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REVIEW ARTICLE

Nature spermidine and spermine alkaloids: Occurrence and pharmacological effects

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KEYWORDS

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Abstract Spermidine and spermine are special polyamines in organisms, and produced *in vivo* by putrescine and S-adenosylmethionine catalyzed by a variety of enzymes. Spermidine and spermine possess multiple amino groups, and are closely related to cell division, growth and survival. Spermidine and spermine alkaloids are widely distributed in plants, bacteria and marine organisms, and can be divided into macrocyclic and open chain according to the skeletons. Spermidine and spermine alkaloids exhibited numerous pharmacological effects such as anti-inflammatory, antibiotics, anti-tumor, anti-Alzheimer and anti-virus. However, up to now, there are few systematic reviews on spermidine and spermine alkaloids. In this review, based on the number of atoms in the ring, we summarized the distributions and pharmacological effects of spermidine and spermine alkaloids. Spermidine and spermine alkaloids have special chemophenetic significances in the plant kingdom, especially the macrocyclic spermidine and spermine alkaloids. Spermidine alkaloids are much more abundant in nature than spermine alkaloids. The pharmacological activities of the open chain spermidine and spermine alkaloids are studied in depth. Polycyclic guanidine spermidine alkaloids, isolated from marine sponge, exhibit great potential in various cancer cells. However, pharmacological studies of macrocyclic spermidine and spermine alkaloids are scarce. Synthesis is an effective way to get more spermidine and spermine alkaloids and their analogues for further study.

1. Introduction

Polyamines are a class of compounds containing two or more amino groups. The most common polyamines with important physiological functions are putrescine, spermidine and spermine (Fig. 1). Spermidine (N-C3-N-C4-N) is widely distributed in organisms and synthesized by putrescine and S-adenosylmethionine. Spermine (N-C3-N-C4-N-C3-N) is a kind of polyamine containing two primary and two secondary amines in its structure (Mude et al., 2022). It is produced *in vivo* by putrescine and S-adenosylmethionine catalyzed by a variety of enzymes. Spermidine and spermine are essential for cell viability, pro-

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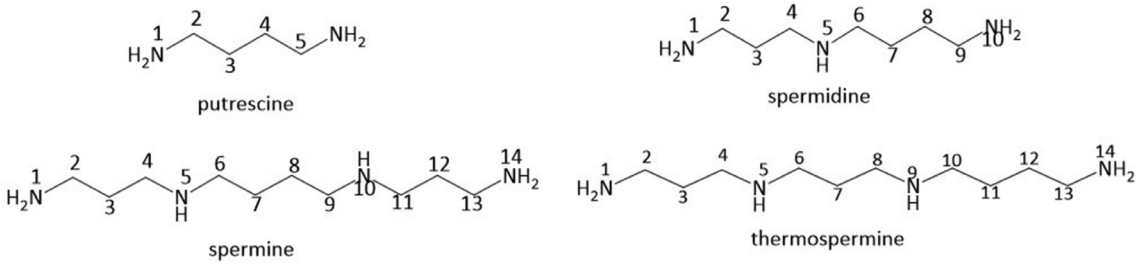


Fig. 1 Chemical structures of putrescine, spermidine, spermine and thermospermine.

liferation, function and differentiation, which possess biological activities such as anti-aging and anti-cancer (Pegg 2014; Madeo et al., 2018).

Spermidine and spermine alkaloids are widely distributed in plants, bacteria and marine organisms, which can be classified into macrocyclic and open chain according to the skeletons (Da Silva and Soengas 2017). Thermospermine is the isomer of spermine converted from spermidine (Fig. 1). Thermospermine alkaloids are also distributed in plants (Park et al., 2017). The spermidine and spermine alkaloids exhibit numerous pharmacological effects such as anti-inflammatory, antibiotics, anti-tumor, anti-Alzheimer and anti-virus. Although a great deal of spermidine and spermine alkaloids have been found during these years, the chemophenetic significances of the spermidine and spermine alkaloids are not clear. Therefore, it is meaningful to find the distribution characteristics of the spermidine and spermine alkaloids, especially macrocyclic spermidine and spermine alkaloids, which are less reported compared with open chain spermidine and spermine alkaloids. Meanwhile, up to now, there are few systematic reviews summarizing the pharmacological effects of the spermidine and spermine alkaloids.

Herein, in this review, we conclude the occurrence and pharmacological effects of the spermidine and spermine alkaloids. The macrocyclic spermidine and spermine alkaloids are classified based on the number of atoms in the ring.

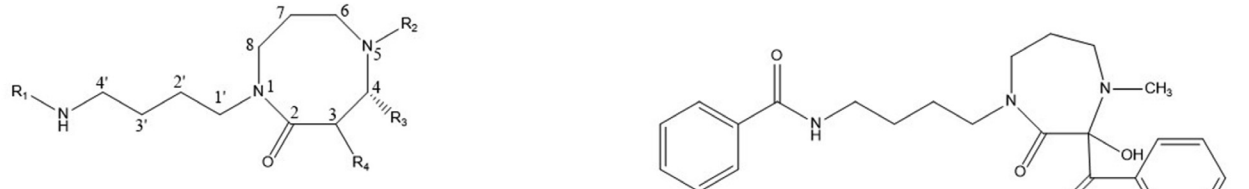
2. Spermidine and spermine alkaloids

2.1. 8-membered ring of spermidine alkaloids

Dovyalicin-type alkaloids are a class of amide alkaloids having a spermidine nucleus (Fig. 2, Table.1). Till now, this type of alkaloids was exclusively isolated from the family salicaceae, genus *Dovyalis* (*D. abyssinica*, *D. macrocalyx*, *D. hebecarpa* and *D. caffra*) (Stærk et al., 2003; Rasmussen et al., 2006; Zaki et al., 2019) and genus *Homalium* (*H. cochinchinensis*) (Addo et al., 2021), and nine members were identified named dovyalicin A, B, C, D, E, F, G, H and I. The dovyalicins have three types of skeletons, with dovyalicin A, B, C, E, G, H and I possessing spermidine as part of a perhydro-1,5-diazocine moiety to form an 8-membered heterocyclic ring, dovyalicin D possessing spermidine as part of a perhydro-1,4-diazepine moiety to form a 7-membered heterocyclic ring, while dovayalicin F is an open-chain spermidine alkaloid. Dovyalicin A, B, E, H and I all have a *C*-4 phenyl group, with the absolute configuration S. They differ in *N*-5 and *C*-4′ groups, with dovyalicin A/N^{-5}(−|-) methyl analogue of dovyalicin E, dovyalicin B *C*-4′ methyl analogue of dovyalicin A, and dovyalicin H and dovyalicin I *C*-4′ trans and cis cinnamoyl analogues of dovyalicin A, respectively. Dovyalicin C is 3-benzoyl analogue of dovyalicin A, with no *C*-4 substituted group. Dovayalicin F has no substituted group in the 8-memberd perhydro-1,5-diazocine ring, with a long side chain at *C*-4′ position. Dovyalicin D possesses a perhydro-1,4-diazepine ring oxygenated at *C*-3 rather than the perhydro-1,5-diazocine ring, and is devoid of optical rotation and presumably racemic. At ambient temperature, dovayalicin F exists as a mixture of cis and trans conformers.

2.2. 13-membered ring of spermidine alkaloids

The spermidine lactam alkaloids with a 13-membered ring have been found mainly in the families of celastraceae, lami-



	R1	R2	R3	R4
dovyalicin A	PhCO-	CH_3	Ph	/
dovyalicin B	CH_3	CH_3	Ph	/
dovyalicin C	PhCO-	CH_3	/	PhCO-
dovyalicin E	PhCO-	/	Ph	/
dovyalicin G	$CH_3(CH_2)_{10}CH{=}CHCO$-	/	/	/
dovyalicin H	(E)-PhCH=CH-	CH_3	Ph	/
dovyalicin I	(Z)-PhCH=CH-	CH_3	Ph	/

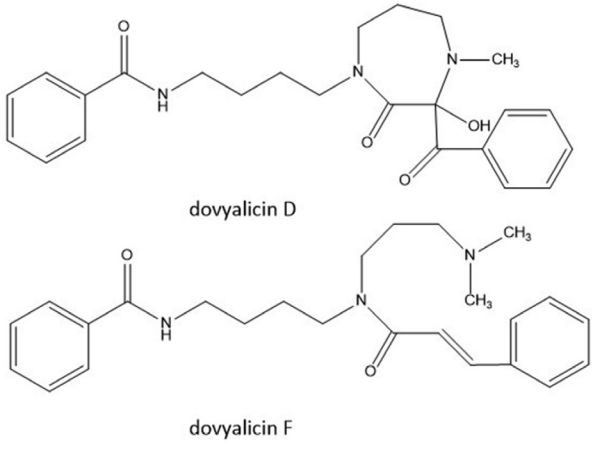


Fig. 2 Chemical structures of 8-membered ring spermidine alkaloids.

Table 1 8-membered ring of spermidine alkaloids.

Compound		plant	part	genus	family	ref
8-membered ring	dovyalicin A	*Dovyalis abyssinica*	leaf, twig	Dovyalis	salicaceae	(Rasmussen et al., 2006)
		Dovyalis hebecarpa	leaf, twig			(Rasmussen et al., 2006)
		Dovyalis macrocalyx	twig			(Stærk et al., 2003; Rasmussen et al., 2006)
	dovyalicin B	*Dovyalis abyssinica*	leaf			(Rasmussen et al., 2006)
		Dovyalis macrocalyx	leaf			(Stærk et al., 2003)
	dovyalicin C	*Dovyalis macrocalyx*	leaf			(Stærk et al., 2003; Rasmussen et al., 2006)
	dovyalicin D	*Dovyalis macrocalyx*	leaf			(Stærk et al., 2003)
	dovyalicin E-F	*Dovyalis abyssinica*	leaf, twig			(Rasmussen et al., 2006)
	dovyalicin G	*Dovyalis caffra*	leaf, twig			(Zaki et al., 2019)
	dovyalicin H-I	*Homalium cochinchinensis*	aerial	homalium	salicaceae	(Addo et al., 2021)

aceae and fabaceae (Fig. 3, Table.2). Most of the spermidine alkaloids with a 13-membered ring differ in substituent groups of *C*-1 and *C*-8. Benzene and its derivatives are common substituents at *C*-8.

Celallocinnine, celacinnine, celafurine and celabenzine differ only in the acyl side chain (Kupchan et al., 1974; Kupchan et al., 1977; Wagner and Burghart 1982; Mahato et al., 1985; Seguineau et al., 1992). Celallocinnine and celacinnine are characterized by the presence of a 13-membered ring reflecting spermidine and cinnamoyl precursorial units at *C*-1. Celallocinnine and celacinnine are *cis*-and *trans*-isomers, the cinnamoyl double bond has cis configuration for celallocinnine and trans configuration for celacinnine. Meefarnine A and B were isolated from *Meehania fargesii* (Murata et al., 2010), with celallocinnine-type and celacinnine-type skeleton, individually. Similar to celallocinnine and celacinnine, they are a pair of *cis*-and *trans*-isomers. Pleurostylin (Wagner and Burghart 1981; Seguineau et al., 1992), isolated from genus *pleurostylia*, represents a structure which spermidine is incorporated in a 13-membered lactam ring to which an additional cinnamoyl residue is fused to yield a 7-membered ring. Two pleurostylin-type alkaloids 7-hydroxypleurostyline, 7′-hydroxy-7′,8′-dihydropleurostyline, along with one celacinnine-type alkaloid 7-hydroxycelacinnine, which exhibit unusual OH substitutions in the macrocycle or the 7-membered ring, were isolated from *pleurostylia opposite* (Seguineau et al., 1992). Caesalpinine A (Mahafo et al., 1983; Mahato et al., 1985), the only known 13-membered spermidine alkaloid isolated from fabaceae family, represents a structure which an hydroxylated cinnamoyl residue is incorporated in the macrocyclic to yield a 5-membered ring.

Celabenzine contains a spermidine unit N^1-linked to a benzoyl group instead of cinnamoyl group. Da silva (Da Silva et al., 2015) found a N^9-methylated celabenzine from *Gymnosporia arenicola* leaf. The three alkaloids cyclocelabenzine, isocyclocelabenzine and hydroxyl-isocyclocelabenzine (Wagner and Burghart 1982) show the 13-membered lactam ring of celabenzine being linked to the benzoyl residue within the spermidine unit. Hydroxyisocyclocelabenzine is the first known spermidine alkaloid with a hydroxy function at the macrocycle. Celafurine has a furan formate moiety, which was only found in *Tripterygium wilfordii* (Kupchan et al., 1977). Recently, a new 13-membered spermidine macrocyclic alkaloid celecarfurine was isolated by our group from the same

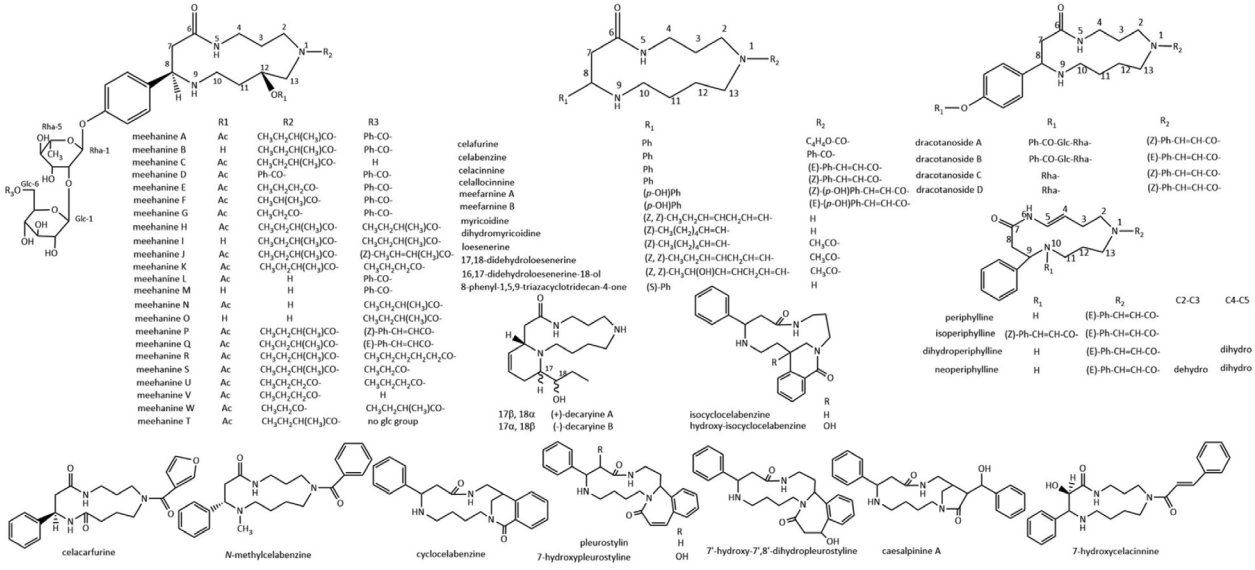


Fig. 3 Chemical structures of 13-membered ring spermidine alkaloids.

Table 2 13-membered ring of spermidine alkaloids.

Compound		plant	part	genus	family	ref
13-membered ring	celacinnine	*Maytenus arbutifolia*	twig	maytenus	celastraceae	(Kupchan et al., 1974)
		Maytenus serrata				(Kupchan et al., 1977)
		Tripterygium wilfordii	root	tripterygium		(Kupchan et al., 1977)
		Pleurostylia opposita	leaf	pleurostylia		(Seguineau et al., 1992)
		Pleurostylia africana				(Wagner and Burghart 1981)
	celallocinnine	*Maytenus arbutifolia*	twig	maytenus	celastraceae	(Kupchan et al., 1974)
		Maytenus serrata				(Kupchan et al., 1977)
		Pleurostylia opposita	leaf	pleurostylia	celastraceae	(Seguineau et al., 1992)
		Caesalpinia digyna		caesalpinia	fabaceae	(Mahato et al., 1985)
		Pleurostylia africana		pleurostylia	celastraceae	(Wagner and Burghart 1981)
	celafurine	*Tripterygium wilfordii*	root	tripterygium	celastraceae	(Kupchan et al., 1977)
	celabenzine	*Tripterygium wilfordii*	root	tripterygium	celastraceae	(Kupchan et al., 1977)
		Maytenus mossambicensis	leaf, twig	maytenus		(Wagner and Burghart 1982)
	7-hydroxypleurostyline, 7-hydroxycelacinnine, 7′-hydroxy-7′,8′-dihydropleurostyline	*Pleurostylia opposita*	leaf	pleurostylia	celastraceae	(Seguineau et al., 1992)
	pleurostylin	*Pleurostylia opposita*	leaf	pleurostylia	celastraceae	(Seguineau et al., 1992)
		Pleurostylia africana				(Wagner and Burghart 1981)
	caesalpinine A	*Caesalpinia digyna*	leaf	caesalpinia	fabaceae	(Mahafo et al., 1983; Mahato et al., 1985)
	cyclocelabenzine, isocyclocelabenzine, hydroxyisocyclocelabenzine	*Maytenus mossambicensis*	leaf, twig	maytenus	celastraceae	(Wagner and Burghart 1982)
	meefarnine A-B	*Meehania fargesii*	whole	meehania	lamiaceae	(Murata et al., 2010)
	N-methylcelabenzine	*Gymnosporia arenicola*	leaf	gymnosporia	celastraceae	(Da Silva et al., 2015)
	celecarfurine	*Tripterygium wilfordii*	root	tripterygium	celastraceae	(Liu et al., 2020)
	myricoidine, dihydromyricoidine	*Clerodendrum myricoides*	whole	clerodendrum	lamiaceae	(Bashwira and Hootele 1988)
	decaryine A, decaryine B, (2S)-2-phenyl-1,5,9-triazacyclotridecan-4-one	*Androya decaryi*	leaf	androya	scrophulariaceae	(Le Lamer et al., 2013)
	loesenerine	*Maytenus loeseneri*	leaf	maytenus	celastraceae	(Díaz et al., 1987)
		Euonymus fortunei	aerial	euonymus		(Wang et al., 2018a)
	17,18-didehydroloesenerine, 16,17-didehydroloesenerin-18-ol	*Maytenus loeseneri*	leaf	maytenus	celastraceae	(Preiss et al., 1988)
	dracotanoside A-D	*Dracocephalum tanguticum*	whole	dracocephalum	lamiaceae	(Wang et al., 2009)
	meehanine A-K	*Meehania urticifolia*	whole	meehania	lamiaceae	(Murata et al., 2009a; Murata et al., 2009b)
	meehanine L-w	*Meehania urticifolia*				
	periphylline, isoperiphylline, dihydroperiphylline, neoperiphylline, perimargine, dihydroperimargine	*Peripterygia marginata*	leaf	peripterygia	celastraceae	(Hocquemiller et al., 1977)

plant (Liu et al., 2020). Celecarfurine is in the 2R-configuration and contains two amide carbonyls in the macrocycle.

Several spermidine alkaloids with no group linked to *N*-1 were found in *Clerodendrum myricoides* (Bashwira and Hootele 1988) and *Androya decaryi* (Le Lamer et al., 2013), which belong to family lamiaceae and scrophulariaceae, respectively. Myricoidine and dihydromyricoidine, with alkenyl linked to C-8, were isolated from *Clerodendrum myricoides*. Myricoidine has two carbon–carbon double bonds (both *cis*-configuration) whereas dihydromyricoidine only has one. Two optical isomers (+)-decaryine A and (-)-decaryine B, along with (-)-(2S)-2-phenyl-1,5,9-triazacyclotridecan-4-one, were isolated from the leaves of *Androya decaryi*. Decaryine A/B represent a structure which a 13-membered lactam ring is fused to a 6-membered ring. Loesenerine, N^1- acetylated dihydromyricoidine, along with two loesenrine-type spermidine alkaloids 17,18-didehydroloesenerine and 16,17-didehydroloesenerin-18-ol were isolated from *Maytenus loeseneri* (Díaz et al., 1987; Preiss et al., 1988).

Several 13-membered cyclic spermidine alkaloidal glycosides have been isolated from leguminous plants *Dracocephalum tanguticum* (Wang et al., 2009) and *Meehania urticifolia* (Murata et al., 2009a; Murata et al., 2009b). Dracotanoside A-D are glycosides of celacinnine and celallocinnine, consisting of two pairs of *cis*-and *trans*-isomers dracotanoside A-B and dracotanoside C-D. The glycosyl moiety of dracotanoside A-B consists of a benzoyl group and two sugar units L-rhamnose and D-glucose, linked to the para position of N-8 benzene ring. Dracotanoside C-D differ with dracotanoside A-B only in the absence of the benzoylated glucopyranosyl unit. 23 spermidine alkaloidal glycosides named meehanine A-W were found in *Meehania urticifolia*. Unlike other 13-membered cyclic spermidine alkaloids, the glycosides have a *C*-12 hydroxy group or *O*-acetyl group. Several moieties such as benzamide, 2-methylbutyramide, butyramide, isobutyramide and propanamide are linked to *N*-1, respectively. All meehanines except meehanine T are diglycosides, possessing two monosaccharide moieties L-rhamnose and β-glucopyranose, with only L-rhamnose in meehanine T. Benzoate, 2-methybutyrate, *trans*-2-methyl-2-butenoate, butyrate, propionate, caproate, cis- and *trans*-cinnamoyl group are linked to *C*-6 of the glucopyranose unit, respectively.

The chirality of the 13-membered cyclic spermidine alkaloids mostly depends on the configuration of *C*-8. All known macrocyclic spermidine alkaloids such as dracotanosides, meehanines and *N*-methylcelabenzine are generally in the 8S-configuration, except that celecarfurine is in the 8R-configuration. In addition, meehanines have a 12R-configuration.

Periphylline and its analogues isoperiphylline, dihydroperiphylline, neoperiphylline, perimargine and dihydroperimargine, which resemble the difference that the spermidine moiety is attached in the opposite manner, were isolated from the leaves of *Peripterygia marginata* (Hocquemiller et al., 1977). Periphylline, isoperiphylline, dihydroperiphylline and neoperiphylline all possess a double bond in the 13-membered ring, while the chemical structure of perimargine and dihydroperimargine had not been fully clarified perhaps due to the limited experiment conditions at that time.

The pharmacological effects of the above spermidine alkaloids with 13-membered ring are less studied and reported. Tang (Tang et al., 2017) utilized a high-throughput *in silico* virtual screening method to find novel medicine formula as matrix metalloproteinase-9 inhibitors. Celacinnine and celallocinnine were qualified to interact with zinc-binding site of matrix metalloproteinase-9. Besides, celacinnine could interact with matrix metalloproteinase-9 related protein that identified by drug-target interaction network analysis. Celafurine could obviously inhibit denosine deaminase activity in HL-60 cell at concentrations of 10, 1 and 0.1 mg/L, with the inhibited activity proportional to the concentration (Wang et al., 2007). Loesenerine activated AMP-activated protein kinase pathway through increasing ADP/ATP ratio by inhibiting mitochondrial respiration, induced increment of glucose uptake in C2C12 cells, and increased glucose consumption in a dose-dependent manner, which exhibited potential hypoglycemic activity (Wang et al., 2018a). *N*-methylcelabenzine was more cytotoxic in cancer-derived cells, although not enough to be considered a cytotoxic agent (Da Silva et al., 2015). In our recent research (Liu et al., 2020), celecarfurine showed remarkable anti-inflammatory effects on IL-1β secretion in LPS-induced rat primary synovial fibroblasts at 10 μM.

2.3. 17-membered ring of spermine alkaloids

The lactam alkaloids with a 17-membered ring are a class of macrocyclic alkaloids having a spermine nucleus (Fig. 4, Table.3). Protoverbine (Guggisberg et al., 2000), which possessed a *C*-11 phenyl group at the unique 17-membered spermine ring, along with its *N*-6, *N*-10-methylene-bridged derivative protomethine, were isolated from *Verbascum pseudonobile*. Several nature products which possess protoverbine-type skeleton had been isolated mainly from genus *verbascum* (*V. pseudonobile, V. phoeniceum and V. nigrum*) and *incarvillea* (*I. sinensis*). Prelandrine (Nezbedova et al., 2001), with a hydroxyl group linked to the para position of *C*-11 benzene ring, was isolated from *Aphelandra squarrosa*. Buchnerine (Lumbu and Hootele 1993), with a methoxy group linked to the para position of *C*-11 benzene ring, along with its derivative *N*-1-*p*-methoxycinnanoylbuchnerine have been isolated from *Clerodendrum buchneri*. Several pairs of trans–cis isomers such as verbacine-verballocine (Drandarov 1995; Chi et al., 1997; Drandarov et al., 1999; Govindan et al., 2019), verbamedine-isoverbamedine (Drandarov and Hesse 2002), verbascenine-verballoscenine (Seifert et al., 1982; Drandarov 1997), verbasitrine-isoverbasitrine (Drandarov et al., 1999) and incasine A-incasine A' (Chi et al., 1997) were isolated, with a cinnamoyl or dimethoxy cinnamoyl group linked to *N*-1. Moreover, verbamedine-isoverbamedine, verbascenine-verballoscenine and incasine A-incasine A' have a *N*-6 formyl, acetyl and imine group, respectively. Verbaskine (Koblicova et al., 1983), also isolated from *Verbascum pseudonobile*, is a *N*-6, *N*-10-carbonyl-bridged derivative of verbacine. Verbametrine and isoverbametrine (Drandarov et al., 1999) are *N*-6, *N*-10-methylene-bridged derivatives of verbasitrine and isoverbasitrine, respectively. Verbamethine (incasine C') and isoverbamethine (incasine C) (Chi et al., 1997; Drandarov et al., 1998; Drandarov et al., 1999; Chi et al., 2007), the *N*-6, *N*-10-methylene-bridged derivatives of verbacine and verballocine, along with incasine B' and incasine B (Chi et al., 1997), the amidinium salts of verbacine and verballocine, were isolated from *Incarvillea sinensis*. The above compounds all have

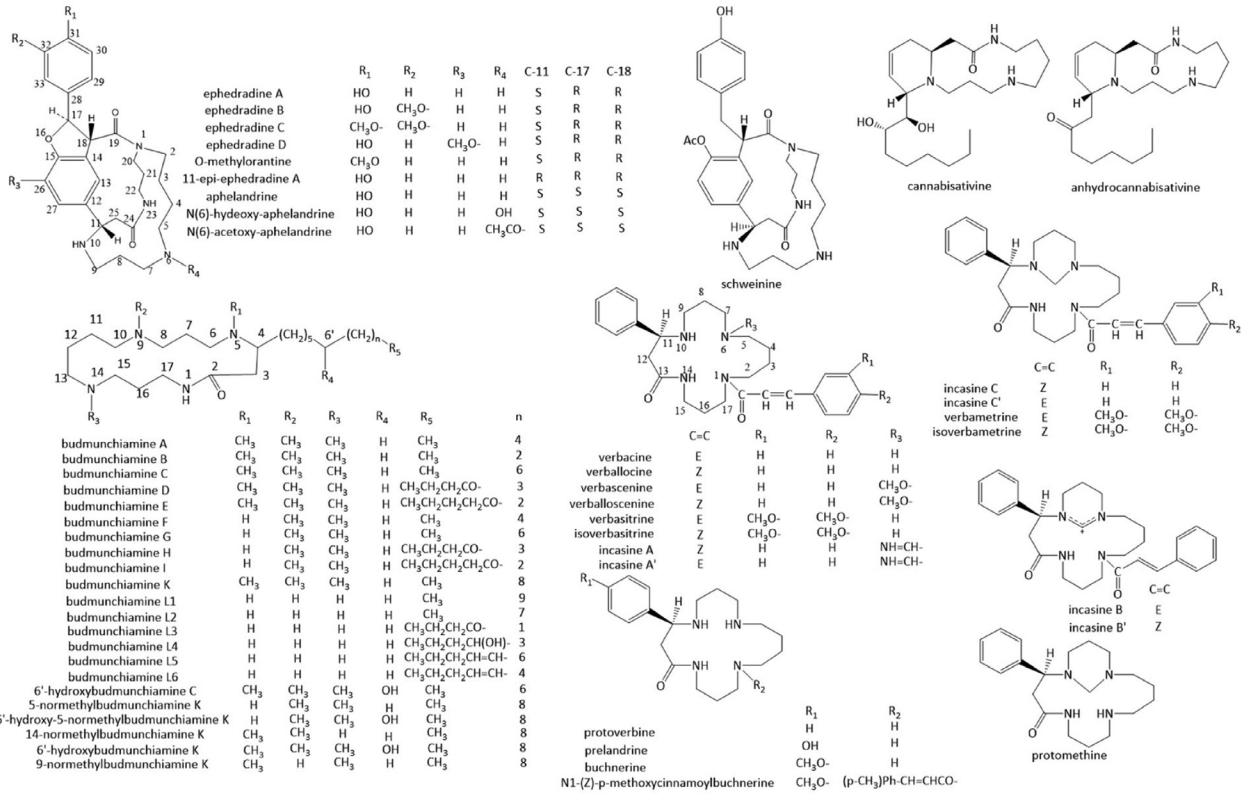


Fig. 4 Chemical structures of 17-membered ring spermine alkaloids.

a S-configuration at *C*-11, except incasine C and C' were in the 11R-configuration. Verbacine exhibited significant cytotoxicity against C6 cells with IC_{50} of 15.09 μg/mL, and was a promising inhibitor of acetylcholinesterase with IC_{50} values of 16.01 μg/mL (Govindan et al., 2019).

Several nature products possessing two special macrocycles and a furan ring have been found in the families of acanthaceae, ephedraceae, and plantaginaceae, among which hydroxylated coumaroyl residue is fused with the *C*-11 benzene ring of the 17-membered lactam ring to yield another 13-membered ring and a furan ring. Aphelandrine and two macrocyclic alkaloids of the aphelandrine type, namely *N*-6-hydroxy-aphelandrine and *N*-6-acetoxy-aphelandrine, were isolated from *Aphelandra fuscopunctata* (Dätwyler et al., 1978; Youhnovski et al., 1999). The alkaloids *O*-methylorantine from *Chaenorhinum minus* (Zhu and Hesse 1988) and *Chaenorhinum villosum* (Dätwyler et al., 1979) have the same constitution as aphelandrine, except that of *O*-methylorantine has a different substituent at *C*-31 (OCH_3 instead of OH), and both compounds have the inverse configuration at *C*-17 and *C*-18. The other alkaloids with a similar backbone to aphelandrine are ephedradine A (Tamada et al., 1979; Zhu and Hesse 1988; Ahmad and Viqar 1990), 11-*epi*-ephedradine A (Ahmad and Viqar 1990), ephedradine B (Hikino et al., 1979; Zhu and Hesse 1988), ephedradine C (Hikino et al., 1980; Zhu and Hesse 1988), and ephedradine D (Hikino et al., 1982), with different substituents at *C*-26, *C*-31 and *C*-32, and 11-*epi*-ephedradine A has an inverse configuration at *C*-11 with ephedradine A. Ephedradine A, B, C and D elicited hypotensive effects in Wistar rats. Ephedradine B was the most potent hypotensive agent among these alkaloids, the hypotensive activity of ephedradine B was exerted mainly by the ganglion blocking action (Hikino et al., 1983). Schweinine (Ahmad and Viqar 1990), similar to ephedradine A, possesses a structure with no furan ring. Chaenorpine (Zhu and Hesse 1988; Zhu et al., 1988) and chaenorhine (Bernhard et al., 1973) represent another structure which caffeoyl residue is fused with the *C*-11 benzene ring of the 17-membered lactam ring to yield a 19-membered ring.

Budmunchiamines, possessing an amide macrocycle invariably substituted by two or three *N*-methyl groups and a homologous side-chain, were isolated from genus *albizia*, fabaceae family (Pezzuto et al., 1991; Pezzuto et al., 1992; Misra et al., 1995; Rukunga and Waterman 1996b; Rukunga and Waterman 1996a; Dixit and Misra 1997). *N*-demethyl derivatives budmunchiamine L1-L6 were isolated as well (Misra et al., 1995; Dixit and Misra 1997). Besides *N*-methyl, the budmunchiamines also differ in the group and length of the aliphatic side chain at *C*-11. 6′-hydroxybudmunchiamine C (Rukunga and Waterman 1996b), 6′-hydroxy-5-normethylbud munchiamine K (Rukunga and Waterman 1996b) and 6′-hydroxybudmunchiamine K (Rukunga and Waterman 1996a) possessed a hydroxyl substitution in the long side chain. Budmunchiamines exhibited significant antibacterial activities. Budmunchiamine A significantly inhibited the growth and fumonisin B1 production by *F. verticillioides* in a dose dependent manner, with the minimum inhibitory concentrations 0.125 mg/mL and minimum fungicidal concentrations 0.25 mg/mL (Thippeswamy et al., 2014). Rukunga (Rukunga and Waterman 1996a) studied the structure–activity relationships of the budmunchiamines, nine budmunchiamines were all active against two gram-positive (*Bacillus subtilis*, *Staphylo-*

Table 3 17-membered ring of spermine alkaloids.

Compound		plant	part	genus	family	ref
17-membered ring	protoverbine, protomethine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Guggisberg et al., 2000)
	prelandrine	*Aphelandra squarrosa*	root	aphelandra	acanthaceae	(Nezbedova et al., 2001)
	buchnerine, *N*-1-(Z)-*p*-methoxycinnamoylbuchnerine	*Clerodendrum buchneri*	leaf	clerodendrum	lamiaceae	(Lumbu and Hootele 1993)
	verbacine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov 1995; Drandarov et al., 1999)
		Melocanna baccifera	fruit, leaf	melocanna	poaceae	(Govindan et al., 2019)
	verballocine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov 1995; Drandarov et al., 1999)
		Incarvillea sinensis	whole	incarvillea	bignoniaceae	(Chi et al., 1997)
	verbasitrine, isoverbasitrine, verbametrine, isoverbametrine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov et al., 1999)
	incasine A, incasine A', incasine B, incasine B'	*Incarvillea sinensis*	whole	incarvillea	bignoniaceae	(Chi et al., 1997)
	incasine C'	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov et al., 1998; Drandarov et al., 1999)
		Incarvillea sinensis	whole	incarvillea	bignoniaceae	(Chi et al., 2007)
	incasine C	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov et al., 1998; Drandarov et al., 1999)
		Incarvillea sinensis	whole	incarvillea	bignoniaceae	(Chi et al., 1997; Chi et al., 2007)
	verbamedine, isoverbamedine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Drandarov and Hesse 2002)
	verbascenine	*Verbascum phoeniceum* *Verbascum nigrum*	aerial	verbascum	scrophulariaceae	(Seifert et al., 1982)
	verballoscenine	*Verbascum phoeniceum*	leaf	verbascum	scrophulariaceae	(Drandarov 1997)
	verbaskine	*Verbascum pseudonobile*	leaf	verbascum	scrophulariaceae	(Koblicova et al., 1983)
	aphelandrine	*Aphelandra squarrosa* *Aphelandra fuscopunctata*	root	aphelandra	acanthaceae	(Dätwyler et al., 1978; Youhnovski et al., 1999)
	N-6-hydroxy-aphelandrine, *N*-6-acetoxy-aphelandrine	*Aphelandra fuscopunctata*	root	aphelandra	acanthaceae	(Youhnovski et al., 1999)
	O-methylorantine	*Chaenorhinum minus*	whole	chaenorhinum	plantaginaceae	(Zhu and Hesse 1988)
		Chaenorhinum villosum				(Dätwyler et al., 1979)
	ephedradine A	*Chaenorhinum minus*	whole	chaenorhinum	plantaginaceae	(Zhu and Hesse 1988)
		NG	aerial	ephedra	ephedraceae	(Tamada et al., 1979)
		Schweinfurthia papilionacea	whole	schweinfurthia	plantaginaceae	(Ahmad and Viqar 1990)
	ephedradine B	*Chaenorhinum minus*	whole	chaenorhinum	plantaginaceae	(Zhu and Hesse 1988)

(*continued on next page*)

Table 3 (*continued*)

Compound	plant	part	genus	family	ref
	NG	aerial	ephedra	ephedraceae	(Hikino et al., 1979)
ephedradine C	*Chaenorhinum minus*	whole	chaenorhinum	plantaginaceae	(Zhu and Hesse 1988)
	NG	aerial	ephedra	ephedraceae	(Hikino et al., 1980)
ephedradine D	*NG*	aerial	ephedra	ephedraceae	(Hikino et al., 1982)
11-*epi*-ephedradine A, schweinine	*Schweinfurthia papilionacea*	whole	schweinfurthia	plantaginaceae	(Ahmad and Viqar 1990)
chaenorpine	*Chaenorhinum minus*	whole	chaenorhinum	plantaginaceae	(Zhu and Hesse 1988; Zhu et al., 1988)
chaenorhine	*Chaenorhinum origanifolium*	aerial	chaenorhinum	plantaginaceae	(Bernhard et al., 1973)
budmunchiamine A	*Albizia lebbek*	seed	albizia	fabaceae	(Dixit and Misra 1997)
	Albizia schimperana	stem bark			(Rukunga and Waterman 1996b)
	Albizia amara	seed			(Pezzuto et al., 1991)
budmunchiamine B-C	*Albizia lebbek*	seed			(Dixit and Misra 1997)
	Albizia amara				(Pezzuto et al., 1991)
budmunchiamine F	*Albizia lebbek*	seed			(Dixit and Misra 1997)
	Albizia amara				(Pezzuto et al., 1992)
budmunchiamine G	*Albizia gummifera*	stem bark			(Rukunga and Waterman 1996a)
	Albizia amara	seed			(Pezzuto et al., 1992)
budmunchiamine D-E, H-I	*Albizia amara*	seed			(Pezzuto et al., 1992)
budmunchiamine L1-L6	*Albizia lebbek*	seed			(Misra et al., 1995; Dixit and Misra 1997)
6′-hydroxybudmunchiamine C, 5-normethylbudmunchiamine K, 6′-hydroxy-5-normethylbudmunchiamine K, 14-normethylbudmunchiamine K	*Albizia schimperana*	stem bark			(Rukunga and Waterman 1996b)
budmunchiamine K, 6′-hydroxybudmunchiamine K, 9-normethylbudmunchiamine K	*Albizia gummifera*	stem bark			(Rukunga and Waterman 1996a)
cannabisativine, anhydrocannabisativine	*Cannabis sativa*	root	cannabis	cannabaceae	(Lotter et al., 1975; Elsohly et al., 1978)

coccus aureus) and two gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria at MIC levels below 80 μg/mL, and showed toxicity to brine shrimp larvae with LC_{50} values below 100 μg/mL. The presence of the hydroxyl in the side chain leads to an appreciable reduction in both antibacterial activity and cytotoxicity. Reduction of the degree of methylation on the macrocycle nitrogens from three to two did not cause a significant loss of antibacterial activity. A mixture of budmunchiamine A-C in the ratio 4: 1: 1 was bactericidal against *Salmonella typhimurium* strain TM677, and found to inhibit the catalytic activity of DNA polymerase, RNA polymerase, and HIV-1 reverse transcriptase (Mar et al., 1991). In addition, two lactam alkaloids cannabisativine and anhydrocannabisativine, with a 17-membered ring spermidine nucleus, were isolated from *Cannabis sativa* (Lotter et al., 1975; Elsohly et al., 1978).

2.4. 24-membered ring of spermidine alkaloids

A spermidine moiety is linked with coumaroyl/caffeoyl/feruloyl groups to form a 24-membered lactam ring, containing two amide carbonyls in the macrocycle (Fig. 5, Table.4). Cad-

abicine, with two trans double bonds, along with cadabicine diacetate, was isolated from *Cadaba farinose* (Ahmad et al., 1985a), *Crataeva nurvala* (Ahmad et al., 1987a) and *Capparis spinose* (Khanfar et al., 2003). Cadabicine totally inhibited ADP, epinephrine-induced platelet aggregation and the plasma clotting at 0.82 mg/mL (Al Kury et al., 1999). Isocodonocarpine (Ahmad et al., 1989), monomethoxy analogue of cadabicine, was isolated from *Capparis decidua*. Monomethoxy and dimethoxy analogues capparisine (Ahmad et al., 1986), capparisinine (Ahmad et al., 1987b) and capparidisine (Ahmad et al., 1985b) were isolated from the same plant, while resemble the difference that the sper-

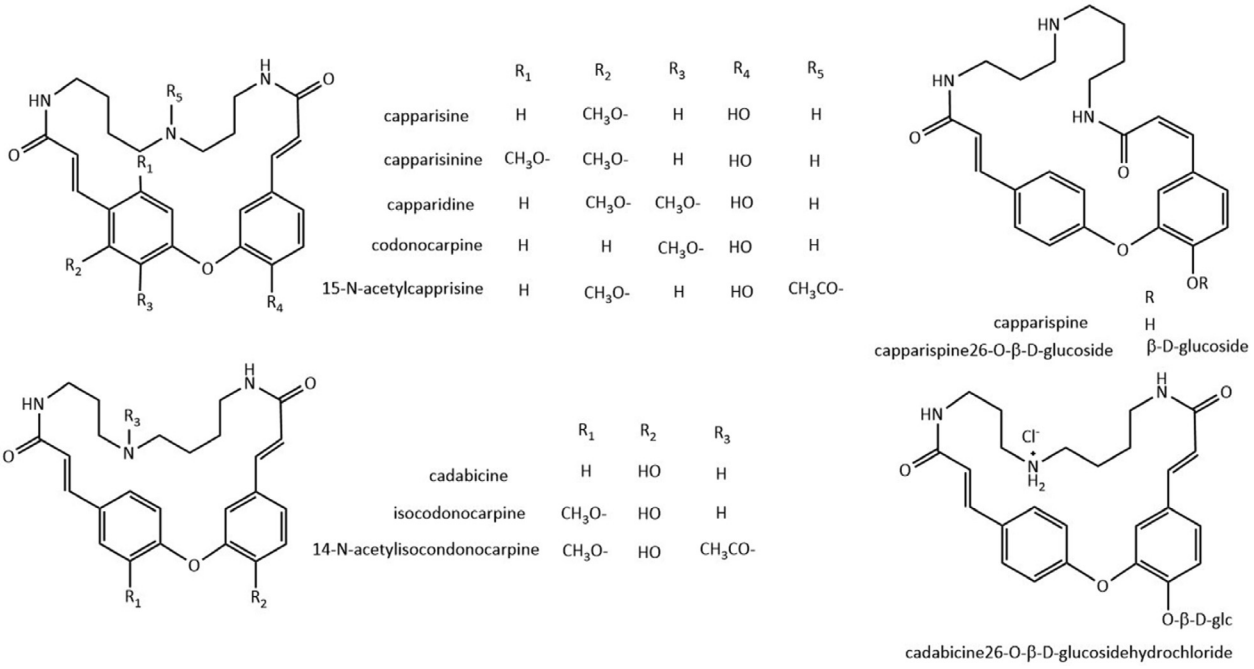


Fig. 5 Chemical structures of 24-membered ring spermine alkaloids.

Table 4 24-membered ring of spermidine alkaloids.

Compound		plant	part	genus	family	ref
24-membered ring	cadabicine	*Cadaba farinosa*	stem bark	cadaba	capparaceae	(Ahmad et al., 1985a)
		Crataeva nurvala	stem bark	crateva		(Ahmad et al., 1987a)
		Capparis spinosa	aerial	capparis		(Khanfar et al., 2003)
	cadabicine diacetate	*Cadaba farinosa*	stem bark	cadaba		(Ahmad et al., 1987a)
		Crataeva nurvala	stem bark	crateva		
	isocodonocarpine	*Capparis decidua*	root bark	capparis		(Ahmad et al., 1989)
	capparisine	*Capparis decidua*	root bark	capparis		(Ahmad et al., 1986)
	capparisinine	*Capparis decidua*	root bark	capparis		(Ahmad et al., 1987b)
	capparidisine	*Capparis decidua*	root bark	capparis		(Ahmad et al., 1985b)
	14-*N*-acetylisocodonocarpine, 15-*N*-acetylcapparisine	*Capparis decidua*	root bark	capparis		(Ahmad et al., 1992)
	capparispine, capparispine26-O-*b*-D-glucoside, cadabicine26-O-*b*-D-glucosidehydrochloride	*Capparis spinosa*	root	capparis		(Fu et al., 2008)
	codonocarpine	*Codonocarpus australis*	bark	codonocarpus	gyrostemonaceae	(Doskotch et al., 1971)

midine moiety is attached in the opposite manner. In addition, two *N*-acetylation analogues 14-*N*-acetylisocodonocarpine and 15-*N*-acetylcapparisine were isolated either (Ahmad et al., 1992). Analogue codonocarpine (Doskotch et al., 1971) was isolated from plant *Codonocarpus australis* of gyrostemonaceae family. Capparidisine possessed cardiovascular activity, exhibiting a dose-dependent depressant effect on heart rate and coronary flow in the isolated rabbit's heart (Rashid et al., 1989).

Capparispine, possessing both trans and cis configuration of the double bonds, along with two glycosides capparispine26-*O*-β-D-glucoside and cadabicine26-*O*-β-D-glucosidehydrochloride, were isolated from *Capparis spinose* (Fu et al., 2008). A cyclic spermidine amide was isolated from *Brassica napus* (Baumert et al., 2005), and the structure is similar to hydroxymethyl derivative of codonocarpine or isocodonocarpine.

2.5. Other membered ring of spermidine and spermine alkaloids

Other membered macrocyclic spermidine and spermine alkaloids have been found in plants (Fig. 6, Table.5). A pair of new macrocyclic spermidine alkaloids, (+)-(S)-scocycamide and (−)-(R)-scocycamide, featured a unique 6/18 fused bicyclic framework with spermidine and catechol units, were isolated from the roots of *Scopolia tangutica* (Wang et al., 2020a). (+)-(S)-scocycamide and (−)-(R)-scocycamide exhibited butyrylcholinesterase inhibition of 18.11 % and 37.83 % at 800 μM, respectively. In addition, they also showed potent antioxidant activity with the oxygen radical absorbance capacity.

Macrocyclic spermine alkaloids pithecolobine 1 and pithecolobine 2 composing of a 19-membered ring were isolated from *Pithecolobium saman* (Wiesner et al., 1952) and *Albizia saman* (Thippeswamy et al., 2014). Pithecolobine 1 completely

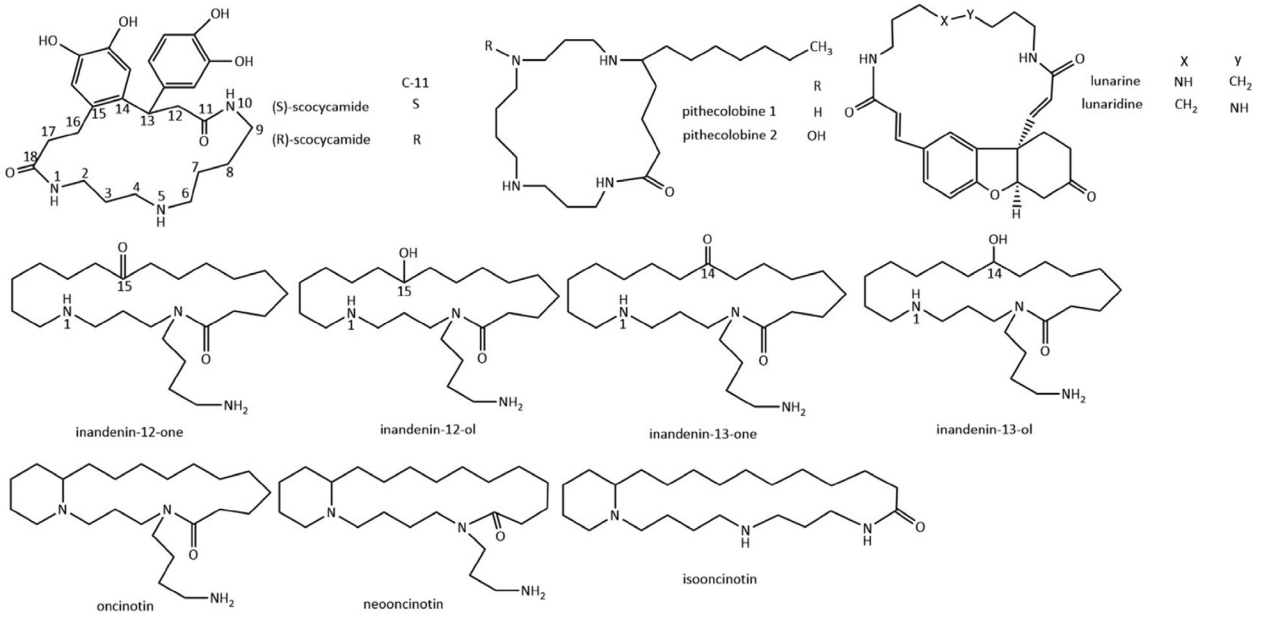


Fig. 6 Chemical structures of other membered ring spermidine and spermine alkaloids.

Table 5 Other membered ring of spermidine and spermine alkaloids.

Compound		plant	part	genus	family	ref
18-membered ring	(S)-scocycamide, (R)-scocycamide	*Scopolia tangutica*	root	scopolia	solanaceae	(Wang et al., 2020a)
19-membered ring	pithecolobine 1	*Pithecolobium saman*	bark	pithecolobium	fabaceae	(Wiesner et al., 1952)
		Albizia saman	leaf	albizia		(Thippeswamy et al., 2014)
	pithecolobine 2	*Pithecolobium saman*	bark	pithecolobium		(Wiesner et al., 1952)
20-membered ring	lunarine	*Lunaria biennis*	seed	peripterygia	celastraceae	(Potier et al., 1963)
		Lunaria rediviva				
	lunaridine	*Lunaria biennis*				(Poupat et al., 1972)
21-membered ring	inandenin-12-one, inandenin-13-one, inandenin-12-ol, inandenin-13-ol	*Oncinotis tenuiloba*	leaf	oncinotis	apocynaceae	(Doll et al., 1995)
	oncinotin	*Oncinotis nitida*	stem bark			(Guggisberg et al., 1974)
22-membered ring	neooncinotin	*Oncinotis nitida*	stem bark	oncinotis	apocynaceae	(Guggisberg et al., 1974)
26-membered ring	isooncinotin	*Oncinotis nitida*	stem bark	oncinotis	apocynaceae	(Guggisberg et al., 1974)

inhibited the fumonisin B1 production by *F. verticillioides* at 0.5 mg/mL *in vitro*, while *in vivo* evaluation showed complete inhibition at 0.5 g/kg *in vivo* (Thippeswamy et al., 2014).

Spermidine alkaloids lunarine (Potier et al., 1963) and lunaridine (Poupat et al., 1972) with a 20-membered ring were isolated from *Lunaria biennis* and *Lunaria rediviva*. The pharmacology of lunarine was first investigated by Henderson in the 1950 s (Henderson and Chen 1950). Lunarine exhibited pharmacological effects on the cardiovascular system, smooth muscle, carbohydrate metabolism, and glandular secretions. Lunarine is a competitive, time-dependent inhibitor of the protozoan oxidoreductase trypanothione reductase, a promising target in drug design against tropical parasitic diseases (Hamilton et al., 2006).

Spermidine alkaloids inandenin-12/13-one and the corresponding alcohols, inandenin-12/13-ol, with two nitrogen atoms in the 21-membered ring, were isolated from *Oncinotis tenuiloba* (Doll et al., 1995). Spermidine alkaloids oncinotin, neooncinotin, and isooncinotin, which possessed a 21-membered, 22-membered, and 26-membered ring, respectively, have been isolated from *Oncinotis nitida* (Guggisberg et al., 1974). The macro ring is naturally divided into two linked rings.

2.6. Open-chain spermidine and spermine alkaloids

Open-chain spermidine and spermine alkaloids are a class of alkaloids with no ring linked to the nitrogen atoms. Several mono-, di-, and tri-substituted spermidines/spermines and tetra-substituted spermines have been found. Open-chain spermidine alkaloids, in which *p*-coumaric acid, caffeic acid, ferulic acid, sinapic acid and benzoic acid are conjugated with spermidine via amide bonds at *N*-1, *N*-5 and *N*-10, are primarily dispersed in the family of solanaceae, and other families fagaceae, pandaceae and asteraceae.

Mono-substituted open chain spermidines such as N^5-benzoylspermidine was isolated from *Oncinotis tenuiloba* (Doll et al., 1994). N^1- and N^8-coumaroyl and feruloyl spermidines were detected in *Solanum dulcamara* (Panagabko et al., 2000). Di-substituted open chain spermidines such as N^1, N^5-di-dihydrocaffeoylspermidine or N^5, N^{10}-di-dihydrocaffeoylspermidine (Gancel et al., 2008; Rodrigues et al., 2013), N^1, N^{10}-di-dihydrocaffeoylspermidine (Sattar et al., 1990; Gancel et al., 2008; Narvaez-Cuenca et al., 2013; Long et al., 2014), N^1, N^{10}-di-benzoylspermidine (Alemayehu et al., 1988), N^1-methoxycaffeoyl, N^{10}-dihydrocaffeoylspermidine (scotanamine B) (Long et al., 2014), N^1, N^{10}-di-dihydroferuloylspermidine (scotanamine C) (Long et al., 2014), N^1-(E)-caffeoyl, N^{10}-dihydrocaffeoylspermidine (scotanamine D) (Long et al., 2014; Yahia et al., 2020; Chen et al., 2021), N^1-(E)-caffeoyl, N^{10}-dihydrocaffeoylspermidine (Long et al., 2014; Zhao et al., 2014), and N^1, N^{10}-ditigiloylspermidine (Schimming et al., 2005) have been found. Scotanamine B exhibited analgesic effects, with moderate agonist activity at the μ-opioid receptor (EC_{50} = 7.3 μM) and induced analgesia in mice (Long et al., 2014). Scotanamine D could inhibit NO production in RAW 264.7 cells stimulated by lipopolysaccharide at 3 μM (Chen et al., 2021). Several *N*, *N*'-di-caffeoyl spermidine isomers were detected from *Solanum melongena* (Whitaker and Stommel 2003), *Nicotiana tabacum* (Camacho-Cristobal et al., 2004) and *Physalis alkekengi* (Wen et al., 2019) by HPLC/MS/MS. However, the structures were not determined because no single compound was obtained. N^1-((4′-O-glycosyl)-sinapoyl), N^{10}-(E, E)-sinapoylspermidine and N^1, N^{10}-di-(E, E)-sinapoylspermidine were isolated from *Arabidopsis thaliana* (Luo et al., 2009). N^1, N^{10}-di-(E, E)-coumaroylspermidine and N^1, N^{10}-di-(E, E)-sinapoylspermidine could modulate plant growth and development (Takahashi et al., 2021). N^1, N^5-di-(E, E)-*p*-coumaroylspermidine was found from *Coix lacryma-jobi* (Xu et al., 2018) and whole grain cereals (Zhang and Peterson 2018), which could improve the content of *T*-AOD and the activity of SOD, CAT and GPx and decrease the content of MDA in HepG2 cells, thus exhibited strong antioxidant activity (Xu et al., 2018). N^1, N^{10}-di-(E, E)-caffeoylspermidine was found from whole grain cereals (Drawbridge et al., 2021).

Certain tri-substituted open chain spermidines have been found in the plants and can be classified by different caffeic acid derivatives either. N^1, N^5, N^{10}-tri-*p*-(E, E, E)-coumaroylspermidine was isolated from *Artemisia caruifolia* (Ma et al., 2001) and *Orostachys japonicas* (Lee et al., 2011). N^1-feruloyl-N^5, N^{10}-di-*p*-(E, E, E)-coumaroyl (keayannidine A), N^1, N^{10}-di-feruloyl-N^5-*p*-(E, E, E)-coumaroyl (keayannidine B), N^1, N^5, N^{10}-tri-(E, E, E)-feruloyl spermidine (keayannidine C) were isolated from *Microdesmis keayana*, pandaceae family. The radical-scavenging activities of keayannidine A-C were found to be significant, although weaker than the positive control quercetin (Zamble et al., 2006). N^1, N^5, N^{10}-tri-dihydrocaffeoylspermidine was isolated from genus solanum (Parr et al., 2005; Gancel et al., 2008; Rodrigues et al., 2013), which exhibited a strong angiotensin I-converting enzyme inhibitory activity with IC_{50} value of 9.55 ppm (Forero et al., 2016). Besides caffeic acid derivatives, tri-substituted open chain spermidines with other substituents have been found. Lyrium spermidine A, with carboxyl group substituted at *N*-5, was isolated from the fruits of *Lycium ruthenicum* (Zhao et al., 2014). N^1, N^{10}-di-benzoyl, N^5-acetamidespermidine, isolated from the leaves of *Banara parviflora* (Moritz et al., 2016), could be biosynthesized by an acetylation using acetyl-CoA with N^1, N^{10}-di-benzoylspermidine. N^1-methylthiocarbonyl-N^5-(E)-cinnamoyl-N^{10}-formylspermidine (chisitine 1) and N^1-benzoyl-N^5-(E)-cinnamoyl-N^{10}-formylspermidine (chisitine 2) were isolated from the leaves of *Chisocheton weinlandii* (Tzourosa et al., 2004).

Open chain spermines which possess four nitrogen atoms, are substituted at N^1, N^5, N^{10} and N^{14}. Mono-substituted N^1-p-coumaroyl spermine was detected in *Solanum dulcamara* (Panagabko et al., 2000). N^1, N^{10}-di-dihydrocaffeoylspermine and N^1, N^5, N^{14}-tri-dihydrocaffeoylspermine were found from *Solanum tuberosum* (Narvaez-Cuenca et al., 2013). *N*, *N*'-di-dihydrocaffeoylspermine isomers were detected from *Physalis alkekengi* (Wen et al., 2019) by HPLC/MS/MS as well. N^1, N^{14}-di-dihydrocaffeoylspermine (kukoamine A) (Funayama et al., 1980; Parr et al., 2005) and N^1, N^{10}-di-dihydrocaffeoylspermine (kukoamine B) (Funayama et al., 1995) were isolated from *Lycium chinense* and *Solanum tuberosum*.

Kukoamines exerted various pharmacological effects such as antioxidant, anti-inflammatory, antidiabetic and neuroprotective. Kukoamines protected bone marrow-derived mesenchymal stem cells from fenton-induced damage via

antioxidant pathways such as electron-transfer, proton-transfer, hydrogen atom transfer, radical-adduct-formation, and Fe^{2+}-chelating. kukoamine B exhibited higher antioxidant levels than kukoamine A (Li et al., 2018a). Kukoamine A showed inhibitory activity on soybean lipoxygenase with IC_{50} 9.5 μM (Hadjipavlou-Litina et al., 2009). Kukoamine A significantly inhibited the production of reactive oxygen species (nitric oxide, prostaglandin E2, cyclooxygenase-2) and inflammatory factors (tumor necrosis factor-α, interleukin-1β, and interleukin-6) in lipopolysaccharide-treated RAW 264.7 macrophage cells (Yang et al., 2016; Wang et al., 2020b). In addition, kukoamine A significantly decreased inflammatory response to carrageenan induced paw edema of carrageenan-treated rats *in vivo* (Hadjipavlou-Litina et al., 2009; Wang et al., 2020b). Bacterial lipopolysaccharide and bacterial DNA/CpG DNA are important pathogenic molecules and drug targets for sepsis. Kukoamine B is a potent dual inhibitor for both LPS and CpG DNA and inhibits their activity *in vitro* and *in vivo*, thus exhibiting anti-sepsis effect (Liu et al., 2011a; Liu et al., 2011b). In LPS-induced septic mice, kukoamine B could protect against lung injury through anti-inflammation, which is related to HMGB1/NF-κB signaling pathway (Ming et al., 2016), protect the function of the small intestine via the Toll-like receptor 4 signaling pathway (Lyu et al., 2015) and protect against liver injury via the activation of NF-κB signaling pathway (Qin et al., 2015). The anti-oxidation and acute inflammation bioactivities of kukoamines may be related to the anti-diabetes properties. Kukoamine B ameliorated high-fat diet/high-fructose-induced insulin resistance and obesity by downregulating lipid accumulation, oxidative stress, and inflammatory factors (Zhao et al., 2020), probably via regulating nuclear transcription factors NF-κB and/or PPAR (Li et al., 2018b). Kukoamine A exhibited similar activities against insulin resistance through inhibiting Srebp-1c and downregulating genes expression (Li et al., 2017). Oxidative-stress and over-activation of *N*-methyl-D-aspartate receptors are important mechanisms of brain injury. Kukoamines could protect against radiation-induced rat brain injury through inhibition of oxidative stress and neuronal apoptosis (Zhang et al., 2016), via activating the PI3-K/Akt/GSK3β pathway (Hu et al., 2015c; Li et al., 2015), and blocking *N*-methyl-D-aspartate receptors in SH-SY5Y cells (Hu et al., 2015a; Hu et al., 2015b). Kukoamine A could ameliorate the neuroinflammatory response and protect neurogenesis after whole-brain irradiation, partially through regulating the activation of NF-κB, AP-1, and PPARδ (Zhang et al., 2017). Kukoamine A was able to protect the brain against injury induced by permanent middle cerebral artery occlusion via mitochondria mediated apoptosis signaling pathway (Liu et al., 2017). Kukoamines have better protective effects on brain degenerative diseases. Kukoamine A protected against neurotoxin-induced Pakinson's disease due to the apoptosis inhibition and iron homeostasis maintaining (Hu et al., 2017; Li et al., 2020b). Alzheimer's disease is an age-related disease characterized by amyloid fibrillogenesis. Kukoamines inhibited aggregation of amyloid β and human islet amyloid polypeptide in a dose-dependent manner. Kukoamine B exhibited stronger inhibitory activities than kukoamine A, and the number of catechol moieties is essential for inhibition of amyloid aggregation (Jiang et al., 2020). Besides, kukoamines also possessed other activities. Kukoamine A showed inhibitory activity against angiotensin I-converting enzyme, thus exerting hypotensive activity (Funayama et al., 1980). Kukoamine A inhibited trypanothione reductase as a mixed inhibitor with K_i = 1.8 μM, K_{ii} = 13 μM) (Ponasik et al., 1995). Kukoamine A also exhibited anti-tumor activity, and inhibited human glioblastoma cell growth and migration *in vitro* and *in vivo* through apoptosis induction and epithelial-mesenchymal transition attenuation by downregulating expressions of 5-Lipoxygenase and CCAAT/enhancer binding protein β (Wang et al., 2016). Kukoamine B exhibited anti-osteoporotic effects, increased the osteoblastic differentiation and mineralized nodule formation of osteoblastic MC3T3-E1 cells, but did not affect osteoclast differentiation, and significantly inhibited OVX-induced bone mineral density loss and restored the impaired bone structural properties in osteoporosis model mice (Park et al., 2019). These differences of kukoamine A and B could be attributed to positional isomeric effects.

N^1, N^{14}-di-feruloyl-N^5-(E, E, E)-*p*-coumaroylspermine (keayanine A), N^1, N^5, N^{14}-tri-(E, E, E)-*p*-coumaroylspermine (keayanine B), N^1-feruloyl, N^5, N^{14}-di-(E, E, E)-*p*-coumaroylspermine (keayanine C) and N^1, N^5, N^{14}-tri-(E, E, E)-feruloylspermine (keayanine D) were isolated from genus *Microdesmis* (Zamble et al., 2007; Roumy et al., 2008). Keayanine A and keayanidine B had significant vasorelaxing properties, stimulating NO production in the vascular bed, probably due to their strong antioxidant activity versus superoxide anion and hydrogen peroxide and to their stimulation of eNOS mRNA expression (Zamble et al., 2009).

Tetra-substituted spermine N^1, N^5, N^{10}, N^{14}-tetra-(E, E, E, E)-*p*-coumaroylspermine was synthesis earlier (Ma et al., 2001) and later isolated from and *Matricaria chamomilla* (Yamamoto et al., 2002) and *Tragopogon tommasinii* (Granica et al., 2015). N^1, N^5, N^{10}, N^{14}-tetra-(E, E, E, E)-*p*-coumaroylspermine inhibited HIV-1 protease more potently than N^1, N^5, N^{10}-tri-*p*-coumaroylspermidine (Ma et al., 2001). cis-trans isomers of N^1, N^5, N^{10}, N^{14}-tetra-*p*-coumaroylspermines (1, 5, 10, 14-(Z, Z, Z, Z), 1, 5, 10, 14-(E, Z, Z, E), and 1, 5, 10, 14-(E, E, E, E)) and N^1, N^5, N^9, N^{14}-tetra-p-coumaroyl thermospermines (1, 5, 9, 14-(Z, Z, Z, Z), 1, 5, 9, 14-(E, Z, Z, E), and 1, 5, 9, 14-(E, E, E, E)) were found in the flowers of *Matricaria chamomilla* (Park et al., 2017). These compounds are potent neurokinin-1 receptor antagonists, and competitively inhibited the binding of substance P and substance P-induced proliferation in breast cancer cell line MDA-MB-453, thus exerting positive effects on substance P/neurokinin-1 receptor-related diseases (Yamamoto et al., 2002; Park et al., 2017).

Compared with other parts of the plant, flowers are abundant in open chain spermidine alkaloids. Di-substituted open chain spermidines such as N^5-caffeoyl, N^{10}-(E)-dihydrocaffeoylspermidine was isolated from the flower of *Lycium barbarum* (Lopatriello et al., 2017). N^1, N^5-di-p-coumaroylspermidine and N^5, N^{10}-di-*p*-coumaroylspermidine were isolated from anthers of *Aphelandra tetraffona* and *Aphelandra chamissoniana* (Werner et al., 1995). Tri-coumaroyl spermidine derivatives, especially N^1, N^5, N^{10}-tri-*p*-(E, E, E)-coumaroylspermidine, and its E-Z isomers were isolated or found in numerous plant flowers belonging to several families (Strack et al., 1990; Werner et al., 1995; Yamamoto et al., 2002; Jiang et al., 2008; Sobolev et al., 2008; Yang et al., 2012; Wiese et al., 2013; Xie et al., 2017; Chen et al., 2018; Mori et al., 2019; Zhou et al., 2021). There are many sper-

midine enantiomers with E (trans) or Z (cis) configurations of the double bonds. Eight E-Z isomers of N^1, N^5, N^{10}-tri-*p*-coumaroylspermidine (EEE, EEZ, EZE, EZZ, ZEZ, ZEE, ZZE, and ZZZ) were isolated from the flower of Japanese apricot tree, *Prunus mume* (Mori et al., 2019). N^1, N^5, N^{10}-tri-*p*-(E, Z, E)-coumaroyl spermidine and N^1, N^5, N^{10}-tri-*p*-(E, Z, Z)-coumaroyl spermidine were named as safflospermidine A and B as well. These tri-coumaroyl spermidines are unstable and could show photoisomerization behavior under sunlight. N^1, N^5-N^{10}-tri-*p*-(Z, Z, E)-coumaroylspermidine and safflospermidine A showed better inhibition effects on serotonin reuptake in rat brain synaptosomes, while N^1, N^5, N^{10}-tri-*p*-(Z, Z, Z)-coumaroylspermidine showed weaker inhibition effect (Yuan et al., 2015). Safflospermidine A and B had a higher antityrosinase activity with IC_{50} of 13.8 and 31.8 μM, respectively (Khongkarat et al., 2020). N^1, N^5, N^{10}-tri-*p*-(Z, Z, E)-coumaroylspermidine is a potent serotonin transporter inhibitor, which possess an inhibitory action on serotonin uptake in S6 cells or in synaptosomes, thus improve neuropsychological disorders (Zhao et al., 2009; Zhao et al., 2010). Both safflospermidine A and B had a higher antityrosinase activity with IC_{50} of 13.8 and 31.8 μM, respectively. N^1, N^5, N^{10}-tri-*p*-(E, E, E) coumaroylspermidine exhibited remarkable hepatoprotective activity in HepG2 cells (Zhou et al., 2021). Coumaroylspermidine extracts from safflower, which included four coumaroylspermidine compounds, N^1, N^5, N^{10}-tri-*p*-coumaroyl spermidine (ZZZ, ZZE, EZE and EEE), exhibited significant anti-depressant effects in rats (Li et al., 2020a). N^1, N^{10}-di-caffeoyl-N^5-*p*-(E, E, E)-coumaroylspermidine, N^1-caffeoyl-N^5, N^{10}-di-*p*-(E, E, E)-coumaroylspermidine and N^1, N^5-di-*p*-coumaroyl-N^{10}-(E, E, E)-caffeoylspermidine were isolated from the bud of *Capparis spinose* (Lopatriello et al., 2017). Coumaroyl di-caffeoylspermidine, feruoyl di-coumaroylspermidine, coumaroyl di-feruoylspermidine and tri-feruoylspermidine were found in plant flowers as well (Yang et al., 2012; Sile et al., 2021). Acyl spermidine N^1-acetyl, N^5, N^{10}-di-*p*-(E, E)-coumaroylspermidine was isolated from *Arachis hypogaea* flowers (Sobolev et al., 2008).

Pollen is the male germ cell of flowering plants and is abundant of spermidine alkaloids. In an early study, the chemical compositions of pollen from 67 species were investigated, N^1, N^{10}-di-(E, E)-feruloylspermidine, N^5, N^{10}-di-(E, E)-feruloylspermidine, N^1, N^{10}-caffeoyl-feruloylspermidine (E, E) and N, N'-di-*p*-coumaroylspermidine existed in the genera *Alnus*, *Betula*, *Corylus*, and *Quercus* (Meurer et al., 1988). N^1-caffeoyl, N^{10}-(E, E)-feruloylspermidine and N^1, N^{10}-di-(E, E)-feruloylspermidine were isolated from the pollen of *Corylus avellana* (Meurer et al., 1986). N^1, N^5-di-*p*-(E, E)-coumaroylspermidine was isolated from *Brassica campestris* pollen (Lv et al., 2013). Isomeric *N*, *N*'-dicoumaroyl, *N*, *N*'-diferuloyl, *N*, *N*'-disinapoyl, *N*-coumaroyl-*N*'-feruloyl, and *N*-feruloyl-*N*'-sinapoyl spermidine derivatives were found in the pollen of *Hippeastrum* × hortorum (Youhnovski et al., 1998). Tri-*p*-coumaroylspermidine, as the main antioxidant components in pollen, was found in numerous plants pollen (Bokern et al., 1995; Lin and Mullin 1999; Sugioka et al., 2018; Adler et al., 2020). N^1, N^{10}-di-*p*-coumaroyl, N^5-(E, E, E)-caffeoylspermidine, N^1, N^5, N^{10}-tri-(E, E, E)-caffeoylspermidine and N^1, N^5, N^{10}-tri-*p*-(E, E, E)-coumaroylspermidine were isolated from the pollen of *Quercus alba* (Walters et al., 2001). N^1, N^{10}-di-*p*-coumaroyl, N^5-(E, E, E)-caffeoylspermidine and N^1, N^5, N^{10}-tri-*p*-(E, E, E)-coumaroylspermidine exhibited antifungal activity, which reduced mycelial growth of the oat leaf stripe pathogen *Pyrenophora avenae* and reduced infection of barley with the powdery mildew fungus *Blumeria graminis* when applied as a post-inoculation treatment (Walters et al., 2001). Human catechol-O-methyltransferase is a key neurotransmitter involved in Parkinson's disease and depression. N^1, N^5, N^{10}-tri-*p*-(E, E, E)- coumaroylspermidine competitively inhibited human catechol-O-methyltransferase activity with an IC_{50} value 16 μM (Miyata et al., 2022). *Quercus dentata*, belonging to the same genus of *Quercus* alba, contains other spermidines such as N^1-*p*-coumaroyl-N^5, N^{10}-di-(E, E, E)-caffeoylspermidine, N^1-feruloyl-N^5, N^{10}-di-(E, E, E)-caffeoylspermidine, N^1-*p*-coumaroyl-N^5-caffeoyl-N^{10}-(E, E, E)-feruloylspermidine, and N^1, N^5-di-*p*-coumaroyl-N^{10}-(E, E, E)-caffeoylspermidine in the pollen (Bokern et al., 1995; Nimtz et al., 1996). Acetyl spermidines were detected in the pollen of *Sambucus nigra*, including two obtained stereoisomers N^1-acetyl-N^5, N^{10}-di-(Z, E)-feruloylspermidine and N^1-acetyl-N^5, N^{10}-di-(E, E)-feruloylspermidine (Kite et al., 2013).

Bee pollen is produced by worker honey bees, which is composed of natural flower pollen mixed with nectar and bee secretions. The chemical components of bee pollen are complicated, and depend on the vegetation at the collection site, as honey bees collect pollen from target plants grown near bee hives. Therefore, the chemical diversity of bee pollen arises from differences in the botanical origins and collection sites resulting in differences in the biological activities and physicochemical properties of pollen, in addition to color, smell, and taste. Di- and tri- substituted hydroxycinnamic acid spermidines with the substituents of *p*-coumaroyl, caffeoyl and feruloyl have been found from been pollen, such as rape bee pollen (Wang et al., 2018b; Zhang et al., 2020), camellia bee pollen (Su et al., 2020), rose bee pollen (Yang et al., 2019) and several other species (Negri et al., 2011). Safflospermidine A-B were isolated from sunflower (*Helianthus annuus*) bee pollen as well (Khongkarat et al., 2020). Phenolamines, from the rape bee pollen, including several di-p-coumaroylspermidines and tri-*p*-coumaroylspermidines, showed better antioxidant activities, and protective effects on HepG2 cells injured by AAPH (Zhang et al., 2020). Tetra-substituted spermines N^1, N^5, N^{10}, N^{14}-tetra-*p*-(E, E, E, E)-coumaroylspermine and N^5-caffeoyl-N^1, N^{10}, N^{14}-tri-*p*-(E, E, E, E)-coumaroylspermine were isolated from a Brazilian bee pollen. N^5-caffeoyl-N^1, N^{10}, N^{14}-tri-*p*-(E, E, E, E)-coumaroylspermine showed the strong free radical-scavenging activity (Ohta et al., 2007).

Several glycosides of spermidine and spermine were found as well. *N*, *N*'-di-dihydrocaffeoylspermidine dihexoside, N^1, N^5 or N^5, N^{10}-di-dihydrocaffeoylspermidine hexoside, N^1, N^{10}-di-dihydrocaffeoylspermidine hexoside and N^1, N^5, N^{10}-tri-dihydrocaffeoylspermidine hexoside were isolated from *Solanum quitoense* (Gancel et al., 2008). Twenty-three open-chain spermidine glycosides named lycibarbarspermidine A-T (Zhou et al., 2016a; Zhou et al., 2016b; Qian et al., 2020; Chen et al., 2021) and lyciamarspermidine A-C (Qian et al., 2020; Chen et al., 2021), along with two open-chain spermine glycosides lyciamarspermine A and B (Qian et al., 2020), have been isolated from *Lycium barbarum*. Lycibarbarspermidines and lyciamarspermidines are *O*-glycosylated products of dicaffeoylspermidine derivatives by one or two β-D-glucopyranose units. Lycibarbarspermidine N and O the cyclization products of dicaffeoylspermidine derivatives. The existing form of dicaf-

feoylspermidine derivatives depends on the pH value of the medium. The addition of CF_3COOH or $NH_3{\cdot}H_2O$ was to isolate and purify these compounds. Thus, the compounds may exist as free base form or ionic form with other acids in the plant. Lycibarbarspermidine A-T all displayed antioxidant capacities. lycibarbarspermidine D, E, and G showed extraordinary potent antioxidant capacities, with the oxygen radical absorbance capacity values of 2.96, 2.71, and 3.07 μM TE/μM, respectively (Zhou et al., 2016b). Lycibarbarspermidines exhibited anti-inflammatory activities (Chen et al., 2021). Lycibarbarspermidine A, C, D, and T could inhibit NO production in RAW 264.7 cells stimulated by lipopolysaccharide. Among them, lycibarbarspermidine C and T could significantly inhibit the level of NO at 3 μM. According to the structure–activity relationship, the monosaccharide substitution decreased the anti-inflammatory activity. The sugar unit which occurred at the C-3′ position could affect the anti-inflammatory activity significantly. The double bond of the caffeic acid derivative part plays an important role in the anti-inflammatory activity either. Lycibarbarspermidine A-T exhibited different levels of anti-Alzheimer's disease activity. Lycibarbarspermidine B, C, F, L, M and O exhibited the short-term memory enhancement capacity close to that of positive control memantine (Zhou et al., 2016b).

Acetyl-lycibarbarspermidine F, and tri-glucosyl derivatives glucosyl-lycibarbarspermidine F, hydroxy-glucosyl-lycibarbar spermidine F were detected in *Lycium barbarum* by UHPLC-QTOF-MS (Mocan et al., 2018). A number of different glycosides of spermidine derivatives were found in *Lycium barbarum*, including several isomers. Different types of spermidines were identified by distinctive MS/MS fragment ions. Despite the lack of structural details, a total of 41 out of 58 spermidines were tentatively characterized, including isomers of dicaffeoyl spermidines, cyclic dicaffeoyl spermidines, and their mono-, di-, tri- and spermidine hexosides (Ahad et al., 2020). Novel dicaffeoylspermine-glucosides isomers with approximately-one hundred different structures, which contains the spermine as polyamine core, rather than spermidine, and 1 to 4 β-D-glucopyranose units attached to different sites, were detected in *Lycium barbarum* (Dos Santos et al., 2022).

Open-chain spermidine and spermine alkaloids have a wide distribution in nature, not only in land plants, but also abundant in microorganism and marine organisms. N^1, N^8-bis(3,4-dihydroxybenzoyl) spermidine, also named pistillarin, was isolated form bacteria *Clavariadelphus pistillaris* and several *Ramaria* species (Steglich et al., 1984), fungus *Penicillium bilaii* (Capon et al., 2007) and *Ramaria subaurantiaca* (Choomuenwai et al., 2013). Pistillarin exhibited antimalarial activity against Plasmodium falciparum (3D7) parasites with IC_{50} 0.23 μM (Choomuenwai et al., 2013). Pistillarin salt, isolated from the fruiting bodies of *Gomphus floccosus*, exhibited a significantly protective effect against DNA damage by hydroxyl radicals generated from the Fenton reaction via iron chelation as well as free radical-scavenging activity (Lee et al., 2010). N^1, N^5-di-dihydrocoumaroyl-N^{10}-acetylspermine (JBIR-125) was isolated from a new species of *Streptomyces* (strain R56-07), which exhibited 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity with an IC_{50} value of 35.1 μM (Kawahara et al., 2012).

Polycyclic guanidine spermidine alkaloids ptilomycalin A (Kashman et al., 1989; Ohtani et al., 1992; Patil et al., 1995; Gallimore et al., 2005; Hua et al., 2007), crabescidin 800 (Jares-Erijman et al., 1991; Berlinck et al., 1993; Tavares et al., 1994; Patil et al., 1995; Chang et al., 2003; Hua et al., 2007), 816 (Jares-Erijman et al., 1991; Berlinck et al., 1993; Jares-Erijman et al., 1993; Patil et al., 1995), 826 (Chang et al., 2003), 830 (Jares-Erijman et al., 1991), 844 (Jares-Erijman et al., 1991), isocrabescidin 800 (Berlinck et al., 1993), 13,14,15-isocrambescidin 800 (Jares-Erijman et al., 1993), crambidine (Berlinck et al., 1993), and fromiamycalin (Chang et al., 2003) have been found in several classes of marine sponges. The structures differed in the number of methylene groups linked to *N*-5, functional groups and stereoisomerism of polycyclic guanidine ring and spermidine ring. Fromiamycalin, different from other ptilomycalin A analogues, which *N*-1 and *N*-5 of the spermidine formed a tetrahydropyrimidine ring. Later, one acyclic guanidine alkaloid, unguiculin A and four pentacyclic alkaloids, ptilomycalin E − H were isolated from the sponge *Monanchora unguiculata* (Campos et al., 2017). The polycyclic guanidine spermidine alkaloids possessed widely pharmacological effects such as anti-tumor, antiviral, and antifungal. Crabescidines exhibited attractive anti-tumor effects. Ptilomycalin A and crambescidine 800 showed significant growth inhibition of 11 different cancer cell lines with GI_{50} values of 0.04–0.19 mg/mL (Hua et al., 2007). Ptilomycalin A shows cytotoxicity against cancer cell lines P388, L1210, KB and MDA-MB-231 with IC_{50} of 0.1, 0.4, 1.3 μg/mL and 4.3 μM, respectively (Ohtani et al., 1992; Tabakmakher et al., 2013). Ptilomycalin E and the mixture of ptilomycalins G and H showed promising cytotoxicity against KB cells with IC_{50} of 0.85 and 0.92 μM, respectively (Campos et al., 2017). Crambescidin 816 was found to be active against HCT-16 human colon carcinoma cells with IC_{50} of 0.24 μg/mL (Berlinck et al., 1993). The anti-tumor mechanisms of crabescidines on cancer cells were investigated. Ptilomycalin A-like induced p53-independent programmed cell death and S-phase cell cycle arrest by activating JNK1/2 and ERK1/2, following AP-1 activation (Dyshlovoy et al., 2016a). Crambescidine 800 induced cell cycle arrest at the G2/M phase and apoptosis of triple negative breast cancer cells by the inhibition of phosphorylation of Akt, NF-κB, and MAPK pathways (Shrestha et al., 2018). Crambescidin 800 induced erythroid differentiation in K562 chronic myelogenous leukemia cells and neurite outgrowth in Neuro 2A neuroblastoma cells (Aoki et al., 2004). Crambescidin-816 inhibited HepG2 cell migration via inhibiting cell–cell adhesion, interfering with the formation of tight junctions, and cell-matrix adhesion (Rubiolo et al., 2014). Crambescidine 816, 830, and 800 strongly inhibited tumor cell proliferation, and disrupted tumor cell adhesion and cytoskeletal integrity promoting the activation of the intrinsic apoptotic signaling (Roel et al., 2016). In addition, ptilomycalin A exhibited antifungal activity against *Candida albicans* with MIC 0.8 μg/mL (Ohtani et al., 1992), and inhibited melanogenesis of *Cryptococcus neoformans in vitro* with an IC_{50} of 7.3 μM through inhibition of biosynthesis of laccase in the melanin biosynthetic pathway (Dalisay et al., 2011). Ptilomycalin F and fromiamycalin exhibited promising activity against *Plasmodium falciparum* with IC_{50} values of 0.23 and 0.24 μM, respectively (Campos et al., 2017). Crambescidine 800 strongly inhibited bacteria *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* with MIC values of 2, 1, 1 μg/mL, respectively (Sun et al., 2015). Crambescidin 800 exhibited the comparable inhibition activity of *Plasmodium falciparum*

Table 6 Open-chain spermidine and spermine alkaloids from land plants.

Compound		plant	part	genus	family	ref
Open-chain	N^5-benzoylspermidine	*Oncinotis tenuiloba*	leaf	oncinotis	apocynaceae	(Doll et al., 1994)
	N^1-coumaroylspermidine, N^1-feruloylspermidine, N^8-coumaroylspermidine, N^8-feruloylspermidine, N^1-coumaroylspermine	*Solanum dulcamara*	leaf, flower	solanum	solanaceae	(Panagabko et al., 2000)
	N^1, N^5, N^{10}-tri-dihydrocaffeoylspermidine	*Solanum sessiliflorum*	fruit	solanum	solanaceae	(Rodrigues et al., 2013)
		Solanum quitoense				(Gancel et al., 2008)
		Solanum tuberosum	tuber	solanum		(Parr et al., 2005)
	N^1, N^5-di-dihydrocaffeoylspermidine	*Solanum sessiliflorum*	fruit	solanum	solanaceae	(Rodrigues et al., 2013)
		Solanum quitoense				(Gancel et al., 2008)
	scotanamine B-C	*Scopolia tangutica*	root	scopolia	solanaceae	(Long et al., 2014)
	scotanamine D	*Scopolia tangutica*	root	scopolia	solanaceae	(Long et al., 2014)
		Lycium barbarum	fruit	lycium		(Chen et al., 2021)
		Hyoscyamus albus	leaf	hyoscyamus		(Yahia et al., 2020)
	N^1, N^{10}-di-dihydrocaffeoylspermidine	*Scopolia tangutica*	root	scopolia	solanaceae	(Long et al., 2014)
		Solanum tuberosum	tuber	solanum		(Narvaez-Cuenca et al., 2013)
		Iochroma cyaneum	herb	iochroma		(Sattar et al., 1990)
		Solanum quitoense	fruit	solanum		(Gancel et al., 2008)
	N^1-(E)-caffeoyl, N^{10}-dihydrocaffeoylspermidine	*Scopolia tangutica*	root	scopolia	solanaceae	(Long et al., 2014)
		Lycium ruthenicum	fruit	lycium		(Zhao et al., 2014)
	N^1, N^{10}-di-benzoylspermidine	*Cassia floribunda*	leaf	cassia	fabaceae	(Alemayehu et al., 1988)
	lyrium spermidine A	*Lycium ruthenicum*	fruit	lycium	solanaceae	(Zhao et al., 2014)
	N^1, N^{10}-di-tigloylspermidine	*Ipomoea nil*	seed	ipomoea	convolvulaceae	(Schimming et al., 2005)
	N, *N*'-di-caffeoylspermidine	*Solanum melongena*	fruit	solanum	solanaceae	(Whitaker and Stommel 2003)
		Nicotiana tabacum	seed	nicotiana		(Camacho-Cristobal et al., 2004)
		Physalis alkekengi	fruit	physalis		(Wen et al., 2019)
	N, *N*-di-dihydrocaffeoylspermine	*Physalis alkekengi*	fruit	physalis	solanaceae	(Wen et al., 2019)
	N^1-((4′-O-glycosyl)-sinapoyl), N^{10}-(E, E)-sinapoylspermidine, N^1, N^{10}-di-(E, E)-sinapoylspermidine	*Arabidopsis thaliana*	seed	arabidopsis	brassicaceae	(Luo et al., 2009)
	N^1, N^5-di-*p*-(E, E)-coumaroylspermidine	*Coix lacryma-jobi*	whole	coix	poaceae	(Xu et al., 2018)
	N^1, N^5, N^{10}-tri-*p*-(E, E, E)-coumaroylspermidine	*Artemisia caruifolia*	aerial	artemisia	asteraceae	(Ma et al., 2001)
		Orostachys japonicus	whole	orostachys	crassulaceae	(Lee et al., 2011)
		Matricaria chamomilla	flower	matricaria	asteraceae	(Yamamoto et al., 2002)
		Aphelandra tetraffona	anther	aphelandra	acanthaceae	(Werner et al., 1995)

(*continued on next page*)

Table 6 (*continued*)

Compound	plant	part	genus	family	ref
	Aphelandra chamissoniana				
	Carthamus tinctorius	flower	carthamus	asteraceae	(Jiang et al., 2008)
	Capparis spinosa	bud	capparis	capparaceae	(Wiese et al., 2013)
	Buddleja officinalis	flower	buddleja	scrophulariaceae	(Xie et al., 2017)
	Crataegi flos	flower	crataegus	rosaceae	(Strack et al., 1990)
	Rosa rugosa	flower	rosa		(Zhou et al., 2021)
	Arachis hypogaea	flower	arachis	fabaceae	(Sobolev et al., 2008)
	Helianthus annuus	pollen	helianthus	asteraceae	(Lin and Mullin 1999)
	Quercus dentata *Quercus alba*	pollen	quercus	fagaceae	(Bokern et al., 1995; Walters et al., 2001)
	Prunus mume	flower	prunus	rosaceae	(Mori et al., 2019)
keayanidine A-B	*Microdesmis keayana*	root	microdesmis	pandaceae	(Zamble et al., 2006)
	Microdesmis puberula				(Roumy et al., 2008)
Keayanidine C	*Microdesmis keayana*	root	microdesmis	pandaceae	(Zamble et al., 2006)
	Microdesmis puberula				(Roumy et al., 2008)
	Sambucus nigra	pollen	sambucus	adoxaceae	(Kite et al., 2013)
N^1, N^{10}-di-benzoyl-N^5-acetamidespermidine	*Banara parviflora*	leaf	banara	salicaceae	(Moritz et al., 2016)
chisitine 1, chisitine 2	*Chisocheton weinlandii*	leaf	chisocheton	meliaceae	(Tzourosa et al., 2004)
N^1, N^{14}-di-dihydrocaffeoylspermine, N^1,N^5, N^{14}-tri-dihydrocaffeoylspermine	*Solanum tuberosum*	tuber	solanum	solanaceae	(Narvaez-Cuenca et al., 2013)
kukoamine A	*Solanum tuberosum*	tuber	solanum	solanaceae	(Parr et al., 2005)
	Lycium chinense	root bark	lycium		(Funayama et al., 1980)
kukoamine B	*Lycium chinense*	root bark	lycium	solanaceae	(Funayama et al., 1995)
keayanine A-D	*Microdesmis puberula* *Microdesmis keayana*	root	microdesmis	pandaceae	(Zamble et al., 2007; Roumy et al., 2008)
N^1, N^5, N^{10}, N^{14}-tetra-*p*-(E, E, E, E)-coumaroylspermine	*Matricaria chamomilla*	flower	matricaria	asteraceae	(Yamamoto et al., 2002; Park et al., 2017)
	Tragopogon tommasinii	aerial	tragopogon		(Granica et al., 2015)
N^1, N^5, N^{10}, N^{14}-tetra-*p*-(Z, Z, Z, Z)-coumaroylspermine, N^1, N^5, N^{10}, N^{14}-tetra-*p*-(E, Z, Z, E)-coumaroylspermine, N^1, N^5, N^9, N^{14}-tetra-*p*-(Z, Z, Z, Z)-coumaroylthermospermine, N^1, N^5, N^9, N^{14}-tetra-*p*-(E, E, E, E)coumaroylthermospermine, N^1, N^5, N^9, N^{14}-tetra-*p*-(E, Z, Z, E)coumaroylthermospermine	*Matricaria chamomilla*	flower	matricaria	asteraceae	(Park et al., 2017)
N^5-(E)-caffeoyl, N^{10}-dihydrocaffeoylspermidine	*Lycium barbarum*	flower	lycium	solanaceae	(Lopatriello et al., 2017)
N^1, N^5-di-(E, E)-*p*-coumaroylspermidine, N^5, N^{10}-di-(E, E)-*p*-coumaroylspermidine	*Aphelandra tetraffona*	anther	aphelandra	acanthaceae	(Werner et al., 1995)
	Aphelandra chamissoniana				
safflospermidine A-B	*Carthamus*	flower	carthamus	asteraceae	(Jiang et al., 2008)

Table 6 (*continued*)

Compound	plant	part	genus	family	ref
	tinctorius				
	Prunus mume	flower	prunus	rosaceae	(Mori et al., 2019)
N^1, N^5-N^{10}-tri-*p*-(Z, Z, E)-coumaroylspermidine	*Carthamus tinctorius*	flower	carthamus	asteraceae	(Jiang et al., 2008; Zhao et al., 2009)
	Prunus mume	flower	prunus	rosaceae	(Mori et al., 2019)
N^1, N^5, N^{10}-tri-*p*-(Z, Z, Z)-coumaroylspermidine	*Carthamus tinctorius*	flower	carthamus	asteraceae	(Jiang et al., 2008)
	Prunus mume	flower	prunus	rosaceae	(Mori et al., 2019)
N^1, N^{10}-di-caffeoyl-N^5-*p*-(E, E, E)-coumaroylspermidine, *N*1-caffeoyl-N^5, N^{10}-di-*p*-(E, E, E)-coumaroylspermidine	*Capparis spinosa*	bud	capparis	capparaceae	(Wiese et al., 2013)
N^1, N^5-di-p-coumaroyl-N^{10}-(E, E, E)-caffeoylspermidine	*Capparis spinosa*	bud	capparis	capparaceae	(Wiese et al., 2013)
	Quercus dentata	pollen	quercus	fagaceae	(Nimtz et al., 1996)
N^1, N^5, N^{10}-tri-*p*-coumaroylspermidine (EEZ, ZEE, ZEZ)	*Prunus mume*	flower	prunus	rosaceae	(Mori et al., 2019)
N^1-acetyl-N^5, N^{10}-di-(E, E)-*p*-coumaroylspermidine	*Arachis hypogaea*	flower	arachis	fabaceae	(Sobolev et al., 2008)
N^1-caffeoyl, N^{10}-(E, E)-feruloylspermidine, N^1, N^{10}-di-(E, E)-feruloylspermidine	*Corylus avellana*	pollen	corylus	betulaceae	(Meurer et al., 1986)
N^1, N^5-di-*p*-(E, E)-coumaroylspermidine	*Brassica campestris*	pollen	brassica	brassicaceae	(Lv et al., 2013)
N^1, N^5, N^{10}-tri-(E, E, E)-caffeoylspermidine	*Brassica campestris*	pollen	brassica	brassicaceae	(Lv et al., 2013)
	Quercus dentata		quercus	fagaceae	(Bokern et al., 1995; Walters et al., 2001)
	Quercus alba				
N^1-*p*-coumaroyl, N^5, N^{10}-di-(E, E, E)-caffeoylspermidine	*Quercus dentata*	pollen	quercus	fagaceae	(Bokern et al., 1995)
N^1, N^{10}-di-*p*-coumaroyl, N^5-(E, E, E)-caffeoylspermidine	*Quercus dentata*	pollen	quercus	fagaceae	(Bokern et al., 1995; Walters et al., 2001)
	Quercus alba				
N^1-feruloyl-N^5, N^{10}-di-(E, E, E)-caffeoylspermidine, N^1-*p*-coumaroyl-N^5-caffeoyl-N^{10}-(E, E, E)-feruloylspermidine	*Quercus dentata*	pollen	quercus	fagaceae	(Nimtz et al., 1996)
N^5, N^{10}-di-(E, E)-feruloylspermidine, N^1-acetyl-N^5, N^{10}-di-(Z, E)-feruloylspermidine, N^1-acetyl-N^5, N^{10}-di-(Z, E)-feruloylspermidine	*Sambucus nigra*	pollen	sambucus	adoxaceae	(Kite et al., 2013)
N, *N*'-di-dihydrocaffeoylspermidine dihexoside, N^1, N^5 or N^5, N^{10}-di-dihydrocaffeoylspermidine hexoside, N^1, N^{10}-di-dihydrocaffeoylspermidine hexoside, N^1, N^5, N^{10}-tri-dihydrocaffeoylspermidine hexoside	*Solanum quitoense*	fruit	solanum	solanaceae	(Gancel et al., 2008)
lycibarbarspermidine A – T	*Lycium barbarum*	fruit	lycium		(Zhou et al., 2016a; Zhou et al., 2016b; Qian et al., 2020; Chen et al., 2021)
lyciamarspermidine A-C	*Lycium barbarum*				(Qian et al., 2020; Chen et al., 2021)
lyciamarspermine A-B	*Lycium barbarum*				(Qian et al., 2020)
acetyl-lycibarbarspermidine F, glucosyl-lycibarbarspermidine F, hydroxy-glucosyl-lycibarbarspermidine F	*Lycium barbarum*				(Mocan et al., 2018)

strain 3D7 to quinine (Lazaro et al., 2006). Crambescidin-816 reduced cell viability in *Saccharomyces cerevisiae* inducing an increment in cell size and DNA content, and apoptosis (Rubiolo et al., 2013). Crambescidin 800 showed a potent protective effect on the cell death of HT22 and neuroblastoma induced by a hypoxic condition or nitric oxide (Suna et al., 2007). Calcium influx is considered the main mechanism responsible for neuronal cell death. Ptilomycalin A could interact with ATP at the ATP binding site of Na^+, K^+-ATPase or Ca^{2+}-ATPase with an IC_{50} of 2 μM and 10 μM, respectively (Ohizumi et al., 1996). Crambescidin 816 was found to have a potent Ca^{2+} antagonist effect and to inhibit the

acetylcholine-induced contraction of guinea pig ileum at very low concentrations (Berlinck et al., 1993). Crambescidin 816 produced its main antagonist effect on L-type Ca^{2+} channels, and partially blocked voltage-gated calcium channels and voltage-dependent sodium channels in cortical neurons (Martin et al., 2013). Crambescidin 816 was proven to be cytotoxic against cortical neurons (Bondu et al., 2012). The cytotoxic effect of crambescidin 816 in cortical neurons may be related to an increase in the cytosolic calcium concentration elicited by the toxin, which is mediated by glutamate receptor activation (Mendez et al., 2017). Furthermore, Crambescidin 800, 816 and 844, fromiamycalin and ptilomycalin A strongly inhibited HSV-1 completely, with diffuse cytotoxicity (Jares-Erijman et al., 1991; Chang et al., 2003; Hua et al., 2007). Ptilomycalin A exhibited anti-HSV activity at a concentration of 0.2 μg/mL (Ohtani et al., 1992).

Monanchomycalin A, B and C, possessing similar structures with crambescidins, were isolated from the Far-Eastern marine sponge *Monanchora pulchra* (Makarieva et al., 2012; Tabakmakher et al., 2013). The anti-tumor activities of monanchomycalin A, B and C were investigated. Monanchomycalin A and B exhibited cytotoxic activities against HL-60 human leukemia cells with IC_{50} values of 120 and 140 nM, respectively (Makarieva et al., 2012). Monanchomycalin C exhibited potency to toxic activities against human breast cancer MDA-MB-231 cells with IC_{50} values of 8.2 μM (Tabakmakher et al., 2013). Monanchoxymycalin A, B and C were isolated from the marine sponge *Monanchora pulchra* either (Tabakmakher et al., 2016; Shubina et al., 2019). Monanchoxymycalin A, B and C exhibited potent cytotoxic activities against cervical epithelioid carcinoma HeLa cells with IC_{50} 2.80 μM, 2.82 μM and 3.50 μM, respectively

Table 7 Open-chain spermidine and spermine alkaloids from other sources.

Compound	source	genus	family	ref
pistillarin	*Clavariadelphus pistillaris*	clavariadelphus	typhulaceae	(Steglich et al., 1984)
	Penicillium bilaii	penicillium	trichocomaceae	(Capon et al., 2007)
	Ramaria subaurantiaca	ramaria	thelephoraceae	(Choomuenwai et al., 2013)
pistillarin salt	*Gomphus floccosus*	gomphus	gomphidiaceae	(Lee et al., 2010)
JBIR-125	*Streptomyces*(strainR56-07)	streptomyces	streptomycetaceae	(Kawahara et al., 2012)
ptilomycalin A	*Ptilocaulis spiculifer*	ptilocaulis	axinellidae	(Kashman et al., 1989; Ohtani et al., 1992)
	Hemimycale	hemimycale	hymedesmiidae	
	Monanchora unguifera	monanchora	crambeidae	(Gallimore et al., 2005; Hua et al., 2007)
	Batzella	batzella	chondropsidae	(Patil et al., 1995)
crambescidin 800	*Monanchora unguifera*	monanchora	crambeidae	(Hua et al., 2007)
	Batzella	batzella	chondropsidae	(Patil et al., 1995)
	Crambe crambe	crambe	brassicaceae	(Berlinck et al., 1993)
	Crambe crambe	crambe	brassicaceae	(Jares-Erijman et al., 1991)
	Monanchora arbuscula	monanchora	crambeidae	(Tavares et al., 1994)
	Monanchora	monanchora	crambeidae	(Chang et al., 2003)
	Monanchora viridis	monanchora	crambeidae	(Shrestha et al., 2018)
	Monanchora ungiculata	monanchora	crambeidae	(Aoki et al., 2004)
	Clathria cervicornis	clathria	microcionidae	(Sun et al., 2015)
crambescidin 816	*Batzella*	batzella	chondropsidae	(Patil et al., 1995)
	Crambe crambe	crambe	brassicaceae	(Berlinck et al., 1993; Jares-Erijman et al., 1993)
	Crambe crambe	crambe	brassicaceae	(Jares-Erijman et al., 1991)
isocrambescidin 800, crambidine	*Crambe crambe*	crambe	brassicaceae	(Berlinck et al., 1993)
crambescidin 830, 844	*Crambe crambe*	crambe	brassicaceae	(Jares-Erijman et al., 1991)
crambescidin 826, fromiamycalin	*Monanchora*	monanchora	crambeidae	(Chang et al., 2003)
13,14,15-isocrambescidin 800	*Crambe crambe*	crambe	brassicaceae	(Jares-Erijman et al., 1993)
unguiculin A, ptilomycalin E – H	*Monanchora ungiculata*	monanchora	crambeidae	(Campos et al., 2017)
monanchomycalin A-C	*Monanchora pulchra*	monanchora	crambeidae	(Makarieva et al., 2012; Tabakmakher et al., 2013)
monanchoxymycalin A-C	*Monanchora pulchra*	monanchora	crambeidae	(Tabakmakher et al., 2016; Shubina et al., 2019)
monanchocidin A-E	*Monanchora pulchra*	monanchora	crambeidae	(Guzii et al., 2010; Makarieva et al., 2011)
didemnidines A, didemnidines B	*Didemnum lahillei*	Didemnum	didemnidae	(Finlayson et al., 2011)
ianthelliformisamine A–C	*Suberea ianthelliformis*	suberea	aplysinellidae	(Xu et al., 2012)
tokaradine C	*Pseudoceratina purpurea*	pseudoceratina	pseudoceratinidae	(Fusetani et al., 2001)
spermatinamine	*Pseudoceratina*	pseudoceratina	pseudoceratinidae	(Buchanan et al., 2007)
pseudoceramine A–C	*Pseudoceratina*	pseudoceratina	pseudoceratinidae	(Yin et al., 2011)
petrobactin	*Marinobacter hydrocarbonoclasticus*	marinobacter	/	(Barbeau et al., 2002)

(Tabakmakher et al., 2016; Shubina et al., 2019). Monanchoxymycalin A and B exhibits cytotoxic activity against breast adenocarcinoma MDA-MB231 cells with IC_{50} values of 5.60 μM and 11.65 μM, respectively (Tabakmakher et al., 2016).

A new class of guanidine alkaloids monanchocidin A-E with an unprecedented skeleton system was isolated from the marine sponge *Monanchora pulchra*. The absolute configuration of the monanchocidin A was later fully determined as 5R, 8S, 10S, 13R, 14S, 15R, 19R, 23R, 37S, 42S, 43R (Shubina et al., 2018). Monanchocidin A-E showed potent cytotoxic activities against HL-60 human leukemia cells with IC_{50} values of 540, 200, 110, 830, and 650 nM, respectively (Guzii et al., 2010; Makarieva et al., 2011). Monanchocidin A showed very modest antibacterial, antifungal, and antiprotozoal activities, and exhibited potent selective activity for the melanoma panel in the NCI cancer cell screening panel (Gogineni et al., 2020). Monanchocidin A exerted antimigratory activity, and was able to overcome cisplatin-resistance of the human germ cell tumor cell line (Dyshlovoy et al., 2014; Dyshlovoy et al., 2015; Dyshlovoy et al., 2016b).

Two new indole spermidines didemnidines A and B, with an indole-3-glyoxylamide moiety linked to the *N*-1 position, were isolated from the New Zealand ascidian *Didemnum* sp. Didemnidine B exhibited mild *in vitro* growth inhibition of *Plasmodium falciparum* with IC_{50} of 15 μM (Finlayson et al., 2011). Ianthelliformisamines A–C were isolated from the marine sponge *Suberea ianthelliformis*, among which ianthelliformisamine A and C belong to spermine and Ianthelliformisamine B belongs to spermidine. Ianthelliformisamine A showed inhibitory activity against the Gram-negative bacterium *Pseudomonas aeruginosa* with an IC_{50} of 6.8 μM and MIC of 35 μM (Xu et al., 2012). Tokaradine C, a positional isomer of lanthelliformisamine B, was isolated from the Japanese marine sponge *Pseudoceratina purpurea* (Fusetani et al., 2001). Spermatinamine (Buchanan et al., 2007) and pseudoceramine A–C (Yin et al., 2011) were also isolated from genus *Pseudoceratina*. Spermatinamin inhibited the activity of isoprenylcysteine methyltransferase with an IC_{50} of 1.9 μM (Buchanan et al., 2007). Spermatinamine and pseudoceramine B significantly inhibited the secretion and enzyme activity of the Yersinia outer protein (Yin et al., 2011). Spermatinamine

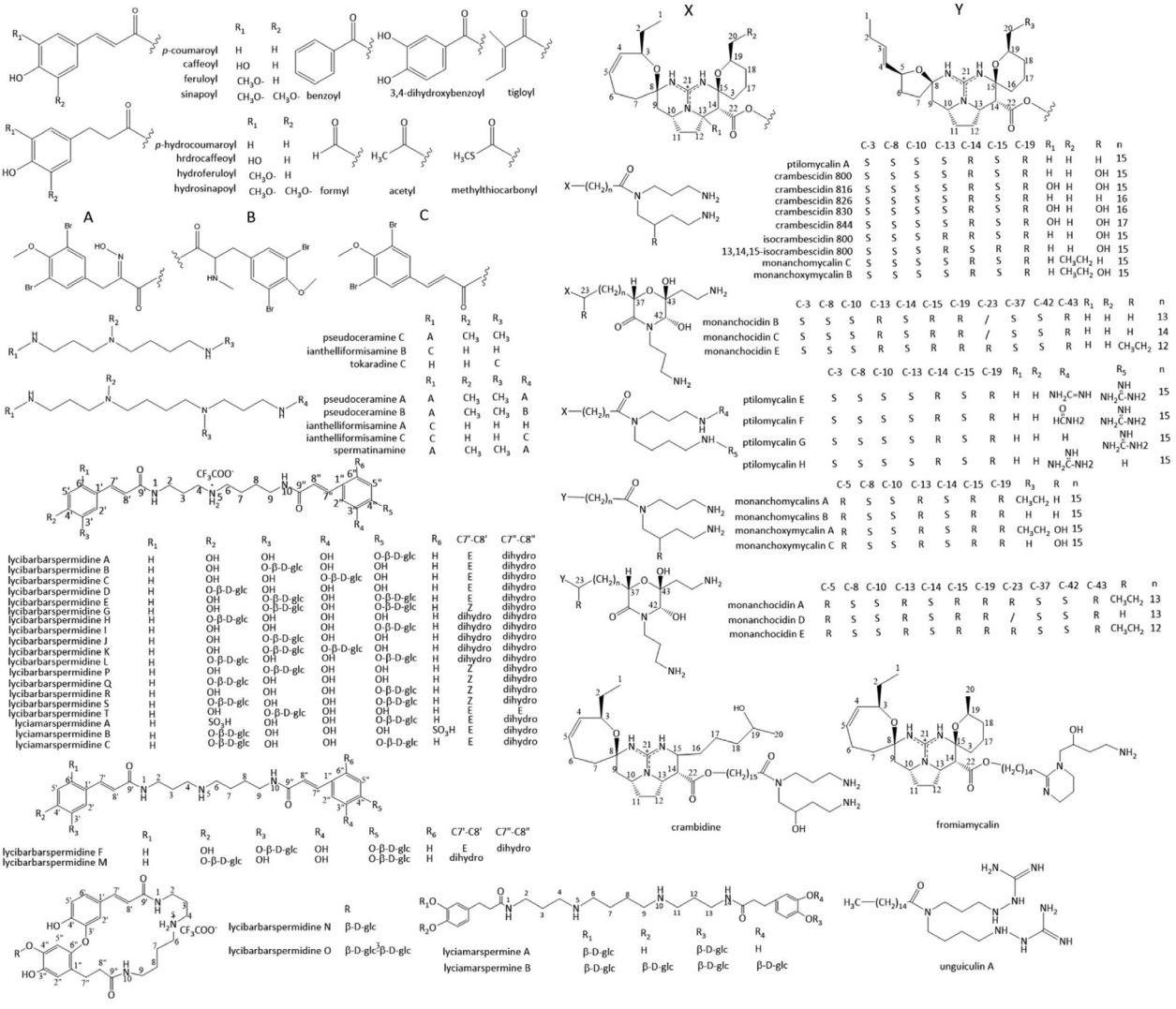


Fig. 7 Chemical structures of open chain spermidine and spermine alkaloids.

also exhibited antimalarial activity against Plasmodium falciparum (3D7) parasites with IC_{50} of 0.23 μM (Choomuenwai et al., 2013).

Petrobactin, composing of two spermidinyl moieties and one citryl moiety, was produced by *Marinobacter hydrocarbonoclasticus*, which could readily undergo a light-mediated decarboxylation reaction when bound to Fe(III) (Barbeau et al., 2002). The open-chain spermidine and spermine alkaloids from land plants and other sources are summarized in Table.6 and Table.7. The substituted groups, along with the structure of open chain alkaloids are included in Fig. 7.

3. Conclusions

In this review, we summarized the occurrence and pharmacological effects of spermidine and spermine alkaloids. Plants, seem to be the main sources of spermidine and spermine alkaloids, especially the macrocylic. Macrocylic spermidine alkaloids are much more abundant in nature than macrocylic spermine alkaloids. Dovyalicin-type alkaloids with an 8-membered ring were manly isolated from genus *Dovyalis* and *Homalium*, salicaceae family. The spermidine lactam alkaloids with a 13-membered ring have been found mainly in celastraceae family. Spermidine alkaloids with 24-membered lactam ring, containing two amide carbonyls in the macrocycle, were isolated from capparaceae family. Almost all the lactam alkaloids with a 17-membered ring are a class of macrocyclic alkaloids having a spermine nucleus.

Many mono-, di-, and tri-substituted spermidines/spermines and tetra-substituted spermines conjugated with hydroxycinnamic acids such as *p*-coumaric acid, caffeic acid, ferulic acid, sinapic acid were found from plants mainly belonging to family solanaceae, asteraceae and fagaceae. Compared with other parts of the plants, pollen is abundant in open chain spermidine and spermine alkaloids. In addition, numerous spermidine and spermine glycosides were detected and isolated from the fruit of *Lycium barbarum*. Marine sponges are abundant in open chain spermidine alkaloids. A great number of guanidine spermidine alkaloids with various skeletons were isolated from the marine sponges. The distribution characteristics of the spermidine and spermine alkaloids have guiding significance in finding new compounds, especially compounds with new skeletons.

A great quantity of the pharmacological effects of the open chain spermidine and spermine alkaloids are reported. anti-oxidative may be the main activity of the caffeic acid derivatives, probably due to the phenolic OH groups of the hydroxycinnamic acids moieties. Polycyclic guanidine spermidine alkaloids, which isolated from the marine sponge, show great potential in various cancer cells. However, pharmacological studies of macrocyclic spermidine and spermine alkaloids are scarce. One reason might be the low contents of the compound obtained. For instance, in our previous study (Zhang et al., 2022), the contents of celacinnine-type alkaloids are about 0.01 mg/g in dry power of *Tripterygium wilfordii*. In addition, some of the compounds were isolated several years ago, and the pharmacological effects were not investigated at that time. Interestingly, some macrocyclic and open chain spermine and spermidine alkaloids exhibited great potential in brain diseases, through inhibition of enzyme activity of acetylcholinesterase and butyrylcholinesterase, and showed protective effects on brain degenerative diseases. Therefore, considering remarkable pharmacological activities, further in-depth studies on the pharmacological effects of the macrocyclic spermidine and spermine alkaloids are required in the future.

In order to obtain more compounds for further study, numerous synthesis methods on the macrocyclic spermidine and spermine alkaloids and their analogues are reported. In the near future, we will summarize these synthesis methods. We hope this review will be helpful for phytochemistry research, especially in finding compounds with attractive pharmacological activities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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