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REVIEW

Expectations of biologically active compounds of the genus *Magnolia* in biomedicine

Jiří Patočka [1], **Jiří Jakl** [2], **Anna Strunecká** [3]

[1] Department of Radiology and Toxicology, Faculty of Health and Social Studies, University of South Bohemia, České Budějovice, Czech Republic
[2] Department of Dendrology and Forest Tree Breeding, Faculty of Forestry and Environment of the Czech University of Agriculture Prague, Czech Republic
[3] Department of Physiology and Developmental Biology, Faculty of Science, Charles University, Prague, Czech Republic

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Summary
Magnolia bark is a highly aromatic herbal material obtained from *Magnolia officinalis* (and other species) of the family Magnoliaceae. In traditional oriental herbal medicine, particularly Chinese medicine, this drug is used for many purposes, especially as a mild tranquillizer. The principal active compounds are the biphenol compounds, magnolol and honokiol, together with other biologically active compounds, which exert numerous and diverse pharmacological actions. Recent research has produced further evidence for the mechanism of their anti-inflammatory, anti-oxidant, antimicrobial, and antitumour activities, and these will be outlined in this review.

Keywords: herbal tranquillizer – honokiol – *Magnolia* – magnolol – obovatol – pharmacology

INTRODUCTION

The genus *Magnolia* is representative of the ancient family *Magnoliaceae*, which has been in existence since the Tertiary period and consists of 120–130 species. Magnolia bark is a traditional Chinese medicine, known under the name *houpu* (from *Magnolia officinalis*), that has been used for thousands of years to treat "stagnation of qi" (low energy), asthma, digestive problems, and emotional distress. Magnolia bark is used as a general anti-stress and anti-anxiety agent. *Magnolia* has also been traditionally used to treat breast cancer.

Houpu is an official herb in the Pharmacopoeia of the People's Republic of China (Pharmacopoeia 1988); the herb is sometimes called chuan *houpu*, because it originally came from the Sichuan area of China. Because traditional Chinese medicine is becoming increasingly popular in many medical contexts in other parts of the world, particularly among patients with cancer, it is important that recent research demonstrates the relevant pharmacological effects of various magnolias and the main pharmacologically active compounds (Ikeda et al. 2003, Yang et al. 2003). Based on the

Jiří Patočka, Department of Radiology and Toxicology, Faculty of Health and Social Studies, University of South Bohemia České Budějovice, 370 01 České Budějovice, Czech Republic
prof.patocka@gmail.com
+ 0420 494 661 014

experimental evidence available so far, it seems likely that *Magnolia* might be helpful in modern medicine (Patočka et al. 2002).

BIOLOGY OF MAGNOLIA GENUS

Various magnolias are distinguished by their many interesting biological features. Current research raises basic questions as to the definition of the genus itself. The genus *Magnolia* consists of about 120-130 species and in the Tertiary period *Magnolias* were common in Europe (Azuma et al. 2001, Kim et al. 2001, Hunt et al. 1998). The majority of *Magnolia* species grow in the temperate and tropical zones of southeastern Asia, while other species grow in the New World. *Magnolia officinalis* is not the only recognised source of magnolia bark; other closely related Asian species of the section *Rytidospermum* Spach are also used in traditional medicine, such as the Japanese *Magnolia obovata* 'Wakoboku' (Ito et al. 1982) or the Chinese *Magnolia rostrata*. However, according to the IUCN Red List these are vulnerable species due to over-harvesting of the bark and habitat destruction (IUCN 2004). *Magnolia* bark was a common ingredient in many formulas, for example 'Saiboku-to' (Maruyana et al. 1998), 'Xiao Zhengqi Tang', 'Maziren Wan', 'Ping Wei San' and 'Shenmi Tang' (Hong-Yen 1980). Some species of *Magnolia* contain magnolol and honokiol, and others lignanoids (Hegnauer 1990). The best-known magnolia, *Magnolia grandiflora*, is a popular plant utilised in Mexican traditional medicine (Bastidas Ramírez et. al. 1998). Another form of *Magnolia* used in medicine is derived from the flower buds (Hu 2000). Currently, China produces about 200 tons of *Magnolia* bark per year (Jinping 2000).

CHEMISTRY OF MAGNOLIA GENUS

The principal substantial compounds present in plants of the *Magnoliaceae* family are different phenolic compounds and terpenoids. Many phenolic compounds have been found in the leaves and bark; for example gallic acid, sennosides A and B, hesperidin, naringin, syringin, and especially two neolignan compounds, magnolol (I) and honokiol (II) (Fig.1). The magnolol content of magnolia bark is generally in the range of 2-10 %, while honokiol tends to occur naturally at 1-5 percent in the dried bark. Magnolol and honokiol are without question pharmacologically the most meaningful constituents of magnolia bark (Watanabe et al. 1983, Liu et al. 2006). From the leaves and bark of *M. obovata,* the novel biphenyl ether lignans, obovatol (III) (Fig. 1) and obovatal were isolated (Ito et al. 1982), together with some sesquiterpene-neolignans, eudesobovatols A and B, eudesmagnolol, eudeshonokiols A and B, clovanemagnolol, and caryolanemagnolol (Fukuyama et al. 1992).

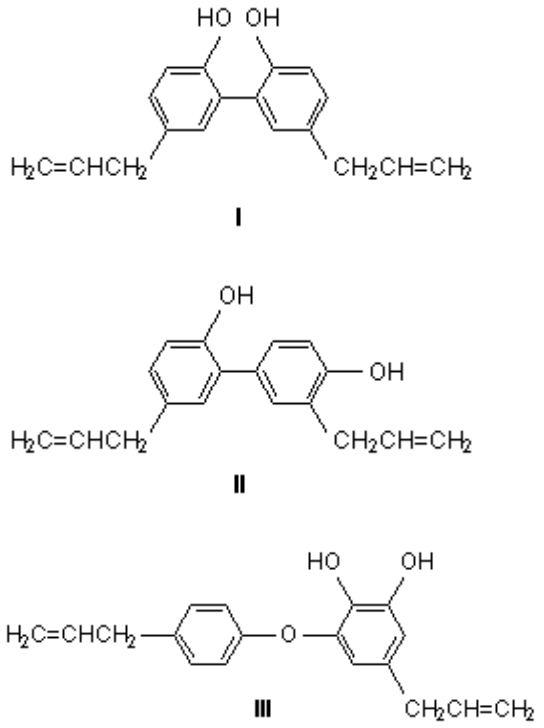

Fig. 1. **Chemical structures of three principal magnolia lignans: magnolol (I), honokiol (II), and obovatol (III)**

Several monoterpenes and sesquiterpenoids have been obtained from the leaves of *Magnolia grandiflora* L, and, on the basis of spectral evidence, their structures determined as α- and β-pinenes, β-eudesmol and bornyl acetate (Tachikawa 2000), 4α, 6α, 10α-trihydroxy-13-acetoxyguaia-11-ene and 12,13-diacetoxyguaia-4α, 6α, 10α, 11-tetraol (Yang et al. 1994). In addition, the known sesquiterpenoid magnograndiolide was also obtained (Luo et al. 2001). Recently, a new sesquiterpenoid was obtained from the leaves of *Magnolia delavayi*. Its structure was determined as 8β-acetoxy-10α-ethyloxy-guaia-4α, 11-diol (Cao et al. 2004). A new tricyclo [4.2.0.0(2,8)] octane-type neolignan, 6-allyl-7- (3,4-dimethoxyphenyl)-2,3-dimethoxy-8-methyl-tricyclo [4.2.0.0(2,8)] oct-3-en-5-one, together with 15 known lignan and neolignan derivatives have been isolated from the flower buds of *Magnolia denudata* DESR (Li et al. 2005).

PHARMACOLOGY OF MAGNOLIA GENUS

Pharmacology of magnolol and honokiol

Magnolol and honokiol, two major phenolic constituents of *Magnolia* species which are abundantly found in the medicinal plants *M. officinalis* and *M. obovata*, show multiple pharmacological effects (Chen et al. 2006). Research has elucidated the underlying mechanism of some of their anti-inflammatory and anti-oxidative effects. It has been found, for example, that magnolol is 1000-fold more potent than α-tocopherol in inhibiting lipid peroxidation in rat mitochondria (Chang et al. 2003). All active *Magnolia* constituents (magnolol, honokiol, obovatol) showed weak inhibition for inducible NO synthase (iNOS) activity, but potent inhibition of iNOS induction and activation of nuclear factor-kappa B (Matsuda et al. 2001). They also inhibit rat liver acyl-CoA: cholesterol acyltransferase (ACAT) with IC_{50} values of 42, 71, and 86 μM, respectively (Kwon et al. 1997). Honokiol may protect the myocardium against ischemic injury and suppress ventricular arrhythmia during ischemia (Tsai et al. 1999). The mechanism of anxiolytic activity of various *Magnolia* extracts has been studied. The observed antimicrobial activity demonstrates the potential of *Magnolias* to be an adjunct in the treatment of periodontitis (Ho et al. 2001).

Anti-inflammatory activity

The reactive oxygen species produced by neutrophils contribute to the pathogenesis of focal cerebral ischemia/reperfusion injury and signal the inflammatory response. Recently it was shown that honokiol has a protective effect against focal cerebral ischemia/reperfusion injury in rats that paralleled a reduction in reactive oxygen species production by neutrophils (Liou et al. 2003). To elucidate the underlying mechanism(s) of the antioxidative effect of honokiol, peripheral neutrophils isolated from rats were activated with phorbol-12-myristate-13-acetate (PMA) or N-formyl-methionyl-leucyl-phenylalanine (fMLP) in the presence or absence of honokiol. Liou et al. (2003) suggested that honokiol inhibited PMA- or fMLP-induced reactive oxygen species production by neutrophils by three distinct mechanisms: (i) honokiol diminished the activity of assembled-NADPH oxidase, a major reactive oxygen species producing enzyme in neutrophils by 40% without interfering with its protein kinase C (PKC)-dependent assembly; (ii) honokiol inhibited two other important enzymes for reactive oxygen species generation in neutrophils, i.e., myeloperoxidase and cyclooxygenase, by 20% and 70%, respectively; (iii) honokiol enhanced by 30%, the activity of glutathione (GSH) peroxidase, an enzyme that triggers the metabolism of hydrogen peroxide (H_2O_2). These data suggested that honokiol, acting as a potent reactive oxygen species inhibitor/scavenger, could achieve its focal cerebral ischemia/reperfusion injury protective effect by modulating enzyme systems related to reactive oxygen species production or metabolism, including NADPH oxidase, myeloperoxidase, cyclooxygenase, and GSH peroxidase in neutrophils.

Magnolol is hypothesized to suppress TNF-alpha production after the endotoxin tolerance induced by sublethal hemorrhage (SLH) and to alter or attenuate subsequent endotoxin tolerance (Liou et al. 2003). Recent results show that the anti-inflammatory effects of magnolol and honokiol are mediated through inhibition of the downstream pathway of MEKK-1 in NF-kappaB activation signalling (Lee et al. 2005). Plasma and tissue TNF-alpha increased after sublethal hemorrhage (SLH); this increase was significantly suppressed by magnolol. Lipid peroxidation and SOD activity increased after SLH; magnolol suppressed the lipid peroxidation but not the SOD activity. In conclusion, magnolol induces an anti-inflammatory response and provides early protection against endotoxin challenge following SLH; however, magnolol attenuates the protraction of endotoxin tolerance and inhibits late protection against endotoxin challenge following SLH (Shih et al. 2004). The anti-inflammatory and neuroprotective effects of magnolol have been demonstrated by other authors (Wang et al. 1995; Lee et al. 2000, Park et al. 2004, Matsui et al. 2005, Lin et al. 2006).

Magnolol inhibited mouse hind-paw oedema induced by carrageenan, and polymyxin B, and reversed the passive Arthus reaction. The recovered myeloperoxidase activity in the oedematous paw was significantly decreased in mice pretreated with magnolol. Suppression of oedema was demonstrated not only in normal mice but also in adrenalectomized animals. Magnolol was less potent in reducing PGD2 formation in rat mast cells than indomethacin. Unlike dexamethasone, magnolol did not increase the liver glycogen level. The results suggest that the anti-inflammatory effect of magnolol was neither mediated by glucocorticoid activity, nor through releasing steroid hormones from the adrenal gland. It is proposed that the action of magnolol is dependent on reducing the level of eicosanoid mediators (Wang et al. 1992).

Antioxidant activity

Magnolol induces apoptosis in rat vascular smooth muscle cells (VSMCs) via the mitochondrial death pathway. This effect is mediated through down-regulation of Bcl-2 protein levels, both *in vivo* and *in vitro*. Magnolol thus shows potential as a novel therapeutic agent for the treatment of atherosclerosis and re-stenosis (Chen et al. 2003).

Magnolol suppressed thromboxane B_2 (TXB_2) and leukotriene B_4 (LTB_4) formation in A23187-stimulated rat neutrophils. Maximum inhibition was obtained with about 10 μM magnolol. Magnolol was more effective in the inhibition of cyclooxygenase (COX) activity than in the inhibition of 5-lipoxygenase (5-LO) activity, as assessed by means of enzyme activity determination *in vitro* and COX and 5-LO metabolic capacity analyses *in vivo*. Magnolol alone stimulated cytosolic phospholipase A_2 ($cPLA_2$) phosphorylation and the translocation of 5-LO and $cPLA_2$ to the membrane, and evoked arachidonic acid (AA) release. These results indicate that magnolol inhibits the formation of prostaglandins and leukotrienes in A23187-stimulated rat neutrophils, probably through a direct blockade of COX and 5-LO activities (Hsu et al. 2004). The hepatoprotective effects of honokiol and magnolol on oxidative stress induced by tert-butylhydroperoxide were probably the result of their antioxidant activity. Honokiol and magnolol also had a protective effect against D-galactosamine-induced hepatotoxicity, which was used as an alternate model to oxidative stress, acting by inhibiting intracellular GSH depletion (Park et al. 2003). Recently a novel synthetically prepared magnolol derivative, 3,3'-bis-allyl-magnolol, was developed as a potential antioxidant for certain diseases (Li et al. 2003).

Anxiolytic activity

The bark of the root and stem of various *Magnolia* species has been used in Traditional Chinese Medicine to treat a variety of disorders including anxiety and nervous disturbances. Honokiol and magnolol have been identified as modulators of the GABA(A) receptors *in vitro* (Squires et al. 1999, Ai et al. 2001). The possible selectivity of honokiol and magnolol on GABA(A) receptor subtypes was demonstrated in a study using ^{3}H-muscimol and ^{3}H-flunitrazepam binding assays on various rat brain membrane preparations and human recombinant GABA(A) receptor subunit combinations. These results indicate that honokiol and magnolol have some selectivity on different GABA(A) receptor subtypes, which could be responsible for the reported *in vivo* effects of these two compounds.

The anxiolytic effect of honokiol, evaluated by means of an elevated plus-maze test, was at least 5000 times more potent than the compound preparation 'Saiboku-to' when mice were treated orally for seven days, and was comparable with the effect of benzodiazepines (Maruyama et al. 1998). Kuribara et al. (1999) compared the anxiolytic potentials of honokiol and water extracts of three *Magnolia* samples using an improved elevated plus-maze in mice. Their results suggest that honokiol is the major constituent responsible for the observed anxiolytic effect of the water extract of *Magnolia,* and that the other components, including magnolol, scarcely influence the effect of honokiol.

Antiarrhythmic activity

Tsai et al. (1996) demonstrated that honokiol may protect the myocardium against ischemic injury and suppress ventricular arrhythmia during ischemia and reperfusion. The experimental ventricular arrhythmia induced by coronary ligation of rats for 30 min were significantly reduced after intravenous pre-treatment (15 min before coronary ligation) with 10^{-7} g/kg magnolol or 10^{-7} g/kg honokiol. However, the antiarrhythmic effect of magnolol or honokiol could be abolished with the pre-treatment of 1 mg/kg nitric oxide inhibitor (L-NAME), but not with pre-treatment of 100 mg/kg aspirin. The abolishment of the beneficial effects of magnolol and honokiol on the myocardium by L-NAME, rather than aspirin, suggests the involvement of an increased nitric oxide synthesis in the protection offered by magnolol and honokiol against arrhythmia during myocardial ischemia (Tsai et al. 1999).

Antimicrobial activity

Three phenolic constituents of *Magnolia grandiflora* L. were shown to possess significant antimicrobial activity using an agar well diffusion assay. Magnolol, honokiol, and 3.5'-diallyl-2'-hydroxy-4-methoxybiphenyl exhibited significant activity against Gram-positive and acid-fast bacteria and fungi (Clark et al. 1981). Magnolol and honokiol have an antimicrobial activity against numerous microorganisms such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, *Capnocytophaga gingivalis*, *Veillonella disper*, *Micrococcus luteus, and Bacillus subtilis* (Chang et al. 1998, Ho et al. 2001).

Both biphenolic compounds, although less potent than chlorhexidine, show a significant antimicrobial activity against these microorganisms, and a relatively low cytotoxic effect on human gingival cells. Thus, it is suggested that magnolol and honokiol might have a potential therapeutic use as a safe oral antiseptic for the prevention and the treatment of periodontal disease (Chang et al. 1998, Ho et al. 2001). Magnolol from *Magnolia officinalis* (cortex) potently inhibited the growth of *Helicobacter pylori* (Bae et al. 1998).

Antitumor activity

The neolignans magnolol and honokiol have been reported to inhibit the growth of several tumour cell lines, both *in vitro* and *in vivo* (Kong et al. 2005). Magnolol has been reported to have anticancer activity (Lin et al. 2001). Magnolol at very low concentrations inhibited DNA synthesis and

decreased cell number in cultured human cancer cells (COLO-205 and Hep-G2) in a dose-dependent manner, but not in human untransformed cells such as keratinocytes, fibroblasts, and human umbilical vein endothelial cells (HUVEC). Magnolol was not cytotoxic at these concentrations and this indicates that it may have an inhibitory effect on cell proliferation in the subculture cancer cell lines (Lin et al. 2002). Magnolol possesses the ability to inhibit tumour growth due to the induction of apoptosis with the activation of caspases (Ikeda and Nagase 2002) and a strong antimetastatic effect due to its ability to inhibit tumour cell invasion (Ikeda et al. 2003). Magnolol induced the reduction of mitochondrial transmembrane potential and the release of cytochrome C into the cytoplasm. Magnolol-induced apoptotic signalling appears to be carried out through mitochondrial alternations to caspase-9, and then downstream effector caspases are activated sequentially. Magnolol could be thus a potentially effective drug for the adjunctive treatment of leukaemia, with low toxicity to normal blood cells (Zhong et al. 2003). These findings warrant further investigation.

Recently Fong et al., (2005) discovered that magnolol and honokiol enhance HL-60 cell differentiation initiated by low doses of 1.25-dihydroxyvitamin D3 (VD3) and all-trans-retinoic acid (ATRA). Cells expressing membrane differentiation markers CD11b and CD14 were increased from 4% in the non-treated control to 8-16% after being treated with 10-30 μM magnolol or honokiol. It is evident that both these neolignans are potential differentiation enhancing agents, which may allow the use of low doses of VD3 and ATRA in the treatment of acute promyelocytic leukaemia (Fong et al. 2005). Honokiol demonstrated weak activity against HIV-1 in human lymphocytes (Amblard et al. 2006).

Magnolol is a strong 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD) inhibitor and, like glycyrrhetinic acid, another 11beta-HSD inhibitor isolated from licorice, induces apoptosis of murine thymocytes via the accumulation of corticosterone. Magnolol has inhibited the enzyme activity in the kidney ($P < 0.0001$) and thymus ($P < 0.002$), while the activity in the liver was not affected. Blood concentrations of corticosterone in the magnolol-treated mice were unexpectedly lower than those in the control animals ($P < 0.002$). This means that the inhibition of 11beta-HSD by magnolol did not increase the systemic level of corticosterone which is relevant to thymocyte apoptosis (Horigome et al. 2001).

Pharmacology of obovatol

The biphenyl ether lignan obovatol from *M. obovata* (Ito et al. 1982) is slightly different from magnolol and honokiol not only chemically but also pharmacologically. Obovatol inhibited the chitin synthase 2 activity of *Saccharomyces cerevisiae* with an IC_{50} of 38 μM. Its derivative, tetrahydroobovatol, inhibited chitin synthase 2 activities under the same conditions with an IC_{50} of 59 μM. These compounds exhibited no inhibitory activity for chitin synthase 3, and showed less inhibitory activity for chitin synthase 1 than for chitin synthase 2 ($IC_{50} > 1$ mM). These results indicated that obovatol and tetrahydroobovatol are specific inhibitors of chitin synthase 2. Furthermore, obovatol and tetrahydroobovatol showed antifungal activities against various pathogenic fungi, with a particularly strong inhibitory activity against *Cryptococcus neoformans* (MIC 7.8 mg/L). The results indicate that obovatol and tetrahydroobovatol can potentially serve as antifungal agents (Hwang et al. 2002).

TOXICOLOGY OF MAGNOLIA GENUS

Magnolia extracts have a two thousand-year-old safety record for use as a Chinese medicine, (Bateman et al. 1998), and no significant toxicity or adverse effects have been reported so far, although no special chronic toxicological studies with magnolol, honokiol, and obovatol have been performed. Very small doses of magnolol and honokiol appear to be safe and effective for anxiety and depression. However, large doses may cause a sedative effect and interact with alcohol, increasing its effects, so driving or operating dangerous equipment should be avoided when taking larger doses of *Magnolia* extract. Further work on the toxicology and potential drug interactions of the constituents of *Magnolia* need to be performed, in order that the useful properties of *Magnolia* species can be realised.

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