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Isolation and Bioactivities of *Stemona* Alkaloid: A Review

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Abstract

Objective/Background: In Chinese, Vietnamese, and Thai traditional medicine of Southeast Asian countries, *Stemonaceae* plants have long been employed. Various studies have proved that these herbal plants contain *Stemona* alkaloids with valuable medicinal value. Although some review articles on *Stemona* alkaloids have appeared in the literature, they are quite outdated. The current study offers a comprehensive review of the isolation and bioactivities of *Stemona* alkaloids. The article might be useful for chemists who work in alkaloid chemistry as well as pharmaceutical areas. **Methods:** "*Stemona* alkaloids" was the most useful keyword to search for literature data. References have been collected from various resources such as Google Scholar, SciFinder, and PubMed. More than 120 electronic publications were obtained from these resources. **Results:** More than 250 *Stemona* alkaloids from 8 groups have been isolated and structurally elucidated from *Stemonaceae* plants. Extracts from these plants as well as isolated compounds possess a wide range of bioactivities, such as antituberculosis, antibacterial, antifungal, and antihelmintic properties activities. **Conclusion:** In this review article, we have summarized 116 studies on the isolation and bioactivities of *Stemona* alkaloids in the literature. More than 250 *Stemona* alkaloid compounds have been isolated and identified. In addition, the article also gives an overview of the bioactivities of *Stemona* alkaloids.

Keywords

pyrrolo[1,2-*a*]azepine, pyrido[1,2-*a*]azepine, stemoamide, stenine, tuberostemospironine, stemoamine, stemofoline, stemocurtisine

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Introduction

The *Stemona* alkaloids are a unique class of naturally occurring alkaloids exclusively isolated from the *Stemonaceae* family, mainly distributed in Southeast Asia.[1] This class of alkaloids is structurally characterized by the presence of a pyrrolo[1,2-*a*]azepine skeleton (Figure 1, n = 1), or a pyrido[1,2-*a*]azepine core structure, the less common type (Figure 1, n = 2).[2]

There are 30 species in 3 genera, *Stemona*, *Croomia*, and *Stichoneuron* of the *Stemonaceae* family. These herbal plants are widely distributed in Southeast Asia, Northern Australia, China, Japan, and Northern America. Extracts from these plants have long been employed in traditional medicine in East Asia, especially 3 species: *S tuberosa*, *S japonica*, and *S sessilifolia*, which were listed in the 2000 edition of the Chinese Pharmacopeia as antitussive medicinal herbs.[3] In Vietnam ("*Bach Bo*"), China ("*Bai Bu*"), and Thailand ("*Non Tai Yak*" or "*Pong Mot Ngam*"), the dried roots from these 3 species have long been utilized to treat coughing and claimed to exhibit antitubercular, antibacterial, antifungal, and antihelmintic properties.[4]

In 2010, the *Stemona* alkaloids were classified into 8 different structural groups by Pilli et al[2] (Figure 2) including stenine (**I**); stemoamide (**II**); tuberostemospironine (**III**); stemoamine (**IV**); parvistemoline (**V**); stemofoline (**VI**); stemocurtisine (**VII**); and a miscellaneous group (**VIII**), formed from those alkaloids which do not possess skeleton mentioned above. The core structures of groups **I** to **VII** are shown in Figure 2.

Phytochemistry

Until now, more than 250 *Stemona* alkaloids have been isolated and structurally elucidated. A large number of *Stemona* alkaloids isolated belong to groups I, II, and VIII. Some *Stemona* alkaloids possess complicated structures and need a long time or even revision to determine the correct configuration. In this section, we discuss the isolation of *Stemona* alkaloids belonging

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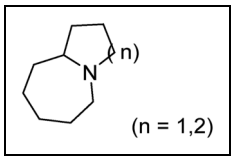


Figure 1. The core structure of the *Stemona* alkaloids.

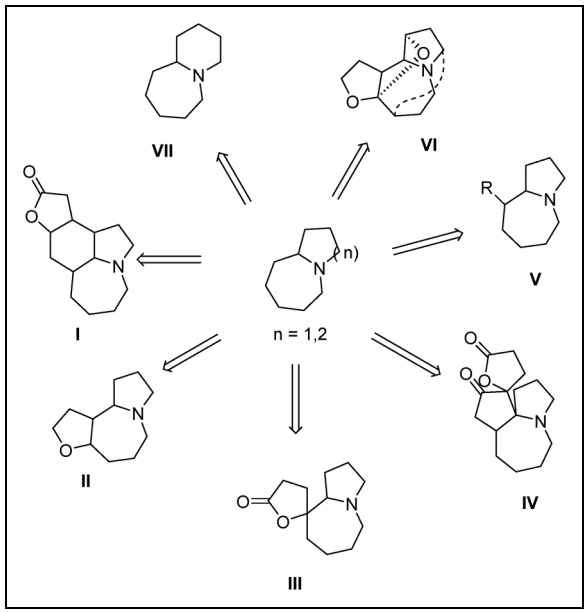


Figure 2. Pilli's classification of the *Stemona* alkaloids.

to each group which were isolated by 2023. Although some review articles on the isolation of *Stemona* alkaloids have been found in the literature,[1,2,5,6] they did not cover recent studies. The article might be useful for chemists who work with the chemistry of natural products as well as pharmacology.

Isolation of Stemona *Alkaloids Belonging to Stenine Group (Group 1)*

The alkaloids in the stenine group possess furo[2,3-*h*] pyrrolo[32,1-*j*,*k*[1]benzazepin-10(2*H*)-one skeleton. Until now, 52 stenine group alkaloids have been isolated and structurally elucidated. Many of these alkaloids contain a γ-lactone ring at C3. Tuberostemonine **1** was the first Stenine *Stemona* alkaloid isolated from *S tuberosa* by Suzuki[7] in 1934, but only until 1967 its structure was fully determined (Figure 3).[8] In 1967, Uyeo et al[9] reported the isolation and structural elucidation of stenine **2** from *Stemona tuberosa* (Figure 3). Tuberostemonine A **3** was discovered by Edwards et al[10] from the rhizomes of *Stentona sessilifolia*. Especially, tuberostemonine A (**3**) displays an (*R*)-absolute configuration at the C-3 position where the γ-butyrolactone moiety is bonded to this stereogenic center (Figure 3). Lin et al[11] isolated tuberosternonol **4**, in which the A-ring has been oxidized to dihydropyrrole, from the roots of *Stenuma tuberosa* (Figure 3). Tuberostemonol (**4**) is the only stenine group alkaloid that possesses a hydroxy group at C-9. Neotuberostemonine **5** and bisdehydroneotuberostemonine **6** were obtained from the roots of *Stemona tuberosa*, collected in Yunnan Province (Figure 3).[12] The A-ring in bisdehydroneotuberostemonine **6** is a pyrrole. Four new *Stemona* alkaloids, namely tuberostemonines B **7** and C **8**, and bisdehydrotuberostemonines B **9** and C **10** were separated by Zou et al[13] from the roots of *Stemona japonica* (Figure 3). In these alkaloids, the ethyl side chain is at the α-position. Isobisdehydrotuberostemonine **11** also known as isodidehydrotuberostemonine and *N*-oxytuberostemonine **12** was achieved by Lin and Fu[14] (Figure 3). Compound **11** possesses a pyrrole ring. Neotuberostemonol (**13**) was isolated by Jiang et al[15] in 2002. Neotuberostemonol differs from tuberostemonol by the β-oriented relative configuration of H-11 and H-12 (tuberostemonol has α-oriented) (Figure 3). 2-Oxostenine (**14**) with a ketone group at C2 was obtained from the roots of *S sessilifolia* and *S mairei*, although full physical data for structure elucidation has not been provided (Figure 3).[16,17] Isostenine (**15**) was co-discovered by Pham et al[17] from the root of *Stemona collinsae.* and by Lin et al from the dried root of *Stemona tuberosa.* Lin et al named it neostigmine (Figure 3).[18] This compound does not contain a γ-lactone ring at C3. In this work, Lin et al also achieved 3 other *Stemona* alkaloids named tuberostemonines H (**16**) and J (**17**), and *epi*-bisdehydrotuberostemonine J (**18**) (Figure 3).[18] Tuberostemonines H and J are distinguished with tuberostemonine in the configurations at C-1, C-9a, C-11, and C-12. H-9 is α-position in tuberostemonine J while the configuration of this hydrogen atom in tuberostemonine and tuberostemonine H is β-oriented. The configuration of *epi*-bisdehydrotuberostemonine J resembles that of tuberostemonine J except for α-oriented H-18 in *epi*-bisdehydroneotuberostemonine J. A pyrrole ring appeared in bisdehydrotuberostemonine J.

In 2006, tuberostemonine K (**19**) was separated from the root tubers of *Stemona tuberosa.*[19] In the same year, tuberostemonine L (**20**) and tuberostemonine M (**21**) were obtained from a root extract of an unidentified *Stemona* species (Figure 3).[20] Two of these alkaloids differ from each other by the configuration of the methyl group at the C3-lactone ring. Later, Hu *et al* reported the isolation and structure elucidation of 2 new alkaloids, didehydrotuberostemonine A (**22**) and tuberostemonine L (**23**) from the roots of *Stemona tuberosa* (Figure 3).[21] These 2 tuberostemonine L (**20**) and tuberostemonine L (**23**) have different configurations, mainly at the 2 lactone rings. Sessilifolines A (**24**) and B (**25**) were isolated from the stems of *Stemona sessilifolia* (Figure 3).[22] Sessilifoline A (**24**) contains an ether linkage, while sessilifoline B has the same configurations as stenine except for the methyl group at C-13. Schinnerl et al[23] obtained tuberostemonine N (**26**) from a mixture of *Stemona* species (Figure 3). In 2008, Lin et al[24] discovered tridehydrotuberostemonine, 9α-bisdehydrotuberostemonine (**27**), and 9α-bisdehydrotuberostemonine A (**28**), from the roots of *Stemona tuberosa* collected from Yunnan Province (Figure 3).

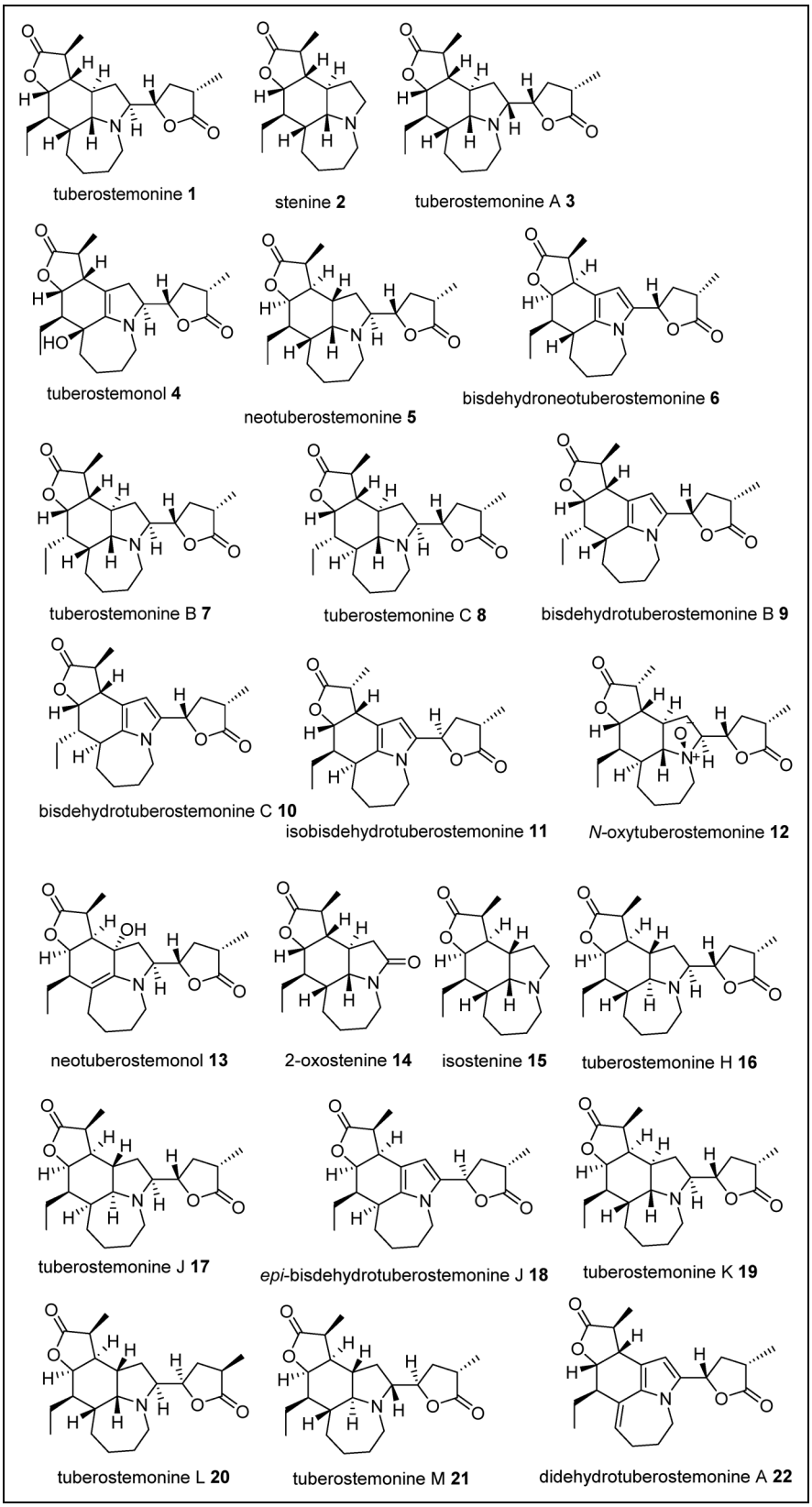
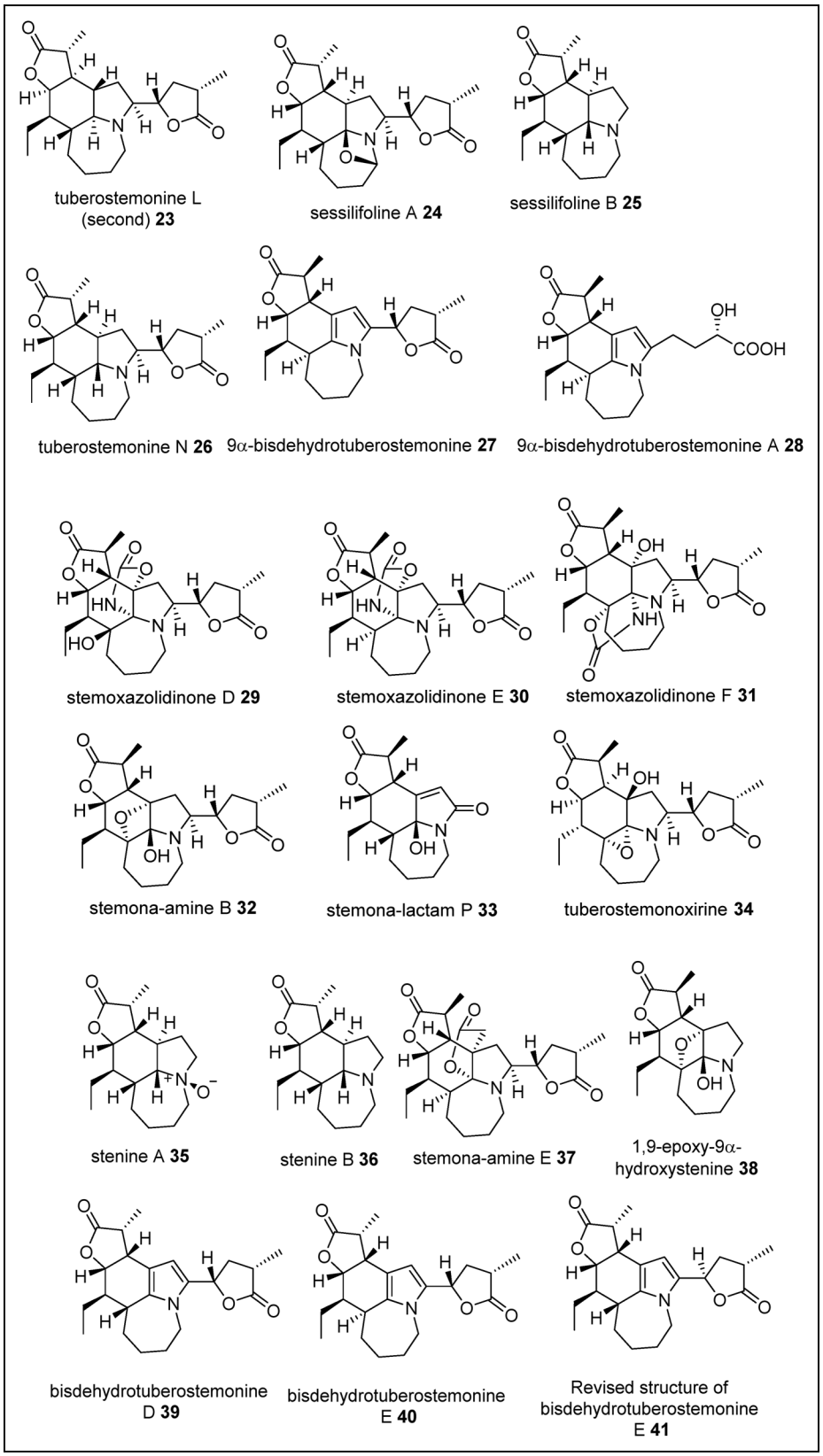


Figure 3. Stenine group alkaloids. (continued)



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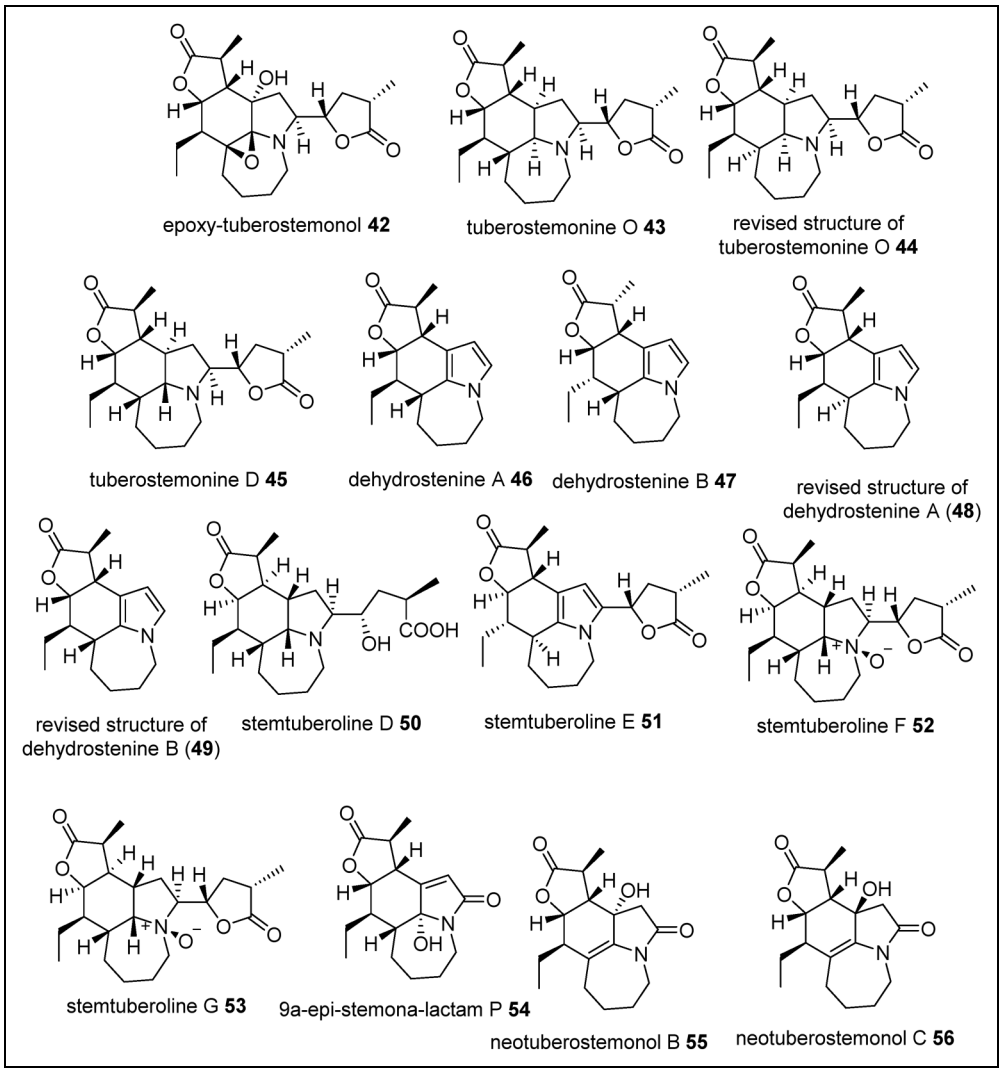


Figure 3. Continued.

9α-Bisdehydrotuberostemonine A was the first sample of tuberostemonine-type alkaloid with an opened ring E, while 9α-bisdehydrotuberostemonine possesses a pyrrole ring. The structure of tridehydrotuberostemonine is the same as didehydrotuberostemonine A (**22**).

Three novel alkaloids, stemoxazolidinones D-F (**29**-**31**), were achieved from the roots of *Stemona sessilifolia* (Figure 3). The structures of stemoxazolidinones D and F were confirmed by X-ray crystallography.[25] These alkaloids possess an oxazolidin-2-one ring and the core skeleton fused together. Hitotsuyanagi et al[26] isolated 2 new alkaloids, stemona-amine B (**32**) and stemona-lactam P (**33**) from the roots of *Stemona tuberosa* (Figure 3). These compounds have a hydroxy group at C9a and stemona-amine B possesses an ether linkage. Tuberostemonoxirine (**34**) containing an epoxy ring was obtained from the roots of *Stemona tuberosa*.[27] Lai et al[28] reported the isolation and structure determination of stenines A (**35**) and stenine B (**36**) from the roots of *Stemona sessilifolia* (Figure 3). Both compounds do not have a lactone ring at C3 and stenine A (**35**) contains an *N*-oxide structure. Stemona-amine E (**37**) was yielded from the roots of *Stemona tuberosa* Lour (Figure 3).[29] This alkaloid contains an additional γ-lactone ring fused to C1 and C9a.

In 2014, Gao et al[30] achieved 3 new alkaloids, named 1,9-epoxy-9*a*-hydroxystenine (**38**), bisdehydrotuberostemonine D (**39**), and bisdehydrotuberostemonine E (**40**), from the roots of *Stemona tuberosa* (Figure 3). Compound **38** has an O-bridge instead of a lactone ring at C3, while the 2 other compounds possess a pyrrole ring. Later, by synthesis, Deng et al[31] revised the structure of bisdehydrotuberostemonine E as **41**. Epoxy-tuberostemonol (**42**) with an oxirane ring at C9 and C9a was obtained from the roots of *S tuberosa*.[32] Kil et al[33] separated tuberostemonine O (**43**) from the roots of *Stemona tuberosa* (Figure 3). Recently, Jiang et al[34] revised structure of tuberostemonine O as **44**, which differs in stereochemistry at C9. Zhang et al[35] isolated tuberostemonine D (**45**) from the

roots of *Stemona tuberosa* (Figure 3). Dong et al[36] discovered 2 new alkaloids, dehydrostenines A (**46**) and B (**47**) from the roots of *Stemona sessilifolia* (Figure 3). Later, Olivier et al[37] revised the structures of dehydrostenines A and B as **48** and **49**, respectively (Figure 3). The compounds have a pyrrole ring but lack a lactone ring at C3. In 2020, Hu et al[38] achieved stemtuberolines D-G (**50**-**53**) from the roots of *Stemona tuberosa* (Figure 3). The *N*-oxide structure appeared in compounds **52** and **53**, while **51** has a pyrrole ring. 9a-*epi*-Stemona-lactam P (**54**) with a double bond at C1, C2, and a hydroxy group at C9a was yielded from the roots of *Stemona tuberosa* (Figure 3).[39] Recently, neotuberostemonols B (**55**) and C (**56**) were isolated from the roots of *Stemona tuberosa* (Figure 3).[40] The alkaloids do not possess a lactone ring at C3.

Isolation of Stemona *Alkaloids Belonging to Stemoamide Group (Group 2)*

The alkaloids in the stemoamide group are characterized by the presence of the 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine nucleus. To date, 65 *Stemona* alkaloids belonging to this group have been isolated. Stemonine (**57**) was the first *Stemona* alkaloid isolated which belongs to stemoamide group 2 and its structure was confirmed by X-ray (Figure 4).[41] Protostemonine (**58**) was isolated by Kondo et al[42] in 1947 and its structure was elucidated by Irie et al[43] in 1970 (Figure 4). Stemoninine (**59**) with a spiro lactone at C11 was obtained by Chu and Kuo[44] for the first time in 1978 and its structure and relative configuration were reported in 1988 (Figure 4).[45] Lin et al isolated stemoamide, the simplest member of this group alkaloid without any lactone ring, (**60**) in 1992 (Figure 4).[9] In 1994, Ye et al[46] achieved 4 *Stemona* alkaloids, namely neostemonine (**61**), bisdehydroneostemonine (**62**), bisdehydroprotostemonine (**63**), and isoprotostemonine (**64**), from the roots of *Stemona japonica,* collected from Zhejiang Province, southern China (Figure 4). All these alkaloids have an unsaturated spironolactone ring connecting at C-11. In compounds **62** and **63**, the A-ring has been oxidized to a pyrrole ring (Figure 4). Compounds **61** and **63** lack a lactone ring at C3. Stemoninoamide (**65**) was separated from the roots of *Stemona tuberosa* (Figure 4).[47] This compound displays an unsaturated spironolactone ring fused at C-11. In 2003, oxyprotostemonine (**66**) and dehydroprotostemonine (**67**) were isolated from 4 *Stemona* species (Figure 4).[48] An ether linkage has appeared in oxyprotostemonine (**66**) and other stereogenic centers are the same as protostemonine. Sessilifoliamide A (**68**) was obtained from the roots of *Stemona sessilifolia* (Figure 4).[49] This compound has a spiro lactone at C11. In 2005, the Ye group discovered 5 *Stemona* alkaloids, bisdehydrostemoninine (**69**), isobisdehydrostemoninine (**70**), bisdehydroneostemoninine (**71**), and bisdehydrostemoninines A (**72**) and B (**73**), from the roots of *Stemona tuberosa* (Figure 4). Bisdehydrostemoninines A (**72**) and B (**73**) have a side chain at the C-3 position, which is reminiscent of the α-methyl-γ-butyrolactone ring. The relative configuration of **72** was determined by X-ray diffraction.[50] In these alkaloids, the A-ring has been transformed into a pyrrole ring. In 2007, the Ye group isolated bisdehydrostemocochinine (**74**), isobisdehydrostemocochinine (**75**), neostemocochinine (**76**), and isoneostemocochinine (**77**) from the roots of *Stemona cochinchinensis* (Figure 4).[51] In compounds **74** and **75**, the A ring is oxidized to a pyrrole ring. Neostemocochinine and isoneostemocochinine differ in configuration at C12. Dihydrostemoninine (**78**) was isolated from the roots of *Stemona sessilifolia* and its structure was confirmed by X-ray single-crystal diffraction.[52] It is a 12, 13-dihydro derivative of stemoninine. Wang et al[53] achieved saxorumamide (**79**) and isosaxorumamide (**80**) from the roots of *Stemona saxorum* collected in Vietnam (Figure 4). These compounds differ from each other only in relative configuration at the C-11–C-12 bond: (11S*, 12S*) for saxorumamide and (11S*, 12R*) for isosaxorumamide. Saxorumamide could be considered as the oxidation product of stemocochinin. Stemoenonine (**81**), oxystemoenonine (**82**), oxystemoninine (**83**), and 9*a*-*O*-methylstemoenonine (**84**) were isolated from the roots of *Stemona tuberosa* (Figure 4).[54] A double bond between C2 and C3 appears in **81**, **82**, and **84**.

Wang et al[55] reported the isolation and structure determination of stemoninines A (**85**) and B (**86**) from the roots of *Stemona sessilifolia* (Figure 4). These compounds display a saturated α-methyl butyrolactone at the spiro position and their configuration differs only at spiro carbon. 13-dimethoxy-11 (*S**),12(*R**)-dihydroprotostemonine (**87**), and neostemofoline (**88**) were isolated from stems and leaves of *Stemona japonica* (Figure 4).[56] Neostemofoline displays the characteristic *n*-butyl side chain at C-3 and an oxygen bridge between C-2 and C-6. Yang et al[57] obtained protostemonamide (**89**) from the roots of *Stemona sessilifolia* (Figure 4). Stemoninone (**90**) with a ketone group at C7 was isolated from the roots of *Stemona tuberosa* (Figure 4).[19] 1-Hydroxyprotostemonine (**91**) was yielded from the root extracts of *Stemona curtisii*.[58] Ramli et al[59] discovered stichoneurines C (**92**), D (**93**), and E (**94**) from extracts of the root and leaf of *Stichoneuron halabalensis* Inthachub collected from Peninsular Malaysia (Figure 4). These compounds have an N-oxide group. Stemona-lactam O (**95**) was isolated from the roots of *Stemona tuberosa*.[24] This compound has a double bond at C2 and C3. Isoneostemocochinine-*N*-oxide (**96**) and neostemocochinine-*N*-oxide (**97**), 2 alkaloids with an N-oxide group, were achieved from the roots of *Stemona cochinchinensis* (Figure 4).[60] Ramli et al[61] separated and identified javastemonines A (**98**) and B (**99**) from the root extracts of *Stemona javanica* (Figure 4). These compounds have a lactone ring attached to C11.

A mixture of novel *Stemona* alkaloids stereo-isomers, stemocochinin (**100**) and isostemocochinin (**101**), was isolated from the roots of *Stemona japonica* Miq (Figure 4).[62] Previously, stemocochinin was reported by Kaltenegger et al,[48] however, its configuration was not determined. Huang et al[63] isolated protostemonine N_4-oxide (**102**), 3-*n*-butylneostemonine (**103**), 10-*epi*-3-*n*-butylneostemonine (**104**), and parvistemonine A (**105**), from the roots of *Stemona parviflora* (Figure 4). The alkaloids possess a butyl side chain at C3. Hu et al[38] discovered

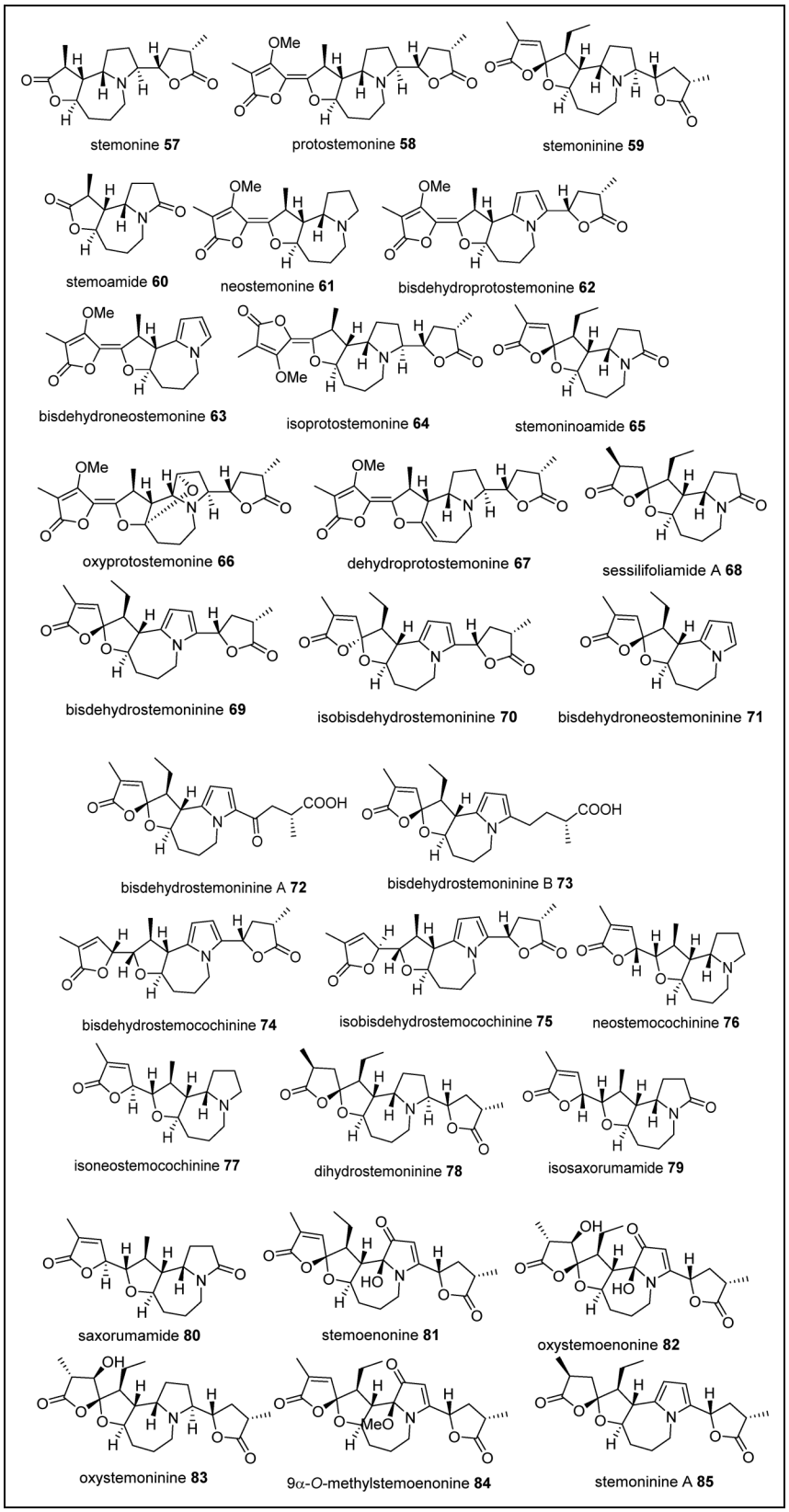
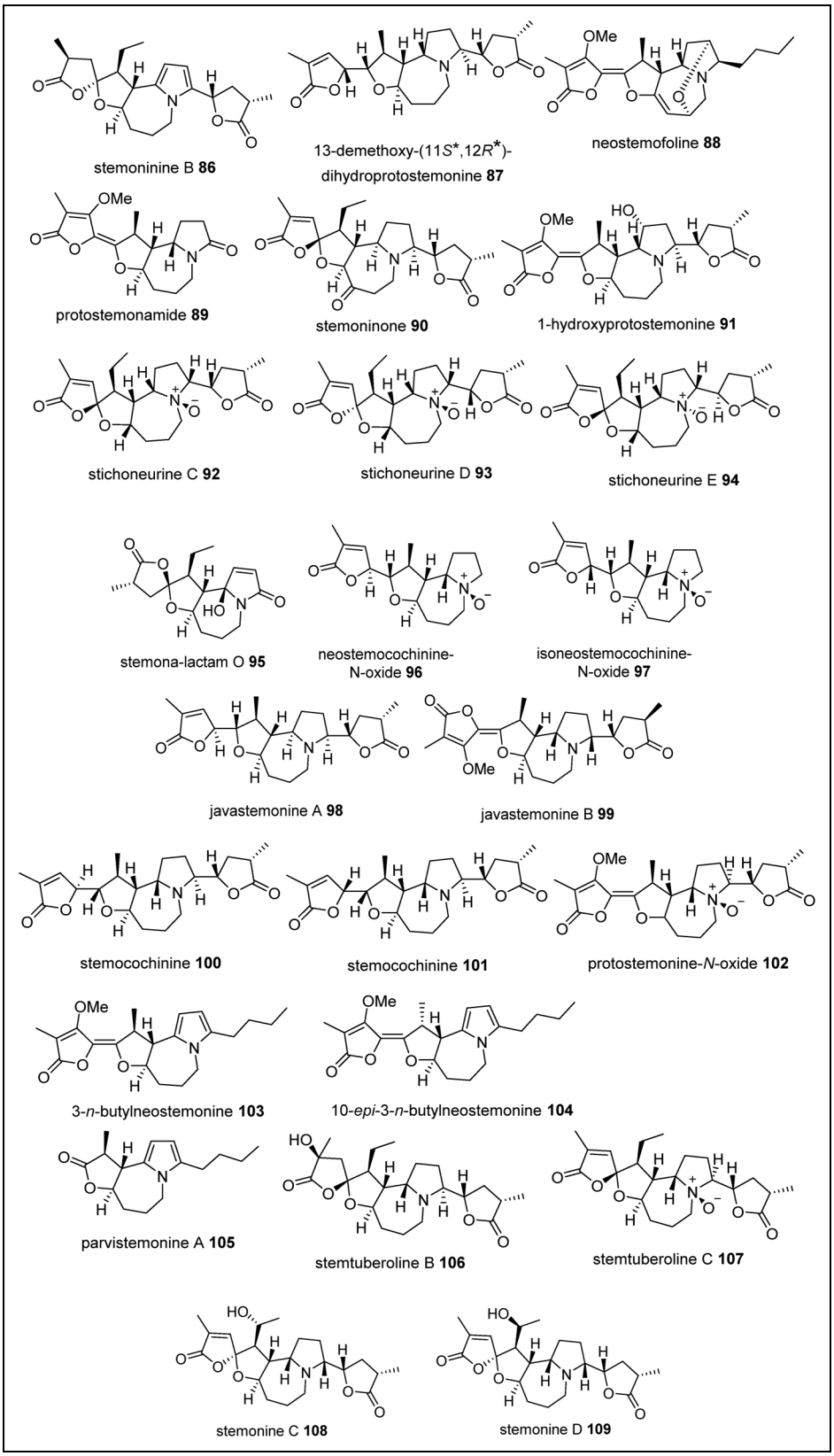


Figure 4. Stemoamide group alkaloids. (continued)



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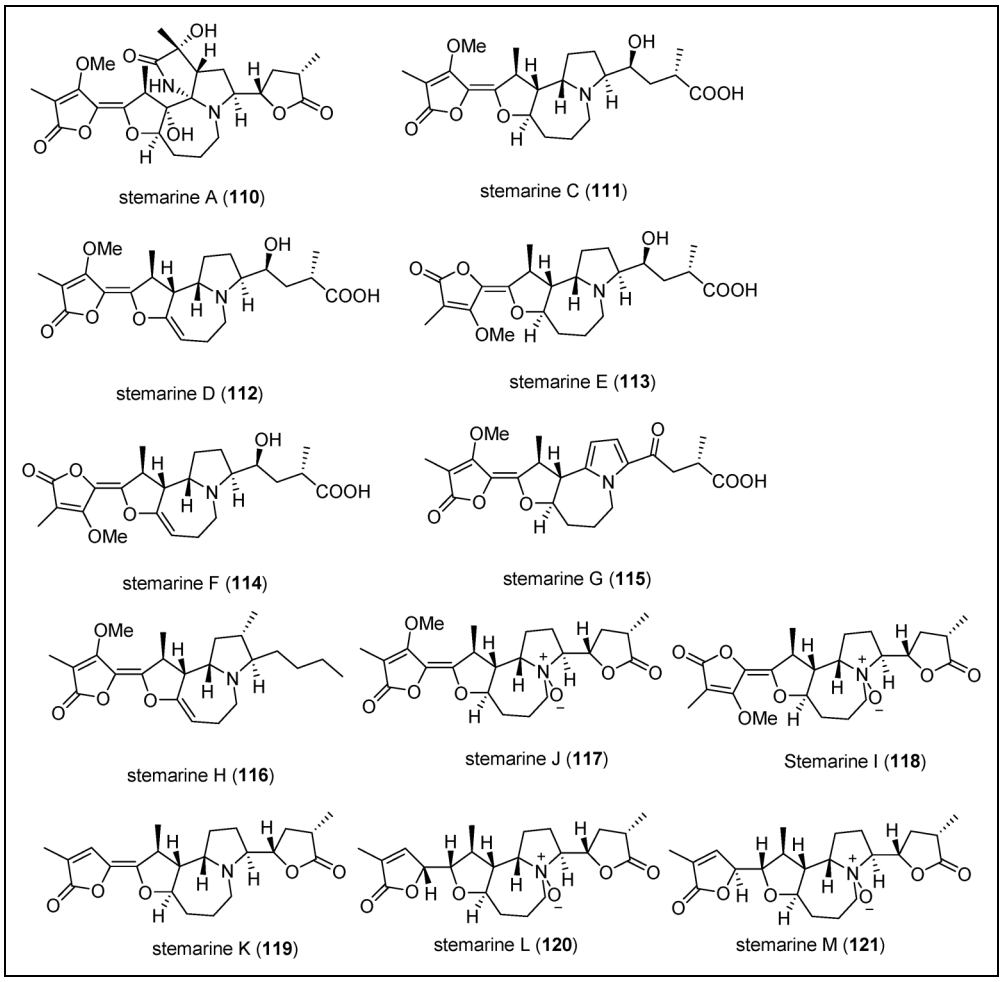


Figure 4. Continued.

stemtuberolines B (**106**) and C (**107**) from the roots of *Stemona tuberosa* (Figure 4). Xu et al[40] described the isolation and structure elucidation of stemonines C (**108**) and D (**109**) from the roots of *Stemona tuberosa* (Figure 4). Recently, 15 novel *Stemona* alkaloids, including stemarine A (**110**) and stemarine C-M (**111-121**) were isolated from the roots of *Stemona mairei* (H.Lév.) K.Krause (Stemonaceae). Their structures were elucidated on the basis of NMR spectra, mass data, and computational study.[64]

Isolation of Stemona *Alkaloids Belonging to Tuberostemospironine Group (Group 3)*

In the tuberostemospironine group, the spiro-γ-butyrolactone moiety is attached to C-9 of its pyrrolo[1,2-*a*]azepine nucleus. Twenty-five tuberostemospironine group alkaloids have been isolated. Stemospironine (**122**) was the first isolated *Stemona* alkaloid belonging to tuberostemospironine group (Figure 5).[65] Croomine (**123**) was yielded from the roots and rhizomes of *Croomia Heterosepala* in 1979 by Noro et al[66] (Figure 5). Xu et al[67] discovered stemotinine (**124**) and isostemotinine (**125**), 2 alkaloids with an ether bridge, from the roots of *Stemona tuberosa* (Figure 5). Bisdehydrocroomine (**126**) with a hydroxy group at C10 also known as didehydrocroomine was obtained by Lin et al[68] (Figure 5). Tuberosternospironine (**127**) was yielded from the roots of *Stenuma tuberosa* by Lin et al[11] The A ring 6α-hydroxycroomine (**128**) was separated from *Stemona tuberosa* (Figure 5).[69] Tuberospironine (**129**) with a hydroxy group at C14 was isolated from *Stemona tuberosa*.[18] Lin et al achieved 10-hydroxycroomine (**130**) and dehydrocroomine (**131**) from the roots of *Stemona tuberosa* collected from Yunnan Province (Figure 5).[24] Recently, the structure of dehydrocroomine was revised as **132**.[34] Sessilifoliamine A (**133**) also known as stemonaamine A was obtained from the roots of *Stemona sessilifolia*.[70] This compound possesses a lactone ring attached to C5 and C6. Hu et al[21] separated tuberostemospiroline (**134**), from the roots of *Stemona tuberosa* (Figure 5). This is the simplest alkaloid belonging to this group.

Dehydroisostemotinine (**135**) with an O-bridge was yielded from the roots of *Stemona tuberosa* collected from Yunnan Province (Figure 5).[71] Tuberospironine A (**136**) (3-*epi*-tuberospironine) with a hydroxy group at C14 was

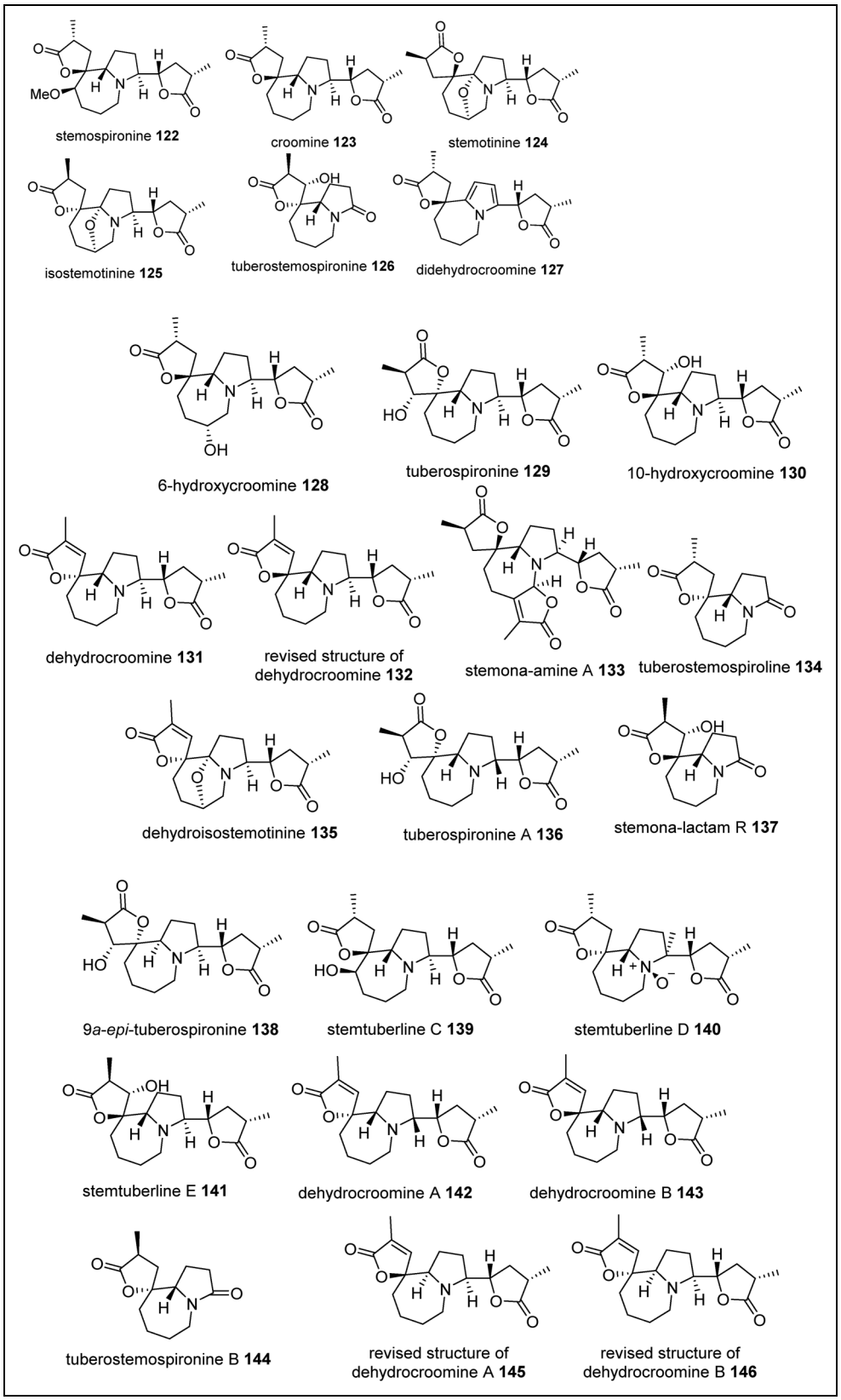


Figure 5. Tuberostemospironine group alkaloids.

discovered from the root extracts of *Stemona tuberosa* Lour. collected from Seram Island, Moluccas Province, Indonesia (Figure 5).[72] Stemona-lactams R (**137**) with a hydroxy group at C10 was obtained from the roots of *Stemona tuberosa* (Figure 5).[26] Yuea et al[27] found 9*a-epi*-tuberospironine (**138**) from the roots of *Stemona tuberosa* (Figure 5). Hu et al[73] achieved 3 novel croomine group alkaloids, stemtuberlines C-E (**139**-**141**), from the roots of *Stemona tuberosa* (Figure 5). Compound **139** has a hydroxy group at C8, while compound **140** possesses an N-oxide group. Dehydrocroomines A (**142**) and B (**143**) and tuberostemospironine B (**144**) were discovered and identified from the roots of *Stemona tuberosa* (Figure 5).[40] Compounds **142** and **143** contain a double bond at C10 and C11. Compound **144** differs from compound **134** in the configuration of the methyl group. Later, structures of dehydrocroomines A and B were revised as **145** and **146**, respectively.[34]

Isolation of Stemona *Alkaloids Belonging to Stemonamine Group (Group 4)*

The stemonamine-type *Stemona* alkaloids are characterized by the presence of the cyclopenta[1,2-*b*]pyrrolo[1,2-*a*]azepine skeleton. Twenty stemonamine-type *Stemona* alkaloids have been isolated and identified until now. Iizuka isolated stemonamine (**147**) and isostenionamine (**148**) isolated from *Stemona japonica* Miq (Figure 6). The structure of **147** was confirmed by X-ray crystal-structure analysis of its hydrochloride form (Figure 6).[74] These compounds do not have a lactone ring at C3. Lin et al[75] reported the isolation and structure elucidation of maistemonine (**149**) and oxymaistemonine (**150**) from *Stemona mairei* collected from Yunnan Province, southwest China (Figure 6). Oxymaistemonine has a hydroxy group at C8. Stemonamide **(151)** and isostemonamide (**152**) were obtained from the roots extract of *Stemona japonica*, collected from Zhejiang Province, China (Figure 6).[76] A ketone group appears at C3 of these compounds. In 2007, 3 new *Stemona* alkaloids, sessilistemonamines A-C (**153**-**155**) with a hydroxy group at C13, were isolated from the roots of *Stemona sessilifolia* (Figure 6).[48] From the roots of *Stemona sessilifolia*, 2 alkaloids, namely isooxymaistemonine (**156**) and isomaistemonine (**157**) were discovered (Figure 6).[77] Compound **157** has a hydroxy group at C8. Ramli et al[78] obtained 2 new stichoneurine-type alkaloids sessilistemonamines E (**158**) and F (**159**), from the root extracts of *Stichoneuron caudatum* (Figure 6). These compounds differ from each other by the configuration of the ethyl group. In 2016, 8-oxo-oxymaistemonine (**160**), 3β-*n*-butylstemonamine (**161**), and 8-oxo-3β-*n*-butylstemonamine (**160**) were isolated from the roots of *Stemona parviflora* (Figure 6).[63] Stemarines B (**163**) was isolated and identified from the roots of *Stemona mairei* (H.Lév.) K.Krause (Stemonaceae).[64] Three hitherto undescribed *Stemona* alkaloids, namely stemajapines A-C (**164-166**) were achieved from the roots of *Stemona japonica* (Blume) Miq. (Stemonaceae). Their structures were elucidated by the analysis of the mass data, NMR spectra, and computational study. Stemjapines A and B differed from maistemonines by the absence of a spiro-lactone ring and skeletal methyl.[79]

Isolation of Stemona *Alkaloids Belonging to Parvistemoline Group (Group 5)*

The parvistemoline-type alkaloids are characterized by the presence of a substituent at C-9 of the pyrrolo[1,2-*a*]azepine nucleus and by the lack of the fused B-C ring system in comparison with the other groups of *Stemona* alkaloids. Thirteen *Stemona* alkaloids belonging to this group have been isolated and structurally elucidated. Parvistemonine (**167**) was the first parvistemoline group alkaloid which was isolated from the roots of *Stemona parviflora* collected in Hainan island, China (Figure 7).[80] Lin et al[81] isolated didehydroparvistemonine (**168**) and parvistemoline (**169**) from *Stemona parviforia* (Figure 7). Compound **168** has a pyrrole ring. Neostemodiol (**170**) was discovered by Ye and Xu[82] (Figure 7). Kakuta et al[49] achieved 3 new *Stemona* alkaloids, sessilifoliamides B-D (**171**-**173**), also known as stemona-lactams B-D, from the roots of *Stemona sessilifolia* (Figure 7). Compound **173** possesses a long side chain. Stichoneurine A (**174**) and B (**175**) were obtained from the lipophilic root extracts of *Stichoneuron caudatum* and *Stemona tuberosa* collected in Thailand (Figure 7).[83] These compounds differ from each other by the configuration of the ethyl group.

Protostemodiol (**176**) was yielded from stems and leaves of *Stemona japonica* (Figure 7).[56] Two new alkaloids, stemaphylline (**177**) and stemaphylline-*N*-oxide (**178**) were produced from a root extract of *Stemona aphylla* (Figure 7).[84] These compounds differ from each other by the N-oxide group. Recently, Hu et al[38] isolated stemtuberoline A (**179**) from the roots of *Stemona tuberosa* (Figure 7).

Isolation of Stemona *Alkaloids Belonging to Stemofoline Group (Group 6)*

The alkaloids of this group possess a complex caged skeleton that has an ether bridge between C2 and C8 and a carbon-carbon bond between C3 and C7. Twenty Stemofoline group alkaloids have been isolated and identified until now. The first isolated *Stemona* alkaloid of this group was stemofoline (**180**) and the structure of this compound was confirmed by X-ray crystallographic analysis (Figure 8).[85] Oxystemofoline (**181**) with a hydroxy group at the end of the butyl side chain and methoxystemofoline (**182**) were obtained from *Stemona parviflo-ria* (Figure 8).[86] The structure of **182** was later revised as isomethoxystemofoline (**183**).[87] Parvistemoninine (**184**) with an ether linkage was identified from *Stemona parvifloria* by Xu et al[88] (Figure 8). 16,17-didehydro-16(*E*)-stemofoline (**185**) also known as didehydroisostemofoline) and 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**186**) also known as isodidehydroisostemofoline) were achieved from the root extract of *Stemona collinsae* (Figure 8).[89] These compounds have a double bond at the butyl side chain. 2-Hydroxystemofoline (**187**) was obtained

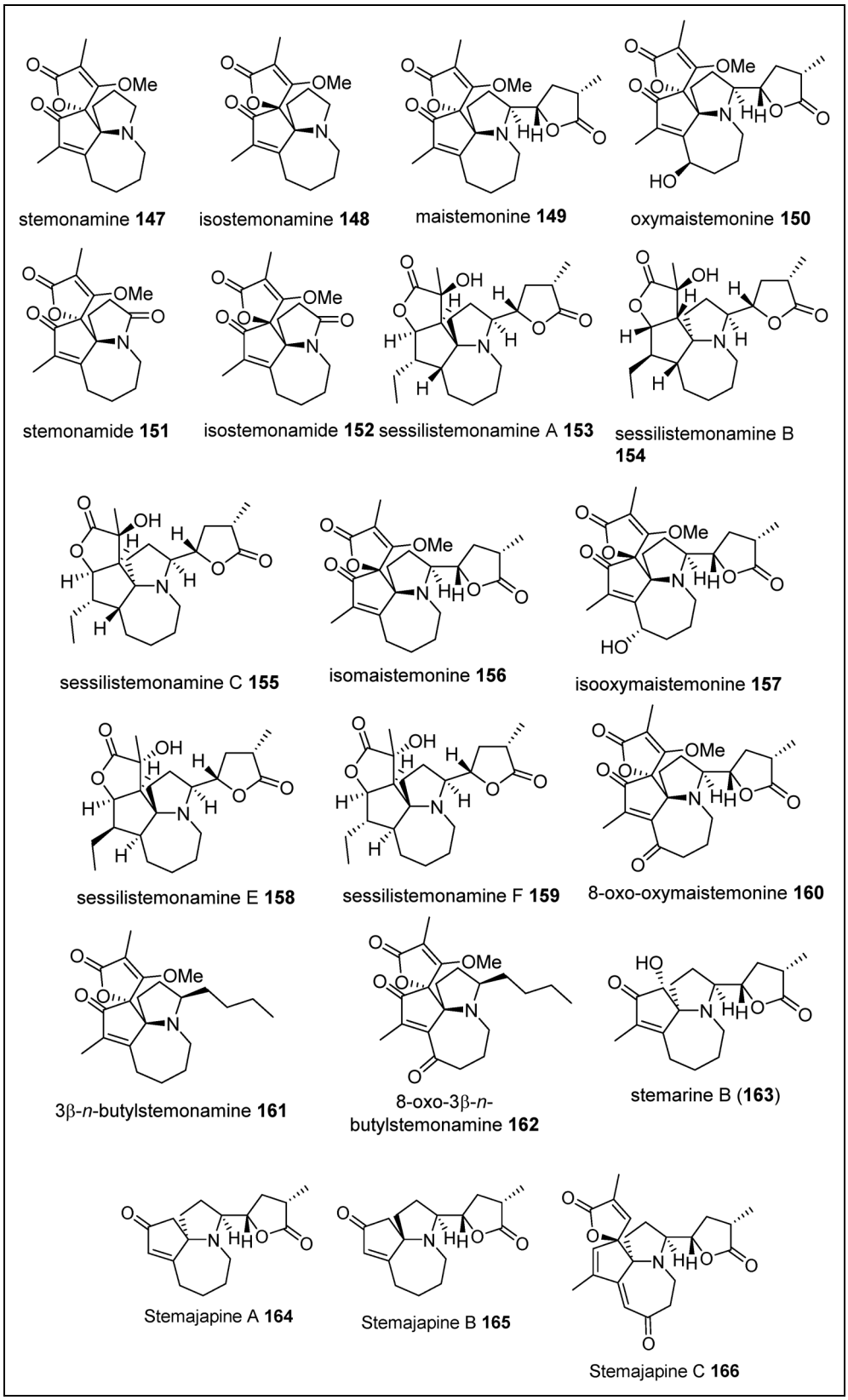


Figure 6. Stemoamine group alkaloids.

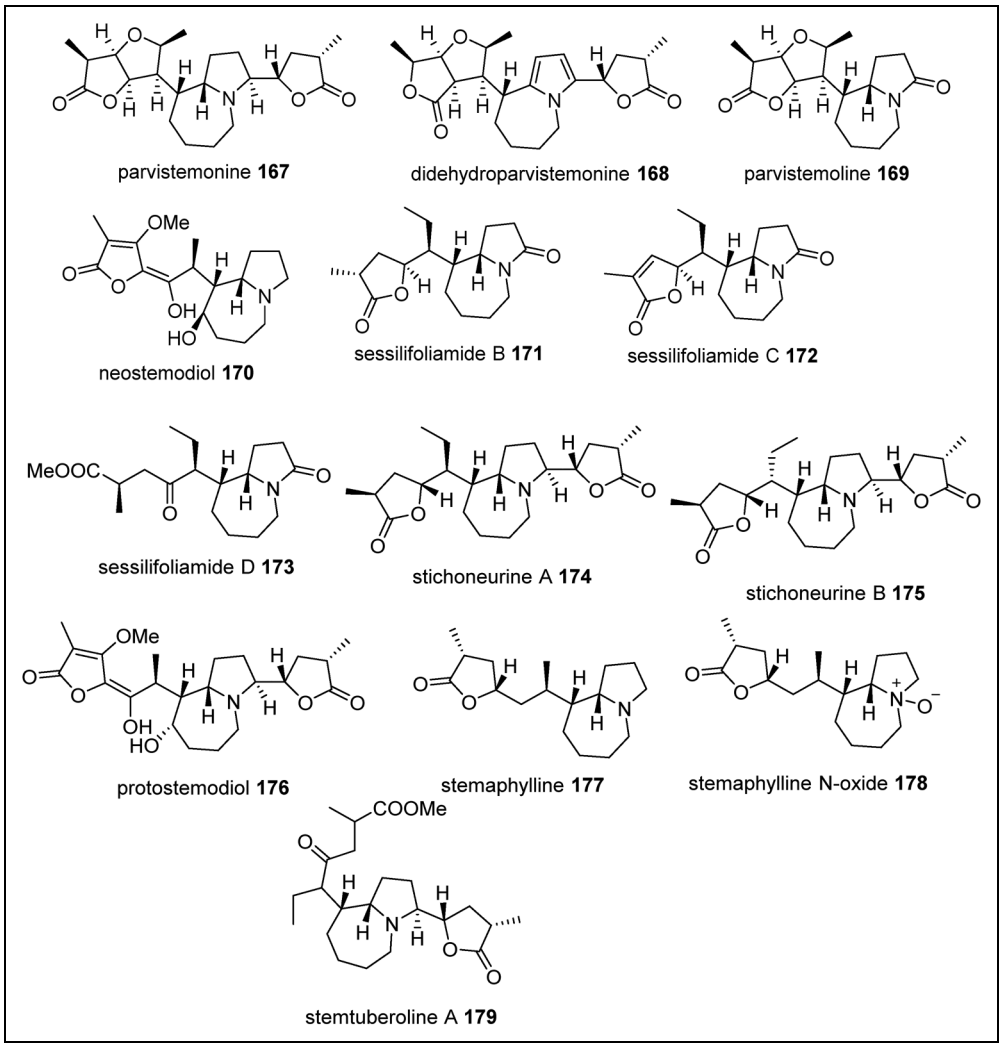


Figure 7. Parvistemoline group alkaloids.

from *Stemona collinsae* and its absolute configuration was confirmed by X-ray crystallography (Figure 8).[90] Two novel dihydrostemofoline alkaloids, 11(*S*),12(*R*)-dihydrostemofoline (**188**) and stemoburkilline (**189**), were isolated from a root extract of *Stemona burkillii* Prain (Figure 8).[91] In 2005, Sastraruji et al demonstrated the isolation and structure elucidation of 6 new stemofoline alkaloids including the first C19 stemofoline alkaloid, methylstemofoline (**190**), (3′*R*)-stemofolenol (**191**), (3′*S*)-stemofolenol (**192**), the first glycosidated *Stemona* alkaloid, stemofolinoside (**193**), 1′,2′-didehydrostemofoline-*N*-oxide (**194**), and (2′*R*)-hydroxystemofoline (**195**), from a root extract of an unidentified *Stemona* species (Figure 8).[92] Compounds **191** and **192** differ from each other by the configuration of the hydroxy group at the side chain. Hydroxystemofoline (**196**) and 16-hydroxystemofoline (**197**) were obtained by Tang et al[57] from stems and leaves of *Stemona japonica* (Figure 8). In **197**, the methyl group at the lactone ring is oxidized to primary alcohol. By semisynthesis, Sastraruji et al[93] proved that (1′*R*)-hydroxystemofoline (**198**), which they isolated and incorrectly reported as (2′*S*)-hydroxystemofoline, is a natural product (Figure 8). (2′*S*)-hydroxy-(11*S*,12*R*)-dihydrostemofoline (**199**) was isolated from the root extracts of *Stemona aphylla* (Figure 8).[94] Huang et al[63] isolated (19*S*)-hydroxy-21-methoxystemofoline (**200**) from the roots of *Stemona parviflora* (Figure 8).

Isolation of Stemona *Alkaloids Belonging to Stemocurtisine Group (Group 7)*

The stemocurtisine group alkaloids display a tetracyclic skeleton with an ether bridge between C-2 and C-8 and a carbon–carbon bond involving C-3 and C-7 of the pyrrolo[1,2-*a*]azepine nucleus. Thirteen alkaloids belonging to this group have been isolated and structurally determined. A new pentacyclic *Stemona* alkaloid, stemocurtisine (**201**) was isolated from a root extract of *Stemona curtisii* (Figure 9).[95] This compound was also discovered by Kaltenegger et al[48] at the same time and named pyridostemin. Along with pyridostemin, stemokerrin

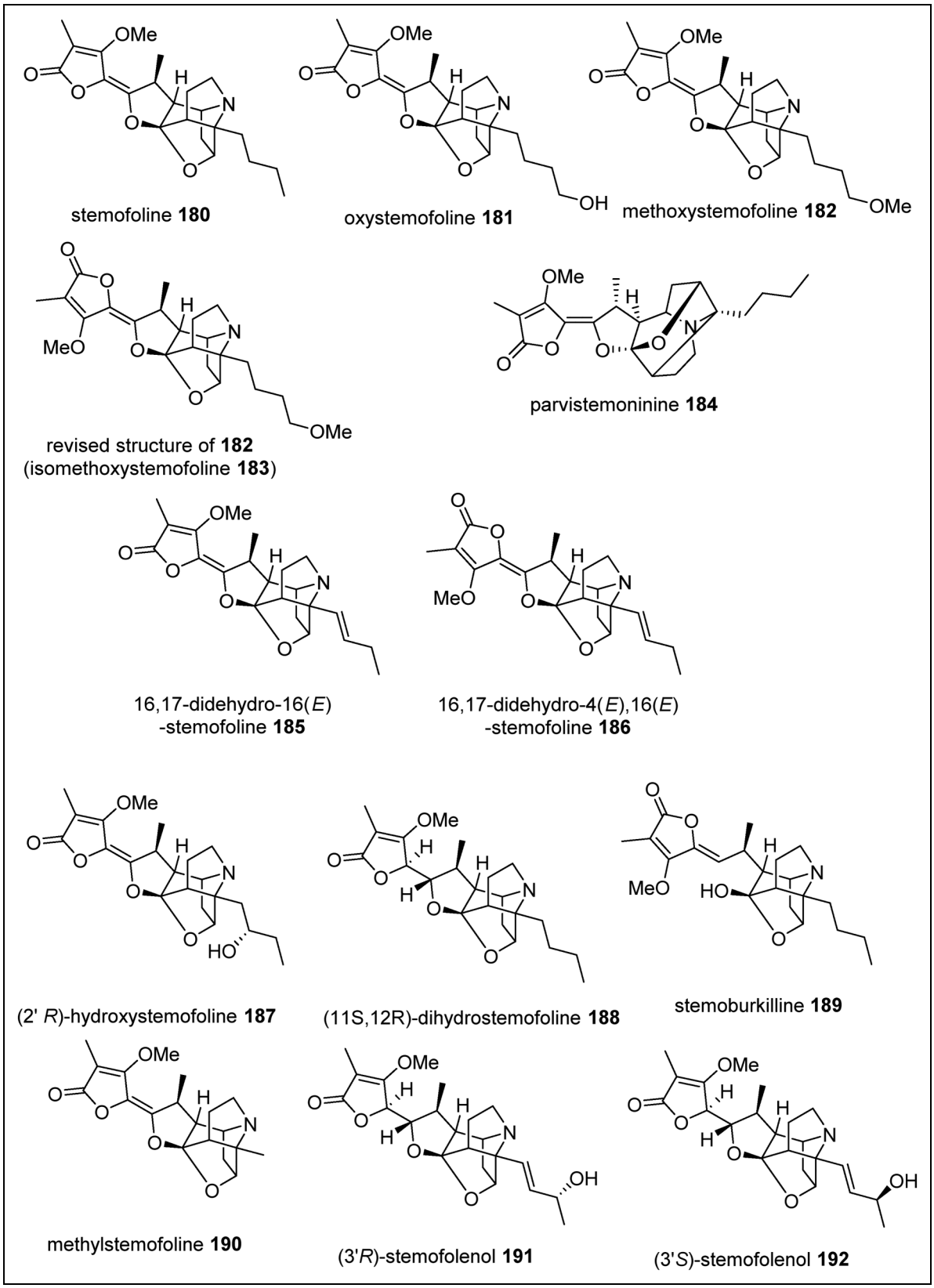


Figure 8. Stemofoline group alkaloids. (continued)

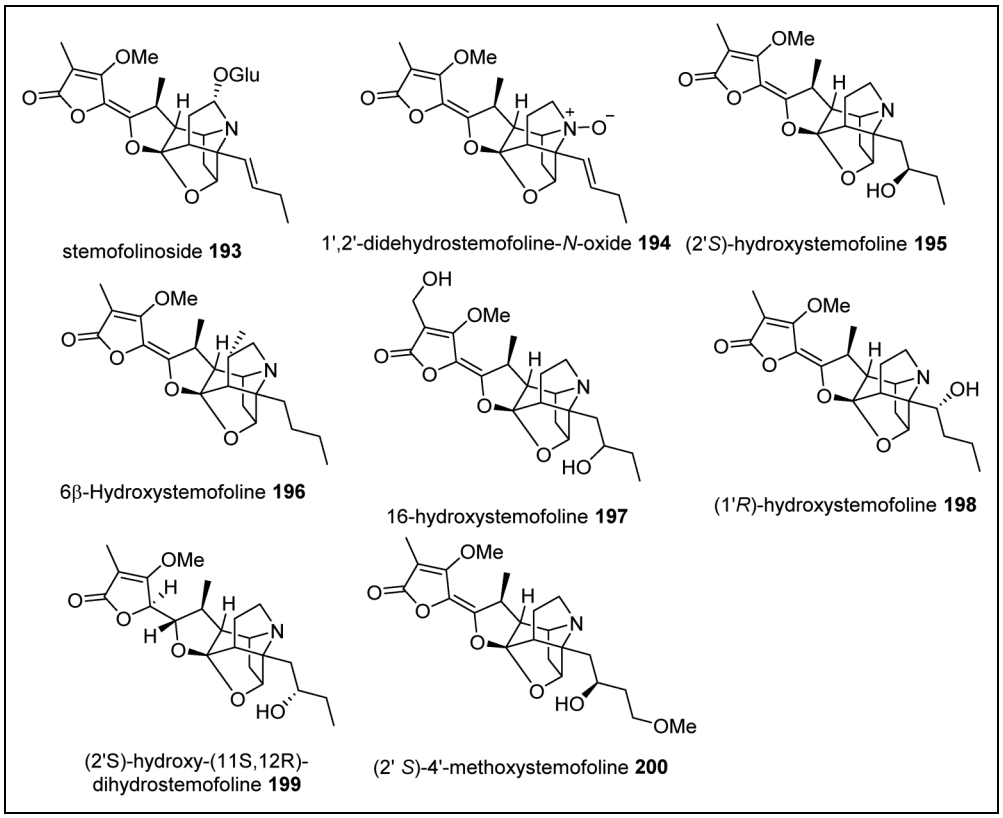


Figure 8. Continued.

(**202**), oxystemokerrin (**203**), oxystemokerrin-*N*-oxide (**204**), and methoxystemokerrin-*N*-oxide (**205**) were isolated from 4 *Stemona* species (Figure 9).[48] Stemokerrin has a double bond at C8 and C9, while oxystemokerrin and oxystemokerrin-*N*-oxide possess an ether bridge. Stemocurtisinol (**206**) with an ether linkage between C1 and C9 was obtained from a root extract of *S curtisii* (Figure 9).[96] Wang et al[53] achieved oxystemokerrilactone (**207**), stemokerrin-*N*-oxide (**208**), and cochinchistemoninone (**209**), from the roots of Vietnamese *Stemona* (Figure 9). Cochinchistemoninone contains a spiro lactone ring. Stemocochinamine (**210**) was yielded from the roots of *Stemona cochinchinensis* (Figure 9).[51] Cochinchistemonine (**211**) was separated from the roots of *Stemona cochinchinensis* collected from northern Vietnam (Figure 9).[97] Guo et al[77] separated and identified stemosessifoine (**212**) from the roots of *Stemona sessilifolia* (Figure 9). Stemocurtisine *N*-oxide (**213**) was isolated from the root extracts of *Stemona curtisii* (Figure 9).[58]

Isolation of Stemona *Alkaloids Belonging to Mislacenous Group (Group 7)*

Fifty-six *Stemona* alkaloids belonging to this group have been isolated and characterized. Oxotuberostemonine (**214**) was separated by Kondo[98] in 1954 and it was confirmed by crystallographic analysis in 1968 (Figure 10).[99] Parvistemoamide (**215**) was obtained by Xu et al[88] from *Stemona parviflora* (Figure 10). Recently, Olivier et al[100] revised the structure of parvistemoamide as stemoamide **60**. Lin et al[11] separated tuberosternonone (**216**) from the roots of *Stenuma tuberosa* (Figure 10). Tuberostemoninol (**217**) was yielded from the roots of *Stemona tuberosa* (Figure 10).[47] The isolation of tuberostemoenone (**218**) was reported by Cui and Lin[101] (Figure 10). Jiang et al[15] discovered neotuberostemoninol (**219**) from *Stemona tuberosa* Lour and its structure was characterized by X-ray crystallography (Figure 10). Parvineostemonine (**220**) was isolated from the stems and leaves of *Stemona parviflora* (Figure 10).[102] Cai and Luo[16] achieved maireistemoninol (**221**), neotuberostemonone (**222**), and epoxytuberostemonone (**223**) from the roots of *Stemona mairei* (Figure 10). Compound **223** contains an oxirane ring. Four new alkaloids, sessilifoliamides E-H (**224-227**) (also known as stemona-lactams E-H) were isolated from the roots of *Stemona tuberosa* (Miq.) Miq, and their configurations were confirmed by X-ray crystallography (Figure 10).[103] Sessilifoliamides E and F differ from each other by a tertiary alcohol, while sessilifoliamide G has an ether bridge.

Sessilifoliamide I (**228**) was produced from the root extracts of *Stemona sessilifolia* (Miq.) and its structure was elucidated by analysis of spectral data and X-ray crystallography (Figure 10).[104] Wang et al[105] obtained sessilistemonamine D (**229**) from the roots of *Stemona sessilifolia* (Figure 10). Lin et al[24] isolated tuberocrooline (**230**) and tuberostemoline (**231**)

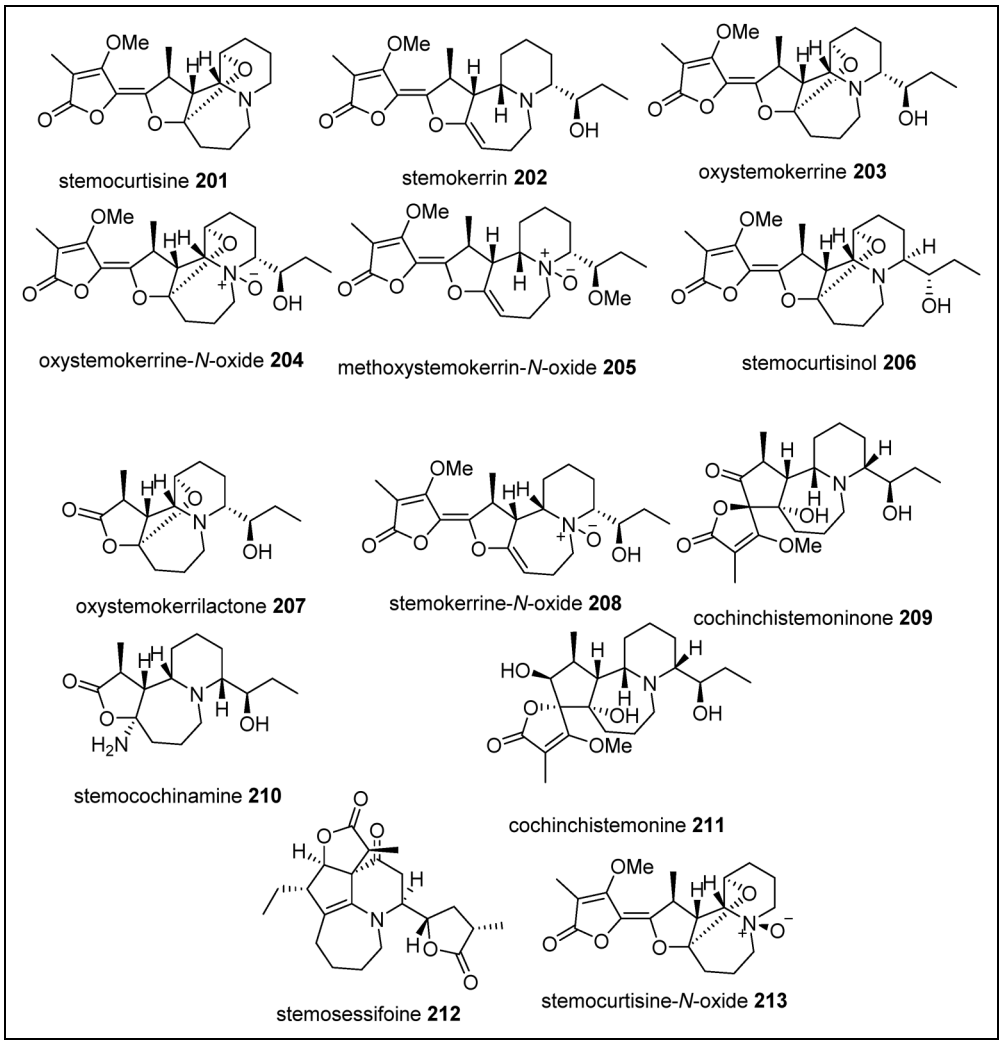


Figure 9. Stemocurtisine group alkaloids.

from the roots of *Stemona tuberosa* collected from Yunnan Province (Figure 10). Sessilifoliamide J (**232**) (also known as stemona-lactam J) having novel alkaloid skeletons was isolated from the roots of *Stemona sessilifolia* and its configuration was confirmed by X-ray crystallography (Figure 10).[49] 1,9*a*-*seco*-stemoenonine (**233**) with a carboxyl group was yielded from the roots of *Stemona tuberosa* by Lin et al.[54] Two new alkaloids, named tuberostemoninol A (**234**) and tuberostemoninol B (**235**) were isolated from *Stemona tuberosa* (Figure 10).[106] These compounds are diastereomers. Two novel *Stemona* alkaloids, sessilifoliamides K (**236**) and L (**237**), with a new pyrido[1,2-*a*]azonine skeleton were obtained from the roots of *Stemona sessilifolia* (Figure 10).[107] Stemoxazolidinones A-C (**238**-**240**) were isolated from the roots of *Stemona sessilifolia* (Figure 10).[25] The only difference between **238** and **239** is the configuration of the ethyl group, while **240** differs from **238** by the stereochemistry of the spiro lactone ring. Hitotsuyanagi et al[26] discovered stemona-lactams M, N, and Q (**241**-**243**) from the roots of *Stemona tuberosa* (Figure 10). The configuration of stemona-lactam M was confirmed by X-ray crystallography (Figure 10). Stemona-amines C (**244**) and D (**245**) were isolated from the roots of *Stemona tuberosa* Lour (Figure 10).[29] The only difference between **244** and **245** is the configuration of the hydroxy group.

A new *Stemona* alkaloid, 6-hydroxy-5,6-seco-stemocurtisine (**246**) was produced from the aerial parts of *Stemona curtisii* collected from Trang Province in Thailand and its configuration was determined by single-crystal X-ray crystallographic analysis (Figure 10).[108] Fukaya et al[109] obtained stemona-lactam S (**247**) from the roots of *Stemona tuberosa* and its absolute stereochemistry was elucidated by analysis of X-ray crystallography and vibrational circular dichroism (Figure 10). Stichoneurines F (**248**) and G (**249**) were achieved from the root extracts of *Stichoneuron caudatum* (Figure 10).[78] Sessilifoliamides E and F differ from each other by a tertiary alcohol. Yue et al[110] discovered stemonatuberone A-C (**250**-**252**), stemonatuberonol A (**253**), and stemonatuberosine A (**254**) from the ethanolic extract of dried root of *Stemona tuberosa* (Figure 10).

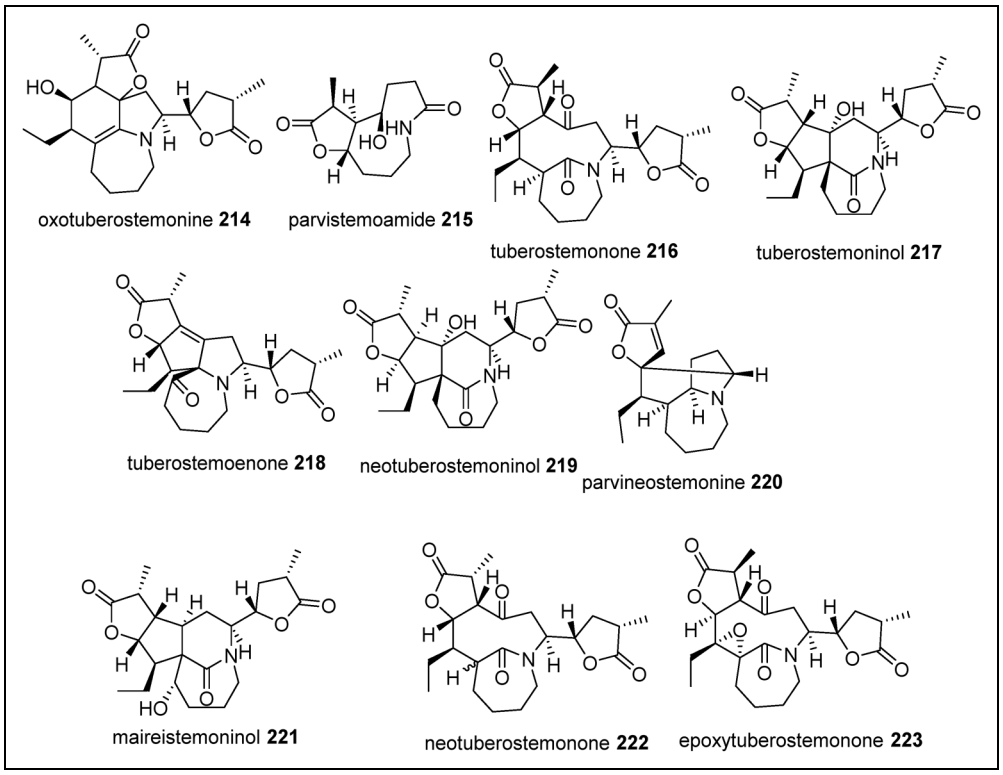


Figure 10. Mislaceneous *Stemona* alkaloids. (continued)

Compounds **250** and **252** are epimers. Neotuberostemoenone (**255**) was produced from the roots of *Stemona tuberosa* (Figure 10).[31] Tuberostemoline A (**256**), tuberostemoline B (**257**), oxotuberostemonine A (**258**), and tuberostemoninol C (**259**) were yielded from the roots of *Stemona tuberosa* (Figure 10).[30] Two new alkaloids, stemona-amines F (**260**) and G (**261**) were obtained from the roots of *Stemona tuberosa* Lour. (Stemonaceae). The relative configuration of stemona-amine F was established by X-ray crystallography (Figure 10).[111] Hu et al[73] discovered stemtuberlines A (**262**) and B (**263**), 2 new alkaloids with a special pyrrolo[32,1-*jk*] benzazepine-12-one skeleton, from the roots of *Stemona tuberosa* (Figure 10).

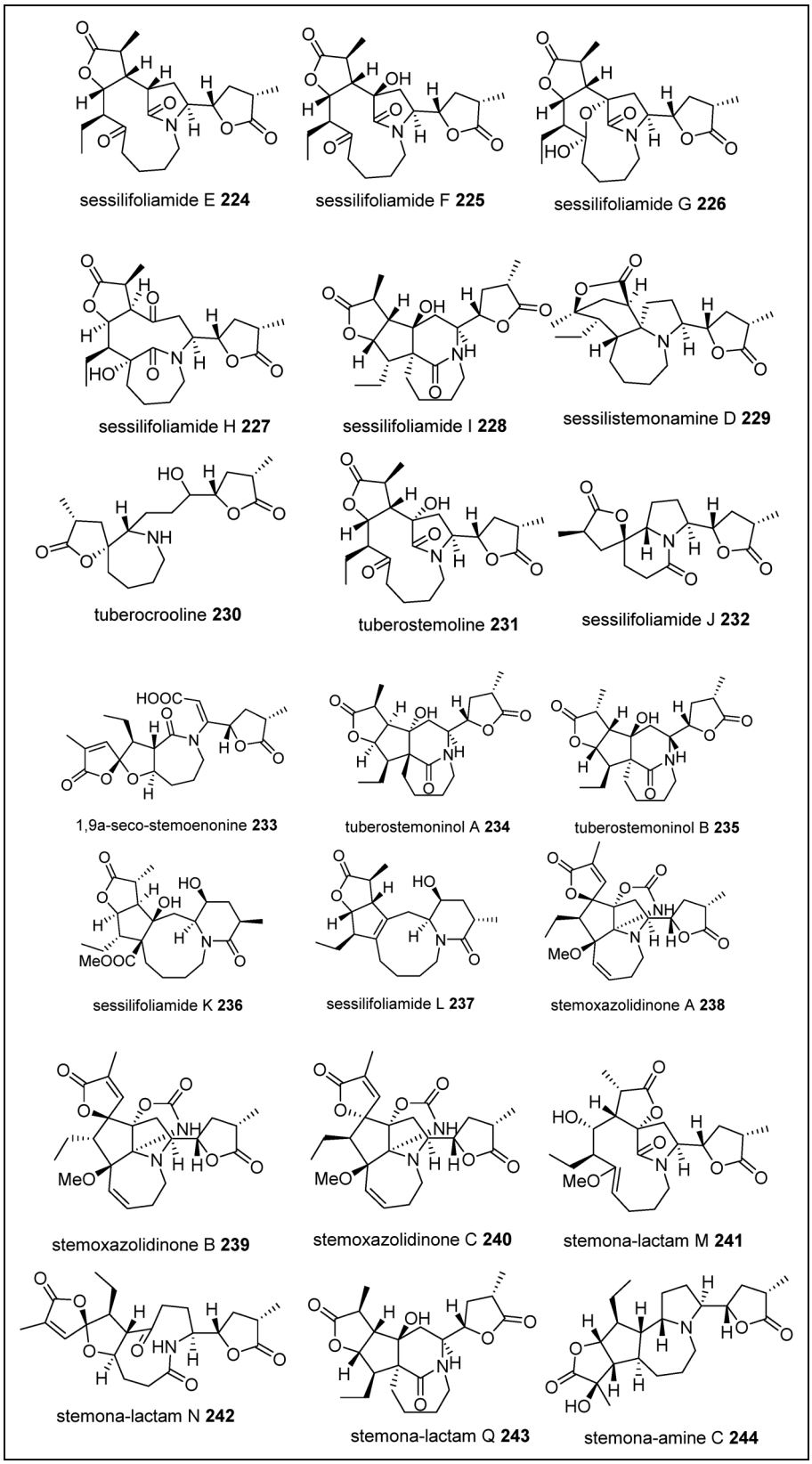
Chalom et al[112] separated a new *Stemona* alkaloid glycoside derivative, 6-hydroxy-5,6-secostemocurtisinoside (**264**) from the ethanolic extract of the aerial parts of *Stemona curtisii* (Figure 10). Tuberostemoline F (**265**) was produced from the roots of *Stemona tuberosa* and its structure was elucidated by spectroscopic data, X-ray single-crystal diffraction, and modified Mosher method (Figure 10).[40] It is the first *Stemona* alkaloid to attach to a sugar molecule. Shi et al[39] achieved atroptuberostemonone (**266**) and 9-deoxo-stemona-lactam F (**267**) from the roots of *Stemona tuberosa* (Figure 10). In this report, the structure of stemonatuberone B was revised to **268**. Recently, stemarines N (**269**) and O (**270**) were isolated from the roots of *Stemona mairei* (H.Lév.) K.Krause (Stemonaceae).[64] The only difference between **269** and **270** is the configuration of the hydroxy group.

Bioactivities of *Stemona* Alkaloids

Insecticidal Activity

Tang et al[56] tested in vitro the insecticidal activity of 6β-hydroxystemofoline **196**, 16-hydroxystemofoline **197**, neostemofoline **88**, protostemodiol **176**, and 13-demethoxy (11*S**,12*R**)-dihydroprotostemonine **87**, and stemofoline **180** against pest insect *Heliothis virescens*. All compounds showed potential activities. Compounds **196**, **197**, **88**, and **180** acted as agonists, whereas **176** and **87** acted as antagonists of the insect nicotinic acetylcholine receptors (nAChRs). The remarkable potential of these stemofolines might be related to the defense system of the *Stemona* plants. Kaltenegger et al[48] reported that lipophilic crude extracts of the roots of *Stemona curtisii* and *Stemona cochinchinensis* exhibited significant insecticidal activity against *Spodoptera littoralis*, whereas moderate activity for *S kerrii* was observed. Among isolated alkaloids, stemofoline **180** was the most active, followed by oxystemokerrin **203** with IC_{50} values of 2.0 and 5.9 ppm, respectively. The accumulation of stemofoline, oxystemokerrin, and dehydroprotostemonine **67** might be responsible for the insecticidal activity of these plants via 2 different modes of action.

The insecticidal properties of the crude extract of *Stemona aphylla* roots and stemaphylline **177**, using a topical application, were screened by Mungkornasawakul et al.[84] Results showed this compound had an equal activity to the positive control, methomyl, while the crude extract showed much lower activity. Sakata et al[65] examined the biological activities of stemospironine



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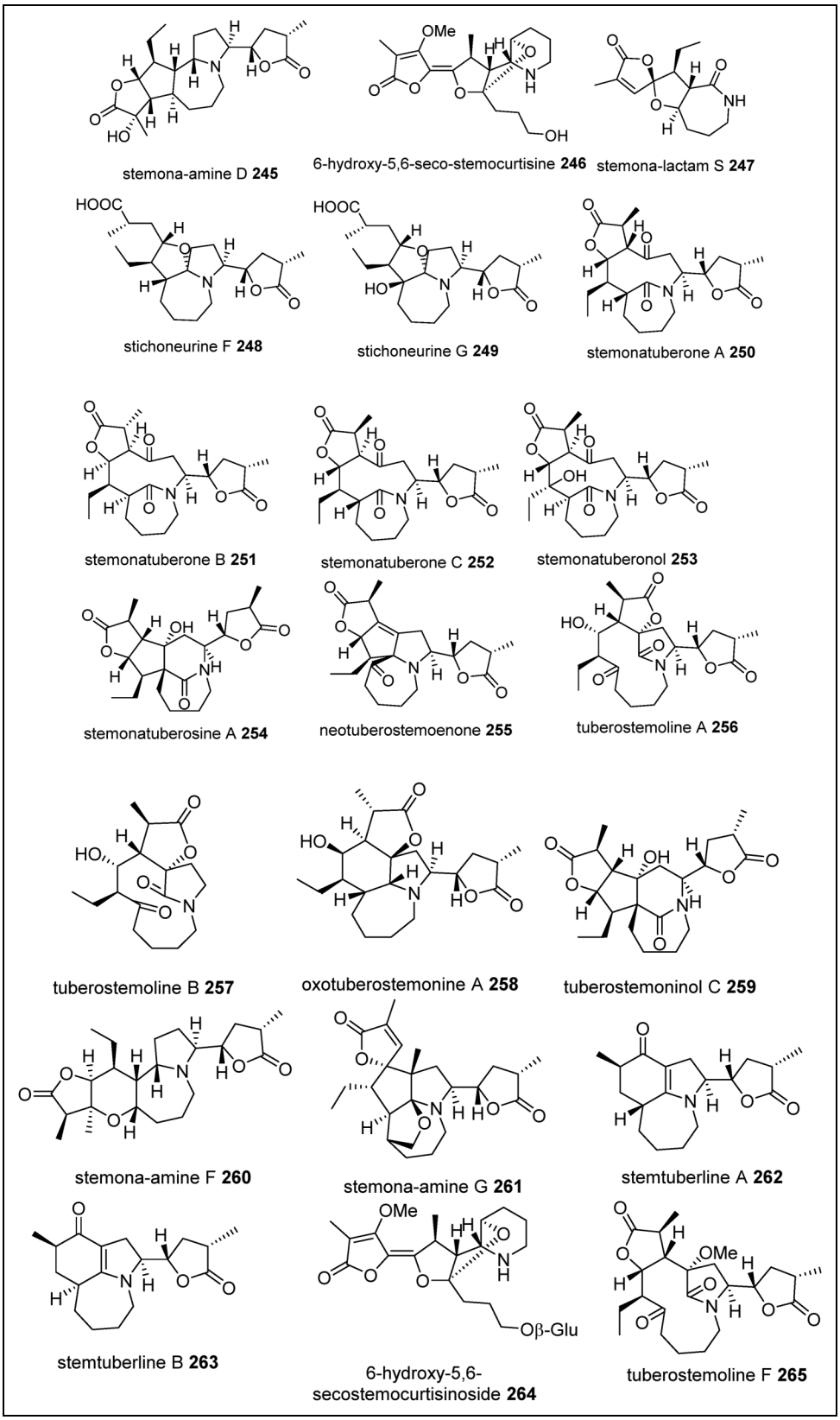

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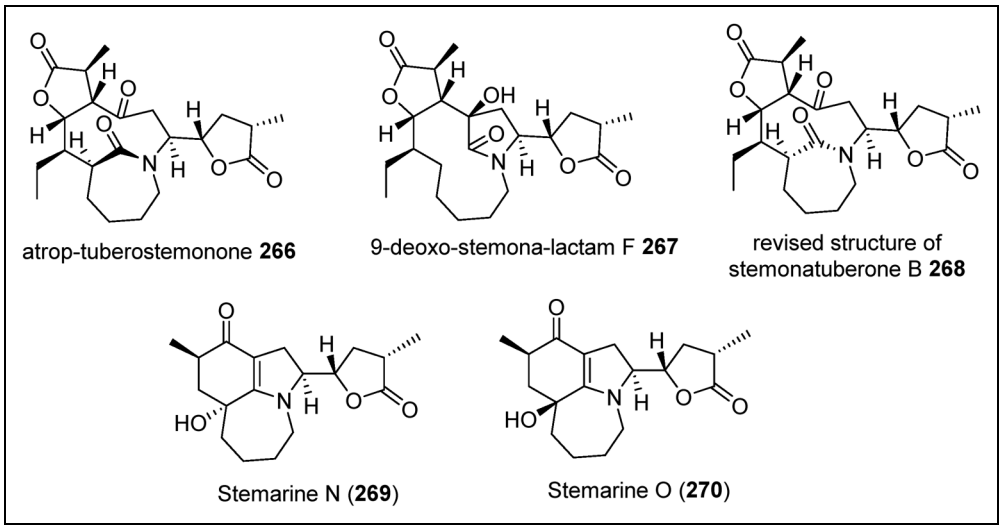

Figure 10. Continued.

and stemofoline against fourth-instar silkworm larvae. Stemofoline was much more active than stemospironine against silkworm larvae (*Bombyx mori* L.) by oral administration. Brem et al[113] indicated that extracts from the leaves and roots of *Stemona collinsae* exhibited strong insecticidal activity compared to those of 2 Aglaia species, a commercial Pyrethrum extract, and azadirachtin. Stemofoline and didehydrostemofoline isolated from extracts exhibited stronger activities than those of Pyrethrum extract. Tuberostemonine showed excellent repellency but no toxic effects.

Jiwajinda et al[89] demonstrated that 16,17-didehydro-16(*E*)-stemofoline (**185**) exhibited better insecticidal activity than stemofoline against diamondback moth larvae. Kongkiatpaiboon et al[114] investigated insecticidal activities against neonate larvae of *Spodoptera littoralis* of 10 *Stemona curtisii* roots and found that stemofoline possessed the highest insecticidal activity with an LC50 value at 2.4 ppm and EC50 at 0.98 ppm. Sakulpanich et al[115] demonstrated that *S collinsiae* root extract displayed insecticidal activity and killed *P ruficornis* in the larval stage via topical administrations and killed adult *P ruficornis* by ingestion administration. The finding suggested that the root extract could be used as a natural insecticide to terminate the life cycle of *P ruficornis*.

Antitussive Activity

In a study described by Lin's group, bisdehydrostemoninine **69** showed remarkable antitussive activity in the citric acid-induced guinea pig cough model ($ID_{50} = 188 \pm 13$ μM).[50] In another report, tuberocrooline **230** and 10-hydroxycroomine **130**, along with croomine **123** and tuberospironine were examined for antitussive activity in the citric acid-induced guinea pig cough model. Croomine **123** was the most potent compound showing a dose-dependent inhibition of coughing with an ID_{50} value of 0.18 mmol/kg.[24] The group also evaluated stemoenonine **81**, 9a-*O*-methylstemoenonine **84**, stemoninoamide **65**, and stemoninine **59** for their antitussive activities. Among them, compounds **65** and **59** displayed good antitussive activity after oral and intraperitoneal administrations with ID_{50} values of 0.33 and 0.26 mmol/kg, respectively.[54]

Stemokerrin was evaluated for antitussive activity using a citric acid-induced guinea pig cough model. It displayed significant antitussive activity, and about 62% cough inhibition was observed at a single intraperitoneal dose of 70 mg/kg.[60] Four alkaloids, neotuberostemonine, tuberostemonine, and tuberostemonine were tested for antitussive activity in the citric acid-induced guinea pig cough model. All of them displayed dose-dependent inhibitory activity after intraperitoneal administration. Tuberostemonine had the same potency via both oral and intraperitoneal dosing, while neotuberostemonine showed significantly lower oral activity than intraperitoneal application. In contrast, tuberostemonine did not show oral activity.[116] Yang et al[57] proved that protostemonine, stemospironine, and maistemonine showed remarkable antitussive activity in a citric acid-induced guinea pig cough model via peripheral administration, while stemonamine had antitussive activity via intracerebroventricular administration.

Five *Stemona* alkaloids including neotuberostemonine (**5**), tuberostemonine H (**16**), tuberostemonine J (**17**), epibisdehydrotuberostemonine (**18**), and neostenine (**15**) isolated from *Stemona tuberosa* were tested for antitussive activity in the guinea pig after cough induction by citric acid aerosol stimulation. Compounds **5** and **15** showed excellent antitussive activity.[18] Xu et al[117] examined the antitussive potency of croomine, neotuberostemonine, stemonine, and tuberostemonine in guinea pigs with citric acid aerosol to induce cough. Neotuberostemonine, tuberostemonine, and stemoninine acted on the peripheral cough reflex pathway, while croomine acted on the central part.

Acetylcholinesterase (AChE) Inhibitory

AChE inhibition is also an important bioactivity of the *Stemona* alkaloids. Sessilistemonamines A-C **153** to **155** and

dihydrostemoninine **78** isolated from the roots of *Stemona sessilifolia* were examined for AChE inhibitory properties by Wang et al.[52] Compounds **153** and **154** displayed moderate activity with IC_{50} values of 68.8 ± 9.5 and 17.1 ± 2.5 μM, respectively but much less than huperzine A (IC_{50} = 0.021 ± 0.016 μM), the reference compound. Stichoneurine E **94**, bisdehydostemoninine A **72**, stemoninine **59**, sessilistemonamine C **155**, and sessilistemonamine A **131** were yielded from *Stichoneuron halabalensis* and evaluated as inhibitors of electric eel and human AChE. Compounds **72** and **59** exhibited moderate inhibitory activity against human AChE with IC_{50} values of 5.52 ± 0.13 and 3.74 ± 0.09, respectively, but less potent than galantamine (IC_{50} = 0.54 ± 1.25 μM), the standard drug.[59]

Kongkiatpaiboon et al[118] evaluated the AChE inhibitory activity of hexane, dichloromethane, and methanol extracts of *Stemona collinsiae* roots as well as isolated *Stemona* alkaloids including didehydrostemofoline and stemofoline. IC50 values on AChE inhibitory activities of hexane, dichloromethane, and methanol extracts were 126.72, 73.78, and > 1000 mg/mL, respectively. IC_{50} values of didehydrostemofoline, stemofoline, and standard galanthamine were 131.3, 102.1, and 1.30 mM, respectively. In a study demonstrated by Qian et al,[22] neotuberostemonine, sessilifoline B, and a mixture of bisdehydrotuberostemonine D and bisdehydrotuberostemonine E displayed potential AChE inhibitory activities in a dosage of 10 mg using huperzine A as a reference drug. Dong et al[36] tested the AChE inhibitory activity of dehydrostenines A and B and concluded that these compounds did not show significant activity.

Mungkornasawakul et al[84] screened the AChE inhibitory activity of crude dichloromethane root extract of *Stemona aphylla* and stemaphylline. The results revealed that the crude extract had higher activity than that of stemaphylline. In a report described by Lai et al,[28] stenine A (**35**) and stenine (**2**) exhibited remarkable anti-AChE activities, with IC_{50} values of 2.1 ± 0.2 μM and 19.8 ± 2.5 μM, respectively. Stichoneurines F (**248**) and G (**249**), sessilistemonamines E (**158**) and F (**157**) were isolated from the root extracts of *Stichoneuron caudatum* and screened for AChE inhibitory activities. Among them, sessilistemonamines E displayed remarkable inhibitory activity with an IC_{50} value of 9.1 ± 0.15 μM.[78] Sastraruji et al[93] demonstrated that (1′*R*)-hydroxystemofoline showed the best AChE inhibition although its activity was weaker than galanthamine, the reference drug. Eight alkaloids including atrop-tuberostemonone, 9-deoxo-stemona-lactam F, 9a-epi-stemona-lactam P, tuberostemonone, tuberostemonine, 2-oxostenine, stemona-amine B, and stemona-lactam Q were examined for their AChE inhibitory activities following Ellman's method using huperzine A as the reference compound (IC_{50} 48.8 nM). Among them, tuberostemonine and 2-oxostenine showed strong activities with IC_{50} values of 66.4 and 81.4 mM, respectively.[39]

Other Bioactivities

Umsumarng et al[119] investigated the MDR modulation effects of alkaloids isolated from *Stemonaceae* plants from the family *Stemona* and *Stichoneuron*. *Stemona* alkaloids including isostmofoline, 11*Z*-didehydrostemofoline, and 11*E*-didehydrostemofoline with core caged ring structure displayed good activity to inhibit P-gp function and increase anti-neoplastic drug sensitivity. In addition, these alkaloids exhibited less toxicity toward normal cells (fibroblast, PBMCs, and RBCs) in in vitro studies. Chanmahasathien et al[120] evaluated stemocurtisine, oxystemokerrine, and stemofoline for synergistic growth inhibitory activity with some anticancer agents including vinblastine, paclitaxel, and doxorubicin of KB-V1 cells. Results revealed that stemofoline exhibited the most inhibitory activity in vitro in the reversal of P-gp-mediated MDR. In addition, the sensitivity of these drugs in a dose- and time-dependent manner in KB-V1 cells was remarkably increased by treatment with stemofoline at different concentrations up to 72 h.

Hu et al[38] described the evaluation for anti-tobacco mosaic virus (TMV) activity of the *Stemona* alkaloids and dehydroisostemoninine was found to exhibit excellent anti-TMV activity with the curative inhibition rate of 84.6% at a concentration of 50 μg/mL. Stemtuberoline also C displayed significant anti-TMV activity with an inhibition rate of 60.48% at the concentration of 50 μg/mL in comparison with ningnamycin, the reference drug (52.89%.).

The anthelminthic activity of tuberostemonine **1** was evaluated against *A cantonensis*, *D canium*, and *F hepatica*. This compound affected the mobility of these helminthic worms.[121] Tuberostemonine was suggested as the major ingredient that is responsible for the insectidal activity of *Stemona tuberosa* against the larvae of *Spodoptera littoralis*.[122] Stemarines C-F, *Stemona* alkaloids possessing a five-carbon carboxylic side chain at C-3, displayed excellent nematocidal activity against *Caenorhabditis elegans*.[64] Pyne et al[96] isolated a new pyrido[1,2-*a*]azepine *Stemona* alkaloids, stemocurtisinol, and known compound oxyprotostemonine from the roots of *S curtisii* and examined for larvicidal activity on malarial carrying mosquito larvae. These alkaloids displayed more significant activity than the crude extract. Among them, oxyprotostemonine was the most active component. Chalom et al[112] examined larvicidal activities against the dengue vector, *Aedes aegypti* of the extract of aerial parts of *Stemona curtisii* and the pure isolated compounds including 6-hydroxy-5,6-secostemocurtisinoside, stemocurtisine, (11*Z*)-1′,2′ didehydrostemofoline, and 6-hydroxy-5,6-seco-stemocurtisine. (11*Z*)-1′,2′ didehydrostemofoline displayed the strongest larvicidal activity with a LC50 value of 2.44 mM. In a study reported by Ramli et al,[61] 3 alkaloids including 13-demethoxy-11(S*), 12(R*)-dihydroprotostemonine, isoprotostemonine, and protostemonine exhibited moderate antiplasmodial activities against the *Plasmodium falciparum* strains, TM4 (IC_{50} values of 17.7 3.7, 16.8 5.4, and 16.0 4.2 mg/mL, respectively) and K1 (IC_{50} values of 16.8 3.1, 14.1 3.7, and 11.9 3.3 mg/mL, respectively).

Twelve *Stemona* alkaloids including stemokerrin, methoxystemokerrin-*N*-oxide, oxystemokerrin, oxystemokerrin-*N*-oxide, pyridostemin (stemocurtisine), dehydroprotostemonine, oxyprotostemonine and stemocochinine, stemofoline,

2′-hydroxystemofoline, protostemonine, and parvistemonine were obtained from 4 *Stemona* species. All of them were evaluated for toxicity and growth inhibition against neonate larvae of *Spodostera littoralis* using 1′,2′-didehydrostemofoline as the reference compound. Stemofoline was found to be the most active, followed by oxystemokerrin (IC_{50} values of 2.0 and 5.9 ppm, respectively).[96]

Xu et al[40] investigated NO production inhibitory effects in LPS-induced RAW 264.7 cells of 29 *Stemona* alkaloids and found that compound dehydrostenine B exhibited equivalent activity to that of the positive drug dexamethasone, while compounds dehydrostenine A, tuberostemonine D, tuberostemonine O, tuberostemoline F, tuberostemoline, and dehydrocroomine displayed a medium inhibitory effect. Stemjapines A and C exhibited strong NO production inhibitory activity with IC_{50} values of 19.7 and 13.8 μM.[79]

Lee et al[123] investigated the inhibitory effect on lipopolysaccharide-induced nitric oxide production of methanol extract of the roots of *Stemona tuberosa* and isolated *Stemona* alkaloids. The results indicated that methanol extract significantly inhibited lipopolysaccharide-induced nitric oxide production in murine BV2 microglial cells. Among tested compounds, bisdehydroneotuberostemonine, *epi*-bisdehydrotuberostemonine J, and bisdehydrotuberostemonine exhibited remarkable inhibitory effects on lipopolysaccharide-induced nitric oxide production in BV2 microglia at 100 μM. In research reported by Huang et al, protostemonine and stemofoline showed strong nematicidal activity against *Panagrellus redivevus*, with IC_{50} values of 0.10 and 0.46 μM, respectively.[59] The bioactivity of *Stemona* alkaloids is also well summarized by Pyne et al.[124,125]

Conclusion

In conclusion, in this review article, we have described the isolation and bioactivity of *Stemona* alkaloids from the *Stemonacea* family. We have summarized more than 110 studies on the isolation and bioactivity of *Stemona* alkaloids in the literature. More than 250 *Stemona* alkaloids have been isolated and identified. Furthermore, the article also focuses on the bioactivities of *Stemona* alkaloids. Revision on the structure of several *Stemona* alkaloids was also presented. Presumably, these activities can help to explain the traditional medicinal application of these plants although further pharmacological studies are needed. In the future, the total syntheses of *Stemona* alkaloids will be discussed and reported.

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