Cassiae semen: A review of its phytochemistry and pharmacology (Review)

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Abstract. *Cassiae* semen (*Leguminosae*), a well-known traditional Chinese medicine, has been used for a number of centuries in areas of Southeast Asia, including Korea, Japan and China. The present review aims to provide updated and comprehensive information, on the botany, phytochemistry and pharmacology of *Cassiae* semen. The available information on *Cassiae* semen was collected using several different resources, including classic books on Chinese herbal medicine and a number of scientific databases, including the China Academic Journals full-text database, PubMed, SciFinder, the Web of Science and Science Direct. To date >70 chemical compounds have been isolated from *Cassiae* semen, and the major components have been determined to be anthraquinones, naphthopyrones and volatile oil. The crude extracts and pure compounds of *Cassiae* semen have been used as effective agents in preclinical and clinical practice due to their beneficial activities, including antihyperlipidemic, antidiabetic, neuroprotective, hepatoprotective, antibacterial, antioxidant and hypotensive activities. With the body of reported data, it has been suggested that *Cassiae* semen has convincing medicinal potential. However, the pharmacological mechanisms of the main bioactive compounds and the association between structure and activity require further investigation.

Contents

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1. Introduction

Cassiae semen, also known as 'Juemingzi' in Chinese, is the dry and mature seed of *Cassia obtusifolia* L. or *C. tora* L., which belong to the *Cassia* genus of *Leguminosae* (1). It is cultivated in Korea, Japan and China, and is commonly consumed as a roasted tea (2,3). In traditional Chinese medicine, it has been used in treatments for hyperlipemia, diabetes mellitus, Alzheimer's disease, acute liver injury, inflammation, photophobia, headache, dizziness and hypertension (4-6).

Phytochemical investigations have isolated and identified >70 compounds, including anthraquinones, naphthopyrones, volatile oils and sterols (7,8). Among these, anthraquinones are the primary functional components and possess a wide spectrum of pharmacological properties (9-11), including antihyperlipidemic, neuroprotective, hepatoprotective, antibacterial and antimutagenic activities (12-14). Naphthopyrones, other primary components, exhibit antidiabetic (15,16), antimicrobial (17), antiestrogenic (18), antiallergic (19) and anthelmintic effects (20). At present, the Pharmacopoeia of the People's Republic of China recommends the use of chrysophanol and aurantio-obtusin as the indicator components, and the quality of *Cassiae* semen is evaluated primarily by assessing the content of these two compounds (1).

The purpose of the present review is to provide comprehensive information on the ethnobotany, phytochemistry and pharmacology of *Cassiae* semen collated from previous studies, in order to facilitate the further study and application of *Cassiae* semen, as well as generate a novel basis for the associations between structure and activity, and their molecular mechanisms of action.

2. Ethnobotany

C. obtusifolia is similar to *C. tora* in terms of botanical morphology. The two are an annual, erect, stout herb, ~1-2 m in length, and their leaves are paripinnate, typically pubescent and are 4-8 cm in length with a conical gland between each of the two lowest pairs of leaflets. Leaflets are formed of 3 leaf

pairs and are glaucous, membranous, glabrous or pubescent, and have obcordate or obovate oblong morphology (2-6 cm long x 1.5-2.5 cm wide); the base is somewhat oblique, usually rounded and there are 8-10 pairs of main nerves. The petiolules are 1.5-2 mm in length and their stipules are linear, pilose and caducous. It blossoms from July to September and produces fruit from September to October. Flowers are usually in subsessile pairs in leaf axils, the pedicels are filiform and are 1-1.5 cm in length. Calyces are ovate, glabrous, membranous and comprised of five-parts; there are five petals, which are pale yellow, oblong, obtuse and the upper petal (standard) is two-lobed. The flowers have 10 stamens, while the upper three are reduced to minute staminodes. The pods are slender, puberulous, subtetragonous, obliquely septate and, are ~15 cm in length and 3-4 mm in width.

However, the seeds of *C. obtusifolia* are a dark brown or green-brown, rhombohedral or short cylindrical, and are 3-7 mm in length and 2-4 mm in width. While *C. tora* seeds are a light brown, shiny, short cylindrical, and are 3-5 mm in length and 2-3 mm in width (1,21).

C. obtusifolia is cultivated in multiple provinces of China, including Henan, Hubei, Shanxi, Sichuan, Zhejiang and Anhui, and also other countries, including Korea, India and Japan. It is primarily distributed in moist and sunny places, in hillside shrubs and in the sandy soil of river banks (21).

As a widely used traditional Chinese medicine, there are some adulterants of this plant, including the seeds of *C. occidentalis* (*Leguminosae*), *C. sophera* (*Leguminosae*) and *Sesbania aculeata Pers* (*Papilionaceae*) (22-24). To date, a number of methods have been developed to identify and distinguish these, including experiential identification, morphological identification, ultraviolet spectrophotometry, the thin layer chromatography method, high performance liquid chromatography (HPLC), HPLC-coupled with time-of-flight and ion trap mass spectrometry, and SDS-PAGE (25-28). Among these methods, the HPLC method is regarded as the most popular method for evaluating the quality and authenticity of *Cassiae* semen. Chrysophanol and aurantio-obtusin are used as the indicator compounds to characterize the quality of this plant and the minimum contents are defined as 0.20 and 0.080%, respectively, in the Pharmacopoeia of the People's Republic of China (1).

3. Phytochemistry

A number of compounds, including anthraquinones, naphthopyrones, volatile oils and sterols, have been isolated from *Cassiae* semen. Anthraquinones and naphthopyrones, which exhibit multiple pharmacological activities, are considered the primary active ingredients of *Cassiae* semen. All compounds isolated from *Cassiae* semen are listed in Table I, and their chemical structures are displayed in Figs. 1-3.

Anthraquinones. *Cassiae* semen contains structurally diverse and biologically active anthraquinones. Thus far, ~53 anthraquinones have been isolated and identified. The predominant anthraquinones are emodin-type anthraquinones, which include emodin, chrysophanol, physcion, aloe-emodin, rhein, obtusin, chryso-obtusin, aurantio-obtusin, obtusifolin, questin, 1-desmethylaurantio-obtusin, 1-desmethylobtusin, 1-desmethylchryso-obtusin, chrysophanol-10,10'-bianthrone, 1,2-dihydroxyanthraquinone, 2-hydroxyemodin-1-methylether, alaternin, 1,3-dihydroxy-6-methoxy-7-methyl anthraquinone, 1-hydroxy-3,7-diformyl anthraquinone, chrysarobin, 8-O-methylchrysophanol, 1-O-methylemodin, 1,2-dimethoxy-8-hydroxy-3-methyl-9,10-anthraquinone and l,2,7-trimethoxyl-6,8-dihydroxy-3-methylanthraquinone (compounds 1-24, respectively; Fig. 1); these have all been isolated from *Cassiae* semen (29-38). There are also many combined anthraquinones (compounds 25-46; Fig. 1), which have been isolated from the seeds of *C. obtusifolia* or *C. tora* (3,7,30,36,39-46).

Naphthopyrones. Naphthopyrones are the other characteristic components in *Cassiae* semen. In 1969, torachrysone, rubrofusarin and rubrofusarin-6-O-β-D-gentiobioside were isolated from *C. tora* seeds (compounds 47-49, respectively; Fig. 2) (47,48). Subsequently, toralactone, rubrofusarin triglucoside, cassiaside, nor-rubrofusarin gentiobioside, cassiaside B, cassiaside C, torachrysone apiglucoside, torachrysone gentiobioside, torachrysone tetraglucoside, cassiatoroside, demethylflavasperone gentiobioside and cassialactone gentiobioside were isolated from *C. tora* seeds (compounds 50-61, respectively; Fig. 2) (17,28,49-51). In addition, cassiaside B and cassiaside C were identified in the seeds of *C. obtusifolia* (52). Other naphthopyrones, including torosachrysone, isotoralactone, cassialactone, cassiaside B_2, cassiaside C_2, nor-rubrofusarin-6-O-β-D (6'-O-acetyl) glucopyranoside and l-hydroxyl-2-acetyl-3,8-dimethoxy-6-O-[β-D-apiofuranosyl-(l→2)-β-D-glucopyranosyl]-naphthalene were also isolated from *C. obtusifolia* seeds (compounds 62-68, respectively; Fig. 2) (19,53-55).

Volatile oils. Li (56) extracted the volatile oils from *Cassiae* semen by steam distillation, and subsequently identified 37 components according to the gas chromatography/mass spectrometry analysis. Among these peaks, the major volatile components were 9-octadecenoic acid (E) (22.15%), n-hexadecanoic acid (12.53%), 9,10-anthracenedione, 1,8-dihydroxy-3-methyl (7.66%), octadecanoic acid (4.56%) and 13-octadecenoic acid methyl ester (Z) (3.84%) (56).

Other compounds. A range of other components have been isolated from *Cassiae* semen, including malvalic acid, sterculic acid, mandelic acid, campesterol, aspidinol and 5,7-dihydroxychromone (compounds 69-74, respectively; Fig. 3) (5,57,58). In addition, the four flavonoid compounds, chrysin, chrysin-7-O-β-D-glucoside, galangin and cyanidenon, were also obtained and identified from *Cassiae* semen (compounds 75-78, respectively; Fig. 3) (58).

4. Pharmacology

Cassiae semen exerts a great variety of pharmacological activities due to its complex bioactive compounds. An overview of the pharmacological studies on *Cassiae* semen is presented in detail in the following sections.

Antihyperlipidemic activity. In traditional Chinese herbal medicine, *Cassiae* semen is used for the prevention and

Table I. Chemical compounds isolated from *Cassiae* semen.

Classification	No.	Chemical component	(Refs.)
Anthraquinones	1	Emodin	(37,38)
	2	Chrysophanol	(34)
	3	Physcion	(34)
	4	Aloe-emodin	(38)
	5	Rhein	(38)
	6	Obtusin	(35)
	7	Chryso-obtusin	(35)
	8	Aurantio-obtusin	(35)
	9	Obtusifolin	(35)
	10	Questin	(36)
	11	1-desmethylaurantio-obtusin	(36)
	12	1-desmethylobtusin	(36)
	13	1-desmethylchryso-obtusin	(36)
	14	Chrysophanol-10,10'-bianthrone	(36)
	15	1,2-dihydroxyanthraquinone	(7)
	16	2-hydroxyemodin-1-methylether	(7)
	17	Alaternin	(29)
	18	1,3-dihydroxy-6-methoxy-7-methyl anthraquinone	(30)
	19	1-hydroxy-3,7-diformyl anthraquinone	(30)
	20	Chrysarobin	(30,31)
	21	8-O-methylchrysophanol	(32)
	22	1-O-methylemodin	(32)
	23	1,2-dimethoxy-8-hydroxy-3-methyl-9,10-anthraquinone	(32)
	24	l,2,7-trimethoxyl-6,8-dihydroxy-3-methylanthraquinone	(33)
	25	Gluco-aurantioobtusin	(39)
	26	Emodin-6-glucoside	(30)
	27	Physcion-8-O-β-D-glucopyranoside	(7,40)
	28	Physcion-8-O-β-gentiobioside	(41)
	29	Emodin-1-O-β-gentiobioside	(41)
	30	Obtusifolin-2-O-β-D-glucoside	(42)
	31	Chysophanol-1-O-β-gentiobioside	(41)
	32	Alaternin-1-O-β-D-glucopyranoside	(7)
	33	Alaternin-2-O-β-D-glucopyranoside	(29)
	34	Aurantio-obtusin-6-O-β-D-glucopyranoside	(43)
	35	Chryso-obtusin-2-O-β-D-glucopyranoside	(7)
	36	Obtusifolin-2-O-β-D-(6'-O-acetyl) glucopyranoside	(44)
	37	Emodin-8-O-β-D-glucopyranoside	(45)
	38	2-methoxyl-chrysophanol-8-O-β-D-glucopyranoside	(46)
	39	1-demethylaurantio-obtusin-2-O-β-D-glucopyranoside	(43)
	40	1,7,8-trimethoxyl-2-hydroxyl-3-methylanthraquinone-2-O-β-D-glucopyranoside	(33)
	41	l,7-diinethoxyl-2,8-dihydroxyl-3-methylanthraquinone-2-O-β-D-glucopyranoside	(33)
	42	l,2,7-trimethoxyl-6,8-dihydroxy-3-methylanthraquinone-6-O-β-D-glucopyranoside	(33)
	43	2,8-dimethoxyl-l,6-dihydroxy-3-methylanthraquinone-6-O-β-D-glucopyranoside	(33)
	44	1-[(β-D-glucopyranosyl-(1→3)-O-β-glucopyranosyl-(1→6)-O-β-D-glucopyranosyl)oxy]-8-hydroxy-3-methyl-9,10-anthraquinone	(42)
	45	1-[(β-D-glucopyranosyl-(1→6)-O-β-glucopyranosyl-(1→3)-O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosyl)oxy]-8-hydroxy-3-methyl-9,10-anthraquinone	(42)
	46	4,6,7-trimethoxyl-aloe-emodin-8-O-β-D-glucopyranoside	(46)
Naphthopyrones	47	Torachrysone	(48)
	48	Rubrofusarin	(47)
	49	Rubrofusarin-6-O-β-D-gentiobioside	(47)

Table I. Continued.

Classification	No.	Chemical component	(Refs.)
	50	Toralactone	(49)
	51	Rubrofusarin triglucoside	(17)
	52	Cassiaside	(50)
	53	Nor-rubrofusarin gentiobioside	(17)
	54	Cassiaside B	(50)
	55	Cassiaside C	(50)
	56	Torachrysone apiglucoside	(17)
	57	Torachrysone gentiobioside	(17)
	58	Torachrysone tetraglucoside	(17)
	59	Cassiatoroside	(51)
	60	Demethylflavasperone gentiobioside	(17)
	61	Cassialactone gentiobioside	(28)
	62	Torosachrysone	(53)
	63	Isotoralactone	(53)
	64	Cassialactone	(53)
	65	Cassiaside B_2	(19)
	66	Cassiaside C_2	(19)
	67	Nor-rubrofusarin-6-O-β-D(6'-o-acetyl) glucopyranoside	(54)
	68	l-hydroxyl-2-acetyl-3,8-dimethoxy-6-O-[β-D-apiofuranosyl-(l→2)-β-D-glucopyranosyl]-naphthalene	(55)
Other compounds	69	Malvalic acid	(5,57)
	70	Sterculic acid	(5)
	71	Mandelic acid	(5)
	72	Campesterol	(5)
	73	Aspidinol	(58)
	74	5,7-dihydroxychromone	(58)
	75	Chrysin	(58)
	76	Chrysin-7-O-β-D-glucoside	(58)
	77	Galangin	(58)
	78	Cyanidenon	(58)

treatment of hyperlipidemia. Several Chinese herbal formulations containing *Cassiae* semen is available in the Chinese market for preventing the formation of atherosclerotic plaques (59). In certain Asian countries, including China and Korea, it is also commonly drunk as a roasted tea to reduce body weight (60,61). Previous studies using mice have evaluated the reductions in blood lipid contents induced by different *Cassiae* semen extracts obtained through different methods, including supercritical fluid extraction, systematic solvents (petroleum ether, ethyl acetate, n-butanol, 70% ethanol and water) and ethanol precipitation following water extraction. The results revealed that the n-butanol and ethyl acetate extracts were the most effective (62,63). In addition, the ethanol and aqueous extracts of *Cassiae* emen significantly decreased the serum levels of total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C), however, they increased the levels of high-density lipoprotein cholesterol (HDL-C) (13,64,65). Similarly, He *et al* (66) reported that treatment with the water extract form of *C. obtusifolia* seeds decreased the blood-lipid level by inhibiting cholesterol synthesis. Cho *et al* (67) demonstrated that soluble fibers from *C. tora* seeds markedly decreased liver TC and TG levels in rats fed with a high-cholesterol diet. The underlying mechanism may be mediated by increasing fecal bile acid excretion and downregulating the production of lipogenic enzymes (67). In addition, soluble fibers decreased the serum levels of TC, TG and LDL-C in patients with type II diabetes without serious adverse effects (2). Liu *et al* (68) revealed that the ethanol extract of *Cassiae* semen upregulated the expression levels of peroxisome proliferator-activated receptor (PPAR)-γ, sterol regulatory element-binding protein-1c, hormone-sensitive lipase and triacylglycerol hydrolase, however, tumor necrosis factor receptor superfamily member 6 was downregulated in adipose tissue. The anti-hyperlipidemia activity of *Cassiae* semen is primarily due to its antioxidant components, such as anthraquinones and polysaccharides. There are a variety of bioactive anthraquinone components in *Cassiae* semen, including chrysophanol, physcion, aurantio-obtusin, obtusifolin and emodin, which have been observed to decrease the levels of TC and TG (69,70). Previous studies have demonstrated that anthraquinones isolated from *Cassiae* semen

Table II. Pharmacological activities of *Cassiae* semen.

Pharmacological activities	Actions	Extracts/compounds	Application	(Refs.)
Anti-hyperlipidemia activity	Reduces blood lipid levels	SFE, systematic solvents (petroleum ether, ethyl acetate, n-butanol, 70% ethanol and water)	*In vivo*	(62,63)
	Decreases the levels of TC, TG and LDL-C; Increases the level of HDL-C	Ethanol and aqueous extracts	*In vivo*	(13,64,65)
	Inhibits the synthesis of cholesterol	Water extract	*In vitro*	(66)
	Increases fecal bile acid excretion and downregulates the production of lipogenic enzymes	Soluble fibers	*In vivo*	(67)
Anti-hyperlipidemia activity	Upregulates the expression levels of PPARγ, SREBP-1c, HSL and TGH; Downregulates the levels of FAS	Ethanol extract	*In vivo*	(68)
	Decreases TC and TG levels	Chrysophanol, physcion, aurantio-obtusin, obtusifolin and emodin	*In vitro*	(69,70)
	Decreases TC, TG and LDL-C levels; Increases HDL-C levels	Anthraquinones	*In vivo*	(73)
	Binds bile acids and reduces the absorption of cholesterol	Water-soluble polysaccharides	*In vitro*	(74)
Anti-diabetic activity	Inhibits AGEs activity	Cassiaside, cassiaside C, rubrofusarin-6-O-β-D-gentiobioside	*In vitro*	(15)
	Inhibits the expression of TGF-1 and ECM proteins	Rubrofusarin-6-O-β-D-gentiobioside, cassiaside	*In vitro*	(16)
	Inhibits AGEs accumulation and, RAGE and COX-2 expression	Methanol extract	*In vitro/vivo*	(75,76)
	Downregulates the expression of TGF-β1, CTGF and smad3, and upregulates the protein expression of smad6	Water extract	*In vivo*	(77)
Neuroprotective activity	Inhibits AChE activity	Ethanol extract	*In vivo*	(6)
	Upregulates the expression of pCREB and BDNF	Ethanol extract	*In vivo*	(78)
	Attenuates secondary calcium dysregulation and cell death	Ethanol extract	*In vivo*	(79)
	Ameliorates the Aβ-induced synaptic dysfunction model	Obtusifolin, alaternin	*In vivo*	(80)
	Inhibits cell damage and protects DA neuronal degeneration	Ethanol extract	*In vitro/vivo*	(81)
	Improves learning and memory capacity; Inhibits MDA and MAO levels; Enhances the level of SOD	Protein and anthraquinone glucosides	*In vivo*	(82)

Table II. Continued.

Pharmacological activities	Actions	Extracts/compounds	Application	Reference
Hepatoprotective activity	Hepatoprotective effects	Methanol extract	*In vitro*	(42,50)
	Increases the serum levels of SOD and decreases the serum levels of AST, ALT and MDA	Aqueous extract	*In vivo*	(85,86)
	Increases the serum levels of SOD and decreases the serum levels of TG, TC, MDA, AST and ALT	Ethanol extract	*In vivo*	(10,87)
Antibacterial activity	Anti-*Staphylococcus aureus;* Anti-*Escherichia coli* K12	Naphthalenes, anthraquinones	*In vitro*	(17)
	Exhibits fungicidal activity against *Botrytis cinerea*, *Erysiphe graminis*, *Phytophthora infestans*, *Puccinia recondita, Phacelia grisea, and Rhizoctonia solani*.	Anthraquinones	*In vitro*	(88)
	Anti-*Helicobacter pylori*	Ethanol and aqueous extracts	*In vitro*	(89)
	Anti-*Clostridium perfringens;* Anti-*E. coli*	1,2-dihydroxyanthraquinone	*In vitro*	(90)
	Anti-*Fusarium oxysporum;* Anti-*B. cinerea*	Chloroform extract	*In vitro*	(91)
Antioxidant activity	Accelerates the oxidation of deoxyribose; inhibits linoleic acid peroxidation	Water extract	*In vitro*	(92,93)
	Scavenges free oxygen radicals	Water extract	*In vitro*	(94)
	Inhibits superoxide radicals	Water-soluble polysaccharides	*In vitro*	(95)
	Decreases MDA serum levels	Water-soluble polysaccharides	*In vitro*	(96)
	Scavenges hydroxyl and superoxide radicals	Water-soluble polysaccharides	*In vitro*	(97)
	Scavenges DPPH radicals	Ethyl acetate fraction	*In vitro*	(98)
	Antioxidant effect	Methanol extract	*In vitro*	(12)
	Scavenges DPPH radicals	Alaternin, cassiaside and rubrofusarin-6-O-β-D-gentiobioside	*In vitro*	(100)
Hypotensive activity	Reduces arterial blood pressure	Water extract	*In vi*vo	(101)
	Hypotensive activity	Water extract	*In vivo*	(103)
	Decreases the blood pressure	Ethanol extract	*In vitro*	(104)
Other activities	Estrogenic activity	70% EtOH extract	*In vitro*	(105)
	Inhibits histamine release from mast cells	Cassiaside C_2	*In vitro*	(19)
	Anti-platelet aggregation	Gluco-aurantioobtusin	*In vitro*	(39)
	Antigenotoxic activity	Water extract	*In vitro*	(106)
	Antimutagenic activity	Anthraquinone aglycones and naphthopyrone glycosides	*In vitro*	(14)

Table II. Continued.

Pharmacological activities	Actions	Extracts/compounds	Application	Reference
	Improves myocardial function and attenuates MI/R-induced injury	Water extract	*In vivo*	(107)

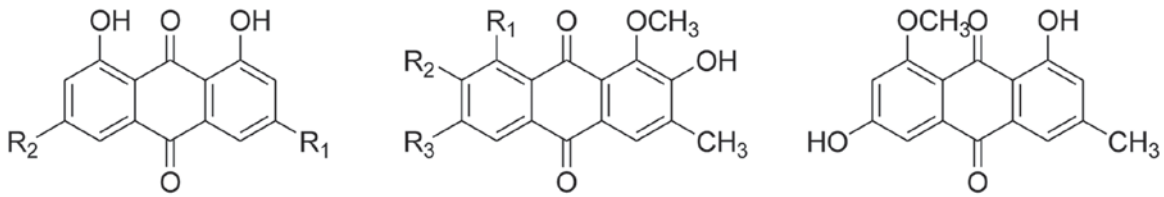
TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PPARγ, peroxisome proliferator-activated receptor; SREBP-1c, sterol regulatory element-binding protein-1c; HSL, hormone-sensitive lipase; TGH, triacylglycerol hydrolase; FAS, tumor necrosis factor receptor superfamily member 6; AGEs, advanced glycation end products; TGF-1, transforming growth factor-1; ECM, extracellular matrix; RAGE, receptor for advanced glycosylation end product; COX-2, cyclooxygenase-2; CTGF, connective tissue growth factor; Smad3/6, mothers against decapentaplegic homolog 3 and 6; AChE, acetylcholinesterase; pCREB, phosphorylated cyclic AMP response element binding protein; BDNF, brain-derived neurotrophic factor; DA, dopaminergic; MDA, malondialdehyde; MAO, monoamine oxidase; SOD, superoxide dismutase; AST, aspartate transaminase; ALT, alanine transaminase; DPPH, 1-diphenyl-2-picrylhydrazyl; MI/R, myocardial ischemia and reperfusion.

were effective substances during hypolipidemic activities (71,72). These results were verified by a previous study, which applied an experimental hyperlipidemic rat model to investigate anthraquinone treatment (80 and 20 mg/kg, per os, for 20 days). The TC, TG and LDL-C levels were significantly reduced in a dose-dependent manner, however, the levels of HDL-C increased. Inhibition of cholesterol synthesis may be one of the underlying mechanisms involved in decreasing blood lipid levels (73). Water-soluble polysaccharides (WSPs) from *Cassiae* semen markedly inhibited the activities of α-amylase and pancreatic lipase, however, protease activity increased. The results demonstrated that WSPs had the ability to bind to bile acids and reduce the absorption of cholesterol, indicating that WSPs may have potential as an effective herbal ingredient in functional food applications (74).

Antidiabetic activity. A number of studies have demonstrated that *Cassiae* semen exhibits anti-diabetic activity. A total of three naphthopyrone glucosides (compounds 49, 52 and 55) isolated from the butanol-soluble extract of *Cassia* semen have been evaluated for their inhibitory activity on advanced glycation end products (AGEs) formation *in vitro*. The results revealed that these compounds possessed more potent inhibitory activity against AGEs compared with the aminoguanidine positive control (15). In addition, rubrofusarin-6-O-β-d-gentiobioside (compound 49) and cassiaside (compound 52) significantly inhibited the expression of transforming growth factor (TGF)-1 and extracellular matrix protein in glomerular mesangial cells cultured under diabetic conditions, suggesting that the active compounds in *Cassiae* semen may be effective in the treatment of renal complications associated with diabetes (16). Similarly, Kim *et al* (75) evaluated the preventive effects of the methanol extract of *Cassia* semen (200 mg/kg/day, for 12 weeks) on the development of diabetic nephropathy in streptozotocin (STZ)-induced diabetic rats. The results indicated that oral treatment with the *Cassia* semen methanol extract inhibited the development of diabetic nephropathy by inhibiting AGEs accumulation, receptor for advanced glycosylation end product and cyclooxygenase-2 expression in the renal cortex of STZ-diabetic rats (75,76). In addition, Zhu (77) reported that the water extract of *Cassia* semen exhibited protective activity against STZ-induced renal fibrosis in diabetic rats. The underlying mechanisms may be associated with its ability to downregulate the expression of TGF-β1, connective tissue growth factor and mothers against decapentaplegic homolog 3 (smad3), as well as upregulating the protein expression of smad6 (77).

Neuroprotective activity. The ethanolic extract from the seeds of *C. obtusifolia* has been reported to have a neuroprotective effect in brain disease models. Kim *et al* (6) suggested that *C. obtusifolia* (25, 50 or 100 mg/kg) significantly attenuated scopolamine or transient bilateral common carotid artery occlusion (2VO)-induced memory impairment. These effects are mediated by the enhancement of the cholinergic nervous system via acetylcholinesterase inhibition in a dose-dependent manner [half maximal inhibitory concentration (IC_{50})=81.6 μg/ml] (6). In addition, *C. obtusifolia* (10 or 50 mg/kg/day) exhibited a neuroprotective effect in a mouse transient global ischemia model due to its anti-inflammatory properties and the induced upregulated expression of phosphorylated cyclic AMP response element binding protein and brain-derived neurotrophic factor (78).

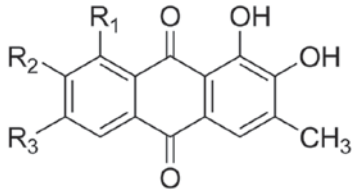
Drever *et al* (79) demonstrated that treatment with *C. obtusifolia* (0.1-10 μg/ml) significantly attenuated secondary calcium dysregulation and cell death induced by N-methyl-D-aspartate and 3-nitropropionic acid in mouse hippocampal cultures, and no significant effect on cell death was induced by incubation with naturally-secreted oligomers of amyloid (A)β. Yi *et al* (80) reported for the first time, that *C. obtusifolia* (10 μg/ml) ameliorated the Aβ-induced synaptic dysfunction model through anti-inflammatory and protein kinase B (Akt)/glycogen synthase kinase-3β pathways. The results suggested that the neuroprotective effect may be attributable to obtusifolin (compound 9) and/or alaternin (compound 17) (80). In a further experiment, *C. obtusifolia* (0.1-1 μg/ml) inhibited cell damage against oxidopamine (6-OHDA)-induced dopaminergic (DA) neural toxicity in PC12 cells through an anti-oxidant and antimitochondrial-mediated apoptosis mechanism. In a mesencephalic DA culture, *C. obtusifolia* (0.1-1 μg/ml) protected the DA cells against 6-OHDA- and N-methyl-4-phenylpyridinium iodide-induced



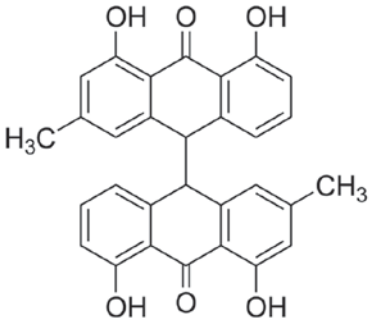
1 R_1=CH_3, R_2=OH
2 R_1=CH_3, R_2=H
3 R_1=CH_3, R_2=OCH_3
4 R_1=CH_2OH, R_2=OH
5 R_1=COOH, R_2=H

6 R_1=OH, R_2=OCH_3, R_3=OCH_3
7 R_1=OCH_3, R_2=OCH_3, R_3=OCH_3
8 R_1=OH, R_2=OCH_3, R_3=OH
9 R_1=OH, R_2=H, R_3=H

10



11 R_1=OH, R_2=OCH_3, R_3=OH
12 R_1=OH, R_2=OCH_3, R_3=OCH_3
13 R_1=OCH_3, R_2=OCH_3, R_3=OCH_3



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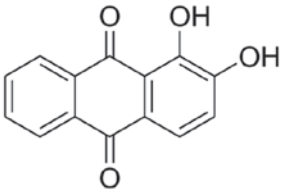

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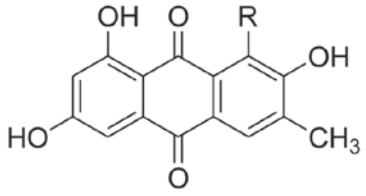
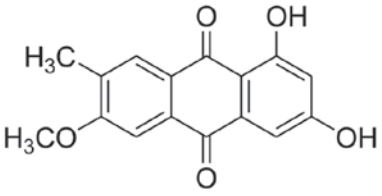


16 R=OCH_3
17 R=OH



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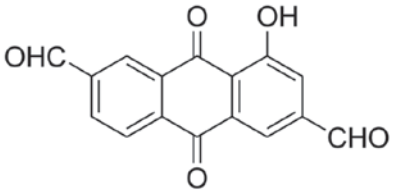

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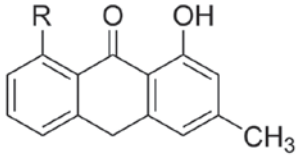
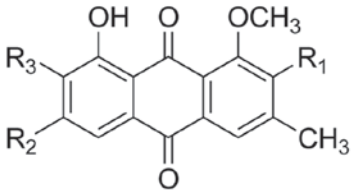
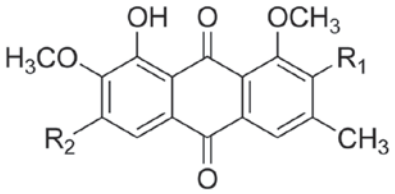


20 R=OH
21 R=OCH_3



22 R_1=H, R_2=OH, R_3=H
23 R_1=OCH_3, R_2=H, R_3=H
24 R_1=OCH_3, R_2=OH, R_3=OCH_3

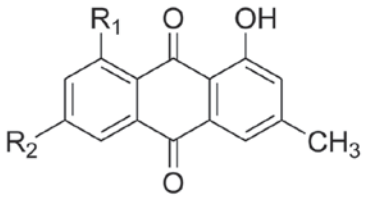


25 R_1=OH, R_2=O-glc

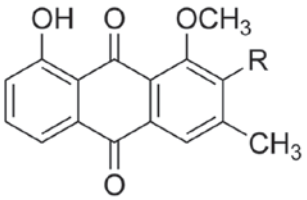
Figure 1. Chemical structures of anthraquinones.

toxicities. In addition, *C. obtusifolia* (50 mg/kg/day for 15 days) significantly protected DA neuronal degeneration in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse Parkinson's disease (PD) model by inhibiting the movement impairment and the loss of DA neurons, indicating that *C. obtusifolia* may be a useful neuroprotective candidate for PD (81). In addition, protein and anthraquinone glucosides from *Cassia* semen improved learning and memory capacity, inhibited the malondialdehyde (MDA) and monoamine oxidase levels, and enhanced the level of superoxide dismutase (SOD) in the cerebrum of senile mice (82).

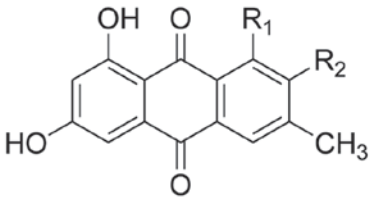
Hepatoprotective activity. It was recorded in the Compendium of Materia Medica that *Cassiae* semen exhibited the functions



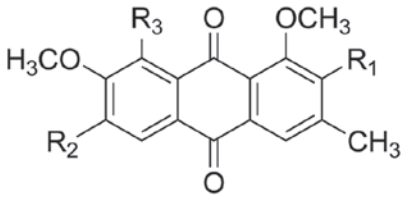
26 R_1=OH, R_2=O-glc
27 R_1=O-glc, R_2=OCH_3
28 R_1= O-glc-glc, R_2=OCH_3
29 R_1= O-glc-glc, R_2=H



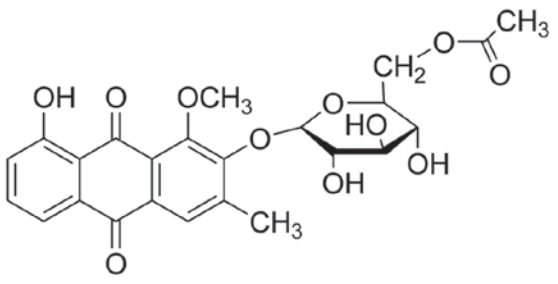
30 R= O-glc



31 R_1= O-glc-glc, R_2=H
32 R_1= O-glc, R_2=OH
33 R_1=OH, R_2=O-glc



34 R_1=OH, R_2= O-glc, R_3=OH
35 R_1= O-glc, R_2=OCH_3, R_3=OCH_3



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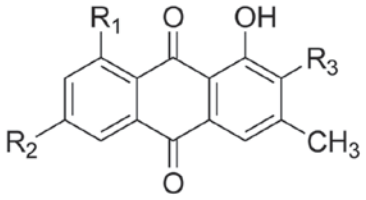
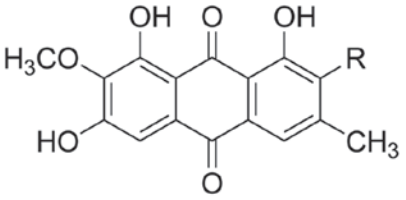
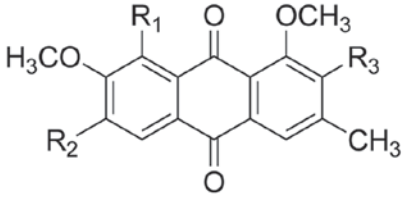


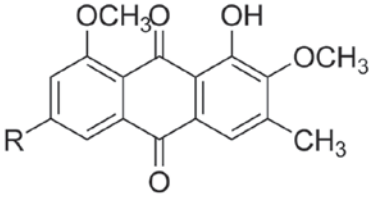
37 R_1= O-glc, R_2=OH, R_3=H
38 R_1= O-glc, R_2=H, R_3=OCH_3



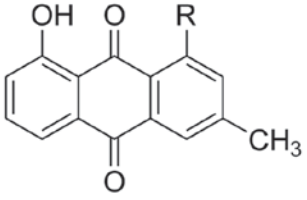
39 R= O-glc



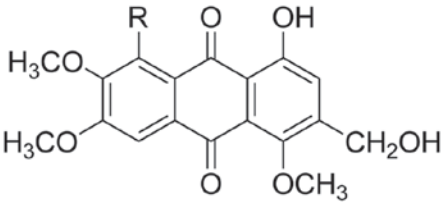
40 R_1=OCH_3, R_2=H, R_3= O-glc
41 R_1=OH, R_2=H, R_3= O-glc
42 R_1=OH, R_2= O-glc, R_3=OCH_3



43 R= O-glc

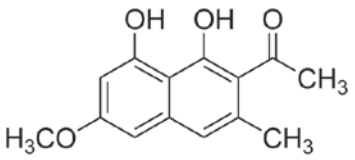


44 R= O-glc-glc-glc
45 R= O-glc-glc-glc-glc



46 R= O-glc

Figure 1. Continued. Chemical structures of anthraquinones.



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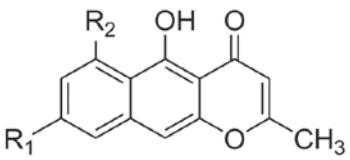
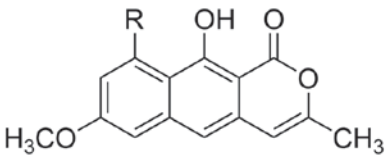
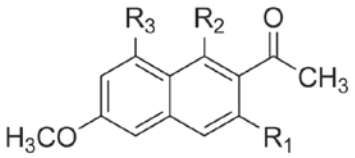


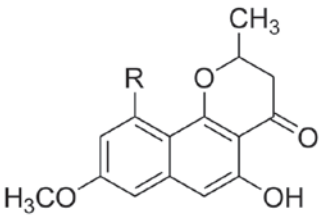
48 R_1=OCH_3; R_2=OH
49 R_1= OCH_3; R_2=O-glc-glc
50 R_1= OCH_3; R_2= O-glc-api
51 R_1= OCH_3; R_2= O-glc-glc-glc
52 R_1=OH; R_2=O-glc
53 R_1=OH; R_2= O-glc-glc



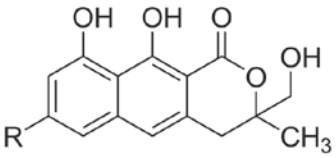
54 R=OH
55 R= O-glc-glc



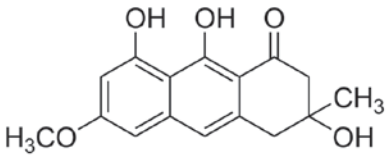
56 R_1=CH_3; R_2=OH; R_3=O-glc-api
57 R_1= CH_3; R_2=OH; R_3= O-glc-glc
58 R_1= CH_3; R_2=OH; R_3= O-glc-glc-glc-glc
59 R_1=O-api; R_2=OCH_3; R_3=O-glc



60 R= O-glc-glc



61 R=O-glc-glc



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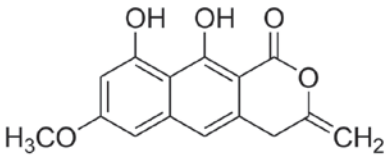

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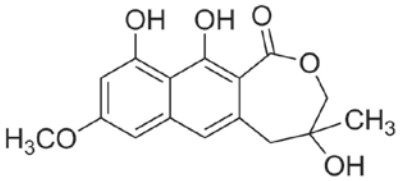

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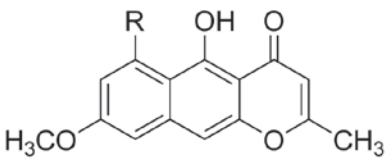
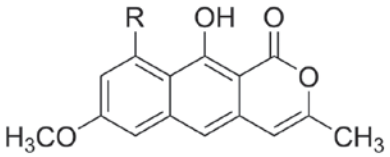
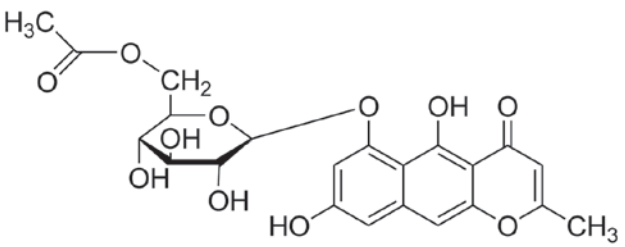


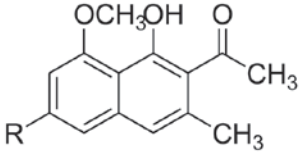
65 R= O-glc-glc-glc-glc



66 R= O-glc-glc-glc-glc



67



68 R=O-glc-api

Figure 2. Chemical structures of naphthopyrones.

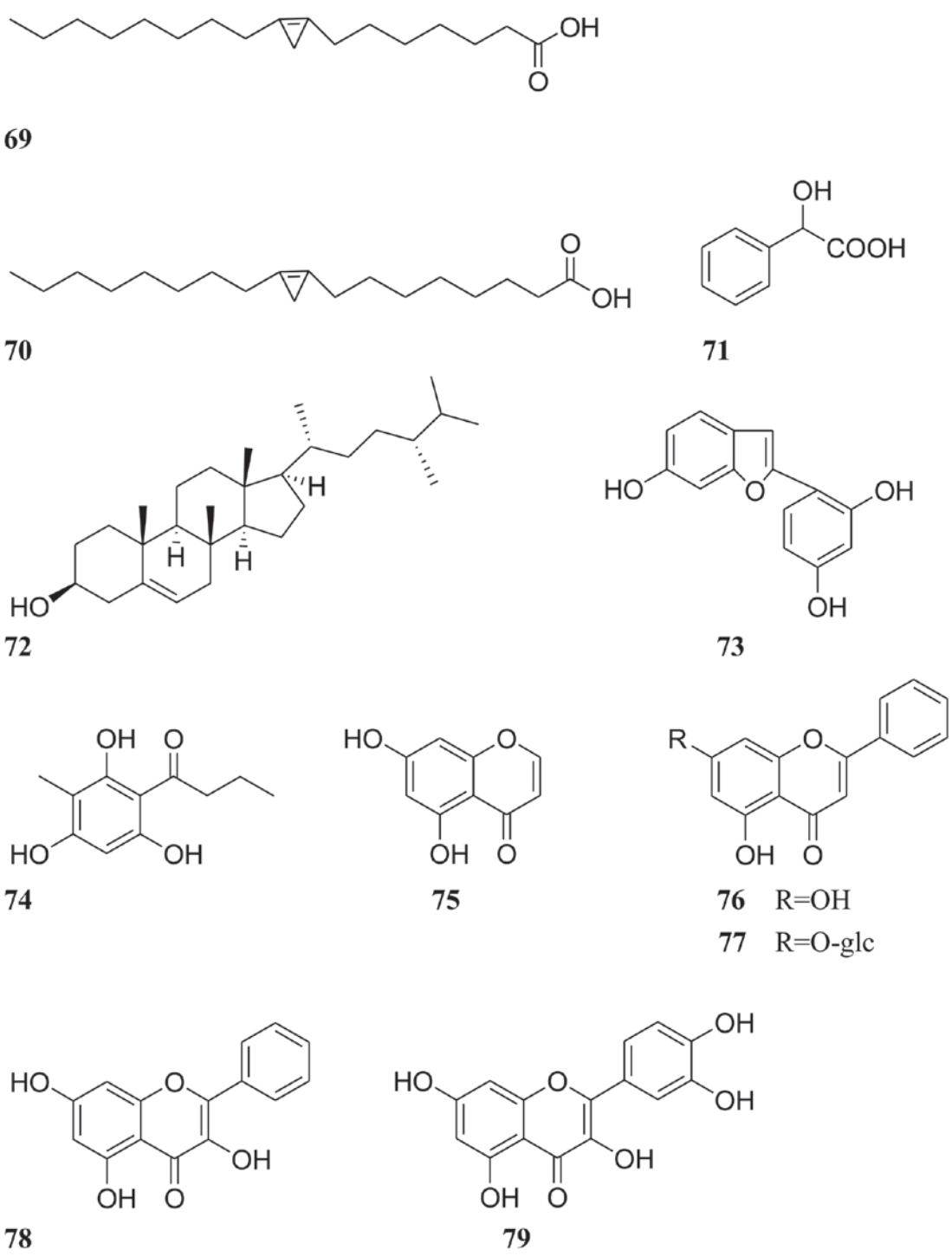


Figure 3. Chemical structures of other compounds.

of nourishing the liver and improving vision (83). In Korea, the aqueous extract of *C. tora* L. seeds has been used for the protection of the liver. A weak anti-hepatotoxic activity in CCl_4-induced mice was observed when the drug was administered orally at a dose of 670 mg/kg (84). The methanol extract of *C. tora* L. seeds exhibited significantly protective effects in primary cultured hepatocytes against CCl_4 and toxicity. A total of two anthraquinone glycosides (compounds 44 and 45) and three naphthoypyrone glycosides (compounds 49, 51 and 53) from the methanol extract of *C. tora* seeds were the primary chemical constituents (42,50). The preventative effects of *Cassiae* semen on acute liver injury in mice induced by CCl_4 have also been investigated (85,86). When compared with the control group, varying concentrations of the aqueous extract of *Cassiae* semen significantly increased the serum levels of SOD, and decreased the serum levels of aspartate transaminase (AST), alanine transaminase (ALT) and MDA. These results indicate that *Cassiae* semen is potentially beneficial in the treatment or prevention of hepatic damage (85,86). In addition, the ethanol extract of *Cassiae* semen has been observed to increase the serum levels of SOD and to decrease the serum levels of TG, TC, MDA, AST and ALT (86). Total

anthraquinones from *Cassiae* semen exhibited a protective effect on alcohol-induced acute liver injury in mice by regulating fat metabolism, improving liver function and increasing the mRNA and protein expression levels of PPAR-γ (10,87).

Antibacterial activity. Antibacterial activity, an important effect of *Cassiae* semen, has been comprehensively investigated. Naphthalenes (compounds 47 and 50) and anthraquinones (compounds 1, 4 and 5) isolated from *C. tora* seeds exhibited significant antibacterial effects on four strains of methicillin-resistant *Staphylococcus aureus* [minimal inhibitory concentration (MIC) was 2-64 μg/ml] and a strain of methicillin-sensitive *S. aureus*. In addition, rhein (compound 5) and torachrysone (compound 47) from the seeds of *C. tora* exhibited antibacterial activity against *Escherichia coli* K12 with MIC values of 512 and 128 μg/ml, respectively (17). Kim *et al* (88) were the first to demonstrate that emodin (compound 1) from *C. tora* seeds has a median lethal dose (LC_{50}) value of 0.102, 0.163, 0.385 and 0.046 g/l against *Rhizoctonia solani*, *Botrytis cinerea*, *Phytophthora infestans* and *Erysiphe graminis*, respectively, and physcion (compound 3) has an LC_{50} value of 0.248, 0.263, 0.518, and 0.073 g/l against *R. solani*, *B. cinerea*, *P. infestans* and *E. graminis*, respectively. In addition, the LC_{50} value of rhein (compound 5) is 0.375, 0.478, and 0.047 g/l against *R. solani*, *B. cinerea* and *P. infestans*, respectively (88).

It has been reported that ethanol and aqueous extracts of *C. obtusifolia* seeds were inhibitory against *Helicobacter pylori* strains (MIC were 100 and 60 μg/ml, respectively) (89). In addition, 1,2-dihydroxyanthraquinone (compound 15) isolated from *C. obtusifolia* seeds was revealed to inhibit the growth of *Clostridium perfringens* and *E. coli*., indicating that this drug exhibited potent growth-inhibiting activities towards human intestinal bacteria (90). Li *et al* (91) demonstrated that the chloroform extract of the seeds of *C. obtusifolia* also exhibited different inhibitory activities against *Fusarium oxysporum* and *B. cinerea* (IC_{50} values were 0.57 mg/ml and 0.97 mg/ml).

Antioxidant activity. The water extract of *C. tora* seeds accelerated the oxidation of deoxyribose induced by Fe^{3+}-EDTA/H_2O_2 and exhibited 94% inhibition of linoleic acid peroxidation at a concentration of 0.2 mg/ml. The underlying mechanisms of this may be mediated by reducing metal ions, scavenging hydroxyl radical and chelating ferrousion (92,93). Xv and Hu (94) demonstrated that the water extract of *Cassiae* semen exhibited a potent ability to scavenge free oxygen radicals [IC_{50} values were 2 mg/ml and 2 μg/ml for hydroxyl radicals (OH^-) and hydrogen peroxide (H_2O_2), respectively]. WSP from *Cassiae* semen (0.022 mg/ml) effectively inhibited superoxide radicals (O^{2-}) induced by pyrogallol autoxidation (95). The inhibitory effects of WSP on serum levels of MDA were used to evaluate its antioxidation capabilities. The results demonstrated that WSP decreased MDA serum levels with an IC_{50} value of 15.80% (96). In another study, Liu *et al* (97) optimized the extraction conditions for WSP of *Cassiae* semen (temperature 80˚C, extraction time 3.5 h, solid-liquid ratio 1:30) and observed that WSP (94.03 μg/ml) had the ability to scavenge hydroxyl and superoxide radicals with scavenging rates of 43.32 and 64.97%, respectively.

In addition, ethyl acetate fraction and n-butanol fraction of *Cassiae* semen were evaluated by DPPH radical scavenging activity. The results revealed that the ethyl acetate fraction had a lower IC_{50} value of 56.4 g/ml, when compared with the value of 80.6 g/ml for n-butanol fraction. 1-Desmethylaurantio-obtusin (compound 11) exhibited good scavenging activity on DPPH with an IC_{50} value of 4.5±0.7 g/ml, while aurantio-obtusin-6-O-β-D-glucopyranoside (compound 34) and questin (compound 10) exhibited moderate antioxidant activity, and their IC_{50} values were 103.2±1.5 g/ml and 185.2±1.8 g/ml, respectively. When compared with these results, chryso-obtusin (compound 7) and aurantio-obtusin (compound 8) demonstrated weaker antioxidant activity (IC_{50} >200 μg/ml) (98). The methanolic extract of *C. tora* seeds exhibited a high antioxidant activity on lipid peroxidation (99). Similarly, in another study, Yen *et al* (12) demonstrated that the methanolic extract of *C. tora* seeds exerted a greater antioxidant activity than the other organic solvents (n-hexane and ethyl acetate). Emodin was also revealed to be an antioxidative component (12). In addition, alaternin (compound 17), cassiaside (compound 52) and rubrofusarin-6-O-β-D-gentiobioside (compound 49) isolated from *C. tora* seeds exhibited good scavenging activity against DPPH radicals with IC_{50} values of 17.59, 32.52 and 18.04 μg/ml, respectively (100).

Hypotensive activity. Aqueous and ethanol extracts of *Cassiae* semen have been reported to possess hypotensive effects (101). Koo *et al* (101) reported that the water extract of *C. tora* seeds (3.75, 7.5, 15, 30, 60 and 250 mg/kg) consistently reduced arterial blood pressure in anesthetized rats. A potential reflex mechanism of this hypotensive action may involve a vagal reflex, which reciprocally inhibits the peripheral vasomotor tone via a reflex reduction in the sympathetic neural outflow to blood vessels (102). In addition, the media portion of the medullary reticular formation has been revealed to be directly involved in the hypotensive effect of *C. tora* seeds (103). Furthermore, the ethanol extract of *Cassiae* semen significantly decreased blood pressure in hypertensive rats by inhibiting receptor-controlled calcium channels on vessels and regulating the secretion of nitric oxide and inducible nitric oxide synthase (104).

Other activities. In addition to the pharmacological effects described above, *Cassiae* semen and its ingredients have other pharmacological effects, including estrogenic, anti-allergic, antigenotoxic, anti-aggregatory, antimutagenic and cardioprotective effects. Some of these effects are discussed briefly below.

The estrogenic activity of *C. obtusifolia* seeds was evaluated by a recombinant yeast screening assay. The results revealed that 70% EtOH extracts of this drug exhibited estrogenic relative potency [half maximal effective concentration (EC_{50}) was 60.2 μg/ml) (105). Cassiaside C_2 (compound 66) isolated from *C. obtusifolia* seeds exhibited a potent anti-allergic activity by inhibiting the histamine release from mast cells induced by antigen-antibody reaction (19). Furthermore, gluco-aurantioobtusin (compound 25) from *C. obtusifolia* seeds possessed potent inhibitory activities against arachidonic-acid-, ADP- and collagen-induced platelet aggregations (39). Wu and Yen (106) demonstrated that the water extract of *C. tora* seeds exhibited potential

antigenotoxic activities against the dietary mutagens Glu-P-1 and TrpP-1 in the Ames test and the Comet assay. The potential mechanisms may be associated with neutralization of the reactive intermediate of Trp-P-1 and an antioxidant effect of the tested compounds (106). Anthraquinone aglycones (compounds 2, 7 and 8) and naphthopyrone glycosides (compounds 49 and 52) from *C. tora* seeds exhibited significant antimutagenic activity *in vitro*. The mechanism associated with these compounds may be mediated via interactions with a microsomal activating system (14). Fu *et al* (107) reported that the water extract of *Cassiae* semen (10 mg/kg/day, for one week) effectively improved myocardial function, and attenuated myocardial ischemia and reperfusion-induced injury and apoptosis in diabetic animals, which is potentially attributable to the reduced plasma lipid levels and the triggered cell survival Akt and extracellular signal-regulated kinases 1/2 signaling.

5. Conclusions

In traditional Chinese medicine, *Cassiae* semen has long been used to clean the liver, brighten the eye, loosen the bowel to relieve constipation, and for the treatment of inflammation, photophobia, headaches, dizziness, hyperlipemia and Alzheimer's disease. In addition, *Cassiae* semen is commonly used in the composition of other herbs. Although modern experiments have confirmed that this drug alone exhibits multiple pharmacological activities, it is important to investigate the molecular mechanisms of *Cassiae* semen combined with other herbs based on traditional uses.

A number of studies have investigated the effective constituents of *Cassiae* semen from different batches and geographical areas. HPLC-fingerprint chromatography is a common method to compare the differences (108-111). Zhang *et al* (3) developed a sensitive and reliable ultra-high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPLC-ESI-MS/MS) method to evaluate the quality of *Cassiae* semen through simultaneous determination of 13 components, providing a novel basis for the overall assessment of the quality of this plant. In addition, a novel nonaqueous capillary electrophoresis method was used for the analysis of aurantio-obtusin, emodin and rhein in *Cassiae* semen with satisfactory results (112). Yang *et al* (113) was the first to simultaneously determine 7 anthraquinones in rat plasma by UHPLC-MS/MS following oral administration of *Cassiae* semen extract. These results may support investigations into the bioactivity mechanism and clinical application of this drug (113). Anthraquinones and naphthopyrones are considered to be the major constituents. Therefore, characteristic compounds or a biological index should be established to evaluate the quality and ensure their clinical application is suitable. In the Pharmacopoeia of the People's Republic of China, chrysophanol and aurantio-obtusin are used as the indicator compounds to characterize the quality of *Cassiae* semen with the minimum contents of 0.20 and 0.080%, respectively (1).

A total of 79 compounds including anthraquinones, naphthopyrones and volatile oil have been isolated and identified from *Cassiae* semen (Table I; Figs. 1-3). It has also been suggested that certain efforts should be made to isolate and identify novel compounds from *Cassiae* semen, in order to strengthen its pharmacological profile to develop it further as a candidate for novel drug developments in the future.

Pharmacological studies have revealed that *Cassiae* semen possesses a variety of biological effects, including anti-hyperlipidemic, anti-diabetic, neuroprotective, hepatoprotective, antimicrobial, anti-oxidant and hypotensive activities (5,90,93,114,115). Extracts and compounds responsible for the pharmacological properties have also been determined, as presented in Table II. Although the pharmacological properties of certain traditional uses of *Cassiae* semen have been validated, these studies were primarily conducted *in vitro* (16,116,117). Therefore, the effects of these compounds require verification *in vivo*. In addition, the association between structure and activity, and the potential synergistic action exerted by the bioactive compounds requires further elucidation. It is anticipated that the comprehensive and current research on the pharmacological activities of extracts, as well as on active molecules isolated from *Cassiae* semen, provided in this review will inspire novel strategies in therapeutics for curing a number of different ailments.

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