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Review:

Biological activity and toxicity of the Chinese herb *Magnolia officinalis* Rehder & E. Wilson (Houpo) and its constituents

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Abstract: Traditional Chinese herbal drugs have been used for thousands of years in Chinese pharmacopoeia. The bark of *Magnolia officinalis* Rehder & E. Wilson, known under the pinyin name "Houpo", has been traditionally used in Chinese and Japanese medicines for the treatment of anxiety, asthma, depression, gastrointestinal disorders, headache, and more. Moreover, *Magnolia* bark extract is a major constituent of currently marketed dietary supplements and cosmetic products. Much pharmacological activity has been reported for this herb and its major compounds, notably antioxidant, anti-inflammatory, antibiotic and antispasmodic effects. However, the mechanisms underlying this have not been elucidated and only a very few clinical trials have been published. In vitro and in vivo toxicity studies have also been published and indicate some intriguing features. The present review aims to summarize the literature on *M. officinalis* bark composition, utilisation, pharmacology, and safety.

Key words: *Magnolia* bark; Houpo; Chinese herb; Traditional Chinese medicine
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1 Introduction

Traditional Chinese medicine (TCM) has a more than 2500-year history and consists of the development of major theories and clinical investigations carried out by generations of practitioners and researchers (Fazel, 1995; Unschuld, 1999; Wang and Li, 2005; Tang *et al*., 2008; Xu *et al*., 2013). Different *Magnolia* have been traditionally used in Chinese and Japanese medicine for thousands of years (Liu *et al*., 2007) and are now widely used internationally. There are three basic materials of frequent application and described in the Chinese pharmacopoeia 2010 (CPC, 2010): the bark of *Magnolia officinalis* Rehder & E. Wilson, called "Houpo" or "Houpu" in Chinese (Houpu, refers to the thick ("hou") bark that is the unadorned ("pu") portion of the plant. The herb is sometimes called "Chuan houpu", because it originally came from the Sichuan area of China. Tuhoupu ("tu" is especially used in Guangxi Province, China) is sometimes used as a substitute (Dharmananda, 2002), the flower bud of *M. officinalis*, called "Houpohua", and the flower bud of *Magnolia biondii* Pamp., *Magnolia denudate* Desr., or *Magnolia sprengeri* Pamp. called "Xinyi" or "Xinyihua". A non-official species, *Magnolia obovata* Thunb., is sometimes described as source material for *Magnolia* bark (Liu *et al*., 2007). In some literature, the flower is wrongly assigned to a non-botanically defined species, erroneously called *Magnolia lactiflora*.

Magnolia trees are mainly distributed in East and Southeast Asia (Cui *et al*., 2013) and are generally very attractive thanks to their fragrant and dazzling flowers (Lee *et al*., 2011). The root and branch bark are collected from April to June and dried in the shade; the stem bark is slightly decocted in boiling water and

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piled up in a wet place until its inner surface becomes purplish-brown or dark brown, softened by steaming, and rolled and dried (CPC, 2010). The dried bark is gray-brown in color with oval lenticles in a longitudinal striation (Fig. 1) and has a fragrant odor, a pungent taste, and is slightly bitter (EPCNF, 2009). The current taxonomic description of the plant is summarized below:

Kingdom: Viridiplantae;

Phylum: Streotophyta;

Class: Eukaryota;

Order: Magnoliales;

Family: Magnoliaceae;

Genus: *Magnolia*

Species: *Magnolia officinalis*, *Magnolia obovata*;

Pharmaceutical name: *Magnoliae* cortex, *Magnolia officinalis* cortex, *Magnolia officinalis* bark;

TCM name: Hou Po or Houpo.

Fig. 1 *Magnolia officinalis* cortex (*Magnolia* bark)

Magnolia bark has been used as a constituent of various traditional Chinese formulas such as "Banxia Houpo Tang" (Table 1), "Xiao Zhengai Tang", "Ping Wei San", and "Shenmi Tang". In China, a number of prescriptions containing Houpo are still in use in modern clinical practice (Yu *et al*., 2012). In Japan, two prescriptions containing *Magnolia* bark, Hange-Koboku-To (Japanese name for Banxia Houpo Tang) (Iwasaki *et al*., 2000) and Saiboku-To (Table 1), are also still in use in modern clinical practice (Li N. *et al*., 2007; Lee *et al*., 2011).

Herbal preparations containing *Magnolia* bark are typically used as decoctions with intakes ranging from 3 to 10 g per person. Various *Magnolia* bark extracts (MBEs) can also be found in the marketplace as ingredients of both dietary supplements, typical recommended use levels ranging from 200 to 800 mg/d per person (EPCNF, 2009), and cosmetic products (Liu *et al*., 2007). The flower bud is used almost exclusively for the treatment of sinus congestion and sinus headaches, and is taken orally or applied topically. *Magnolia* bark, on the other hand, has a very wide range of applications as will be detailed in the present review; it has been used in Chinese and Japanese traditional medicines for the treatment of gastrointestinal (GI) disorders, anxiety, depression, nervous disorders, asthma, and allergic disease, as well for the alleviation of headaches, muscular pain, and fever (Dharmananda, 2002; Amblard *et al*., 2007; Li N. *et al*., 2007; Liu *et al*., 2007; Lee *et al*., 2011).

Table 1 Examples of traditional Chinese and Japanese formulas containing *Magnolia*

Traditional Chinese and Japanese formulas	Plants
Banxia Houpo Tang (Chinese)	*Pinellia*[a] (*Pinellia ternate* Thunb.): 6.0 g
(Iwasaki *et al*., 2000)	Hoelen[a] (*Poria cocos* Wolf): 3.0 g
	Magnolia (*Magnolia obovata* Thunb.): 3.0 g
	Perilla (*Perilla frutescens* Britton var. *acuta* Kudo): 2.0 g
	Ginger[a] (*Zingiber officinale* Roscoe): 1.0 g
Saiboku-To (Japanese)	Bupleuri[a] (*Bupleurum falcatum* L.): 7.0 g
(Bielory *et al*., 2004)	*Pinellia*[a] (*Pinellia ternata* Thunb.): 5.0 g
	Hoelen[a] (*Poria cocos* Wolf): 5.0 g
	Scutellaria[a] (*Sculellaria baicalensis* Georgi): 3.0 g
	Magnolia (*Magnolia obovata* Thunb.): 3.0 g
	Zizyphi[a] (*Zizyphus jujuba* Miller var. *inermis* Rehder): 3.0 g
	Ginseng[a] (*Panax ginseng* C.A. Meyer): 3.0 g
	Glycyrrhiza[a] (*Glycyrrhiza uralensis* Fisch.): 2.0 g
	Perilla (*Perilla frutescens* Britton var. *acuta* Kudo): 2.0 g
	Zingiberis[a] (*Zingiber officinale* Roscoe): 1.0 g

[a] Although these herbs are part of herbal formulae implicated in hepatotoxicities (Teschke *et al*., 2014; 2015; 2016; Zhu *et al*., 2016), the causality assessment is most often lacking

2 Phytochemicals isolated from *Magnolia*

Up till now, more than 250 kinds of ingredients have been isolated from the cones, bark, flowers, and leaves of the genus *Magnolia* (Cui *et al*., 2013). Chemical investigations of the cortex of *M. officinalis* and *M. obovata* led to the isolation of several major phenolic compounds, notably the neolignan derivatives magnolol (5,5'-diallyl-2,2'-dihydroxybiphenyl) and honokiol (5,3'-diallyl-2,4'-dihydroxybiphenyl) (Table 2), which are considered the two principal phenolic compounds in the bark and the main active constituents (Dharmananda, 2002; Li N. *et al*., 2007; EPCNF, 2009).

As well as these well-known lignans magnolol and honokiol, alkaloids are a group of interesting secondary metabolites of this species, which produces mainly isoquinoline-type alkaloids, the majority of which are aporphine and benzylisoquinoline derivatives (Yan *et al*., 2013). *Magnolia* bark also contains volatile oils, the major constituents of which are the sesquiterpenoid alcohols, α-, β-, and γ-eudesmol (about 95% of the essential oil). Specific components in the bark and the proportions of those constituents significantly differ depending on harvesting sites and period (EPCNF, 2009).

2.1 Lignans

Major significant bioactive components isolated from the bark of *M. officinalis* or *M. obovata* appear to be the polyphenolic neolignans, magnolol and honokiol (Kong *et al*., 2005; Amblard *et al*., 2007; Lin *et al*., 2011). Magnolol was named after its source, genus *Magnolia* plants, and honokiol was named after "Honoki", a Japanese name of *M. obovata* Thunb. (Maruyama and Kuribara, 2000). Magnolol and honokiol are two hydroxylated biphenolic isomers (neolignans, $C_{18}H_{18}O_2$) (Lin *et al*., 2007), the *ortho-ortho*-C-C and *ortho-para*-C-C dimers of 4-allylphenol, respectively (Kong *et al*., 2005) (Table 3).

Commercially available *Magnolia* bark extracts appear to be marketed based on their high phenolic content, with magnolol and honokiol ranging from 40% to 90% of total polyphenols; the evaluation of the quality of commercial Houpo samples, according to region, harvesting, and processing, is effectively based on a quantitative determination of the levels of magnolol and honokiol in the bark (EPCNF, 2009).

Table 2 Major constituents of *Magnolia* bark (Dharmananda, 2002)

Component	Parts where found
Essential oil	Bark (3000–10 000 ppm)*
Bornyl-acetate	Essential oil (terpene)
Camphene	Essential oil (terpene)
Caryophyllene epoxide	Essential oil (terpene)
Eudesmols	Bark
α-Eudesmol	Essential oil (terpene)
β-Eudesmol	Essential oil (terpene)
γ-Eudesmol	Essential oil (terpene)
Cryptomeridiol	Essential oil (terpene)
α-Pinene	Whole plant (terpene)
β-Pinene	Whole plant (terpene)
Polyphenol	
Bornyl-magnoliol	Whole plant (lignan)
Caffeic acid	Whole plant
Cyanidin	Whole plant (anthocyanidin)
Honokiol	Whole plant (lignan)
Quercetin	Whole plant (flavonoid)
Kaempferol	Whole plant (flavonoid)
Magnolol	Bark (lignan)
Alkaloid	About 1% of the bark
Anonaine	Whole plant (aporphine)
Liriodenine	Whole plant (aporphine)
Magnocurarine	Whole plant (benzyltetrahydroisoquinoline)
Magnoflorine	Whole plant (benzyltetrahydroisoquinoline)
Michelalbine	Whole plant (aporphine)
Salicifoline	Whole plant (phenethylamine)
Mineral	
Copper	Bark (8 ppm)
Calcium	Bark (6350 ppm)
Iron	Bark (120 ppm)
Magnesium	Bark (690 ppm)
Manganese	Bark (120 ppm)
Potassium	Bark (2560 ppm)
Sodium	Bark (27 ppm)
Zinc	Bark (9 ppm)

* ppm: 1 ppm=1 mg/L

The Chinese (CPC, 2010) and European pharmacopoeia (Council of Europe, 2013) require a minimum of 2.0% of the total amount of honokiol and magnolol, with reference to the dried drug. Other neolignans include 4-*O*-methylhonokiol (0.012% in *M. obovata* and 0.0003% in *M. officinalis* bark) and obovatol (only found in *M. obovata* at 0.33%) (Lee *et al*., 2011).

2.2 Alkaloids

Other bioactive polar compounds from *Magnolia* bark are alkaloids (about 1% of the bark), mainly benzyltetrahydroisoquinoline and aporphine types (Yu *et al*., 2012), based on the precursor amino acids tyrosine and dopa. Alkaloids that possess an isoquinoline skeleton are among the most common of all alkaloids.

From the bark of *M. officinalis*, different tertiary and quaternary alkaloids have been isolated and structurally elucidated (Yan *et al*., 2013), including (1) the aporphine alkaloids *N*-methylcoxylonine, (*S*)-magnoflorine, magnofficine, (*R*)-asimilobine, corytubérine, anonaine, liriodenine and (2) the benzyltetrahydroisoquinoline alkaloids (*R*)-magnocurarine, (*S*)-tembetarine, lotusine, (*R*)-oblongine, reticuline (Guo *et al*., 2011; Yan *et al*., 2013). Magnoflorine and magnocurarine are considered as the major and most potent of *Magnolia* bark alkaloids (Dharmananda, 2002) (Tables 4 and 5).

Alkaloids are found in leaves (at full maturation or beginning of fall), branches, and bark of *Magnolia* species (Ziyaev *et al*., 1999). These alkaloids include tertiary and the highly polar quaternary ammoniums.

Table 3 Chemical properties of lignans magnolol, honokiol, and obovatol (NCBI, 2016)

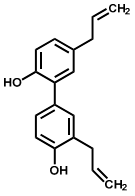
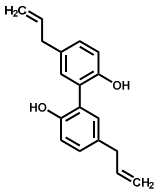
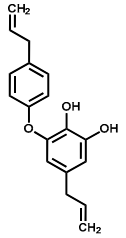
Name	Chemical structural formula	IUPAC name	Synonym	Molecular formula	Molecular weight (g/mol)
Honokiol		2-(4-Hydroxy-3-prop-2-enylphenyl)-4-prop-2-enylphenol	5,3'-Diallyl-2,4'-dihydroxybiphenyl	$C_{18}H_{18}O_2$	266.3
Magnolol		2-(2-Hydroxy-5-prop-2-enylphenyl)-4-prop-2-enylphenol	5,5'-Diallyl-2,2'-dihydroxybiphenyl	$C_{18}H_{18}O_2$	266.3
Obovatol		5-Prop-2-enyl-3-(4-prop-2-enylphenoxy)benzene-1,2-diol	5,5'-Diallyl-2,2'-dihydroxybiphenyl	$C_{18}H_{18}O_3$	282.3

Table 4 Chemical properties of the alkaloids magnoflorine and magnocurarine (NCBI, 2016)

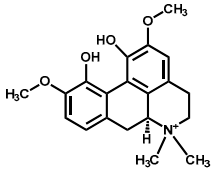
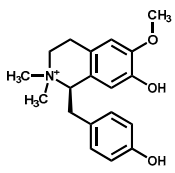
Name	Chemical structural formula	IUPAC name	Molecular formula	Molecular weight (g/mol)
Magnoflorine		(6a*S*)-2,10-dimethoxy-6,6-dimethyl-5,6,6a,7-tetrahydro-4H-dibenzoquinoline-6-ium-1,11-diol	$C_{20}H_{24}NO_4^+$	342.4
Magnocurarine		(1*R*)-1-[(4-hydroxyphenyl) methyl]-6-methoxy-2,2-dimethyl-3,4-dihydro-1H-isoquinolin-2-ium-7-ol	$C_{19}H_{24}NO_3^+$	314.4

Table 5 Content of magnocurarine in *Magnolia officinalis* bark (Dharmananda, 2002)

Species	Collection site	Magnocurarine (% (w/w) in bark)
Magnolia officinalis	Zhenping, Shaanxi	0.150
Magnolia officinalis	Hanzhong, Shaanxi	0.103
Magnolia officinalis	Ansi, Hubei	0.127
Magnolia officinalis	Nanjiang, Sichuan	0.060
Magnolia officinalis var. *biloba*	Jinggangshan, Jiangxi	0.060
Magnolia officinalis var. *biloba*	Guilin, Guangxi	0.025
Magnolia officinalis var. *biloba*	Lishui, Zhejiang	0.201

3 Biological activity

Magnolia bark has not only been used historically in traditional Chinese and Japanese medicine, but also in American and Indian medicine; the bark has been listed in the American Pharmacopeia as bitter tonic and antimalarial (Davis, 1981; Li N. *et al*., 2007). More recently, *Magnolia* bark has been used as a component of dietary supplements and topically applied cosmetics (Li N. *et al*., 2007; Liu *et al*., 2007).

Various pharmacological activities (anti-cancer, anti-stress, anti-anxiety, antidepressant, antioxidant, anti-inflammatory, and hepatoprotective) have been investigated for *Magnolia* bark and its constituents. However, most often the mechanisms underlying these pharmacological effects have not been elucidated (Lee *et al*., 2011) (Fig. 2).

3.1 Cytotoxic activity: eventual therapeutic application in cancer?

Cancer represents a major health problem worldwide. In 2012, the World Health Organization (WHO) recorded 14 million new cases of cancer and 8.2 million cancer-related deaths, with 4.3 million under the age of 70 years (WHO, 2016). Significant progress in the fight against cancer still calls for both advances in cancer diagnosis and development of preventive and therapeutic strategies (Arora *et al*., 2012). Herbal therapies from alternative and complementary medicines may hold a key to such advances; for example, TCM proposes preparations to treat cancers, but the effective component(s) or their mode of action at cellular and molecular levels is largely unknown (Yang *et al*., 2003).

Studies in in vitro and animal models have shown that *Magnolia* components, especially the neolignans honokiol and magnolol, are able to target many pathologically relevant pathways (Arora *et al*., 2012). These findings have increased interest in using neolignans as possible novel chemotherapeutic agents; notably, mechanistic studies have been carried out on honokiol to assist the development of novel synthetic analogues and to provide clues for rational combinations with conventional chemo- or radiotherapy (Fried and Arbiser, 2009).

3.1.1 Mechanisms of action

As Arora *et al.* (2012) recapped, cancer progresses through a series of genetic and epigenetic aberrations leading to dysregulation of key cell signaling pathways involved in growth, malignant behavior, and therapy-resistance. Honokiol and its analogs target multiple signaling pathways, including nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), epidermal growth factor (EGFR, also called ErbB1), mammalian target of rapamycin (mTOR, a protein kinase centrally involved in the control of cell metabolism, growth, and proliferation), and the caspase-mediated common pathway, which modulate cancer initiation and progression (Kumar *et al.*, 2013). Also, to fight cancer, lignans-induced apoptosis seems to be a key feature (Lee *et al.*, 2011).

The ubiquitous transcription factors, NF-κB and STAT3, control the expression of a wide array of genes notably involved in development, cell growth, and differentiation, immunity, metabolism, inflammation, and cancer (Grivennikov and Karin, 2010). Aberrant activation of these transcription factors is not only common in many malignancies, in both the early and late developmental steps (Arora *et al.*, 2012), but also in tumorigenesis, metastasis, and angiogenesis through the induction of genes participating in malignant conversion and tumor promotion (Lee *et al.*, 2011). In many tumors, a constitutive activation of NF-κB modulates the expression of anti-apoptotic

(upregulation) and pro-apoptotic (downregulation) genes and activates cell cycle and proliferation (Garg and Aggarwal, 2002; Karin, 2006; Lee *et al.*, 2011; Arora *et al.*, 2012). STATs notably participate in oncogenesis, through upregulation of genes encoding apoptosis inhibitors and cell cycle regulators (Yu *et al.*, 1995; Buettner *et al.*, 2002). Lignans, especially honokiol, have been shown to affect NF-κB signaling, not through a direct effect on NF-κB-DNA binding, but upstream of NF-κB activation, at the level of IKK, the inhibitor of κB (IκB) kinase (Fried and Arbiser, 2009). They inhibit NF-κB activation through the suppression of protein kinase B (AKT), which prevents IKK activation, IκBα phosphorylation, and NF-κB nuclear translocation. STAT3 can be inhibited by lignans through interleukin-6 (IL-6), one of the many growth factors that modulate its expression, and by the repression of upstream protein tyrosine kinases, cellular sarcoma (c-Src), Janus kinase 1 (JAK1), and JAK2 (Fried and Arbiser, 2009; Arora *et al.*, 2012).

EGFR is a membrane receptor, a glycoprotein with tyrosine kinase activity, which is frequently overexpressed and/or amplified in various cancer types. Aberrant EGFR signaling has been shown to promote cell survival and proliferation (Arora *et al.*, 2012). Failure to attenuate receptor signaling by receptor downregulation can also lead to cellular transformation; the mechanisms by which EGFR becomes oncogenic are numerous, often specific for each cancer type (Zandi *et al.*, 2007). Studies in several human cells, obtained from breast cancer, melanoma, and head and neck squamous cell carcinoma, indicate that a growth inhibitory effect of lignans is associated with down-modulation of EGFR signaling and phosphorylation (Fried and Arbiser, 2009; Arora *et al.*, 2012; Kaushik *et al.*, 2012).

In most cancer cells, but also in the carcinogenic process, an aberrant activation of mTOR is primarily caused by the activation of the phosphatidyl-inositol 3-kinase (PI3K)-AKT pathway (Guertin and Sabatini, 2007). It is suggested that lignans, and especially honokiol, may suppress the activation of mTOR and its downstream signaling, resulting in apoptosis induction, by inhibiting the extracellular signal-regulated kinases (ERK) and AKT pathways or by upregulating phosphatase and tensin homolog (PTEN) (Liu *et al.*, 2008; Fried and Arbiser, 2009; Lee *et al.*, 2011; Arora *et al.*, 2012; Kaushik *et al.*, 2012).

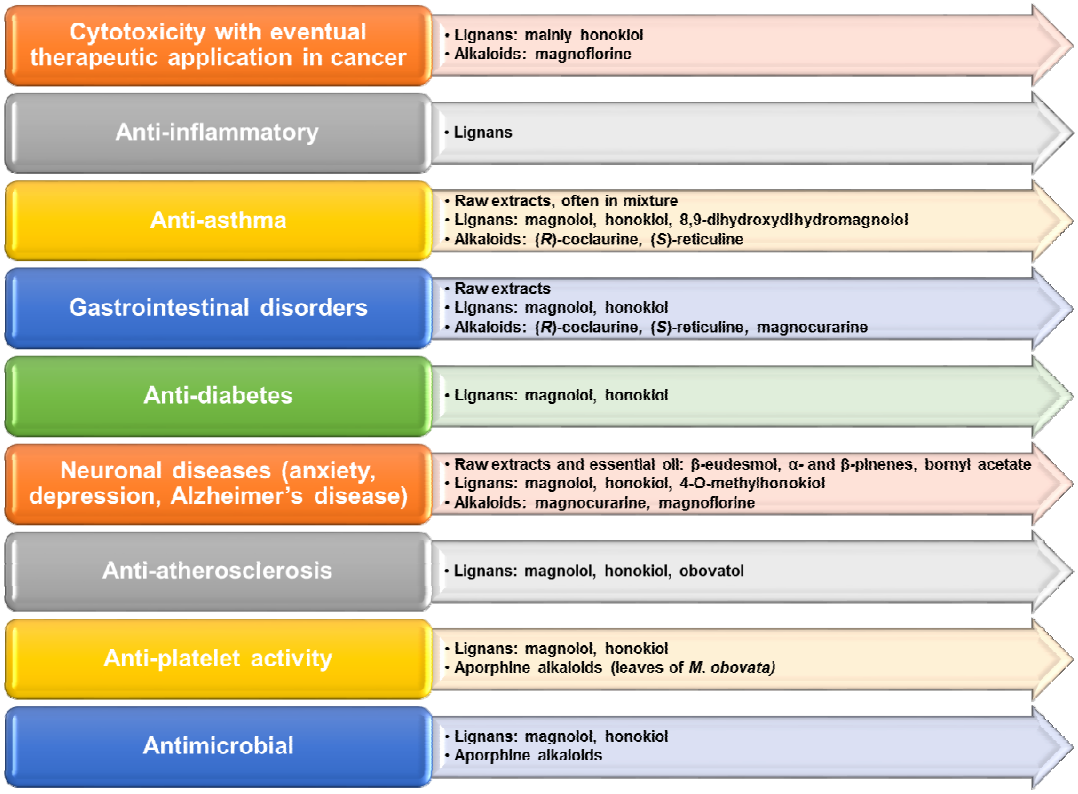


Fig. 2 Therapeutic interest of *Magnolia*: reported extracts and compounds associated with biological activities

3.1.2 Cytotoxic activity of *Magnolia* lignans

Several constituents of *M. officinalis*, mainly lignans, have been widely reported to be cytotoxic, which is a possible clue to new anti-cancer compounds (Lee *et al*., 2011). At low concentrations (up to 3 μmol/L), they can induce apoptosis in human cancer cell lines, whereas they do not inhibit the growth of human untransformed cells (Kong *et al*., 2005). Honokiol was reported to possess higher activity than magnolol in the induction of apoptosis (Kong *et al*., 2005). Obovatol increased the susceptibility to chemotherapeutic agents at low concentrations, around 5 μmol/L (Lee S.Y. *et al*., 2009) (Table 6).

3.2 Anti-inflammatory activity

Inflammation, a protective response involving immune cells, blood vessels, and molecular mediators, is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (Ferrero-Miliani *et al*., 2007). Generally, the production of inflammatory molecules is triggered by mitogenic stimulation with various bacterial products, such as lipopolysaccharides (LPS). Various signaling cascades composed of pattern recognition receptors (e.g. Toll-like receptor 4 (TLR4)), non-receptor type tyrosine kinases (eg. Src and Syk), serine/threonine kinases (protein kinase C (PKC), PKA, PI3K, and AKT), MAPK, and various redox-sensitive transcription factors, such as NF-κB, are regarded as critical components participating in the process (Kim and Cho, 2008; Simmonds and Foxwell, 2008).

Nitric oxide (NO·), a physiological mediator of endothelial cell relaxation, also plays a key role in the inflammatory pathway. Synthesised by many cell types involved in immunity and inflammation, through the inducible NO· synthase (iNOS), in response to pro-inflammatory cytokines and bacterial LPS, NO· is a major defense molecule, toxic against infectious organisms, and is a key player in the pathogenesis of a variety of inflammatory diseases (Lee *et al*., 2011). NO· notably regulates the functional activity, growth and death of many immune and inflammatory cell types including macrophages, T lymphocytes, antigen-presenting cells, mast cells, neutrophils, and natural killer cells (Coleman, 2001; Ricciardolo *et al*., 2004; Garcia and Stein, 2006; Tripathi *et al*., 2007).

Table 6 Cytotoxic activities of *Magnolia* compounds (Lee *et al*., 2011)

Compound	Cell line or animal model	IC_{50} (μmol/L)	Reference
Magnolol	COLO-205 (human colon carcinoma cell line)	50–100	Lin *et al*., 2001
	HCT116 (human colorectal carcinoma cell line)	60	Lee D.H. *et al*., 2009
	HeLa (human cervix adenocarcinoma cell line)	12.4–49.9	Syu *et al*., 2004
	HepG2 (human liver cancer cell line)	100	Lin *et al*., 2001
	RKO (human rectal carcinoma cell line)	47.8	Chen *et al*., 2004
	H460 (human lung carcinoma cell line)	20–40	Li H.B. *et al*., 2007
	OVCAR-3 (human ovarian carcinoma cell line)	12.4–49.9	Syu *et al*., 2004
	PC-3 (human prostate metastatic cell line)	60	Lee D.H. *et al*., 2009
Honokiol	RKO (human rectal carcinoma cell line)	38.8	Wang *et al*., 2004
	H460 (human lung carcinoma cell line)	41.1	Yang *et al*., 2002
	SW480 (human colorectal carcinoma cell line)	48.7	Yang *et al*., 2002
	LS180 (intestinal human colon adenocarcinoma cell line)	41.9	Yang *et al*., 2002
	CH27 (human lung squamous carcinoma)	40.9	Yang *et al*., 2003
	PC-3 (human prostate metastatic cell line)	20–40	Hahm and Singh, 2007
	MCF-7 (human breast adenocarcinoma cell line)	15–20	Li L. *et al*., 2007
	SCC4 (human tongue squamous cell carcinoma)	25	Ahn *et al*., 2006
	MKN45 (human gastric cancer cell line)	20–40	Sheu *et al*., 2007
Obovatol	SW620 (human colon metastatic cell line)	5	Lee S.Y. *et al*., 2009
	HCT116 (human colorectal carcinoma cell line)	5	Lee S.Y. *et al*., 2009
	LNCaP (androgen-sensitive human prostate adenocarcinoma cell line)	5	Lee S.Y. *et al*., 2009
	PC-3 (human prostate metastatic cell line)	5	Lee S.Y. *et al*., 2009
	HT1080 (fibrosarcoma cell line)	20	Lee *et al*., 2007
Magnoflorine	HepG2 (human liver cancer cell line)	1.2	Mohamed *et al*., 2010

IC_{50}: concentrations for 50% inhibition of cell growth

The factor NF-κB (Section 3.1) promotes the transcription of genes involved in pro-inflammatory responses. In macrophages, NF-κB is activated by inflammatory extracellular signals such as LPS, IL-1 and tumor necrosis factor α (TNF-α), and regulates a number of inflammatory genes, inducing further inflammatory mediators, including NO· and cytokines (Zhang *et al*., 2013). A second major transcription factor, the activator protein 1 (AP-1), an ubiquitous dimeric protein complex composed of Jun and Fos subfamilies (Curran and Franza, 1988), is also activated by many pathophysiological stimuli, including LPS, reactive oxygen species (ROS), mitogenic growth factors, inflammatory cytokines, growth factors of the transforming growth factor-β (TGF-β family, ultraviolet (UV) and ionizing irradiation, cellular stress, antigen binding, and neoplastic transformation. In response to different stimuli, AP-1 is able to activate different sets of genes for differentiation, proliferation, apoptosis (Wisdom, 1999), and inflammation (Newton and Dixit, 2012) responses.

Within the repertoire of protein kinase cascade networks, the MAPK family contains at least 3 protein kinases in series that culminate in the activation of a multifunctional MAP kinase (Pearson *et al*., 2001). MAP kinases are major components of pathways controlling embryogenesis, cell differentiation, cell proliferation and cell death (Pearson *et al*., 2001), and play a significant role in carcinogenesis and in leukocytes' recruitment to sites of inflammation (Herlaar and Brown, 1999). As for AP-1, the MAPKs differentially activate inflammatory pathways, depending on the stimuli and cell types (Lee *et al*., 2011).

The cyclooxygenase 2 (COX2), induced in cells by proinflammatory cytokines and growth factors, is also increased in certain inflammatory states. COX2 is a key enzyme in the synthesis of pro-inflammatory eicosanoids (prostaglandins (PGs), thromboxanes (TBXs), leukotrienes, etc.).

As discussed in the previous section, the NO production, the expressions of iNOS, IL-1β, TNF-α and COX, and the generation of eicosanoids, in addition to the activation levels of MAPKs, AP-1, and NF-κB pathways, may reflect the degree of inflammation and have become important indicators with which to assess inflammatory and anti-inflammatory processes (Lee *et al*., 2011). An impressive series of studies has shown that all of these major indicators are positively impacted by *Magnolia* lignans, even if the full anti-inflammatory mechanisms have not yet been elucidated (Choi *et al*., 2007; Lin *et al*., 2007; Munroe *et al*., 2007; Kang *et al*., 2008; Lee *et al*., 2011). Upregulating signaling cascades composed of Ras, Raf, and MAPK, downregulating the activation of NF-κB, and blocking NF-κB activation mediated by CD40 and latent membrane protein 1 are speculated to be the action mechanism of *Magnolia* lignans (Lin *et al*., 2007; Kim and Cho, 2008; Lee *et al*., 2011).

Among the lignans (Table 7), honokiol and magnolol were notably shown to inhibit the formation of eicosanoids (prostaglandin D2 (PGD2), PGE2, leukotriene C4 (LTC4), LTB4, and thromboxane B2 (TXB2)), probably through inhibition of phospholipase A2, COX, 5-lipoxygenase, LTC4 synthase, and LTA4 hydrolase activities (Lin *et al*., 2007).

3.3 Therapeutic activity in asthma

Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person (WHO, 2016). According to WHO estimates, 235 million people suffer from asthma, with prevalences ranging from 1% to 18% across countries. Moreover, it represents one of the most prevalent chronic conditions among children. In addition to large financial burdens, asthma also leads to serious health consequences and compromises life quality (Lin *et al*., 2015).

Table 7 Anti-inflammatory lignans from *Magnolia* (Lee *et al*., 2011)

Compound	Cell line	In vivo	Concentration/dose	Reference
4-Methoxyhonokiol		Mice	20–100 mg/kg	Zhou *et al*., 2008
Honokiol		Mice	3 mg/mouse	Munroe *et al*., 2007
Magnolol		Mice	10 mg/kg	Wang *et al*., 1992
4-Methoxyhonokiol	RAW (murine macrophage cell line)		1–30 μmol/L	Zhou *et al*., 2008
Obovatol	RAW (murine macrophage cell line)		1–5 μmol/L	Choi *et al*., 2007

The causes of asthma are not completely understood and the pathology cannot be cured, but appropriate management can control the disorder (WHO, 2016). In China as well as throughout Asia, myths and misconceptions on Western medicine and corticosteroids are prevalent, resulting in non-adherence to conventional treatments and in the recourse to traditional herbal medicines (Hon *et al*., 2015). For example, Saiboku-To, a Japanese mixture of ten different herbal extracts (Table 1) that include *M. officinalis*, has been investigated for corticosteroid-dependent severe asthma to reduce the maintenance doses of corticosteroids. This herbal complex medicine is also known for its use in general bronchial asthma (Lee *et al*., 2011) and the TCM herb "Houpo" (bark of *M. obovata* and/or *M. officinalis*), is widely used for the treatment of chest tightness and asthma (Ko *et al*., 2003). Homma *et al*. (1993) suggested that magnolol, as an inhibitor of 11β-hydroxysteroid dehydrogenase and T-lymphocyte proliferation, might be responsible for the therapeutic effect of Saiboku-To resulting in corticosteroid-sparing.

The effects of *Magnolia* on asthma are from two types: (1) *M. officinalis* (as well as Saiboku-To) inhibits human lymphocyte blastogenesis, in vitro, in a dose-dependent way. It seems to have anti-asthmatic effect through suppression of type IV (lymphocyte-mediated) allergic reaction (Lee *et al*., 2011); (2) *Magnolia* extracts induce bronchodilatation by a muscle relaxation that is associated with a Ca^{2+} antagonist effect, probably due to magnolol and honokiol. Moreover, alkaloids such as (*R*)-coclaurine and (*S*)-reticuline inhibit acetylcholine (ACH)-induced contraction of muscles (Ko *et al*., 2003; Lee *et al*., 2011). The effects of honokiol and magnolol on muscular contractile responses and intracellular Ca^{2+} mobilization were investigated in the non-pregnant rat uterus; both lignans (at concentrations 1–100 μmol/L) inhibited spontaneous and uterotonic agonists (carbachol, PGF-2α, and oxytocin), and an experimental Ca^{2+} channel activator in a concentration-dependent manner. The inhibition rate of honokiol on spontaneous contractions appeared to be slower than that of magnolol-induced responses (Lu *et al*., 2003) (Table 8).

3.4 Treatment of gastrointestinal disorders

Diseases of the GI tract are highly common and varied, including irritable bowel syndrome, functional dyspepsia, abdominal pain, abdominal bloating, nausea, vomiting, diarrhoea, constipation, etc., which have a substantial effect on quality of life and healthcare costs (Hu *et al*., 2009). *M. officinalis* is commonly used in TCM for treating such GI disorders, probably through an antispasmodic effect that results in relaxation of GI tract smooth muscles (Chan *et al*., 2008; Lee *et al*., 2011).

Among various regulatory factors that modulate smooth muscle motility in GI tracts, ACH and serotonin (5-hydroxytryptamine, 5-HT) are considered as major neurotransmitters that regulate the GI motility. Magnolol and honokiol significantly inhibit 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 $CaCl_2$; both behave as non-competitive muscarinic antagonists. Magnolol and honokiol inhibited contractions induced by ACH (in Ca^{2+}-free medium) and extracellular Ca^{2+}-dependent contractions induced by ACH; this Ca^{2+} blockade effect is also discussed for anti-asthmatic effects in Section 3.3 (Lu *et al*., 2003; Chan *et al*., 2008; Jeong *et al*., 2009; Lee *et al*., 2011; Herrmann *et al*., 2014).

Alkaloids may also confer some of the antispasmodic effect of *Magnolia* bark when used in high-dose decoctions to alleviate bronchiole spasms and intestinal spasms. Magnocurarine was investigated as a potential muscle relaxant drug in Japan (Dharmananda, 2002) (Table 9).

Table 8 In vitro effects of *Magnolia* compounds active in asthma treatment (Lee *et al*., 2011)

Compound	Dose	Effect	Reference
Magnolol and 8,9-dihydroxydihydromagnolol	11.26–26.29 μmol/L (IC_{50})	Inhibition of lymphocytes blastogenesis	Taniguchi *et al*., 2000
Magnolol and honokiol	0.1–100.0 μmol/L	Muscle relaxation (through Ca^{2+} channels)	Ko *et al*., 2003
(*R*)-coclaurine and (*S*)-reticuline	0.25–0.50 mmol/L	Muscle relaxation (through Ca^{2+} channels)	Kimura *et al*., 1989

IC_{50}: concentrations for 50% inhibition of cell growth

Table 9 *Magnolia* compounds active in GI disorders (Lee *et al*., 2011)

Compound	Dose	Effect	Reference
Magnolol and honokiol	0.1–100.0 μmol/L (human prostate stromal cells WPMY-1 and porcine trachea); 1–1000 μmol/L (guinea pig)	Muscle relaxation (through Ca^{2+} voltage-operated channels)	Ko *et al*., 2003; Herrmann *et al*., 2014
(*R*)-coclaurine and (*S*)-reticuline	0.25–0.50 mmol/L (isolated guinea pig papillary muscle)	Muscle relaxation (through Ca^{2+} voltage-operated channels)	Kimura *et al*., 1989
Magnocurarine	13.8 mg/kg (rabbit)	Muscle relaxation (through Ca^{2+} voltage-operated channels)	Chang and But, 1987

3.5 Treatment of diabetes

Magnolia plants have been used as Korean and Brazilian complementary and alternative medicines for the treatment of diabetes and diabetic complications; it has been shown that long-term supplementation of honokiol and magnolol ameliorates body fat accumulation, insulin resistance, and adipose inflammation in high-fat fed mice (Kim *et al*., 2013). Honokiol and magnolol reduce fasting blood glucose and plasma insulin levels in type 2 diabetic rats without altering body weight, and induce glucose uptake in adipocytes. Honokiol also enhances insulin signaling pathways such as the Ras/ERK1/2 and phosphoinositide-3-kinase/AKT signaling pathways, and ameliorates alcoholic steatosis by blocking fatty acid synthesis regulated by the sterol regulatory element-binding protein 1c (SREBP1c) (Kim *et al*., 2013). An ethanolic extract of the *Magnolia* cortex showed an in vitro inhibitory effect on the formation of advanced glycation endproducts (AGEs), which play an important role in the development of diabetic complications. Furthermore, magnolol inhibits AGE formation and sorbitol accumulation in streptozotocine-induced diabetic rats (Sohn *et al*., 2007). Honokiol and magnolol also improve both glucose and lipid metabolisms and inhibit acyl-CoA cholesterol acyltransferase (ACAT), which catalyzes the formation of cholesteryl esters from cholesterol and long-chain fatty acyl-CoA. Magnolol can activate the peroxisome proliferator-activated receptor γ (PPARγ) as a ligand, induce adipocyte differentiation, and enhance insulin-stimulated glucose uptake in animal models (Lee *et al*., 2015).

3.6 Effects on neuronal disease

The bark of *M. officinalis* is one of the most important traditional herbal medicines in China and Japan used to treat clinical depression and anxiety-related disorders (Nakazawa *et al*., 2003). Even the oldest known TCM book, *Shennong Bencao Jing*, mentions this tranquilizing action (Tachikawa *et al*., 2000). Kampo preparations, such as Hange-Koboku-To, Yoku-Kan-san, Saiboku-To, and Kami-Kihi-To, have been historically prescribed for conditions akin to clinical depression, anxiety-related disorders, such as anxiety neurosis, insomnia, and anxiety hysteria, as well as for thrombotic stroke and GI complaints (Maruyama *et al*., 1998). The ingredients that have been reported to possess pharmacological effects on the nervous systems are β-eudesmol, α- and β-pinenes, and bornyl acetate, as essential oils; magnolol and honokiol, as diphenyl compounds; and magnocurarine and magnoflorine, as alkaloids (Tachikawa *et al*., 2000). Metabolites formed by the gut flora have been proposed as the actual active agents (Nakazawa *et al*., 2003).

3.6.1 Treatment of anxiety

Anxiety disorders are considered the most common psychiatric diagnoses affecting between 10% and 30% of the general population. Excess anxiety can be debilitating and lower the quality of life (Wittchen and Hoyer, 2001; Lee *et al*., 2011). Despite well-known side effects such as sedation, muscle relaxation, amnesia, and dependence, benzodiazepines are extensively used for the treatment of several forms of anxiety (Wittchen and Hoyer, 2001). Various herbal medicines, traditionally used for tranquillo-sedative effects, are now being investigated as anxiolytic drugs, including the bark of *M. officinalis* (Lee *et al*., 2011).

The central depressant effects of lignans may contribute not only to an anticonvulsant effect but also, at low doses, to an anxiolytic activity. This can be partially attributed to their interaction with the γ-aminobutyric acid receptor A ($GABA_A$), a known

target for benzodiazepines and other anxiolytics. The activity of hippocampal glutamic acid decarboxylase (GAD), an enzyme involved in GABA synthesis, is significantly increased in honokiol-treated mice, suggesting that honokiol may alter the brain's synthesis of GABA. $GABA_A$ receptors have subunit heterogeneity that influences their function; magnolol and honokiol were found to modulate all receptors, regardless of their sub-units, but receptors with the δ-subunit were 2 to 3 times more sensitive (Alexeev *et al*., 2012; Chen *et al*., 2012; Woodbury *et al*., 2013).

3.6.2 Treatment of depression

Depression is a mood-altering disease affecting energy, sleep, appetite, libido, and the ability to function. The symptoms of depression include an intense feeling of sadness, hopelessness, despair, and the inability to experience pleasure in usual activities (Lee *et al*., 2011). Most common anti-depressant drugs (tricyclic/polycyclic antidepressants, selective serotonin reuptake inhibitor, monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, lithium) potentiate the action of monoamines (norepinephrine, dopamine, and serotonin) in the brain, an observation that resulted in the so-called "theory of monoamines" that postulates an association between depression and monoamine depletion. Efforts in the field are still sorely needed, as recent studies indicate that about 30% of depressive patients fail to respond satisfactorily to antidepressant treatment.

In vitro radioligand binding and cellular functional assays revealed that *Magnolia* bark supercritical carbon dioxide extracts interact with the adenosine A1 receptor, dopamine transporter, and dopamine D5 receptor (antagonist activity), serotonin receptors (5-HT1B and 5-HT6, antagonist activity) and the GABA benzodiazepine receptor at a concentration of 100 μg/ml or lower (Koetter *et al*., 2009). Honokiol and magnolol exhibit neurotrophic function by enhancing hippocampal ACH release, and magnolol modulates the central serotonergic activity (Nakazawa *et al*., 2003). Major receptors of biogenic amine neurotransmitters (dopamine, noradrenaline, serotonin, and histamine) are coupled with G-proteins, activating or inhibiting adenylate cyclase. Honokiol and magnolol could normalize the biochemical abnormalities in brain serotonin and its metabolites, serum corticosterone levels, and platelet adenylate cyclase activity via up-regulating the cyclic adenosine monophosphate pathway (Waymire, 1997; Lee *et al*., 2011).

3.6.3 Effects on Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia. There are no available treatments that stop or reverse the progression of the disease, which worsens as it progresses, and eventually leads to death (WHO, 2016). Studies of patients with AD have revealed ACH-depleted cerebral regions; centrally acting cholinergic drugs have been reported to increase the ACH levels in these brain regions affected by AD and to improve cognition and memory. Maintaining ACH levels in brain, by antagonizing the activity of acetylcholinesterase (ACHE), the enzyme that degrades ACH, is one of the few therapeutic options in AD patients, which could be important to delay the aggravation of the disease (Lee *et al*., 2011). However, ACHE inhibitors have limitations, including short half-lives, peripheral cholinergic side effects, and notable hepatotoxicity (Lee *et al*., 2011). Beside ACH depletion, abnormal phosphorylation of the protein tau, oxidative stress, and altered protein processing resulting in abnormal β-amyloid peptide (Aβ) accumulation are associated with the progressive development of AD, leading to neuronal cell death (Zaki *et al*., 2014).

Ethanol extracts of *M. officinalis* and 4-*O*-methylhonokiol were found to dose-dependently attenuate the scopolamine-induced increase in ACHE activity in the cortex and hippocampus of mice and inhibited ACHE activity in vitro (Lee *et al*., 2010). Beside ACH depletion, oxidative damages are also associated in the progressive development of AD. Actually, oxidative stress-induced neuronal cell death by accumulation of Aβ is a critical pathological mechanism in AD. The antioxidants honokiol, magnolol, and 4-*O*-methylhonokiol significantly decrease Aβ-induced cell death; these neuroprotective effects are possibly mediated through reduced ROS production as well as suppression of intracellular calcium elevation and inhibition of caspase-3 activity (Hoi *et al*., 2010; Woodbury *et al*., 2013). Lignans are also able to decrease the activity of β-secretase, preventing the release of Aβ from amyloid precursor protein (APP) (Lee *et al*., 2010).

3.7 Therapeutic activity in cardiovascular diseases

Cardiovascular diseases (CVDs), a group of disorders of the heart and blood vessels, are the prime cause of death worldwide (WHO, 2016). The cardiovascular protection potentiality of *M. officinalis* due to its antioxidant components was described around the 1990s (Lo *et al*., 1994). A role for oxidative stress has been postulated in many CVDs as ROS contribute to cardiovascular lesions by promoting inflammation, altering vasomotion, inducing cell death, causing platelet aggregation, and stimulating vascular smooth muscle cell (VSMC) proliferation; induced vascular stenosis, cell death, and inflammation are major progressive factors in cardiovascular dysfunctions (Lee *et al*., 2011). The potential of *M. officinalis* to afford cardiovascular protection was attributed to its antioxidant components, including lignans and, notably, honokiol and magnolol. Those effects are dose-related, and are the consequence of different molecular mechanisms' regulation (Ho and Hong, 2012).

3.7.1 Effects in atherosclerosis

Atherosclerosis is a condition, in which plaques made of cholesterol, fatty substances, cellular waste products, calcium, and fibrin build up inside the arteries (AHA, 2016). Oxidized low-density lipoproteins (LDL) induce arterial wall cells to produce chemotactic factors, adhesion molecules, cytokines, and growth factors that play a role in the development of these plaques (Young and Woodside, 2001; Lee *et al*., 2011). Honokiol was shown to alleviate the detrimental effects of oxidized LDL, reducing the expression of endothelial iNOS and adhesion molecules, and attenuating the induced cytotoxicity, apoptosis, ROS generation, intracellular calcium accumulation, the subsequent mitochondrial membrane potential collapse, cytochrome c release, and activation of caspase-3 in human umbilical vein endothelial cells (HUVECs) (Ou *et al*., 2006). Moreover, magnolol effects include protection of the cardiovascular system by interfering with ROS generation (Lee *et al*., 2011). *Magnolia* compounds with an anti-atherosclerosis effect were listed in Table 10 (Lee *et al*., 2011).

3.7.2 Anti-platelet activity

Magnolia compounds have been known for more than 20 years to interfere in some major pathways of platelet activation/inhibition: (1) TBXs, some of the most powerful agonists for platelet activation and major contributors to thrombus formation; TXB2, whether induced by collagen, arachidonic acid, or thrombin, is inhibited by magnolol and honokiol; also five aporphine alkaloids isolated from leaves of *M. obovata*, *N*-acetylanonaine, *N*-acetylxylopine, *N*-formylanonaine, liriodenine, and lanuginosine, show potent antiplatelet activities, probably by interfering with TXA2 production and/or binding (Teng *et al*., 1988; Pyo *et al*., 2003; Ho and Hong, 2012); (2) the activation of PPAR isoforms (α, β/δ, and γ), a pathway known to inhibit platelet aggregation; magnolol (20–60 μmol/L) dose-dependently enhances the activity and intracellular level of PPAR-β/γ in platelets (Shih and Chou, 2012); and (3) the cytosolic Ca^{2+} influx and/or mobilization from intracellular stores that plays a crucial role in the platelet responses to various agonists (Lee *et al*., 2011); the rise of intracellular calcium caused by arachidonic acid or collagen is suppressed by both magnolol and honokiol (Teng *et al*., 1988; Pyo *et al*., 2003; Lee *et al*., 2011).

3.8 Antimicrobial activities

Antibiotic treatments have become a cornerstone for human health; however, due to long, wide, and irrational applications of antibacterial agents in treatments in various fields other than in the clinic, resistant strains have evolved as problematic pathogens and now pose a serious challenge. In the fight against these resistant pathogens, plant extracts heavily exploited in different civilizations (Amblard *et al*., 2007; Zuo *et al*., 2015) could yield clues to new therapeutic options (Okusa *et al*., 2014; Rasamiravaka

Table 10 Anti-atherosclerosis effects of *Magnolia* lignans (Lee *et al*., 2011)

Compound	Dose (μmol/L)	Subject	Reference
Honokiol	2.5–20.0	HUVEC (human umbilical vein endothelial cell)	Ou *et al*., 2006
	25–150	HASMC (human aortic smooth muscle cell)	Lee *et al*., 2006
Magnolol	1–10	Rat cardiac fibroblasts	Chen *et al*., 2006
Obovatol	1–5	Rat VSMC (vascular smooth muscle cell)	Lim *et al*., 2010

et al., 2014; Ngezahayo *et al*., 2015; Ngezahayo *et al*., 2016).

The antimicrobial activities of honokiol and magnolol, the main constituents of *M. officinalis*, were effective against Gram-positive bacteria, such as *Streptococcus mutans* (Bang *et al*., 2000), *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus faecalis*, *Escherichia coli*, *Salmonella typhimurium*, *Bacillus anthracis*, *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Micrococcus luteus*, *Bacillus subtilis*, *Capnocytophaga gingivalis*, *Veillonella disper*, but also against fungal strains such as *Candida albicans* as a representative fungus for candidiasis, *Trichophyton mentagrophytes* for superficial dermatomycosis and *Cryptococcus neoformans* for deep dermatomycosis. The lignans showed a significant antimicrobial activity against these microorganisms with minimum inhibitory concentrations (MICs) ranging 10–240 μmol/L (Chang *et al*., 1998; Bang *et al*., 2000; Ho *et al*., 2001; Hu *et al*., 2011).

Lignans, mainly honokiol and magnolol, have marked dose-dependent antimicrobial effects (Table 11) (Kim *et al*., 2015). Previous studies have shown that phenolic compounds can affect microbial growth by altering microbial cell permeability and permitting the loss of macromolecules. Once the phenolic compounds have crossed the cell membrane, interactions with membrane enzymes and proteins will cause an opposite flow of protons, affecting cellular activity. It has also been suggested that phenols react primarily with the phospholipid components of the cell membrane, causing an increase in permeability (Hu *et al*., 2011; Zuo *et al*., 2015). For antiviral activity of aporphine alkaloids, they were shown to interfere with the viral replicative cycle. Although DNA synthesis was reduced, their exact target remains to be elucidated (Boustie *et al*., 1998).

4 Toxicity

All effective drugs may produce adverse drug reactions, and herbal medicines are no exception. Their long-standing use as traditional medicines has probably allowed the elimination of the most toxic drugs but special attention must be paid to insidious toxicities which are not easily detectable by tradipraticians or pharmacovigilance, including genotoxicity, carcinogenicity, and developmental toxicity (Ouédraogo *et al*., 2012; Zhang *et al*., 2012; Williamson *et al*., 2015). With the current worldwide increase in the use of herbal products, increasing numbers of side effects, some of them very serious, are emerging, raising concerns about the general safety of herbal products (Liu *et al*., 2014).

Magnolia toxicity has been studied in vitro and in vivo. Results from these studies are summarized in Tables 12–14 (Li N. *et al*., 2007).

5 Clinical research on *Magnolia*

Despite a well-documented use of *Magnolia* in TCM and a wealth of in vitro and in vivo pharmacological studies, there are practically no clinical studies published in English. A PubMed database search with the terms “Magnolia” [MESH] AND “Clinical Study” [Publication Type] yields only 10 papers (in Feb. 2017). Most of them deal with oral cavity applications of *Magnolia* bark extracts, as dentifrice (Hellstrom and Ramberg, 2014), tablets (Porciani *et al*., 2014). or chewing gum (Porciani and Grandini, 2012). In menopausal women, the addition of a *Magnolia* bark extract to isoflavones, lactobacilli, calcium, and vitamin D_3 induced positive effects on insomnia, irritability, anxiety, depressed mood, asthenia, and loss of libido; adverse events were comparable in treated

Table 11 Antimicrobial effect of *Magnolia officinalis* compounds

Compound	Concentration	Microorganisms	Reference
Honokiol	94–188 μmol/L	*C. albicans*, *T. mentagrophytes*, and *C. neoformans* Funga strains	Bang *et al*., 2000
	11–15 μmol/L	*Propionibacterium acnes* bacteria strain (Gram+)	Zuo *et al*., 2015
	60–240 μmol/L	*Staphylococcus aureus* bacteria strain (Gram +)	Zuo *et al*., 2015
Magnolol	94–188 μmol/L	*C. albicans*, *T. mentagrophytes*, and *C. neoformans* fungal strains	Bang *et al*., 2000
	34 μmol/L	*Propionibacterium acnes* bacteria strain (Gram+)	Park *et al*., 2004
	60–240 μmol/L	*Staphylococcus aureus* bacteria strain (Gram+)	Zuo *et al*., 2015
Aporphine alkaloids	1.1 μg/ml	*Herpes simplex* virus (HSV-1) Poliovirus	Mohamed *et al*., 2010

Table 12 *Magnolia* bark extracts (MBEs) in vitro genotoxicity

Assay	Subject	Effects	Reference
Ames test	*Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537) with and without S9 fraction	MBE did not increase the mean number of revertants with or without metabolic activation, for both *S. thyphimirium* and *E. coli* strains, in comparison to the spontaneous reversion rate in the negative control at concentrations from 18.75 to 300 μg/plate	Li N. *et al*., 2007
	Tryptophan-requiring *Escherichia coli* mutant WP2 *uvrA* with and without S9 fraction	The number of revertants could not be counted for *S. typhimurium* strains TA1535 and TA1537 at concentrations of 150 and 300 μg/plate due to excessive cytotoxicity	
Chromosomal aberration assays	CHO (Chinese hamster ovary cell)	Exposure for 3 h to MBE at concentrations of 0–30 μg/ml in the absence of a metabolic activation system (S9) and 0–7 μg/ml with S9 did not induce chromosomal aberrations, whereas higher concentrations were cytotoxic and did not allow for analysis of aberrations. Extended exposure for 18 h without metabolic activation at concentrations up to 15 μg/ml also resulted in a negative response	Zhang *et al*., 2008
	V79 cell (derived from Chinese hamster lung tissue)	Treatment for 6 and 24 h, with concentrations up to 52 and 59 μg/ml, in the absence and presence of S9, did not increase the incidence of chromosomal aberrations compared to negative controls	
Measurement of H2AX histone phosphorylation (DNA double strand break detection)	FHs 74 Int (human intestinal epithelial cells)	*Magnolia officinalis* aqueous extract (1 mg/ml) caused DNA damages detected by immunofluorescence but not by whole-cell ELISA assay	Nachtergael *et al*., 2015
Measurement of DNA degradation (by staining and quantifying DNA with PI)	HK-2 (human proximal tubule epithelial cell)	Treatments of HK-2 cells with 10 μmol/L magnolol or honokiol alone increased DNA degradation	Bunel *et al*., 2016

Table 13 *Magnolia* bark extracts (MBEs) in vivo toxicity assessment

Assay	Subject	Effects	Reference
Genotoxicity assessment (micronucleus test)	Swiss Albino (CD-1) mice	No statistically significant increase in the number of micronucleated polychromatic erythrocytes in any of the MBE-treated groups compared to the negative control group at either time point	Li N. *et al*., 2007
Acute toxicity	Mice	Oral LD_{50} of MBE >50 g/kg	Liu *et al*., 2007
	Swiss Albino (CD-1) mice	No mortalities and no clinical signs of toxicity were observed in animals given 2500 mg MBE/kg body weight (BW)	Li N. *et al*., 2007
	Dogs (1 g/kg i.v.)	No mortality	Chang and But, 1986
Short-term toxicity	Sprague-Dawley rats (animals received orally MBE at levels of 0, 60, 120, or 240 mg/kg BW per day during 21 d)	Increase of absolute and relative thyroid weight and increase of relative kidney weight in female of high-dose group compared to their respective controls	Liu *et al*., 2007
		Slight fatty degeneration of the liver in 5/10 of the 240 mg/kg BW per day group (4 females and 1 male)	
		Food consumption significantly reduced in Week 3 in females from the high-dose group	
		Lack of toxicity following dietary administration of MBE at doses up to 480 mg/kg BW per day	
Subchronic toxicity	Sprague-Dawley rats (animals received orally MBE at levels of 0, 60, 120, or 240 mg/kg BW per day during 90 d)	No mortality, ophthalmic abnormalities were found	Liu *et al*., 2007
		In males, significantly higher weight gains in the 120 and 240 mg/kg BW groups were observed	
		Significant increase of blood total bilirubin and sodium values in all groups compared to the control group	
		Slight fatty degeneration and sporadic focal necrosis in the liver of 11/40 animals (4 females and 7 males) in the 240 mg/kg BW group	
		Lack of toxicity following dietary administration of MBE at doses up to 240 mg/kg BW per day	

Table 14 *Magnolia* bark toxicity in human subjects

Magnolia preparation	Subject	Observation	Reference
Dietary supplement containing extracts of *M. officinalis* and *Phellodendron amurense* (for weight management)	22 subjects	Only 1/22 subjects reported side effects such as heartburn, shaking hands, perilabial numbness, sexual dysfunction and thyroid dysfunction. No explanation for the evaluation of these effects as being possibly related to treatment was provided	Garrison and Chambliss, 2006b
Preparation containing 60 mg *Magnolia* bark extract and 50 mg magnesium (24-week period)	89 menopausal women	Preparation was well tolerated by 94% of subjects	Mucci *et al*., 2006
Chinese multi-herbal preparations		Some mixtures containing *Magnolia* are reported to be hepatotoxic	Teschke *et al*., 2014; 2015; 2016

(334 women) and control (300 women) groups (Agosta *et al*., 2011). In a similar group of women, *Magnolia* extract and magnesium alleviated psycho-affective and sleep disturbances (Mucci *et al*., 2006). On 26 healthy, overweight (BMI 25 to 34.9 kg/m^2), premenopausal female adults, a proprietary blend of extracts of *M. officinalis* and *Phellodendron amurense* reduced temporary, transitory anxiety but was not effective in reducing long-standing feelings of anxiety or depression; no adverse effects were observed (Kalman *et al*., 2008). This mixture was investigated in a similar woman group for weight management (Garrison and Chambliss, 2006). In a non-comparative study, as an add-on therapy in 148 patients with mild to moderate asthma using inhaled corticosteroids, an extract of *Magnoliae flos* had a beneficial effect on asthma control (Park *et al*., 2012).

The well-demonstrated pharmacological properties of *Magnolia* constituents probably warrant further clinical studies; the cytotoxicities and cell cycle activities of lignans represent, however, an attention point. It would be interesting to evaluate the Chinese literature for study designs and results, notably in terms of safety.

6 Conclusions

Traditional Chinese herbal drugs have been used for thousands of years of Chinese history. Currently they still serve as one of the most important available health resources, prescribed in tandem with Western medical treatment. In general, the therapeutic benefits of TCM from established combination prescriptions have survived the test of time (Yang and Chen, 1997).

Magnolia bark has been used historically in traditional Asian remedies for thousands of years without apparent indications of safety concern. Various extracts derived from *Magnolia* bark are also widely available in dietary supplement products at recommended doses of 200 to 800 mg/d per person. *Magnolia* ingredients have indisputably a wide variety of pharmaceutical properties. It is now necessary to identify the constituents, delineate possible mechanisms, and justify routes and formulations (Lee *et al*., 2011).

Considering previous studies about *Magnolia* bark extract toxicity, its security seems to be assured. However, the high potentiation of aristolochic acid (AA) genotoxicity by *M. officinalis* was recently demonstrated. This co-genotoxicity of *Magnolia* and *Aristolochia* may lead to an explanatory factor for the "Chinese herb nephropathy" cases, rapid onset and tragic intoxications observed specifically in Belgium in the 1990s (Vanherweghem *et al*., 1993). Since the recognition of the high nephrotoxicity and carcinogenicity of AAs, *Aristolochia* species have been classified as human carcinogens (International Agency for Research on Cancer, 2002); banned from many markets, they should no longer be used. Nevertheless, this potentiation warrants further studies as it could bring regulatory authorities to take into account indirect genotoxicities in their safety assessment schemes (Nachtergael *et al*., 2015; Bunel *et al*., 2016).

It is now necessary to establish suitable modern standards, techniques, and methods to evaluate the safety of such herbal products alone and in association. Herbal preparations will thereby be used more safely and effectively.

Compliance with ethics guidelines

Mélanie POIVRE and Pierre DUEZ declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：厚朴及其成分的生物活性和毒性

概　要：中草药已在中国药典中使用了数千年。木兰属的厚朴，主要用于治疗焦虑、哮喘、抑郁症、胃肠道疾病、头痛。其树皮提取物是目前市售的食品补充剂和化妆品的主要成分。厚朴及其主要成分具有多种药理活性，具有抗氧化、抗炎、抗生素和抗痉挛作用。然而，相关机制尚未明确，临床试验也鲜有报道。体外和体内毒性研究已经发现了一些有趣的特征。本文旨在总结关于厚朴的成分、利用、药理学和安全性的文献。

关键词：木兰树皮；厚朴；中草药；中药