Daphniphyllum Alkaloids: Recent Findings on Chemistry and Pharmacology

Haifeng Wu1, Xiaopo Zhang1, Lisheng Ding1, Shilin Chen1,3, Junshan Yang1, Xudong Xu1
1 Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
2 Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, China
3 Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

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- Daphniphyllum
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Abstract

The unique polycyclic fused ring systems of Daphniphyllum alkaloids, along with their extensive bioactivities, make this family of alkaloids especially attractive targets for total synthesis and biogenetic studies. Successive discoveries of new alkaloids with unprecedented skeletons have made a great contribution to structural diversities of alkaloids elaborated by plants of the genus Daphniphyllum. By the end of 2008, more than 200 alkaloids belonging to 14 different skeletal types have been isolated from different parts of plants of thirteen Daphniphyllum species. These alkaloids show cytotoxic, antioxidant, vasorelaxant, and antiplatelet activating factor effects. The plausible biosynthetic pathways for Daphniphyllum alkaloids have been proposed and biomimetic total syntheses of some alkaloids completed. To provide an update of the previous reviews published in 2009, new structures, synthesis, and bioactivity of Daphniphyllum alkaloids reported in recent years are presented in this article. In the meantime, an additional 54 novel alkaloids have been isolated and identified. Among them, some possess unprecedented frameworks. Several inspired organic syntheses were completed.

Introduction

Daphniphyllum alkaloids, triterpenoid alkaloids with highly variable polycyclic skeletons, are characteristic constituents of the genus Daphniphyllum. Daphniphyllum, referring to Daphne and leaf in Greek, is the sole genus in the Daphniphyllaceae family, including about 30 species of dioecious evergreen trees and shrubs mainly distributed from India to Japan and from central China to New Guinea [1]. About ten species were found in China, some of which are traditionally used in the treatment of asthma, rheumatism, and snakebites. The isolation of the first C30-type Daphniphyllum alkaloid, daphnimarine from D. macropodum, was reported by Yagi in 1909 [2]; however, the structure remained unresolved. The systematic investigation of Daphniphyllum alkaloids began in the 1960s. Three new alkaloids, daphnicaline, daphnicadine, and daphnicamine, were isolated from the seeds of D. calycinum, Niu-Er-Fon (in Chinese) by Fang et al. [3]. Niu-Er-Fon is a poisonous plant growing in southern China. Its seed oils are only used as biodiesel because of toxicity. The authors measured the melting points and proposed the molecular formulae of these alkaloids. Subsequently, an investigation of the Hong Kong species of D. calycinum and D. glaucescens resulted in the isolation of another three new alkaloids, calycine, glaucescine, and glaucescinine [4]. The 1H-NMR spectrum of calycine was reported. In 1966, the structures of several alkaloids from D. macropodum were determined with X-ray analysis of their hydrobromide by Hirata et al. [5–7]. Since then, more than 200 Daphniphyllum alkaloids have been isolated from the genus Daphniphyllum until the end of 2008. The initial five skeletal types have been expanded to 14 main types. These alkaloids show cytotoxic, antioxidant, vasorelaxant, and antiplatelet activating factor (PAF) effects. The unusual ring systems of Daphniphyllum alkaloids, together with their biological aspects, make this family of alkaloids especially attractive targets for total synthesis and biogenetic studies. In 1986, the first total synthesis of a Daphniphyllum alkaloid, (+)-methyl homodaphniphyllate, was completed by Heathcock et al. [8]. Subsequently, a series of total syntheses were reported [9–11]. A biosynthetic pathway for Daphniphyllum alkaloids was also proposed and several biomimetic total syntheses of some Daphniphyllum alkaloids were conducted by Heathcock.

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and coworkers [12–18]. Considering structural peculiarities of Daphniphyllum alkaloids, Yamamura et al. successively reviewed the isolation, structural elucidation, and chemical and biological properties of Daphniphyllum alkaloids in 1975 and 1986 [19, 20]. Thereafter, the application of modern chromatographic and spectroscopic techniques greatly facilitated the further discoveries of Daphniphyllum alkaloids. In 2003, Kobayashi and Morita summarized reports published during the 15-year period between 1987 and 2002 [21]. From then on, 66 new alkaloids from 11 species of Daphniphyllum had been reported until 2007, and about two-thirds of these alkaloids were isolated from the Chinese species of Daphniphyllum by Chinese researchers. Li and Guo published a mini-review highlighting progress over that period [22]. In 2009, the two comprehensive reviews were published, respectively [23, 24]. Both thoroughly summarized chemical structures, biological activities, biosynthesis, and organic synthesis of all reported Daphniphyllum alkaloids. Since then, an additional 54 novel alkaloids have been isolated from nine species of the Daphniphyllum genus. Some of these alkaloids belong to the known skeleton, while others possess unprecedented frameworks. In addition, several elegant organic syntheses were also completed. To provide an update of the previous reviews, this article focuses on new structures, synthesis, and biological activities of Daphniphyllum alkaloids reported in the past few years (2009–present).

**Phytochemistry**

Daphniphyllum alkaloids possess complex polycyclic ring systems represented by a fused pentacyclic, hexacyclic, heptacyclic, or octacyclic skeleton or an aza-adamantane nucleus. Most of these alkaloids were derived from six molecules of the mevalonic acid pathway via a squalene-like intermediate except for a few that originated from amino acids. According to the structural classification proposed by Kobayashi, Daphniphyllum alkaloids are divided into 14 main structural types including daphniphyllines, secodaphniphyllines, yuzurimines, daphnilactone A, daphnilactone B, yuzurines, bukittinggines, daphnezomines, daphnicyclidins, daphmanidins, daphniglaucins, calyciphyllines, paxdaphnines, and daphlongeranines A and B, as shown in Fig. 1. The classification of recently isolated alkaloids basically follows that of previous reviews, but the newly obtained skeletons have been added (Table 1).

**Fig. 1** Skeletons of Daphniphyllum alkaloids.
Yuzurimine-type alkaloids contain 22 carbon atoms commonly with a C-9–C-10 double bond, and C-22 is mostly a methyl ester of a carboxyl group. Recently, nine new yuzurimine-type alkaloids, calycinumine A (4) [28], 9,10-epoxycalycinine A (5) [27], calycinumine B (6) and K (7) [29], 4,21-deacetyl-deoxyyuzurimine (8) [30], daphnezomine T (9) [26], daphhimalenine B (10) [31], daphangustifoline B (11) [32], and daphhimalenine C (12) [33] have been reported (Fig. 2). Calycinumine A (4) is the first example of a C-22-nor yuzurimine-type alkaloid and its structure was confirmed by a single-crystal X-ray diffraction. Macropodumines J (6) and K (7) [29], 4,21-deacetyl-deoxyyuzurimine (8) [30], daphnezomine T (9) [26], daphhimalenine B (10) [31], daphangustifoline B (11) [32], and daphhimalenine C (12) [33] have been reported (Fig. 2). Calycinumine A (4) is the first example of a C-22-nor yuzurimine-type alkaloid and its structure was confirmed by a single-crystal X-ray diffraction. Macropodumines J (6) and K (7) [29], 4,21-deacetyl-deoxyyuzurimine (8) [30], daphnezomine T (9) [26], daphhimalenine B (10) [31], daphangustifoline B (11) [32], and daphhimalenine C (12) [33] have been reported (Fig. 2).

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kaloid without a branched C1 unit at C-5. Daphangustifoline B (11) is the first alkaloid with a benzyl group in the genus of *Daphniphyllum*. Biogenetically, daphnezomine T (9) might be generated from an intermediate-like portdamacrine B, which could be derived from yuzurimine by the elimination of acetic acid from C-3–C-4 and hydrolysis of acetyl ester at C-21, via the oxidative decarboxylation of the aforementioned intermediate and subsequent oxidation might yield daphnezomine T (9) (Fig. 3).

**Yuzurine**

Different from other *Daphniphyllum* alkaloids with 22 C-atoms, yuzurine-type alkaloids have 23 carbons in their frameworks with a methyl group attached to the nitrogen atom. In the last few years, nineteen yuzurine-type alkaloids, 17-hydroxydaphnigraciline (13) [25], daphlongamines I (14) and J (15) [34], daphlongeranines F (16) [35], daphlongeranines D (17) and E (18) [36], daphmalenines A (19) and B (20) [37], daphnioldhamine A (21) [38], and daphmacromines A–J (22–31) [39], have been obtained (Fig. 4). Daphmalenines A (19) and B (20) are biogenetically related yuzurine-type *Daphniphyllum* alkaloids of the rare (14R,15S) series, possessing an unusual penta- or tetracyclic ring system, respectively. Daphmalenine B (20) is the first seco-10,17-yuzurine-type *Daphniphyllum* alkaloid. The absolute configurations of daphmalenines A (19) and B (20) were determined on X-ray diffraction by using the Flack parameter and computational methods, respectively. Daphmalenines A (19) and B (20) could be originated from the common imine intermediate, which involves an alternative route during the process of the formation of the C-14–C-15 bond. Daphnioldhamine A (21) might be generated from the common intermediate, which involved an oxidative reaction to form the ether linkage between C-21 and C-9, and the C=O group at C-11. Daphnioldhamine A (21) is the first *Daphniphyllum* alkaloid with a transannular effect and was easily tautomerized under acidic or alkaline conditions. The structure of daphmacromine A (22) was confirmed by single-crystal X-ray diffraction.

**Bukittinggine**

Two new bukittinggine-type alkaloids, dapholdhamine A (32) [40] and angustimine (33) [41], were isolated (Fig. 5). Dapholdhamine A (32) is closely related to bukittinggine. Angustimine (33) is an intramolecular salt featuring an unprecedented hexacyclic fused skeleton through the cleavage of a C-6–C-7 bond and the formation of a C-6–N bond. The biosynthetic origin of angustimine (33) could be traced back to a bukittinggine-type alkaloid, caldaphnidine P, which would give an intermediate after hydrolysis yielding angustimine (33) via a cascade of chemical reactions by involving the key steps of a C-6–C-7 bond cleavage and a C-6–N bond formation.

**Daphnezomine A**

Daphnezomine A-type alkaloids possess a unique aza-adamantane core with an amino ketal bridge. Dapholdhamine B (34) was a zwitterion isolated from the leaves of *D. oldhami* [40] (Fig. 5).

**Daphnezomine F**

Daphnezomine F-type alkaloids possess a characteristic 1-azabicyclo[5.2.2]undecane ring system. Two new daphnezomine F-type alkaloids, daphnezomine U (35) [26] and daphlongeranine C (36) [36], were obtained (Fig. 5). Daphlongeranine C (36) is the first daphnezomine F-type alkaloid obtained from the fruits of *D. longeracemosum*.

**Daphnezomine L**

Two new daphnezomine L-type alkaloids, daphnezomine L methyl ester (37) [25] and calycinumine B (38) [28], were reported (Fig. 5). Daphnezomine L methyl ester (37) is structur-
ally close to a hypothetical biogenetic intermediate between the seco-daphniphylline and daphniphylline skeletons. Calycinumine B features an unprecedented heteroatom-containing adamantane-like western hemisphere of the daphnezomine L-type alkaloid.

Daphnicyclidin

Daphnicyclidin-type alkaloids are a group of rare C-22 fused hexa- or pentacyclic nor-Daphniphyllum alkaloids. Five new daphnicyclidin-type alkaloids, dapholdhamines C and D (39), caldaphnidine H (40), angustifolimine (42) [41], and paxiphylline C (43) [43], were reported (Fig. 5). Angustifolimine (42) represents the second diamino Daphniphyllum alkaloid. Paxiphylline C (43) was the first Daphniphyllum alkaloid with an O-methylcarbonate group. Recently, the absolute configurations of two known compounds, macropodumines B and C, were determined by comparison between the experimental CD spectra and the TDDFT-calculated ones [44].
Daphniglaucin A
A new daphniglaucin A-type alkaloid, daphangustifoline A (44), was isolated from the whole plant of *D. angustifolium* [32] (Fig. 5). Daphangustifoline A (44) was a zwitterion containing a 1-azoniatetracyclo[5.2.2.01,6.04,9]undecane ring system.

Calyciphylline A
Calyciphylline A-type alkaloids are a group of rare C-22 fused hexacyclic nor-*Daphniphyllum* alkaloids, biosynthesized by the fission of the C-1–N bond of a yuzurimine-type alkaloid and the formation of a new bond between C-4 and nitrogen. Calyciphylline A-type alkaloids possess a 6/5/5/7/5/6-membered ring system and an oxo group on C-1. Eight new calyciphylline A-type alkaloids, subdaphnidine A (45) [25], daphlongamines E–G (46–48) [45], daphhimalenine D (49) [33], and paxiphyllines D (50) and E (51) [43], were reported (Fig. 6). Paxiphyllines D (50) and E (51) are the N-oxide form of longistylumphylline A and daphnilongeranine A, respectively.

Calyciphylline B
Calyciphylline B-type alkaloids are a group of rare C-22 fused-pentacyclic yuzurimine-type nor-*Daphniphyllum* alkaloids. Most of them contained a six-member lactone ring. A new calyciphylline B-type alkaloid, daphlongamine H (52), was reported (Fig. 6) [45].

Others
In addition, two new structural types are reported. Daphhimalenine A (53), closely related to the yuzurimine-type alkaloids, was obtained from *D. himalense* [31]. Daphhimalenine A (53), with a rearranged C-21 skeleton, contains a unique 1-azabicyclo[5.2.1]decane ring system with the cleavage of the C-1–C-8 bond (Fig. 6). The absolute configuration of daphhimalenine A (53) was assigned by computational methods. Daphhimalenine A (53) was biogenetically related to daphhimalenine B (10). After dehydration, daphnezomine T (9) could further convert to the key carbonium intermediate C, which finally underwent a carbocation rearrangement to afford a 1-azabicyclo[5.2.1]decane ring system in daphhimalenine A (53) (Fig. 3). Daphenylline (54), closely related to the calyciphylline A-type alkaloids, was obtained from *D. longerasemus* (Fig. 5) [46]. Daphenylline (54), possessing an unprecedented rearranged 22-nor-calyciphylline skeleton, has an expanded neohexatomic ring with C-13 connected to C-1 instead of C-8 as usual. The absolute configuration of daphenylline (54) was elucidated on the basis of computational approaches. Daphenylline (54) might be biosynthesi-
cally generated from daphnilongeranin C, which could be reduced and dehydrated to form a ring expanded intermediate E via the Wagner-Meerwein rearrangement. Then the intermediate F could be involved in the elimination of the carboxyl group at C-21 by decarboxylase to generate intermediates G or H with a double bond between C-13 and C-14 or between C-14 and C-15, followed by one or two steps of syn-[1,3] sigmatropic rearrangement to yield daphenylline (54) (Fig. 7).

Synthesis

The intriguing structures of *Daphniphyllum* alkaloids have been challenging organic chemists since the first *Daphniphyllum* alkaloid was unambiguously elucidated in the 1960s. The way in which the nitrogen atom(s) in *Daphniphyllum* alkaloids is (are) incorporated in nature can inspire the synthetic chemist to pursue a biomimetic approach [47]. Heathcock’s biomimetic synthesis of the daphniphylline alkaloids is state-of-the-art work with a characteristic elegance and simplicity reminiscent of nature’s approach to formidable structures [48]. Total synthesis has still been assuming a serious role in biology and medicine. A new synthetic strategy is increasingly focused on preparing complex molecules in the most efficient manner possible. In 2011, the first total synthesis of a daphmanadin A-type alkaloid, (+)-daphmanadin E, was reported by Weiss et al. [49]. Daphmanadin A-type alkaloids possess an unprecedented hexacyclic structure including a fused dihydropyrrole along with an embedded deca- or octahydrocyclopentazulene (oxide) around a central bicyclo[2.2.2]octane. The authors used an elegant strategy involving rapid access to an enantiomerically pure bicyclo[2.2.2]octadione and elaboration around its periphery by implementing two Claisen rearrangements, a diastereoselective hydroboration and a cobalt-catalyzed enolate R-vinylation [51]. Li and coworkers constructed a [6–6–6–5] bridged ABCD tetracyclic skeleton via a stereoselective intramolecular 2-azaallyl anion cycloaddition in only 8 steps [52]. Additionally, Yang et al. completed the construction of 6-substituted spiro[4.5]decane, an important structural motif, using the tandem semipinacol-type 1,2-carbon migration/aldol reaction [53].

Cascade reactions are a useful method for the construction of polycyclic skeletons, which are important cores for biological activities [54]. Coldham et al. reported the first synthesis of the core ring system of the yuzurinine-type alkaloids by a cascade of condensation, cyclization, and intramolecular dipolar cycloaddition reactions [55]. In another study, a similar approach was successfully extended to bridged tricyclic compounds, yuzurinine B, daphnilactone B, and bukittinggine [56]. In 2009, two reports about asymmetric synthesis of cores common in daphnicycladin-A-type alkaloids were published. Ikeda and coworkers first described an enantiocontrolled access to the tricyclic intermediate corresponding to the BCD portion [6–5–7] of daphnicycladin A through the highly diastereoselective conjugate addition of nitromethane, an Ireland-Claisen rearrangement, and a tandem acyliminium/Mannich-type reaction [57]. In another report, theaza-Cope-Mannich reaction and ring-closing metathesis were used as key steps in the assembly of intermediates containing rings A–D [58].

In addition, a new type of template-assisted cyclization for the formation of crownaphane bearing the azaheterocyclic fragment with the same core structure of 2-azabicyclo[2.2.2]oct-2-ene was described [59]. An asymmetric synthesis of the ABCD ring system of daphnilactone B is also reported [60]. A tricyclic substructure of the tetracyclic nitrogen core of the daphniglaucins was synthesized by an oxidative activation of the allyl side chain of a bicyclo[1.1.0]butylmethylamine, a spontaneous intramolecular formal Alder-ene reaction, and a selective cyclization of a triol intermediate [61].
Bioactivities

The cytotoxicity of some *Daphniphyllum* alkaloids against different human tumor cell lines was evaluated (Table 2). Daphnangustifoline B (12) showed weak inhibition of tumor growth against the HL-60 (human promyelocytic leukemia), MCF-7 (human breast adenocarcinoma), and A549 (human lung adenocarcinoma) cell lines [32]. Daphnilongeridine exhibited cytotoxicity against several tumor cell lines with IC50 values in the range of 2.4–9.7 µM and against the HMEC (human microvascular endothelial) cell line with an IC50 of 2.7 µM [25]. In addition, daphmaclycines A–J (23–32) in vitro displayed pesticide activities against brine shrimp (*Artemia salina*) at 100 mg/L, and the corrected lethality ranged from 40.98% to 70.90%. Two known alkaloids, deoxyyuzurimine and yuzurimine C, showed higher corrected lethality values of 81.81% and 80.56%, respectively [39]. It is likely that the *Daphniphyllum* alkaloids play an important role in the protection of the plants which produce them against attacking insects [29]. Daphtedinine C exhibited the most potent insecticidal effect against *Plutella xylostella* and a moderate effect against *Heliothis virescens*, while deoxyyuzurimine and daphnicyclidin D showed weak insecticidal effects against *Aphis gossypii*. Recently, Zhang et al. found that deoxycalyciphylline B was mainly responsible for the hepatotoxicity of *D. calycinum* [62].

Conclusions

So far, more than 250 alkaloids have been reported from 15 species of the *Daphniphyllum* genus. It is highly likely that further phytochemical investigations on the other species will result in many more isolations of *Daphniphyllum* alkaloids with structural variations. Total syntheses of *Daphniphyllum* alkaloids are now underway, and the biosynthesis of *Daphniphyllum* alkaloids requires thorough studies to elucidate the intermediates and the relevant enzymes. The biological activities of *Daphniphyllum* alkaloids should be extensively investigated. In addition, plants of the genus *Daphniphyllum* produce structurally diverse and complex alkaloids, which should play an important role for the plant itself from the evolutionary perspective.
role of these alkaloids in the life cycle of the plant should also be paid much more attention.

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Conflict of Interest

The authors have no conflicts of interest.

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