Review articles

Magnolol: A multifunctional compound isolated from the Chinese medicinal plant *Magnolia officinalis*

Yung-Hsiang Chen\textsuperscript{a,b}, Po-Hsun Huang\textsuperscript{c,d}, Feng-Yen Lin\textsuperscript{e}, Wen-Chi Chen\textsuperscript{b}, Yuh-Lien Chen\textsuperscript{f}, Wei-Hsian Yin\textsuperscript{d,g}, Kee-Ming Man\textsuperscript{a,h,i,}, Po-Len Liu\textsuperscript{j,}**

\textsuperscript{a} Department of Anesthesiology, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan
\textsuperscript{b} Graduate Institute of Integrated Medicine, Departments of Urology and Medical Research, China Medical University, Taichung, Taiwan
\textsuperscript{c} Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan
\textsuperscript{d} Department of Medicine, Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan
\textsuperscript{e} Department of Internal Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
\textsuperscript{f} Institute of Anatomy and Cell Biology, National Taiwan University, Taipei, Taiwan
\textsuperscript{g} Heart Center, Cheng-Hsin General Hospital, Taipei, Taiwan
\textsuperscript{h} Department of Life Sciences, National Chung Hsing University, Taichung, Taiwan
\textsuperscript{i} Graduate Institute of Geriatric Medicine, Anhui Medical University, Hefei, China
\textsuperscript{j} Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, 100, Shih-Chuan 1st Rd., Kaohsiung 80708, Taiwan

Received 29 June 2011; received in revised form 6 September 2011; accepted 12 September 2011

Abstract

Introduction: Chinese herbs are widely used as important remedies in Oriental integrative medicine. Magnolol is a small polyphenolic molecule with low toxicity that is isolated from the herb genus *Magnolia*. In preclinical experiments, magnolol was found to have anti-oxidative, anti-inflammatory, anti-tumorigenic, anti-diabetic, anti-microbial, anti-neurodegenerative and anti-depressant properties. Magnolol can also effectively regulate pain control, hormonal signalling, gastrointestinal and uterus modulation as well as provide cardiovascular and liver protective effects.

Materials and methods: We briefly conducted PubMed and MEDLINE database reviews for articles that related to magnolol.

Results: The major biological mechanisms of action and potential health benefits of magnolol are described.

Conclusions: These health benefits of magnolol have provided an increased interest in bringing this herbal compound to the clinic as a novel therapeutic agent. Knowledge of the multiple activities of magnolol can assist with the development of magnolol derivatives and the design of clinical trials that will maximize the potential benefit of magnolol in the patient setting.

© 2011 Published by Elsevier GmbH.

Keywords: Antioxidant; Chinese medicine; Inflammation; Integrative medicine; Magnolol

Introduction

Magnolol (Fig. 1) is a polyphenolic compound derived from *Magnolia officinalis*, a plant commonly associated with Chinese (Kampo) herbs (Fig. 2)\textsuperscript{[1]}. In the 1990s, it was discovered that magnolol could inhibit hydroxyl radicals and lipid peroxidation\textsuperscript{[2–5]}. Now it is known that magnolol and methanolic extracts of *Magnolia* exhibit anti-oxidative, anti-inflammatory, anti-tumorigenic, anti-diabetic, anti-microbial, anti-neurodegenerative and anti-depressant properties. These compounds also regulate hormones, possess positive gastrointestinal and uterus modulatory effects, as well as exhibit cardiovascular and liver protective effects. They can also be effective in controlling pain (Fig. 3)\textsuperscript{[6]}. The knowledge of magnolol’s multiple biological activities is encouraging for the development of magnolol derivatives as well as the design of clinical trials that will maximize the potential benefit of magnolol administration in a patient setting.

\* Corresponding author at: Tungs’ Taichung MetroHarbor Hospital, 699, Sec. 1, Chungchi Rd., Wuchi, Taichung 435, Taiwan.

\** Corresponding author.

E-mail addresses: manJimmy60@hotmail.com (K.-M. Man), kisa@kmu.edu.tw (P.-L. Liu).

1876-3820/ – see front matter © 2011 Published by Elsevier GmbH.
Materials and methods

The authors searched PubMed and MEDLINE for articles in English using keywords (alone and in various combinations) in the following categories:

- Magnolia genus related keywords (such as magnolol and honokiol).
- Integrative medicine related keywords (complementary/alternative/integrative medicine, traditional Chinese medicine, ethno-botanical survey, herbs, herbal, nutritional/dietary supplements).

We also performed a manual search of the reference lists in identified publications. Subsequently, one researcher selected the eligible studies and assessed the relevance of each publication. In this short review article, the recent findings regarding the biological effects of the antioxidative molecule magnolol were selected and reviewed.

Results

General antioxidative effects

The ability of magnolol to inhibit oxidative stress was first demonstrated in vitro. Rate constants for competition reactions between hydroxyl radicals and biphenyl compounds including magnolol were estimated [3]. It is thought that chemical mechanisms by which magnolol may function involves a peroxide intermediate followed by a phenolic hydroxyl group attacking the peroxide carbon chain, yielding a pentose or hexose ring and water [7]. Magnolol scavenges hydroxyl radicals that are generated by ultra-violet (UV) irradiation and inhibits UV-induced mutation in Salmonella [4]. The ability of magnolol to inhibit lipid peroxidation was demonstrated in ex vivo experiments involving rat heart/liver mitochondria and human sperm [5,8]. Magnolol is approximately 1000 times more potent than α-tocopherol [5,9] in its ability to inhibit lipid peroxidation in the heart mitochondrion and 340 times more potent in rat liver mitochondria [8]. With in vivo animal studies, it was observed that magnolol protects against small intestinal, cerebral and hind limb ischemia-reperfusion injuries [10–13].

Anti-inflammatory and anti-anaphylaxis effects

Previous data shows that magnolol can inhibit inflammatory enzyme/cytokine production, nuclear factor (NF)-κB activation and leukocyte activation, which indicates that magnolol could have anti-inflammatory properties at clinically achievable concentrations [7]. Magnolol exhibits leukocyte suppression, anti-inflammation and analgesic effects via decreased myeloperoxidase activity [14], decreased eicosanoid mediator activity [15–17] and decreased leukotriene formation [18–23]. Histamine release [21,24], as well as nitric oxide (NO), tumour necrosis factor-α (TNF-α), basic fibroblast growth factor, matrix metalloproteinase-1 and interleukin (IL)-4 production are also decreased [25–27]. Magnolol inhibits passive cutaneous anaphylactic reactions [25], skin photoaging [27], neurogenic inflammation, as well as dorsal skin and ear edema [28].

Magnolol is also used traditionally in the treatment of chest tightness and asthma [18–23]. The magnolol-induced inhibition on tracheal smooth muscle contraction and excitability of airway myocytes are due to the inhibition of Ca²⁺ influx [29,30]. Due to these potential health benefits, there is a definite increased interest in utilizing magnolol in the clinic as a novel anti-inflammatory and anti-anaphylaxis agent.

Anti-cancer properties

Konoshima et al. were the first to demonstrate the effect of magnolol against skin cancer in mice [31]. Magnolol can successfully induce apoptosis in tumour cells, including, cultured human hepatoma and colon [32] cancer cells, lung squamous [33] and thyroid [34] carcinoma, melanoma [35,36], fibrosarcoma, mononocytic leukaemia [35,37,38] and prostate [39] cancer cells [40]. Li et al. reported that magnolol in human non-small lung cancer cells, induced cell death, not by an apoptotic pathway but rather by autophagy [41]. Magnolol successfully inhibits experimentally induced liver and spleen metastasis using lymphoma and melanoma models [42] (Fig. 4).
Cardiovascular protection effects

Teng et al. were the first to demonstrate, in rabbit, that magnolol can inhibit the aggregation of platelet-rich plasma that was induced by collagen and arachidonic acid [43]. It was concluded that the anti-platelet effect of magnolol is due to an inhibitory effect on thromboxane formation as well as the inhibition of intracellular calcium mobilization [44].

Vascular smooth muscle cell (VSMC) contraction, proliferation and migration play important roles in the development of cardiovascular diseases [45]. Chen et al. showed that magnolol induced apoptosis in VSMCs via the mitochondrial apoptotic pathway [46]. Wu et al. also showed the apoptotic pathway and anti-oxidant effect might mediate the inhibition of cell growth [47].

Restenosis is a common complication after balloon angioplasty. A number of cytokines, chemotactic and growth factors may be involved. Previous studies illustrated that magnolol treatment significantly inhibited Cu²⁺-induced low density lipoprotein (LDL) oxidation in cholesterol-fed rabbits and reduced atheroma formation [48]. These data suggest that magnolol could be a potential novel therapeutic agent for the treatment of restenosis [49].

The adhesion of leukocytes to the vascular endothelium, mediated by adhesion molecules, is a pivotal early event in atherogenesis [50]. Also, due to its anti-inflammatory and anti-oxidant properties, magnolol may play important roles in the prevention of atherosclerosis and inflammatory responses in vivo [51]. More recently, magnolol was found to inhibit cardiac fibroblast proliferation by interfering with reactive oxygen...
species generation [52]. These results provide a therapeutic basis for the development of magnolol as an anti-oxidative and anti-inflammatory agent for vascular disorders including atherosclerosis (Fig. 5).

Anti-neurodegenerative effects

The protective effect of magnolol against hypoxia-induced cell injury in cortical neuron–astrocyte mixed cultures has been examined. This is the first report demonstrating the protective effect of magnolol against chemical hypoxic damage or necrotic cell death of neurons using cortical neuron–astrocyte mixed cultures [53]. Lee et al. further demonstrated that the protective effects of magnolol against brain damage by potassium cyanide (KCN) or KCN plus lipopolysaccharide in hypoglycemic media might involve the inhibition of prostaglandin E2 (PGE2) production; however, inhibition of nitric oxide generation did not appear to play a major role in this protective response [54]. Lin et al. also reported that the neuroprotective effects of magnolol might be related to its anti-oxidative actions. By antagonizing the toxicity induced by excitatory amino acids, this herbal compound could potentially be used to treat neurodegenerative diseases [55].

Magnolol was identified as a modulator of γ-aminobutyric acid (GABA)A receptor subtypes, due to its ability to selectively interact with GABA_A receptors in vitro. Selective interaction with GABA_A receptors provides a mechanism that might explain some of the magnolol regulated in vivo neuroprotective effects [56]. Furthermore, magnolol prevents age-related learning and memory impairment by preserving cholinergic neurons in the forebrain, suggesting magnolol may have potential therapeutic applications to various neuronal disorders such as Alzheimer’s disease.

Depressant and anti-depressant effects

Watanabe et al. was the first to report that magnolol had centrally acting muscle relaxant activity [57] which produced spindle discharges in sensory and motor cortex electroencephalograms and inhibited midbrain reticular formation- and hypothalamus-stimulated responses in the neo- and palaeocortex electroencephalograms. These results indicated that magnolol can depress the ascending activating systems as well as depress the activity of the spinal cord [2,58]. Tsai et al. examined the possibility that magnolol might elicit its depressant effect by modulating central serotonergic activity and concluded that the suppression of brain 5-hydroxytryptamine (HT) release by magnolol was site-specific, and the suppression of cortical 5-HT release by magnolol did not occur due to 5-HT autoreceptors at the 5-HT terminals [59].

On the other hand, Nakazawa et al. indicated that magnolol acted similar to other anti-depressants [60]. Recently, Xu et al. reported on the anti-depressant-like effects of oral administration of a honokiol and magnolol mixture in well-validated models of depression in rodents [61]. These results suggested that the synergistic anti-depressant-like effects of magnolol might be mediated simultaneously by the regulation of serotonergic and gastroenteric system functions. These findings also provided a potential pharmacological basis for the clinical anti-depressant application of magnolol.

GI and uterus modulation effects

The effects of magnolol on muscular contractile responses and intracellular Ca^{2+} mobilization were investigated in the non-pregnant rat uterus. It was reported by Lu et al. that magnolol
might be a putative Ca\(^{2+}\) channel blocker and could be of potential value in the treatment of gynaecological dysfunctions associated with uterine muscular spasm and dysmenorrhoea [62]. Zhang et al. showed that the inhibitory effects of magnolol on the contractility of smooth muscles isolated from gastric fundus strips in rats and isolated ileum of guinea pigs was associated with calcium-antagonistic effects that suggest magnolol could improve the gastric emptying of a semi-solid meal and intestinal propulsive activity in mice [63]. The influence of magnolol on the contractile activity of isolated colonic (ileum) muscle strips in the guinea pig helped elucidate a mechanism by which magnolol might function. Magnolol was found to block receptor-operated cation and voltage dependent Ca\(^{2+}\) channels. Also, through the inhibition of the InsP3-sensitive and ryanodine-sensitive pathways, magnolol can also block calcium release from the sarcosomal membrane [64,65]. These data show that magnolol exerts therapeutic effects on gastrointestinal disease through relaxation of the GI tract smooth muscles.

Yang et al. investigated the protective effects of magnolol on sepsis-induced inflammation and intestinal dysmotility and concluded that magnolol prevented sepsis-induced suppression of intestinal motility in rats. The potential mechanism for this effect is likely due to the ability of magnolol to modulate self-amplified inflammatory events and block oxidative stress in the intestine [66].

Liver protective effects

Chiu et al. investigated the ability of magnolol to suppress the generation of oxygen free radicals and improve the viability of cold-preserved warm-reperfused rat livers. They concluded that magnolol was an effective antioxidant and suppressed lipid peroxidation in rat liver mitochondria, indicating that in solution, magnolol could be used a protective rinse for transplanted organs against unwanted lipid peroxidation during reperfusion [8]. The protective effect of magnolol on the liver was performed in vitro with tertiary butyl hydroperoxide- and \(\gamma\)-galactosamine-induced hepatocyte injury as well as in vivo with acetaminophen-induced liver damage in rats. These studies indicate the potential interest of magnolol in the treatment of toxic acute liver failure [67,68]. By upregulating the anti-apoptotic Bcl-XL gene and through the suppression of the Bcl-xS gene, magnolol also induced an anti-apoptotic effect in the liver and was protective against ischemia and reperfusion (I/R) induced liver injury [69]. Moreover, Yin et al. also suggested that Magnolia officinalis might be a promising candidate for the development of a therapeutic agent for alcohol-induced liver disease [70].

Anti-diabetic complication effects

Sohn et al. investigated the effect of magnolol on type 2 diabetic Goto–Kakizaki rats and reported that the use of magnolol could result in good blood glucose control and prevent or retard the development of diabetic complications [71]. Moreover, Choi et al. showed magnolol exhibited binding affinity to peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\)); however, the activity of magnolol was weaker than rosiglitazone. In mature 3T3-L1 adipocytes, magnolol increased basal and insulin-stimulated glucose uptake. These results suggest that magnolol could improve insulin sensitivity through the activation of PPAR-\(\gamma\) [72].

Hormone regulation effects

Hsieh et al. investigated the effects of magnolol on thermoregulation and hypothalamic release of 5-HT by in vivo microdialysis performed in normothermic rats and in febrile rats treated with IL-1\(\beta\). Their data suggest that magnolol decreases body temperature by reducing 5-HT release in the rat hypothalamus [73]. Tachikawa et al. showed the crude extract of Magnolia bark inhibited the secretion of catecholamines from bovine adrenal chromaffin cells that were stimulated by acetylcholine, indicating that the inhibitory effect may be associated with its pharmacological effect on the nervous system [74]. Chen et al. focused on the identification of the mechanism responsible for the effect of magnolol on corticosterone production and found a pathway by which magnolol could induce the expression of steroidogenic acute regulatory protein, which is involved in the rate-limiting step in steriodogenesis [75].

Pain control effects

Lin et al. demonstrated that magnolol effectively alleviated formalin-induced inflammatory pain without motor and cognitive side effects, suggesting the use of magnolol in the potential treatment of inflammatory pain [76]. The same group also investigated the anti-nociceptive effects of magnolol on animal paw licking responses as well as the effect on thermal hyperalgesia, which is induced by glutamate receptor agonists in mice. They demonstrated that magnolol effectively decreased the inflammatory pain through the inhibition of nociception provoked by NMDA receptor and mGluR5 activation [77].

Anti-microbial effects

Clark et al. were the first to examine the anti-microbial activity of magnolol using an agar-well diffusion assay. They found that magnolol exhibited significant activity against fungi as well as Gram-positive and acid-fast bacteria [78,79]. Magnolol is also a potent inhibitor of Helicobacter pylori growth [80]. Together with the previously known antibacterial activity against Propionibacterium acnes, it is suggested that magnolol may be used as a possible safe and effective acne-mitigating agent [81].

Discussion

Magnolol has multifunctional properties mediated by several mechanisms of actions. The development of other polyphenolic agents such as curcumin is hindered by poor absorption and rapid excretion [7,82]; however, significant systemic levels of magnolol were observed in preclinical models. Magnolol can also cross the blood–brain barrier [83,84]. In other words magnolol exhibits a desirable spectrum of bioavailability that is generally
not observed with other herbal compounds. Understanding the mechanism and safety of magnolol is required for the future therapeutic use of this compound. Further insights into the signalling network modulated by magnolol may provide the basis for novel research that can exploit magnolol for future prevention and treatment of human disease. Safety during long-term administration, combined with its cost and future therapeutic potential, make it an ideal agent for both prevention and therapy of chronic illnesses, either alone or in combination with other medications. Clinical trials are necessary to understand the true effectiveness and safety of magnolol in humans. Magnolol analogues with improved pharmacokinetic and pharmacodynamic properties will also help in the development of novel pharmacological compounds for the treatment of numerous disorders and will be important in future clinical trials.

Conclusions

These health benefits of magnolol have increased the interest in bringing this herbal compound to the clinic as a novel therapeutic agent. Knowledge of the multiple activities of magnolol can assist with the development of novel derivatives and the design of clinical trials that will maximize the potential benefit of magnolol in the patient setting.

Financial support

Grants NSC 100-2320-B-039-008-MY2 and NSC 100-2320-B-037-009 from the National Science Council, grant CMU100-NSC-05 from China Medical University, and grant DOH100-TD-B-111-004 from the Taiwan Department of Health Clinical Trial and Research Center of Excellence.

Conflict of interest

None.

References


