생 약 학 회 지
Kor. J. Pharmacogn.
17(1) : 78~84 (1986)

The Glycosides of Araliaceaus Drugs and their Biological Activities

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Abstract—Among the Araliaceae plants indigenous to Korea, those whose medicinal usage are comparatively high have been selected in this serial studies. Chiisanoside and acanthoside D were isolated and identified from the *Acanthopanax chinensis* leaves and root bark. Chiisanoside and acanthoside D have been found to have the lowering S-GPT, S-GOT value and BSP-retention rate and survival rate, anti-histaminic effect in the toxic state through the bio-pharmacological experiments. α-hederin, hederagenin pentaglycoside were isolated both stem bark of *Kalopanax pictum* Nakai var. *magnificum* and *Kalopanax pictum* Nakai var. Max. respectively. Syringoside, acanthoside D were also isolated from the root bark of *Acanthopanax koreanum*. The biological activity of ginsenoside Rb_1, Rg_1, Re were examined. Ginsenoside Rb_1, Rg_1, Re promotes the antileaking effect in X-ray (Co 60) irradiated toxic state.

Keywords—Araliaceae • *Acanthopanax chiisanensis* • *Acanthopanax koreanum* • acanthoside D • chiisanoside • syringoside • *Kalopanax pictum* Nakai *var. magnificum* • *K. pictum* Nakai *var.* Max • α-hederin • hederagenin pentaglycoside • biological activities • BSP-retention rate • S-GPT, S-GOT lowering effect • survival effect • anti-histaminic action • anti-leaking effect.

For many years, we have been attracted by the biological activities of Korean Ginseng. In this context, I have developed interest in the chemically effective components of various plants belonging to the Araliaceae family and we have been conducting research in this area over the past several years. Compared with the sparse distribution of the Araliaceous plants across the world, the naturally growing Araliaceous plants and their distributions in Korea very high. This is the very motive behind my starting the research on this theme.

Among the Araliaceous plants indigenous to Korea, those whose medicinal usages are comparatively high have been selected and tabulated in Table I. Among them, the stem bark or root bark of *Acanthopanax* spp.[1)] is known as Acanthopanacis cortices which is used for the medicinal purposes. It is called wujiapi in China. Among these plants, there are two extraordinary species indigenous to Korea that induced my special interest. The stem bark of *Kalopanax* spp. is called Kalopanacis cortex in Korea and it is used for the medicinal purposes. It is, referred to as Haitongpi in China. It is interesting to know that this plant is a

Table I. Araliaceous plants which is indigenous to Korea and used as the folk medicines

Acanthopanax chiisanensis Nakai
Acanthopanax Koreanum Nakai
Acanthopanax rufinerve Nakai
Acanthopanax seoulensis Nakai
Acanthopanax sessiliflorum Seem
Acanthopanax Siboldianum Makino
Kalopanax pictum Nakai
Kalopanax pictum Nakai *var. magnificum* Nakai
Kalopanax pictum Nakai *var. Maximowiczi* Nakai
Kalopanax pictum Nakai *var. typicum* Nakai
Eleutherococcus asperatus Koid.
Eleutherococcus senticosus Max.
Hedera Tobleri Nakai
Panax Schinseng Nees
Tetrapanax papyriferum Koch

quite differet plant from Haiton-Pi which is used in China or Taiwan.

The distribution of the *Eleutherococcus asperatus* is confined to the northern part of our country while the distribution of the *Eleutherococcus senticosus* is comparatively wide spread in the mountaneous regions of the southern part of Korea and cultivated in some areas of the region. Extract preparations separated from this plant is called Siberian ginseng in the Soviet Russia and it is exported to European countries. It is, however, erraneous to call it Siberian ginseng in terms of the scientific justification. Nevertheless, its biological activities are widely promoted as having the similar biological activities as those of *Panax ginseng.*

Hedera Tobleri is a plant widely distributed in the southern region of Korea. Its medicinal components are similar to those of hederagenin glycoside and ginsenosides.[2] This is really an interesting reality. It is because hederagenin compounds are contained in *Acanthopanax* spp., *Kalopanax* spp. and *Hedera* spp. • Accordingly, *Hedera Tobleri* is placed somewhere between *Acanthopanax* spp. and *Kalopanax* spp. and *Eleutherococcus* spp. are the containment of lignan glycosides in all of these plants. Above observations have been validated through the extraction, isolation, identification of their constituencies in terms of their biological activities.

A Study on the Chemical Constituent of *Acanthopanax Koreanum* Nakai and its Pharmaco-Biological Activities[3]

Two glycosides, assumed to be one of the potential active principles, is isolated from the root bark of *Acanthopanax Koreanum* Nakai, identified to be acanthoside D, $C_{34}H_{46}O_{18}$, mp 242°C, and syringoside, $C_{17}H_{24}O_9$, mp 192°C. Acanthoside D has been found to have S-GPT, S-GOT lowering effect, BSP-retention rate and survival rate in the toxic state through the biopharmacological experiments.

Table II. The effects of acanthoside D on the S-GPT and S-GOT activities of rabbits intoxicated with 95% carbon tetrachloride at the time of 24 hrs. ($p<0.04$)***

liver enzyme	Carmen units	
	Control group*	Acanthoside D dosing group**
S-GPT	320.0±1.0	146.0±2.0
S-SOT	336.6±1.5	124.0±4.8

*Control group only CCl_4(0.1 ml/kg) i,p, inj.
**Acanthoside 5 mg orally before 3 hrs from CCl_4 inj.
***According to Mann-Whitney test.

Table III. Survival rates of mice affected by acanthoside D

Group	Number of animal	Number of Death	Survival rates*
control**	10	7	30
acanthoside D dosing group	10	3	70

*Measured at the time of 24hrs after intoxicated with ephedrine hydrochloride (390 mg/kg. Lethal dose)
**Only ephedrine hydrochloride i,p, inj.
***Acanthoside D 5 mg/kg orally before 3 hrs from ephedrine intoxication.

Table IV. BSP retention equivalent at the time of 30 min after BSP injection

Item \ Animal group	Control group**	Acanthoside D dosing group***
BSP retention equivalent*	83.5±2.0%	28.0%3.0

*Measured at time of 48hrs after intoxicated with 95% CCl_4 0.1 ml/kg
**Only CCl_4 0.1 ml/kg i,p, administration
***Acanthoside 5 ml/kg before 3 hrs from CCl_4 injection

A New Glycosyl Ester of a 3,4-Secotriterpene from Korean Medicinal Plant, *Acanthopnanx Chiisanensis* (Araliaceae)[4]

From leaves and stem-bark of Korean medicinal plant, *Acanthopanax chiisanensis*, a new glycoside was isolated and its structure was established as the α-L-rhamnopyranosyl (1→4)-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl ester of 1(R)-hydroxy-3,4-seco-lup-4(23), 20(30)-dien-3, 11 α-olactone. This is the first example of a naturally occurring glycoside of 3,4-seco-triterpene.

The Biological Activity of a new Glycoside, Chiisanoside from *Acanthopanax chiisanensis* Nakai Leaves[5]

A new glycoside was isolated from *Acanthopanax chiisanensis* Nakai (*Araliaceae*) leaves and its biological activity was investigated. $C_{48}H_{76}O_{19}$, m.p. 208~209° and named chiisanoside.

Chiisanoside exhibited non-toxic effects and significant antihitaminic activity. It was found that chiisanoside showed the antidiabetic activity against epinehrine-and alloxan-induced diabetes, decreased the toxicity of LD_{50} by ephedrine hydrochlorde and promoted the elimination of chloramphenicol from blood. Chiisanoside also increased the survival rate in rats intoxicated by carbon tetrachloride from death and led to re-establishment of normal enzymatic function. In the histopathological studies, chiisanoside improved fatty degeneration and parenchymal cell necrosis of the liver induced by carbon tetrachloride in rats(Table V~IX).

Table V. Antihistaminic activity of ethanol and water extracts of *Acanthopanax chiisanensis* leaves and its glycoside, chiisanoside in rats

	No. of animals	Dose, mg/kg			Evan's blue centent in fresh intestine, μg/g	% Inhibition of the dye leakage	Antihistaminic activity
		Chiisanoside, oral	Histamine, i.v.	Evan's blue, i.v.			
Normal[a]	10	—	—	100	136.42±5.52[c]	64.31	1.00
Control[a]	10	—	0.006	100	382.23±14.25	—	—
Chiisanoside[b]	10	10	0.006	100	342.52±13.25*	10.39	0.16
	10	20	0.006	100	246.46±9.45*	35.52	0.55
EtOH extract[b]	10	1,000	0.006	100	314.47±12.33*	17.73	0.27
	10	2,000	0.006	100	273.02±16.45	22.40	0.35
Water extract[b]	10	1,000	0.006	100	296.60±14.50*	22.40	0.35
	10	2,000	0.006	100	337.55±12.25*	1-.69	0.18

a. Normal and control groups: received orally 0.9% NaCl.
b. Test groups: received orally chiisanoside or extracts suspended in water 30 min before administration of histamine.
c. Mean±S.D.
*Significant at $p<0.01$ vs. control group.

Table VI. Average blood sugar levels in rabbits induced with epinephrine after oral administration of chiisanoside

	Dose mg/kg	Blood sugar, mg/dl					
		Time (hrs.)					
		0	0.5	1	2	3	4
Control[a]	—	97.9±2.1	158.4±4.1	128.5±4.2	106.5±5.4	97.8±3.7	92.1±2.5[c]
Chiisanoside[b]	10	98.4±3.2	127.2±3.5**	120.4±3.2**	98.5±4.1**	95.4±4.2	91.2±3.5
	20	97.4±2.4	140.5±2.9**	115.3±3.0**	96.9±3.2**	93.4±2.5*	89.3±4.1*

a. Control: received orally 0.9% NaCl.
b. Test group: received orally chiisanoside suspended in water 30 min before induction with a 0.05 ml/kg i.v. dose of epinephrine HCl solution (1 : 1000).
c. Mean±S.D. No. of animals in each group was 10.
*Significant at $p<0.05$ vs. control group.
**Significant at $p<0.01$ vs. control group.

Table VII. Average blood sugar levels in rabbits induced with alloxan after oral administration of chiisanoside

	Dose mg/kg	Blood sugar, mg/*l*				
		Time(days)				
		0	1	3	7	5
Control[a]	—	96.5±4.1	23.5±3.5	378.5±21.2	240.5±19.5	194.4±20.5[c]
Chiisanoside[b]	10	97.4±5.4	36.44±1*	304.5±25.6*	200.5±15.6*	161.5±10.6*
	20	98.1±4.5	45.5±5.5*	265.5±31.5*	170.4±20.3	145.4±13.1*

a. Control:received orally 0.9% NaCl.
b. Test group: received orally chiisanoside suspended in water 30min before induction with 2.6 m*l*/kg i.v. dose of 5% alloxan solution.
c. Mean±S.D. No. of animals in each group was 10.
*Significant at $p<0.05$ vs. control group.

Table VIII. Changes of elmination half-life($t_{\frac{1}{2}}$) of chloramphenicol after oral administration of chiisanoside

	Oral dose mg/kg	Elimination half-life (hrs.)
Control[a]	—	2.16
Chiisanoside[b]	10	1.70*
	20	1.52*

a. Control: received orally 0.9% NaCl.
b. Test group: received orally chiisanoside suspended in water 30 min before administration of a 50 mg/kg i.v. dose of chloramphenicol.
c. Mean±S.D.
No. of animals in each group was 10.
*Significant at $p<0.01$ vs. control group.

Pharmaco-Biological Action of Ginsenoside Rb_1, Rg_1 and Re

Ginseng glycosides separated by Elyakow *et al.*, which were used by I. I. Brekhman in his experiments did not cover all varieties of ginseng glycosides. Therefore, I.I. Brekhman's research and his resultant contention leave much to be reinforced when the remaining

Table IX. Effect of ethanol and water extracts of *Acanthopanax chiisanensis* and chiisanoside on enzymatic activities, liver weight and survival rate in rats intoxicated with carbon tetrachloride

	Dose mg/kg	Enzymatic activities (Reitman-Frankel unit/dl) S-GOT	S-GPT	$\frac{\text{Liver weight}}{\text{Body weight}} \times 100$	Survival rate, %
Normal	—	75.8±6.5	31.5±3.2	4.13±0.55[c]	100
Control[a]	—	177.4±25.4	66.9±8.4	7.13±0.45	80
Chiisanoside[b]	10	126.4±15.5*	60.0±10.0**	5.55±0.33*	95
	20	96.6±14.2*	50.0±4.2*	5.00±0.50*	100
EtOH extract[b]	1.000	157.5±21.3	62.2±8.5	5.82±0.54*	90
	2.000	154.2±20.0*	55.5±4.2*	5.26±0.45*	95
Water extract[b]	1.000	148.2±20.0*	61.5±4.5**	5.71±0.40*	90
	2.000	158.5±19.2**	66.6±5.5	6.04±0.55*	70

a. Control group: received orally 0.9% NaCl.
b. Test group: received orally chiisanoside or extract suspended in water daily for 5 days after intoxication of a 4 ml/kg subcutaneous dose of 50% carbon tetrachloride in olive oil daily for 4 days.
c. Mean±S.D. No. of animals in each group was 20.
*Significant at $p<0.01$ vs. control group. **Significant at $p<0.05$ vs. control group.

Table X. The effect of ginsenosides on the S-GOT and S-GPT activities of rabbits intoxicated with 95% CCl_4 at the time of 24 hours (Karmen unit)

	Control*	Rb_1**	Rg_1**	Re**
S-GOT	351.0±8.5	149.3±14.6	174.5±17.2	165.0±11.9
S-GPT	325.8±8.1	252.5±23.5	270.0±9.5	248.0±12.6
			(p 0.004)***	

Rb_1: Ginsenoside-Rb_1 Rg_1: Ginsenoside-Rg_1 Re: Giesenoside-Re
*Only CCl_4 (0.1 ml/kg) i.p. inj.
**Ginsenoside: 5 mg/kg orally before 3 hrs from CCl_4 inj.
***According to Mann-Whitney U test. Animal number of each groups were five.

Table XI. BSP retention equivalents of rabbit affected by ginsenosides (Unit: %)

	Control**	Rb_1***	Rg_1	Re
BSP retention eqivalent*	83.6±2.5	25.8±6.8	22.7±1.7	23.8±1.6

Rb_1: Ginsenoside-Rb_1 Rg_1: Ginsenoside-Rg_1 Re: Ginsenoside-Re
*Measured at the time of 48 hours after intoxicated with 95% CCl_4 inj.
**Only CCl_4 (0.1 ml/kg) i.p. inj.
***Glycosides: 5 mg/kg orally before 3 hours from CCl_4 inj. respectively.
Animal numbers of each group were five

varieties of ginseng glycosides are taken into consideration. It is, therefore, consequently regarded significant to attempt comparison of pharmacological and biological activities by employing other methods of investigation of biological activities of various properties of ginseng glycosides.

In this respect, from among intoxicated animals, particularly, the liver functions as an index, of course, inclusive of relative comparison between serum GPT and serum GOT, the measurement of retained BSP along with the influence on the metabolic rate of medicines. After having induced

Table XII. Survival rates of mice affected by ginsenosides

Group	Number of animal	Number of death	Survival rate* (%)
Rb_1**	10	4	60
Rg_1	10	5	50
Re	10	3	70
Control***	10	7	30

Rb_1: Ginsenoside-Rb_1 Rg_1: Ginsenoside-Rg_1 Re: Ginsenoside-Re
*Measured at the time of 24 hrs after-intoxicated with ephedrine HCl (390 mg/kg: lethal dose)
**Glycosides: 5 mg/kg orally before 3hrs from ephedrine HCl intoxication.
***Only ephedrine HCl i.p. inj.

Table XIII. Protective effect of ginsenosides on the increased in the capillary permeability of rat intestine after 24hrs. of irradiation

Group	Evan's blue content of intestine(μg/g of evacuated fresh intestine)	Inhibition of the dye leakage(%)	Protective activity against irradiation
Normal	107.49±11.9	41.92	1.00
γ-irradiation alone	185.07±20.6	—	—
γ-irradiation+Ginsenoside Rb_1	155.12±12.4	16.18	0.39
γ-irradiation+Ginsenoside Re	127.78±18.6	30.96	0.74
γ-irradiation+Ginsenoside Rg_1	110.86±12.6	40.10	0.96

Six rats were used in each group. All values are significant.
1) Ginsenosides were administered orally the dose of 40 mg/kg before 12 hours of irradiation
2) intraperitoneally the dose of 20 mg/kg after 3 hours of irradiation and
3) orally the dose of mg/kg after 6 hours of irradiation.
Evan's blue 1% (wt/vol) in 0.85% (wt/vol) NaCl solution had been injected at 0.5 ml/100 g (IV) 30 minutes before the animals were sacrificed.

a toxic state (by administration of a lethal dose of ephedrine hydrochloride and γ-ray radiation exposure) the effect of glycoside on the survival rate and protective activities of the test animals. (Table X~XIII).

Chemical Constituents of *Kalopanax Pictum* Nakai var *Magnificum* Nakai[7] —Two Triterpenoid Glycosides From the Stem Bark—

From the methanol extract of the stem bark of *Kalopanax pictum* Nakai var. *magnificum* Nakai (Araliaceae), two triterpenoid glycosides were isolated from the two fractions and characterized based on the physical chemical properties and spectroscopic evidences.

Compound I $C_{41}H_{66}O_{12}$ mp 247~249°C, $[\alpha]_D$+18.0(pyridine) was isolated from the ethylacetate fraction and identified as hederagenin 3-O-α-L-Rhamnopyranosyl(1→2)-α-L-arabinopyranoside.

Compound II $C_{59}H_{96}O_{26}$ mp 226~228°C, $[\alpha]_D$-8.0(pyridine) was isolated from the butanol fraction and identified as 3-0-α-L-Rhamnopyranosyl (1→2) arabinopyranosyl hederagenin 28-0-α-L-Rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside.

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