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## Therapeutic applications of compounds in the *Magnolia* family

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### ABSTRACT

The bark and/or seed cones of the *Magnolia* tree have been used in traditional herbal medicines in Korea, China and Japan. Bioactive ingredients such as magnolol, honokiol, 4-O-methylhonokiol and obovatol have received great attention, judging by the large number of investigators who have studied their pharmacological effects for the treatment of various diseases. Recently, many investigators reported the anti-cancer, anti-stress, anti-anxiety, anti-depressant, anti-oxidant, anti-inflammatory and hepatoprotective effects as well as toxicities and pharmacokinetics data, however, the mechanisms underlying these pharmacological activities are not clear. The aim of this study was to review a variety of experimental and clinical reports and, describe the effectiveness, toxicities and pharmacokinetics, and possible mechanisms of *Magnolia* and/or its constituents.

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## 1. Introduction

The *Magnolia* bark is an herbal material obtained from *Magnolia officinalis* and from other species of the Family Magnoliaceae. The

attractive features of a *Magnolia* tree generally include fragrant and dazzling flowers and petiolate leaves with large stipules, which at first surround the stem, but fall off later and leave a characteristic scar around the node. Among *Magnolia* species, *M. obovata* and *M. officinalis* are very

**Abbreviations:** ACh, acetylcholine; AChE, acetylcholinesterase; AIF, apoptosis inducing factor; ATP, adenosine triphosphate; Bax, Bcl2-associated protein; Bcl2, B-cell lymphoma protein-2; B-CLL, B-cell chronic lymphocytic leukemia; CDK, cyclin-dependent kinase; CFA, complete Freud's adjuvant; Cg, carrageenan; COX, cyclooxygenases; ERK, extracellular signaling-regulated kinase; GABA, gamma-aminobutyric acid; IL, interleukin; IAP, inhibitor of apoptosis protein; iNOS, inducible NO synthase; i.v., intravenous; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LMP1, latent membrane protein1; LPS, lipopolysaccharides; MAPK, mitogen activated protein kinases; Mcl-1, myeloid-cell leukemia sequence 1; mGluR5, metabotropic glutamate 5 receptors; NGF, nerve growth factor; NO, nitric oxide; NMDA, N-methyl-D-aspartic acid; PARP, poly (adenosine diphosphate-ribose) polymerase; PG, prostaglandins; PGE2, prostaglandin E2; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SAMP8, senescence-accelerated-prone 8; SSRI, selective serotonin reuptake inhibitors; TNF, tumor necrosis factor; TPA, tissue plasminogen activator; VSMC, vascular smooth muscle cell; TXA, thromboxanes; XIAP, X-linked inhibitor of apoptosis protein.

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**Table 1**  
Main components of Magnoliaceae plants and their major characteristics.

Components	MW	Contents on methanol or ethanol extract					Major characteristics
		<i>M. obovata</i> (Matsuda et al., 2001)	<i>M. obovata</i> (Min, 2008)	<i>M. obovata</i> (Choi et al., 2009)	<i>M. officinalis</i> (Yahara et al., 1991)	<i>M. officinalis</i> (Lee et al., 2009e)	
Magnolol 5,5'-diallyl-2,2'-dihydroxybiphenyl	266.3 (C <sub>18</sub> H <sub>18</sub> O <sub>2</sub> )	7.65%	2%	0.78%	1%	1.25%	Anti-cancer and anti-inflammatory effects. Anxiolytic and anti-depressant effects, anticonvulsant and anti-nociceptive effects. Anti-stroke. Neurite outgrowth effects. Anti-platelet effects. Relaxation of smooth muscle. Anti-asthmatic effects. Anti-oxidant activity.
Honokiol [2-(4-hydroxy-3-prop-2-enylphenyl)-4-prop-2-enylphenol]	266.3 (C <sub>18</sub> H <sub>18</sub> O <sub>2</sub> )	0.55%	1.25%	1.25%	0.17%	1.81%	Anti-cancer and anti-inflammatory effects. Anxiolytic and anti-depressant effects, anticonvulsant and antinociceptive effects. Anti-stroke. Neurite outgrowth effects. Anti-platelet effects. Relaxation of smooth muscle. Anti-asthmatic effects. Anti-oxidant activity.
4-O-methylhonokiol 2-[4-Methoxy-3-(2-propenyl)phenyl]-4-(2-propenyl)phenol	280.4 (C <sub>19</sub> H <sub>20</sub> O <sub>2</sub> )	0.012%	0.21%	0.13%	0.0003%	1.24%	Anti-stroke, neurite outgrowth effects, anti-inflammatory effects, anti-oxidative, anti-Alzheimer effects.
Obovatol [5-prop-2-enyl-3-(4-prop-2-enylphenoxy)benzene-1,2-diol]	282.3 (C <sub>18</sub> H <sub>18</sub> O <sub>3</sub> )	0.33%	0.125%	0.078%	–	–	Anti-cancer effects, anxiolytic effects, anti-inflammatory effects, and anti-oxidant activity.
Eudesmagnolol		0.12%					
Clovanemagnolol		0.0075%					
Caryolanemagnolol		0.0055%					
Eudeshonokiols A		0.0023%					
Eudeshonokiols B		0.0022%	0.0025%				
Eudesobovatols A		0.054%					
Eudesobovatols B		0.031%	0.00125%				
Magnolianin		2.2%					
Syringin		0.36%	0.0125%				
Liriodendrin		0.14%					
(+)-syringaresinol 4'-O-β-D-glucopyranoside		0.027%			0.0016%		
Caryophyllene oxide		0.018%					
α-eudesmol		0.12%					
β-eudesmol		0.22%					
γ-eudesmol		0.11%					
Coumaric acid			0.00075%				
Magaldehyde B			0.0075%		0.02%		
Sinapic aldehyde					0.0078%		
Syringaresinol					0.081%		

important in traditional Chinese and Japanese herbal medicine. The Chinese name for the herb is Houpu, and it has been used in traditional formulas containing *Magnolia* bark such as Banxia Houpu Tang (Luo et al., 2000), Xiao Zhengai Tang, Ping Wei San and Shenmi Tang (Hsu & Hsu, 1980). In Japan, both prescriptions containing *Magnolia* bark, Hange-koboku-to (Sugaya et al., 1983; Iwasaki et al., 2000) and Sai-boku-to (Fukushima, 1997), are still in use in modern clinical practice. *Magnolia* bark and flower has been used for treatment of gastrointestinal disorders, anxiety and allergic disease in Chinese and Japanese traditional medicines. These applications included quantitative determination of major chemical constituents of *Magnolia* tree and the therapeutic effects of its constituents. *Magnolia* bark was reported to contain several biologically active compounds such as magnolol, honokiol, 4-*O*-methylhonokiol, obovatol and other neolignan compounds, which have many diverse functions. Systemically, the bark showed anti-cancer effects (Choi et al., 2002), anti-inflammatory effects (Kang et al., 2008) and anti-oxidant actions (Kong et al., 2000). In the central nervous system, it showed anti-stress, anti-anxiety (Weeks, 2009), anti-depressant (Xu et al., 2008), anti-Alzheimer and anti-stroke effects. In the cardiovascular system, it showed vascular relaxation, and anti-atherosclerosis and anti-platelet effects. In the gastrointestinal system, it showed anti-esophageal obstruction, anti-gastric ulcer, anti-diarrhea and hepatoprotective effects (Park et al., 2006). In addition, magnosalin, a compound isolated from 'Shin-i' (*Flos magnoliae*), showed anti-arthritis (Kobayashi et al., 1998), anti-angiogenic (Kobayashi et al., 1996) and anti-inflammatory effects (Kimura et al., 1992b). Although these effects are well-known, the mechanisms of action have not yet been established. The aim of this study was to review the data from a variety of experimental and clinical reports and describe the effectiveness of *Magnolia* and possible mechanisms for *Magnolia* and/or its constituents.

## 2. Components of *Magnolia*

*Magnolia* has been used in a number of traditional medicine preparations in China and Japan. Banxia Houpu Tang (Luo et al., 2000), Xiao Zhengai Tang, Ping Wei San, Shenmi Tang (Hsu & Hsu, 1980), Hange-koboku-to (Sugaya et al., 1983; Iwasaki et al., 2000) and Sai-boku-to (Fukushima, 1997) are examples of *Magnolia*-containing medicinal preparations. To rationalize the use of these plants as medicines and add to its tremendous value in traditional health-care systems, several species of *Magnolia*, especially *M. officinalis*, *M. obovata* and *M. biondii*, have been the subject of numerous phytochemical and pharmacological investigations over the last century. The genus *Magnolia* is a rich source of several biologically active compounds. It is reported to have at least 255 different ingredients, such as alkaloids, coumarins, flavonoids, lignans, neolignans, phenylpropanoids and terpenoids (Ito et al., 1982; Tachikawa et al., 2000). Among these, several neolignan ingredients including magnolol, honokiol, 4-*O*-methylhonokiol and obovatol have been the focus of studies on various pharmacological effects of *Magnolia*.

Methanolic extracts of Japanese *M. obovata* was subjected to HPLC to determine levels of several neolignans, magnolol (7.65%), honokiol (0.55%), 4-*O*-methylhonokiol (0.012%) and obovatol (0.33%) (Matsuda et al., 2001). Moreover, Min (2008) found that methanolic extracts of Japanese *M. obovata* were composed of magnolol (2%), honokiol (1.25%), 4-*O*-methylhonokiol (0.21%) and obovatol (0.125%). Choi et al. (2009) found that methanolic extracts of Korean *M. obovata* were composed of magnolol (0.78%), honokiol (1.25%), 4-*O*-methylhonokiol (0.13%) and obovatol (0.078%). Yahara et al. (1991) found that methanolic extracts of Chinese *M. officinalis* were composed of magnolol (1%), honokiol (0.17%) and 4-*O*-methylhonokiol (0.0003%). We recently found that ethanolic extracts of Chinese *M. officinalis* were composed of magnolol (1.25%), honokiol (1.81%) and 4-*O*-methylhonokiol (1.24%) (Lee et al., 2009e). These quantitative and qualitative differences of components from *Magnolia* bark are proposed to be due to studying different *Magnolia*

species, different extracting solvents and different analytic methods or different growing areas. For example, obovatol was extracted from *M. obovata* but not from *M. officinalis* (Table 1). The structure of magnolol was determined to be 5,5'-diallyl-2,2'-dihydroxybiphenyl. The structure of honokiol was determined to be 3,5'-diallyl-4,2'-dihydroxybiphenyl (Bang et al., 2000). The structure of obovatol was determined to be 4',5'-diallyl-2,3-dihydroxybiphenyl ether. The structure of 4-*O*-methylhonokiol was determined to be 3,5'-diallyl-2'-hydroxy-4-methoxybiphenyl which has been referred to as 4-methoxyhonokiol or 6'-*O*-methylhonokiol (Yahara et al., 1991; Min, 2008; Zhou et al., 2008; Oh et al., 2009), as shown in Fig. 1. Also from Magnoliaceae plants are methyl caffeate, denudatin B, sinapyl alcohol, the germacranolide sesquiterpene lactones (costunolide, parthenolide and costunolide dipoxide) and lignans (eudesmin, magnolin, yangambin and epimagnolin B. These were isolated as novel compounds (el-Ferly & Chan, 1978; Teng et al., 1990; Pyo et al., 2002; Choi et al., 2004; Kim et al., 2009). In addition, to increase the activity of *Magnolia*-originated components, novel derivatives have been synthesized and combined with other drug/delivery systems for magnolol (Wang et al., 2002; Li et al., 2003), honokiol (Amblard et al., 2007; Hou et al., 2008; Kim et al., 2010; Zheng et al., 2010) and obovatol (Yu et al., 2009). Therefore, it is important to develop isolation methods to increase the effects and activities of each component.

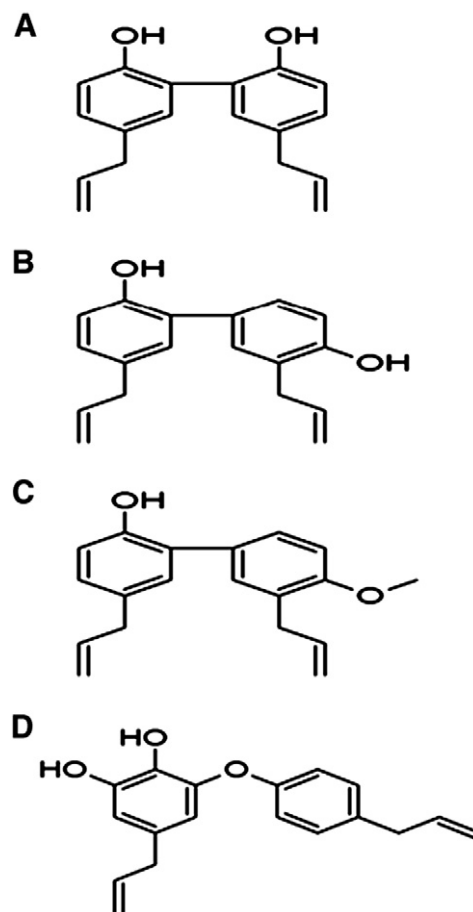


Fig. 1. Chemical structures of (A) magnolol, (B) honokiol, (C) 4-*O*-methylhonokiol and (D) obovatol.

**Table 2**  
Anti-cancer activities of active compounds from *Magnolia* families.

Compound	Cell lines or animal models	IC <sub>50</sub>	Effects	References	
Magnolol	COLO-205	100 μM	Induction of apoptosis	Lin et al., 2001, 2002	
	COLO-205	50 μM	Activation of the CaM/Ras/Raf-1/ERK pathway	Hsu et al., 2007	
	HCT116	60 μM	Apoptosis via inhibiting the EGFR/P13K/Akt signaling pathway	Lee et al., 2009a	
	RKO	12.47 μg/ml	Less toxicity to normal cells and potent anti-cancer activity	Chen et al., 2004	
	COLO-205-implanted nude mice	100 μM	Inhibition of the proliferation of tumor cells	Lin et al., 2002	
	RKO-implanted nude mice	80 mg/kg	Less toxicity to normal cells and potent anti-cancer activity	Chen et al., 2004	
	Hep-G2	100 μM	Induction of apoptosis and inhibition of the proliferation of tumor cells	Lin et al., 2001, 2002	
	HepG2	3.3–13.3 μg/ml	Significant anti-VRE activity and moderate cytotoxicity against the cancer cell lines	Syu et al., 2004	
	CH27	80–100 μM	Induction of apoptosis	Yang et al., 2003	
	H460	20–40 μM	Blockade of the PI3K/PTEN/Akt pathway by autophagy	Li et al., 2007a	
	OVCAR-3	3.3–13.3 μg/ml	Significant anti-VRE activity and moderate cytotoxicity against ovarian cancer cell lines	Syu et al., 2004	
	HeLa	3.3–13.3 μg/ml	Significant anti-VRE activity and moderate cytotoxicity against ovarian cancer cell lines	Syu et al., 2004	
	CGTH W-2	80 μM	Apoptosis via the cytochrome-c/caspase 3/PARP/AIF and PTEN/Akt/caspase 9/PARP pathways and necrosis via PARP activation	Huang et al., 2007	
	5637	40–60 μM	Inhibition of TNF-α-induced MMP-9 expression	Lee et al., 2008a	
	PC-3	60 μM	Apoptosis via inhibiting the EGFR/P13K/Akt signaling pathway	Lee et al., 2009a	
	U373	100 μM	Inhibition of cell proliferation through up-regulation of p21/Cip1	Chen et al., 2009a	
	L5178Y-ML25	2–10 mg/Kg	Inhibition of tumor cell invasion and metastasis	Ikeda et al. 2003	
	Honokiol	B16-BL6	2–10 mg/Kg	Inhibition of tumor cell invasion and metastasis	Ikeda et al. 2003
		RKO	10.33 μg/ml	Apoptosis through a p53-independent pathway	Wang et al., 2004
		SW480	12.98 μg/ml	Apoptosis through a p53-independent pathway	Wang et al., 2004
LS180		11.16 μg/ml	Apoptosis through a p53-independent pathway	Wang et al., 2004	
CH27		40.9 μM	Modulation of Bcl-X1 and Bad proteins, release of mitochondrial cytochrome c and caspase-3	Yang et al., 2002	
H460		41.1 μM	Modulation of Bcl-X1 and Bad proteins, release of mitochondrial cytochrome c and caspase-3	Yang et al., 2002	
H1299		34.7 μM	Modulation of Bcl-X1 and Bad proteins, release of mitochondrial cytochrome c and caspase-3	Yang et al., 2002	
H1299		25 μM	Apoptosis through inhibition of invasion via modulation of NF-κB activation	Ahn et al., 2006	
WI-38		60.5 μM	Modulation of Bcl-X1 and Bad proteins, release of mitochondrial cytochrome c and caspase-3	Yang et al., 2002	
LL/2		17.7 μM	Enhancement of tumor cell radiosensitivity in vitro and in vivo	Hu et al., 2008	
LL/2 bearing-tumor model		25 mg/kg	Enhancement of tumor cell radiosensitivity in vitro and in vivo	Hu et al., 2008	
Cisplatin-sensitive (A2780s) -resistant (A2780cp) cancer cells		36 μM, 34.7 μM	Increased susceptibility of cisplatin-resistant human ovarian cancer cells	Luo et al., 2008	
Cisplatin-sensitive (A2780s) -resistant (A2780cp) cancer cells implanted mice		10 mg/kg	Increased susceptibility of cisplatin-resistant human ovarian cancer cells. Inhibition of both A2780s and A2780cp ovarian cancer cell growth. Prolongation of the survival of tumor-bearing mice.	Luo et al., 2008	
PC-3		20 or 40 μM	G <sub>0</sub> -G <sub>1</sub> phase cell cycle arrest through suppression of retinoblastoma protein level/phosphorylation and inhibition of E2F1 transcriptional activity	Hahm and Singh, 2007	
LNCaP.		20 or 40 μM	G <sub>0</sub> -G <sub>1</sub> phase cell cycle arrest through suppression of retinoblastoma protein level/phosphorylation and inhibition of E2F1 transcriptional activity	Hahm and Singh, 2007	
MCF-7/ADR		5–25 μM	Down-regulation of P-glycoprotein expression	Xu et al., 2006	
MCF-7		15–20 μM	Induction of necrotic cell death through the mitochondrial permeability transition pore	Li et al., 2007b	
A293		25 μM	Apoptosis through inhibition of invasion via modulation of NF-κB activation	Ahn et al., 2006	
HEK293		15–20 μM	Induction of necrotic cell death through the mitochondrial permeability transition pore	Li et al., 2007b	
SCC4		25 μM	Apoptosis through inhibition of invasion via modulation of NF-κB activation	Ahn et al., 2006	
MKN45	20–40 μM	Induction of the GRP94 cleavage-associated apoptotic response	Sheu et al., 2007		
MKN45-implanted nude mice	0.5–1.5 mg/kg	Induction of the GRP94 cleavage-associated apoptotic response	Sheu et al., 2007		
U937	55 μM	Inhibition of TNF-α-stimulated NF-κB activation and NF-κB regulated gene expression through suppression of IKK activation	Tse et al., 2005		

Table 2 (continued)

Compound	Cell lines or animal models	IC <sub>50</sub>	Effects	References
Honokiol	RAW 264.7	25 $\mu$ M	Apoptosis through inhibition of invasion via modulation of NF- $\kappa$ B activation	Ahn et al., 2006
	B-CLL	38 $\mu$ M	Induction of caspase-dependent apoptosis	Battle et al., 2005
	MM	30.0–37.5 $\mu$ M	Apoptosis via both caspase-dependent and -independent pathway	Ishitsuka et al., 2005
	HL-60	55 $\mu$ M	Inhibition of TNF- $\alpha$ -stimulated NF- $\kappa$ B activation and NF- $\kappa$ B regulated gene expression through suppression of IKK activation	Tse et al., 2005
	HL-60	15–20 $\mu$ M	Induction of necrotic cell death through the mitochondrial permeability transition pore	Li et al., 2007b
	KBM-5	25 $\mu$ M	Apoptosis through inhibition of invasion via modulation of NF- $\kappa$ B activation	Ahn et al., 2006
	U266	25 $\mu$ M	Apoptosis through inhibition of invasion via modulation of NF- $\kappa$ B activation	Ahn et al., 2006
Obovatol	SW620	5 $\mu$ M	Increased susceptibility to chemotherapeutic agents	Lee et al., 2009c
	SW620 implanted nude mice	5 mg/kg	Increased susceptibility to chemotherapeutic agents	Lee et al., 2008b
	HCT116	5 $\mu$ M	Increased susceptibility to docetaxel	Lee et al., 2009c
	SW620- implanted nude mice	5 mg/kg	Inhibition of colorectal cancer growth by blocking tumor cell proliferation and inducing apoptosis	Lee et al., 2008b
	LNCaP	5 $\mu$ M	Increased susceptibility to docetaxel	Lee et al., 2009c
	PC-3	5 $\mu$ M	Increased susceptibility to chemotherapeutic agents	Lee et al., 2009c
	HT1080	20 $\mu$ M	Blocking of migration and invasion by inhibition of MMP-2 expression and activity	Lee et al., 2007

### 3. Therapeutic applications in cancer

#### 3.1. Effects on cancer

Individual constituents of *Magnolia* have been reported by many investigators to have anti-cancer effects (Table 2). In vitro, honokiol induced caspase-dependent cell death in B-cell chronic lymphocytic leukemia (B-CLL) cells, and it was more toxic to B-CLL cells than to normal mononuclear cells, suggesting increased susceptibility of the malignant cells (Battle et al., 2005). Low levels (10–40  $\mu$ M) of magnolol in human lung squamous carcinoma CH27 cells inhibited proliferation of the cells; high levels (80–100  $\mu$ M) induced apoptosis of CH 27 cells (Yang et al., 2003). In addition, magnolol dose-dependently (0–40  $\mu$ M) decreased cell numbers in a human glioblastoma cancer U373 cell line (Chen et al., 2009a). Twenty-four hours treatment of CGTH W-2 thyroid carcinoma cells with 80  $\mu$ M magnolol led to about 50% of cells showing apoptotic features and 20% showing necrotic features (Huang et al., 2007). Obovatol dose-dependently (1–5  $\mu$ M) inhibited the proliferation of vascular smooth muscle cells (VSMCs) from rat aorta that was induced by platelet-derived growth factor. This is an in vitro model of proliferative disease of the arterial intima that did not exhibit any cellular toxicity or apoptosis (Lim et al., 2010). Obovatol (10–25  $\mu$ M) inhibited cancer cell growth in prostate cells (LNCaP and PC-3) and colon cancer cells (SW620 and HCT116), although cytotoxic activity was not observed in normal cells up to 50  $\mu$ M (Lee et al., 2008c). Honokiol had an anti-angiogenic effect in an in vitro proliferation assay of the transformed endothelial cell lines SVR. Honokiol treatment (3 mg/day) in an in vivo model of angiosarcoma-implanted nude mice showed an anti-tumor effect, a decrease of 50% in tumor growth (Bai et al., 2003). Obovatol (5 mg/kg/day) in human colorectal carcinoma SW620 cells implanted in nude mice for 20 days inhibited tumor growth; there was a 50% decrease in tumor volume and a 44.6% decrease in tumor weight at the end of the experiment and no adverse health effects (Lee et al., 2008b). Honokiol (80 mg/kg) in a human colorectal carcinoma cell line (RKO) implanted in Balb/c nude mice displayed anti-cancer activity – it inhibited tumor growth and prolonged the lifespan of tumor-bearing mice (Chen et al., 2004). Both magnolol and a methanol extract of *M. officinalis* exhibited remarkable inhibitory effects in a murine model of skin tumor promotion (Konoshima et al., 1991; Hibasami et al., 1998; Maruyama et al., 1998). Recently, anti-proliferative activities of

obovitol, namely in vivo neointimal formation, were found in a rat carotid artery injury model. Two days after injury, in vivo medial VSMC proliferation (assessed by in situ BrdU labeling) was significantly inhibited in the obovatol-treated groups (100  $\mu$ g and 1 mg). The angiographic mean luminal diameters of the obovatol-treated groups were significantly larger than that of the control group. The obovatol-treated groups showed significant reductions in neointimal formation versus the control group (Lim et al., 2010). Treatment with 2 mg honokiol/mouse (thrice a week) in PC-3-implanted nude mice significantly retarded growth of PC-3 xenografts without causing weight loss. Tumors from honokiol-treated mice exhibited a markedly higher count of apoptotic bodies, a reduced proliferation index, and neovascularization compared with control tumors (Hahm et al., 2008). In COLO-205-implanted nude mice that formed solid tumors, administration of magnolol (100 mg/kg, 5 times/week for 2 weeks) led to profound regression (up to 85%) of these tumors (Lin et al., 2002).

#### 3.2. Mechanisms of action in cancer

Inhibition of apoptosis is a key feature of cancer development (Hanahan & Weinberg, 2000; Taylor et al., 2008). In particular, the intrinsic apoptosis pathway is initiated by mitochondrial cytochrome c release into the cytosol. Cytochrome c release is regulated by the pro-apoptotic B-cell lymphoma protein-2 (Bcl2) family of proteins such as Bcl2-associated protein (Bax), Bid and Bak and by the anti-apoptotic Bcl2 family of proteins such as Bcl2 and Bcl-x<sub>l</sub>. Apoptosis via caspase activation is also significant in cancer development (Fischer et al., 2007). Therefore, it has been proposed that controlling apoptosis could be an important strategy in the development of new cancer treatments (Jiang & Wang, 2004; Ledgerwood & Morison, 2009).

The anti-cancer mechanism of *Magnolia* has been reported to be associated with cleaved poly (adenosine diphosphate-ribose) polymerase (PARP) and modulation of caspase cascades and three subfamilies of Bcl2, Bax, and BH-3 (Choi et al., 2002; Yang et al., 2003; Chen et al., 2004; Battle et al., 2005; Huang et al., 2007; Hahm et al., 2008; Lee et al., 2008a). Honokiol-induced B-CLL cell apoptosis was characterized by activation of caspases-3, -8 and -9 and cleavage of PARP. Exposure of B-CLL cells to honokiol resulted in up-regulation of Bax and down-regulation of the expression of the key survival protein myeloid-cell leukemia sequence 1 (Mcl-1), which is associated with response to

**Table 3**  
Therapeutic applications for neuronal disease.

Compounds	Dose	Subjects	Effects	References
<i>Anxiolytic effect</i>				
Extracts of <i>M. officinalis</i> and Phellodendron amurense (Relora®)	250 mg/3 times daily	20–50 years old female adults	Reduction of temporary and transitory anxiety	Kalman et al., 2008
<i>Magnolia</i> bark extract with magnesium	60 mg with 50 mg	Menopausal women	Efficacy on psycho-affective and sleep disturbance through interaction with GABA system	Mucci et al., 2006
Honokiol	0.2 mg/kg	Mice	Reduction of anxiety	Kuribara et al., 2000a
Obovatol	0.2–1 mg/kg	Mice	Reduction of anxiety by GABA-benzodiazepine receptor mediated Cl <sup>-</sup> channel opening	Seo et al., 2007; Ma et al., 2009
Obovatol	0.05–0.2 mg/kg	Mice	Prolongation of sleeping time by GABA-benzodiazepine receptor mediated Cl <sup>-</sup> channel activation	Ma et al., 2009
Honokiol and magnolol	5 μM	Rat brain membrane	Activation of GABAergic system	Squires et al., 1999
Dihydrohonokiol-B	1 mg/kg	Mice.	Reduction of anxiety by stimulation of GABA <sub>C</sub> receptors and of the GABA <sub>A</sub> -benzodiazepine receptor complex	Kuribara et al., 2000b; Irie et al., 2001; Liu et al., 2008
Dihydrohonokiol-B	1–100 ng/ml	Rat hippocampal neurons	Protection of neurons from ammonia-induced increases in [Cl <sup>-</sup> ] <sub>i</sub> by stimulation of GABA <sub>C</sub> receptors	Irie et al., 2001
Dihydrohonokiol-B	10 ng/ml	Rat hippocampal neurons	Prevention of Aβ-induced aggravation of glutamate neurotoxicity through GABA <sub>C</sub> receptor stimulation	Liu et al., 2005
<i>M. officinalis</i> Rehder extract	10–100 μg/ml	Dopamine, serotonin and GABA receptor proteins	Interaction with adenosine A(1) and potentiating the GABA activated chloride current	Koetter et al., 2009
<i>Antidepressant effects</i>				
Mixture of honokiol and magnolol	20 mg/kg	Chronic unpredictable mild stress of rats	Elevation of serotonin levels	Koetter et al., 2009; Qiang et al., 2009
Magnolol and dihydroxydihydromagnolol	50–100 mg/ kg	Rats	Attenuation of depression	Nakazawa et al., 2003
Magnolol and honokiol	20 and 40 mg/ kg	Mice and rats	Attenuation of depression by normalization of serotonin and its metabolites and platelet adenylate cyclase activity	Xu et al., 2008
Magnolol and honokiol	15 and 30 mg/kg	Mice	Attenuation of depression by significant increase of serotonin and in noradrenaline	Yi et al., 2009
<i>Therapeutic effects to neurodegenerative disorders</i>				
Magnolol and honokiol	10 and 1 mg/kg	SAMP8 mice	Prevention of age-related learning and memory impairment	Matsui et al., 2009
Magnolol and honokiol	100 μM	Rat hippocampal neurons	Concentration-dependent enhancement of K <sup>+</sup> -evoked ACH release	Tsai et al., 1995; Hou et al., 2000
Magnolol and honokiol	1–100 μM	Rat hippocampal neurons	Increase of extracellular ACH release	Tsai et al., 1995; Hou et al., 2000
Ethanol extract of <i>M. officinalis</i> and 4-O-methylhonokiol	5 or 10 mg/kg, or 0.75 or 1.5 mg/kg	Mice	Prevention of memory impairment by attenuation of the scopolamine-induced increase of ACHE activity	Lee et al., 2009e
<i>Prevention of neurotoxicities</i>				
Honokiol	1–100 mg/kg	Mice	Reduced lethality of NMDA by reduction of oxidative stress	Cui et al., 2007
Magnolol and honokiol	0.1–10 μM	Rat cerebellar granule cells	Protection of neurons against hydrogen peroxide-induced toxicity	Lin et al., 2006
4-O-methylhonokiol and ethanol extract of <i>M. officinalis</i>	1–10 mg/kg	Mice	Suppression of Aβ <sub>1–42</sub> -induced mice memory impairment by suppression of ROS and Aβ generation	Lee et al., 2009b
<i>Neurotrophic effects</i>				
4-O-methylhonokiol	1 or 10 μM	Rat embryonic neuronal cells	Release of Nerve growth factor (NGF) and Brain-derived neurotrophic factor	Lee et al., 2009d
(+)-eudesmin	50 μM	PC12 cells	Enhanced NGF-induced neurite-bearing activity	Yang et al., 2006
Honokiol	0.1–10 μM	Rat cortical neurons	Increase of neurite outgrowth	Fukuyama et al., 2002; Zhai et al., 2005
Honokiol	0.1–10 μM	Rat cortical neurons	Promotion of neurite outgrowth	Fukuyama et al., 2002; Zhai et al., 2005
<i>Therapeutic effects to strokes</i>				
Honokiol	10 μg/kg	Mice	Protection of ischaemic reperfusion injury by preservation of mitochondrial oxidative stress	Chen et al., 2007
Honokiol	0.1 or 1.0 μg/kg	Rats	Amelioration of focal cerebral ischemia-reperfusion injury by Anti-oxidative and anti-inflammatory effects	Liou et al., 2003
Magnolol	20 or 40 mg/kg	Rats	Impressive effects against heatstroke reactions by attenuating free radical formation and lipid peroxidation	Chang et al., 2003

Table 3 (continued)

Compounds	Dose	Subjects	Effects	References
<i>Antinociceptive effects</i>				
Obovatol	1–5 $\mu$ M	LPS-activated RAW 264.7	Inhibition of NO production through the inhibition of NF- $\kappa$ B/MAPK activity	Choi et al., 2007
Magnolol and honokiol	5 or 10 mg/kg, i.p. or 0.1–1.0 $\mu$ g/paw	Mice	Inhibition of glutamate, NMDA and mGlu5 receptors and suppression of PGE2 generation	Lin et al., 2009
Magnolol	20 or 40 mg/kg	Rats	Inhibition of heatstroke by attenuation of free radical formation and lipid peroxidation	Chang et al., 2003
<i>Anticonvulsant effects</i>				
Ethyl ether and hydroalcoholic extract of <i>M. grandiflora</i> L. seeds	250 mg/kg and 200 mg/kg	Rats	Prolongation of sleeping time	Bastidas Ramirez et al., 1998; Nakazawa et al., 2003; Sy et al., 2008
Honokiol	1–100 $\mu$ M	Rat cerebrocortical synaptosomes	Prevention of seizures by inhibition of glutamate and intracellular Ca <sup>2+</sup> signals	Bastidas Ramirez et al., 1998; Nakazawa et al., 2003; Sy et al., 2008

treatment in B-CLL patients (Battle et al., 2005). Honokiol induced apoptosis of RKO cells through activation of caspase cascades (Chen et al., 2004). Honokiol-induced apoptosis of human prostate cancer cells (PC-3, LNCaP and C4-2) was correlated with the induction of Bax, Bak, and Bad and with a decrease in Bcl-xL and Mcl-1 protein levels (Hahm et al., 2008). Magnolol-induced apoptosis in human lung squamous carcinoma CH27 cells was related to increased expression of Bad, Bcl-X<sub>s</sub>, caspases-3, -6, and -9 and JNK and to down-regulation of the expression of Bcl-X<sub>L</sub> and ERK (Yang et al., 2003). Magnolol-induced CGTH W-2 thyroid carcinoma cell death was characterized by an increase in levels of activated caspases and of cleaved PARP (Huang et al., 2007). Consistent with the induction of apoptosis in prostate and colon cancer cells, obovatol increased the expression of Bax, caspase-3 and caspase-9, whereas it inhibited the expression of Bcl-2 (Lee et al., 2008b). Costunolide, a compound isolated from the stem and bark of *M. sieboldii*, induced apoptosis in human promonocytic leukemia U937 cells; the apoptosis was demonstrated to be induced by depleting intracellular thiols modulated by Bcl-2 (Choi et al., 2002). Individual constituents of *Magnolia* had anticancer effects through cell cycle arrest related to activation of the p21 pathway (Lin et al., 2002; Chen et al., 2009a; Lim et al., 2010). Magnolol-induced COLO-205 cell cycle arrest occurred when the cyclin–cyclin-dependent kinases (CDKs) system was inhibited, just when p21 protein expression was augmented (Lin et al., 2002). Magnolol treatment of U373 cells arrested the cells at the G0/G1 phase of the cell cycle, decreased protein levels of cyclins A and D1, and increased protein levels of p21/cip1. The CDK2–p21/Cip1 complex was increased, and the CDK2 kinase activity was decreased in magnolol-treated U373 cells (Chen et al., 2009a). Inhibition of cell proliferation and cell death induced by *Magnolia* components was reported to occur through the inhibition of NF- $\kappa$ B activity (Tse et al., 2005; Kim et al., 2007; Lee et al., 2008a, 2009a).

NF- $\kappa$ B mediates tumorigenesis, angiogenesis and metastasis through the expression of genes participating in malignant conversion and tumor promotion (Garg and Aggarwal, 2002; Greten et al., 2004; Pikarsky et al., 2004). Constitutive activation of NF- $\kappa$ B is found in most tumors, and activated NF- $\kappa$ B up-regulates anti-apoptotic genes and/or down-regulates apoptotic gene expression (Garg and Aggarwal, 2002). Therefore, inactive NF- $\kappa$ B results in an increase in the expression of apoptotic genes such as Bax, caspase-3, caspase-9, and a decrease in anti-apoptotic genes such as Bcl2, COX-2, c-Fos, c-Jun, X inhibitor of apoptosis protein (XIAP) and inhibitor of apoptosis protein (IAP) (Aggarwal et al., 2006a,b). The inactivation of NF- $\kappa$ B is supposed to be an attractive target for anti-cancer therapy (Baldwin, 2001; Yamamoto and Gaynor, 2001; Collett and Campbell, 2006).

Obovatol inhibited TNF- $\alpha$  and 12-O-tetradecanoylphorbol-13-acetate-induced transcriptional and DNA binding activities of NF- $\kappa$ B in prostate and colon cancer cells. Subsequently, obovatol decreased translocation of p65 and p50 into the nucleus via a decrease in the phosphorylation of I $\kappa$ B. Consistent with the induction of apoptosis,

obovitol increased the expression of apoptotic genes Bax, caspase-3, and caspase-9, whereas it inhibited the expression of anti-apoptotic genes such as Bcl2, IAP-1 and XIAP as well as the cell proliferation marker genes COX-2, c-Fos, c-Jun and cyclin D1 (Lee et al., 2008c). Obovatol also resulted in synergistic acceleration of docetaxel-induced cell death of prostate and colon cancer cells, and the combination significantly inhibited NF- $\kappa$ B activities as well as expression of NF- $\kappa$ B target apoptotic cell death proteins; but it decreased anti-apoptotic cell death proteins (Lee et al., 2009c). Honokiol treatment blocked TNF- $\alpha$ -induced NF- $\kappa$ B activation in four different cancer cell lines (U937, HL-60, MCF-7 and HeLa). Honokiol did not directly affect NF- $\kappa$ B: DNA binding, but honokiol inhibited TNF- $\alpha$ -stimulated phosphorylation and degradation of the cytosolic NF- $\kappa$ B inhibitor I $\kappa$ B $\alpha$  (Tse et al., 2005). Both magnolol and honokiol had an additional anti-cancer effect – they induced apoptosis via up-regulation of phosphatase and tensin homolog (PTEN) and down-regulation of Akt (Huang et al., 2007; Liu et al., 2008). In particular, magnolol induced apoptosis via the cytochrome-c/caspase 3/PARP/apoptosis inducing factor (AIF) and PTEN/Akt/caspase 9/PARP pathways and induced necrosis via PARP activation (Huang et al., 2007). PTEN, a well-known tumor suppressor gene, reduced phosphorylation of focal adhesion kinase (FAK), suppressed invasion and metastasis formation, and increased survival in an animal model (Gautam et al., 2003). PTEN seems to function by negatively regulating the action of phosphatidylinositol 3-kinase and its downstream substrate Akt (Cantley & Neel, 1999; Ramaswamy et al., 1999). Loss of PTEN function could result in increased Akt activity and suppression of apoptosis (Stambolic et al., 1998; Ramaswamy et al., 1999). Magnolol activated PTEN and inactivated Akt by decreasing levels of phosphorylated PTEN and phosphorylated Akt in CGTH W-2 thyroid carcinoma cells (Huang et al., 2007). Honokiol (10, 20 or 30  $\mu$ M for 3 h) decreased the phosphorylation of Akt and increased the level of its inhibitor PTEN in MCF-7, MCF-7/adr and BT-474 cell lines (Liu et al., 2008).

#### 4. Therapeutic applications for neuronal disease

##### 4.1. Effects on and mechanisms in anxiety

Anxiety disorders, which are highly prevalent worldwide, are considered the most common psychiatric diagnoses, affecting between 10 and 30% of the general population (Rice & Miller, 1998; Greenberg et al., 1999; Wittchen & Hoyer, 2001). Excess anxiety can be debilitating and lower the quality of life.

Benzodiazepines have been extensively used for the treatment of several forms of anxiety, although these compounds have well-known side effects such as sedation, muscle relaxation, amnesia, and dependence (Jordan et al., 1996; Rickels & Schweizer, 1997). The development of new anxiolytics has been an area of interest. Recently,

various types of herbal medicines have been used as anxiolytic drugs (Rex et al., 2002).

The bark of *M. officinalis* has been used in traditional Chinese medicine to treat a variety of mental disorders including depression in China and Japan (Watanabe et al., 1983; Maruyama et al., 1998; Nakazawa et al., 2003). The researchers based in traditional medicine have focused their efforts toward the antidepressant, anxiolytic and sedative effects of *M. officinalis*-contained decoctions (Table 3) (Xu et al., 2008; Weeks, 2009). Kuribara et al. (2000a) studied honokiol derived from *Magnolia*; seven daily treatments of 0.2 mg/kg honokiol produced an anxiolytic effect measured as an elevated plus-maze test. *Magnolia*-free preparations did not have any anxiolytic effects. Oral administration of obovatol (0.2, 0.5 and 1.0 mg/kg) increased the percentage of entries into open arms and the percentage of time spent in the open arms, compared with that of a saline-treated group. These anxiolytic-like effects were reversed by flumazenil, a benzodiazepine receptor antagonist, suggesting that the anxiolytic-like effects of obovatol interacted with the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex (Seo et al., 2007). In a randomized, parallel, placebo-controlled clinical study, Relora® (250 mg, 3 times daily, for 6 weeks), an extract mixture of *M. officinalis* and *Phellodendron amurense* was more effective than placebo in reducing temporary, transitory anxiety as measured by the Spielberg STATE-TRAIT anxiety questionnaire in healthy women (Kalman et al., 2008). A controlled, randomized, multicentre study showed the efficacy of a rational formulation containing Estromineral serena® (60 mg of *Magnolia* bark extract and 50 mg of magnesium) for 24 weeks on psycho-affective and sleep disturbances in symptomatic menopausal women (Mucci et al., 2006). Flushing, nocturnal sweating, palpitations, insomnia, asthenia, anxiety, mood depression, irritability, vaginal dryness, dyspareunia, and libido loss, significantly decreased in severity and frequency after the fourth week of Estromineral serena® (Mucci et al., 2006). On the other hand, *M. officinalis* extracts were demonstrated to have an affinity for adenosine A(1) and potentiated the GABA-activated chloride current at the benzodiazepine subunits of the GABA receptor, consistent with traditional anxiolytic activities (Koetter et al., 2009). Co-administration of dihydrohonokiol-B, a derivative of honokiol, with diazepam led to an enhanced anxiolytic-like efficacy. Moreover, as with diazepam, the anxiolytic-like effect of the dihydrohonokiol-B was reduced by flumazenil, the benzodiazepine receptor antagonist, but not bicuculline, a GABA<sub>A</sub> antagonist. These results suggest that the dihydrohonokiol-B acts at the benzodiazepine recognition site of the GABA<sub>A</sub>-benzodiazepine receptor complex (Kuribara et al., 2000b). In other research, a GABA<sub>C</sub> receptor blocker, (1,2,5,6-tetrahydropyridin-4-yl)methyl-phosphinic acid inhibited the protective effects of dihydrohonokiol-B toward ammonia-induced increases in intracellular Cl<sup>-</sup> concentrations and Aβ-induced decreases in neuronal Cl<sup>-</sup>-ATPase activity (Irie et al., 2001; Liu et al., 2005). In animal behavioral research, the honokiol-induced prolongation (0.2 mg/kg/day for 1 week) of time in the open arms of the maze was almost equivalent to the effect of a single treatment with diazepam (1 mg/kg). The honokiol-induced effect was inhibited by flumazenil (0.3 mg/kg) and bicuculline (0.1 mg/kg), and by CCK-4 (50 µg/kg) and caffeine (30 mg/kg). However, the co-administration of diazepam with caffeine enhanced the effect, and diazepam completely reversed the effect of CCK-4. These facts suggest that the anxiolytic mechanism of honokiol is somewhat different from that of diazepam (Kuribara et al., 1998). As an intriguing result, Squires et al. (1999) reported that honokiol and magnolol increase the binding of [<sup>3</sup>H]muscimol (a GABA<sub>A</sub> agonist) in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low affinity sites. In a related article, Ma et al. (2009) reported that magnolol may enhance pentobarbital-induced sleeping behaviors through the activation of the GABAergic system. Also, anxiolytic-like effects of obovatol appeared to be mediated by the GABA-benzodiazepine receptor Cl<sup>-</sup> channel opening (Seo et al., 2007) and obovatol potentiated pentobarbital-induced sleeping time through GABA receptors/Cl<sup>-</sup> channel activation (Ma et al., 2009). We recently found

that 4-*O*-methylhonokiol showed anxiolytic effects, and its effect was related to GABA-benzodiazepine receptor Cl<sup>-</sup> channel opening (unpublished data). These data suggest that components of *Magnolia* could be used for anxiety, and its effect may be related with GABA receptor/Cl<sup>-</sup> channel activation.

#### 4.2. Effects on and mechanisms in depression

Depression is a pervasive mood-altering disease affecting energy, sleep, appetite, libido and the ability to function. The symptoms of depression are an intense feeling of sadness, hopelessness, despair, and the inability to experience pleasure in usual activities. Most common anti-depressant drugs potentiate the action of norepinephrine, dopamine and serotonin in the brain. Several classes of antidepressant such as tricyclic/polycyclic antidepressants, SSRI, monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors as well as lithium salts have been used (Eby & Eby, 2010).

Between 29% and 46% of patients with depression who are treated with antidepressants fail to respond fully; they have treatment-resistant depression (Papakostas, 2005). In addition, SSRI cause side effects such as nausea, diarrhea, agitation and headaches. SSRIs were reported to double the risk of suicidal behaviour (Stone et al., 2009). Tricyclic antidepressants cause dry mouth, blurred vision, drowsiness, dizziness, tremors, sexual problems, skin rash, and weight gain or loss. Monoamine oxidase inhibitors cause several side effects including hepatitis, heart attack, stroke and seizures. To overcome these side effects, therapeutic methods have included other antidepressant materials such as omega-3 fatty acids (Appleton et al., 2006), dehydroepiandrosterone (Wolkowitz et al., 1999; Schmidt et al., 2005; Nair et al., 2006), zinc (Nowak et al., 2003, 2005), lithium (Court & Nelson, 1996), magnesium (Eby & Eby, 2006), *Eleutherococcus senticosus* (Deyama et al., 2001; Kurkin et al., 2006), Saffron (the flowers of *Crocus sativus*) (Wang et al., 2010), inositol (vitamin B<sub>8</sub>) (Taylor et al., 2004), Kanna (*Sceletium tortuosum*) (Smith et al., 1996), bach flower remedies and Australian bush flower essences (Ernst, 2002), and green/white Tea (Niu et al., 2009). However, the effects of these materials are not yet established. New clinical and pharmacological strategies that are focusing on new drug development must be developed.

Treatments with magnolol and dihydroxydihydromagnolol [50–100 mg/kg, intraperitoneal (i.p.)] attenuated forced swim-induced experimental depression in mice (Nakazawa et al., 2003). Treatment (20 and 40 mg/kg) with a mixture of honokiol and magnolol to rats induced the same effects as in the forced swimming test and the tail suspension test and reversed the chronic mild stress-induced reduction in sucrose consumption to prevent anhedonia (Xu et al., 2008). Yi et al. (2009) showed that treatment (30 mg/kg) with a mixture of honokiol and magnolol decreased immobility in the forced swimming test and tail suspension test in mice after one- and two-week treatments. Furthermore, the anti-depressant effect was increased by co-administration of ginger rhizome. Although ginger rhizome (19.5 or 39 mg/kg) alone was ineffective, the combination of an ineffective dose of 39 mg/kg ginger rhizome with 15 mg/kg mixture of honokiol and magnolol was the most effective, and produced a synergistic action on behaviors after a two-week treatment (Yi et al., 2009). The results suggest that a mixture of honokiol and magnolol with ginger rhizome creates a synergistic anti-depressant action by attenuating abnormalities in serotonergic and noradrenergic functions. A mixture of 20 mg/kg honokiol, 20 mg/kg magnolol and 14 mg/kg ginger rhizome exhibited significant synergistic effects on the sucrose intake increase and on the immobility time reduction in rats under chronic unpredictable mild stress. The mixture of honokiol and magnolol elevated serotonin levels in various brain regions, and ginger rhizome reduced gastric mucosa cholecystokinin and serum gastrin levels in rats under chronic unpredictable mild stress (Qiang et al., 2009). These results suggest that the

synergistic anti-depressant-like effects of a mixture of honokiol and magnolol with ginger rhizome might be mediated simultaneously by regulation of serotonergic and gastrointestinal system functions.

An extract of *M. officinalis* and a mixture of *Ziziphus spinosa* were investigated for pharmacological target. In vitro radioligand binding and cellular functional assays revealed to interact with the adenosine A(1) receptor, dopamine transporter and dopamine D(5) receptor (antagonist activity), serotonin receptors [5-HT(1B) and 5-HT(6) antagonist activity] and the GABA benzodiazepine receptor at a concentration of 100 µg/ml or lower (Koetter et al., 2009).

On the other hand, drugs which selectively bind to the serotonin transporter, which are known as SSRIs, were effective in treating anxiety, panic, compulsive behavior and depression in humans by elevating synaptic serotonin levels (Yamauchi et al., 2006; Baghai et al., 2009). The results support the traditional conclusion that *M. officinalis* bark and *Ziziphus spinosa* seed have anxiolytic and sleep-inducing activities (Koetter et al., 2009). Additionally, the effect of corticotrophin releasing factor in modulating the activity of noradrenergic neurons may provide a link between environmental trigger factors and central noradrenergic dysfunction. Such a link may be a basis for the development of novel anti-depressants (Leonard, 1997). So, an increase in serotonin and a synergistic increase in noradrenaline may be related to the anti-depressant function of *Magnolia* extracts. Xu et al. (2008) reported that a mixture of honokiol and magnolol (20 and 40 mg/kg) significantly attenuated chronic mild stress-induced alterations in the 5-hydroxyindolacetic acid (serotonin metabolite)/serotonin ratio in hippocampus and nucleus accumbens, and decreased chronic mild stress-induced corticosterone elevation in serum to normalize the hypothalamic-pituitary-adrenal hyperactivity. It also reversed chronic mild stress-induced reductions in platelet adenylate cyclase activity via up-regulating the cyclic adenosine monophosphate pathway. It is known that biogenic amine neurotransmitters (dopamine, noradrenaline, serotonin and histamine) act through adenylate cyclase (Wollemann, 1980) and drugs that enhance brain serotonin function increase serum corticosterone concentrations (Fuller, 1996). Thus, honokiol and magnolol could normalize the biochemical abnormalities in brain serotonin and its metabolites, serum corticosterone levels, and platelet adenylate cyclase activity, suggesting that they also may be involved in the anti-depressant effects of these plant constituents. These data show that components of *Magnolia* could be applicable to depressed patients, and their anti-depressant effects may be related to modulation of neurotransmitters.

#### 4.3. Effects on and mechanisms in Alzheimer disease

Studies of patients with AD have revealed depleted brain levels of acetylcholine. Centrally acting cholinergic drugs have been reported to increase the regional cerebral blood flow of acetylcholine (ACH) in the brain regions affected by AD (Namba et al., 1971). Thus, maintaining acetylcholine levels in brain is important for the cure of AD patients. One way to do this is blocking the activity of acetylcholinesterase (ACHE), the enzyme that degrades ACH. The cholinesterase inhibitors donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate are the currently approved drugs for treatment of AD patients (Ellis, 2005). However, ACHE inhibitors have limitations including their short half-lives and excessive side effects caused by activation of peripheral cholinergic systems, as well as hepatotoxicity, which is the most frequent and important side effect of these drugs (Farlow et al., 1992; Knapp et al., 1994; Rogers et al., 1998; Lahiri et al., 2002). For this reason, alternative and complementary therapies are needed. AD is also characterized by cerebral parenchyma deposition of amyloid beta peptide (Aβ) (Weiner et al., 2000). Oxidative damage of macromolecules is associated with accumulation of Aβ in the progressive development of AD (Frank & Gupta, 2005; Nishida et al., 2008; Rezaei-Zadeh et al., 2008), and is a critical event in Aβ-induced neuronal cell death (Yatin et al., 1998; Drouet et al., 2000; Butterfield &

Lauderback, 2002; Jang & Surh, 2002). Many studies have reported that antioxidants might reduce Aβ accumulation, and thereby reduce neuronal cell death and memory impairment (Liou et al., 2003; Lin et al., 2006; Kim et al., 2009; Lee et al., 2010). Our previous studies also showed that theanine and epigallo catechin-3-gallate (EGCG), which have anti-oxidative properties, protected memory impairment in mice through the reduction of Aβ accumulation (Kim et al., 2009; Lee et al., 2009a,b,c,d,e). Since neuroinflammation is also a critical contributor to the development of AD (Lee et al., 2008a,b,c), anti-inflammatory agents could also be applicable to the treatment of AD.

Various researchers have recently reported that compounds from *Magnolia* may have potential therapeutic applications to various neurodegenerative disorders (Matsui et al., 2009). Senescence-accelerated-prone 8 (SAMP8) mice exhibit early-onset impaired learning and memory (Nomura & Okuma, 1999). Age-related learning and memory impairment in SAMP8 mice was prevented by daily treatment for 14 days with either magnolol (10 mg/kg) or honokiol (1 mg/kg). Additionally, a 14-day treatment with either drug enhanced phosphorylation of Akt in the forebrain at 2 months of age and prevented age-related cholinergic deficits (Matsui et al., 2009). When 100 µM of honokiol or magnolol was perfused into rat hippocampus via a dialysis probe, extracellular ACH release was markedly increased to 165.5% and 237.83% of basal levels, respectively. The results suggest that honokiol or magnolol may enhance in vivo hippocampal acetylcholine release (Hou et al., 2000). In the same manner, honokiol enhanced K<sup>+</sup>-evoked ACH release directly on hippocampal cholinergic terminals via receptors other than the M2 cholinergic subtype (Tsai et al., 1995). Additionally, we found that an ethanol extract of *M. officinalis* and 4-*O*-methylhonokiol dose-dependently attenuated the scopolamine-induced increase in ACHE activity in the cortex and hippocampus of mice and inhibited ACHE activity in vitro with an IC<sub>50</sub> of 12 nM (Lee et al., 2009e). Considering these results and the ones on anti-oxidants information (the other main section in this paper), the ability of *Magnolia* constituents to protect the brain against neurodegenerative implications and syndromes seem to be related to an increase in ACH release, phosphorylation of Akt, anti-oxidative function and a decrease in ACHE release. Oxidative stress is also an important factor that can induce neuronal damage, modulate intracellular signaling, and ultimately lead to neuronal death by apoptosis or necrosis (Behl & Moosmann, 2002; Calabrese et al., 2009; Jellinger, 2009). Constituents of *Magnolia* have been reported to be effective against the development of neurodegenerative implications, preventing diverse toxin attacks by anti-oxidative mechanisms (Lin et al., 2006; Cui et al., 2007; Lee et al., 2009b). It has been reported that honokiol and magnolol may protect neurons against toxicity induced by hydrogen peroxide, glutamate and N-methyl-D-aspartic acid (NMDA), suggesting anti-oxidative actions (Lin et al., 2006). In in vivo and in vitro models, 4-*O*-methylhonokiol prevented Aβ<sub>1-42</sub>-induced apoptotic cell death by suppression of reactive oxygen species (ROS) generation as well as β-secretase expression and generation of Aβ (Lee et al., 2009b). In vivo, oral administration (3 mg/kg) of honokiol for 3 days reduced 60% lethality in NMDA-treated mice to 10%, and alleviated the behavioral signs of NMDA neurotoxicity. Moreover, honokiol pretreatment restored levels of total glutathione, thiobarbituric acid-reactive substances and cytosolic glutathione peroxidase activity in brain tissue, indicating that honokiol can prevent oxidative stress in brain (Cui et al., 2007). Additionally, oral pretreatment of ethanol extracts of *M. officinalis* (2.5, 5 and 10 mg/kg) and 4-*O*-methylhonokiol (1 mg/kg) in the drinking water for 5 weeks protected against the memory impairments induced in mice by intraventricular treatment with Aβ<sub>1-42</sub> (0.5 µg/mouse, i.c.v.) (Lee et al., 2009b). Compounds in *Magnolia* have also been reported to have effects on neurite outgrowth (Fukuyama et al., 2002; Zhai et al., 2005; Yang et al., 2006; Lee et al., 2009d). The compound 4-*O*-methylhonokiol has the ability to induce neurite outgrowth via increases in neurotrophic factor levels

**Table 4**  
Anti-inflammatory effects of *Magnolia*.

Compounds	Dose	Subjects	Effects	References
Ethanol extract, dichloromethane fraction and the isolated compound costunolide from <i>M. ovata</i>	72.35, 5.8, and 0.18 mg/kg	Mice	Inhibition of Cg-induced paw edema	Kassuya et al., 2009
Ethanol extract, dichloromethane fraction and the isolated compound costunolide from <i>M. ovata</i>	30, 4.5, and 0.15 mg/kg	Mice	Inhibition of LPS-induced fever	Kassuya et al., 2009
Methanol extract of <i>M. kobus</i>	0.05–5 µg/ear	Mice	Suppression of ear swelling in TPA-induced skin inflammation	Kang et al., 2008
4-methoxyhonokiol	1–30 µM	RAW 264.7	Inhibition of LPS-mediated NF-κB activation by inhibition of p38 MAP kinase signaling pathways and inhibition of NF-κB activation	Zhou et al., 2008; Oh et al., 2009
4-methoxyhonokiol	20 or 100 mg/kg	Mice	Inhibition of acute inflammation and dye leakage. Inhibition of Cg-induced paw swelling. Inhibition of TPA-induced ear thickness and ear weight	Zhou et al., 2008; Oh et al., 2009
4-methoxyhonokiol	2.5–10 µM	RAW 264.7	Inhibition of LPS (1 µg/ml)-induced NO generation by inhibition of the NF-κB pathway	Zhou et al., 2008; Oh et al., 2009
4-methoxyhonokiol	0.1–1 mg/ear	Mice	Inhibition of TPA-induced inflammatory ear edema formation, NF-κB activity, and iNOS and COX-2 expression	Zhou et al., 2008; Oh et al., 2009
Honokiol	3 mg/mice	Mice	Stabilization of the severity of collagen-induced arthritis	Munroe et al., 2007
Magnolol	–	Mice	Inhibition of mouse hind-paw edema and decreases in acetic acid-induced writhing responses	Wang et al., 1992, 1995; Kuo et al., 2010
Magnolol	10 mg/kg	Mice	Inhibition of mouse hind-paw edema by inhibition of iNOS, COX-2, prostaglandin E2, thromboxane B2, leukotriene B4, and NF-κB activation	Wang et al., 1995
Magnolol	1 or 5 µM	Mice	Reduction of TPA-induced NFκB and DNA binding	Kuo et al., 2010
Obovatal	1–5 µM	RAW 264.7	Inhibitory effect on NO production	Choi et al., 2007
Epimagnolin B	5–20 µM	VSMC	Inhibitory effect on NO production and COX-2 expression via NF-κB activity	Kim et al., 2007
Magnosalin	2.39–48.9 µM	Synovial cells	Inhibition of proliferation of synovial cells via inhibition of IL-1α stimulated action	Takahashi et al., 1996; Kobayashi et al., 1998

through ERK activation (Lee et al., 2009d). (+)-Eudesmin can induce neurite outgrowth from PC12 cells by stimulating up-stream mitogen activated protein kinases (MAPK), protein kinase C (PKC) and protein kinase A (PKA) pathways (Yang et al., 2006). Also, honokiol acts as a neurotrophic factor that plays an important role in differentiation, survival and maintenance through modulation of neurite outgrowth (Fukuyama et al., 2002; Zhai et al., 2005; Chen et al., 2009c). Its mechanism may be that honokiol activates phospholipase C and then inositol 1,4,5-triphosphate, which mobilizes intracellular Ca<sup>2+</sup> stores. Subsequently, the increase in cytoplasmic free Ca<sup>2+</sup> in neuronal cells activates Ca<sup>2+</sup>/calmodulin-dependent kinase II, which presumably enhances ERK1/2 phosphorylation (Zhai et al., 2005). Considering all factors, several components in *Magnolia* seem to have neurotrophic effects against neurodegenerative diseases as well as against various nerve injuries via mitogen activated ERK kinase (MEK). We recently found that 4-O-methylhonokiol prevented memory dysfunction in APPsw mice and PS2 mutant mice via increases in Aβ clearance and inhibition of ERK activation in the brain (unpublished data). Taken together, these data show that components of *Magnolia* could be useful in the treatment of Alzheimer's disease.

#### 4.4. Effects on and mechanisms in stroke

A stroke, known medically as a cerebrovascular accident (CVA), is the third leading cause of death in the U.S. and the leading cause of adult disability (Lloyd-Jones et al., 2010). Strokes occur when the blood supply to a part of the brain is suddenly interrupted by occlusion (an ischemic stroke) or by hemorrhage (a hemorrhagic stroke). The ischemic stroke occurs due to a reduction in blood flow due to thrombosis, embolism, or hypoperfusion. The hemorrhagic stroke occurs when a blood vessel in the brain bursts, spilling blood into the spaces surrounding the brain cells, or when a cerebral aneurysm ruptures. Both ischemic and hemorrhagic strokes commonly induce tissue infarction, due to failure of blood and oxygen supplies to parts of the brain. Failure of blood and

oxygen supplies induce defects in anaerobic metabolism in brain tissue, and then a rapid drop in adenosine triphosphate (ATP) levels. In the absence of biochemical energy, cells begin to lose the ability to maintain electrochemical gradients. Consequently, there is a massive influx of calcium into the cytosol, a massive release of glutamate from synaptic vesicles, lipolysis, calpain activation, and the arrest of protein synthesis. Additionally, removal of metabolic wastes is slowed (Raichle, 1983). Mitochondrial ATP depletion results in neuronal cell death. The ATP production is essential for maintaining ion pumping activity of Na<sup>+</sup>, K<sup>+</sup>-ATPase, which regulates the ionic concentration gradients in neurons for stimulating the generation of action potentials. Accumulating results indicate that this enzyme is the most sensitive to ROS and thus to changes in ATP production (Zhan & Yang, 2006). An initial event in cerebral ischemia is ROS production, which induces oxidation of cellular proteins, DNA and lipids (Dirnagl et al., 1999; Moro et al., 2005).

Pharmacologic therapies for these strokes are to normalize blood flow after it is determined whether the patient has ischemic or hemorrhagic stroke. For an ischemic stroke caused by a thrombus (blood clot), removing the blockage of blood flow via thrombolysis is primarily required. Thrombolytic drugs/fibrinolytics such as (i) plasminogen activators: r-tPA (Saver, 2006), UPA, streptokinase, anistreplase, monteplase, (ii) other serine endopeptidases: aniclod (Hennerici et al., 2006), fibrinolysin, and (iii) brinase are used. Antiplatelet drugs such as (i) glycoprotein IIb/IIIa inhibitors, (ii) ADP receptor/P2Y12 inhibitors, (iii) prostaglandin analogue (PGI2), (iv) COX inhibitors, (v) thromboxane inhibitors and (vi) phosphodiesterase inhibitors are also used. Anticoagulants such as (i) vitamin K antagonists, (ii) factor Xa inhibitors (heparin, oligosaccharides, heparinoid, xabans), (iii) direct thrombin (II) inhibitors (hirudin, argatroban, dabigatran, melagatran, and ximelagatran) are commonly used (Healey et al., 2008; Sacco et al., 2008; Singer et al., 2008; Verro et al., 2008). Moreover, brain pathogenesis due to the loss of oxygen and substrate can be ameliorated by treatment with anti-oxidants such as green tea or its components (Scott et al., 1993; Yoshino &

Murakami, 1998; Hong et al., 2000, 2001; Arab & Liebeskind, 2010), vitamin E (Chang et al., 1998; Tagami et al., 1998; Cherubini et al., 2000), ginkgo biloba extract (Pietri et al., 1997; Calapai et al., 2000; Louajri et al., 2001), red wine/resveratrol (Mizutani et al., 2000a,b; Huang et al., 2001), niacin (vitamin B3) (Mokudai et al., 2000; Sakakibara et al., 2000; Maynard et al., 2001) and isoflavones (Jenkins et al., 2000; Djuric et al., 2001).

Constituents of *Magnolia* have been reported to be effective against syndromes associated with rapid nerve cell loss such as those occurring in stroke. Anti-oxidative mechanisms are thought to be involved (Chang et al., 2003; Liou et al., 2003; Chen et al., 2007). Administration of honokiol (10 µg/kg) twice, 15 min before and 60 min after cerebral ischemia in mice resulted in significant reductions in brain infarct volume and in synaptosomal production of ROS. The decreases in synaptosomal mitochondrial membrane potential, synaptosomal mitochondrial metabolic function and tissue Na<sup>+</sup>, K<sup>+</sup>-ATPase activities observed in the ischemic brains were also attenuated by honokiol treatment (Chen et al., 2007). Additionally, Liou et al. (2003) showed an ameliorating effect of honokiol against focal cerebral ischemia-reperfusion injury that can be attributed to its anti-oxidative and anti-inflammatory actions. These actions are mediated, at least in part, by limiting lipid peroxidation and reducing neutrophil activation/infiltration that may be primed/activated during the injury. In a related paper by Chang et al. (2003), magnolol inhibited heatstroke reactions, and attenuated free radical formation and lipid peroxidation.

#### 4.5. Additional effects on and mechanisms in neuronal disease

It has been reported that compounds of *Magnolia* have anti-nociceptive effects (Choi et al., 2004; Lin et al., 2009). Sinapyl alcohol, the result of in vivo transformation of syringin, was particularly potent in a mouse analgesic model, suggesting a link between anti-nociceptive effects and suppression of inflammatory mediators [NO, PGE2, TNF-α, inducible Nitric oxide synthase (iNOS), COX-2] (Choi et al., 2004). In a comparative study of two *Magnolia* constituents, honokiol (5 and 10 mg/kg) and magnolol (5 and 10 mg/kg) were administered 20 min prior to formalin (25 µl of 2.5%) injection in the mouse hindpaw. The time spent licking the hindpaw was measured in 5 min intervals through the first phase (0–5 min) and second phase (10–40 min) of the formalin test. Honokiol and magnolol did not affect total licking time in the first phase, but inhibited total licking time in the second phase compared with a corn oil control (Lin et al., 2007). Honokiol and magnolol reduced licking behavior and thermal hyperalgesia of mice that had been induced by glutamate, NMDA and CHPG, agonists of metabotropic glutamate 5 receptors (mGluR5). This suggested that the anti-nociceptive actions of honokiol and magnolol is related to inhibition of glutamate receptors including both NMDA and mGlu5 receptors. Also, intraplantar application (i.pl.) of honokiol and magnolol (0.5–1.0 µg/paw) reduced PGE2- and substance P-induced thermal hyperalgesia (Lin et al., 2009). Substance P is a major neurotransmitter for pain signaling (Ueda, 1999). Prostaglandins, which are inflammatory mediators, also enhance the release of glutamate and substance P from peripheral afferent nerve fiber terminals (Millan, 1999). Like their inhibition of glutamate, NMDA and mGlu5 receptors, and nociceptive neurotransmitter, their anti-nociceptive effects may also be related to suppression of inflammatory mediators including PGE2. Anticonvulsant effects of *Magnolia* have been reported (Bastidas Ramirez et al., 1998; Lin et al., 2005). Both honokiol and magnolol significantly increased NMDA-induced seizure thresholds determined by mice tail-vein infusion of NMDA (10 mg/ml) (Lin et al., 2005). The ethyl ether and hydroalcoholic extract of *M. grandiflora* L. seeds orally administered in a single dose of 250 mg/kg (calculated on a lipidic base) or 200 mg/kg, abolished the extensor reflex of maximal electricity-induced seizure tests in, respectively, 50% and 40% of rats (Bastidas Ramirez et al., 1998).

Anticonvulsant mechanisms of *Magnolia* components may be related to inhibition of the release of excitatory amino acid transmitters such as glutamate, or to amino acid-evoked intracellular Ca<sup>2+</sup> signals in neurons. Glutamate antagonists selective for NMDA or non-NMDA receptors are used as potent anticonvulsants nowadays (Loscher, 1998). Sy et al. (2008) reported that honokiol potently inhibited 4-aminopyridine (4-AP)-evoked glutamate release from isolated nerve terminals and this effect resulted from a reduction in vesicular exocytosis. According to Lin et al. (2005), honokiol and magnolol showed the same potency and efficacy in decreasing glutamate-evoked intracellular Ca<sup>2+</sup> signals, but honokiol was more potent than magnolol in inhibiting NMDA-evoked intracellular Ca<sup>2+</sup> signals in cultured rat cerebellar granule cells. Moreover, magnolol-induced inhibition of glutamate mediated Ca<sup>2+</sup> signaling was reduced in the presence of non-NMDA receptor antagonists, but the inhibitory effect of honokiol on glutamate-evoked intracellular Ca<sup>2+</sup> signals was not. This indicated that honokiol is more selective for NMDA receptors than magnolol. These data suggest that components of *Magnolia* could be useful for treatment of disorders such as stroke, pain, convulsions and seizures.

## 5. Therapeutic applications in inflammatory disease

### 5.1. Effects on inflammatory disease

*Magnolia* constituents are reported to have anti-inflammatory effects (Table 4). Kimura et al. (1992b) investigated about anti-inflammatory effects of nine crude drugs containing “Kakkon-to-ka-senkyu-shin’i” against adjuvant-induced air pouch granuloma in mice, and revealed the effects were induced by magnolia via serial combination therapies of the components. Magnosalin, a compound derived from *Flos Magnoliae*, was reported to have inhibitory effect against the proliferation of synovial cells from rheumatoid MRL/1 and collagen-induced arthritis mice, and rheumatoid arthritis patients via inhibition of IL-1α stimulated action (Takahashi et al., 1996; Kobayashi et al., 1998). The ears of BALB/c mice were pretreated with vehicle and the indicated concentrations of a methanol extract of *M. kobus* (0.05, 0.5 or 5 µg/ear) for 30 min. Tissue plasminogen activator (TPA; 300 ng/ear, dissolved in vehicle) was applied to induce skin inflammation. After 4 h, the increase in ear thickness was measured. Topical application of a methanol extract of *M. kobus* suppressed ear swelling in a TPA-induced skin inflammation model (Kang et al., 2008). Dried and powdered trunk bark (424 g) of *M. ovata* was extracted at room temperature successively with hexane and ethanol. The solvents were removed under reduced pressure to yield crude extracts in hexane (1.5 g) and ethanol (ethanol extract from *M. ovata*, EEMO, 22.5 g). A part of the EEMO (10.0 g) was dissolved in ethanol–water (1:1) and partitioned with dichloromethane. The dichloromethane layer was separated and the solvent evaporated to give 1.54 g of residue (DCM fraction). The oral administration of EEMO, DCM and costunolide inhibited carrageenan (Cg)-induced paw edema of mice (ID<sub>50s</sub>: 72.4, 5.8 and 0.18 mg/kg, respectively) (Kassuya et al., 2009). To investigate 4-methoxyhonokiol’s anti-inflammatory effect, an acetic acid-induced vascular permeability test in mice was performed using a modification of a method originally devised by Whittle (1964). Doses of 20 and 100 mg/kg 4-methoxyhonokiol (i.p.) and 50 mg/kg dexamethasone (i.p.) had a significant effect against acute inflammation induced by acetic acid. Inhibition of dye leakage rates was 32.2, 37.4 and 40.9% respectively. In order to further evaluate the in vivo (mice) anti-inflammatory effects of 4-methoxyhonokiol, a Cg-induced paw edema test was employed. Maximal edema formation was observed 1 h after 1% Cg injection, and treatment with 4-methoxyhonokiol dose-dependently inhibited Cg-induced paw swelling. In particular, treatment with 4-methoxyhonokiol at 100 mg/kg (i.p.) significantly suppressed edema formation 1 h after edema induction, the inhibitory rate being 31.7% (Zhou et al., 2008). Additionally, topical application of

0.1, 0.5 and 1 mg 4-methoxyhonokiol immediately before TPA (1 µg/10 µl of acetone) treatment to the ears of mice inhibited TPA-induced increases in ear thickness and ear weight (Oh et al., 2009). To investigate honokiol's anti-inflammatory effect, female C57BL/6 and mCD40-latent membrane protein1 (LMP1) Tg mice were either left naive or immunized with 100 µg of CII (type II chicken collagen)/complete Freund's adjuvant (CFA, 5 mg/ml H37 RA heat-killed mycobacteria) or CFA only. Some of the mice receiving CII/CFA were injected i.p. with 3 mg/mouse/day honokiol suspended in 20% intralipid, starting at day 21 postimmunization. Paw swelling and clinical scores were determined for each paw every 3–4 days from days 21 to 70 postimmunization. In vivo, honokiol stabilized the severity of symptomatic collagen-induced arthritis in both CD40-LMP1 transgenic mice and their congenic C57BL/6 counterparts. Overall, honokiol-treated CII/CFA mice had at least 25% less paw swelling and 50–66% lower clinical scores compared with mice that received CII/CFA alone (Munroe et al., 2007). Wang et al. (1992) showed that magnolol also inhibited mouse hind-paw edema induced by diverse compounds and reversed a passive arthritis reaction.

## 5.2. Mechanisms of action in inflammation

Generally, inflammatory mechanism has been reported as discussed later. NOS enzymes are classified into two groups, one type, cNOS, is constitutively present in several cell types (e.g. neurons and endothelial cells) (Kirkeboen et al., 1999). In contrast, iNOS, which is expressed in various cell types including VSMCs, macrophages, hepatocytes and astrocytes, is induced in response to pro-inflammatory cytokines and bacterial lipopolysaccharide (LPS). Expression of iNOS catalyzes the formation of large amounts of NO, which plays a key role in the pathogenesis of a variety of inflammatory diseases (Ricciardolo et al., 2004; Cuzzocrea, 2006; Malinski, 2007). NF-κB is a transcription factor that promotes the transcription of genes involved in pro-inflammatory responses (Simmonds & Foxwell, 2008). In macrophages, NF-κB was activated by inflammatory extracellular signals such as LPS, interleukin-1 (IL-1) and TNF-α, and regulated a number of inflammatory genes producing inflammatory mediators such as NO (Muller et al., 1993). Like NF-κB, AP-1 is also activated by many pathophysiological stimuli, including LPS, cytokines and ROS (Matsuda & Hattori, 2006). MAPKs are a group of signaling molecules that also appear to play important roles in inflammatory processes and have been reported to differentially activate them depending on the stimuli and cell types (Suh et al., 2006). Salvemini et al. (1993) demonstrated that the enhanced release of prostaglandins that follows inflammatory mechanisms was nearly entirely driven by NO. Leukotrienes are released in inflammatory reactions and in immediate hypersensitivity reactions and its mechanism involves stimulation of the biosynthesis of prostaglandins and thromboxanes (Sirois & Borgeat, 1984). Additionally, a number of studies have shown that COX activity is increased in certain inflammatory states and is induced in cells by proinflammatory cytokines and growth factors (Bailey et al., 1985; Sano et al., 1992). Therefore, NO production, expression of iNOS, IL-1β, TNF-α and COX, and generation of prostaglandins, thromboxanes and leukotrienes, in addition to activating MAPKs, AP-1 and NF-κB, may reflect the degree of inflammation and may provide indicators with which to assess inflammatory processes.

Anti-inflammatory mechanisms of *Magnolia* have been reported to be associated with the suppression of NO production, the expression of iNOS, IL-1β, TNF-α and COX, the generation of prostaglandins, thromboxanes and leukotrienes, and the activation of MAPKs, AP-1 and NF-κB (Wang et al., 1995; Choi et al., 2007; Munroe et al., 2007; Kang et al., 2008; Zhou et al., 2008; Kim et al., 2009; Oh et al., 2009; Kuo et al., 2010). A methanol extract of *M. kobus* 1–10 µg/ml inhibited LPS (300 ng/ml)-induced production of NO and IL-1β in RAW 264.7 cells, a murine macrophage-like cell line (Kang et al., 2008). In addition, TNF-α secretion and expression of mRNA for iNOS, IL-1β and TNF-α were also

suppressed (Kang et al., 2008). The ingredient 4-methoxyhonokiol (10 and 30 µM) significantly inhibited LPS (1 µg/ml)-induced NO production as well as protein and mRNA expression of iNOS and COX-2 in RAW 264.7 cells. Furthermore, 4-methoxyhonokiol inhibited LPS-mediated nuclear NF-κB activation via the prevention of IκB phosphorylation and degradation. In mice, 4-methoxyhonokiol (20 and 100 mg/kg, i.p.) also inhibited LPS (10 mg/kg, i.p.)-induced plasma NO release (Zhou et al., 2008). In other research, consistent with its inhibition of LPS (1 µg/ml)-induced NO generation in macrophage RAW 264.7 cells, 4-methoxyhonokiol (2.5–10 µM) also inhibited the activity of NF-κB and the expression of iNOS. Additionally, topical application of 4-methoxyhonokiol (0.1–1.0 mg/ear) inhibited TPA-induced NF-κB activity, and iNOS and COX-2 expression (Oh et al., 2009). In the same manner, magnolol inhibited TPA-induced NF-κB activity, and iNOS and COX-2 expression in mouse skin, and obovatol inhibited NO production related to the down-regulation of NF-κB activity in RAW 264.7 cells (Choi et al., 2007; Kuo et al., 2010). Choi et al. (2007) demonstrated that obovatol also inhibits NF-κB/MAPK activity in LPS-activated RAW 264.7 cells. Moreover, magnolol has been reported to reduce both prostaglandin E2 and leukotriene B4 levels in the pleural fluid of a mouse model of pleurisy. In a rat isolated peripheral neutrophil suspension, magnolol (3.7 µM) suppressed A23187-induced thromboxane B2 and leukotriene B4 formation (Wang et al., 1995). As a novel chemical, epimagnolin B also inhibited the production of NO and prostaglandin E2 and the expression of iNOS and COX-2 through suppression of IκBα degradation and nuclear translocation of the p65 subunit of NF-κB in BV-2 cells, a murine microglial cell line (Kim et al., 2009). Honokiol treatment of mouse B-cell lines expressing the human CD40-LMP1 chimeric receptor abrogated CD40- and LMP1-mediated NF-κB and AP-1 activation, and decreased TNF-α and IL-6 production (Munroe et al., 2007) These results suggest that the anti-inflammatory properties of honokiol could be valuable for blocking the autoimmune response.

## 6. Therapeutic application to the cardiovascular system

### 6.1. Effects and mechanisms in atherosclerosis

A role for oxidative stress has been postulated in many cardiovascular diseases (Lehucher-Michel et al., 2001; Young & Woodside, 2001; Ungvari et al., 2005). ROS can promote inflammation, alter vasomotion, induce cell death, cause platelet aggregation, and stimulate VSMC proliferation (Yao et al., 1993; Harrison, 1997; Griendling & Ushio-Fukai, 1998; Dimmeler et al., 1999; Lavrovsky et al., 2000). All of these events are thought to contribute to cardiovascular lesion formation. In particular, it has been reported that oxidized low-density lipoprotein (LDL) induces arterial wall cells to produce chemotactic factors, adhesion molecules, cytokines, and growth factors that have a role to play in the development of plaque related to atherosclerosis (Huang et al., 1999; Kita et al., 1999; Young & Woodside, 2001).

*Magnolia* constituents including honokiol and magnolol have been evaluated as antioxidants (Haraguchi et al., 1997; Kang et al., 2007). Honokiol ameliorated oxidized LDL-diminished endothelial NOS protein expression, and reduced oxidized LDL-induced adhesion molecules in human umbilical vein endothelial cells (HUVECs) (Ou et al., 2006). Furthermore, honokiol attenuated oxidized LDL-induced cytotoxicity, apoptosis, ROS generation, intracellular calcium accumulation, the subsequent mitochondrial membrane potential collapse, cytochrome c release and activation of caspase-3 in HUVECs (Ou et al., 2006). These results show that honokiol can prevent vascular lesion complications including oxidized LDL-induced dysfunction. Also, magnolol seems to have protective effects in the vascular system, including the inhibition of cardiac fibroblast proliferation by interfering with ROS generation (Liou et al., 2009). Chen et al. (2006) suggested that the inhibition of endothelial adhesion molecule expression by antioxidant agents such as magnolol may serve a potential therapeutic strategy to reduce clinical

atherosclerosis. *Magnolia* constituents have cell cycle arrest effects related to activation of the p21 pathway (Lin et al., 2002; Chen et al., 2009a; Lim et al., 2010). Lee et al. (2006) demonstrated that honokiol-dependent VSMC growth inhibition in vitro results from p21-mediated cell cycle arrest, suggesting clinical approaches to reducing atherosclerosis. Lin et al. (2009) recently demonstrated that obovatol isolated from *Magnolia* can inhibit VSMC proliferation in vitro and in vivo via a p21-dependent cell-cycle arrest mechanism and also suggested the possibility that it can act as an anti-proliferative drug for angioplasty restenosis and atherosclerosis.

Magnolol treatment of TNF- $\alpha$ -induced VSMCs induced (a) declines in extracellular signal-regulated kinase (ERK) 1/2 activity, (b) G1 cell cycle arrest, (c) induced the expression of p21WAF1, but (d) resulted in a decrease in CDKs and cyclones involved in G1 progression. Magnolol strongly inhibited matrix metalloproteinase-9 (MMP-9) expression through the transcription factors NF- $\kappa$ B and AP-1 in TNF- $\alpha$ -induced VSMC (Kim et al., 2007). Obovatol treatment of VSMC blocked the cell cycle in G1 phase by down-regulating the expression of cyclins and CDKs, and selectively up-regulating the expression of p21Cip1, a CDK inhibitor (Lim et al., 2010).

Magnosalin and magnoshinin, compounds from Flos magnolia were investigated about inhibitory effects against angiogenesis and pouch granuloma formation. It was showed selective inhibitory effects of angiogenesis by magnosalin and of granuloma formation by magnoshinin (Kimura et al., 1990). Furthermore, the magnosalin and magnoshinin showed anti-proliferative and anti-angiogenic effects using rat endothelial cells (Kimura et al., 1992a; Kobayashi et al., 1996).

## 6.2. Anti-platelet effects and mechanisms

*Magnolia* constituents have been known to have anti-platelet activity. Pyo et al. (2002) reported that methyl caffeate had 3–4 fold higher anti-platelet potency than acetylsalicylic acid (ASA) and that the activities of obovatol and honokiol were comparable to ASA, whereas magnolol and syringin showed only mild effects. In other studies of Teng et al. (1988), magnolol and honokiol inhibited the aggregation and ATP-mediated release of rabbit platelet-rich plasma that had been induced by collagen and arachidonic acid. Teng et al. (1990) reported that denudatin B, an isomer of kadsurenone isolated from *M. gargesii*, inhibited the aggregation and ATP release of washed rabbit platelets caused by platelet-activating factor (PAF) in a concentration-dependent manner.

Thromboxanes (TXAs) are considered to be one of the most powerful agonists for platelet activation and a major contributor to thrombus formation. Therefore, inhibition of the synthesis or the action of TXAs is a theoretically effective means for treatment of atherothrombotic disorders. This has been demonstrated by clinical evidence that drugs such as aspirin, picotamide and ridogrel, are beneficial for patients with acute coronary syndromes and myocardial infarction (The Ridogrel Versus Aspirin Patency Trial (RAPT) investigators, 1994; Jneid et al., 2003; Eriksson et al., 2009). Cytosolic Ca<sup>2+</sup> mobilization also plays a crucial role in platelet activation and aggregation. During platelet activation, the increase of [Ca<sup>2+</sup>]<sub>i</sub> as a result of either Ca<sup>2+</sup> influx or release from intracellular stores is fundamental to the platelet response to various agonists (Jackson et al., 2003; Varga-Szabo et al., 2009). Additionally, PAF has been known to exert effects on platelet aggregation and secretion (Kroegel, 1988; Chao & Olson, 1993). Teng et al. (1988) reported that denudatin B played a role as a PAF antagonist. In addition, it was reported that TXA B2 formation caused by collagen, arachidonic acid or thrombin was in each case inhibited by magnolol and honokiol. The rise of intracellular calcium caused by arachidonic acid or collagen was also suppressed by the two *Magnolia*-derived constituents (Teng et al., 1988). Teng et al. (1988) concluded that the anti-platelet effect of magnolol and honokiol is due to an inhibitory effect on TXA formation

and also to an inhibition of intracellular calcium mobilization. In view of these facts, Magnoliaceous plants seem to have several anti-platelet chemicals related to its PAF antagonistic effect or its inhibition of TXA formation and intracellular calcium mobilization.

## 7. Additional therapeutic applications

### 7.1. Therapeutic applications in gastrointestinal disorders

It has been suggested that constituents of *Magnolia* can exert therapeutic effects on gastrointestinal disease through relaxation of gastrointestinal tract smooth muscles that is associated with a Ca<sup>2+</sup> antagonistic effect (Zhang et al., 2005; Bian et al., 2006). Magnolol and honokiol significantly inhibited the contractility of isolated gastric fundus strips of rats treated with ACH or serotonin, and of isolated ileum in guinea pigs treated with ACH or CaCl<sub>2</sub>; both of them behaved as non-competitive muscarinic antagonists. Magnolol and honokiol inhibited contractions induced by ACH in Ca<sup>2+</sup>-free medium and extracellular Ca<sup>2+</sup>-dependent contractions induced by ACH (Zhang et al., 2005). In other research, it was confirmed that magnolol dependently inhibited carbachol or serotonin induced muscle contractions in guinea pig colon muscle strips at concentrations ranging from 1 to 100  $\mu$ M (Bian et al., 2006).

In human studies (Oikawa et al., 2005, 2009), each subject received Hange-koboku-to containing 5 extracts (Pinelliae tuber, HOLELEN, Magnoliae cortex, Perillae herba, Zingiberis rhizome) 3 times daily as 7.5 g oral supplements before meals for 2 weeks. A significant increase in gastric emptying rate was observed in both healthy volunteers and in patients with functional dyspepsia. The extract also reduced bowel gas in functional dyspepsia, suggesting a reduction in abdominal bloating. Thus, gastrointestinal symptoms (abdominal pain, indigestion and constipation) closely related to abdominal bloating were decreased in subjects with functional dyspepsia. In view of these findings, *Magnolia* components alone or in combination with others appear to exert therapeutic utility on functional dyspepsia. However, further research is necessary.

### 7.2. Therapeutic applications in asthma

Saiboku-To, the herbal complex medicine that includes *M. officinalis*, is also known for its use in bronchial asthma (Taniguchi et al., 2000). It was found that magnolol and 8, 9-dihydroxydihydromagnolol from *M. officinalis* as well as Saiboku-to inhibited concanavalin A-induced human lymphocyte blastogenesis in vitro in a dose-dependent fashion and magnolol inhibited picryl chloride-induced mouse ear swelling in vivo. It was concluded that these preparations have anti-asthmatic effects through suppression of type IV (lymphocyte-mediated) allergic reaction. Tsuruga et al., 1991 also showed that extracts of the flower buds of *M. salicifolia* have anti-allergy effects in a passive cutaneous anaphylaxis (PCA) test. In other research, magnolol and honokiol (0.1–100  $\mu$ M) inhibited carbachol- and high K<sup>+</sup>-induced muscle contractions in a concentration-dependent fashion in porcine trachea but did not affect basal muscle tension. Magnolol and honokiol concentration-dependently decreased the Ca<sup>2+</sup>-dependent muscle contraction induced by high K<sup>+</sup> induced depolarization. Muscle contractions elicited by caffeine, an inhibitor of calcium release from intracellular calcium stores, were not altered by magnolol or honokiol. In conclusion, the relaxant effects of magnolol and honokiol on porcine tracheal smooth muscle suggest blockade of Ca<sup>2+</sup> influx through voltage-operated Ca<sup>2+</sup> channels rather than Ca<sup>2+</sup> release from intracellular Ca<sup>2+</sup> stores (Ko et al., 2003). Kimura et al. (1983, 1989) showed that D-coclaurine, D-reticuline, 1-N-methylcoclaurine and yuzirine, were isolated from the dried buds of *M. salicifolia* Maxim, inhibited ACH-induced contraction of frog skeletal muscle, and the other components, (+)-R-coclaurine and (+)-S-reticuline, have negative inotropic effects in papillary muscles of guinea pigs. In view of these findings, some

constituents of Magnoliaceae plants seem to have anti-asthmatic actions through mechanisms related to anti-allergic reaction, especially type IV, or mechanisms associated with the blockade of  $\text{Ca}^{2+}$  influx, mainly through voltage-operated  $\text{Ca}^{2+}$  channels.

### 7.3. Therapeutic applications in liver disease

Oxidative stress is involved in the pathogenesis of chronic liver diseases including alcohol- or drug-induced hepatotoxicity, iron overload, hepatitis and hepatocarcinoma development, but molecular mechanisms are not established (Nitti et al., 2008). *Magnolia* components have hepatoprotective effects due to their antioxidant activity (Park et al., 2003, 2006; Chen et al., 2009b). In rat primary hepatocytes, honokiol and magnolol inhibited cellular leakage of lactate dehydrogenase (LDH) and aspartate aminotransferase, cell death, lipid peroxidation, ROS generation and intracellular glutathione depletion induced by tertbutylhydroperoxide. It was presumed that their antioxidant activity was the reason. They also had a protective effect against D-galactosamine-induced hepatotoxicity, an alternative model of oxidative stress. They inhibited the depletion of intracellular glutathione, an antioxidant (Park et al., 2003). Park et al. (2006) showed that honokiol pretreatment 5 min before glycochenodeoxycholic acid treatment inhibited the generation of intracellular reactive oxygen species, reduced activation of caspases-8, -9 and -3, reduced cleavage of poly-(ADP-ribose) polymerase, reduced stress-activated protein kinase/c-jun-NH2-terminal kinase phosphorylation, and resulted in an anti-apoptotic protective effect in primary cultured rat hepatocytes. In other research, hepatoprotective effects of magnolol against acetaminophen-induced toxicities representing histological changes, lipid peroxidation, glutathione depletion in liver tissue, and elevated levels of aspartate aminotransferase, alanine aminotransferase and LDH in serum were confirmed (Chen et al., 2009b). These data also indicate that components of *Magnolia* could have hepatoprotective effects.

## 8. Safety and toxicity of *Magnolia* ingredients

Although *Magnolia* bark has been used for a long time in Chinese and Japanese traditional medicines, it is important to investigate the toxicity or adverse effects of *Magnolia* bark and its ingredients. The mutagenicity of an ethanol extract (94% magnolol and 1.5% honokiol) of *Magnolia* bark was evaluated in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and in the *Escherichia coli* mutant, WP2uvrA. In a mutagenicity study, the *Magnolia* bark extract did not increase the mean number of revertants per plate of any *S. typhimurium* strain or the *E. coli* strain, with or without metabolic activation, in comparison to the spontaneous reversion rate in the negative control. The authors concluded that *Magnolia* bark extract is not mutagenic in the aforementioned *S. typhimurium* and *E. coli* strains under their experimental conditions (Li et al., 2007a,b,c). The genotoxicity of an ethanol extract (94% magnolol and 1.5% honokiol) of *Magnolia* bark extract was studied in two in vitro chromosomal aberration assays in Chinese hamster ovary (CHO) cells and Chinese hamster lung tissue (V79) cells. In CHO and V79 cells, treatment of *Magnolia* bark extract in the absence and presence of S9 did not increase the incidence of chromosomal aberrations compared to negative controls. The authors concluded that *Magnolia* bark extract is not genotoxic under the conditions of the in vitro chromosomal aberration assays in CHO and V79 cells (Zhang et al., 2008). In addition, a micronucleus test was performed in male and female Swiss Albino (CD-1) mice that were 7–9 weeks of age. Oral administration (625–2500 mg/kg) of ethanol extracts (94% magnolol and 1.5% honokiol) of *Magnolia* bark did not affect the ratio of immature to total erythrocytes, and the number of micronucleated polychromatic erythrocytes did not significantly increase in any groups treated with *Magnolia* bark extracts compared to the negative control group (Li et al., 2007a,b,c).

The oral LD<sub>50</sub> of the crude product of the *Magnolia* cortex evaluated by the National Research Institute of Chinese Medicine was >50 g/kg and 8.5 g/kg following i.p. injection in mice (Ueng et al., 1997). This demonstrates the low oral toxicity of *Magnolia* bark extract. In a subacute toxicity study, administration of 5 or 10 g/kg of *Magnolia* bark extract for 14 days resulted in decreased alanine aminotransferase and creatinine levels and increased BUN levels in male rats, but no differences were noted in any other measured parameters (Ueng et al., 1997; Yang & Chen, 1998). In another study, female and male Sprague–Dawley rats (6–7 weeks old, 100–120 g of body weight) were administered *Magnolia* bark extract (94% magnolol and 1.5% honokiol) orally (60–480 mg/kg/day for 21 days or 60–240 mg/kg/day for 90 days). The extracts were obtained by a supercritical carbon dioxide extraction method. There were no treatment-related effects on clinical observations, macroscopic or microscopic findings, hematology, clinical chemistry, urine chemistry, or organ weight measurements. There were no deaths or significant differences in body weight or weight gain (Liu et al., 2007). These results showed that *Magnolia* bark extract has very low toxicity and very few adverse effects. However, it will be necessary to investigate toxic and adverse effects at therapeutic doses in various species, over a broad range of doses and using various routes of administration.

## 9. Pharmacokinetics and pharmacodynamics of *Magnolia* ingredients

### 9.1. Pharmacokinetics of *Magnolia*

The major ingredients of *Magnolia* are magnolol, honokiol, obovatol and 4-*O*-methylhonokiol. Pharmacokinetic and pharmacodynamic studies have mainly been done for magnolol and honokiol. The pharmacokinetics of magnolol were evaluated after intravenous (i.v.) injection of 2, 5 and 10 mg/kg to male Sprague–Dawley rats. The half-lives in the plasma samples were  $54.1 \pm 5.14$ ,  $49.05 \pm 5.96$  and  $49.58 \pm 6.81$  min, respectively (Tsai et al., 1994b). After i.v. injection of honokiol (5 and 10 mg/kg) to male Sprague–Dawley rats, the half-lives of disposition in the plasma samples were  $49.22 \pm 6.68$  and  $56.2 \pm 7.30$  min, respectively (Tsai et al., 1994a). These results indicate that magnolol and honokiol have similar pharmacokinetic characteristics, and their half-lives of disposition are almost dose-independent and of first-order. The half-lives of magnolol in rabbit ( $14.5 \pm 1.77$  min for 5 mg/kg i.v. bolus administration, and  $15.7 \pm 3.00$  min for 76  $\mu\text{g}/\text{kg}/\text{min}$  i.v. infusion) were approximately one-third of those in rats (Tsai et al., 1994b). However, the results in rabbits also support the idea that the pharmacokinetics of disposition of magnolol, and probably of honokiol, are first-order independently of the administration routes, doses and animal species. Chen et al. (2004) investigated pharmacokinetics of honokiol after i.p. injection of 250 mg/kg in BALB/c mice. The maximum plasma concentration of honokiol was observed at  $27.179 \pm 6.252$  min, and the elimination half-life was  $5.218 \pm 0.861$  h. After 10 min of magnolol (5 mg/kg, i.v.) administration to rat, brain concentrations of magnolol showed no significant differences among various regions (cerebral cortex, olfactory bulb, hippocampus, striatum, cerebellum, brain stem and rest of brain) (Tsai et al., 1996).

### 9.2. Pharmacodynamics of *Magnolia*

Magnolol was metabolized to isomagnolol (the propenyl side chains being transformed to allyl groups), hydrogenated and hydroxy derivatives, glucuronides and sulfates (Tsai et al., 1995, 1996). It was suggested that tissue enzymes and intestinal bacterial enzymes are involved in the metabolism of orally administered magnolol.

Hattori et al. (1984, 1986) determined the metabolites of magnolol after repeated oral administration to rats using high-performance liquid chromatography and liquid chromatography–mass spectrometry. The urinary and fecal metabolites of magnolol were tetrahydromagnolol

(M1), 5-(1-propen-1(E)-yl)-5'-propyl-2,2'-dihydroxybiphenyl (M2), 5-allyl-5'-propyl-2,2'-dihydroxybiphenyl (M3), isomagnolol (5,5'-di(1-propen-1(E)-yl)-2,2'-dihydroxybiphenyl) (M4), and 5-allyl-5'-(1-propen-1(E)-yl)-2,2'-dihydroxybiphenyl (M5). In feces 24 h after the first administration of 50 mg/kg magnolol only a small amount of metabolites were detected, but magnolol was recorded as a major constituent (22% of the administered dose). Isomagnolol and tetrahydromagnolol, however, increased in amount almost linearly from 48 to 72 h accompanied by a significant decrease in the amount of magnolol. The former metabolite became constant in amount after 96 h, but the latter increased further and reached a maximum level after 120 h. The elution patterns of urinary metabolites of orally administered magnolol were essentially similar to those observed for the fecal metabolites. However, the in vitro incubation of magnolol with rat bacteria did not yield tetrahydromagnolol, suggesting that intestinal bacteria under

anaerobic conditions mostly use isomerization of magnolol but not its reduction (hydrogenation).

Hattori et al. (1986) evaluated the metabolism of [ring-14 C] magnolol after a single oral administration. There were two peaks of blood radioactivity levels at 15 min and 8 h, suggesting an enterohepatic circulation of magnolol and its metabolites. A major metabolite excreted in the bile was [ring-14C]magnolol-2-O-glucuronide. After oral and i.p. administration of [ring-14C]magnolol, most of the radioactivity was eliminated into the feces and urine within the first 12 h in each case.

## 10. Conclusion

The bark of *Magnolia* plants has been used historically in traditional herbal medicines in Asia for thousands of years. As

**Table 5**  
Other therapeutic effects of *Magnolia*.

Compounds	Dose	Subjects	Effects	References
<i>Anti-atherosclerosis effects</i>				
Honokiol	2.5–20 μM	HUVECs	Prevention of oxidative modification of LDL and expression of NOS	Ou et al., 2006
Magnolol	1–10 μmol/l	Rat cardiac fibroblasts	Inhibition of cardiac fibroblast proliferation and endothelial adhesion	Chen et al., 2006; Liou et al., 2009
Honokiol	25–150 μM	Human aortic smooth muscle cells (HASMC)	Inhibition of VSMC proliferation	Lee et al., 2006
Obovatol	1–5 μM	Rat VSMCs	Down-regulation of the expression of cyclins and CDKs, and up-regulation of the expression of p21 <sup>Cip1</sup>	Lim et al., 2010
Obovatol	0.1 or 1 mg	Rat carotid artery injury model	Blockade of the cell cycle in G <sub>1</sub> phase	Lim et al., 2010
Denudatin B, mangnolol and honokiol	10 μg/ml	Rabbit platelets	Inhibition of aggregation and ATP release from platelets	Teng et al., 1988; Teng et al., 1990
Magnosalin	0.3–3 μg/ml	Rat endothelial cells	Inhibition of progression phase in endothelial cells proliferation	Kimura et al., 1992a
Magnoshinin	0.1–3 μg/ml	Rat endothelial cells	Inhibition of progression phase in endothelial cells proliferation	Kimura et al., 1992a
<i>Relaxation of gastrointestinal (GI) tract smooth muscles</i>				
Magnolol and honokiol	10 <sup>-5</sup> –10 <sup>-3</sup> , or 10 <sup>-6</sup> –10 <sup>-4</sup> mol/L	Isolated gastric fundus strips of rats	Inhibition of gastric fundus contraction	Zhang et al., 2005
Magnolol and honokiol	10 <sup>-5</sup> –10 <sup>-3</sup> , or 10 <sup>-6</sup> –10 <sup>-4</sup> mol/L	Terminal ileum segments of guinea pigs	Inhibition of guinea pig ileum contraction	Zhang et al., 2005
Magnolol and honokiol	0.5–20, or 0.5–20 mg/L	Mice	Prevention of gastric nuclide retention	Zhang et al., 2005
<i>Therapeutic possibility in functional dyspepsia</i>				
Mixture of Pinelliae tuber, HOLELEN, Magnoliae cortex, Perillae herba and Zingiberis rhizome)	7.5 g/day	Healthy volunteers and patients with functional dyspepsia (FD).	Reducing delays in gastric emptying	Oikawa et al., 2005
Mixture of Pinelliae tuber, HOLELEN, Magnoliae cortex, Perillae herba and Zingiberis rhizome	7.5 g/day	Healthy volunteers and patients with functional dyspepsia (FD).	A significant increase in gastric emptying rate and bowel gas reduction	Oikawa et al., 2009
<i>Anti-asthmatic effects</i>				
Magnolol and 8, 9-dihydroxydihydromagnolol	IC50: 3.0–7.7 μg/ml	Concanavalin A-induced human lymphocytes	Inhibition of lymphocyte blastogenesis	Taniguchi et al., 2000
Magnolol and 8, 9-dihydroxydihydromagnolol	100 mg/kg	Picryl chloride-induced mouse ear	Inhibition of ear swelling and allergic mediation	Taniguchi et al., 2000
Magnolol and honokiol	0.1–100 μM	Porcine trachea	Relaxation of porcine tracheal smooth muscle through voltage-operated Ca <sup>2+</sup> channels	Ko et al., 2003
(+)-R-coclaurine	0.25–0.50 mM	papillary muscles of guinea pigs	Negative inotropic action in papillary muscles of guinea pigs	Kimura et al., 1989
(+)-S-reticuline	0.25–0.50 mM	papillary muscles of guinea pigs	Negative inotropic action in papillary muscles of guinea pigs	Kimura et al., 1989
<i>Liver protection</i>				
Honokiol	40–10 μM	Primary cultured rat hepatocytes	Protection against apoptosis induced by glycochenodeoxycholic acid	Park et al., 2006
Magnolol	0.01–1 mg/kg	Rats	Protection against acetaminophen-induced toxicities	Chen et al., 2009b
Magnolol and honokiol	20–1 μM	Rat hepatocytes	Protection against tertiary butyl hydroperoxide- or D-galactosamine-induced toxicity	Park et al., 2003

described in this review, in vitro and in vivo as well as clinical trials have demonstrated that the constituents of *Magnolia* bark may be important traditional medicines for treating a variety of conditions such as cancer, neuronal disease, inflammatory disease and cardiovascular disease. *Magnolia* bark contains at least 255 different ingredients, including alkaloids, coumarins, flavonoids, lignans, neolignans, phenylpropanoids and terpenoids. Although most studies have focused on magnolol, honokiol, obovatol and 4-*O*-methylhonokiol in the various constituents, other components may also have therapeutic effects. Recent studies have focused on anti-cancer effects, and effects on anxiety, depression, Alzheimer's disease, stroke, inflammatory disease, cardiovascular disease, gastrointestinal disorders, asthma and liver disease. Studies have demonstrated diverse mechanisms for *Magnolia* constituents.

Anti-cancer effects of *Magnolia* ingredients indicate that it up-regulates expression of apoptotic genes and/or down-regulates expression of anti-apoptotic genes, arrests cell cycle mechanisms related to activation of the p21 pathway, and inhibits NF- $\kappa$ B activity. The bark of *M. officinalis* has been used in traditional Chinese medicine to treat a variety of mental disorders (Watanabe et al., 1983; Maruyama et al., 1998; Nakazawa et al., 2003). Studies also showed that the components useful for anxiety may cause to GABA receptor/Cl<sup>-</sup> channel activation, while those useful for depression may be related to modulation of neurotransmitters. *Magnolia* ingredients also have neurotrophic effects against Alzheimer's disease as well as against nerve injuries (via MEK). Anti-oxidative effects and normalization of mitochondrial functions of *Magnolia* ingredients could protect cells and ameliorate cellular damage due to brain ischemia. Anti-inflammatory mechanisms of *Magnolia* have been reported to be associated with the suppression of NO production, the expression of iNOS, IL-1 $\beta$ , TNF- $\alpha$  and COX, and the activation of MAPKs, AP-1 and NF- $\kappa$ B. Anti-atherosclerosis effects (Table 5) of *Magnolia* ingredients have been reported to be associated with anti-oxidative effects and cell cycle arrest. Anti-platelet effects of magnolol and honokiol are due to the inhibitory effects on TXA formation and inhibition of intracellular Ca mobilization.

These ingredients have a wide variety of pharmaceutical properties. It is now necessary that we identify the constituents, delineate possible mechanisms, and justify routes and formulations. We hope this review provides a foundation for further studies to assess mechanisms underlying the effects of *Magnolia* ingredients, and clinical applications of these components.

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