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Mini Review

Discovery of Novel Alkaloids from *Magnolia* Genus: A Literature Review from 2002-2024

Tegar Achsendo Yuniarta [1*]

Rosita Handayani [2]

[1] Department of Drug Discovery and Development, Faculty of Pharmacy, Universitas Surabaya, Surabaya, East Java, Indonesia
[2] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, East Java, Indonesia

*email: tegar.achsendo@staff.ubaya.ac.id; phone: +6289506181250

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Abstract

The genus *Magnolia*, encompassing hundreds of globally distributed species, has a long-standing history in traditional medicine for treating diverse ailments. These species are particularly renowned for their rich array of bioactive compounds, notably alkaloids. This study provides a comprehensive summary of novel alkaloid compounds identified in various *Magnolia* species within recent years. Through a targeted literature review utilizing Google Scholar and PubMed (2002–2024), we pinpointed nine novel alkaloids and one nitrogen-based compound isolated from four distinct *Magnolia* species. These newly discovered compounds exhibited promising bioactivities, including significant antiplatelet and anti-acetylcholinesterase effects. Structurally, the majority of these compounds belong to the aporphine and benzylisoquinoline classes, although some display unique configurations, such as glycosidic or N-oxide alkaloids. This review aims to bridge a critical gap in the existing scientific literature regarding the comprehensive documentation of novel alkaloid secondary metabolites found across the diverse *Magnolia* genus.

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INTRODUCTION

The genus *Magnolia*, a member of the family Magnoliaceae and order Magnoliales, comprises an estimated 100 to 200 species globally[1,2]. These species are geographically widespread, with a native range spanning East and Southeast Asia, North and Central America, and the West Indies[3]. Throughout history, *Magnolia* plants have been deeply embedded in human culture and traditions, holding significant historical and cultural importance worldwide[4-8].

Many *Magnolia* species are well-regarded for their pharmacological properties and have been staples in traditional medicine systems. For example, various parts of *M. officinalis* and *M. obovata* are extensively used in Chinese and Japanese traditional medicine to treat conditions such as diarrhea and flatulence[4,9]. Similarly, several *Magnolia* species have long been utilized for medicinal purposes by various indigenous tribes in Mexico and Central America[5,10]. Notably, early versions of the United States Pharmacopoeia once listed *M. virginiana* and *M. tripetala* as official drugs for the treatment of malaria, rheumatism, gout, and respiratory ailments[11].

Among the diverse phytochemicals produced by the genus, alkaloids stand out as a particularly exciting group of secondary metabolites. These nitrogenous, cyclic organic compounds are primarily derived from the shikimate or mevalonate metabolic pathways[12]. In *Magnolia* plants, alkaloids are predominantly found with an isoquinoline-type scaffold, though smaller numbers belong to the protoalkaloid group[1]. These compounds have demonstrated a wide array of notable bioactivities, including inotropic, dopaminergic, anti-acetylcholinesterase, and antiviral effects[13-15]. Although Sarker *et al.*[1] published a foundational database on *Magnolia* secondary metabolites including alkaloids in 2002, there remains a critical

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gap in the comprehensive documentation of novel alkaloids discovered since the turn of the century. This mini-review, therefore, aims to bridge this information gap by summarizing the novel alkaloids isolated from *Magnolia* species from the beginning of the 21st century to the present.

SEARCH STRATEGY

A comprehensive literature search was conducted in September 2024 using the Google Scholar and PubMed databases. The search was limited to a timeframe from 2002, corresponding to the publication of the Sarker database[1], to 2024. The specific search terms "novel alkaloid Magnolia" and "new alkaloid Magnolia" were employed to identify relevant studies. Initially, articles were screened based on their titles and abstracts to confirm the presence of newly reported alkaloids from the *Magnolia* genus. Subsequently, selected articles were subjected to a full-text review to extract detailed information on the compounds. This methodical approach ultimately identified a total of six research articles, from which nine novel alkaloid compounds were isolated from four distinct *Magnolia* species. These compounds are further discussed in detail in the following section.

ALKALOIDS SCAFFOLD IN MAGNOLIA

The alkaloids found within the genus *Magnolia* are broadly classified into two primary groups: 'true alkaloids', which possess an isoquinoline core, and protoalkaloids (**Figure 1**). The former group is further subdivided into three distinct scaffolds: aporphine, benzylisoquinoline, and bisbenzylisoquinoline. As of 2002, a total of 40 alkaloids had been identified, comprising six amino alkaloids (protoalkaloids) and 34 isoquinoline-based compounds[1].

The benzylisoquinoline scaffold is a cornerstone chemotype commonly found in various plant alkaloids. These compounds are structurally significant as they serve as the foundational building blocks for the diversification of other *Magnolia* alkaloids. Through intramolecular C-C coupling and intermolecular C-O reactions, benzylisoquinoline structures can be converted into aporphine or bisbenzylisoquinoline scaffolds, respectively[16,17]. Examples of benzylisoquinoline alkaloids found in *Magnolia* include magnocurarine, armepavine, and reticuline[18]. The aporphine scaffold, a 4-H-dibenzo[de,g]quinoline structure, is a derivative of benzylisoquinoline, with its four-ring system and a nitrogen atom located in the B ring[19]. The formation of the C ring from a benzylisoquinoline precursor is catalyzed by the enzyme CYP80G[16]. Aporphine alkaloids are typically found in two forms: aporphine itself, which has a methyl group on the nitrogen atom, and noraporphine, which lacks this methyl group. Representative aporphine alkaloids isolated from the genus include anonaine, asimilobine, liriodenine, nornuciferine, and roemerine[20].

The bisbenzylisoquinoline scaffold, as its name suggests, is composed of two benzylisoquinoline units linked by a biphenyl or an ether bond. The synthesis of this complex structure is catalyzed by CYP80A1[21]. To date, only three bisbenzylisoquinoline compounds with an ether bond—magnolamine, magnoline, and oxycanthine—have been isolated from *Magnolia* species[1]. In contrast, protoalkaloids, also known as amino alkaloids, are distinguished by a nitrogen atom positioned outside the heterocyclic ring, thus not classifying them as true heterocyclic compounds[22]. This class of alkaloids often serves as a precursor for the formation of larger, more complex molecules. Salicifoline is one of the six protoalkaloids frequently identified across numerous *Magnolia* species[12].

NEW ALKALOIDS FOUND IN MAGNOLIA (2002-2024)

Magnolia obovata

Magnolia obovata (Thunb.), a species native to Japan that can grow up to 30 meters, has a rich cultural history and has spread to continents like Eurasia and North America. Known as the Japanese big-leaf *Magnolia*, its dried bark has been used in traditional medicine and its leaves to wrap food[4,23]. While many of its alkaloid compounds are well-documented, a few novel ones have been recently isolated and characterized.

In a 2003 study, two new alkaloids, N-acetylxylopine and N-formylanonaine, were successfully isolated from a methanol extract of *M. obovata* leaves[24]. Both compounds, along with the previously known N-acetylanonaine, belong to the aporphine

class of alkaloids. The structural difference between these two new compounds lies in their carbonyl group and the C9 position (**Figure 2**). When tested for their effect on platelet aggregation, N-acetylxylopine demonstrated a dual mechanism by inhibiting both TXA2 production and its receptor binding, whereas N-formylanonaine acted solely by suppressing TXA2 production. It is important to note that while they are new isolates from *M. obovata*, these compounds are not entirely novel as they have been found in other species, such as *Talauma gitingensis*[25], *Hexalobus monopetalus*[26], and *Tinospora crispa*[27]. Further research has revealed additional bioactivities for these compounds; N-acetylxylopine has shown potential as an antinociceptive agent in the peripheral nervous system[28], while N-formylanonaine exhibits micromolar activity as a mushroom tyrosinase inhibitor and radical scavenger[29].

A separate study successfully isolated another novel alkaloid, isolaureline N-oxide, from a chlorocarbon-based solvent extract of *M. obovata* leaves[30]. This compound is a N-oxide alkaloid that is structurally related to isolaureline, also an aporphine. The presence of a nitroso moiety distinguishes this alkaloid, which is formed through an oxidation reaction during the alkaloid's biosynthesis[31].

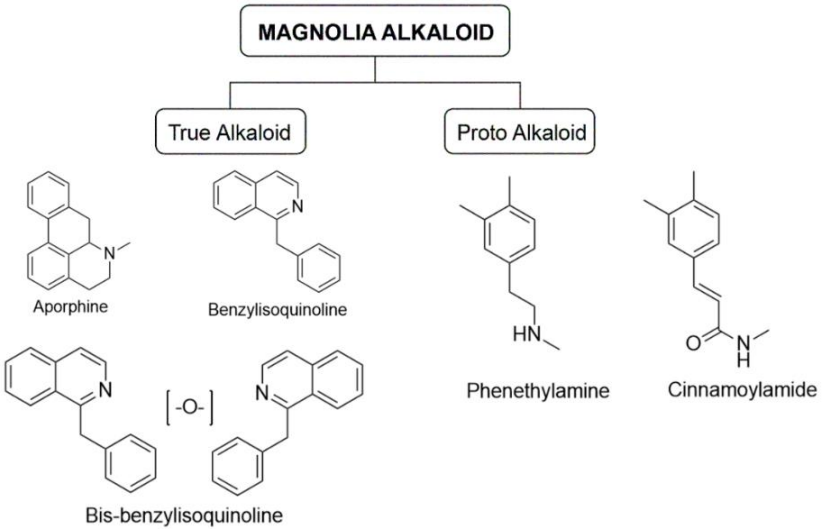


Figure 1. Structure of various chemotypes of alkaloid found in *Magnolia* genus.

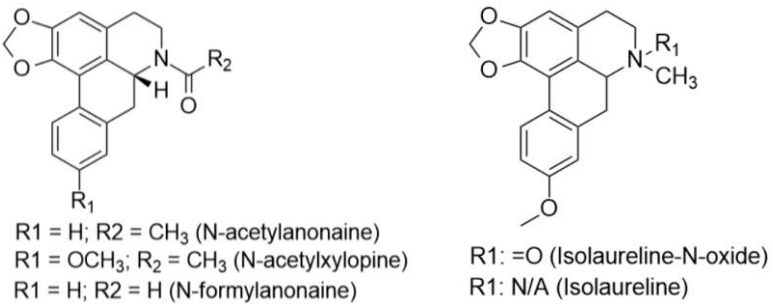
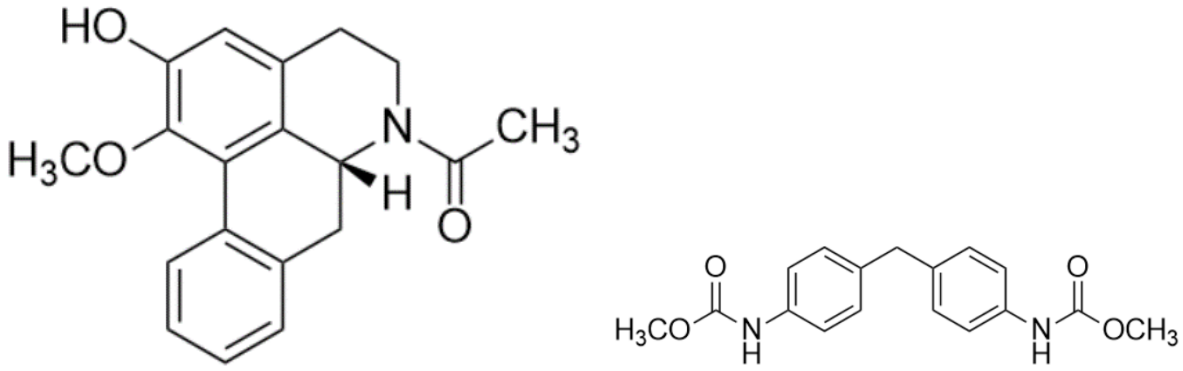


Figure 2. 2D structure of N-acetylanonaine, N-acetylxylopine, and N-formylanonaine (**a**), as well as isolaureline N-oxide, and isolaureline (**b**).

Magnolia kachirachirai

Magnolia kachirachirai Dandy is an endangered tree species endemic to southeastern Taiwan, with populations facing fragmentation and habitat loss due to human encroachment[32]. While a variety of alkaloids were previously isolated from this plant in the 1960s[1], more recent research has continued to uncover novel compounds. In 2011, a study successfully isolated and characterized a new aporphine alkaloid named kachirachiranine from the plant's bark. The extraction process involved methanol, followed by a chloroform-water partition, with the target compound being isolated from the chloroform phase[33]. Structurally, kachirachiranine is closely related to N-formylanonaine, as both contain a formyl group attached to a nitrogen atom (**Figure 3**). The key structural difference lies in the absence of a methylenedioxy group in the A ring of kachirachiranine.

Another unique compound, dimethyl 4,4'-methylenebis(4,1-phenylene)diurethane, was also isolated for the first time from a natural source in this study[33]. Due to the position of its exocyclic nitrogen atom, this compound can be provisionally categorized as a protoalkaloid. However, its classification as a true alkaloid remains ambiguous, as the definition of alkaloids is often tied to their specific biosynthetic pathways[22]. This compound and its derivatives have since been identified in other plant species, such as *Iphiona aucheri*[34].

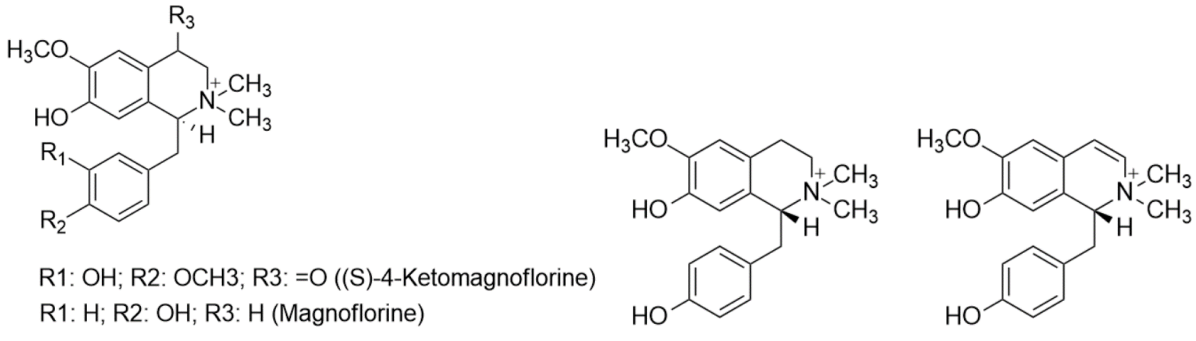


a **b**

Figure 3. 2D structure of kachirachiraine (**a**) and dimethyl 4,4'-methylenebis(4,1-phenylene)diurethane (**b**).

Magnolia officinalis

Magnolia officinalis Rehd. et Wils, a tree native to the forests of northern and central China, is recognized for its two subspecies, *M. officinalis* subsp. *officinalis* and *M. officinalis* subsp. *biloba*, which exhibit minor ecological distinctions[35]. This species has been classified as endangered, primarily due to the widespread illicit harvesting of its bark, a key ingredient in the traditional Chinese medicine preparation known as Houpu[9,32]. In a 2013 study, researchers successfully isolated two novel alkaloids from the ethanolic bark extract of the plant[18]. The isolation process involved an initial chloroform extraction, followed by sequential purification using ion exchange and column chromatography of the aqueous fraction. The two compounds, (S)-4-ketomagnoflorine and (R)-3,4-dehydromagnocurarine, are structurally related to the well-known alkaloids magnoflorine and magnocurarine. Their unique features include the presence of a carbonyl group and a double bond in the B-ring, respectively (**Figure 4**). Interestingly, (R)-3,4-dehydromagnocurarine has also been reported in another plant species, *Portulaca oleacera*[36].



a **b** **c**

Figure 4. 2D structure of (S)-4-ketomagnoflorine and magnoflorine (**a**), magnocurarine (**b**), and (R)-3,4-dehydromagnocurarine (**c**).

A recent study successfully isolated a novel alkaloid, magnofficine, from an ethanolic extract of *M. officinalis* bark. The isolation procedure involved a unique approach where the dried plant material was first treated with aqueous hydrochloric acid, followed by a cationic exchange step. The resulting aqueous extract was then diluted with ethanol, concentrated, and subsequently partitioned with dichloromethane before undergoing column chromatography for purification[37]. Structurally, magnofficine is a member of the aporphine class of alkaloids, distinguished by a unique N-methyltyramine moiety attached to ring A of its structure (**Figure 5**).

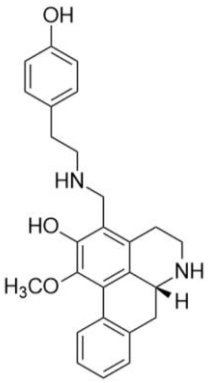
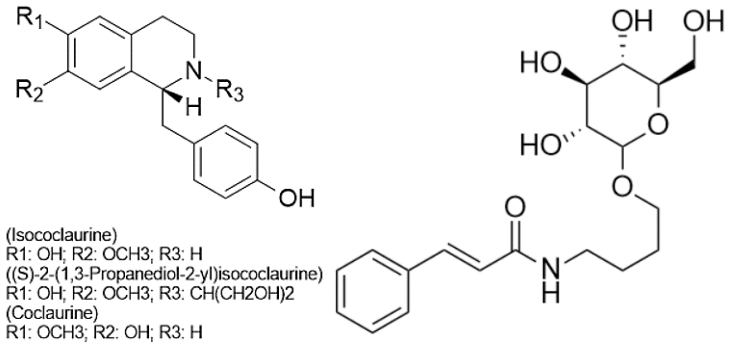


Figure 5. 2D structure of magnofficine.

Magnolia biondii

Magnolia biondii Pamp. is a tree species that is widely cultivated in northern China and is known for its traditional medicinal uses, including analgesic, anti-inflammatory, antibacterial, and anti-allergy properties[38]. In a significant study from 2020, two novel alkaloids were successfully isolated from an acetone extract of its flower buds: 4,4'-dihydroxy-3-methoxy-paucine-4'-O-β-D-glucopyranoside and (S)-2-(1,3-propanediol-2-yl)-isococlaurine (**Figure 6**). The isolation process involved sequential solvent extraction followed by column chromatography, with the butanol fraction yielding these two distinct compounds[39]. The first compound is particularly noteworthy as it represents the first glycosidic alkaloid discovered in the *Magnolia* genus. It is a paucine cinnamoylamide alkaloid, found in *Nicotiana tabacum* flower[40], structurally similar to magnolamide but uniquely featuring a monosaccharide moiety[1]. The second novel compound is a derivative of isococlaurine, an alkaloid analogue that, while found in other plant species, had not previously been reported in *Magnolia*[41,42]. Both of these compounds were evaluated for their inhibitory activity against acetylcholinesterase and demonstrated promising activity in the micromolar range[39].



a **b**

Figure 6. 2D structure of (S)-2-(1,3-propanediol-2-yl)-isococlaurine, isococlaurine, and coclaurine (**a**) as well as 4,4'-dihydroxy-3-methoxy-paucine-4'-O-β-D-glucopyranoside (**b**).

CONCLUSION

This review systematically summarizes the discovery of nine novel alkaloids and one nitrogen-based compound isolated from various *Magnolia* species over the past two decades. Our analysis confirms that while many of these compounds adhere to established structural scaffolds like aporphine and benzylisoquinoline, a subset exhibits unique frameworks, including glycosidic alkaloids and N-oxide aporphines. Beyond their structural novelty, several of these compounds demonstrate promising biological activities, such as antiplatelet and acetylcholinesterase inhibitory effects. These findings underscore the significant potential of the *Magnolia* genus as a source of novel secondary metabolites with a wide range of bioactivities. Furthermore, this review contributes to a more comprehensive understanding of the alkaloid metabolite profile within *Magnolia* plants, which can inform and guide future phytochemical and pharmacological research.

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AUTHORS' CONTRIBUTION

Conceptualization: Tegar Achsendo Yuniarta, Rosita Handayani
Data curation: Tegar Achsendo Yuniarta, Rosita Handayani
Formal analysis: Rosita Handayani
Funding acquisition: -
Investigation: Tegar Achsendo Yuniarta, Rosita Handayani
Methodology: Tegar Achsendo Yuniarta
Project administration: Tegar Achsendo Yuniarta
Resources: Tegar Achsendo Yuniarta, Rosita Handayani
Software: -
Supervision: -
Validation: -
Visualization: Tegar Achsendo Yuniarta
Writing - original draft: Tegar Achsendo Yuniarta, Rosita Handayani
Writing - review & editing: Tegar Achsendo Yuniarta

DATA AVAILABILITY

SMILES structures of magnolia alkaloids, including those in the article are available in CSV format on GitHub (https://github.com/tegarachsendo/magnodb).

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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