REVIEW

Department of Pharmacognosy[1], School of Pharmacy, Second Military Medical University, Shanghai; Department of Pharmacy[2], School of Pharmacy, Fujian University of Traditional Chinese Medicine, Fuzhou, P.R.China

Acanthopanax senticosus: review of botany, chemistry and pharmacology

LinZhang Huang[1,2], HongFang Zhao[1,2], BaoKang Huang[1], ChengJian Zheng[1], Wei Peng[1], LuPing Qin[1]

Received August 9, 2010, accepted September 17, 2010

LuPing Qin, Department of Pharmacognosy, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai, 200433, P.R. China
qinsmmu@126.com; lpqin@smmu.edu.cn

Pharmazie 66: 83–97 (2011) *doi: 10.1691/ph.2011.0744*

Acanthopanax senticosus (Rupr. et Maxim) Harms (Araliaceae), also called Siberian Ginseng, *Eleutherococcus senticosus*, and *Ciwujia* in Chinese, is a widely used traditional Chinese herb that could invigorate *qi*, strengthen the spleen, and nourish kidney in the theory of Traditional Chinese Medicine. With high medicinal value, *Acanthopanax senticosus* (AS, thereafter) is popularly used as an "adaptogen" like *Panax ginseng*. In recent decades, a great number of chemical, pharmacological, and clinical studies on AS have been carried out worldwide. Several kinds of chemical compounds have been reported, including triterpenoid saponins, lignans, coumarins, and flavones, among which, phenolic compounds such as syringin and eleutheroside E, were considered to be the most active components. Considerable pharmacological experiments both *in vitro* and *in vivo* have persuasively demonstrated that AS possessed anti-stress, anti-ulcer, anti-irradiation, anticancer, anti-inflammatory and hepatoprotective activities, etc. The present review is an up-to-date and comprehensive analysis of the botany, chemistry, pharmacology, toxicity and clinical trials of AS.

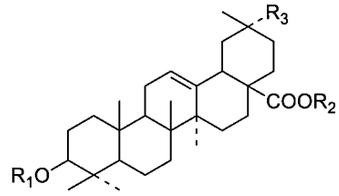
1. Introduction

Acanthopanax senticosus (AS, thereafter) (also known as *Eleutherococcus senticosus*, Siberian ginseng, and Ciwujia) is a hardy shrub, approximately six-meter high, native to the northeastern region of China, Korea, and Japan, and the far-eastern region of Russia. It is a medicinal herb that belongs to the family of Araliaceae and is also known as a powerful tonic herb with an impressive range of health benefits. This medicinal plant is especially popular in China and Russia. Currently, it remains one of the traditional Chinese medicines in the Pharmacopoeia of the People's Republic of China. AS is efficient in invigorating the liver and kidney, replenishing the vital essence, and strengthening bones, and can be used to relieve symptoms of transient cerebral ischemia attacks, cerebral arteriosclerosis, cerebral thrombosis and cerebral embolism caused by a deficiency in the liver and kidney. In addition, it is used to treat coronary heart disease, angina pectoris, combined neurosis and the menopausal syndrome (China 2005). Also, it is well known to be highly effective in treating various conditions, including stress-induced pathophysiologic changes (Fujikawa et al. 1996) and inflammation. This review tries to show the advances in botany, chemistry, pharmacology, adverse reactions, and clinical trials of AS in the last decade, on the basis of two other similar reviews of this plant (Davydov and Krikorian 2000; Deyama et al. 2001).

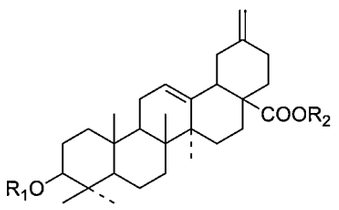
2. Botany of *Acanthopanax senticosus*

Acanthopanax senticosus (AS) or *Eleutherococcus senticosus*, is also called *Ciwujia* in Chinese, and Siberian ginseng in the Siberian Taiga region. Although not as popular as Asian ginseng, the medicinal use of *AS* dates back 2,000 years according to Chinese medicine records. It was first introduced into the American herb market in the late 1970 s as "*Wuchaseng*" and "*Wujiaseng*". And it is commonly called eleuthero, and was previously marketed in the United States as Siberian Ginseng as it has properties similar to those of *Panax ginseng*. However, AS is only distantly related to the true ginseng species (*Panax ginseng* and *P. quinquefolius*) and possesses entirely different, unrelated chemical constituents. So in May 2002, the United States Congressional amendment to the Federal Food, Drug and Cosmetic Act eliminated any confusion regarding what is true ginseng. Currently, only the genus *Panax* can be called ginseng on labeling or in advertising, marketing eleuthero as Siberian Ginseng in the United States is therefore illegal. (Winston and Maimes 2007)

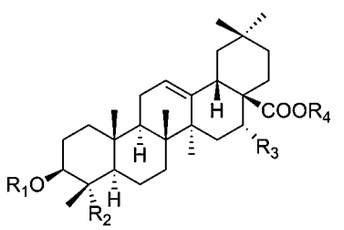
The herb grows in mixed and coniferous mountain forests, forming low undergrowth or is found in groups in thickets and edges. Shrubs of *AS* are to 6 m tall. Branches with dense to scattered, slender, terete, bristlelike prickles. Petiole 3–12 cm, slender, sometimes with fine prickles; petiolule of central leaflet (0.6–1.22 cm), usually brownish pubescent; leaflets (3−5), elliptic-obovate or oblong, 5–13 × 3–7 cm, papery, abaxially pubescent on veins, adaxially with scattered hairs, secondary veins 6 or 7 pairs, conspicuous on both surfaces, base broadly cuneate, margin sharply biserrate, apex shortly acuminate or acuminate. Inflorescence terminal, a solitary or compound umbel, borne on leafy shoots, usually with 2–6 umbels together; peduncles 5–7 cm, glabrous; pedicels 1–2 cm, glabrous or slightly pubescent at base. Calyx subentire or with 5 inconspicuous teeth, glabrous. Corolla purple-yellow. Ovary



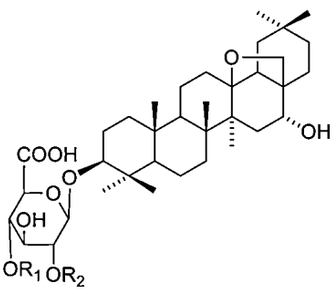
	R_1	R_2	R_3
1	-ara(1-2)-Glc	-Glc(1-6)-Glc-(1-4)-rha	CH_3
3	-ara(1-2)-rha	-Glc(1-6)-Glc-(1-4)-rha	CH_2OH
4	-ara(1-2)-Glc	-Glc(1-6)-Glc(-6Ac)-(1-4)-rha	CH_2OH
16	-ara(1-2)-Glc	H	CH_3
12	-ara	-Glc(1-6)-Glc(-6Ac)(1-4)-rha	CH_2OH
8	-ara	-Glc(1-6)-Glc(1-4)-rha	CH_3
9	-ara(1-2)-rha	-Glc(1-6)-Glc(-6Ac)(1-4)-rha	CH_3
10	-ara	-Glc(1-6)-Glc(-6Ac)(1-4)-rha	CH_3
14	-ara(1-2)-rha	-Glc(1-6)-Glc(1-4)-rha	CH_3
15	-ara(1-2)-rha	H	CH_3
18	H	H	CH_2OH
22	-ara-Glc	-Glc-Glc(-6Ac)-rha	CH_3
23	-ara-rha	H	COOH
28	-ara-rha	H	CH_2OH
29	-GlcA	H	CH_3
33	-GlcA	-Glc	CH_3
38	-Glc	-Glc(-6)-Glc	CH_3
39	-rha(1-2)-ara	-Glc(1-6)-Glc	CH_3
40	-rha(1-4)-ara	-rha(1-4)-Glc(1-6)-Glc	CH_3



	R_1	R_2
2	-ara(1-2)-Glc	-Glc(1-6)Glc(1-4)-rha
5	-ara(1-2)-rha	-Glc(1-6)Glc(1-4)-rha
6	-ara	-Glc(1-6)Glc(1-4)-rha
7	-ara(1-2)-rha	-Glc(1-6)Glc(-6Ac)(1-4)-rha
11	-ara	-Glc(1-6)Glc(-6Ac)(1-4)-rha
13	-ara(1-2)-rha	H
17	H	H
21	-ara-Glc	-Glc-Glc(-6Ac)-rha



	R_1	R_2	R_3	R_4
24	-GlcA	CH_3	-OH	-Glc
26	-ara-rha	CH_3	-OH	-Glc-Glc-rha
30	-GlcA	CH_2OH	H	H
31	-6-O-methyl-GlcA	CH_2OH	H	H
32	-GlcA	CHO	H	H
34	-GlcA	CH_2OH	H	-Glc
35	-6-O-methyl-GlcA	CH_2OH	H	-Glc
36	-GlcA	CHO	H	-Glc
37	H	CH_2OH	H	-Glc



	R1	R2
19	-Glc-(1-3)-Gal	-Rha
20	-Rha-(1-4)-Rha-(1-4)-[O-Rha-(1-2)]-Glc	H

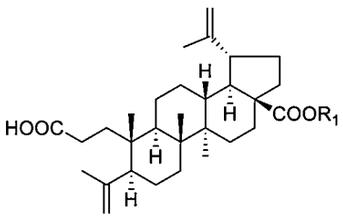
5-carpellate; styles united into a column. Fruit ovoid-globose, ca. 8 mm; styles persistent, ca. 1.5 mm. Fl. Jun–Jul, fr. Aug–Oct. (Wu and Raven 2007)

This plant is distributed in Amur, Khabarovsk, Primorye, Sakhalin of Russian Far East, Hebei, Heilongjiang, Henan, Jilin, Liaoning, Shaanxi, Shanxi, Sichuan of China, also in Japan and Korea. In Traditional Chinese Medicine, it is efficient in invigorating *qi* and strengthening the spleen, tonifying kidney to relieve mental strain. AS is therefore found use in the treatment of symptoms like *yang* deficiency of spleen and kidney, body weak and hypodynamia, poor appetite, aching of waist and knee, insomnia and dreaminess and so on. Eleuthero was originally used by people in the Siberian Taiga region to increase performance and quality of life and to decrease infections, in Russia.

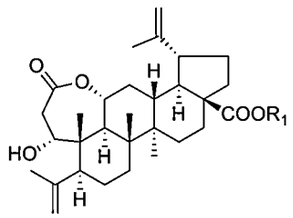
3. Chemical constituents

Brekhman (1968, 1976) performed the earliest phytochemical and pharmacological studies on Siberian ginseng. AS was originally discovered in search for a drug that could substitute the expensive Korean ginseng. However, AS showed marked difference from Korean ginseng in the main components. The active components of the former were considered to be lignans, while saponins were the most bioactive constituents in Korean ginseng.

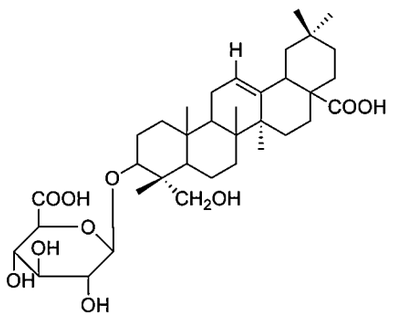
Many chemical constituents have been isolated from AS since the late 1960 s, by several groups from Germany, Japan, China and Korean, etc. In this section, we describe the main constituents and the up-to-date pharmacological studies of AS.



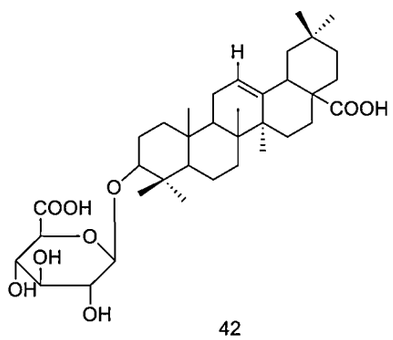
25 R_1 = -Glc-Glc-rha



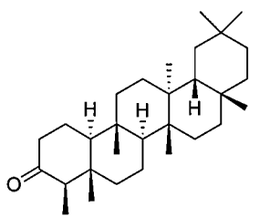
27 R_1 = -Glc-Glc-rha



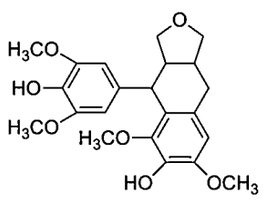
41



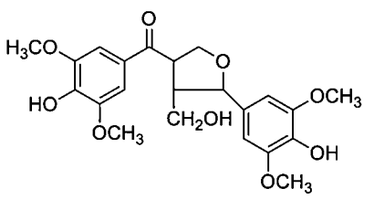
42



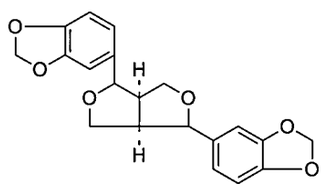
43



44



45



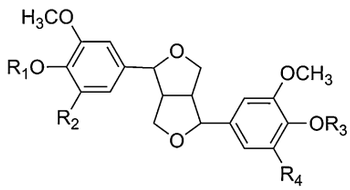
46

3.1. Volatile compounds (essential oils)

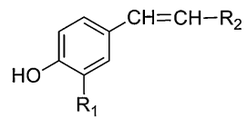
Limited work has been carried out on the volatile components of *AS*. Its essential oils were isolated by hydrodistillation and analyzed by GC/Qms, GC/FTIR and GC/oaTOFMS (Yu et al. 2006). The oil yield of the root of *AS* was 0.05%, and 68 GC peaks were identified qualitatively with the aid of analysis of GC/FTIR and GC/oaTOFMS. Among the 68 GC peaks, the contents of 20 components are more than 1%. Isocaryophyllene and caryophyllene oxide occupied 9.97% and 16.4% of the total volatile oils, respectively. Other components identified in essential oil in high amounts (>2%) included n-octadecanol, manoyl oxide, 9,17-octadecadienal, tetradecanal, humulene oxide, humulene, β-farnesene, (E,E)-2.4-decadienal, linalool, p-cymene, 2-n-pentylfuran, α-pinene, n-heptaldehyde and so on. To our knowledge, there are no reports yet about the pharmacological effects of essential oils from AS.

3.2. Triterpenoid saponins

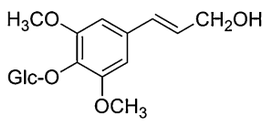
Since the first study of *AS* in 1950 s, many triterpenoid saponins have been isolated and identified from different parts of this plant. Somewhat later, in the 1980s (Shao et al. 1989) ciwujianosides A_1, A_2, A_3, A_4, B, C_1, C_2, C_3, C_4, D_1, D_2, D_3, E have been isolated from the leaves of *AS*. Ciwujianosides D_1 and C_1 were found to possess significant inhibitory effect on histamine release induced by anti-immunoglobulin E in a concentration-dependent manner (Umeyama et al. 1992). After that, Jiang et al. (2006) also obtained three new compounds called acanthopanaxosides A, B, C, along with sessiloside and tauroside that were first reported from this species. They also evaluated the biological effect of these compounds against pancreatic lipase. Ciwujianoside C_1, tauroside H1,3-*O*-alpha-rhamnopyranosyl-(1-2)-alpha-arabinopyranosyl mesembryanthemoidigenic acid, acanthopanaxoside C, sessiloside, and chiisanoside were found



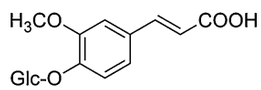
	R_1	R_2	R_3	R_4
47	-Glc	OCH_3	-Glc	OCH_3
48	-Glc	OCH_3	-OH	OCH_3
49	H	H	-Glc	H
50	-Glc	OCH_3	H	OCH_3
51	-Glc	H	-Glc	H
52	-Glc	H	-Glc	OCH_3



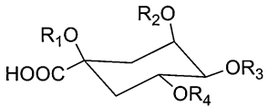
	R_1	R_2
58	-OH	-COOH
59	-OMe	-CHO
60	-OH	-COOEt

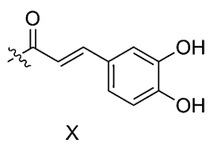


53



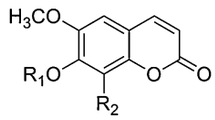
61



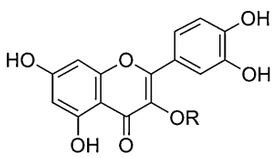


X

	R_1	R_2	R_3	R_4
54:	H	H	H	X
55:	X	H	H	X
56:	H	X	H	X
57:	H	H	X	X



	R_1	R_2
62 :	H	$-OCH_3$
63:	-Glc	$-OCH_3$
64:	H	H
65:	-Glc(1-6)-rha	$-OCH_3$



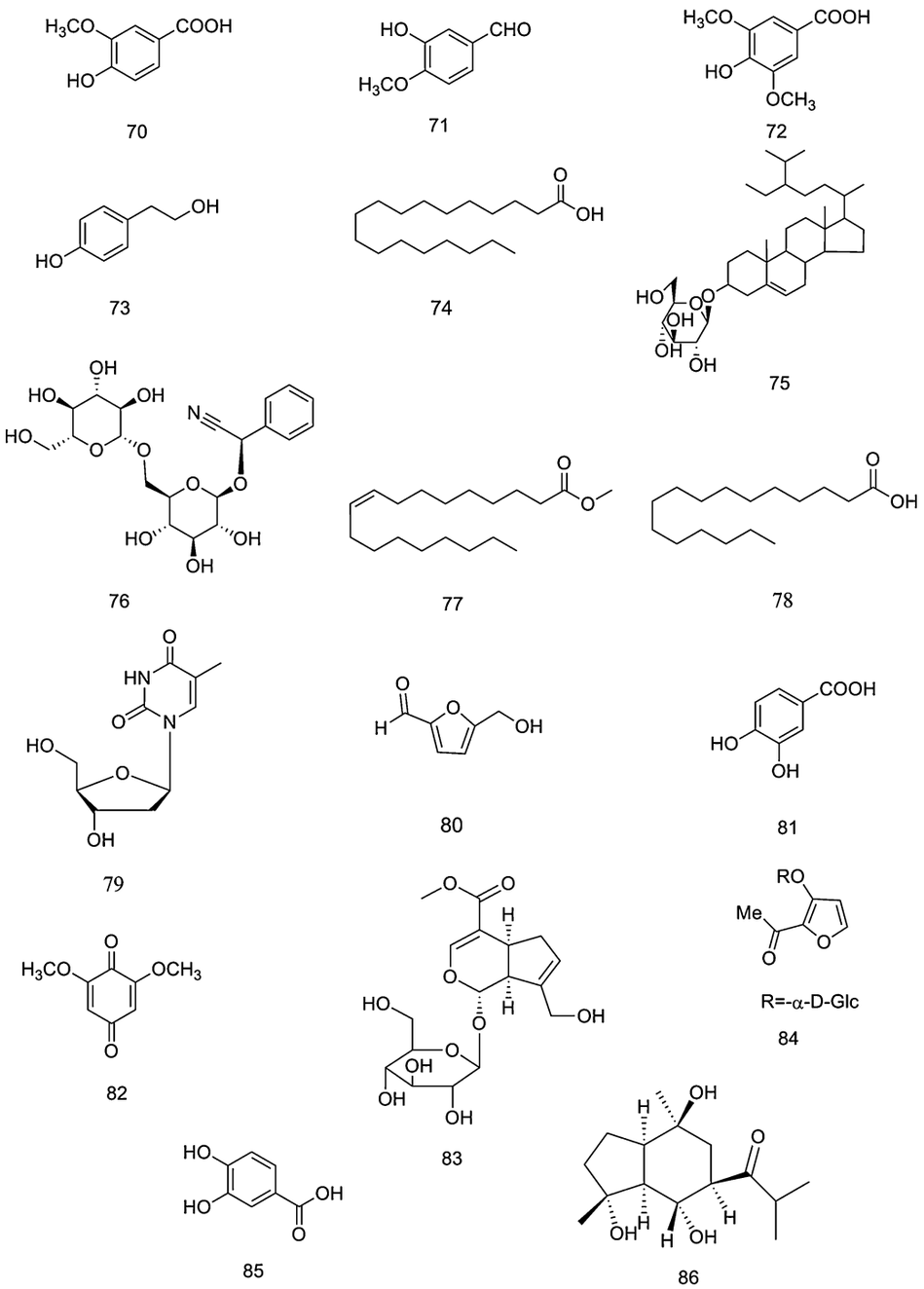
	R
66:	-Rha
67:	-Gal
68:	H
69:	-Rha-Glc

to inhibit pancreatic lipase activity *in vitro*. In comparison, ciwujianosides C_2, D_2, C_4, and C_3 and hederasaponin B enhanced this enzyme. (Li et al. 2007) isolated sixteen triterpenoid saponins from the fruits of *AS*, including a new compound, acanthopanaxoside E, which was established as 3-*O*-beta-D-glucuronopyranosyl echinocystic acid 28-*O*-beta-D-glucopyranoside on the basis of various spectroscopic analyses and chemical degradation, along with silphioside F, hederagenin 3-*O*-beta-D-glucuronopyranoside 6'-*O*-methyl ester, gypsogenin 3-*O*-beta-D-glucuronopyranoside and so on. Moreover, those crude saponin fractions were proved to possess inhibitory activity on pancreatic lipase, a key enzyme in lipid digestion. The major triterpenoid in commercial eleutherococcus material is oleanane-type triterpenoid saponins (Fig.). Other kinds of saponins are listed in the Table.

3.3. Lignans

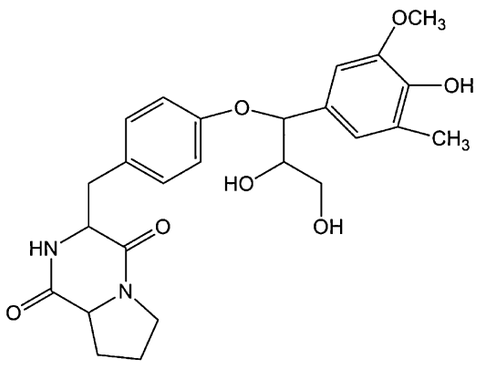
Lignans have been suggested to be evolutionarily-derived by elaboration of the phenylpropanoid pathway for a plant's own "benefits", as its own immunoprotection and protection, as it were, from harmful free radicals (Lewis and Davin 1994). AS not only synthesizes lignans such as syringin, syringoresinol and sesamin, but also makes and accumulates lignan precursors such as cell wall-bound hydroxycinnamic acid-caffeic acid and other intermediate compounds of lignan synthesis such as coniferylaldehyde (Davydov and Krikorian 2000). New compounds, neociwujiapenol (Wu et al. 1999). ciwujiatone (Wu et al. 1997). eleutheroside E2 (Li et al. 2001), have been obtained from various parts of this plant. Also, 3',5'-*O*-dicaffeoylquinic acid, 4',5'-*O*-dicaffeoylquinic acid (Tolonen et al. 2002). feruloyl sucrose (Wu et al. 1999). (+)-pinoresinol-*O*-β-D-glucoside, (+)-syringaresinol-*O*-β-D-glucoside, (+)-pinoresinlo-di-*O*-β-D-glucoside and (+)-medioresinol-di-*O*-β-D-glucoside(Nishibe et al. 1990) were first separated from *AS*. For more detailed information about lignan compouds 44 to 61 see Table.

Eleutheroside B (syringin) is the main active lignan of *AS*, which has anti-radiation (Zhang et al. 1990), immunopotentiating/immunostimulatory (Kapil and Sharma 1997), immunomodulatory (Cho et al. 2001), hypoglycemic (Niu et al. 2008), antihyperglycemic (Niu et al. 2007), anti-oxidant (Lee et al. 2004), anti-inflammatory (Lanza et al. 2001), and anti-fatigue (Chen et al. 2008), effects. Also syringin was proved to be active in protecting against neuritic atrophy and cell death under Abeta

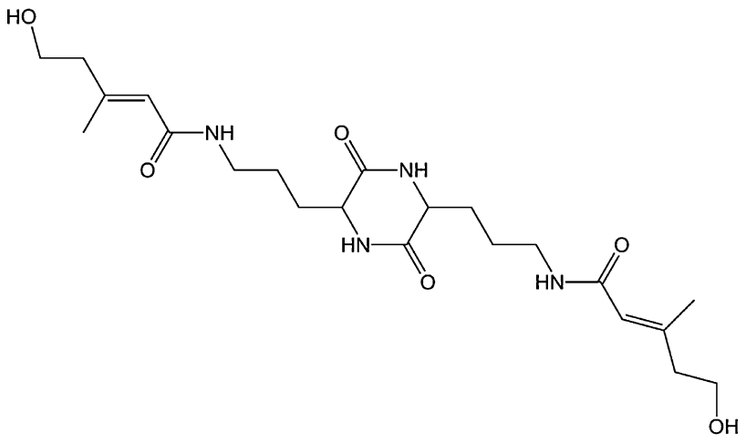


treatment (Tohda et al. 2008). Besides, sesamin have the effect of suppressing the growth and inducing apoptosis in human stomach cancer KATOIII cells (Hibasami et al. 2000). Moreover, hypocholesterolemic (Hirata et al. 1996), anti-cancer (Hirose et al. 1992), immunostimulatory (Nonaka et al. 1997), and heptoprotective effects (Akimoto et al. 1993) were reported for lignans. In addition, eleutheroside E possesses significant anti-inflammatory effects, which were further studied. Tokiwa et al., (2006) examined the effects of eleutheroside E on gene expression of inflammatory mediators and DNA binding activity of transcription factors in IL-1-stimulated human synovial sarcoma cell line SW982 cells. They found that eleutheroside E suppressed the gene expression of IL-6, matrix metalloproteinase (MMP-1), and cyclooxygenase(COX)-2 at lower concentrations than eleutheroside B and isofraxidin, which also inhibited MMP-1 promoter activity, transcription factors NF- κ B and AP-1 binding activities. All those results suggested that eleutheroside E may exert an antiflammatory effect by suppressing the gene expression of inflammatory proteins through inhibiting NF-κ B and AP-1 binding activities (Tokiwa et al. 2006). The pharmacological effects of other kinds of lignan compounds like caffeic acid have been already elucidated in a previous review (Davydov and Krikorian 2000).

Syringin, is thought to be the best marker compound for quality assurance of the Shigoka, the rhizome of *Eleutherocuccus senticosus*, from the viewpoint of its pharmacological activ-



87



88

ity (Maruyama et al. 2008). It is reported that the contents of eleutheroside B and E in stems were higher than those in roots (Kang, et al. 2001).

Pharmacokinetic studies showed that, blood drug level-time curves of eleutheroside E and eleutheroside B in Wistar rats following administration of an *Eleutherococcus* injection into the femoral vein were shown to fit a three-compartment model. The half-life ($t_{1/2}$) was 4.662 h for eleutheroside E and 2.494 h for eleutheroside B. The concentration of eleutheroside E and eleutheroside B varied in different tissues: $C_{liver} > C_{kidney} > C_{spleen} > C_{heart}$ and $C_{kidney} > C_{liver} > C_{heart}$ (Feng et al. 2006)

HPLC analysis revealed that the total eleutherosides were significantly higher in leaves of field grown plants as compared to that in somatic embryo of different stages. However, the content of eleutheroside B, eleutheroside E and eleutheroside E_1 was higher than that in other developmental stages. This result indicates that an efficient protocol for the mass production of *Eleutherococcus sessiliflorus* biomass can be achieved by bioreactor culture of somatic embryos and can be used as a source of medicinal raw materials (Shohael et al. 2005).

3.4. Coumarins

Compared with other kinds of compouds, only few coumarin compouds were reported from this plant. Isofraxidin, isofraxidin- 7-*O*-β-D-glucoside (Nishibe et al. 1990), scopoletin (Kurkin et al. 1992), and eleutheroside B_2 (Li et al. 2009) were isolated. Isofraxidin is one of the main bioactive constituents in the roots of *AS*, which has antifatigue, antistress, and immuno-accommondating effects (Sun et al. 2007). Aldose-reductase-inhibitory, antileukemic, antimalarial, cancer-preventive and choleretic effects of isofraxidin have been recorded in Dr. Duke's phytochemical and ethnobotanical databases. Scopoletin exhibited a potent inhibitory effect on rabbit platelet aggregation induced by four types of agent, ADP, PAF, sodium arachidonate and/or collagen (Okada et al. 1995). However, some researchers classified parts of lignans and coumarins as phenolic compounds, which include syringic acid, vanillin, p-coumaric acid, caffeic acid, ferulic acid, chlorogenic acid, coniferin, syringin, coniferyl alcohol, isofraxidin, isofraxidin glucoside, syringaresinol, syringaresinol diglucoside (Kurkin et al. 1991), sinapyl alcohol 4-*O*-(2'-*O*-α-L-apioxyl-β-D-glucopyranoside), scopoletin, protocatechuic acid, protocatechuic acid 3'-*O*-β-D-glucopyranoside (Kurkin et al. 1992). Among them, most of the compounds were isolated for the first time from this plant.

3.5. Flavones

Four flavonoids, including hyperin, quercitrin, quercetin, and rutin, were isolated from AS, and the later three were

first reported from the leaves of this plant. Those compounds were identified in terms of electrospray tandem mass spectrometry(ESI-MS^n) data (Mao-Lian et al. 2002). Moreover, it was found that the content of quercetin together with its derivatives was more than 37.25%. However, the total flavonoids varied due to different harvest periods, different areas, and different processing methods. It is reported that the highest content of total flavonoids was detected in the four-year-old *AS* collected in tiexi and dried in the sun (Wang et al. 2005).

3.6. Polysaccharides

Acanthopanacis senticosi Polysaccharides (ASPs) were comprised of glucose, fructose, arabinose etc. Fang et al. (1985) isolated two homogeneous polysaccharides from the alkaline aqueous extract of AS, a glucan with a mean M of 150 000 and a heteroxylan with a mean M of 30,000. Both of them were proved to enhance phagocytosis in various immunological tests. In general, ASPs was extracted by hot water then precipitated with alcohol. When the quantity of alcohol was equal to the volume of ASPs filtrate, the production yield will be the highest. They do not only inhibit the lipid peroxidation but also produce some reductive effect to the erythrocyte membrane (Qing-fan et al. 2005). ASPs can also enhance the expression of OGG1 mRNA and protect the hippocampal neurons from oxidative stress injury (Bo et al. 2009). and possess anticancer effects.

3.7. Other compounds

Vanillic acid, isovanillin, tyrosol, octadecnoic acid, daucosterol, amygdaloside, methyl oleate, aethylis oleas and palmitic acid, thymidine,(Li et al. 2001) protocatechuic,(Kurkin et al. 1992) oplopanone B (Li et al. 2009) and eleutherazine A, B(Li et al. 2010) were also isolated from *AS*. More detailed information was listed in the Table (70−88).

4. Pharmacology research

4.1. Anti-inflammatory activity

AS is frequently used in TCM for inflammatory diseases. Its stem bark extract may be partly responsible for the anti-inflammatory function. Since exposing of mouse peritoneal macrophages to AS extract significantly suppressed superoxide anion production induced by zymosan in a dose-dependent manner, meanwhile, it also significantly inhibited hydrogen peroxide production induced by phorbol 12-myristate 13-acetate (PMA) in a dose-dependent manner. Intraperitoneal administration of AS extract to KM mice reduced the ex vivo production of zymosan induced-superoxide anion and PMA-induced hydrogen peroxide by their peritoneal macrophages (Lin et al. 2008). Isofraxidin, isolated from AS, slightly inhibited the growth of SW982 cells at 450 μM, but significantly suppressed the gene expression of IL-1β, IL-6, MMP-1, and COX-2 at 135 μM as well as at 450 μM, also suppressed IL-6 production. These results suggest that isofraxidin exhibits anti-inflammatory effects (Yamazaki et al. 2004). Compared with the effects of the three active components (+)-syringaresinol-di-*O*-β-D-glucoside(SR), syringin and isofraxidin isolated from the stem bark of AS, on inflammatory function in SW982 human synovial sarcoma cell system, isofraxidin had significant inhibitory effects on cell growth; SR suppressed the production of IL-6 at lower concentrations than syringin and isofraxidin, SR and syringin significantly suppressed the production of prostaglandin E_2, while isofraxidin suppressed only slightly. SR was more potent than syringin and isofraxidin at inhibiting the expression of IL-1β, IL-6, cyclooxygenase (COX)-2 and matrix metalloproteinases (MMP)-1 mRNA, but was less potent than syringin at inhibiting the expression of MMP-2. Furthermore, SR significantly reduced MMP-1 promoter luciferase activity and DNA-binding activity of transcriptional factors AP-1 and NF-kappa B. In conclusion, these results suggested that SR modulates the inflammatory process involved in arthritis by suppressing various gene expression through inhibiting AP-1 and/or NF-kappaB activities (Yamazaki et al. 2007).

4.2. Anticancer/antitumor activities

The aqueous extract of AS is able to inhibit tumor metastasis prophylactically as well as therapeutically, and its antitumor effect is associated with activation of macrophages and NK cells (Yoon et al. 2004). The polysaccharides from AS can inhibit the proliferation of S180 mice sarcoma and K562 human chronic myelogenous leukemia cells. That means that the antitumor action of AS is not only related to the action of enhancing the body immune function but also related to the changes of the cell membrane (Tong et al. 1994).

4.3. Hepatoprotective effects

Intraperitoneally injected water-soluble polysaccharides extracted from AS, can attenuate fulminant hepatic failure induced by D-galactosamine/lipopolysaccharide in mice. They significantly lowered serum levels of tumor necrosis factor-α, aspartate transaminase and alanine transaminase, improved the histologic changes in liver, inhibited hepatocyte apoptosis and, suppressed the lethality induced by D-galactosamine/lipopolysaccharide (Park et al. 2004).
The 30 kDa glycoprotein (GF-AS) isolated from the stem bark of AS was studied on the protective effect against acute and chronic alcohol-induced hepatotoxicity. The outcomes showed that GF-AS significantly increases the activities of alcohol-metabolizing enzymes, including alcohol dehydrogenase, microsomal ethanol metabolizing system, and acetaldehyde dehydrogenase in rats acutely treated with alcohol. GF-AS also increases the activities of antioxidant enzymes and glutathione levels. Collectively, GF-AS may alleviate alcohol-induced hepatotoxicity through increasing ethanol and lipid metabolism, as well as antioxidant defense systems in livers injured by acute- and chronic-alcohol intake (Choi et al. 2006). Recently, Smalinskiene et al. (2009) showed that AS 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.

4.4. Immunodulator

An ethanolic extract of AS was found to influence cytokine synthesis of activated whole blood cultures of ten healthy volunteers, and the release of IL-4, IL-5 and IL-12 was significantly inhibited, suggesting that the preparation possesses immunomodulatory potency (Schmolz et al. 2001). In addition, the whole ethanolic fluid extract of AS was able to induce and enhance interleukin-1 and interleukin-6 but not interleukin-2 production *in vitro* (Steinmann et al. 2001).
In vitro, lymphocytes treated with an AS preparation produced an immune-boosting effect both in cancer patients and healthy controls (Kupin and Polevaia 1986). AS has an *in vitro* effect on the activation and proliferation of immunocompetent cells, also on the production of key cytokines and immune activation markers. A standardized fixed combination of *Andrographis paniculata* and AS extracts when investigated in cultivated whole blood cells showed higher increase in formation of

Table: Chemical compounds isolated from Acanthopanax senticosus

Classification	NO.	Chemical component	Part of plant	Reference
Triterpenoid saponins	1	Ciwujianosides A1(new)	Leave	Chunjie et al. (1989)
	2	Ciwujianosides A2(new)	Leave	Chunjie et al. (1989)
	3	Ciwujianosides A3(new)	Leave	Chunjie et al. (1989)
	4	Ciwujianosides A4(new)	Leave	Chunjie et al. (1989)
	5	Ciwujianosides B(new)	Leave	Chunjie et al. (1988)
	6	Ciwujianosides C1(new)	Leave	Chunjie et al. (1988)
	7	Ciwujianosides C2(new)	Leave	Chunjie et al. (1988)
	8	Ciwujianosides C3(new)	Leave	Chunjie et al. (1988)
	9	Ciwujianosides C4(new)	Leave	Chunjie et al. (1988)
	10	Ciwujianosides D1(new)	Leave	Chunjie et al. (1988)
	11	Ciwujianosides D2(new)	Leave	Chunjie et al. (1988)
	12	Ciwujianosides D3(new)	Leave	Chunjie et al. (1989)
	13	Ciwujianosides E(new)	Leave	Chunjie et al. (1988)
	14	Hederasaponin B 3-O-α-Rhamnopyranosyl-(1→2)-α-arabin	Leave	Chunjie et al. (1988)
	15	Opyranosyl oleanolic acid	Leave	Chunjie et al. (1988)
	16	Saponin P_E	Leave	Chunjie et al. (1989)
	17	30-Norolean-12,20(29)-dien-28-oic acid	Leave	Chunjie et al. (1989)
	18	29-Hydroxyoleanolic acid	Leave	Chunjie et al. (1989)
		3β-{O-β-D-Glucopyranosyl-(1→3)-O-β-D-Galactopyranosyl-(1→4)-{O-α-L-rham nopyranosyl-(1→2)}-O-β-D-glucuronopy ranosyl}-16α-hydroxy-13β,28-epoxyoleanan	Root	Kujawa et al. (1991)
	19	3β-{O-α-L-		
	20	Rhamnopyranosyl-(1→4)-O-α-L-rhamnopyranosyl-(1→4)-[O-α-L-rhamnopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→x)-O-β-D-glucuronopyra nosyl}-16α-Hydroxy-13β,28-epoxyoleanane	Root	Kujawa et al. (1991)
	21	Acanthopanaxoside A(new)	Leave	Wenhong et al. (2006)
	22	Acanthopanaxoside B(new)	Leave	Wenhong et al. (2006)
	23	Acanthopanaxoside C(new)	Leave	Wenhong et al. (2006)
	24	Acanthopanaxoside E	Fruit	Fang et al. (2007)
	25	Sessiloside(first)	Leave	Wenhong et al. (2006)
	26	Tauroside $H_{1(first)}$	Leave	Wenhong et al. (2006)
	27	Chiisanoside	Leave	Wenhong et al. (2006)
	28	3-O-α-Rhamnopyranosyl-(1→2)-α-arabinopyranosyl mesembryanthemoidi-genic acid	Leave	Wenhong et al. (2006)
	29	Silphioside F (first)	Fruit	Fang et al. (2007)
	30	Copteroside B	Fruit	Fang et al. (2007)
	31	hederagenin 3-O-β-D-glucuronopyranoside 6'-O-methyl ester(first)	Fruit	Fang et al. (2007)
	32	Gypsogenin 3-O-β-D-glucuronide(first)	Fruit	Fang et al. (2007)

Table: (*Continued*)

Classification	NO.	Chemical component	Part of plant	Reference
	33	Silphioside G(first)	Fruit	Fang et al. (2007)
	34	Ilexoside XLVIII(first)	Fruit	Fang et al. (2007)
	35	Hederagenin 3-O-β-D-glucuronopyranosyl methyl ester-28-O-β-D-glucopyranoside (first)	Fruit	Fang et al. (2007)
	36	3-O-β-D-Glucuronopyranosylgypsogenin 28-O-β-D-glucopyranoside (first)	Fruit	Fang et al. (2007)
		37 Hederagenin28-O-β-D-glucopyranoside(first)	Fruit	Fang et al. (2007)
	38	Hemsgiganoside B(first)	Fruit	Fang et al. (2007)
	39	Anhuienside C (first)	Fruit	Fang et al. (2007)
	40	Eleutheroside L	Fruit	Fang et al. (2007)
	41	Hederagenin-3-O- β -glucuronopyranoside (first)	Seed	Jie et al. (2005)
		42. oleanolicacid-3-O- β -glucuronopyranoside(first)	Seed	Jie et al. (2005)
	43	Friedelin	Stem, leave	Liangjiu et al. (1981)
Lignans	44	Neociwujiaphenol(new)	Stem, leave	Lijun et al. (1999)
	45	Ciwujiatone(new)	Stem, leave	Lijun et al. (1997)
	46	Sesamin	Root, bark	Yuqing et al. (1991)
	47	Eleutheroside E	Root	Xingcong et al. (2001)
	48	Eleutheroside E2(new)	Root	Xingcong et al. (2001)
	49	(+)-Pinoresinol-O-β-D-glucoside(first)	Stem, bark	Sansei et al. (1990)
	50	(+)-Syringaresinol-O-β-D-glucoside(first)	Stem, bark	Sansei et al. (1990)
	51	(+)-Pinoresinlo-di-O-β-D-glucoside(first)	Stem, bark	Sansei et al. (1990)
	52	(+)-Medioresinol-di-O-β-D-glucoside(first)	Stem, bark	Sansei et al. (1990)
	53	Syringin(eleutheroside B)	Root	Xingcong et al. (2001)
	54	Chlorogenic acid	Stem, bark	Sansei et al. (1990)
	55	1',5'-O-Dicaffeoylquinic acid	Seed	Tolonen et al. (2002)
	56	3',5'-O-Dicaffeoylquinic acid(first)	Seed	Tolonen et al. (2002)
	57	4',5'-O-Dicaffeoylquinic acid(first)	Seed	Tolonen et al. (2002)
	58	Caffeic acid		Davydov, krikorian. (2000)
	59	Coniferyl aldehyde		Davydov, krikorian. (2000)
	60	Caffeic acid ethyl ester		Davydov, krikorian. (2000)
	61	Feruloyl sucrose(first)	Stem, leave	Lijun et al. (1999)
Coumarins	62	Isofraxidin	Stem, bark	Sansei et al. (1990)
	63	Isofraxidin-7-O-β-D-glucoside	Stem, bark	Sansei et al. (1990)
	64	Scopoletin	Bark	Kurkin et al. (1992)
	65	Eleutheroside B_2(new)	Aerial parts	Zhifeng et al. (2009)
Flavonoids	66	Quercitrin	Leave	Maolian et al. (2002)
	67	Hyperoside	Leave	Maolian et al. (2002)
	68	quercetin	Leave	Maolian et al. (2002)
	69	Rutin	Leave	Maolian et al. (2002)
Other compounds	70	Vanillic acid	Stem	Yanguang et al. (2002)
	71	Isovanillin	Stem	Yanguang et al. (2002)
	72	Syringic acid	Stem	Yanguang et al. (2002)
	73	Tyrosol	Stem	Yanguang et al. (2002)
	74	Octadecanoic acid	Root, bark	Yuqing et al. (1991)
	75	Daucosterol	Root, bark	Yuqing et al. (1991)
	76	Amygdaloside	Root, bark	Yuqing et al. (1991)
	77	Methyl oleate(first)	Root, bark	Yuqing et al. (1989)
	78	Palmitic acid(first)	Root, bark	Yuqing et al. (1989)

Table: (*Continued*)

Classification	NO.	Chemical component	Part of plant	Reference
	79	Thymidine	Root	Xingcong et al. (2001)
	80	5-Hydroxymethylfurfural	Stem	Jiyoung et al. (2004)
	81	3, 4-Dihydroxybenzonic acid	Seed	Hye sook yun et al. (1987)
	82	2,6-Dimethoxy-p-benzoquinone(first)	Stem, bark	Sansei et al. (1990)
	83	Geniposide	Boot	Zican et al. (2003)
	84	3-O-α-D-Glucopyranoside	Root	Xingcong et al. (2001)
	85	Protocatechuic acid	Bark	Kurkin et al. (1992)
	86	Oplopanone B(new)	Aerial parts	Zhifeng et al. (2009)
	87	Eleutherazine A(new)	Aerial parts	Zhifeng et al. (2010)
	88	Eleutherazine B(new)	Aerial parts	Zhifeng et al. (2010)

TNF-alpha and beta-MG compared to individual pure extracts (Panossian et al. 2002).

4.5. Anti-ulcer effects

Fujikawa et al. (1996), studied the pharmacological effect of the stem bark of AS on the stress-induced gastric ulcer, and found that a single oral administration of the aqueous extract did not show any protective effect on gastric ulcer. However, a protective effect was observed in a dose-dependent manner after oral administration of the extract for 2 weeks. Furthermore the n-butanol extract used for oral administration for 2 weeks showed an obvious inhibiton of 61.1% on gastric ulcer. This study indicated that the protective effect of the stem bark of AS on gastric ulcer may be partially due to those of chlorogenic acid and syringaresinol di-*O*-β-D-glucoside.

4.6. Anti-allergic effects

AS 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 anti-dinitrophenyl IgE-induced tumor necrosis factor-alpha (TNF-alpha) production from mast cells in a concentration-dependent manner (Yi et al. 2001; Yi et al. 2002). Komasa et al. (2004) observed that AS possessing anti-allergic effects since it can lower histamine releasing and inhibit the pigment leak in a dose-dependent manner.

4.7. Anti-irradiation effects

AS extract was slightly radiation protective, but less than gingseng saponin (Ben-Hur and Fulder 1981). However, Yonezawa et al. (1989) showed that the AS extract significantly increased the survival ratio and leukocyte count within the period of the death. Cerebral hemorrhage after 4 Gy*4 was diminished by the extract. Recovery of leukocytogenesis seems much more important for survival at split-dose irradiation than at single acute irradiation. A further study and found that oral administration of polysaccharides from AS dose-dependently reduced the irradiation-induced injury on rats studied, and showed a protective effect against irradiation-induced loss of body weight, white cell counts, food and water intake, reduce MDA level and raise antioxidase activity (SOD, GSH-Px) ($p < 0.05$, $p < 0.01$). It may be concluded that polysaccharides from AS possess a good irradiation-protective effect(Li and Zhou 2007).

4.8. Anti-fatigue effects

An aqueous extract of AS prolonged swimming time of rats in a forced swimming test or in a chronic swimming. Syringaresinol di-*O*-β-D-glucoside may be responsible in part of the pharmacological effect (Nishibe et al. 1990). Moreover, the extract of AS cannot only increase stress resistance, but also increase the mean lifespan of the nematode *C. elegans* in a dose-dependent way (Wiegant et al. 2009). Facchinetti et al. (2002) conducted a double-blind study in order to investigate study the effect of AS on psychological distress. The result showed that AS is able to reduce cardiovascular responses to stress in healthy young volunteers, while placebo was ineffective.

The anti-fatigue effect of AS on biogenic monoamine levels in the rat brain was determined. Outcomes showed that a single or 2 week administration of AS showed a marked increase in the dopamine (DA) level only in the striatum. However, noradrenaline (NA) levels were increased by a single dose of AS in a wide range of brain regions such as the cortex, hypothalamus, striatum, hippocampus, substantia nigra and pons. When administered for 2 weeks no increase in NA levels was seen in these brain regions, except for an increase in the frontal cortex and anterior hypothalamus. The above results suggested that AS may act by regulating NA and DA levels in specific brain regions related to stress response and Parkinson's disease (Fujikawa et al. 2002). In addition, the reduction of exercise-induced serotonin synthesis and tryptophan expression in the dorsal raphe may lead to the increase of time to exhaust by treadmill running (Rhim et al. 2007).

AS was also involved in stress-related brain loci (Soya et al. 2008). A study showed that c-Fos accumulated in both the supraoptic nuclei (SON) and Para ventricular nuclei (PVN), which regulate stress response, after AS administration. Only the caudal regions in the nucleus of the solitary tract, a locus innervating both the SON and PVN, were activated.

4.9. Inhibitory activity on nitrite production

Syringin, a kind of phenyl-propanoid glycosides, in the AS, not only plays a role in stimulating rat-blood macrophages to perform phagocytosis, but also enhanced the generation of the NO molecules (Lin et al. 2007a). However, Lin et al. (2007b) showed that the extract of AS inhibited NO production in murine macrophages *in vitro* and *in vivo*. Moreover, AS can significantly attenuate LPS-induced iNOS expression, but not COX-2 expression, and it also downregulate inflammatory iNOS

expression by blocking JNK and Akt activation (Jung et al. 2007).

Experiments were carried out to study the effects of AS extract on NO production and inducible nitric oxide synthase (iNOS) gene expression in lipopolysaccharide (LPS) plus interferon-gamma(IFN-gamma)-stimulated RAW264.7 macrophages and investigated its mechanisms of anti-inflammatory activity. The result was that AS significantly suppressed NO production and iNOS gene expression in a dose-dependent manner. Besides, AS suppresses iNOS gene expression through the inhibition of intracellular peroxides production, which has been implicated in the activation of NF-kappaB (Lin et al. 2008).

4.10. Effects on bone metabolism

The effect of AS extract on the development of glucocorticoid-induced osteoporosis was studied. Through observing the changes of rats' urinary excretion of calcium and hydroxyproline after receiving AS extract for 10–30 days, Kropotor et al. (2002) found that in rats receiving LESG for 10–30 days urinary excretion of calcium and hydroxyproline decreased by 3.7–1.4 times and 51–18%, respectively, compared to the control ($p < 0.05$). These results suggested that during steroid-induced osteoporosis the preventive effect of the AS is comparable to that of ipriflavone which is highly effective in the therapy of osteoporosis in clinical and experimental studies. Meanwhile, an investigation on the effects of AS on bone remodeling and bone mineral density in Korean postmenopausal women was conducted. AS extract group showed a significant increase in serum osteocalcin levels compared to the control group. Obviously, it had beneficial effects on bone remodeling, while no significant adverse effects were observed (Hwang et al. 2009).

4.11. Neuroprotective effects

The neuroprotective effects of AS were investigated in transient middle cerebral artery occlusion (MCAo, 90 min occlusion, 24 h reperfusion) of Sprague-Dawley rats. The infarct volume was significantly reduced by 36.6% after peritoneal injection of AS (100 mg/kg) compared with the control. In the immunohistochemical study, AS markedly inhibited both cyclooxygenase-2 and OX-42 expressions in the penumbral region 24 h after MCAo. These results indicate that AS has a neuroprotective effect by inhibiting inflammation and microglial activation in brain ischaemia (Bu et al. 2005; Bu et al. 2010). Moreover, eleutheroside B was proved to protect against neuritic atrophy and cell death under Abeta treatment. Subsequent treatment with the methanol extract and the water extract of AS (10-1000 ng/ml) resulted in significant axonal and dendritic regenerations and reconstruction of neuronal synapses in rat cultured cortical neurons damaged by amyloid beta (Abeta)(25-35) (Tohda et al. 2008).

4.12. Antioxidant effects

Pretreatment of rats with AS extract administered orally for 30 days reduced the NO and lipid peroxidation levels, increased the activities of catalase and GSH-Px (Yokozawa et al. 2003), suggesting the capability of scavenging reactive oxygen radicals. Moreover, AS was the most effective scavenger of peroxynitrite (ONOO-), and the MeOH extract of it had the highest ferric reducing antioxidant power (Chen et al. 2010). Those data supported that AS acted as a strong antioxidant in addition to exerting anti heat environmental stress effects (Kim et al. 2010).

Furthermore, eleutheroside B was responsible for a moderate free radical scavenging activity on DPPH (Lee et al. 2004). *Acanthopanax* senticosides B was found to protect cardiomyocytes against oxidative-stress injury induced by H_2O_2 through reduction of lipid perosidation and enhancement of the activity of antioxidant defense (Liang, Yu et al. 2010).

4.13. Enzyme inhibition

AS showed to produce an inhibition of hexobarbital metabolism *in vitro* and *in vivo*, that was due to the enzyme inhibit rather than induct (Medon et al. 1984). As for increasing and decreasing the stress response effect of AS, the possible mechanism was by increasing occupancy of positive and negative feedback stress hormone receptors by their natural lignans due to inhibition of specific enzymes which function to limit receptor occupancy. Specifically, it is suggested that AS inhibits catechol-O-methyl transferase, which reside in close proximity to stress hormone receptors and catalyse the degradation of stress hormones into inactive compounds (Gaffney et al. 2001). In addition, silphiside F, copteroside B, hederagenin 3-*O*-β-D-glucuronopyranoside 6'-*O*-methyl ester and gypsogenin 3-*O*-β-D-glucuronide from the AS showed pancreatic lipase inhibition activity. Further study indicated that the free carboxylic acid group at position 28 in the structure is responsible for the enhancement of inhibition of pancreatic lipase activity (Li et al. 2007).

4.14. Hypoglycaemic activity

Intragastric administrations of AS extract in mice induced a hypoglycemic response, without gross pharmacological effects (Medon et al. 1981). Eleutheroside B has abilities to enhance glucose utilization and lower plasma glucose level in rats suffering from insulin deficiency (Liu et al. 2008; Niu et al. 2008), and to raise the release of Ach from nerve terminals, which in turn to stimulate muscarinic M3 receptors in pancreatic cells and augment the insulin release to result in plasma glucose lowering action (Liu et al. 2008). However, another pathway to decrease the level of plasma glucose was also discovered. Eleutheroside B can enhance the secretion of beta-endorphin from adrenal medulla to stimulate peripheral micro-opioid receptors resulting in a decrease of plasma glucose in diabetic rats lacking insulin, but in the presence of micro-opioid receptor antagonists and/or in the micro-opioid receptor knockout diabetic mice, it had no effects (Niu et al. 2007). Similarly, the insulinotropic effect on the plasma glucose regulation is impaired in conscious rats with a regular sympathetic tone, in contrast, when the sympathetic tone was inhibited in anesthetized animals, a plasma glucose lowering effect accompanied by an increase of plasma insulin and C-peptide were obtained (Niu et al. 2008).

4.15. Other pharmacological effects

4.15.1. Anti-steatosis

A 50% ethanol extract of AS was found to reduce body weight and insulin resistance in high fat diet-induced hyperglycemic and hyperlipidemic ICR mice. To evaluate the anti-steatosis action of AS, insulin-resistant ob/ob mice with fatty livers were treated with AS ethanol extract for an 8 week-period. The results showed that AS reversed the hepatomegaly, lowered circulating glucose and lipids, and enhanced insulin action in the liver. These changes culminated in inhibition of triglyceride synthesis in non-adipose tissues including liver and skeletal muscle. Gene expression studies confirmed reductions in glucose 6-

phosphatase and lipogenic enzymes in the liver (Park et al. 2006).

4.15.2. Antiviral and antibacterial effect

It is believed that AS extract inhibits the productive replication of all RNA viruses studied so far, including human rhinovirus (HRV), respiratory syncytial virus (RSV) and influenza A virus in cell cultures. However no effects were observed on the DNA type viruses (Glatthaar-Saalmller et al. 2001). Chiisanogenin, isolated from the leaves of AS, showed broad but moderate antibacterial activities against G (+) and G (−) bacteria, the minimum inhibitory concentration (MIC) being in the range of 50-100 mg/ml (Lee et al. 2003).

5. Adverse effects, toxicity and contraindications

There is a case report about a man whose digoxin serum level increased when he added Siberian ginseng and decreased when the Siberian ginseng was stopped (McRae 1996). However, Awang et al. (1996) suspected that the apparent rise in the patient's serum digoxin levels was due to a contribution from cardiac glycosides in periploca sepium, a toxic plant that contains cardiac glycosides and pregnancy-type steroids and a common substitute for AS (Awang 1996). But, the latest study showed that the apical-to-basolateral (A-to-B) transport of digoxin, a P-glycoprotein (P-gp) substrate, was significantly increased by the addition of AS extract in a concentration-dependent manner. In contrast, the A-to-B transport of cephalexin, a peptide transporter substrate, was significantly decreased by the addition of AS extract in the same manner. The study was based on the interaction between AS and other drugs which focus on the effect of AS extract on intestinal drug transporter(P-gp), and peptide transporter activities in Caco-2 cells. Those results showed that P-gp and peptide transporter activities are suppressed by AS extract addition in a non-competitive manner (Takahashi et al. 2010).

Maruyama et al. (2008) analyzed the nuclear ribosomal DNA internal transcribed spacer sequence of the AS available on the Japanese and Chinese markets and found that at least 3 species were used as the source plant of the commercial Shigoka, the rhizome of AS. Only 70% of all samples were made from the correct species. Another contraindication reported was platelet aggregation inhibited by 4-dihydroxybenzoic acid from the AS (Yun-Choi et al. 1987). Recently, a report from Swedish researchers showed that AS combined with Purple coneflower and Malabar nut would result in adverse reactions including urticaria, angioedema and anaphylactic reaction, exanthema, increased hepatic enzymes, fever, various (Jacobsson et al. 2009).

6. Clinical trials

When clinical trials were undertaken to study the effects of *Panax ginseng* and AS on competitive club level endurance athletes, no significant change in testosterone, cortisol or TCR (testosterone to cortisol ratio) was observed in *Panax ginseng* group but, in the AS group, TCR decreased by 28.7%. This result suggested that AS increased rather than decreased hormonal indices of stress (Gaffney et al. 2001).

AS proved to short on the period of recovery from children's dysentery when added to monomycin in a study of 100 cases (Vereshchagin 1978). The number of immunocompetent cells, specially T lymphocytes were increased (mainly helper/inducer type, but also cytotoxic and natural killer cells) after administration of an ethanolic AS preparation to volunteers for 6-month (Bohn et al. 1987). Moreover, cellular defence, physical fitness and lipid metabolism were also affected (Szołomicki et al. 2000).

7. Conclusion

AS was widely adapted as a nourishment treatment in Chinese folk medicine. It gained considerable advocacy and use among a fairly broad Soviet population after its introduction to the general Soviet medical community. The Chinese Pharmacopeia recorded it as a formula agent, used widely in Traditional Chinese Medicine. However, in Western countries, it was not adopted for a nourishing agent. AS was once called Siberian Ginseng, which meanz that it had been characterized as a weaker, much less effective substitute for *Panax ginseng*. Due to plenty of research work conducted by Western scientists, this herbal medicine is now widely used in Western countries as an alternative medicine. Since Brekhman et al. (1968, 1976) performed the first studies on AS, this plant attracted more and more attention of scientists worldwide, who not only isolated chemical components but also evaluated pharmacological activities. This medicinal plant is rich in phenolic compounds which were regarded as the most active constituents, such as eleutheroside B (syringin) and eleutheroside E, responsible for various pharmacological properties of AS. These phenolic compounds possess anti-stress, antioxidant and anti-inflammatory effects, etc. Other bioactive compounds like triterpenoid saponins, flavones, polysaccharides have also been isolated and identified from various parts of this plant. Currently, many kinds of AS preparations were available on the market, like Siberian tea, Ciwujia injection, extract of Eleutherococcus etc. That indicates that AS, as an effective adaptogen herbal medicine just like *Panax ginseng*, has attracted the eyes of people around the world. Further studies on AS should be conducted regarding its bioactive constituents and their mechanism of action.

References

Akimoto K, Kitagawa Y, Akamatsu T, Hirose N, Sugano M, Shimizu S, Yamada H (1993) Protective effects of sesamin against liver damage caused by alcohol or carbon tetrachloride in rodents. Ann Nutr Metab 37: 218–224.

Awang D (1996) Siberian ginseng toxicity may be case of mistaken identity. Canad Med Assoc J 155: 1237.

Ben-Hur E, Fulder S (1981) Effect of Panax ginseng saponins and Eleutherococcus senticosus on survival of cultured mammalian cells after ionizing radiation. Am J Chin Med 9: 48–56.

Bo D, Ying T, Li Y (2009) Effects of acanthopanacis senticosi polysaccharides on expression of OGG1 mRNA in hippocampal neurons damaged by oxidative stress. Chin J Gerontol 29: 396–399.

Bohn B, Nebe C, Birr C (1987) Flow-cytometric studies with Eleutherococcus senticosus extract as an immunomodulatory agent. Arzneimittelforschung 37: 1193–1196.

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

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

Bu Y, Jin Z, Park S, Baek S, Rho S, Ha N, Park S, Kim S, Kim H (2005) Siberian ginseng reduces infarct volume in transient focal cerebral ischaemia in Sprague-Dawley rats. Phytother Res 19(2): 167–169.

Bu Y, Kwon S, Kim YT, Kim MY, Choi H, Kim JG, Jamarkattel-Pandit N, Dore S, Kim SH, Kim H (2010) Neuroprotective effect of HT008-1, a prescription of traditional Korean medicine, on transient focal cerebral ischemia model in rats. Phytother Res 24: 1207–1212.

Chen C, Ribaya-Mercado J, McKay D, Croom E, Blumberg J (2010) Differential antioxidant and quinone reductase inducing activity of American, Asian, and Siberian ginseng. Food Chem 119: 445–451.

Chen L, Xiao-yan W, Xu-wei H, Hai-tao F, Shan-yi Q (2008) Determination of eleutheroside B in antifatigue fraction of Acanthopanax senticosus by HPLC. China J Chin Materia Medica 23: 2800–2802.

Pharmacopoeia Commission of People's Republic of China (2005). Pharmacopoeia of the People's Republic of China (2005). Beijing, Chemical Industry Press.

Cho J, Nam K, Kim A, Park J, Yoo E, Baik K, Yu Y, Park M (2001) *In-vitro* and *in-vivo* immunomodulatory effects of syringin. J Pharm Pharmacol 53: 1287–1294.

Choi J, Yoon T, Kang K, Lee K, Kim W, Suh Y, Song J, Jung M (2006) Glycoprotein isolated from Acanthopanax senticosus protects against hepatotoxicity induced by acute and chronic alcohol treatment. Biol Pharm Bull 29: 306–314.

Davydov M, Krikorian AD (2000) Eleutherococcus senticosus (Rupr. & 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 Pharmacol Sin 22: 1057–1070.

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.

Fang J, Proksch A, Wagner H (1985) Immunologically active polysaccharides of Acanthopanax senticosus. Phytochemistry 24: 2619–2622.

Feng S, Hu F, Zhao J, Liu X (2006) Determination of eleutheroside E and eleutheroside B in rat plasma and tissue by high-performance liquid chromatography using solid-phase extraction and photodiode array detection. Eur J Pharm Biopharm 62: 315–320.

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.

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 B, H $^{\cdot\cdot 1}$gel H, Rich P (2001) 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 B, Hügel H, Rich P (2001) 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.

Glatthaar-Saalmüller B, Sacher F, Esperester A (2001) Antiviral activity of an extract derived from roots of Eleutherococcus senticosus. Antiviral Res 50: 223–228.

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 7: 1213–1216.

Hirata F, Fujita K, Ishikura Y, Hosoda K, Ishikawa T, Nakamura H (1996) Hypocholesterolemic effect of sesame lignan in humans. Atherosclerosis 122: 135–136.

Hirose N, Doi F, Ueki T, Akazawa K, Chijiiwa K, Sugano M, Akimoto K, Shimizu S, Yamada H (1992) Suppressive effect of sesamin against 7, 12-dimethylbenz [a]-anthracene induced rat mammary carcinogenesis. Anticancer Res 12: 1259–1265.

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

Hwang YC, Jeong IK, Ahn KJ, Chung HY (2009) The effects of Acanthopanax senticosus extract on bone turnover and bone mineral density in Korean postmenopausal women. J Bone Miner Metab 27: 584–590.

Jacobsson I, Jönsson A, Gerdén B, Hägg S (2009) Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 18: 1039–1047.

Jiang W, Li W, Han L, Liu L, Zhang Q, Zhang S, Nikaido T, Koike K (2006) Biologically active triterpenoid saponins from Acanthopanax senticosus. J Nat Prod 69: 1577–1581.

Jung C, Jung H, Shin Y, Park J, Jun C, Kim H, Yim H, Shin M, Bae H, Kim S (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.

Kang J, Linh P, Cai X, Kim H, Lee J, Kim Y (2001) Quantitative determination of eleutheroside B and E from Acanthopanax species by high performance liquid chromatography. Arch Pharm Res 24: 407–411.

Kapil A, Sharma S (1997) Immunopotentiating compounds from Tinospora cordifolia. J Ethnopharmacol 58: 89–95.

Kim KJ, Hong HD, Lee OH, Lee BY (2010) The effects of Acanthopanax senticosus on global hepatic gene expression in rats subjected to heat environmental stress. Toxicol.(Epub ahead of print)

Komasa Y, Mizoguchi T, Kubota H, Takekoshi H (2004) Anti-allergic Effects of Acanthopanax senticosus root extract and Perilla frutescens seed extract. Jpn J Complement Alternat Med 1: 95–101.

Kropotov A, Kolodnyak O, Koldaev V (2002) Effects of Siberian ginseng extract and ipriflavone on the development of glucocorticoid-induced osteoporosis. Bull Exp Biol Med 133: 252–254.

Kupin V, Polevaia E (1986) Stimulation of the immunological reactivity of cancer patients by Eleutherococcus extract. Vopr Onkol 32: 21–26.

Kurkin V, Evstratova R, Zapesochnaya G (1992) Phenolic compounds of the bark of Eleutherococcus senticosus. Chem Nat Compd 28: 512–513.

Kurkin V, Zapesochnaya G, Bandyshev V (1991) Phenolic compounds of Eleutherococcus senticosus. Chem Nat Compd 27: 755–756.

Lanza A, Martinez M, Matellano L, Carretero C, Castillo L, Sen A, Benito P (2001) Lignan and phenylpropanoid glycosides from Phillyrea latifolia and their *in vitro* anti-inflammatory activity. Planta Med 67: 219–223.

Lee S, Shin D, Oh K, Shin K (2003) Antibacterial compounds from the leaves ofAcanthopanax senticosus. Arch Pharm Res 26: 40–42.

Lee S, Son D, Ryu J, Lee Y, Jung S, Kang J, Lee S, Kim H, Shin K (2004) Anti-oxidant activities of acanthopanax senticosus stems and their lignan components. Arch Pharm Res 27: 106–110.

Lewis N, Davin L (1994) Evolution of Lignan and Neolignan Biochemical Pathways, Washington, DC: American Chemical Society.

Li F, Li W, Fu H, Zhang Q, Koike K (2007) Pancreatic lipase-inhibiting triterpenoid saponins from fruits of Acanthopanax senticosus. Chem Pharm Bull 55: 1087–1089.

Li X, Barnes D, Khan I (2001) A new lignan glycoside from Eleutherococcus senticosus. Planta Med 67: 776–777.

Li X, Zhou A (2007) Preparation of polysaccharides from Acanthopanax senticosus and its inhibition against irradiation-induced injury of rat. Carbohydr Polym 67: 219–226.

Li ZF, Wu ZH, Chen G, Zhang QH, Pei YH (2009) Two new compounds from Acanthopanax senticosus Harms. J Asian Nat Prod Res 11: 716–719.

Li ZF, Xu N, Feng BM, Zhang QH, Pei YH (2010) Two diketopiperazines from Acanthopanax senticosus Harms. J Asian Nat Prod Res 12: 51–55.

Liang Q, Yu X, Qu S, Xu H, Sui D (2010) Acanthopanax senticosides B ameliorates oxidative damage induced by hydrogen peroxide in cultured neonatal rat cardiomyocytes. Eur J Pharmacol 627: 209–215.

Lin C, Hsieh S, Hsu S, Chang C (2007) Hot pressurized water extraction of syringin from Acanthopanax senticosus and *in vitro* activation on rat-blood macrophages. Biochem Eng J 37: 117–124.

Lin Q, Jin L, Cao Z, Lu Y, Xue H, Xu Y (2008) Acanthopanax senticosus suppresses reactive oxygen species production by mouse peritoneal macrophages *in vitro* and *in vivo*. Phytother Res 22: 740–745.

Lin Q, Jin L, Cao Z, Xu Y (2008) Inhibition of inducible nitric oxide synthase by Acanthopanax senticosus extract in RAW264. 7 macrophages. J Ethnopharmacol 118: 231–236.

Lin Q, Jin L, Ma Y, Shi M, Xu Y (2007) Acanthopanax senticosus inhibits nitric oxide production in murine macrophages *in vitro* and *in vivo*. Phytother Res 21: 879–883.

Liu K, Wu Y, Liu I (2008) Release of acetylcholine by syringin, an active principle of Eleutherococcus senticosus, to raise insulin secretion in Wistar rats. Neurosci Lett 434: 195–199.

Mao-Lian C, Feng-Rui S, Ming-Quan G, Zhi-Qiang L, Shu-Ying L (2002) Identification of the Flavonoid Constituents from Leaves of Acanthopanax Senticosus Harms. Chem J Chin Univ 23: 805–808.

Maruyama T, Kamakura H, Miyai M, Komatsu K, Kawasaki T, Fujita M, Shimada H, Yamamoto Y, Shibata T, Goda Y (2008) Authentication of

the traditional medicinal plant Eleutherococcus senticosus by DNA and chemical analyses. Planta Med 74: 787–789.

McRae S (1996) Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. Canad Med Assoc J 155(3): 293–295.

Medon P, Ferguson P, Watson C (1984) Effects of Eleutherococcus senticosus extracts on hexobarbital metabolism *in vivo* and *in vitro*. J Ethnopharmacol 10: 235–241.

Medon P, Thompson E, Farnsworth N (1981) Hypoglycemic effect and toxicity of Eleutherococcus senticosus following acute and chronic administration in mice. Acta Pharmacol Sinica 2: 281–285.

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.

Niu H, Hsu F, Liu I (2008) Role of sympathetic tone in the loss of syringin-induced plasma glucose lowering action in conscious Wistar rats. Neurosci Lett 445: 113–116.

Niu H, Hsu F, Liu I, Cheng J (2007) Increase of endorphin secretion by syringin, an active principle of Eleutherococcus senticosus, to produce antihyperglycemic action in type 1-like diabetic rats. Horm Metab Res 39: 894–898.

Niu H, Liu I, Cheng J, Lin C, Hsu F (2008) Hypoglycemic effect of syringin from Eleutherococcus senticosus in streptozotocin-induced diabetic rats. Planta Med 74: 109–113.

Nonaka M, Yamashita K, Iizuka Y, Namiki M, Sugano M (1997) Effects of dietary sesaminol and sesamin on eicosanoid production and immunoglobulin level in rats given ethanol. Biosci Biotechnol Biochem 61: 836.

Okada Y, Miyauchi N, Suzuki K, Kobayashi T, Tsutsui C, Mayuzumi K, Nishibe S, Okuyama T (1995) Search for naturally occuring substances to prevent the complications of diabetes. II: Inhibitory effect of coumarin and flavonoid derivatives on bovine lens aldose reductase and rabbit platelet aggregation. Chem Pharm Bull 43: 1385–1387.

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 E, Nan J, Zhao Y, Lee S, Kim Y, Nam J, Lee J, Sohn D (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.

Park S, Lee S, Kang S, Chung S (2006) Acanthopanax senticosus reverses fatty liver disease and hyperglycemia in ob/ob mice. Arch Pharm Res 29: 768–776.

Qing-fan M, Xiao-kun Y, Mu-yun X, Ming-liang L, Zhi-hui G, Hao F, Yu-zhuo C, Li-rong T (2005) Extraction of Acanthopanacis senticosi polysaccharides and their antioxidative effect. J Jilin Univ (Science Edition) 43: 683–686.

Rhim Y, Kim H, Yoon S, Kim S, Chang H, Lee T, Lee H, Shin M, Shin M, Kim C (2007) Effect of Acanthopanax senticosus on 5-hydroxytryptamine synthesis and tryptophan hydroxylase expression in the dorsal raphe of exercised rats. J Ethnopharmacol 114: 38–43.

Schmolz M, 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 is modulated by an extract from Eleutherococcus senticosus L. roots. Phytother Res 15: 268–270.

Shao C, Kasai R, Xu J, Tanaka O (1989) Saponins from leaves of Acanthopanax senticosus Harms., Ciwujia. II: Structures of ciwujianosides A1, A2, A3, A4 and D3. Chem Pharm Bull 37: 42–45.

Shohael A, Chakrabarty D, Yu K, Hahn E, Paek K (2005) Application of bioreactor system for large-scale production of Eleutherococcus sessiliflorus somatic embryos in an air-lift bioreactor and production of eleutherosides. J Biotechnol 120: 228–236.

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. Ann N Y Acad Sci 1171 (Natural Compounds and Their Role in Apoptotic Cell Signaling Pathways): 314–320.

Soya H, Deocaris C, Yamaguchi K, Ohiwa N, Saito T, Nishijima T, Kato M, Tateoka M, Matsui T, Okamoto M (2008) Extract from Acanthopanax senticosus Harms (Siberian Ginseng) activates NTS and SON/PVN in the rat brain. Biosci Biotechnol Biochem 72: 2476–2480.

Steinmann G, Esperester A, Joller P (2001) Immunopharmacological *in vitro* effects of Eleutherococcus senticosus extracts. Arzneimittelforschung 51: 76–83.

Sun H, Lv H, Zhang Y, Wang X, Bi K, Cao H (2007) A rapid and sensitive UPLC-ESI MS method for analysis of isofraxidin, a natural antistress compound, and its metabolites in rat plasma. J Sep Sci 30: 3202–3206.

Szołomicki J, Samochowiec L, Wójcicki J, Droździk M (2000) The influence of active components of Eleutherococcus senticosus on cellular defence and physical fitness in man. Phytother Res 14: 30–35.

Takahashi T, Kaku T, Sato T, Watanabe K, Sato J (2010) Effects of Acanthopanax senticosus HARMS extract on drug transport in human intestinal cell line Caco-2. J Nat Med 64: 55–62.

Tohda C, Ichimura M, Bai Y, Tanaka K, Zhu S, Komatsu K (2008) Inhibitory Effects of Eleutherococcus senticosus Extracts on amyloid beta (25-35)-Induced Neuritic Atrophy and Synaptic Loss. J Pharmacol Sci 107: 329–339.

Tokiwa T, Yamazaki T, Sakurai S (2006) Anti-inflammatory effect of eleutheroside E from Acanthopanax senticosus. Foods Food Ingred J Jpn 211: 576–582.

Tolonen A, Joutsamo T, Mattlla S, Kämäräinen T, Jalonen J (2002) Identification of isomeric dicaffeoylquinic acids from Eleutherococcus senticosus using HPLC-ESI/TOF/MS and 1H-NMR methods. Phytochem Anal 13: 316–328.

Tong L, Huang T, Li J (1994) Effects of plant polysaccharides on cell proliferation and cell membrane contents of sialic acid, phospholipid and cholesterol in S 180 and K 562 cells. Zhongguo Zhong xi yi jie he za zhi 14: 482–484.

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.

Vereshchagin I (1978) Treatment of dysentery in children with a combination of monomycin and Eleutherococcus. Antibiotiki 23: 633–636.

Wang ZQ, Wang ZY, Chen LC, Tan XM, JJ M (2005) Studies on different harvest periods and different processing methods of acanthopanx senticosus from different producing areas. Res Inf Trad Chin Med. 7: 13–15.

Wiegant F, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post J (2009) Plant adaptogens increase lifespan and stress resistance in C. elegans. Biogerontology 10: 27–42.

Winston D, Maimes S (2007) Adaptogens: Herbs for Strength, Stamina, and Stress Relief. Rochester, Vermont: Healing Arts Press.: 1–336.

Wu ZY, Raven P (2007) Flora of China. Science Press and Missouri Botanical Garden Press, Beijing and St Louis. Vols 13: 466–472.

Wu L, Gao H, Zheng J, Liu K, Yian S, Jiang L (1999) A Study on a new lignan of Acanthopanax senticosus (Rupr. et Maxim.) Harm. J Shenyang Pharm Univ 16: 58-59.

Wu L, Ruan L, Zheng J, Wang F, Ding F, Gong H (1999) Studies on chemical constituents from Acanthopanax senticosus (rupr. et maxim.) harms. Acta Pharm Sinica 34: 841–846.

Wu L, Zheng J, Liu K, Shen Y (1997) A new lignan of Acanthopanax senticosus (Rupr. et Maxim.) Harm. Chin J Med Chem 7: 274–275.

Yamazaki T, Shimosaka S, Sakurai M, Matsumura T, Tsukiyama T, Tokiwa T (2004) Anti-inflammatory effects of a major component of Acanthopanax senticosus Harms, isofraxidin. Jpn J Electrophor 48: 55–58.

Yamazaki T, Shimosaka S, Sasaki H, Matsumura T, Tukiyama T, Tokiwa T (2007) (+)-Syringaresinol-di-O-[beta]-d-glucoside, a phenolic compound from Acanthopanax senticosus Harms, suppresses proinflammatory mediators in SW982 human synovial sarcoma cells by inhibiting activating protein-1 and/or nuclear factor-[kappa] B activities. Toxicol *In vitro* 21: 1530–1537.

Yi J, Hong S, Kim J, Kim H, Song H, Kim H (2002) Effect of Acanthopanax senticosus stem on mast cell-dependent anaphylaxis. J Ethnopharmacol 79: 347–352.

Yi J, Kim M, Seo S, Lee K, Yook C, Kim H (2001) Acanthopanax senticosus root inhibits mast cell-dependent anaphylaxis. Clin Chim Acta 312: 163–168.

Yokozawa T, Rhyu D, Chen C (2003) Protective effects of Acanthopanax radix extract against endotoxemia induced by lipopolysaccharide. Phytother Res 17: 353–357.

Yonezawa M, Katoh N, Takeda A (1989) Radiation protection by Shigoka extract on split-dose irradiation in mice. J Radiat Res 30: 247–254.

Yoon T, Yoo Y, Lee S, Shin K, Choi W, Hwang S, Ha E, Jo S, Kim S, Park W (2004) Anti-metastatic activity of Acanthopanax senticosus extract and its possible immunological mechanism of action. J Ethnopharmacol 93: 247–253.

Yu W, Zhang H, Huang W, Chen J, Liang X (2006) Analysis of the volatile oil from the stem of Acanthopanax senticosus (Rupr. et Maxim.) harms with several hyphenated methods of chromatography. Front Chem China 1: 193–198.

Yun-Choi H, Kim J, Lee J (1987) Potential inhibitors of platelet aggregation from plant sources, III. J Nat Prod 50: 1059–1064.

Zhang R, Qian J, Yang G, Wang B, Wen X (1990) Medicinal protection with Chinese herb-compound against radiation damage. Aviat Space Environ Med 61: 729–731.