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Review

Constituents and pharmacological effects of *Eucommia* and Siberian ginseng

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KEY WORDS medicinal plants; Chinese traditional medicine; lignans; glucosides; terpenes; stress; anti-hypertensive agents; peptic ulcer; fatigue

ABSTRACT

The bark and leaves of *Eucommia ulmoides* Oliv (*Eucommiaceae*) and "Siberian ginseng" (Ezoukogi in Japanese) prepared from the root bark or stem bark of *Eleutherococcus senticosus* Maxim (*Acanthopanax senticosus* Harms) have been used as tonic and anti-stress drug. The extracts of *Eucommia* showed anti-hypertensive, anti-complementary, anti-oxidative, and anti-gastric ulcer effects, and promoting collagen synthesis, accelating granuloma formation, and other pharmacological effects. The Siberian ginseng exhibited anti-fatigue, anti-stress, immuno-enhancing effect, CNS activity, and anti-depressive effect. By now, 40, 28, and 10 compounds have been isolated from *Eucommia ulmoides* bark, *Eucommia ulmoides* leaves, and Siberian ginseng, respectively, and their structures were elucidated. Their pharmacological activities were mainly due to lignans and iridoid glycosides.

INTRODUCTION

It is well known that stress causes various disorder in bioregulatory, autonomic nervous, endocrine, and immuno systems, and anti-stress drugs restore ordinary healthy conditions. Many medicinal plants has been used for tonic, and some of them showed enhancing host resistance to various stress. Radix Ginseng, root of *Panax ginseng* C A Mey (*Araliaceae*) is one of the most famous herbal medicines, and has been used for tonic and anti-stress medicine. Several plants were used as the substitute of Radix Ginseng, and called attaching the word ginseng such as "desert ginseng"; *Cistanche* herba, the whole body of *Cistanche deserticola* Y C Ma (*Cistancheae*). The root of *Eleutherococcus senticosus* Harms (= *Acanthopanax senticosus*) (*Araliaceae*) also has been called as "Siberian ginseng", and similarly used as ginseng.

We reviewed the constituents and their pharmacological effects of two popular medicinal plants, Siberian ginseng and *Eucommia*.

EUCOMMIA

As well as *Panax ginseng*, Cortex Eucommiae (named Duzhong or Tuchung in Chinese and Tochu in Japanese), the bark of *Eucommia ulmoides* Oliv (*Eucommiaceae*), has been used as traditional medicine in Japan, China, and Korea. The pharmacological effects of Cortex Eucommiae was recorded as strengthening the internal organs, bones, and muscles, and preventing senescence in the old famous texts, Shennong Bengcao Jing[1] and Bengcao Gangmu[2]. It is also described as a tonic, analgesic, sedative, dieuretic, lumbago, and antihypertensive medicines in the modern books, Chinese Pharmacopeia[3], Manual of Chinese Medicines[4], Chinese Materia Medica[5], and a project of UNESCO[6]. Cortex Eucommiae is made from the bark of 15 – 20 years old *Eucommia ulmoides* Oliv trees, so it is very expensive in the market. There are some reports on the regeneration of the bark after peeling off[7-9]. Since 1970s, the leaves of *Eucommia ulmoides* has been used instead of the bark as a antihypertensive medicine. The use of the leaves brought

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the benefit to be able to collect leaves annually. The bark and leaves contain common iridoid and lignan compounds, so the leaves have been used similarly as the bark, for tonic and antihypertensive. Recently, various studies on *Eucommia ulmoides* Oliv have been developed[10,11]. *Eucommiaceae* family consists of *Eucommia ulmoides* Oliv, which are male and female trees. The character and cultivation method of *Eucommia ulmoides* Oliv were shown in books[12-14]. The barks are classified 4 types according to their surface pattern[11]. Type 1: with smooth surface; 2: with slight crack surface; 3: with deep crack surface; 4: with tortoise shell-like crack surface.

Most barks in the market belong to type 1. The ordinary *Eucommia ulmoides* Oliv barks contain 6 % – 16 % of ethanolic extract and 0.1 % – 0.5 % of pinoresinol di-*O*-β-*D*-glucopyranoside (9). The more abundant of 9 and more productive, quickly growing *Eucommia ulmoides* Oliv trees were selected and seperated into five groups, named Huazhong 1 – 5[12]. Cortex Eucommiae is prepared from more than 15 years old *Eucommia ulmoides* Oliv uree. The bark is peeled off in growing season, from June to August in Japan, Korea, and China. Because in this season, the bonding of bark to heart wood is weaker, the bark is easily dried and the color of inner bark turns to violet-black[15]. The color of crude drug is often important for its quality. In the case of Cortex Eucommiae, the color of inner bark is prescribed as dark violet[3-5]. It seemed to be produced by intracellular enzyme. The relation between iridoid glycosides content and color was reported by different preparation, the coloration of the inner bark was prevented by irradiation of microwave, or immediate dipping in boiling water[15]. In our experiment, adding of acidic or basic solution also prevented the coloration. On the other hand, dipping the bark in boiling water or steaming after several hours from peeling off accelerated the turning to black.

SIBERIAN GINSENG

The crude drug "Siberian ginseng" (*Eleutherococcus*), prepared from the root bark of the Siberian plant, *Eleutherococcus senticosus* Maxim (*Acanthopanax senticosus* Harms), has long been used in empirical oriental medicine for the nonspecific enhancement of resistance in humans and animals. At the first, this Siberian ginseng was discovered in search for a drug that could replace the rather expensive Korean ginseng. But it was shown that phytochemically the main components of Siberian ginseng (lignans) markedly differ from those of the Korean ginseng (saponins). The first phytochemical and pharmacological studies of this drug were based on Russian studies by Brekhman and his group. In Hokkaido (Japan), in order to preserve natural resources from the point of exhaustion, the stem bark of *Eucommia senticosus* (Japanese name: Ezoukogi) has been also used as a Siberian ginseng in place of the root bark. It was observed that the water extract from the stem bark exhibited a prolonged effect on the exercise time to exhaustion in chronic swimming stressed rats. This section describes the main constituents of Siberian ginseng and the up-to-date pharmacological studies of the Siberian ginseng as anti-stress drug.

CONSTITUENTS OF *EUCOMMIA ULMOIDES* OLIV AND SIBERIAN GINSENG

Constituents of *Eucommia ulmoides* Oliv bark

Eucommia ulmoides Oliv contains gutta[16], polyisoprenoid[17], iridoids, and lignans. We reported the isolation and structual determination of 39 compounds from the bark[18-24], which were listed in Tab 1.

The air-dried bark of *Eucommia ulmoides* Oliv (10 kg, commercial crude drug produced in China) was chopped and extracted with 20 L of 50 % MeOH, three times, under reflux. The extract was treated as usual way, and gave ethyl acetate extract (45 g), *n*-butanol extract (60 g), and water-soluble extract (480 g) successively. Each extracts were subjected to ion exchange resin, Diaion HP-20 (Mitsubishi Chemical Co Ltd) and silica gel column chromatography, gel filtration and preparative HPLC. The ethyl acetate extract gave compounds 1, 10, 21, 22, and 30 – 37. The *n*-butanol extract afforded compounds 18, 19, 23, 24, and 25 – 29. The water-soluble extract gave compounds 2 – 17, 20, and 25. We reported the structure elucidation of compounds 1 – 37 in the previous papers[18-23]. The structures of 38 and 39 were also elucidated as (+)-pinoresinol vanillic acid ether diglucopyranoside (38) and (+)-syringaresinol vanillic acid ether diglucopyranoside (39), respectively[24]. The main components of the bark are iridoids and lignans. The former are the same with those of the leaf. They are listed in Tab 1, and their structures are shown in Chart 1. β-Sitostero-*O*-β-*D*-glucoside was also isolated[25].

Tab 1. The isolated compounds from Cortex Eucommiae.

No	Compound name
1	Methyl chlorogenate
2	(−)-Olivil 4′,4″-di-*O*-β-*D*-glucopyranoside
3	Eucommioside I
4	Geniposidic acid
5	(+)-1-Hydroxypinoresinol 4′, 4″-di-*O*-β-*D*-glucopyranoside
6	Caffeic acid
7	Dehydrodiconiferyl alcohol 4,γ-di-*O*-β-*D*-glucopyranoside
8	Aucubin
9	(+)-Pinoresinol di-*O*-β-*D*-glucopyranoside
10	Hedyotol C 4″,4‴-di-*O*-β-*D*-glucopyranoside
11	(+)-Medioresinol di-*O*-β-*D*-glucopyranoside
12	(−)-Olivil 4″-*O*-β-*D*-glucopyranoside
13	(−)-Olivil 4′-*O*-β-*D*-glucopyranoside
14	Eucommiol
15	(+)-Syringaresinol di-*O*-β-*D*-glucopyranoside
16	Guaiacylglylglycerol β-syringaresinol ether 4″,4‴-di-*O*-β-*D*-glucopyranoside
17	Citrusin B
18	(+)-1-Hydroxypinoresinol 4″-*O*-β-*D*-glucopyranoside
19	(+)-1-Hydroxypinoresinol 4′-*O*-β-*D*-glucopyranoside
20	Geniposide
21	*erythro*-Dihydroxydehydrodiconiferyl alcohol
22	*threo*-Dihydroxydehydrodiconiferyl alcohol
23	*erythro*-Guaiacylglycerol
24	*threo*-Guaiacylglycerol
25	(+)-Pinoresinol *O*-β-*D*-glucopyranoside
26	Eucommin A
27	(+)-Cyclo-olivil
28	(+)-Syringaresinol *O*-β-*D*-glucopyranoside
29	(−)-Olivil
30	Dihydrodehydrodiconiferyl alcohol
31	Guaiacylglycerol-β-coniferyl aldehyde ether
32	Genipin
33	(+)-1-Hydroxypinoresinol
34	(+)-Pinoresinol
35	(+)-Epipinoresinol
36	(+)-Medioresinol
37	(+)-Syringaresinol
38	(+)-Pinoresinol vanillic acid ether diglucopyranoside
39	(+)-Syringaresinol vanillic acid ether diglucopyranoside
40	β-Sitosterol *O*-β-*D*-glucopyranoside

Compound 1 – 39 were reported in references 18 – 24 and compound 40 was in reference 25.

Constituents of *Eucommia ulmoides* Oliv stem The constituents of the stem of *Eucommia ulmoides* Oliv were reported as follows; 5-hydroxy-2-fusaldehyde, eucommiol (14), 1-deoxyeucommiol (41), geniposide (20), geniposidic acid (4), koaburaside (1,4-dihydroxy-2, 6-dimethoxybenzene-4-*O*-β-*D*-glucopyranoside), syringin (69), coniferin, glucose, and sucrose[26].

Constituents of *Eucommia ulmoides* Oliv leaves *Eucommia ulmoides* leaves contains iridoids, lignans, flavons, phenols, and terpenes[27-35]. They are shown in Tab 2. Some of them are commonly contained in the bark and stem.

Tab 2. The isolated compounds from *Eucommia ulmoides* leaves.

No	Compound name
3	Eucommioside I
14	Eucommiol
41	1-Deoxyeucommiol
42	Epieucommiol
43	Asperuloside
44	Asperulosidic acid
45	Deacetylasperulosidic acid
46	Scandoside 10-*O*-acetate
47	Ulmoidol
48	Ursolic acid
49	Catechin-(7, 8-b, c)-4α-(3, 4-dihydroxyphenyl)-2(3H)-pyranone
50	Catechin-(7, 8-b, c)-4β-(3, 4-dihydroxyphenyl)-2(3H)-pyranone
51	Kaempferol
52	Astragalin
53	Kaempferol 3-*O*-rutinoside
54	Kaempferol 3-*O*-(6″-acetyl)-glucopyranoside
55	Quercetin
56	Quercetin 3-*O*-glucopyranoside
57	Quercetin 3-*O*-xylopyranosyl-(1→2)-glucopyranoside
58	Catechol
59	Pyrogallol
60	Protocatechuric acid
61	*p-trans* Coumaric acid
62	Guaiacylglycerol
63	3-(3-Hydroxyphenyl)propionic acid
64	3-(3,4-Dihydroxyphenyl)propionic acid
65	Chlorogenic acid
66	3-*O*-Feruloylquinic acid

Constituents of Siberian ginseng In order to clarify the constituents of Siberian ginseng, the extraction and separation were carried out in the following manner. Dry powdered bark was extracted four times with hot methanol. The methanol solution was evaporated to a small volume under reduced pressure, diluted with water and then filtered. The filtrate was extracted successively with ether, chloroform, and 1-butanol. The ether extract was subjected to column chromatography on silica gel, eluted with a benzene-chloroform solvent system to give isofraxidin. The chloroform extract was subjected to column chromatography on silica gel, eluted with a chloroform-ethanol solvent system to give 2,6-dimethoxy-*p*-benzoquinone (68). The *n*-butanol extract was subjected to column chromatography on silica gel, eluted with a chloroform-ethanol solvent system to give (+)-

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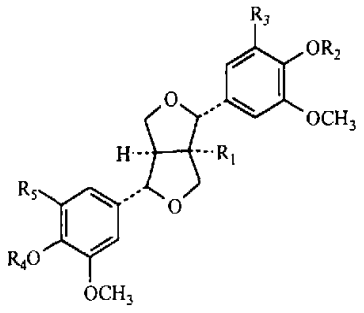
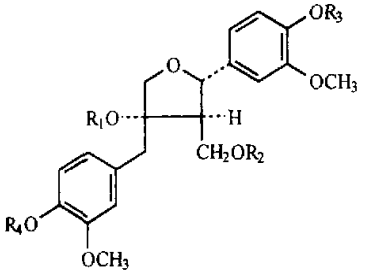
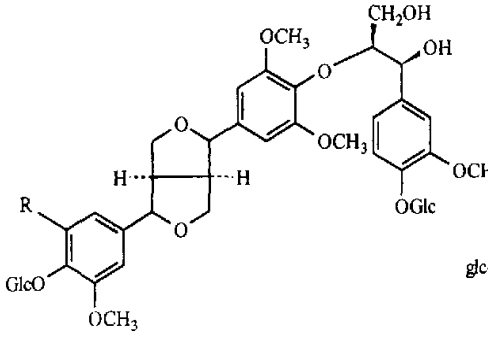


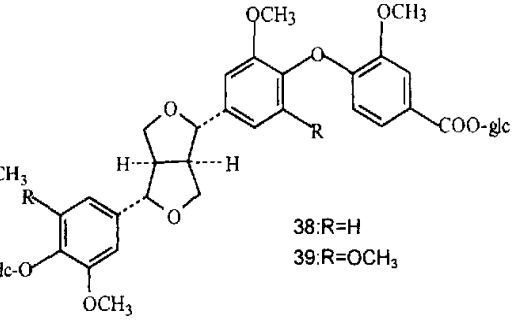
No.	R1	R2	R3	R4	R5
34	H	H	H	H	H
25	H	glc	H	H	H
9	H	glc	H	glc	H
36	H	H	OCH_3	H	H
26	H	glc	OCH_3	H	H
11	H	glc	OCH_3	glc	H
37	H	H	OCH_3	H	OCH_3
28	H	glc	OCH_3	H	OCH_3
15	H	glc	OCH_3	glc	OCH_3
33	OH	H	H	H	H
19	OH	glc	H	H	H
18	OH	H	H	glc	H
5	OH	glc	H	glc	H



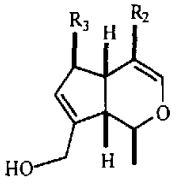
No.	R1	R2	R3	R4
27	H	H	H	H
13	H	H	glc	H
12	H	H	H	glc
2	H	H	glc	glc

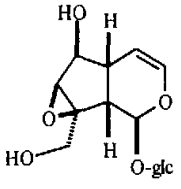


10:R=H
16:R=OCH_3

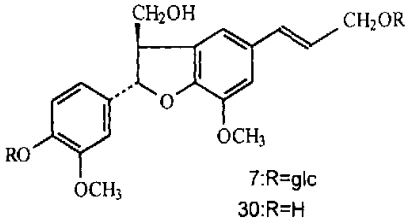


38:R=H
39:R=OCH_3





Catalpol

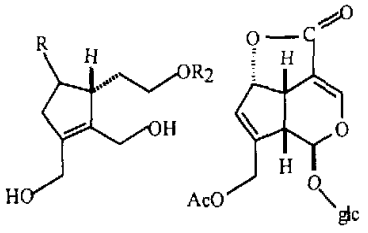


7:R=glc
30:R=H

4:R_1=glc,R_2=COOH,R_3=H
8:R_1=glc,R_2=H,R_3=OH
20:R_1=glc,R_2=$COOCH_3$,R_3=H
32:R_1=R_3=H,R_2=$COOCH_3$

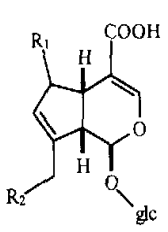
Chart 1. Structure of the compounds isolated from *Eucommia ulmoides* Oliv.

Terpenoids

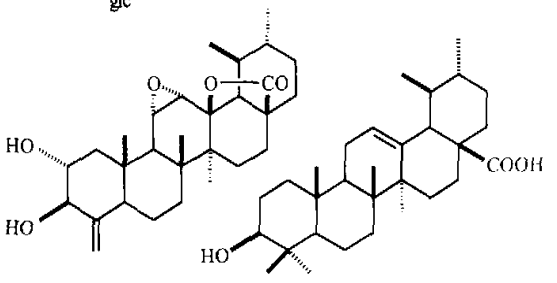


3:R_1=—OH,R_2=glc
14:R_1=—OH,R_2=H
41:R_1=R_2=H
42:R_1=⋯OH,R_2=OH

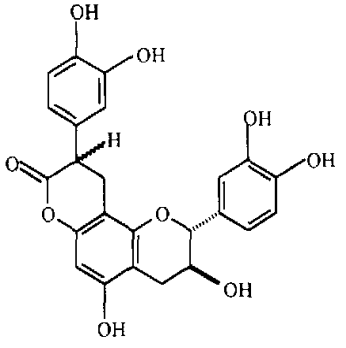
43



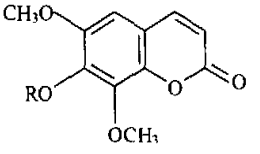
44:R_1=⋯OH,R_2=OAc
45:R_1=⋯OH,R_2=OH
46: R_1=—OH,R_2=OAc



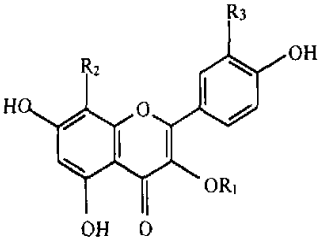
47 48



Catechins α β
49:4α-H
50:4β-H

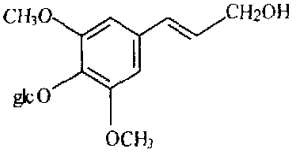


67: R=H
70: R=glc

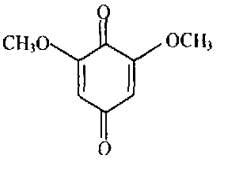


Flavonoids

51:R_1=R_2=R_3=H
52:R_1=glc,R_2=R_3=H
53:R_1=glc-rham,R_2=R_3=H
54:R_1=6"-acetyl-glc,R_2=R_3=H
55:R_1=R_2=H,R_3=OH
56:R_1=glc,R_2=H,R_3=OH
57:R_1=glc-xyl,R_2=H,R_3=OH

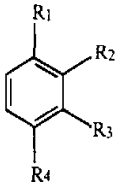


69

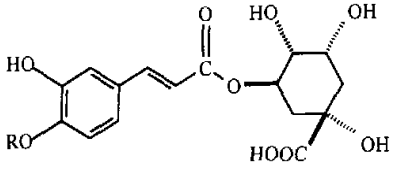


68

Phenolic Derivatives



58:R_1=R_2=OH, R_3=R_4=H
59:R_1=R_2=R_3=OH, R_4=H
60:R_1=R_2=OH,R_3=H, R_4=COOH
61:R_1=OH,R_2=R_3=H, R_4=CH=CH-COOH
62:R_1=OH,R_2=OCH_3,R_3=H, R_4=CH(OH)-CH(OH)-CH_2OH
63:R_1=R_3=H,R_2=OH, R_4=CH_2-CH_2-COOH
64:R_1=R_2=OH,R_3=H, R_4=CH_2-CH_2-COOH



65:R=H
66:R=CH_3

Chart 1. continued

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syringaresinol di-*O*-β-*D*-glucoside (eleutheroside E, 15), syringin (eleutheroside B, 69), chlorogenic acid (65), (+)-pinoresinol *O*-β-*D*-glucoside (25), (+)-syringaresinol *O*-β-*D*-glucoside (28), (+)-pinoresinol di-*O*-β-*D*-glucoside (9), and (+)-medioresinol di-*O*-β-*D*-glucoside (11), respectively. The aqueous residue extract was chromatographed on Sephadex LH-20 with water to give isofraxin 7-*O*-β-*D*-glucoside (eleutheroside B1, 70)[36]. The constituents of Siberian ginseng are listed in Tab 3 and the content of the main components in Siberian ginseng is shown in Tab 4.

Tab 3. The isolated compounds from Siberian ginseng.

No	Compound name
9	(+)-Pinoresinol di-*O*-β-*D*-glucopyranoside
11	(+)-Medioresinol di-*O*-β-*D*-glucopyranoside
15	(+)-Syringaresinol di-*O*-β-*D*-glucopyranoside
25	(+)-Pinoresinol *O*-β-*D*-glucopyranoside
28	(+)-Syringaresinol *O*-β-*D*-glucopyranoside
65	Chlorogenic acid
67	Isofraxidin
68	2,6-Dimethoxy-*p*-benzoquinone
69	Syringin
70	Isofraxidin 7-*O*-β-*D*-glucopyranoside

Tab 4. Content of main constituents (mg/100 g) in parts of Siberian ginseng.

No	Bark		Leaf
	Root	Stem	
15	96.4	53.2	-
65	274.6	96.7	62.1
67	5.5	5.4	2.2
69	41.4	22.6	2.4
70	20.1	3.2	-

PHARMACOLOGICAL EFFECTS OF *EUCOMMIA ULMOIDES* OLIV AND SIBERIAN GINSENG

Antihypertensive effect The decoction and tincture of *Eucommia ulmoides* Oliv bark showed the antihypertensive effect[3-5,37-42]. Compound 9 was reported as the antihypertensive compound[43]. We investigated the hypotensive activity of the fractions and components of *Eucommia ulmoides* bark[44] (Tab 5 and Chart 2). The water extract of *Eucommia ulmoides* bark and its *n*-butanol extracted residue showed the hypotensive activity in anesthetized sponteneous hypertensive rat (SHR) in iv. Compound 4 and 25 showed stronger activity (++), and dehydrodiconiferyl alcohol 4,γ'-di-*O*-β-*D*-glucopyranoside (7), citrusin B (17), and

Tab 5. Effect of constituents of Cortex Eucommiae on blood pressure in anesthetized SHR.

No	Dose/mg·kg^{-1}	Hypotensiona
Water extract	16.7	++
n-BuOH extract	16.7	++
Residue-1	16.7	+
Residue-2	16.7	++
HP-20, 30 % MeOH eluate	16.7	++
HP-20 100 % MeOH eluate	16.7	+
2	30.0	-
3	30.0	-
4	30.0	++
5	30.0	-
7	30.0	+
8	30.0	Pressor
9	30.0	-
11	30.0	Pressor
12	30.0	-
13	30.0	-
14	30.0	-
20	30.0	-
25	30.0	++
32	30.0	+

Hypotention: + (5-10 mmHg), ++ (20-40 mmHg), - (no effect).

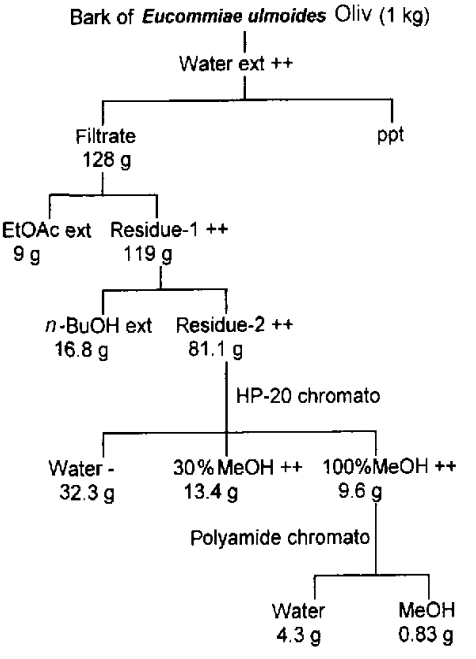

Chart 2. Hypotensive effect of Cortex Eucommiae fractions.

genipin (32) showed the moderate activity (+). Compound 9 showed no activity. Compounds 4 and 25 accelerated the respiration in SHR. The *Eucommia ulmoides* leaves extract also showed the hypotensive activity in rat[45], SHR[46], and clinical[47,48] and has been used for hypotensive. Japanese Ministry of Health and Welfare authorized it as a food for specific health use for prevention of hypertensive and the effect is mainly belong to 4.

Anticomplementary effect The anticomplementary effect of the components of *Eucommia ulmoides* Oliv bark was examined[49]. As shown in Tab 6, in the lignans, eucommin A (26), (+)-syringaresinol *O*-β-*D*-glucoside (28), and (+)-epipinoresinol (35) exhibited the moderate anticomplementary activity (24 % ~ 27 %) at the concentration of 1.5 g/mL. The lignan glucosides were more active than their aglucones in each series of lignans. In the iridoids, 32 showed the strongest inhibitory activity (75.3 %), on the other hand, 20 exhibited the weak activity (23 %) as well as other iridoids. Since it was quite probable that the hemiacetal moiety present in 32 was responsible for the anticomplementary activity, compounds 4 and 8 were subjected to enzymatic hydrolysis with β-glucosidase, and the activity of their hydrolysate were assessed. Both hydrolysate exhibited remarkable activity as 32 (Tab 7). It seems that the hemiacetal moiety plays an important role in the manifestation of the anticomplementary activity of iridoids.

Tab 6. Anticomplementary activity of *Eucommia ulmoides* constituents[1].

No	Inhibition/ %	No	Inhibition/ %
2	18.7 ± 1.5	20	23.0 ± 8.8
3	17.3 ± 6.9	23,24	19.3 ± 6.6
4	14.3 ± 3.0	25	9.0 ± 1.5
5	18.3 ± 2.7	26	27.7 ± 1.2
8	21.7 ± 8.1	28	27.7 ± 4.8
9	12.0 ± 0.6	29	4.3 ± 1.9
10	15.0 ± 3.0	30	11.7 ± 1.2
11	13.7 ± 0.7	31	8.3 ± 1.2
13	18.0 ± 5.0	32	75.3 ± 1.8
14	20.7 ± 8.1	34	3.3 ± 0.9
15	18.3 ± 2.7	35	24.7 ± 6.2
17	1.7 ± 1.2	37	2.7 ± 0.9
		Catalpol[2]	7.7 ± 2.0

1) Data are expressed as $x \pm s_x$ of three experiments.
2) Catalpol was not isolated from *Eucommia ulmoides*.

Tab 7. Anticomplementary activity of enzymatic hydrolysates of iridoids[1].

Original iridoids	Inhibition/ %
4	87.3 ± 2.3
8	89.3 ± 0.9
Catalpol[2]	> 90
β-Glucosidase	5.0 ± 1.0
D-Glucose	1.3 ± 0.7

1) Data are expressed as $x \pm s_x$ of three experiments.
2) Catalpol was not isolated from *Eucommia ulmoides*.

Anti-oxidative effect It is well known that free radicals attack the unsaturated fatty acid and prepare peroxide, and resulting in decrease of membrane fluidity, of enzyme and receptor activity. Free radicals attack DNA and cause mutation leading to cancer. Anti-oxidative compounds scavenge free radicals and prevent the peroxide-induced diseases, such as heart attack and cancer.

The aqueous extract of *Eucommia ulmoides* leaves, row and roasted Cortex Eucommiae showed anti-oxidative activity[50]. The inhibitory activity of the extracts on the linoleic acid peroxidation measured by thiocyanate method followed the order; leaves (99.9 %), roasted cortex (95.9 %), and row cortex (77.2 %) at 60 h of incubation. The thiobarbituric acid reactive substance (TBARS) values followed the same order above, on the inhibitory activities of liposomal and microsomal lipid peroxidation. Pinoresinol (34) showed inhibitory activity against peroxidation in rat liver microsomes, and syringaresinol (37) showed no effect[51]. Compounds 34 and 37 exhibited stronger LDL-oxidation inhibitory activity than probucol, which is a cholesterol-lowering drug with antioxidant activity and reduce atherosclerosis in animals[52].

Anti-fatigue effect Siberian ginseng have been used extensively in Russia as an adaptogen whose properties are the ability to increase a nonspecific body resistance to stress, fatigue, and disease[53]. The pharmacological effect of the water extract of Siberian ginseng on the exercise time to the point of exhaustion in chronic swimming stressed rats was examined[36]. For 25 d, the extract (500 mg · kg^{-1} · d^{-1}) was orally administered every day at the same hour of the day. From d 15 after the first administration, the swimming stress was given to the rats under the same conditions at the same hour of the day and continued for 6 trial times every other day. Fig 1A showed the effect of the extract

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on the exercise time to exhaustion in the chronic swimming stressed rats. A significant difference was observed between the control group and the extract-treated group on and after the 4th trial (d 21 after the first administration). This result indicates that the extract may protect rats from fatigue induced by chronic swimming stress. Compound 15 also showed the same effect (Fig 1B), but 65 exhitited no effect (Fig 1C). The effect of the Siberian ginseng extract on hepatic glycogen level was evaluated on exhaustion time in chronic swimming stressed rats[54]. Decrease in hepatic glycogen level due to chronic swimming stress was greatly suppressed in the extract-treated group. Exhaustion time in the 15-treated group was significantly longer on and after the 6th trial. However, no significant difference in hepatic glycogen level was observed. Hepatic glycogen level in 65-treated group was significantly suppressed. A water extract of Siberian ginseng, 15 and 69 were examined for their effect on physical conditions in mice subjected to acute oscillation. The drugs were given orally to mice 10 min before or immediately after the enforced exercise. The fatigued state was evaluated by rectal temperature, body and grip tones (sliding angle and spring balance), motor coordination (rotating rod), and exploratory and spontaneous movements (exploratory movement and motor activity tests). The extract of Siberian ginseng served to prevent the stress-induced decrease in rectal temperature and body and grip tones, and to accelerate recovery from decreases in body and grip tones. Compound 69 functioned to prevent the stress-induced decreases in grip tone and exploratory movement, and to accelerate recovery from the decreases in grip tone, exploratory movement and spontaneous movement, and 15 functioned to prevent the stress-induced decreases in exploratory and spontaneous movements and to accelerate recovery from such conditions[55].

Stress reducing effect Experiment of healthy human subjects of the Siberian ginseng extract have demonstreated stress-reducing activities without any adverse effects[56]. In restrained cold-water stressed rats, the water extract of Siberian ginseng and 15 displayed an anti-gastric ulcer effect[57]. Compound 4, a main component of *Eucommia* leaf, also, exhibited the anti-ulcer effect as shown in Fig 2.

The oral pre-administration of the extract in a dose of 500 mg/kg showed an increase in serum prolactin and serum growth hormone concentrations in the male rats under the non-stress condition[58]. In a study to analyze the protective mechanism on the gastric ulcer by the

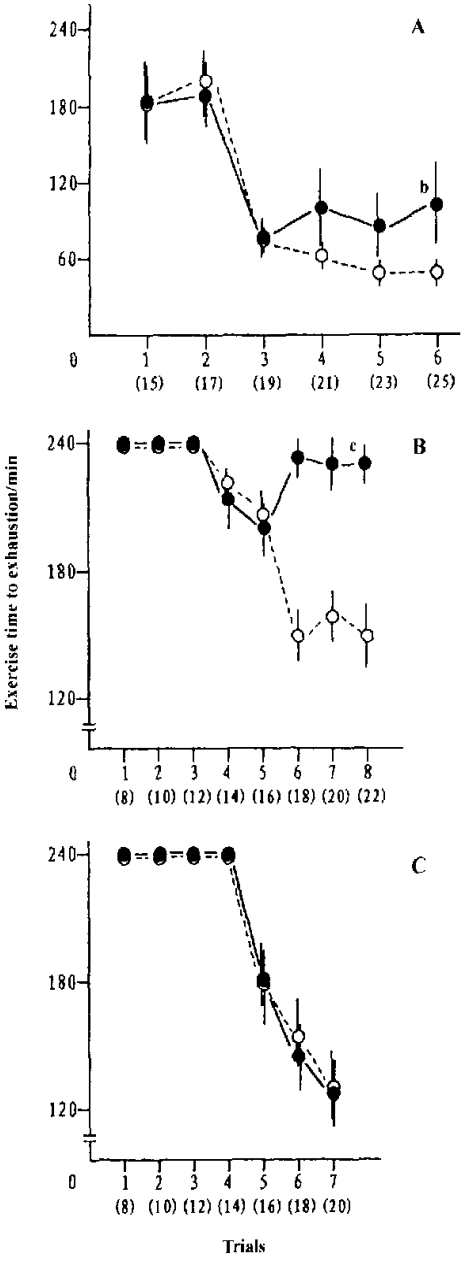

Fig 1. Effect of water extract of Siberian ginseng stem bark (A), (+)-syringaresionol di-*O*-β-*D*-glucoside (B), and chlorogenic acid (C) on exercise time to exhaustion in chronic swimming stressed rats. $n = 9-12$ rats. $\bar{x} \pm s_{\bar{x}}$. $^bP < 0.05$, $^cP < 0.01$ *vs* control. Figure in brackets indicates day after the first administration. (●) Treated; (○) Control.

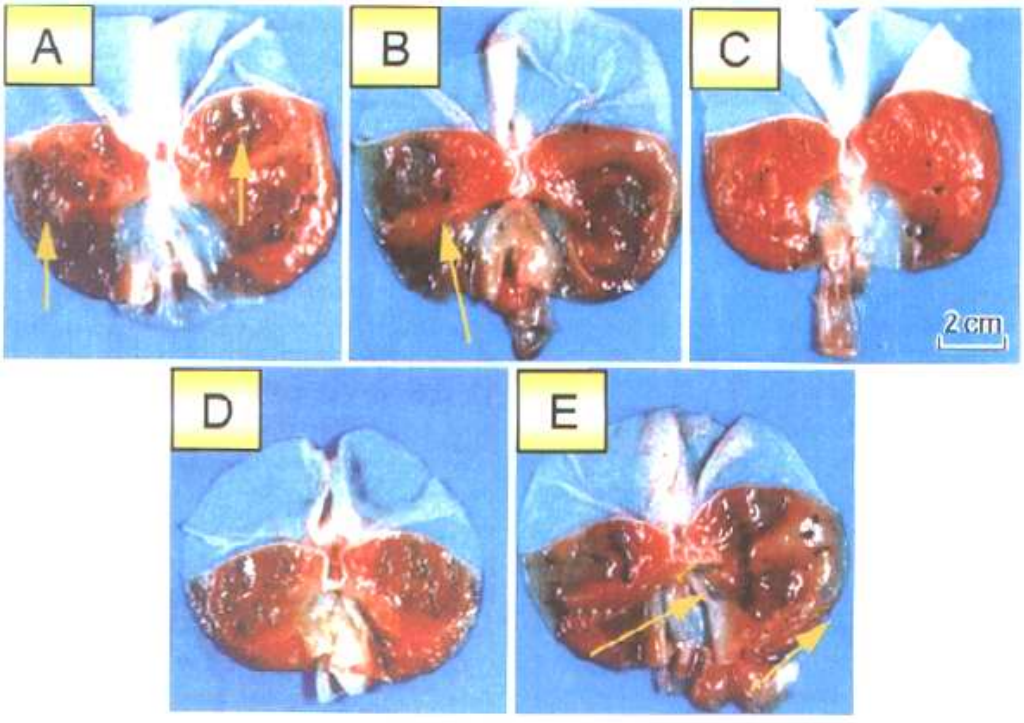

Fig 2. Anti-gastric ulcer effect of geniposidic acid (*po*) in water restrained stressed rats. A: 50 mg·kg^{-1}·d^{-1}; B: 75 mg·kg^{-1}·d^{-1}; C: 100 mg·kg^{-1}·d^{-1}; D: Intact control; E: Stress control.

extract via the prolactin and growth hormone receptors in the brain, the central actions of rat prolactin and growth hormone as inhibitors to the occurrence of the restrain stress in water-induced gastric ulcer were investigated to obtain the results that the extract enhanced the peripheral level of prolactin and the increase in prolactin could act through the rat prolactin receptor at the paraventricular nucleus and the ventromedial hypothalamus to inhibit the gastric ulcer development by restrain stress in water. The administration of the extract of *Eucommia ulmoides* bark and 4 prevented the decrease of sex and learning behaviors in chronic hanging stressed mice. Compound 9 prevented the decrease of learning behavior, and Siberian ginseng 15, 20, and 69 prevented the decrease of sex behavior[59,60]. Compounds 4, 20, and 32 prevented the decrease of sex and learning behaviors and the enlargement of adrenal glands in chronic hanging stressed mice. Compounds 4 and 20 prevented the decrease of rectal temperature, but Compound 32 promoted the decrease[61].

Effect on the anabolic, gonadal, and adrenal synthesis systems The extract of *Eucommia ulmoides* bark increased the adaptation ability. Administration of the extract significantly increased the relative weight of adrenal gland, androgen secretion from the reticular layer of the adrenal cortex, and promoted protein anabolic action in castrated rats[62]. Administration of the extract of *Eucommia ulmoides* bark in male rats, which were hindlimb-suspended, showed significantly higher concentration of serum testosterone, the testicular cAMP level and 24 h urinary excretion of 17-ketosteroid than those of controls. There were no significant differences between the treated and control groups in serum leuteinizing hormone (LH), and in the weight per body weight of kidneys, adrenal and testis. It seems that the administration of the extract of *Eucommia ulmoides* bark inducing high serum testosterone concentrations in hindlimb-suspended rats, might directly act on testicular and adrenal functions[63]. Administration of the extract of *Eucommia ulmoides* bark and 20 increased the adrenal gland and testis in male Wistar rats, during the exercise load using tread mill[64]. Similarly, the extract of *Eucommia ulmoides* leaves increased them[65].

As an anabolic activity of adaptogens in animal models, direct stimulatory effects on DNA, RNA or protein synthesis have been described. Swimming for 15

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min inhibited nuclear DNA-dependent RNA polymerase activity in the liver and skeletal muscles of rats. Siberian ginseng (15 mg/kg, ip) administered 1 h before swimming delayed the inhibition of RNA polymerase and accelerated its restoration during rest[66].

The extract of *Eucommia ulmoides* leaves were administerted in a model of a "Pixu Zheng" syndrome in traditional Chinese medicine, caused by a long term administration of the senna extract, and increased the relative weight of organ to body weight in the liver, thymus, adrenals, testis, and small intestine, and decreased in submandibular glands[67].

Promoting effect on collagen synthesis Decline of collagen synthesis is seemd to be relative to aging. A rat fed with a lower protein diet showed the decrease of collagen synthetic activity. Administration of the extract of *Eucommia ulmoides* leaves improved the collagen synthesis in collagen synthetic activity-reduced model rat[68]. Compound 4 and 8, the common components of *Eucommia ulmoides* bark and leaf, promoted the collagen synthesis[69]. Administration of the extracts of the fresh *Eucommia* bark and Cortex Eucommiae (crude drug; air-dried) also increased granuloma formation and collagen synthesis. The former extract has a stronger effect than the latter. The active compounds proved to be 20 and eucommiol (14), besides 4 and 8 in collagen synthesis[70].

Accelerating effect on granuloma formation Administration of aqueous extract of *Eucommia ulmoides* leaves stimulated granuloma formation in normal rats[71]. The wound healing process is devided into four phases as follows: exudation, proliferation, fibroblastion, and maturation. Granulation is a characteristic of the second stage of wound healing. Collagen deposition in granuloma showed the advance to early wound healing, and has been described as a result of elevated collagen synthesis.

Improvement in the turnover rate of the stratum corneum Administration of the water soluble extract of methanol extract of *Eucommia ulmoides* Oliv leaves and Compound 4 improved the turnover rate of the stratum corneum in false aged model rat[69,72]. It seems that this effect is due to 4, one of the major components of the bark and leaf of *Eucommia ulmoides* Oliv.

Inhibitory activity on nitrite production Nitrite shows various bioactivities and plays important role in living body. Macrophage is one of nitrite-producers. Superfluous nitrite production often promote the inflamation. The aqueous and methanolic extracts of *Eucommia ulmoides* Oliv showed the inhibitory activity on nitrite production stimulated by lipopolysaccharide/interferon-γ in murine peritoneal macrophages[73].

Immuno-enhancing effect Oral administration of the water extract of Siberian ginseng to rats under non-stress and cold-water stress caused a significant enhancement of β-endorphin level in plasma (Tab 8)[74]. A similar effect was also observed in human beings. In addition, oral administration of Compound 15 to rats caused the enhancement of β-endorphin level in plasma. Simura *et al* reported that there are opioid receptors on T-lymphocyte and that the immune reaction is enhanced when the opioid receptors on T-lymphocyte are filled with sufficient concentration of β-endorphin[75]. So the therapeutic effect of Siberian ginseng as a tonic medicine may be due to the enhancement of the immune reaction. Actually, a double-blind study with 36 human subjects has shown that Siberian ginseng improves non-specific immune reactivities as determined by quantitative flow-cytometry. Immunocompetent cells, in particular T-lymphocytes and natural killer cells were found to be markedly increased after administration of the extracts for four weeks[76].

Tab 8. Effect of the water extract of Siberian ginseng on rat plasma β-endorphin levels (pg/mL) under non-stress and cold-water stress cold-water stress.

Condition	Control	Administration ($500\ mg \cdot kg^{-1} \cdot d^{-1}$, *po*)
Non-stress	16.83 ± 1.30	$30.17 \pm 4.70^{1)}$
Cold-water stress	10.60 ± 1.79	$20.60 \pm 3.48^{2)}$

Each value represents the $x \pm s_x$ of 6 samples.
1) Significantly different from control group, $P < 0.05$.
2) Significantly different from control group, $0.05 < P < 0.1$.

CNS activity The mental ability is improved by administration of adaptogens. Animal experiments have shown that administration of extracts (0.05 – 1 mg/kg, sc, and 0.02 – 2 mg/kg, iv) can cause electroencephalogram alterations that may be taken as evidence for stimulatory CNS effects[77]. A two-week course of the extract (1 mL/kg, *po*) in rats led to increases in noradrenaline and serotonin in the brain[78]. Peroral application of 500 mg/kg for 7 weeks of water extract led to improvement in learning and memory abilities in an active avoidance rat model[79]. Compound 15 showed the potent effect on neurite outgrowth of a cultured cell line of paraneuron, PC12h cells[80]. In this respect, it

may be one of the reasons for improved mental ability following administration of adaptogens that the component of the anti-stress crude drug has the same activity on the paraneuronal cells as neurotrophic factors such as the nerve growth factor.

Antidepressive effect Due to the close connections between stress and the development depressions, the forced swimming test, which has been developed to evaluate the efficacy of antidepressive drugs[81], is also used to evaluate the efficacy of putative adaptotgenic drugs. If a mouse is forced to swim on a small glass cylinder freely floating in water it will desperately try initially to escape or to swim. The leaf of Siberian plant, *Eleutherococcus senticosus*, contains hyperoside, flavonol glycoside[82], which showed remarkably activity in the forced swimming test[83]. The Siberian ginseng was also shown to produce an inhibition (66 %) of hexobarbital metabolism, *in vitro*, as compared to controls[84]. Isofraxidin in the bark and hyperoside in the leaf of Siberian ginseng are respectively reported as effective sedative components[85].

Anti-inflammatory effect Anti-inflammatory activity of iridoids was tested by using the carrageenan-induced mouce paw edema and the tetradecanoylphorbol-acetate (TPA)-induced mouse ear edema models. Compound 8 inhibited the edema significantly at a dose of 100 mg/kg and at 1 mg/ear, respectively, in both experiments[86].

Analgesic effect Compounds 20 and 32 inhibited the writhing behavior in mice induced by acetic acid[86].

Compound 34, isolated from *Eucommia ulmoides* Oliv[18] and from *Fagracea racemosa* Jack ex Wall, showed a dose-dependent inhibition of the acetic acid-induced writhing in mice[87].

Relaxation effect The root of Todopan Pouk (*Fargraceae racemosa* Jack ex Wall, *Loganiceae*) has been used as a pain killer in Borneo and Malaysia, and for the treatment of fever in Malaysia and India[88]. The methanolic extract of Todopan Pouk exhibited a relaxation effect on norepinepherine-induced contraction in rat aortic strips at 0.2 mg/mL. Three active components were isolated from and determined as, 34, 35, and (+)-lariciresinol[87]. Two former compounds, 34 and 35 were isolated from *Eucommia ulmoides* Oliv bark[18].

Antibacterial activity Compound 8 in the presence of β-glucosidase, and aucubigenin exhibited the antimicrobial activity against *Staphylococcus aureus* 209P JC-1. Compound 8 showed no activity in the absence of β-glucosidase. Several iridoids with hemiacetal structure showed the microbial activity in the same condition[89]. The hemiacetal moiety plays an important role in the manifestation of antimicrobial activity, likewith in the anticomplementary activity.

Other activities Compound 15 showed a marked effect on the inhibitory activity against beef heart cAMP phosphodiesterase, which is expected act as therapeutic agents such as antipsychotics, antianxiety, and antihypertensive drugs[90]. (+)-Syringaresinol (37), which is an aglycone of 15 and 28, showed a potent radical-scavenging activity, which may lower the risk of cancer. Compound 37 prevented the formation of advanced glycation end products, which may reduce development of diabetic complications.

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杜仲和西伯利亚人参的化学成分及药理作用

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