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The Ethnomedicinal Uses of Magnoliaceae from the Southeastern United States as Leads in Drug Discovery

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Abstract

In Asia and North America, members of the family Magnoliaceae have been and are presently used extensively in indigenous herbal medicine. Many taxa of the genus *Magnolia* produce lignans and sesquiterpene lactones, some with considerable *in vitro* bioactivities. This review focuses on selected natural products of the genus *Magnolia* from the southeastern United States with demonstrated biological and pharmacological properties. Ethnomedicinal data obtained from the Native Americans of the southeastern United States correlate well with the results of pharmacological investigations.

Keywords: Magnolia, ethnobotany, ethnomedicine, sesquiterpene lactones, lignans.

Introduction

The family Magnoliaceae consists of 12 woody genera, of which *Magnolia* (incl. *Talauma*), *Liriodendron*, *Michelia* and *Aromadendron* have been used in traditional folk medicine in Asia and North America. The contemporary center of diversity for Magnoliaceae is located in the tropical regions of southeastern Asia, although species of *Magnolia* and *Liriodendron* also occur in North America. Because of the disjunct range of *Magnolia*, ethnomedicinal data are reported from Eastern Asia and from the southeastern U.S. and Mexico. Due to the fact that *Magnolia* and *Liriodendron* have the greatest ethnomedicinal value within the Magnoliaceae, considerable phytochemical work has been done primarily on these genera. Members of the Magnoliaceae contain secondary metabolites such as phenolic compounds, sesquiterpene lactones, monoterpenes, alkaloids, and volatile oils. This review deals with the ethnomedicinal use of *Magnolia* and *Liriodendron* native to the southeastern U.S. with examples for potential medicinal use of their lead compounds.

The ethnomedicinal use of *Magnolia* in the southeastern United States

In the southeastern United States, the genus *Magnolia* is represented by eight species (Morin, 1997; Duncan & Duncan, 1988). These native trees are characterized by fragrant flowers and an aromatic and bitter tasting bark (Griffith, 1847; Small, 1933). *Magnolia grandiflora* L. (southern magnolia, laurel) and *M. virginiana* L. (*M. glauca* L., sweetbay, beaver-tree) are evergreen trees which are mainly found in the coastal plain ecophysiographic region. The deciduous *M. pyramidata* L. (pyramid magnolia) is located in maritime areas throughout the coastal plain of the Gulf of Mexico, whereas *M. ashei* Weatherby (Ashe's magnolia), the rarest magnolia species in the U.S., is found only in six counties of the Florida panhandle. The range of *M. macrophylla* Michx. (great-leaf magnolia) extends in bottomland woods and ravines from the southern coastal plain north into Kentucky. The highly morphologically variable *Magnolia acuminata* L. (*M. cordata* Michx.), the cucumber tree, ranges from the coastal region northward to Ontario, Canada. *Magnolia tripetala* L. (umbrella magnolia) occurs in upland regions and the interior part of the Southeast while *M. fraseri* Walt. (mountain magnolia) is only found in the Appalachian Mountains.

Magnolia virginiana, the sweetbay magnolia or beaver tree (since its bark is a chief food of beavers), may appear as a deciduous and multi-trunked northern variety and a single-trunked and evergreen southern variety (McDaniel, 1966; Treseder, 1978). It was used to treat various ailments among

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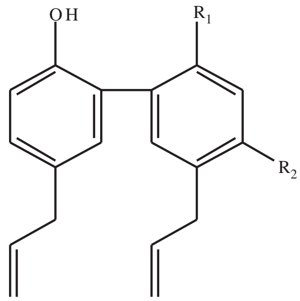
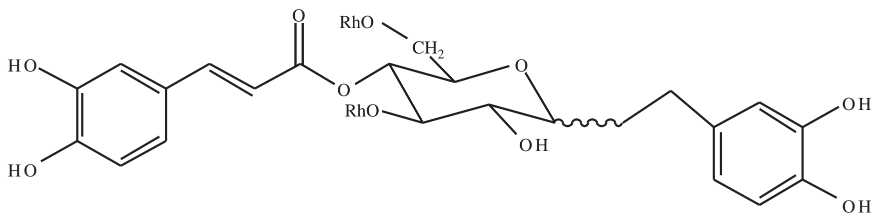


1 R_1 = H, R_2 = OH : Honokiol
2 R_1 = H, R_2 = OMe : Methylhonokiol
3 R_1 = OH, R_2 = H : Magnolol



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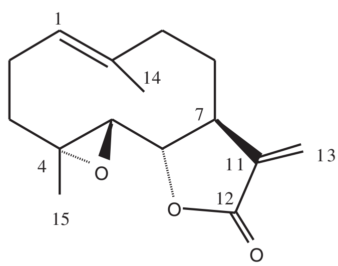

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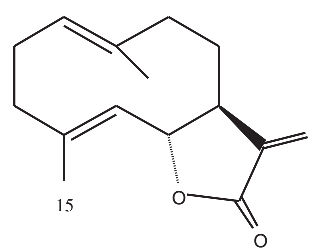

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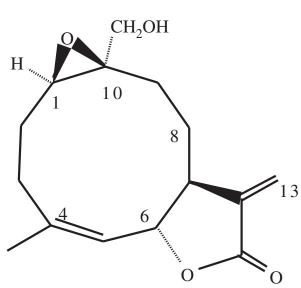

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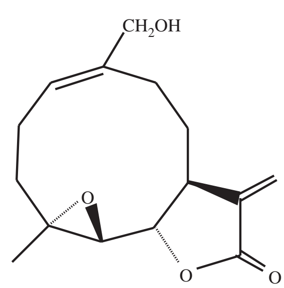

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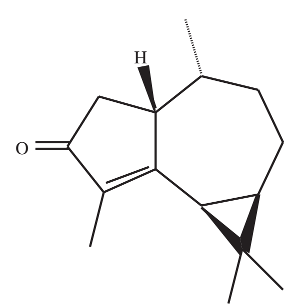

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Figure 1. Structures of componrds **1–9**.

the Indian tribes of the southeastern U.S. The root and stem bark, as well as the branches were prepared as bitter tonics with considerable power against autumnal fever and rheumatism. Furthermore, they were applied as a laxative and sudorific in a warm decoction or as an agent against paroxysms of intermittent fever in cold decoctions, powder, or tinctures. A tincture of the cones and seeds was used for the same purposes (Bolyard, 1981; Speck et al., 1942; Michaux, 1805). The strong odor of the flowers is described as causing chest oppression in some people (Millspaugh, 1975). The

Houma Indians of Louisiana made a tea from leaves of the sweetbay to prevent chills, to 'warm the blood', and to cure colds (Speck, 1941). Early pharmacological investigations supported the aromatic, diaphoretic, and astringent properties of this tree and revealed a bradycardia after uptake of the bark (Price, 1802). Powdered roots were reported as being used as a diaphoretic in the treatment of rheumatism, pleurisy, cough, and even consumption, while powdered bark was utilized against remittent, intermittent, and typhoidal fever (Price, 1802; Vogel, 1970). The latter usage reports promoted interest in investigating *Magnolia* as a potential native and adequate substitute for the rare and expensive Peruvian bark (*Aristolochia trilobata* L.) and the colombo (*Jateorhiza columba* Miers.).

A decoction of the bark of *M. grandiflora* (katlaha) was used by the Chocktaw Indians of Louisiana as a remedy against itching due to 'prickly heat' (Bushnell, 1909). Taylor (1940) reports the same indication as well as its use against dropsy by the Koasati, although the medicinal properties of *Magnolia* do not seem to support these applications (Taylor, 1940).

The Iroquois, who apparently had a highly diversified system of herbal medicine, used the inside of the bark from the east side of the trunk of *M. acuminata* as a remedy against toothache (Speck et al., 1942; Herrick, 1978 and 1995). Michaux (1805) reports its use by the inhabitants of Pennsylvania and Virginia in the preparation of a strong and bitter tasting fever created by steeping the fruits of *M. acuminata* in whiskey. The use of bark infusions of *M. acuminata* and *M. macrophylla* by the Cherokee as an analgesic for curing stomachache and cramps is reported (Moerman, 1998). *Magnolia virginiana*, *M. acuminata* and *M. tripetala* were recognized in the U.S. Pharmacopoeia (2nd list, 1820–94) for treating rheumatism (Hutchens, 1991).

The medicinal properties of *M. acuminata*, *M. tripetala,* and *M. macrophylla* are described to be approximately the same as those of *M. grandiflora* and *M. virginiana*, and the species may be substituted for one another for medical preparations (Griffith, 1847). However, modern chemical analysis shows that the chemistry of *M. virginiana* may be different from the chemistry of the other species. In general, *M. virginiana* was considered to have the most powerful actions, and *M. acuminata* was classified as the most active species against several types of rheumatism. The dosage for the treatment of these ailments should be rather high, with about five teaspoons of powdered bark being used daily (Crellin & Philpott, 1990).

Some of the Asian *Magnolia* species are of great value in herbal medicine. For example, the bark of Chinese *M. officinalis* Rehd. & Wils. is known as a tonic and stimulant and is used against anorexia, nausea, dysentery, and other ailments. *M. denudata* Desr. from China is used as a diaphoretic and febrifuge (Hocking, 1997).

Another genus within the Magnoliaceae, the tulip tree or yellow poplar (*Liriodendron tulipifera* L.), was used by the native Indians of North America. Although its bark is less aromatic than the bark of magnolia, it was a preferred tonic with similar medical properties. Powdered bark, especially root bark, is reported to be useful as a febrifuge in paroxysmal fevers (Griffith, 1847), and it was also used as a febrifuge in the Houma medicine (Millspaugh, 1975). The Cherokees applied it as an anthelminthic, anti-diarrheal, anti-rheumatic, and against miscellaneous diseases (Herrick, 1995). Other applications included the treatment of dyspepsia and dysentery. The tulip tree is also listed in the U.S. Pharmacopoeia (2nd list). A closely related member of the genus *Liriodendron* from China, *L. chinense* (Hemsl.) Sargent, is well known for its antipyretic effects (Vogel, 1970).

The chemistry of *Magnolia*

The presence of active bitter principles in the bark of magnolia species was recognized more than 150 years ago. In 1842, analyses of an extract from *M. virginiana* provided a volatile oil, a resin, and a crystalline substance named liriodendrine (Griffith, 1847; Hocking, 1997). It may correspond to the known lignan glycoside derivative liriodendrin that was found in many plants. Today, knowledge of the chemistry, biology and pharmacology of the magnolias from the southeastern U.S. is substantial. The main classes of natural products present in the magnolias include phenolic biphenyls and other structural types of lignans as well as sesquiterpene lactones (Fig. 1). For most species, minor amounts of alkaloids, fatty acids, and coumarins have also been reported (Hegnauer, 1990).

Phenylpropanoids

The phenylpropanoids (lignans, norlignans, and neolignans) of magnolia can be found in all non-woody parts of the plant. The different structural types of phenylpropanoids have a wide variety of biological activities including cytotoxic, antitumor, anti-viral, anti-microbial, anti-inflammatory, antifungal, insecticidal, and other properties (Song & Fischer, 1999; Clark et al., 1981). The majority of phenylpropanoids occurring in the southeastern magnolias belong to the biphenyl-type lignans. Honokiol (**1**), mono-*O*-methylhonokiol (**2**) and magnolol (**3**) are found in abundance in the seed oil and the bark of *M. grandiflora* (El-Feraly & Chan, 1978; El-Feraly & Li, 1978; Nitao et al., 1991; Rao & Davis, 1982) and are the major lignans in the leaves of the northern variety of *M. virginiana*. These compounds show anti-fungal and anti-bacterial activities (Nitao et al., 1991). Moreover, magnolol is an inhibitor of the 11β-hydroxysteroid dehydrogenase, a steroid metabolic enzyme which plays a key role in the maintenance of glucocorticoid homeostasis (Horigome et al., 2001). Magnolol seems to act more specifically than the known inhibitor glycyrrhetinic acid, which causes side effects like high blood pressure. The phenolic compounds can also occur as glycosides, such as magnolidin (**4**) and syringin, which are the major glycosidic components in the bark of *M. grandiflora* (Rao, 1975; Rao & Wu, 1978; Rao & Juneau, 1975).

The neolignan and biphenylic compounds produced by the northern variety of *M. virginiana* act as remarkable deterrents protecting the plant against many insect herbivores, although certain silkmoths (Saturniidae) are specialized to using *M. virginiana* leaves as a sole food source (Nitao et al., 1992; Johnson et al., 1996; Johnson, 1998). Lignan derivatives from other species, which had been reported for the treatment of rheumatism (e.g., *Podophyllum*, *Acanthopanax*), seem to be responsible for the anti-rheumatic effect of *Magnolia* rather than the sesquiterpene lactones as previously assumed (Chung & Kim, 1986; Larsen et al., 1989; Heptinstall & Awang, 1998). Some synthetic lignans are in use as anti-pyretic drugs (Kimura et al., 1993). Many lignans show effects of remarkable cytotoxicity (Lee, 1999). Magnolol is strongly inhibitory against proliferation of tumor cells *in vitro* (Wiedhopf et al., 1973; Kim & Ryu, 1999) and it inhibits mouse skin tumor promotion (Konoshima et al., 1991). Recent investigations of the pharmacological properties of magnolol also revealed that it has a cardioprotective effect (Huang et al., 2000). Dibenzocyclooctadiene-type lignans have been found recently in *M. pyramidata* (Song et al., 2000). Due to the diversity of the lignans found in *Magnolia*, it can be expected that further significant activities will be discovered in various biological test systems. It must be anticipated that the aqueous decoction of plant parts and the preparation of alcoholic extracts may result in slightly different patterns of active compounds. In most of the *in vitro* and *in vivo* assays, pure compounds or non-aqueous extracts were tested. Therefore, bioassays of polar constituents of *Magnolia* could reveal new and novel pharmacological effects.

Sesquiterpene lactones

The biological interest in sesquiterpene lactones is mainly directed towards their anti-tumor, anti-leukaemia, and anti-inflammatory properties (Hall et al., 1979, 1980). More recently, their antifungal properties were investigated (Wedge et al., 2000). Among the sesquiterpene lactones, parthenolide, helenalin, and related compounds have been extensively studied (Hehner et al., 1999; Grippo et al., 1992). In *Magnolia* species, as well as in *Liriodendron*, germacranolides such as parthenolide (**5**), costunolide (**6**), and melampolides (e.g., melampomagnolides **7**, **8**) occur in the bark, leaves and fruits (El-Feraly & Chan, 1978; El-Feraly, 1984). Parthenolide has been shown to be the most active principle of feverfew [*Tanacetum parthenium* (L.) Schultz] and Tansy (*T. vulgare* L.), and it is found in many other species of the Asteraceae (Bruneton, 1999). Interestingly, many species of the Asteraceae containing high amounts of sesquiterpene lactones have been used in traditional herbal medicines of indigenous people for similar purposes to the *Magnolia* species (Speck, 1937; Hamel & Chiltoskey, 1975). The parthenolide content of the dried leaves of *M. grandiflora* can be nearly 3%, whereas its content in feverfew is about 0.01–1% (Cutlan et al., 2000). Parthenolide was found to act as a cytostatic (Ross et al., 1999) and it inhibits the activation of the transcription factor NF-κB, which plays a key role in inflammatory processes (Hehner et al., 1999). It has been shown that parthenolide, due to its α-methylene-γ-lactone structure, suppresses lipopolysaccharide-stimulated protein tyrosine phosphorylation in murine macrophages (Hwang et al., 1996). This is a key step in the genesis of inflammatory processes. The sesquiterpene lactones in the bark and leaves are also effective deterrents against insects (Castro et al., 2000) and phytopathogens (Fischer, 1991). Besides parthenolide and costunolide, peroxyparthenolide and peroxycostunolide were also found in *M. grandiflora* (El-Feraly et al., 1977, 1979). These compounds also show considerable cytotoxic activity. The melampolides-type melampomagnolide A (**7**) and B (**8**) are found in the southern magnolia in lower concentrations than parthenolide and costunolide (Macias et al., 1992). They may play a role in allelopathy (Song et al., 1998), but their cytotoxic properties are still unknown. The annual variation pattern in the occurrence of parthenolide, costunolide, and costunolactol in the southern variety of *M. virginiana* has been studied. Parthenolide and costunolactol show an inverse relationship with a parthenolide maximum occurring in July/August (Song et al., 1998). It is significant to point out that the southern and the northern varieties of *M. virginiana* show distinctly different chemical profiles. The southern *M. virginiana* var. *australis* produces sesquiterpene lactones and lacks phenolic lignans (Song et al., 1998), whereas the northern *M. virginiana* var. *virginiana* produces mainly phenylpropanoids but no sesquiterpene lactones (Nitao et al., 1999). Both varieties have different morphological characteristics as well.

Cyclocolorenone (**9**), a sesquiterpene ketone, was found in *M. grandiflora* and shows significant phytotoxic as well as anti-bacterial and anti-fungal activity (Jacyno et al., 1991). This supports the observation that magnolia trees are generally not affected by fungal pathogens. Moreover, the phytotoxic effect shown in the inhibition of plant seedlings (wheat coleoptile assay) may explain the observation that there is essentially no plant growth under *M. grandiflora* trees. Cyclocolorenone is also found in *Ledum* species (Belousova et al., 1989) and in liverworts such as *Bazzania trilobata* (Nagashima et al., 1996). Both *Ledum* and *Bazzania* can build up monocultures in their habitat.

Volatile oils contributing to the floral odors of the southeastern magnolia and tulip tree have been intensively studied with regard to their taxonomic significance, (Thien et al., 1975).

Outlook

The genus *Magnolia* is known to contain a great variety of natural products with significant pharmacological properties. The ethnobotanical records of members of *Magnolia* and related taxa, which were commonly used by indigenous people, correlate well with recent pharmacological data of their pure natural products. Therefore, ethnobotanical data may serve as a point of departure for biological investigations of natural products in the search for new drug leads. Structurally similar substances may be found in different species of *Magnolia*. This seems to support the notion that these species could be used interchangeably for the treatment of similar ailments. However, the presence of different structural types of natural products in the northern and southern varieties of *Magnolia virginiana* (lignans versus sesquiterpene lactones), as well as annual variations of the main constituent in the southern variety, parthenolide, may complicate reliable predictions. Magnolias represent an excellent, fast growing renewable resource and produce large amounts of structurally and biologically interesting compounds. Investigations of *Magnolia* species that have not yet been phytochemically analyzed have shown a great potential for the discovery of new and novel drugs. Additionally, pure compounds isolated previously from *Magnolia* species should be tested in newly developed bioassays for possible leads in medicine and/or agriculture. There still exist opportunities in the discovery of new medicinal drugs from these long used medicinal plants.

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