Inhibitory effects of *Eleutherococcus senticosus* extracts on amyloid β (25-35)-induced neuritic atrophy and synaptic loss. J. Pharmacol. Sci., 107: 329-339.doi:10.1254/jphs.08046FP.

Tolonen A, Joutsamo T, Mattlla S, Kämäräinen T, Jalonen J (2002). Identification of isomeric dicaffeoyquinic acids from *Eleutherococcus senticosus* using HPLC-ESI/TOF/MS and ^{1}H-NMR methods. Phytochem. Anal., 13: 316-328. doi.10.1002/pca.663.

Umeyama A, Shoji N, Takei M, Endo K, Arihara S (1992). Ciwujianosides D1 and C1: powerful inhibitors of histamine release induced by anti-immunoglobulin E from rat peritoneal mast cells. J. Pharm. Sci., 81: 661-662.

Wiegant FAC, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA (2009). Plant adaptogens increase lifespan and stress resistance in *C. elegans*. Biogerontology, 10: 27-42. doi:10.1007/s10522-008-9151-9.

Winston D, Maimes S (2007). Adaptogens: Herbs for Strength, Stamina, and Stress Relief. Healing Arts Press, Rochester, Vermont, Pp. 85-86.

Yang DS, Cha MH, Kang BJ, Oh SW, Kim YE, Yoon YS (2003). A study on the longitudinal bone growth of growth-stimulating material with *Eleutherococcus senticosus*. Korean J. Food Sci. Technol., 35: 702-707.

Yang SJ, Shin JS, Kang CH (2004). Extraction of acanthoside-D from *Acanthopanax* cortex using supercritical carbon dioxide. Korean J. Biotechnol. Bioeng., 19: 284-287.

Yi JM, Hong SH, Kim JH, Kim HK, Song HJ, Kim HM (2002). Effect of *Acanthopanax senticosus* stem on mast cell-dependent anaphylaxis. J. Ethnopharm., 79: 347-352.

Yu CY, Kim SH, Lim JD, Kim MJ, Chung IM (2003). Intraspecific relationship analysis by DNA markers and in vitro cytotoxic and antioxidant activity in *Eleutherococcus senticosus*. Toxicol. Vitro, 17: 229-236.