

Daphniphyllum Alkaloids: Recent Findings on Chemistry and Pharmacology

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Key words

- *Daphniphyllum*
- Daphniphyllaceae
- alkaloids
- synthesis
- biological activity

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, daphnimacrine from *D. macropodum*, was reported by Yagi in 1909 [2]; however, the structure remained unresolved. The systematic investigation of *Daphniphyllum* alkaloids began in the 1960 s. 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 al-

kaloids. 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 glaucescine [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

received April 7, 2013
revised June 22, 2013
accepted Sept. 16, 2013

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DOI <http://dx.doi.org/10.1055/s-0033-1351024>
Published online November 8, 2013
Planta Med 2013; 79: 1589–1598 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0032-0943

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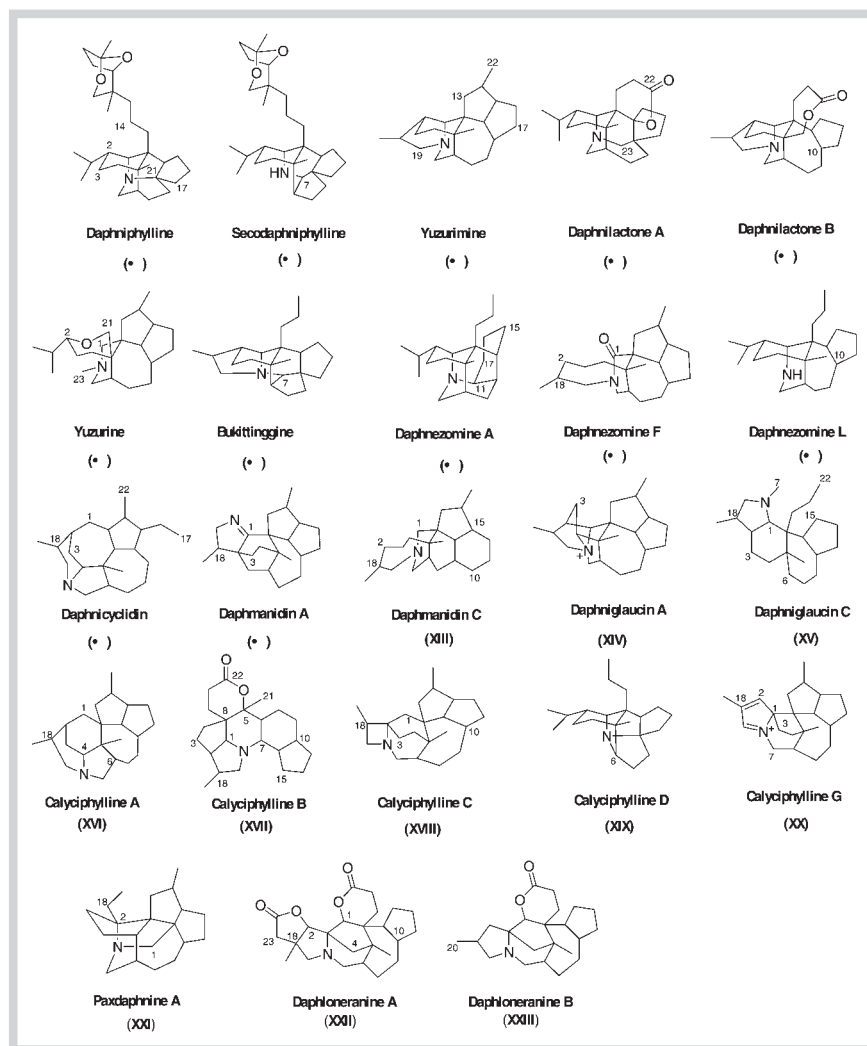


Fig. 1 Skeletons of *Daphniphyllum* alkaloids.

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**).

Daphniphylline

Daphniphylline-type alkaloids possess 22 carbon cores with or without the C8 side chain. The C8 unit consists of 6-oxabicyclo[3.2.1]octane or 2,8-dioxabicyclo[3.2.1]octane. Three novel daphniphylline-type alkaloids, 11-hydroxycodaphniphylline (**1**) [25], daphnezomine V (**2**) [26], and homodaphniphyllate (**3**) lacking

Table 1 *Daphniphyllum* alkaloids reported in recent years.

No.	Compounds	Sources	Parts	Ref.
1	11-Hydroxycodaphniphylline	<i>D. subverticillatum</i> Merr.	leaves	[25]
2	Daphnezomine V	<i>D. humile</i> Maxim. ex Franch.	leaves and branches	[26]
3	Homodaphniphyllate	<i>D. calycinum</i> Benth.	stems and leaves	[27]
4	Calycinumine A	<i>D. calycinum</i> Benth.	twigs	[28]
5	9,10-Epoxycalycinine A	<i>D. calycinum</i> Benth.	stems and leaves	[27]
6	Macropodumine J	<i>D. macropodum</i> Miq.	bark	[29]
7	Macropodumine K	<i>D. macropodum</i> Miq.	bark	[29]
8	4,21-Deacetyl-deoxyyuzurimine	<i>D. macropodum</i> Miq.	bark	[30]
9	Daphnezomine T	<i>D. humile</i> Maxim. ex Franch.	leaves and branches	[26]
10	Daphhimalenine B	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[31]
11	Daphangustifoline B	<i>D. angustifolium</i> Hutch.	whole plants	[32]
12	Daphhimalenine C	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[33]
13	17-Hydroxydaphnigraciline	<i>D. subverticillatum</i> Merr.	leaves	[25]
14	Daphlongamine I	<i>D. longeracemosum</i> Rosenth.	fruits	[34]
15	Daphlongamine J	<i>D. longeracemosum</i> Rosenth.	fruits	[34]
16	Daphlongeranine F	<i>D. longeracemosum</i> Rosenth.	fruits	[35]
17	Daphlongeranine D	<i>D. longeracemosum</i> Rosenth.	fruits	[36]
18	Daphlongeranine E	<i>D. longeracemosum</i> Rosenth.	fruits	[36]
19	Daphmalenine A	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[37]
20	Daphmalenine B	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[37]
21	Daphnioldhamine A	<i>D. oldhami</i> (Hemsl.) Rosenth.	fruits	[38]
22	Daphmacromine A	<i>D. macropodum</i> Miq.	leaves and stems	[39]
23	Daphmacromine B	<i>D. macropodum</i> Miq.	leaves and stems	[39]
24	Daphmacromine C	<i>D. macropodum</i> Miq.	leaves and stems	[39]
25	Daphmacromine D	<i>D. macropodum</i> Miq.	leaves and stems	[39]
26	Daphmacromine E	<i>D. macropodum</i> Miq.	leaves and stems	[39]
27	Daphmacromine F	<i>D. macropodum</i> Miq.	leaves and stems	[39]
28	Daphmacromine G	<i>D. macropodum</i> Miq.	leaves and stems	[39]
29	Daphmacromine H	<i>D. macropodum</i> Miq.	leaves and stems	[39]
30	Daphmacromine I	<i>D. macropodum</i> Miq.	leaves and stems	[39]
31	Daphmacromine J	<i>D. macropodum</i> Miq.	leaves and stems	[39]
32	Dapholdhamine A	<i>D. oldhami</i> (Hemsl.) Rosenth.	leaves	[40]
33	Angustimine	<i>D. angustifolium</i> Hutch.	twigs	[41]
34	Dapholdhamine B	<i>D. oldhami</i> (Hemsl.) Rosenth.	leaves	[40]
35	Daphnezomine U	<i>D. humile</i> Maxim. ex Franch.	leaves and branches	[26]
36	Daphlongeranine C	<i>D. longeracemosum</i> Rosenth.	fruits	[36]
37	Daphnezomine L methyl ester	<i>D. subverticillatum</i> Merr.	leaves	[25]
38	Calycinumine B	<i>D. calycinum</i> Benth.	twigs	[28]
39	Dapholdhamine C	<i>D. oldhami</i> (Hemsl.) Rosenth.	leaves	[40]
40	Dapholdhamine D	<i>D. oldhami</i> (Hemsl.) Rosenth.	leaves	[40]
41	Caldaphnidine H	<i>D. calycinum</i> Benth.	leaves and stems	[42]
42	Angustifolimine	<i>D. angustifolium</i> Hutch.	twigs	[41]
43	Paxiphylline C	<i>D. paxianum</i> Rosenth.	twigs and leaves	[43]
44	Daphangustifoline A	<i>D. angustifolium</i> Hutch.	whole plants	[32]
45	Subdaphnidine A	<i>D. subverticillatum</i> Merr.	leaves	[25]
46	Daphlongamine E	<i>D. longeracemosum</i> Rosenth.	leaves	[45]
47	Daphlongamine F	<i>D. longeracemosum</i> Rosenth.	leaves	[45]
48	Daphlongamine G	<i>D. longeracemosum</i> Rosenth.	leaves	[45]
49	Daphhimalenine D	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[33]
50	Paxiphylline D	<i>D. paxianum</i> Rosenth.	twigs and leaves	[43]
51	Paxiphylline E	<i>D. paxianum</i> Rosenth.	twigs and leaves	[43]
52	Daphlongamine H	<i>D. longeracemosum</i> Rosenth.	leaves	[45]
53	Daphhimalenine A	<i>D. himalense</i> (Benth.) Muell.-Arg	leaves	[31]
54	Daphenylline	<i>D. longeracemosum</i> Rosenth.	fruits	[46]

the C8 unit [27], were recently isolated (● Fig. 2). Daphnezomines V (2) was an *N*-oxide form of daphnilongeranin D.

Yuzurimine

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],

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. Macropodumine J (6) contains a nitrile group, which is relatively rare in naturally occurring alkaloids. Daphnezomine T (9) is the first al-

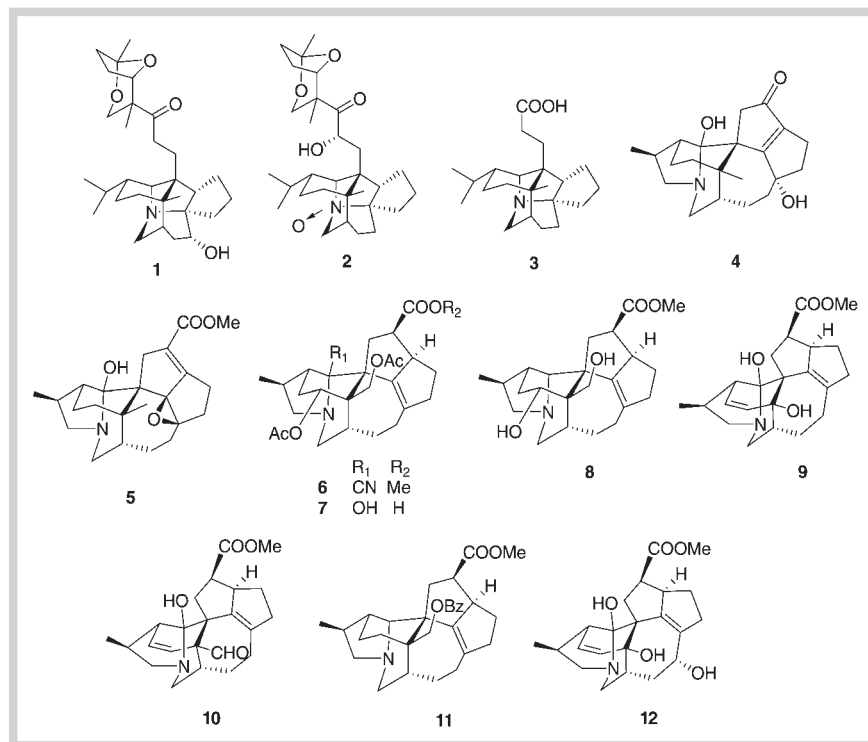


Fig. 2 Daphniphylline and yuzurimine-type alkaloids.

kaloid without a branched C_1 unit at C-5. Daphangustifoline B (**11**) is the first alkaloid with a benzyl group in the genus *Daphniphyllum*. Biogenetically, daphnezimine T (**9**) might be generated from an intermediate-like pordamacrine 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 loss of the C1 branch at C-5. Daphmalenine B (**10**) might undergo oxidation to give intermediate A, and then oxidative decarboxylation of the aforementioned intermediate and subsequent oxidation might yield daphnezimine 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], daphlongeranine 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 (14*R*,15*S*) 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.

Daphnezimine A

Daphnezimine 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).

Daphnezimine F

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

Daphnezimine L

Two new daphnezimine L-type alkaloids, daphnezimine L methyl ester (**37**) [25] and calycinumine B (**38**) [28], were reported (● Fig. 5). Daphnezimine L methyl ester (**37**) is structur-

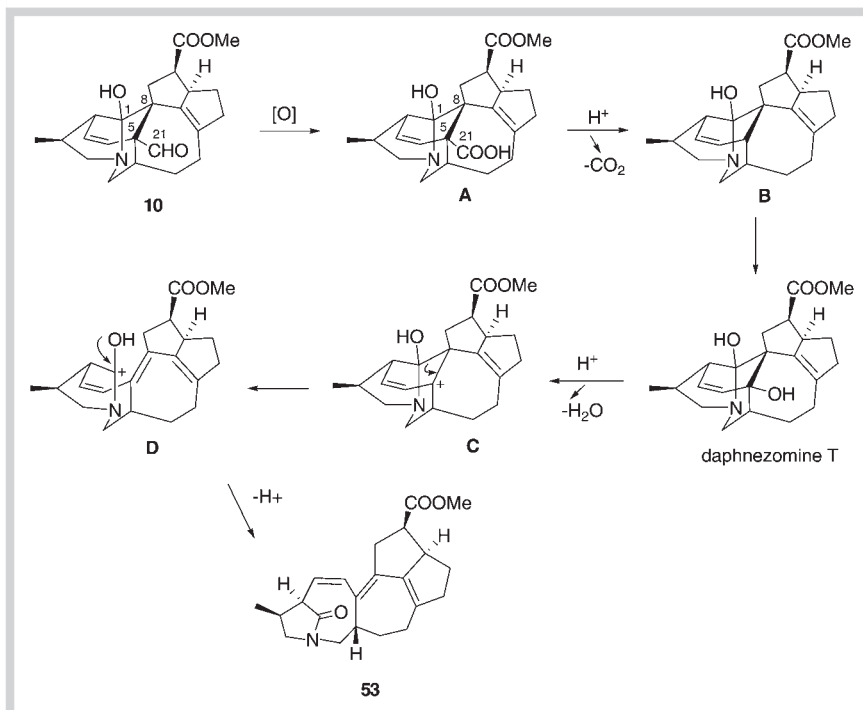


Fig. 3 Plausible biosynthetic pathway of daphnezomine T (9), daphhimalenine B (10), and daphhimalenine A (53).

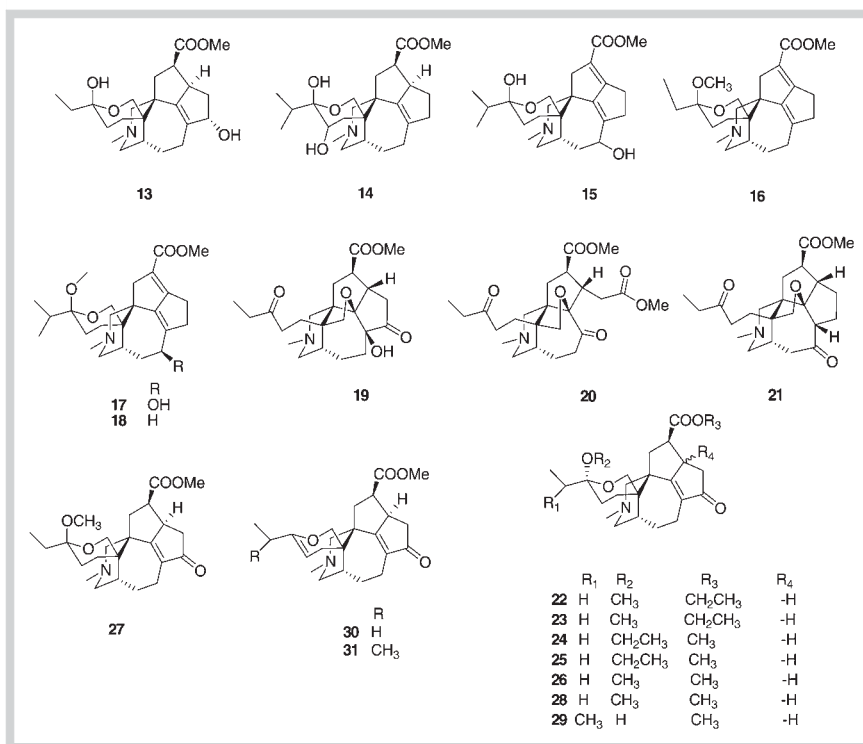


Fig. 4 Yuzurine-type alkaloids.

ally close to a hypothetical biogenetic intermediate between the secodaphniphylline and daphniphylline skeletons. Calycinumine B (38) 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 (39) and D

(40) [40], caldaphnidine H (41) [42], 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].

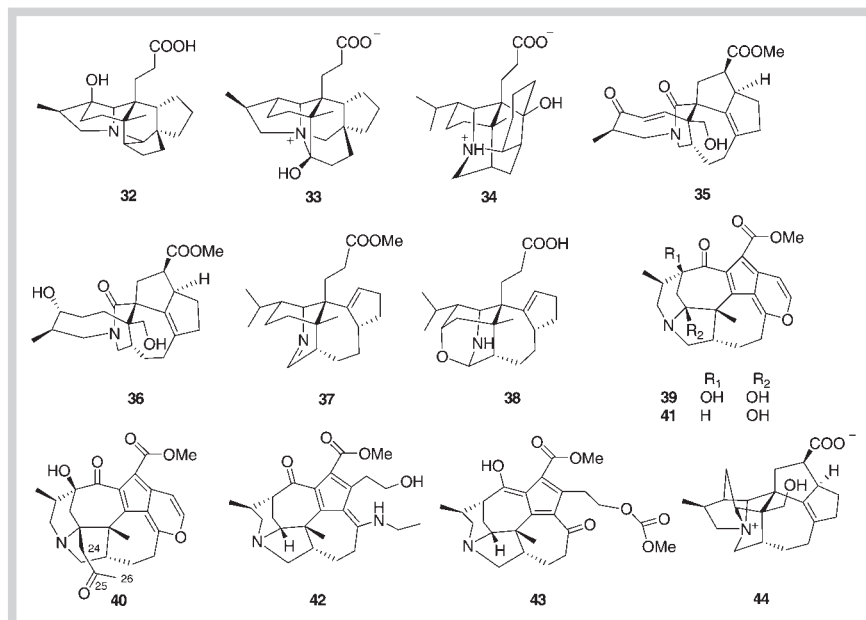


Fig. 5 Bukittinggine, daphnezomine A, daphnezomine F, daphnezomines L, daphnicyclidin, and daphniglaucin A-type alkaloids.

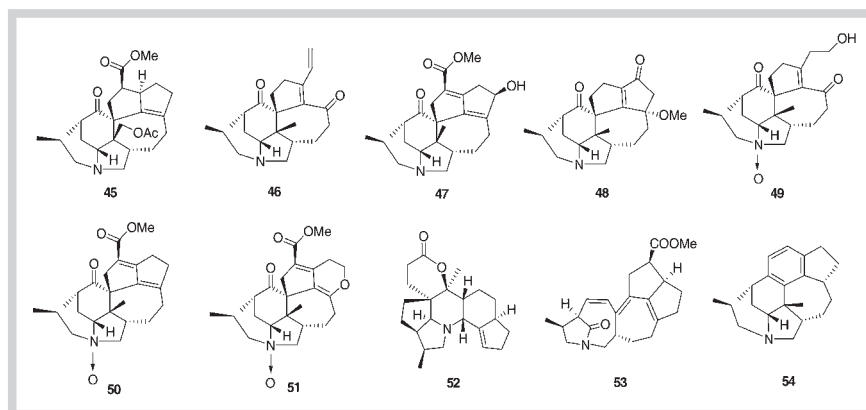


Fig. 6 Calyciphylline A, calyciphylline B, and other type alkaloids.

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[5.2.2.0^{1,6}.0^{4,9}]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 C₂₂ 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. longeracemosum* (● 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 biosyntheti-

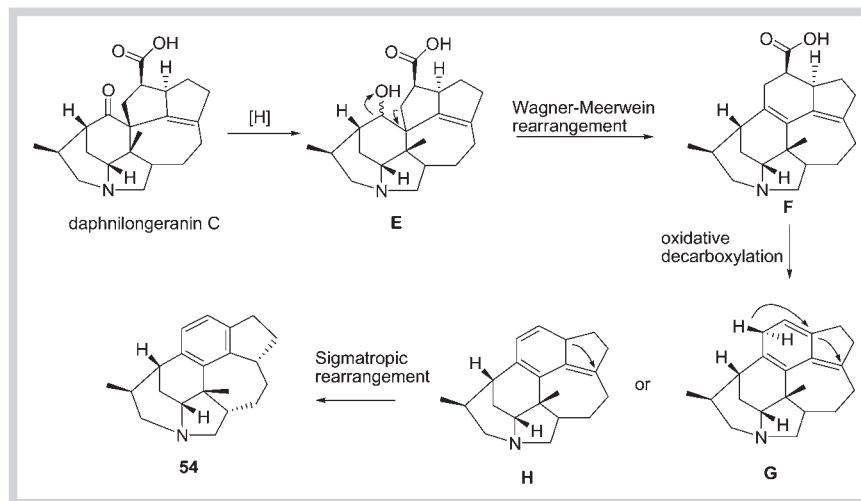


Fig. 7 Plausible biosynthetic pathway of daphenylline (54).

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 daphmanidin A-type alkaloid, (+)-daphmanidin E, was reported by Weiss et al. [49]. Daphmanidin 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 alkyl-Heck cyclization (● Fig. 8).

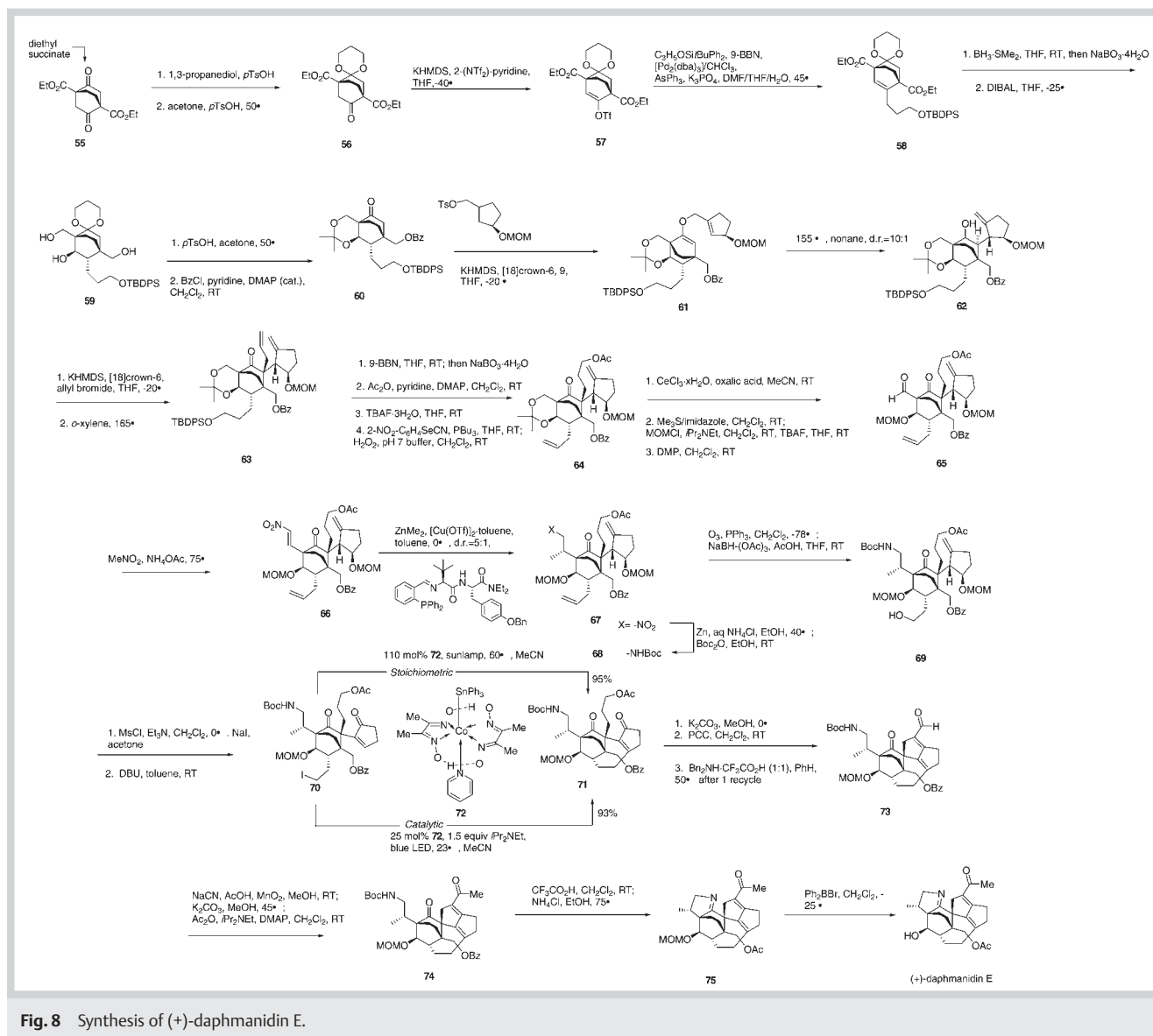
For a successful total synthesis, a robust and practical route for the expedient construction of common cores in highly complex molecules is a prerequisite. Recently, the rapid assembly of the structural motif in *Daphniphyllum* alkaloids was fruitfully completed. In 2012, several strategies for constructions of different moieties present in the calyciphylline A-type alkaloid are reported. Darses et al. developed a synthetic strategy for the construction of the [7-5-5] tricyclic core using a key intramolecular Pauson-Khand reaction (IPKR) [50]. Subsequently, the synthesis

of daphnilongeranin B and daphniyunnine D would be completed via late stage, base-mediated, double-bond migration and a regio- and stereoselective radical allylic oxygenation based on a DEF tricyclic ring system (● Fig. 9). In another study, an efficient and scalable synthesis of a bowl-shaped [6-6-5] skeleton was developed from a readily available carvone derivative through a seven-step sequence involving an aza-Michael addition and Pd-catalyzed enolate R-vinylation [51]. Li and coworkers constructed a [6-6-6-5] bridged ABCE 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 yuzurimine-type alkaloids by a cascade of condensation, cyclization, then intramolecular dipolar cycloaddition reactions [55]. In another study, a similar approach was successfully extended to bridged tricyclic compounds, yuzurimine B, daphnilactone B, and bukittinggine [56].

In 2009, two reports about asymmetric synthesis of cores common in daphnicyclidin-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 daphnicyclidin A through the highly diastereoselective conjugate addition of nitromethane, an Ireland-Claisen rearrangement, and a tandem acyliminium/Mannich-type reaction [57]. In another report, the aza-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 crownophane 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). Daphnagustifoline 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 IC_{50} values in the range of 2.4–9.7 μM and against the HMEC (human microvascular endothelial) cell line with an IC_{50} of 2.7 μM [25]. In addition, daphmacromines 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. Biological/ecological

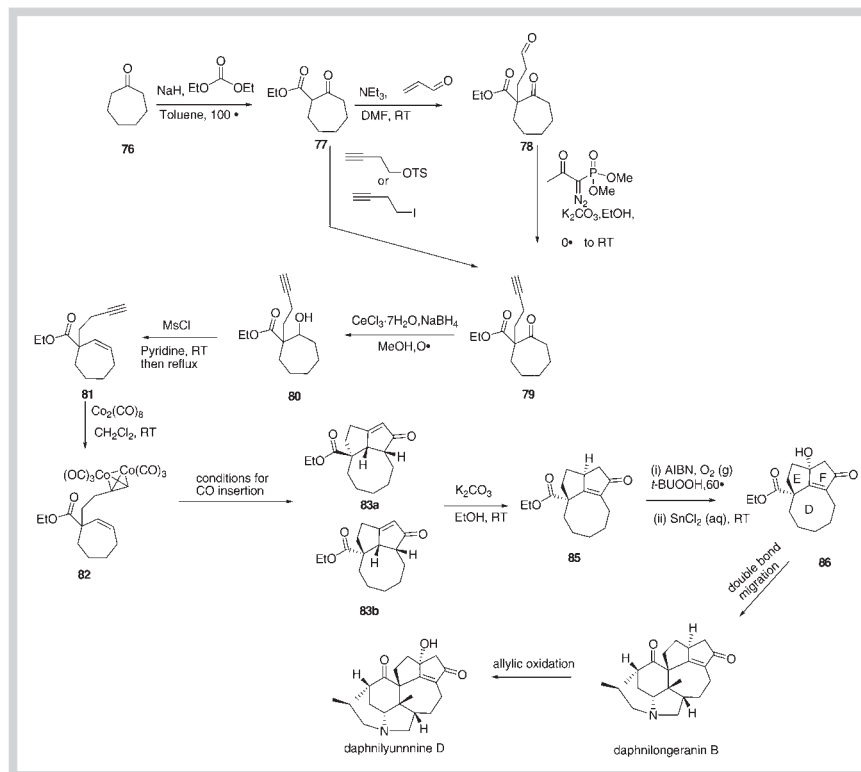


Fig. 9 Synthesis of the tricyclic core.

Table 2 Bioactivity of *Daphniphyllum* alkaloids obtained recently.

Compounds	Cytotoxicity (IC ₅₀ /μM)						References
	HL-60	MCF-7	A549	P-388	BEL-7402	HMEC	
Daphangustifoline B	weak	weak	weak	–	–	–	[32]
Daphnilongerinine	9.5	–	–	2.4	9.7	2.7	[25]

role of these alkaloids in the life cycle of the plant should also be paid much more attention.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 81102770), Chinese Traditional Medicine Researches of Special Projects (No. 200707007), the technological large platform for comprehensive research and development of new drugs in the Twelfth Five-Year “Significant New Drugs Created” Science and Technology Major Projects (No. 2012ZX09301-002-001-026), and the chemical composition of the digital library of traditional Chinese medicine for drug discovery in the Twelfth Five-Year “Significant New Drugs Created” (No. 2011ZX09307-002-01) is gratefully acknowledged.

Conflict of Interest

The authors have no conflicts of interest.

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