MAGNOLIA

(Magnolia officinalis)

An Overview of the Research and Clinical Indications

Lise Alschuler, ND, FABNO

plant intelligence.®
PROFESSIONAL RESOURCES

90LTT032

This herb research review is intended to be used by authorized health care practitioners, clinicians, pharmacists, physicians, and any other professionally trained persons who may provide medical advice to patients or consumers. The information presented has been obtained from research of reference books, clinical and scientific published papers, and other published works. The lay reader is advised to consult a licensed health care practitioner regarding the information contained herein.

BACKGROUND AND USES

Magnolia, Magnolia officinalis, is a deciduous tree native to China. The bark, stripped from the stems, branches and roots of the tree have been historically used in Traditional Chinese Medicine and Japanse Kampo medicine. The traditional use of Magnolia bark, or Houpo, rely upon its bitter, warm and aromatic qualities for the treatment of digestive complaints such as indigestion, flatulence and loss of appetite, as well as lung issues such as cough and asthma.[1,2] Magnolia bark extract has also been in traditional Chinese and Japanese medicines for its sedative and anxiolytic actions for the treatment of anxiety, depression and seizures.[3] The modern day uses of Magnolia officinalis mimic these usages with emphasis on the neurological and anti-inflammatory properties of this bark extract.

In the United States of America, Magnolia officinalis has been granted "Generally Recognized as Safe" (GRAS) status by the FDA.

ACTIVE CONSTITUENTS

Numerous constituents of Magnolia officinalis have been identified, which include: phenolic glycosides, phenolic acids and nonsesquiterpenoids[4] as well as numerous alkaloids.[5] The two major bioactive constituents of Magnolia are magnolol and honokiol, which are bi-phenolic lignan isomers, making up 1 to 10% of the dried bark extract.[6] Honokiol and magnolol possess a phenol ring, a structure found in the anesthetic propofol, which may explain some of the pharmacologic actions of magnolia.

MECHANISM OF ACTION

Magnolia extract has a variety of medicinal actions. Most of the activity of magnolia is attributed to the magnolol and honokiol. Both of these compounds are considered active and similar in effect. Both magnolol and honokiol enhance the activity of $GABA_A$ receptors and neurotransmission. This action lends anxiolytic, sedative, neuroprotective, and anti-convulsant effects. Contributing to the anxiolytic effects is the inhibition of dopamine transporter activity and reduced dopamine and serotonin receptor binding affected by both magnolol and honokiol.[7] These polyphenols have also been shown to inhibit glutamate receptor activity.[8] Both honokiol and magnolol have been shown to increase acetylcholine release in the hippocampus, which creates anti-depressive and analgesic effects.[9] The neuroprotective properties of honokiol have been demonstrated in rodent models with intravenous administration, specifically, reducing neurotoxicity in seizure disorder and cerebral infarction.[10] The neuroprotective effects have been attributed to honokiol's inhibition of reactive oxygen species production, inhibition of neutrophil infiltration, and neurotrophic activity.

Another important area of medicinal activity of magnolia extract is signal transduction modification. Honokiol has been shown to inhibit a number of transcription factors including nuclear factor kappa B (NF-kβ), signal transducer and activator of transcription 3 (STAT3), epidermal growth factor receptor (EGFR) and mammalian target of rapamycine (mTOR).[11] Aberrant activation of these transcription factors had been documented in many malignancies. Thus, the broad-spectrum inhibition by honokiol likely underlies its observed anti-proliferative, anti-tumor and anti-inflammatory effects. Further anti-inflammatory effects have been documented from Magnolia officinalis bark extract. The extract reduces interleukin-6 and interleukin-8 from bacterial stimulated fibroblasts.[12]

An experimental indication for magnolia is in the management of hyperglycemia. This is due to the fact that honokiol is a proliferator-activated receptor gamma ($PPAR_Y$) partial agonist.[13] $PPAR_Y$ is a transcription factor that regulates lipid and glucose metabolism particularly in adipose tissue. Partial PPAR agonists have the net effect of lowering blood sugar without triggering adipogenesis as do full PPAR agonist drugs.

RESEARCH SUMMARY

Anxiolytic and Sedative Properties

A prospective, two-group, parallel, randomized double-blind, placebo-controlled trial of 26 adult females with anxiety tested the anxiolytic effects of 6 weeks of an oral preparation that combined Magnolia officinalis extract (standardized to not less than 1.5% honokiol) and Phellodendron amurense extract (standardized to not less than 0.1% berberine).[14] Each participant ingested 250mg of the extract combination three times daily or placebo. The Magnolia and Phellodendron combination significantly reduced transitory anxiety as measured by the State-Trait Anxiety Inventory compared to placebo but was not effective in reducing long-standing anxiety or depression. There were no safety concerns observed in the study.

Magnolol, through its activation of the $GABA_A$ receptor has been demonstrated in mice to promote sleep.[15] Sleep latency is reduced and the non-REM and REM phases of sleep are increased under the influence of magnolol administered via intraperitoneal injection at a dose of 25mg/kg. The sedative effects of Magnolia extract have been further demonstrated in humans. The effects of Magnolia extract and Magnesium were studied in a 24-week controlled, randomized multicenter study with 89 symptomatic menopausal women with sleep or mood alterations.[16] Each participant either took one daily tablet of soy isoflavones (60mg), Lactobacilli (500 million spores, and included in order to assist in the metabolism of the isoflavones), Magnolia bark extract (60mg), magnesium (50mg), calcium (141mg) and vitamin D3 (5µg), or control (calcium and vitamin D3). Menopausal symptoms were rated by the subjects and their physicians. At

study end, all menopausal symptoms, namely hot flushes, nocturnal sweating, palpitations, insomnia, anxiety, asthenia, depression, irritability, loss of libido, vaginal dryness, dyspareunia were significantly improved with the combination tablet over calcium and vitamin D3 alone ($p<0.001$). This study indicated the efficacy of soy isoflavones, Magnolia extract and magnesium in improving sleep quality in addition to improving other menopausal symptoms.

Chemopreventive properties

The majority of the anti-cancer studies related to Magnolia officinalis have been conducted on the constituent honokiol. There have been several cancer types studied. A mouse study of ultraviolet irradiated mice found that topical application of honokiol (3mg per mouse) resulted in 80% reduction in tumor size and 62% reduction in malignant progression of papillomas to skin carcinomas.[17] Honokiol has been shown to inhibit the growth of breast cancer cell lines in a dose-dependent manner regardless of their estrogen, progesterone, Her2neu or p53 status.[18] Honokiol arrests cell cycle, induces apoptosis and suppresses Ras activation (a major activator of cell survival and proliferation in some cancers). Honokiol has been shown to cause apoptosis of prostate cancer cells and to inhibit the growth of prostate cancer-associated stromal fibroblasts.[19] Honokiol has also been shown to inhibit the growth of human colorectal cells[20], gastric cancer cells[21] and pancreatic cells.[22]

Magnolol also has chemopreventive actions. One observed mechanism for this cancer preventive action is the inhibition of angiogenesis (blood vessel growth). One of the major triggers of angiogenesis to tumors is local tissue hypoxia. Magnolol attenuates hypoxia induced angiogenesis by inhibiting hypoxia-inducible factors-1α (HIF-1α) and vascular endothelial growth factor (VEGF).[23]

Chemotherapeutic properties

Honokiol is a radiosensitizer. Lung carcinoma cells pre-treated with liposomal honokiol for 24 hours prior to radiation treatment showed a two-fold enhancement of radiation. This effect has been further documented in animals who experienced a reduction in tumor volume of 78% when co-treated with radiation and honokiol compared to a reduction in tumor volume of 42% from radiation therapy alone.[24] A similar synergistic effect of honokiol was demonstrated with cisplatin in lung and ovarian tumor models.[25,26] Honokiol has been shown to downregulate the expression of P-glycoprotein in breast cancer cells.[27] This down-regulation maintains cellular sensitivity to the cytotoxic effects of chemotherapy. Honokiol administered to mice bearing ovarian cancer tumors demonstrated decreased angiogenesis and significant inhibition of tumor growth compared to control mice.[28] Honokiol crosses the blood brain barrier and inhibits glioma growth in mouse models.[29]

Anti-inflammatory: Gingivitis

The anti-inflammatory activities of magnolia bark extract have clinical applications in the prevention of gingivitis. A randomized double-blind study enrolled 120 healthy adults at high risk for dental caries as demonstrated by high salivary mutans streptococci concentration ($\geq 10^5$ CFU/ml) and gum bleeding on probing >25%. Subjects were randomized to chew gum with magnolia extract, xylitol gum or control gum. Salivary and gingival examinations were done at baseline, after 7 days and after 30 days of gum use. The magnolia gum significantly reduced plaque acidogenicity, mutans streptococci concentration and gingival bleeding compared to xylitol and control gums.[30] These results were confirmed in another controlled, double-blind study of 123 adults that compared sugar-free chewing gum with gum containing zinc acetate (0.012% by weight) and magnolia bark extract (0.15% by weight) on oral volatile sulfur-containing compounds (indication of plaque-forming bacteria). The zinc and magnolia gum reduced the volatile sulfur-containing compounds by 27.6% one hour after 10-minutes of chewing compared to 6.9% in the gum-only group, ($p<0.05$).[31]

Weight management

The partial $PPAR_{\gamma}$ agonist actions, combined with the anxiolytic actions of magnolia extract indicate its use in the management of obesity. A randomized, double-blind, placebo-controlled clinical study of 28 premenopausal, healthy, overweight females assessed the impact of Magnolia officinalis and Phellodendron amurense capsules on weight gain.[32] These participants all scored above the national mean on self-reported anxiety and this age group typically eats more in response to stressful situations. Subjects took 250mg capsules three times daily for 6 weeks or placebo. There was a significant weight gain during the study for the placebo group (P < ,01), but no significant weight gain for the group receiving extracts of M. officinalis and P. amurense (P < .89). Stated in a different way, 75% of the control group gained weight versus only 37% of the treatment group. Additionally, the treatment group experienced decreased bedtime cortisol levels, while the placebo experienced increased bedtime cortisol. The weight management effects may have stemmed from the reduction of cortisol levels and associated stress-induced eating.

Alcoholic fatty liver

Excessive alcohol consumption is known to precipitate liver damage due to fatty infiltration, inflammation, fibrosis and ultimately cirrhosis. The fatty infiltration, or steatosis, is the earliest response of the liver to chronic alcohol consumption. Sterol regulatory element-binding protein-1c (SREBP-1c) is a transcription factor that regulates lipid homeostasis and has been implicated in alcoholic steatosis. Steatosis can develop into steatohepatitis under the influence of inflammatory cytokines such as TNFa.

Magnolia officinalis extract given by feeding tube to ethanol-fed rats at 45mg/kg per day completely reversed all serum markers of steatosis, and liver histology from the sacrificed animals demonstrated complete reversal of alcohol-induced steatosis.[33] These effects are presumed to be due to suppression of TNF-α and superoxide anion production and the inhibition of SREBP-1c activation. Thus, magnolia holds promise as a therapy for alcoholic fatty liver.

CLINICAL INDICATIONS, PRACTITIONER DOSING, CONTRAINDICATIONS AND TOXICITY

Clinical Indications

- Anxiety
- Insomnia
- Cancer risk reduction
- Radio- and chemosensitizing agent
- Relief of menopausal symptoms
- Reduction of plaque formation and gingivitis
- Weight management, especially with stress-induced eating as contributing factor
- Prevention and reversal of fatty liver, and specifically alcoholic steatosis

Dosage range

Honokiol and magnolol are not readily soluble in water. Once absorbed, they are largely metabolized in the liver to glucuronidated and sulphated compounds, of which up to 50% is secreted in the bile and the remainder is transported systemically bound to plasma proteins.[34] Honokiol and magnolol are distributed widely have been demonstrated to cross the blood-brain barrier. The pharmacokinetics have been studied in rodent models, but are yet to be defined in humans.[35] In rats, intravenous injection of honokiol 5–10 mg/kg has a plasma terminal 1/2 life of approximately 40–60 min.[36]

Dosing recommendations are not well elucidated. Current dosing recommendations target 300 mg of Magnolia extract daily in divided doses. However, doses as low as 60mg of Magnolia extract may be effective.

Contraindications

Having been granted “Generally Recognized as Safe” (GRAS) status in the United States of America by the Food and Drug Administration (FDA), Magnolia officinalis is well tolerated by most people.

Patients taking anticoagulant medication or with clotting disorders such as hemophilia or von Willebrand’s deficiency should avoid using this botanical agent as honokiol is a potent inhibitor of arterial thrombosis.[37]

Toxicity

Toxicological studies on honokiol and Magnolia bark extract have not shown any pathological effects in the primary sites of distribution: liver, lung, kidney, spleen, brain, heart, pancreas, intestines, or bone marrow after intravenous or oral administration.[38] Furthermore, no genotoxic effects have been observed in cellular studies.[39]

CONCLUSIONS

The overall botanical medicine benefit profile for Magnolia officinalis makes it a viable botanical agent for optimizing neurological function with a specific indication for anxiety and insomnia. Magnolia reduces oxidative stress and inflammation in brain, oral cavity and liver. Magnolia has specific chemopreventive actions in a variety of cancer types and acts synergistically with therapeutic radiation and chemotherapy. Magnolia also reduces weight gain secondary to stress-induced over-eating.

Magnolia officinalis appears to be a safe herb for medicinal use, as it has been used safely and effectively in traditional Asian medicine for hundreds of years.

ABOUT THE AUTHOR

Lise Alschuler is a naturopathic doctor with board certification in naturopathic oncology and has been a practicing since 1994. She graduated from Brown University with an undergraduate degree in Medical Anthropology and received a doctoral degree in naturopathic medicine from Bastyr University. Dr. Alschuler is past-President of the American Association of Naturopathic Physicians and a founding and current board member of the Oncology Association of Naturopathic Physicians. She also currently serves as President Emeritus on the board of the Naturopathic Post-Graduate Association. Dr. Alschuler works as an independent consultant in the area of practitioner and consumer health education. She maintains a naturopathic oncology part-time practice out of Naturopathic Specialists, based in Scottsdale AZ. Previously, she was the department head of naturopathic medicine at Midwestern Regional Medical Center – Cancer Treatment Centers of America. She was also the clinic medical director and botanical medicine chair at Bastyr, as well she was on the faculty of Southwest College of Naturopathic Medicine.

Dr. Alschuler is the co-author of The Definitive Guide to Cancer: An Integrative Approach to Prevention, Treatment and Healing, and The Definitive Guide to Thriving After Cancer: A Five-Step Integrative Plan to Reduce the Risk of Recurrence and Build Lifelong Health. She co-created FiveToThrivePlan.com, and co-hosts a radio show, Five To Thrive Live! on the Cancer Support Network about living more healthfully in the face of cancer. She calls Tucson AZ and Chicago, IL home. Learn more at drlise.net.

REFERENCES

[1] Hahm, E-R, Arlotti, JA, Marynowski SW and Singh SV. Honokiol, a Constituent of Oriental Medicinal Herb Magnolia officinalis, Inhibits Growth of PC-3 Xenographs In vivo in Association with Apoptosis Induction. Clin Cancer Res. 2008;14:1248.
[2] Yan R., Wang W., Guo J. et al. Studies on the Alkaloids of the Bark of Magnolia officinalis: Isolation and On-line Analysis by HPLC-ESI-MS. Molecules. 2013;18:7739.
[3] Alexeev M, Grosenbaugh D, Mott D, and Fisher J. The natural products magnolol and honokiol are positive allosteric modulators of both synaptic and extra-synaptic GABAA receptors. Neuropharmacology. 2012;62(8):2507.
[4] Yan RY, Liu HL, Zhang JY, Yang B. Phenolic glycosides and other constituents from the bark of Magnolia officinalis. J Asian Nat Prod Res. 2013 Aug 5. [Epub ahead of print]
[5] Yan R, Wang W, Guo J, Liu H, et al. Studies on the alkaloids of the bark of Magnolia officinalis: isolation and on-line analysis by HPLC-ESI-MS(n). Molecules. 2013 Jul 3;18(7):7739.
[6] Alexeev M, Grosenbaugh D, Mott D, and Fisher J. The natural products magnolol and honokiol are positive allosteric modulators of both synaptic and extra-synaptic GABAA receptors. Neuropharmacology. 2012;62(8):2507.
[7] Koetter U, Barrett M, Lacher S, Abdelrahman A, Dolnick D. Interactions of Magnolia and Ziziphus extracts with selected central nervous system receptors. J Ethnopharmacol. 2009; 124:421.
[8] Lin YR, Chen HH, Ko CH, Chan MH. Differential inhibitory effects of honokiol and magnolol on excitatory amino acid-evoked cation signals and NMDA-induced seizures. Neuropharmacol. 2005; 49:542.
[9] Tsai TH, Westly J, Lee TF, Chen CF, Wang LC. Effects of honokiol and magnolol on acetylcholine release from rat hippocampal slices. Planta Med. 1995; 61:477
[10] Woodbury A., Yu S, Wei L, Garcia P. Neuro-modulating effects of honokiol: a review. Frontiers Neuro. 2013;4(130):1-6.
[11] Arora S., Singh S., Piazza G. Contreras C. et al. Honokiol: a novel natural agent for cancer prevention and therapy. Curr Mol Med. 2012;12(10):1244.
[12] Walker JM, Maitra A, Walker J, Ehrnhoefer-Ressler MM, et al. Identification of Magnolia officinalis L. bark extract as the most potent anti-inflammatory of four plant extracts. Am J Chin Med. 2013;41(3):531-44.
[13] Atanas G., Wang J, Gu S., Bu J. et al. Honokiol: A non-adipogenic $PPAR_Y$ agonist from nature. Biochim Biophys Acta. 2013;1830(10):4813.
[14] Kalman D, Feldman S, Feldman R, Schwartz H. et al. Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind, placebo-controlled clinical trial. Nutr J. 2008;7:11.
[15] Chen C-R, Zhou X-Z, Luo Y-J, Huang Z-L, et al. Magnolol, a major bioactive constituent of the bark of Magnolia officinalis, induces sleep via the benzodiazepine site of GABAA receptor in mice. Neuropharmacology. 2012;63:1191.
[16] Mucci M, Carraro C, Mancino P, Monti M, et al. Soy isoflavones, lactobacilli, Magnolia bark extract, vitamin D3 and calcium. Minerva Ginecol. 2006;58:323.

[17] Chilampalli S, Zhang X, Fahmy H, Kaushik RS, et al. Chemopreventive effects of honokiol on UVB-induced skin cancer development. Anticancer Res. 2010; 30:777.
[18] Wolf I, O'Kelly J, Wakimoto N, Nguyen A, Amblard F, Karlan BY, et al. Honokiol, a natural biphenyl, inhibits in vitro and in vivo growth of breast cancer through induction of apoptosis and cell cycle arrest. Int J Oncol. 2007; 30:1529.
[19] Hahm ER, Arlotti JA, Marynowski SW, Singh SV. Honokiol, a constituent of oriental medicinal herb magnolia officinalis, inhibits growth of PC-3 xenografts in vivo in association with apoptosis induction. Clin Cancer Res. 2008; 14:1248.
[20] Wang T, Chen F, Chen Z, Wu YF, Xu XL, Zheng S, et al. Honokiol induces apoptosis through p53-independent pathway in human colorectal cell line RKO. World J Gastroenterol. 2004; 10:2205.
[21] Liu SH, Shen CC, Yi YC, Tsai JJ, Wang CC, Chueh JT, et al. Honokiol inhibits gastric tumourigenesis by activation of 15-lipoxygenase-1 and consequent inhibition of peroxisome proliferator-activated receptor-gamma and COX-2-dependent signals. Br J Pharmacol. 2010; 160:1963.
[22] Arora S, Bhardwaj A, Srivastava SK, Singh S, McClellan S, Wang B, et al. Honokiol arrests cell cycle, induces apoptosis, and potentiates the cytotoxic effect of gemcitabine in human pancreatic cancer cells. PLoS One. 2011; 6:e21573.
[23] Chen MC, Lee CF, Huang WH, Chou TC. Magnolol suppresses hypoxia-induced angiogenesis via inhibition of HIF-1α/VEGF signaling pathway in human bladder cancer cells. Biochem Pharmacol. 2013 May 1;85(9):1278.
[24] Hu J, Chen LJ, Liu L, Chen X, Chen PL, Yang G, et al. Liposomal honokiol, a potent anti-angiogenesis agent, in combination with radiotherapy produces a synergistic antitumor efficacy without increasing toxicity. Exp Mol Med. 2008; 40:617
[25] Jiang QQ, Fan LY, Yang GL, Guo WH, Hou WL, Chen LJ, et al. Improved therapeutic effectiveness by combining liposomal honokiol with cisplatin in lung cancer model. BMC Cancer. 2008; 8:242.
[26] Liu Y, Chen L, He X, Fan L, Yang G, Chen X, et al. Enhancement of therapeutic effectiveness by combining liposomal honokiol with cisplatin in ovarian carcinoma. Int J Gynecol Cancer. 2008; 18:652.
[27] Liu H, Zang C, Emde A, Planas-Silva MD, Rosche M, Kuhnl A, et al. Anti-tumor effect of honokiol alone and in combination with other anti-cancer agents in breast cancer. Eur J Pharmacol. 2008; 591:43.
[28] Li Z, Liu Y, Zhao X, Pan X, Yin R, Huang C, et al. Honokiol, a natural therapeutic candidate, induces apoptosis and inhibits angiogenesis of ovarian tumor cells. Eur J Obstet Gynecol Reprod Biol. 2008; 140:95.
[29] Wang X, Duan X, Yang G, Zhang X, Deng L, Zheng H, et al. Honokiol crosses BBB and BCSFB, and inhibits brain tumor growth in rat 9L intracerebral gliosarcoma model and human U251 xenograft glioma model. PLoS One. 2011; 6:e18490.
[30] Campus G, Cagetti MG, Cocco F, Sale S, et al. Effect of a sugar-free chewing gum containing magnolia bark extract on different variables related to caries and gingivitis: a randomized controlled intervention trial. Caries Res. 2011;45(4):393-9.

[31] Porciani PF, Grandini S. The effect of zinc acetate and magnolia bark extract added to chewing gum on volatile sulfur-containing compounds in the oral cavity. J Clin Dent. 2012;23(3):76.
[32] Garrison R, Chambliss WG. Effect of a proprietary Magnolia and Phellodendron extract on weight management: a pilot, double-blind, placebo-controlled clinical trial. Altern Ther Health Med. 2006 Jan-Feb;12(1):50.
[33] Yin H-Q, Je Y-T, Kim Y-C, Shin Y-K, et al. Magnolia officinalis Reverses Alcoholic Fatty Liver by Inhibiting the Maturation of Sterol Regulatory Element-Binding Protein-1c. J Pharmacol Sci. 2009;109:486.
[34] Arora S., Singh S., Piazza G. Contreras C. et al. Honokiol: a novel natural agent for cancer prevention and therapy. Curr Mol Med. 2012;12(10):1244.
[35] Lee YJ, Lee YM, Lee CK, Jung JK, et al. Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther (2011) 130(2):157.
[36] Tsai TH, Chou CJ, Cheng FC, Chen CF. Pharmacokinetics of honokiol after intravenous administration in rats assessed using high-performance liquid chromatography. J Chromatogr B Biomed Appl. 1994;655(1):41.
[37] Hu H, Zhang XX, Wang YY, Chen SZ. Honokiol inhibits arterial thrombosis through endothelial cell protection and stimulation of prostacyclin. Acta Pharmacol Sin. 2005;26(9):1063. 1745- 7254.2005.00164.x
[38] Arora S., Singh S., Piazza G. Contreras C. et al. Honokiol: a novel natural agent for cancer prevention and therapy. Curr Mol Med. 2012;12(10):1244.
[39] Zhang B, Maniatis T, Song Y, Zhang W, Zhang X, Li N, et al. Evaluation of magnolia bark extract in chromosomal aberration assays. Mutat Res. 2008; 654:133.