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Review

Natural Compounds with Antioxidant Activity: Recent Findings from Studies on Medicinal Plants†

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Abstract – Reactive oxygen species potentially cause damage to cellular components including lipids, protein and DNA; this oxidative damage plays a key role in the pathogenesis of neurodegenerative disease, cardiovascular disease, metabolic disease and cancer. On the basis of the oxidative stress hypothesis, a number of studies have been performed to search for an efficient and safe antioxidant. Although in vitro studies have provided promising results, only a limited number of natural and synthetic antioxidants have been developed for clinical application due to their low efficacy and side-effects. Thus, the discovery of new antioxidants with marked efficacy and safety has attracted worldwide attention in recent decades. Since plants are recognized as important sources of natural antioxidants, our research has focused on the discovery of new naturally occurring antioxidants from medicinal plants. The purpose of this review is to open a new prospect in the field of search for natural antioxidants from medicinal plants by summarizing our recent findings. Using in vitro bioassay systems such as 2,2-diphenyl-1-picrylhydrazyl, superoxide radical scavenging tests and lipid peroxidation models, we have tested over than 350 species of medicinal plants for their antioxidant activity and selected several of them for further investigation. During the research on the discovery of effective natural antioxidants from the medicinal plants selected, we have isolated several new and known antioxidant compounds that include stilbene glycosides, phenolic glycosides, flavonoids, oligostilbenes, and coumarins. Our results suggest that the presence of antioxidant compounds in the medicinal plants might be associated with the traditional use to treat inflammation, cardiovascular disease and various chronic diseases.

Keywords – Reactive oxygen species, Natural antioxidants, Medicinal plants, Stilbene glycosides, Phenolic glycosides, Flavonoids, Oligostilbenes, Coumarins

Introduction

Reactive oxygen species (ROS) are highly reactive due to the presence of unstable electrons. Superoxide radical (O_2^-), one of the most well-known ROS, is produced under normal metabolism of oxygen by NAD(P)H oxidase, cyclooxygenase (COX), lipoxygenase (LOX), xanthine oxidase (XO) and the mitochondrial ubiquinone-cytochrome b cycle (Augustyniak *et al*., 2010). The O_2^- is then stabilized by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2), which is further neutralized to H_2O by catalase, glutathione peroxidase (GPX), or via the Fenton reaction (Augustyniak *et al*., 2010). Although the H_2O_2 is not a free radical, it is recognized as a ROS because of its ability to generate hydroxyl radical (HO·), the most reactive and harmful ROS. Lipid peroxidation is a well known consequence of the reaction of HO· with lipid molecules. The process of lipid peroxidation is initiated by the abstraction of a hydrogen atom from an unsaturated fatty acyl chain. Under aerobic conditions, the carbon-scentered lipid radical (L·) reacts with oxygen to give rise to a lipid peroxyl radical (LOO·), which further propagates the peroxidation chain reaction by taking a hydrogen atom from other unsaturated fatty acids (Davies, 2000). The resulting lipid hydroperoxide (LOOH) can decompose into several ROS including lipid alkoxyl radical (LO·), lipid epoxides, and aldehydes (e.g. malonyldialdehyde, 4-hydroxynonenal) (Davies, 2000). Since polyunsaturated fatty acids in cell membranes are particularly vulnerable to this process, it is speculated that the lipid peroxidation by ROS is detrimental to cellular functions and leads to further problems. Similar oxidative

†Dedicated to professor KiHwan Bae for his leading works on bioactive natural products.

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damage can occur in other biomolecules including proteins, sugars and DNA (Evans and Halliwell, 1999). Several lines of evidence indicate that the formation of oxidized proteins and DNA adducts in severe oxidative conditions may not undergo appropriate degradation and replacement/repair, and may instead cross-link with one another or form covalent bonds, which cause an inflammatory immune responses and cell death (Davies, 2000). Therefore, oxidative damage of the cellular components including lipids, proteins and DNA has been implicated in the pathogenesis of neurodegenerative disease, cardiovascular disease, metabolic disease, cancer and aging (Evans and Halliwell, 1999; Kamat *et al*., 2008; Roberts and Sindhu, 2009).

On the basis of the oxidative stress hypothesis in various degenerative diseases and aging, a number of studies have been performed to search for an efficient and safe antioxidant. Although in vitro studies have provided promising results, only a limited number of natural and synthetic antioxidants have been developed for clinical application due to their low efficacy and side-effects (Augustyniak *et al*., 2010). Thus, the discovery of new antioxidants with high efficacy and safety has attracted worldwide attention in recent decades (Augustyniak *et al*., 2010). Natural products have attracted our attention to develop new antioxidants because of our belief that natural antioxidants are better and safer than synthetic ones. Plants provide a rich source of natural antioxidants. Since plants generate ROS as by-products in the photosynthetic process, it is assumed that they have a defensive system of secondary metabolic products to protect themselves from oxidative damage (Augustyniak *et al*., 2010). Accordingly, plants are recognized as an important resource containing antioxidants and so it would be meaningful to seek antioxidants from plants (Augustyniak *et al*., 2010). Since medicinal plants have been clinically used for a long time, with regard to safety, our study has focused on the discovery of new naturally occurring antioxidants from medicinal plants. The purpose of this review is to open a new prospect in the field of search for natural antioxidants from medicinal plants by summarizing our recent findings. Here, we provide with our representative results chronologically focusing on the chemical structures of antioxidant compounds isolated from several medicinal sources, along with their in vitro antioxidant properties.

Sorbus commixta – *Sorbus commixta* Hedlund (Rosaceae) is a shrub growing in the base of mountainous regions and usually grows 6-8 m in height. The stem barks of *S. commixta* have been used in traditional medicine as a tonic and to treat various respiratory diseases (Bae, 2001). The fruits have also been used as a laxative as well as a gargle for sore throats, inflamed tonsils and hoarseness (Bae, 2001). The biphenyls acuparin and its 2'- and 4'-oxygenated derivatives have been reported as phytoalexins of the genus *Sorbus* (Kokubun *et al*., 1995). Previous phytochemical investigations on this plant have resulted in the isolation of triterpenes, lignans and flavonoids (Na *et al*., 2002). Recently, its extract was demonstrated to have beneficial effects on atherosclerosis (Sohn *et al*., 2005) and a protective effect on hepatic lipid peroxidation in an acute-alcohol treated model (Lee *et al*., 2006a). In our preliminary tests, a MeOH extract from the stem barks of *S. commixta* showed DPPH radical scavenging activity. Bioassay-guided fractionation of the MeOH extract led to the isolation of two flavanol glycosides, whose structures were determined as catechin-7-*O*-β-D-xylopyranoside and catechin-7-*O*-β-D-apiofuranoside (Fig. 1) (Na *et al*., 2002). As shown in Table 1, two isolates scavenged the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and O_2^- radicals effectively and inhibited the lipid peroxidation as well (Na *et al*., 2002).

Pleuropterus ciliinervis – As part of an ongoing study to identify novel antioxidant compounds from medicinal plants, the roots of *Pleuropterus ciliinervis* Nakai (Polygonaceae) were found to have strong antioxidant activity. The roots of *P. ciliinervis* have been used in traditional medicine, known as "Hasuo", to treat inflammation, bacterial infections, suppurative dermatitis and gonorrhea (Namba, 1993; Xiao *et al*., 2002). Stilbenes, anthraquinones and flavonoids have been isolated from the genus *Pleuropterus* (Han and Cho, 1981; Yoshizaki *et al*., 1987; Tang and Eisenbrand, 1992). Twelve compounds including two new stilbenes, (*E*)-pieceid-2"-*O*-gallate and (*E*)-pieceid-2"-*O*-coumarate, a new naphthopyrone, pleuropyrone A and nine known compounds including, *trans*-resveratrol, pieceid, (±)-catechin, (–)-lyoniresinol-3a-*O*-β-D-glucopyranoside, (+)-lyoniresinol-3a-*O*-β-D-glucopyranoside, stigmast-4-en-3-one, β-sitosterol, physcion and emodin were isolated from the roots of *P. ciliinervis* (Fig. 1). The isolates were tested for their antioxidant scavenging effects on DPPH and superoxide radicals in addition to their ability to inhibit lipid peroxidation. Of these, (*E*)-pieceid-2"-*O*-gallate exhibited potent antioxidant scavenging activity against DPPH and O_2^- radicals, and inhibited lipid peroxidation (Table 1). Our results show that the galloyl group in stilbene plays an essential role in antioxidant activity, while the glycosylation of stilbene reduces the activity (Lee *et al*., 2003; Min *et al*., 2003).

Table 1. Antioxidant activities of natural compounds isolated from medicinal plants

Affiliation	Compounds	Radical scavenging activities				Inhibitory activities		Reference
		DPPH (IC_{50})	O_2 (IC_{50})	$ABTS^{\bullet+}$ (IC_{50})	NO (% inhibition)	Lipid peroxidation (IC_{50})	Soybean lipoxygenase type I (IC_{50})	
Stilbene	piceatannol	82.6 ± 5.3 32.5 ± 0.6	49.5 ± 5.0			0.8 ± 0.01 15.1 ± 0.72	66.1 ± 2.49	Na *et al*., 2009; Do *et al*., 2009
	pieceid	82.4				67.2		Lee *et al*., 2003
	resveratrol	38.9 81.2 ± 1.2	51.1			3.3 28.9 ± 0.60	22.5 ± 0.53	Lee *et al*., 2003; Do *et al*., 2009
	(*E*)-pieceid-2-*O*-gallate	16.5	23.9			4.3		Lee *et al*., 2003
	(E)-pieceid-2-*O*-coumarate	84.3	74.6			5.1		Lee *et al*., 2003
Oligostilbene	(+)-ampelopsin A	> 250				> 250	27.4 ± 0.08	Do *et al*., 2009
	(+)-ampelopsin F	207.5 ± 2.8				> 250	17.2 ± 0.27	Do *et al*., 2009
	cis-amurensin B	175.1 ± 1.1				44.3 ± 0.80	16.3 ± 0.52	Do *et al*., 2009
	trans-amurensin B	121.2 ± 1.1				39.6 ± 1.10	12.1 ± 0.32	Do *et al*., 2009
	r-2-viniferin	103.5 ± 1.6				31.9 ± 0.40	6.39 ± 0.08	Do *et al*., 2009
	trans-ε-viniferin	62.5 ± 0.8				36.1 ± 0.90	16.9 ± 0.23	Do *et al*., 2009
Flavonoid	isoliquiritigenin	> 200	185.8 ± 15.6			15.0 ± 1.0		Na *et al*., 2009
	2',4'-dihydroxy-4-methoxychalcone	> 200	> 200			22.4 ± 2.7		Na *et al*., 2009
	(+)-catechin	42.7 ± 2.8 22.6 ± 2.1	56.8 ± 5.9 3.8 ± 0.6	2.93 ± 0.1		16.2 ± 0.9		Na *et al*., 2009; Thuong *et al*., 2010a
	catechin-7-*O*-β-D-xylopyranoside	3.6 ± 0.2	8.5 ± 0.9			9.0 ± 0.8		Na *et al*., 2002
	catechin-7-*O*-β-D-apiofuranoside	4.0 ± 0.3	9.2 ± 1.0			9.2 ± 0.9		Na *et al*., 2002
	afzelin	123.5 ± 3.7	116.1 ± 7.9			33.7 ± 2.1		Na *et al*., 2009
	myricetin-3-*O*-(2''-*O*-galloyl)--L-rhamnopyranoside	20.2 ± 1.1	21.4 ± 3.1			7.9 ± 0.7		Na *et al*., 2009
	myricitrin	32.7 ± 0.9	64.0 ± 4.9			11.3 ± 0.7		Na *et al*., 2009
	quercetin	9.4 ± 2.1						Do *et al*., 2009
	quercitrin	44.3 ± 1.3	71.6 ± 4.5			13.8 ± 0.9		Na *et al*., 2009
	syringetin-3-*O*-rutinoside	96.5 ± 2.3	159.1 ± 7.4			49.0 ± 2.3		Na *et al*., 2009
	syringetin-3-*O*-(2''-*O*-galloyl)-rutinoside	43.5 ± 2.2	69.1 ± 2.4			19.3 ± 1.2		Na *et al*., 2009
	gossypetin-8-*O*-β-D-xylopyranoside	35.3 ± 4.1	5.5 ± 0.5		41.7 ± 0.2			Thuong *et al*., 2007
	rhodalidin	> 100	40.1 ± 6.6		43.4 ± 10.8			Thuong *et al*., 2007
	rhodalin	> 100	17.7 ± 0.8		39.0 ± 13.6			Thuong *et al*., 2007
Coumarin	aesculetin	17.2 ± 2.8	2.3 ± 0.4	2.45 ± 0.02		15.8 ± 1.9		Thuong *et al*., 2010a
	aesculin	> 200	> 200	0.38 ± 0.02				Thuong *et al*., 2010a
	fraxetin	39.9 ± 2.8	1.1 ± 0.2	0.85 ± 0.01		26.3 ± 2.1		Thuong *et al*., 2010a
	fraxin	> 200	> 200	0.41 ± 0.03				Thuong *et al*., 2010a
	scopoletin	> 200	> 200	1.57 ± 0.02		93.5 ± 6.9		Thuong *et al*., 2010a
	daphnetin	20.6 ± 2.3	3.2 ± 0.4	2.15 ± 0.2		17.8 ± 2.2		Thuong *et al*., 2010a
	umbelliferone	> 200	26.7 ± 2.8	0.53 ± 0.05		187.2 ± 13.1		Thuong *et al*., 2010a
	cleomiscosin A	> 200	29.2 ± 1.7	1.03 ± 0.08				Jin *et al*., 2007
	cleomiscosin C	> 200	6.7 ± 0.9	2.07 ± 0.04				Jin *et al*., 2007

Table 1. Continued

Affiliation	Compounds	Radical scavenging activities				Inhibitory activities		Reference
		DPPH (IC_{50})	O_2 (IC_{50})	$ABTS^{\bullet+}$ (IC_{50})	NO (% inhibition)	Lipid peroxidation (IC_{50})	Soybean lipoxygenase type I (IC_{50})	
Phenolic Compounds	ethyl gallate	35.3 ± 4.0	79.7 ± 7.1			35.4 ± 3.1		Na *et al*., 2009
	methyl gallate	28.8 ± 1.6	89.6 ± 7.6			38.3 ± 3.6		Na *et al*., 2009
	arbutin	> 100	> 100		0			Thuong *et al*., 2007
	2,6-di-*O*-galloylarbutin	3.6 ± 0.2	14.0 ± 1.2		0			Thuong *et al*., 2007
	populoside			1.67		115.64		Zhang *et al*., 2006
	populoside A			2.07		45.82		Zhang *et al*., 2006
	populoside B			1.13		45.27		Zhang *et al*., 2006
	populoside C			1.55		31.17		Zhang *et al*., 2006
	tremulacin			0.12		> 200		Zhang *et al*., 2006
	tremuldin			0.24		> 200		Zhang *et al*., 2006
	salicin			0.21		> 200		Zhang *et al*., 2006
	grandidentatin			1.27		141.12		Zhang *et al*., 2006
	salireposide			1.01		56.67		Zhang *et al*., 2006
	coumaroyl-β-D-glucoside			0.78		42.26		Zhang *et al*., 2006
	3,4-di-*O*-caffeoylquinic acid	13.4 ± 1.1						Hung *et al*., 2006
	methyl 3,4-di-*O*-caffeoyl quinate	14.1 ± 0.4						Hung *et al*., 2006
	3,5-di-*O*-caffeoylquinic acid	18.2 ± 0.5						Hung *et al*., 2006
	methyl 3,5-di-*O*-caffeoyl quinate	10.6 ± 0.2						Hung *et al*., 2006
	4,5-di-*O*-caffeoylquinic acid	10.4 ± 0.5						Hung *et al*., 2006
	methyl 4,5-di-*O*-caffeoyl quinate	12.6 ± 1.0						Hung *et al*., 2006
	1-(4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2-hydroxyethanone	> 100	> 100		31.0 ± 10.5			Thuong *et al*., 2007
	pleuropyrone A	> 100	>100			> 100		Min *et al*., 2003
	(–)-lyoniresinol-3a-*O*-β-D-glucopyranoside	45.7	>100			37.4		Min *et al*., 2003
	(+)-lyoniresinol-3a-*O*-β-D-glucopyranoside	42.6 86.1 ± 5.3	>100 >200			39.1 67.1 ± 5.3		Na *et al*., 2009 Min *et al*., 2003
Positive Control	α-tocopherol	6.7 ± 0.3 20.7	>100			15.6 ± 1.9 5.3 9.8 ± 0.50		Na *et al*., 2002; Min *et al*., 2003; Ha *et al*., 2009
	ferulic acid	56.4 ± 4.6	>200	1.89 ± 0.05				Jin *et al*., 2007; Thuong *et al*., 2010a
	caffeic acid	25.3 ± 2.2 31.1 ± 1.9	35.6 ± 4.3 45.6 ± 5.3	1.92 ± 0.08 1.98		>200		Zhang *et al*., 2006; Thuong *et al*., 2007; Hung *et al*., 2006; Jin *et al*., 2007; Thuong *et al*., 2010a
	BHA	4.8 ± 0.2 58.0 ± 3.6	24.6 ± 3.2 127.8 ± 7.5			10.8 ± 0.7 1.0 ± 0.01		Na *et al*., 2002 Na *et al*., 2009
	BHT	50.8 ± 3.6 145.8 ± 6.7	120.8 ± 7.5	0.80		11.88		Min *et al*., 2003; Zhang *et al*., 2006; Thuong *et al*., 2007; Hung *et al*., 2006
	baicalein						23.4 ± 0.48	Ha *et al*., 2009

Reynoutria sachalinensis – *Reynoutria sachalinensis* (Fr. Schm.) Nakai is a perennial shrub which is distributed in Korea, China and Japan. The roots of *R. sachalinensis* and *R. japonica* have been used as a traditional medicine Reynoutriae Radix to treat arthralgia, jaundice caused by damp-heat, amenorrhea, mass formation in the abdomen, cough with profuse expectoration, scalds, burns, traumatic injuries, carbuncles and scores (Bae, 2001). Bioassay-guided fractionation of the MeOH extract of *R. sachalinensis* flower using the DPPH assay led to the isolation of three anthraquinones and three flavonoids. Their structures were identified as emodin, emodin-8-*O*-β-D-glucopyranoside, physcion-8-*O*-β-D-glucopyranoside, quercetin-3-*O*-α-L-arabinofuranoside, quercetin-3-*O*-β-D-galactopyranoside and quercetin-3-*O*-β-D-glucuronopyranoside (Fig. 1). Study of the antioxidant activities of the

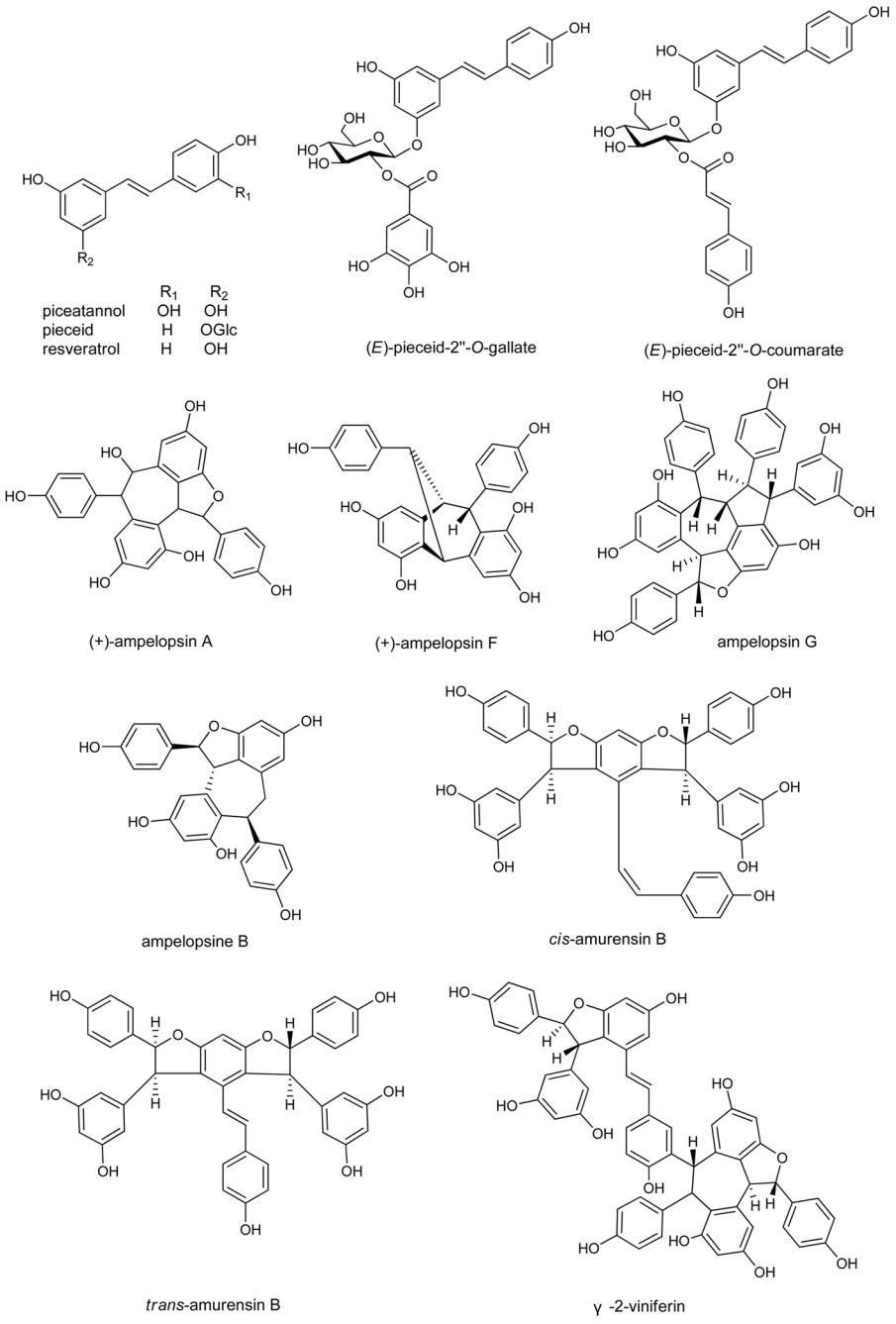
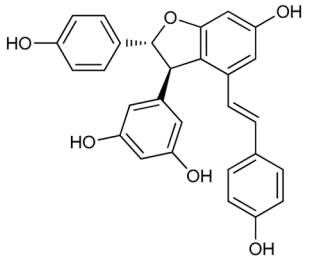
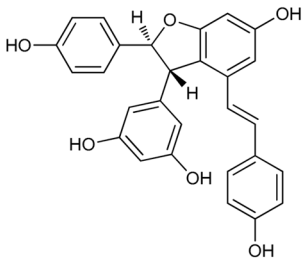


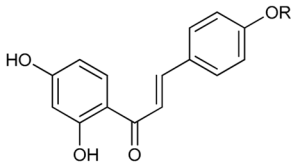
Fig. 1. Chemical structures of antioxidant compounds isolated from medicinal plants.



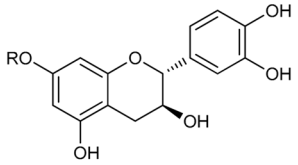
ε -viniferin



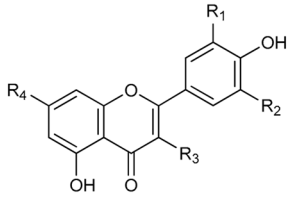
trans-ε -viniferin



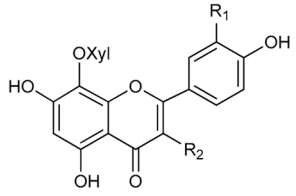
isoliquiritigenin	R=H
2',4'-dihydroxy-4-methoxychalcone	R=CH_3



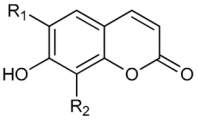
(+)-catechin	R=H
(+)-catechin-7-O-β-D-xylopyranoside	R=xylose
(+)-catechin-7-O-β-D-apiofuranoside	R=apiose



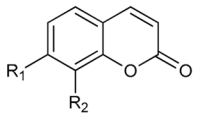
	R_1	R_2	R_3	R_4
afzelin	H	H	ORha	OH
luteolin	H	OH	H	OH
luteolin-7-*O*-β -D-glucoside	H	OH	H	OGlc
myricetin	OH	OH	OH	OH
myricetin-3-*O*-(2''-*O*-galloyl) -α -L-rhamnopyranoside	OH	OH	*O*-(2-*O*-galloyl) -Rha	OH
myricitrin	OH	OH	ORha	OH
quercetin	H	OH	OH	OH
quercitrin	OH	H	ORha	OH
syringetin-3-*O*-rutinoside	OCH_3	OCH_3	*O*-Glc-*O*-Rha	OH
syringetin-3-*O*-(2''-*O*-galloyl)-rutinoside	OCH_3	OCH_3	*O*-(2-*O*-Galloyl) -Rha	



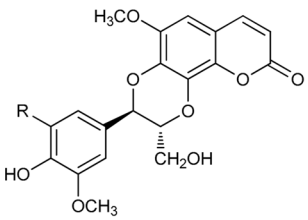
	R_1	R_2
gossypetin-8-*O*-β -D-xylopyranoside	OH	OH
rhodalidin	H	OGlc
rhodalin	H	OH



	R_1	R_2
aesculetin	OH	H
aesculin	OGlc	H
fraxetin	OCH_3	H
fraxin	OCH_3	OGlc
scopoletin	OCH_3	OH



	R_1	R_2
coumarin	H	H
daphnetin	OH	OH
herniarin	OCH_3	H
umbelliferone	OH	H



	R
cleomiscosin A	H
cleomiscosin C	OCH_3

Fig. 1. Continued

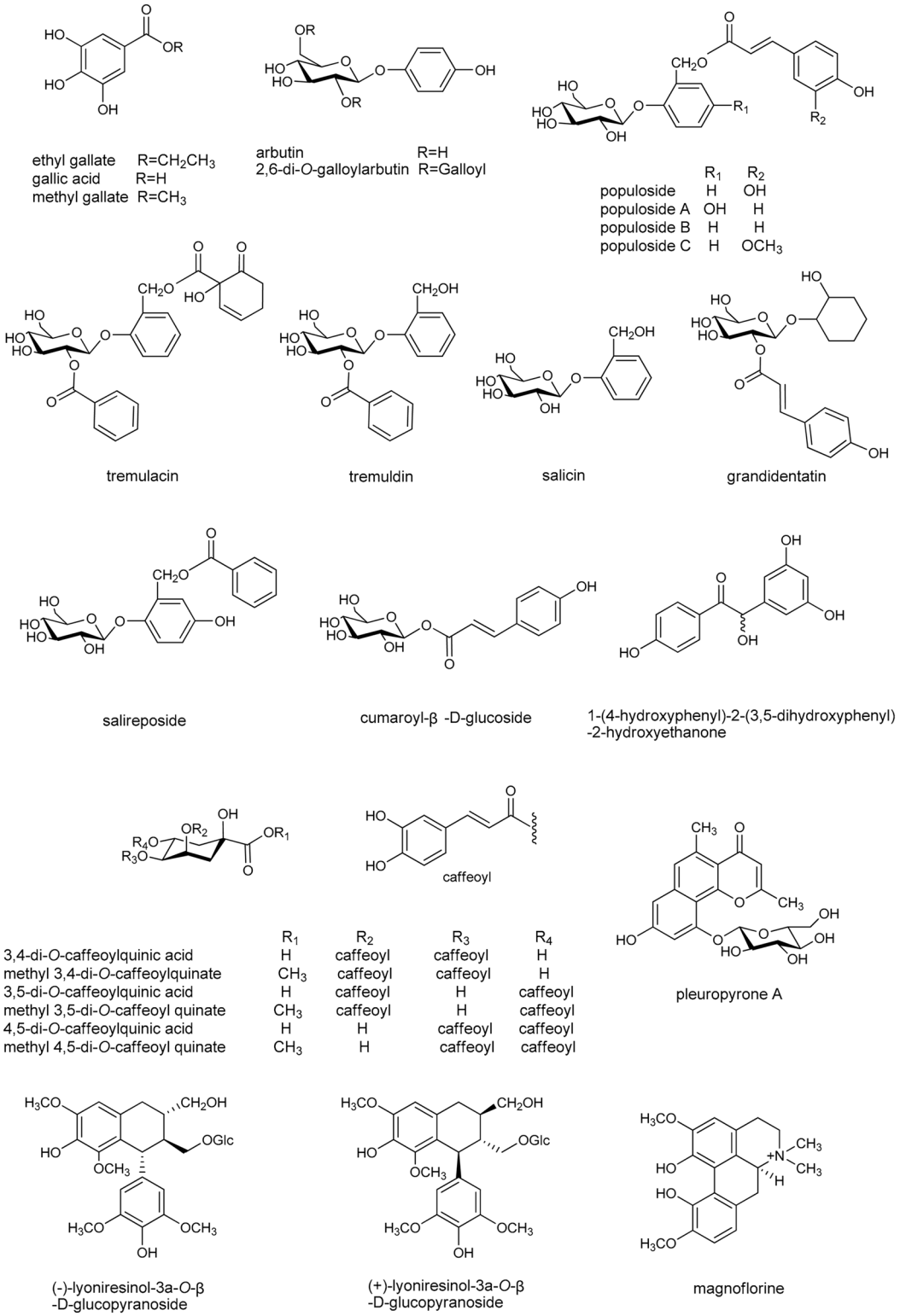


Fig. 1. Continued

isolates demonstrated that quercetin-3-*O*-α-L-arabinofuranoside, quercetin-3-*O*-β-D-galactopyranoside, and quercetin-3-*O*-β-D-glucuronopyranoside had anti-radical activity against DPPH with IC_{50} values of 64.3, 54.7, and 46.2

μM, respectively, as well as anti-radical activity against O_2^-, with IC_{50} values of 6.0, 6.7, and 4.4 μM, respectively. Interestingly, they were also effective in the inhibition of low density lipoprotein (LDL) oxidation with IC_{50} values of 3.8, 3.2, and 5.4 μM, respectively (Zhang *et al*., 2005).

Weigela subsessilis – The genus *Weigela*, a member of the family Caprifoliaceae, is comprised of roughly twelve species (Chang, 1997). All of these plants are widespread and cultivated specifically in Korea, Japan and Northern China. Among them, four species namely, *W. hortensis, W. praecox, W. florida,* and *W. subsessilis* have been found in Korea (Chang, 1997). Although *W. subsessilis* is a widespread, endemic species in Korea, it has been rarely reported for use in folk medicine (Park *et al*., 2006). Recent phytochemical studies on the leaves of this plant have resulted in the isolation of flavonoids, coumarins, and triterpenoids. The flavonoids isolated from this plant were reported as kaempferol-*O*-3-α-L-(3-*O*-acetyl)-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside, sutchuenoside A, kaempferitrin, astragalin, kaempferol 7-*O*-rhanmnoside and kaempferol-3-*O*-α-L-rhanmnosyl-7-*O*-β-D-glucoside (Won *et al.,* 2004). Four coumarins, scopoletin, cleomiscosin A, scopolin and fraxin were also isolated from these leaves (Won *et al*., 2004; Thuong *et al*., 2005). Eight ursane-type triterpenoids, asiatic acid, corosolic acid, esculentic acid, ilekudinol A, ilekudinol B, pomolic acid, ursolic acid and weigelic acid, were isolated from an EtOAc-soluble extract of the leaves of *W. subsessilis* (Thuong *et al*., 2006). In our continuing study, we found that the coumarins isolated from *W. subsessilis* inhibited LDL oxidation mediated by either catalytic copper ions (Cu^{2+}) or free radicals generated with the azo compound 2,2-azobis-(2-amidinopropane)dihydrochloride (AAPH). Of the coumarins tested, scopoletin and cleomiscosin A increased the lag time of conjugated diene formation and inhibited the generation of thiobarbituric acid reactive substances (TBARS) in a dose-dependent manner. In addition, it was found that scopoletin and cleomiscosin A had the capacity to protect the fragmentation of apolipoprotein B-100 (apoB-100). These results suggest that *W. subsessilis* and its active coumarins, scopoletin and cleomiscosin A may have a role to play in preventing the LDL oxidation involved in atherogenesis (Thuong *et al*., 2005).

Dipsacus asper – *Dipsacus asper* Wall, belongs to Dipsacaceae, is a perennial herb growing in the moist fields and mountains (Namba, 1993). The species has long been used as a tonic and anti-inflammatory agent for the treatment of low back pain, knee pain, rheumatic arthritis, traumatic hematoma, and bone fractures (Zhou *et al.,* 1981; Wang, 1999). Previous authors reported the isolation of several triterpenoid saponins, iridoid glycosides and sterols from this plant (Kouno *et al.,* 1990; Jung *et al.,* 1993; Namba, 1993). Pharmacological studies have demonstrated that the saponins from *D. asper* possess anticomplementary, antinociceptive and neuroprotective activities (Suh *et al.,* 2000). The species has also been reported to be effective in treating vitamin E deficiency (Xie *et al.,* 1994). The extract of *D. asper* can enhance the antioxidant status of blood and liver in rodents (Wong *et al.,* 1996), which may also contribute to its effectiveness in ischemic heart disease (Li *et al.,* 2010). Our activity-guided fractionation of the MeOH extract from the roots of *D. asper* led to the isolation of six phenolic compounds including 3,4-di-*O*-caffeoylquinic acid, methyl 3,4-di-*O*-caffeoyl quinate, 3,5-di-*O*-caffeoylquinic acid, methyl 3,5-di-*O*-caffeoyl quinate, 4,5-di-*O*-caffeoylquinic acid and methyl 4,5-di-*O*-caffeoyl quinate (Fig. 1). The free radical scavenging activities of compounds were analyzed with the DPPH assay and all the compounds exhibited potent antioxidant activities against DPPH radical formation (Table 1). When LDL (100 μg/ml in PBS) was incubated with Cu^{2+} alone, the lag time was 25 min, whereas, in the presence of 2.5 μM of compounds, the lag phase was retarded to 390, 335, 350, 385, 330, and 380 min, respectively. In the presence of caffeic acid used as a positive control, lag phase decreased to 230 min. Thus, at the same concentration, these compounds were more effective than caffeic acid in inhibiting LDL oxidation. The oxidation of LDL initiated by Cu^{2+} was also measured by the formation of malondialdehyde (MDA) using the TBARS assay. All the compounds tested markedly reduced the formation of TBARS, which was comparable to conjugated diene formation. All the compounds exhibited significant inhibitory activities against Cu^{2+}-mediated LDL oxidation (Table 2).

Populus davidiana – The genus *Populus* belonging to the Salicaceae family is comprised of more than 100 species, which are distributed in temperature zones and subtropical regions. Among these, *Populus davidiana* Dode [*P. tremela.* L. var. *davidiana* (Dode) Schneid.] is distributed throughout Korea, Northern China and Siberia (Bae, 2001). The plant has been used traditionally for treatment of various diseases including diarrhea, paralysis, pulmonary disease, pox and variola (Bae, 2001). Some phenolic glycosides and flavonoids have been isolated from this plant (Zhou *et al*., 2002). Previous phytochemical studies have also revealed the presence of phenolic glycosides (Erickson *et al*., 1970; Asakawa *et al*., 1977; Mattes *et al*., 1987; Jossang *et al*., 1994; Picard *et al*.,

Table 2. Inhibitory effect of natural compounds on LDL and/or HDL oxidation

Affiliation	Compounds	LDL - oxidation			HDL - oxidation			Reference
		Lag-time[a] (min)	TBARS, IC_{50} (M)		Lag time (min)	TBARS, IC_{50} (M)		
			Cu^{2+}-mediated	AAPH-mediated		Cu^{2+}-mediated	AAPH-mediated	
	Blank	24						Thuong *et al.*, 2005
	DMSO	52			38			
Oligostilbene	ampelopsine B	118	3.0 ± 1.2	6.1 ± 1.8	105	3.9 ± 1.2	8.2 ± 2.0	Ngoc *et al.*, 2008
	ε-viniferin	136	1.7 ± 1.0	3.2 ± 1.3	128	2.4 ± 1.1	5.7 ± 1.9	Ngoc *et al.*, 2008
Coumarin	fraxetin	554	2.5 ± 0.2					Thuong *et al.*, 2009
	fraxin	29	>200	>200				Thuong *et al.*, 2005
	esculetin	520	2.8 ± 0.2					Thuong *et al.*, 2009
	scopoletin	42	57.4 ± 4.4	37.3 ± 2.6				Thuong *et al.*, 2005
	cleomiscosin A	112	13.1 ± 2.5	26.8 ± 1.8				Thuong *et al.*, 2005
Phenolic	3,4-di-*O*-caffeoylquinic acid		2.1 ± 0.2					Hung *et al.*, 2006
Compounds	methyl 3,4-di-*O*-caffeoyl quinate		1.9 ± 0.1					Hung *et al.*, 2006
	3,5-di-*O*-caffeoylquinic acid		2.3 ± 0.1					Hung *et al.*, 2006
	methyl 3,5-di-*O*-caffeoyl quinate		2.0 ± 0.3					Hung *et al.*, 2006
	4,5-di-*O*-caffeoylquinic acid		2.3 ± 0.3					Hung *et al.*, 2006
	methyl 4,5-di-*O*-caffeoyl quinate		1.8 ± 0.2					Hung *et al.*, 2006
Alkaloid	magnoflorine				123	2.3 ± 0.2	6.2 ± 0.5	Hung *et al.*, 2007
Positive Controls	BHT	>240	3.0 ± 0.4 2.3 ± 0.1	10.1 ± 1.4				Hung *et al.*, 2006; Thuong *et al.*, 2005
	caffeic acid	471	5.2 ± 1.0					Hung *et al.*, 2006; Thuong *et al.*, 2009
	α-tocopherol	97	23.4 ± 2.7 22.9 ± 1.2					Hung *et al.*, 2006; Thuong *et al.*, 2005
	vitamin C				97	10.5 ± 0.8	18.7 ± 1.5	Hung *et al.*, 2007
	vitamin E	75	20.9 ± 2.4		145 83	1.8 ± 0.2 4.3 ± 1.2	4.4 ± 0.5 10.2 ± 1.9	Hung *et al.*, 2007; Ngoc *et al.*, 2008

[a]Lag-times (min) were obtained when each compound was tested at a concentration of 5 mM.

1994), flavonoids (Pearl and Darling, 1970) and organic acids in other species of the genus *Populus*. Our phytochemical investigation of the EtOAc-soluble fraction of a *P. davidiana* MeOH extract has resulted in the isolation of three new phenolic glycosides, populosides A-C, and seven known phenolic glycosides namely, populoside, tremulacin, tremuldin, salicin, grandidentatin, salireposide and coumaroyl-β-D-glucoside (Fig. 1). The compounds were tested for their radical scavenging activities against an azo radical, $ABTS^{\bullet+}$. Of these, the populosides A-C, populoside, grandidentatin, salireposide and coumaroyl-β-D-glucoside exhibited antioxidant activities in this assay with higher quenching abilities with TEAC of 2.07 ± 0.02, 1.13 ± 0.02, 1.55 ± 0.01, 1.67 ± 0.03, 1.27 ± 0.02, 1.01 ± 0.02 and 0.78 ± 0.01, respectively (Table 1) (Zhang *et al*., 2006).

Acer okamotoanum – The genus *Acer* is a member of family Aceraceae. These plants are widespread specifically in Korea, Japan, China and Manchuria (Moon *et al.,* 2004). These plants are comprised of 15 species in Korea, which are primarily maple trees growing in mountainous regions. In particular, *Acer okamotoanum* is an endemic Korean maple species, growing in the mountains of Ullung island. Most species are deciduous, but a few in southern Asia and the Mediterranean region are evergreen (Van *et al*., 1999). The leaf, branch and root of some species in this genus have been used in folk medicine for the treatment of arthralgia and fractures (Kim *et al*., 1998a). Previous phytochemical studies on this plant resulted in the isolation of some flavonol glycosides and phenolic compounds, along with their anti-HIV-1 integrase activities (Kim *et al*., 1998b). In our investigation, two compounds, cleomiscosins A and C, were isolated from the EtOAc-soluble fraction of a MeOH extract of the leaves and twigs of *A. okamotoanum* by column chromatography. These isolates have been shown to exhibit antioxidant activities against lipid peroxidation (Yun *et al*., 2001). Recently, Thuong *et al*. (2005) reported the inhibitory effect of cleomiscosins A on LDL oxidation. However, although its antioxidant activity against LDL oxidation has been reported, the mechanism by which it inhibits LDL oxidation is still poorly understood. Here, we found that cleomiscosins C dose-dependently inhibits LDL oxidation mediated by either catalytic Cu^{2+} or free radicals generated with the azo compound AAPH with IC_{50}s 29.5 and 11.9 μM, respectively. By electrophoretic analysis, we also observed that cleomiscosins C protects apoB-100 against Cu^{2+}-induced fragmentation (65.3% inhibition at 5 μM) (Table 2). Furthermore, fluorescence analyses clearly indicated that both cleomiscosins A and C protect against the oxidative modification of apoB-100 induced by either Cu^{2+} or HOCl (cleomiscosins A, IC_{50} 13.4 and 8.1 μM, respectively; cleomiscosins C, IC_{50} 23.6 and 3.9 μM, respectively). These findings suggest that cleomiscosins A and C could be beneficial in preventing LDL oxidation in atherosclerotic lesions (Jin *et al*., 2007).

Coptidis Rhizoma – Magnoflorine is a quaternary alkaloid with an isoquinoline skeleton isolated from Coptidis Rhizoma, the rhizomes of *Coptis japonica* (Ranunculaceae). The antioxidant activity of magnoflorine was investigated with respect to its structural features and physico-chemical properties to inhibit free radical peroxidation. In this study, the susceptibility of high density lipoprotein (HDL) to in vitro Cu^{2+}- and AAPH-induced lipid peroxidation in the presence of magnoflorine was examined. Also, the presence of magnoflorine with Cu^{2+}-oxidized HDL in preventing LDL oxidation was studied to investigate whether the inclusion protects LDL from oxidative modifications. Magnoflorine exerted an inhibitory effect against Cu^{2+}-induced lipid peroxidation of HDL, as shown by prolongation of lag time from 62 to 123 min at the concentration of 3.0 μM. It also inhibited the generation of TBARS in the dose-dependent manner with IC_{50} values of 2.3 - 0.2 μM and 6.2-0.5 μM by either catalytic Cu^{2+} or thermo-labile radical initiator (AAPH), respectively (Table 2). Separately, Cu^{2+}-oxidized HDL lost the antioxidant action but the inclusion of magnoflorine with Cu^{2+}-oxidized HDL protected LDL oxidation and increased with increasing magnoflorine concentration. The results suggest that magnoflorine may have a role to play in preventing the HDL oxidation. Magnoflorine is an alkaloid bearing two free phenolic groups. The presence of an aromatic-OH group may be responsible for their antioxidant efficiency, similarly to other phenolic antioxidants (Bors *et al*., 1990), *via* a chain-breaking mechanism by donation of the phenolic hydrogen. Moreover, magnoflorine had a lower O-H bond dissociation energy and the highest occupied molecular orbital surroundings of the reaction center, which have been identified as important requisites for both chelating and radical scavenging activities as well as explaining the higher antioxidant efficiency of the former compound (Hung *et al*., 2007).

Sedum takesimense – *Sedum* species is a large genus belongs to Crassulaceae family. *Sedum takesimens* Nakai is an endemic plant, commonly known as 'seomkirincho' among other 20 *Sedum* species in Korea. It is an edible plant common to Ulleung Island and has light green leaves on thick stems and a yellow flower blooming in the summer. It has been documented as either a vegetable

or folk medicine for treatment of many diseases (Bae, 2001). There are many reports about the phytochemical constituents such as alkaloids, flavonoids, phenols, phenolic acids, carbohydrates, amino acids and coumarins of some *Sedum* species (Stevens *et al*., 1996; Kim *et al*., 1996). However, 1-(4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2-hydroxyethanone, gossypetin-8-*O*-β-D-xylopyranoside, 2,6-di-*O*-galloylarbutin were first time isolated from *Sedum takesimense* along with 11 known phenolic constituents (Fig. 1). Especially, gossypetin-8-*O*-β-D-xylopyranoside and 2,6-di-*O*-galloylarbutin exhibited strong scavenging activities against DPPH and O_2^- radicals as well as significant inhibitory effects on lipid peroxidation (IC_{50} 14.0 and 10.8 μM, respectively) and LDL oxidation induced by Cu^{2+} (IC_{50} 5.7 and 3.3 μM, respectively). Further, the activity of 2,6-di-*O*-galloylarbutin was much higher than BHT in the REM analysis. In this study, some structure-activity relationships were also exhibited. As shown in table 1, the anti-lipid peroxidation ability of 1-(4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2-hydroxyethanone was much less than that of resveratrol, suggesting that a modification of the double bond reduced its activity. Besides, the anti-oxidant activity of the flavonol glycoside, gossypetin-8-*O*-β-D-xylopyranoside, was significantly stronger than that of rhodalin and rhodalidin due to the ortho-hydroxyl group in the B-ring (Hou *et al*., 2004a, b). Interestingly, 2,6-di-*O*-galloylarbutin had a remarkable free radical quenching capacity as well as inhibitory effects on both lipid peroxidation and LDL oxidation as compared to either gallic acid or arbutin. This indicated that the addition of galloyl groups significantly increased the anti-oxidant activity of 2,6-di-*O*-galloylarbutin (Thuong *et al*., 2007).

Cercis chinensis – The genus *Cercis* of Leguminosae is comprised of over 6 species distributed in temperate zones. *Cercis chinensis* Bunge, a deciduous shrub, is widely distributed in southeast China (Mu *et al*., 2007). Earlier phytochemical investigations on *C. chinensis* revealed the presence of phenolic compounds (Mu *et al*., 2007; Na *et al.,* 2009). Flavonoids such as kaempferol, quercetin and myricetin, as well as their glycosides have been reported as constituents of this genus (Salantino *et al.,* 2000). The stem bark, root bark and stem of *C. chinensis* have been used to promote blood circulation in addition to treating dysmenorrhea, edema, bruising and various injuries (Bae, 2001). Its flowers are used to treat rheumatic ache and its fruits are used to treat coughs (Mu *et al*., 2007). In vitro antioxidant-guided fractionation of the EtOH extract led to the isolation and identification of twenty phenolic compounds including a new flavonol glycoside. In this report, the isolation and structure determination of the new compound and the evaluation on the antioxidant activity was described. The EtOH extracts from the stems and leaves of *C. chinensis* Bunge (Leguminosae) showed significant antioxidant activity in our preliminary screening. Antioxidant activity-guided fractionation of the EtOH extract of *C. chinensis* led to the isolation of a new flavonol glycoside, syringetin-3-*O*-(2"-*O*-galloyl)-rutinoside, together with nineteen known compounds which were identified as isoliquiritigenin, liquiritigenin, 2',4'-dihydroxy-4-methoxychalcone, resveratrol, piceatannol, gallic acid, methyl gallate, ethyl gallate, myricetin, afzelin, quercitrin, myricitrin, myricetin-3-*O*-(2"-*O*-galloyl)-α-L-rhamnopyranoside, syringetin-3-*O*-rutinoside, (+)-catechin, (–)-epicatechin-3-*O*-gallate, (–)-epigallocatechin-3-*O*-gallate, (–)-lyoniresinol-3a-*O*-β-D-xylopyranoside and (+)-lyoniresinol-3a-*O*-β-D-glucopyranoside by comparing their spectral data with those previously reported. Myricetin, myricetin-3-*O*-(2"-*O*-galloyl)-α-L-rhamnopyranoside, (–)-epicatechin-3-*O*-gallate, and (–)-epigallocatechin-3-*O*-gallate exhibited potent scavenging activities to DPPH· and O_2^- at very low concentrations. Their ability to inhibit lipid peroxidation initiated by Fe^{2+}/ascorbate in rat brain homogenates was examined. Piceatannol exhibited potent lipid peroxidation inhibitory activities with IC_{50} value of 0.8 ± 0.01 μM which was comparable to the positive control BHA (1.0 ± 0.01 μM) (Table 1). Resveratrol, myricetin, myricetin-3-*O*-(2"-*O*-galloyl)-α-L-rhamnopyranoside, (–)-epicatechin-3-*O*-gallate, and (–)-epigallocatechin-3-*O*-gallate also inhibited iron-induced lipid peroxidation at low concentrations (Table 1). Replacement of the hydroxyl groups at the C-3', 5' of B-ring by methoxyl groups in syringetin-3-*O*-rutinoside led to a loss in antioxidant activity. The new flavonol glycoside, syringetin-3-*O*-(2"-*O*-galloyl)-rutinoside, which possesses a galloyl moiety at the C-2" position, was more effective than syringetin-3-*O*-rutinoside, which showed strong antioxidant activities against DPPH radical, superoxide radical and lipid peroxidation with IC_{50} values of 43.5 ± 2.2, 69.1 ± 2.4, and 19.3 ± 1.2 μM, respectively (Table 1) (Na *et al*., 2009).

Rhubarb – Rhubarb is the rhizomes of *Rheum undulatum* L., *R. palmatum* L., *R. tanguticum* Maxim., *R. officinale* Baill., and *R. coreanum* Nakai, an important and well-known medicinal origin plant which has been used in traditional medicine for the treatment of blood stagnation as well as a purgative agent (Bae *et al*., 2001). Previously, a number of natural stilbene and anthraquinone derivatives were identified as the main components with many activities such as anti-inflammatory, anti-

diabetic, anti-allergic, cytotoxicity, anti-carcinogenic and antioxidant effects (Kim *et al*., 1999; Matsuda *et al*., 2001; Choi *et al*., 2005; Song *et al*., 2006). Since ampelopsin B and -viniferin, two oligostilbenes isolated from rhubarb (Fig. 1), has not been studied for their protective effect on human lipoproteins against lipid peroxidation, the objective of our study was to verify their beneficial properties toward cardiovascular disease by protecting human lipoproteins. Both ampelopsin B and -viniferin exerted inhibitory activities against Cu^{2+}- and AAPH-induced LDL oxidation, as exhibited by a prolongation in lag time from 52 to 118 and 136 min, respectively. They and also increased the lag time from 38 to 105 and 128 min for HDL oxidation, respectively, at the concentration of 3.0 μM (Table 1). With respect to the generation of TBARS, both isolates inhibited LDL oxidation mediated by either catalytic Cu^{2+} or the thermolabile radical initiator (AAPH) in a dose-dependent manner with IC_{50} values of 3.6 and 6.0 μM for ampelopsin B, and 1.7 and 3.2 μM for -viniferin, respectively (Table 1). In addition, the compounds also showed strong ability to protect HDL oxidation induced by both Cu^{2+} and AAPH with low IC_{50} values (Table 2). The results suggest that the isolated oligostilbenes may have a role in preventing lipoprotein oxidation (Ngoc *et al*., 2008)

Vitis amurensis – *Vitis amurensis* (Vitaceae) is widely distributed, wild-growing grape species in Korea, China and Japan. The root and stem have been used in traditional medicine to relieve pains from injury, cancer, stomach ache, neuralgic pain and abdominal pain (Huang and Lin, 1999). In recent studies, it has been reported that the root possesses anti-inflammatory (Huang *et al*., 2000; Huang *et al*., 2001), anti-tumor (Lee *et al*., 2006b), and anti-aging activities (Lastra and Villegas, 2005) in addition to preventing Alzheimer's disease (Jang *et al*., 2007). To date, phytochemical studies of the root have found resveratrol, four dimers and two trimers of resveratrol including: amurensin A, (+)-ε-viniferin, the ampelopsins A and D as well as amurensin B and ampelopsin E respectively (Huang and Lin, 1999). Further a resveratrol dimer, amurensin H (Huang *et al*., 1999a), a resveratrol trimer, amurensin G (Huang *et al*., 1999b), two resveratrol trimers and two resveratrol pentamers, amurensins C-F, respectively (Huang *et al*., 2000), ten resveratrol tetramers, amurensins I-M, (+)-hopeaphenol, vitisin A, (+)-vitisifuran A, and heyneanol A have been isolated (Huang *et al*., 2001). In our previous study, eleven resveratrol derivatives including a new oligostilbene, *cis*-amurensin B, were isolated from the leaf and stem of *V. amurensis* (Fig. 1) and examined for their antioxidant capacities, as well as anti-inflammatory effects for the first time. Stilbenes and oligostilbenes displayed moderate anti-lipid peroxidation activities, but all the isolates exhibited strong $ABTS^{\bullet+}$ radical scavenging activities in the dose-dependent manner (Table 1). In addition, the isolates showed stronger inhibitory capacities against soybean lipoxygenase type I than that of baicalein, a positive control (Table 1). Of the isolates, *r*-2-viniferin exhibited the strongest scavenging activity against $ABTS^{\bullet+}$ radical with a TEAC value of 5.57, and the most potential inhibitory effect on soybean lipoxygenase with the IC_{50} value of 6.39 M (Table 1). Furthermore, our findings suggest that the chemical compositions isolated from the leaf and stem are almost similar to those isolated from the root of *V. amurensis*. Therefore, the results may explain, in part, the uses of both the leaf and stem, as well as the root of *V. amurensis* in Korean traditional medicine (Do *et al*., 2009).

Natural coumarins – Coumarins are derivatives of cinnamic acid with a benzo--pyrone skeleton (Murray, 1989; Bruneton, 1999) that are widely found in the plant kingdom. More than 1300 coumarins have been isolated and reported from natural sources, particularly from the families Rutaceae, Apiaceae, Fabaceae, and Asteraceae (Bruneton, 1999; Murray, 1989). Previously, the free radical-quenching capacities and anti-lipid peroxidation activities of various coumarins have been investigated (Paya *et al*., 1992; Martin *et al*., 1996). Our phytochemical studies on four Korean medicinal plants, *Fraxinus rhynchophylla* Dence, *Angelica dahurica* Fischer ex Hoffmann, *Evodia daniellii* (Benn.) Hemsl. and *Peucedanum japonicum* Thunb. resulted in the isolation of 17 coumarins (Fig. 1). Since there have been several reports on the antioxidant activities of coumarins, it is expected that studies these compounds might be beneficial for new uses as well as in traditional remedies. We studied the antioxidant activities and the structure-activity relationships of coumarins isolated from four Korean medicinal plants and four purchased coumarins. The free radical scavenging and lipid peroxidation assays revealed that five phenolic coumarins, scopoletin, aesculetin, fraxetin, umbelliferone and daphnetin possessed considerable antioxidant activities (Table 1). The coumarins having a catechol group showed significant free radical scavenging activities and inhibitory effects on lipid peroxidation, indicating that the catechol group significantly contributed to the antioxidant activities of coumarins (Fig. 1). In contrast, the sugar moiety markedly reduced the activities of coumarin glycosides. The results also demonstrate that the α-pyrone ring of coumarins

significantly enhanced the capacity of inhibiting oxidative reactions of the coumarins (Thuong et al., 2009; Thuong *et al.,* 2010). In addition, fraxetin, a coumarin, was found to inhibit LDL oxidation at lower concentrations and also induce antioxidant enzymes via Nrf2/ARE activation (Thuong *et al*., 2009).

Conclusion

Oxidative damage to biomolecules including lipids, proteins and DNA is known to be involved in the pathogenesis of neurodegenerative disease, cardiovascular disease, metabolic disease, cancer and aging. However, although in vitro studies have provided promising results, only a very limited number of antioxidants have been developed for clinical use (Augustyniak *et al*., 2010). It is possible that complex factors may contribute to this apparent loss of effect in clinical applications. Despite the fact that the development of effective antioxidant drugs is difficult, it is fascinating to search for new antioxidants from medicinal sources because they can provide pharmacological evidence for the treatment of chronic diseases which might be associated with their antioxidant actions. In order to find out new and effective natural antioxidants, we have prepared extracts from over 350 species of medicinal plants and evaluated their in vitro antioxidant activities using DPPH, superoxide radicals scavenging and lipid peroxidation assays. During our search for antioxidant compounds from the medicinal plants selected, we have isolated several new and known antioxidant compounds which include stilbene glycosides, phenolic glycosides, flavonoids, oligostilbenes and coumarins. Our results suggest that the presence of antioxidant compounds in the medicinal plants might be associated with their traditional use to treat inflammation, cardiovascular disease and various chronic diseases. More studies are required to demonstrate that the antioxidant compounds have beneficial effects in degenerative disease models by further investigating their mechanism of action.

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