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Ten years of advances in the chemistry and bioactivities of natural C_{19}-diterpenoid alkaloids

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C_{19}-diterpenoid alkaloids (DAs) constitute the most representative and largest class of DAs and have long been a popular focus of natural product research. In the past ten years (2015–2024), approximately 354 new C_{19}-DAs have been reported, composing eight structural subtypes, among which aconitine-type DAs are the most common, followed by lycoctonine-type DAs. In addition, several rare substituents and novel skeletons have been reported, demonstrating the rich structural diversity of this class. C_{19}-DAs are distributed only among *Aconitum* and *Delphinium* plants in the Ranunculaceae family, with a highly regular distribution pattern within these groups. Natural C_{19}-DAs exhibit various physiological activities, including antitumor, anti-inflammatory, analgesic, and antimicrobial activities. In summary, the diverse structures and biological activities of C_{19}-DAs highlight the great potential of this type of compound as lead compounds in drug discovery; in particular, the antitumor and anti-inflammatory effects of C_{19}-DAs merit further in-depth study.

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1. Introduction

DAs (diterpenoid alkaloids) are heterocyclic compounds in which the C-19 or C-20 of a tetracyclic or pentacyclic diterpene is linked to the nitrogen atom of β-aminoethanol, methylamine or ethylamine.[1] DAs can be divided into four main types according to the number of carbon atoms in the parent nucleus, namely, C_{18}-, C_{19}-, C_{20}-, and bis-DAs. C_{19}-DAs, once known as norditerpenoid alkaloids, are the most representative type of DA structure; they were the first type of DA to be discovered, and the greatest number of reported DA compounds are in this group.[2] Aconitine, which was isolated from *Aconitum napellus* by Geiger PL in 1833, was the first reported DA and is the best-known compound of this class. The discovery of aconitine not only marked the beginning of the study of DAs but also played an important role in the history of natural medicinal chemistry. C_{19}-DAs have a polycyclic fused cage skeleton with abundant substituents at multiple positions. The complex chemical structures of these materials have long attracted the persistent and intense research interest of chemists in the fields of natural products and organic synthesis.[3,4] In the approximately two centuries since the discovery of aconitine, more than 900 natural C_{19}-DAs have been reported, including eight structural subtypes with rich structural diversity.

The distribution of C_{19}-DAs is limited to plants from the genera *Aconitum* and *Delphinium* in the family Ranunculaceae. Many plants from these two genera have a long history of medicinal use worldwide, such as the famous traditional Chinese medicines (TCMs) Fuzi (processed lateral roots of *A. carmichaelii*), Chuanwu (processed mother roots of *A. carmichaelii*), Caowu (processed roots of *A. kusnezoffii*), and Xueshangyizhihao (*A. brachypodum*).[5,6] *Delphinium* plants are also widely used medicinally to treat bruises, rheumatism, toothache, and enteritis.[7] C_{19}-DAs are recognized as characteristic active components of these medicinal plants. C_{19}-DAs have various pharmacological activities, in particular, significant anti-inflammatory and analgesic effects. In China, two C_{19}-DAs have been used clinically as analgesics, namely, 3-acetylaconitine, discovered in *A. flavum*, and crassicauline A, discovered in *A. crassicaule*. The successful development and wide application of these C_{19}-DA drugs originating from traditional medicines have encouraged researchers to conduct further and in-depth chemical and pharmaceutical research on these types of compounds.[8–10] In the past ten years (2015–2024),

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approximately 354 new natural C_{19}-DAs have been discovered that exhibit significant physiological activities, including anti-tumor, anti-inflammatory, analgesic, antimicrobial, and cholinesterase inhibition. To better promote the development and application of C_{19}-DAs and their related medicinal plant resources, in this paper, we have specifically investigated the chemical structural characteristics, distribution, and biological characteristics of C_{19}-DAs from natural sources reported in the past ten years.

2. Structure and classification

C_{19}-DAs can be divided into eight subtypes according to their parent core structure and substituent groups (Fig. 1). Aconitine-type (**A**) and lycoctonine-type (**B**) C_{19}-DAs are the two most important subtypes, accounting for approximately 70% of the total number of C_{19}-DAs. These two structure subtypes differ in the presence of a 7-oxygenated substituent; aconitine-type DAs (**A**) do not contain this substituent, whereas lycoctonine-type DAs (**B**) do. Pyro-type C_{19}-DAs (**C**) refers to molecules with $\Delta^{8,15}$ or 15-keto groups, which are obtained from aconitine-type DAs by eliminating 8-OAc or 15-oxygenated substituents. Lactone-type DAs (**D**) refer to C_{19}-DAs with a six-membered lactone C ring, which are obtained through Baeyer–Villiger oxidation of aconitine-type DAs. Typically, franchetine-type DAs (**E**) have a *N*-C-17–*O*-C-6 *N*,*O*-mixed acetal group. Recently, franchetine-type DAs with *N*-C-17–*O*-C-7 or *N*-C-19–*O*-C-6 *N*,*O*-mixed acetal groups have also been reported. Seco-type DAs (**F**)

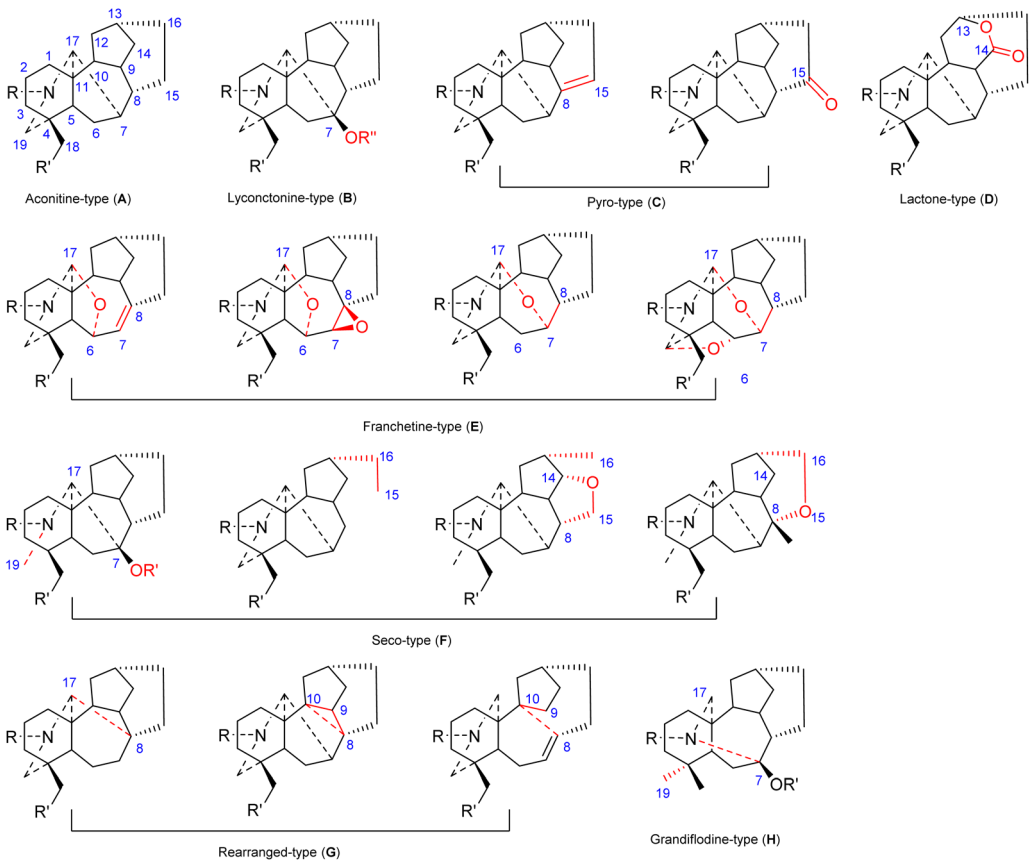

Fig. 1 Structure types of C_{19}-DAs.

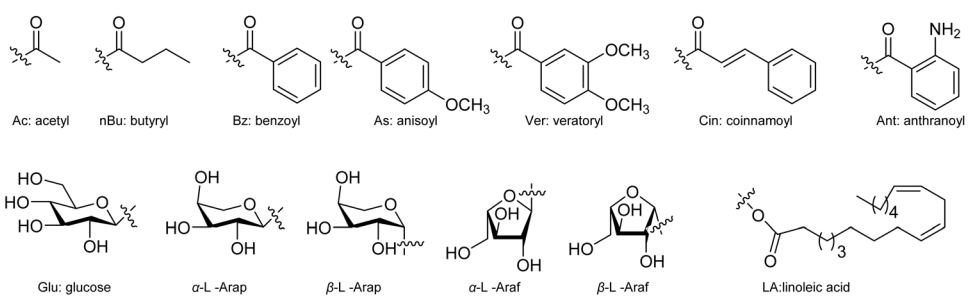

Fig. 2 Structures of common substituents in C_{19}-DAs.

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include 7,17-seco-type, 4,19-seco-type, 8,15-seco-type, and 15,16-seco-type C_{19}-DAs. The rearranged-type DAs (**G**) mainly include acoseptine-type, vilmoraconitine-type and vilmorine A-type DAs. Grandiflodine-type C_{19}-DAs (**H**) are a newly reported type of C_{19}-DA scaffold. The names, subtypes, plant sources and references of 354 natural C_{19}-DAs reported in the past ten years (2015.01–2024.12) are listed in Table S1. Herein, the structural features of C_{19}-DAs are discussed by category.

2.1. Aconitine-type C_{19}-DAs (A)

Aconitine-type DAs are the most important type of C_{19}-DAs, with the largest number of reported compounds (192) in the past 10 years. Aconitine-type DAs are reported mainly from the genus *Aconitum*, with only approximately 10 DAs isolated from the genus *Delphinium* (**A17**, **A23**, **A25**, **A75**, **A76**, **A85**, **A86**, **A126**, **A145**, and **A147**). According to the form of the N atom, natural aconitine-type C_{19}-DAs can be further divided into 162 amines (**A1–A162**), one *N*,*O*-mixed acetal compound (**A163**), two *N*-oxide derivatives (**A164–A165**), seven amide/lactam compounds (**A166–A172**), 17 imines (**A173–A191**), and one quaternary ammonium salt (**A192**) (Fig. 3). Specifically, uncinatine D (**A76**), isolated from *D. uncinatum*, has a *N*-ethanol substituent,[11] and szechenyianine E (**A168**) from *A. szechenyianum* has a *N*-hexyl group.[12] The degree of oxidation of aconitine-type C_{19}-DAs is generally lower than that of lycoctonine-type C_{19}-DAs; aconitine-type DAs usually have oxygenated substituents at C-1, C-8, C-14, and C-16, followed by C-18, C-6, C-3, C-10, C-13 and C-15. Rarely, pseudostapine B (**A74**) from *A. pseudostapfianum*[13] and refractines D–K (**A89–A96**) from *A. refractum*[14] feature an OH-5 group, whereas villosudine B (**A121**) from *A. franchetii* has an OH-2 group.[15] In addition, sepaconitine (**A122**) and lappaconine (**A123**) from *A. barbatum*[16] have an OH-9 group. Typically, C_{19}-DAs possess an oxygenated substituent at C-16, most often a methoxy group. However, in austroyunnanine B (**A124**)[17] and apetaldine E (**A148**),[18] the oxygenated substituents at C-16 were eliminated, generating a $\Delta^{15,16}$ group. In addition, 8-dehydroxylbikhaconine (**A32**), isolated from *A. ouvrardianum*, is characterized by the lack of an oxygenated substituent at C-8.[19]

The most common substituents in C_{19}-DAs are OCH_3, OH and its esters, including Ac (acetyl), Bz (benzoyl), As (anisoyl), Vr (veratroyl), Cin (cinnamoyl), and anthranoyl groups and their derivatives (Fig. 2). In general, the OAc and aroyl groups are located mainly at C-8 and C-14, whereas anthranoyl groups and their derivatives are commonly placed at C-18. A series of compounds including brevicanines A–D (**A151–A154**), isolated from *A. brevicalcaratum*,[20] and novolunines A–B (**A155–A156**), isolated from *A. novoluridum*,[21] have a 2-(2-methyl-4-oxoquinazolin-3-yl)benzoate group linked to C-18.

A series of C_{19}-DAs containing sugar substituents have been reported, including refractine L (**A105**), isolated from *A. ouvrardianum*,[19] aconicarmichosides E–L isolated from *A. carmichaelii* (**A106–A108**, **A110–A114**, **A114**, **A116**)[22] and aconicarmichosides A–C (**A109**, **A113**, **A115**).[23] The glycosyl types include β-D-Glu, α-L-Arap, β-L-Arap, α-L-Araf, and β-L-Arap. The substitution position is typically at C-14,[23,24] although aconicarmichoside E (**A106**), isolated from *A. carmichaelii*,[24] is linked with β-L-Araf at C-1. In addition, carmichasine A (**A118**), which was isolated from *A. carmichaelii*,[25] possesses a rare cyano group at C-19. 19*R*-Acetonyltalatisamine (**A119**), isolated from *A. ouvrardianum*,[19] and hemaconitine D (**A120**), isolated from *A. hemsleyanum*,[26] have an

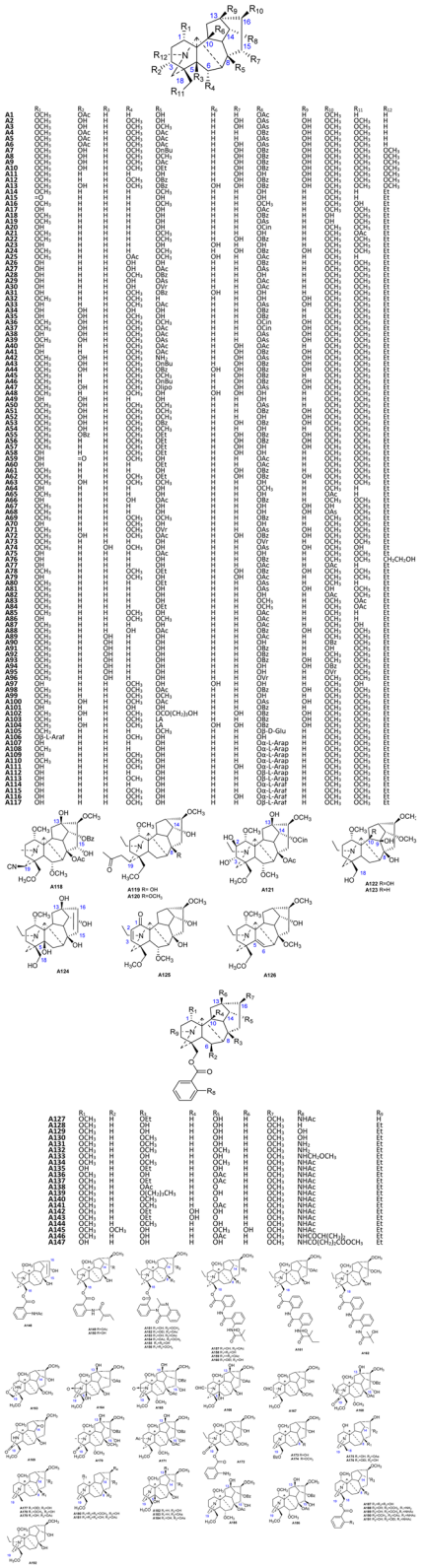

Fig. 3 The structures of aconitine-type C_{19}-DAs (A1–A192).

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acetonyl (CH_2COCH_3) at C-19, which may be artifacts. A few components containing double bonds have also been reported; for example, lasiandroline (**A125**), isolated from *A. nagarum*, contains an α,β-unsaturated ketone,[27] and jadwarine B (**A126**), isolated from *D. denudatum*,[28] contains a Δ5,6 group. In addition, two compounds, namely, sinchiangensine A (**A104**), isolated from *A. sinchiangense*,[29] and refractine L (**A105**), isolated from *A. refractum*, are esterified by a long-chain fatty acid at C-8.[14]

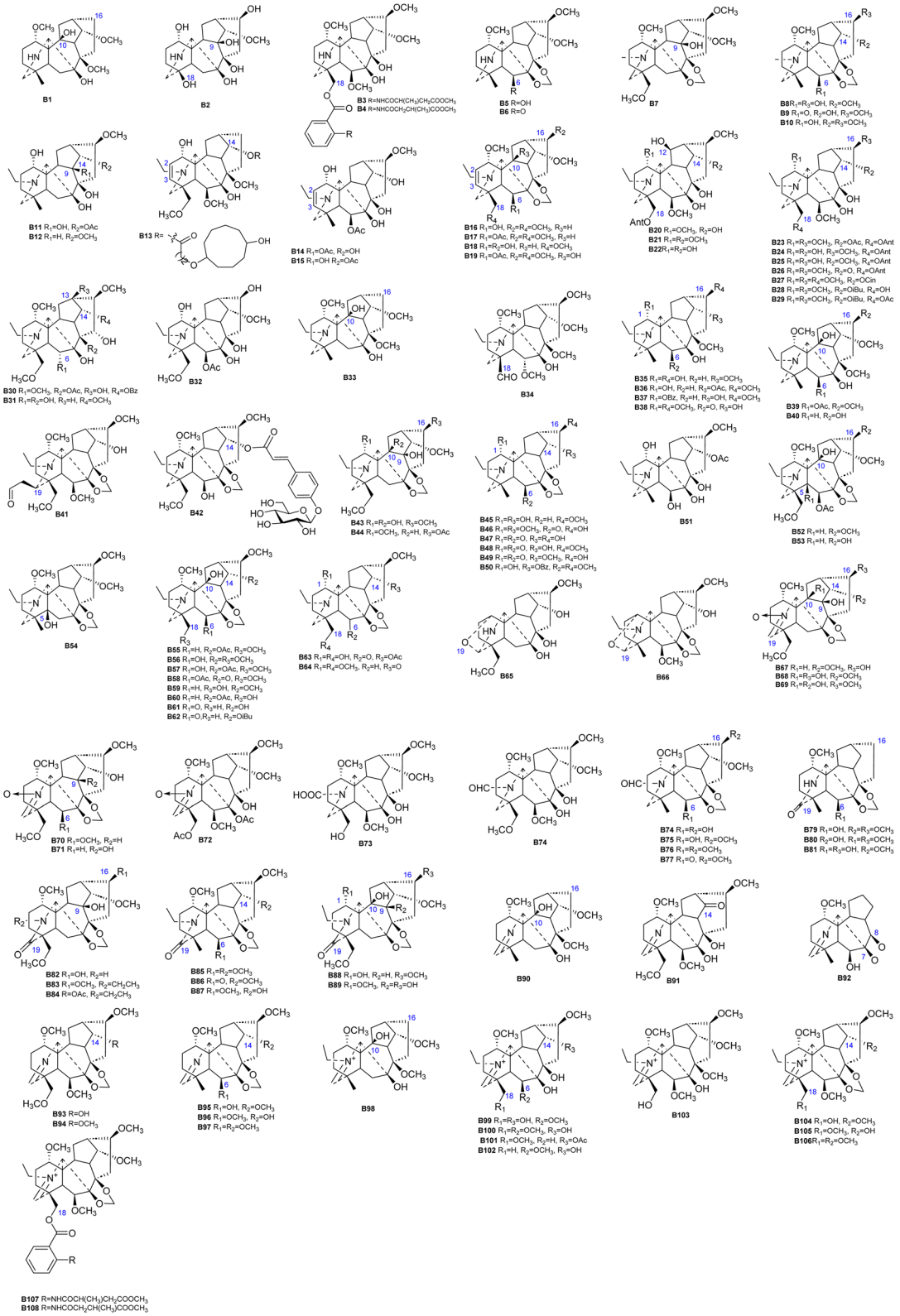

Fig. 4 Structures of lycoctonine-type C_{19}-DAs (**B1–B108**).

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2.2. Lycoctonine-type C_{19}-DAs (B)

The number of lycoctonine-type DAs is second only to that of aconitine-type DAs, with 108 published in the past ten years (Fig. 4). Lycoctonine-type DAs have been isolated mainly from *Delphinium*, with only approximately 9 compounds reported from *Aconitum*. In terms of the form of the N atom, the reported lycoctonine-type C_{19}-DAs included 64 amines (**B1–B64**), two *N*,*O*-mixed acetal compounds (**B65–B66**), 6 *N*-oxide derivatives (**B67–B72**), 17 amide/lactam compounds (**B73–B89**), 8 imines (**B90–B97**), and 11 quaternary ammonium salts (**B98–B108**). Seven lycoctonine-type DAs (**B13–B19**) containing a $\Delta^{2,3}$ group have been reported. The degree of oxidation of lycoctonine-type DAs is generally greater than that of aconitine-type DAs, whose C-1, C-6, C-7, C-8, C-10, C-14, C-16, and C-18 carbons often undergo oxidative substitution. Rarely, ajacisine A (**B20**), isolated from *D. ajacis*,[30] and ajacisine B (**B21**),[30] ajacisine G (**B22**),[31] and grandifloline D (**B52**), isolated from *D. grandiflorum*, have an OH-12 substitution,[32] whereas grandifloline F (**B53**)[32] and elapaciline (**B54**), isolated from *D. elatum* cv. Pacific Giant,[33] have an OH-5 group.

A series of C_{19}-DAs isolated from *D. pachycentrum* by our group, pachycentine B (**B33**) and pachycentine C (**B1**),[10] are characterized by the lack of an oxygenated substituent at C-16. Lycoctonine-type DAs have fewer kinds of substituents, and the most common substitutions are OCH_3, OH, and OCH_2O, whereas 7,8-OCH_2O can be considered a characteristic substituent of lycoctonine-type C_{19}-DAs. Except for the anthranoyl group and its derivatives, aroyl groups are rare in lycoctonine-type C_{19}-DAs. Iliensine A (**B42**), from *D. iliense*, possesses a rare *E*-*p*-hydroxy cinnamoyl group.[34] In addition, majusine D (**B13**), whose C-14 is esterified by 3-((5-hydroxycyclononyl)oxy) propanoic acid, was discovered in *D. majus*.[35] Pseudonidine B (**B41**), isolated from *D. pseudoaemulans*,[36] has an acetonyl group linked to C-19, which may be an artificial product.

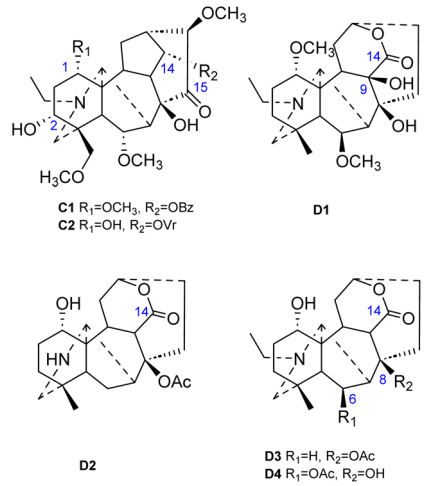

Fig. 5 Structures of pyro- and lactone-type C_{19}-DAs.

2.3. Pyro-type C_{19}-DAs (C)

Pyro-type DAs are C_{19}-DAs containing a $\Delta^{8,15}$ or a 15-keto group. These DAs were originally isolated from processed aconite and are considered thermal decomposition products of aconitine-type C_{19}-DAs containing an OH-15 group.[37] In recent years, only two alkaloids of this type have been reported, namely, nagaconitine B (**C1**)[38] and nagarumine D (**C2**),[17] both of which were isolated from *A. nagarum* and have a 15-keto group (Fig. 5).

2.4. Lactone-type C_{19}-DAs (D)

Lactone-type C_{19}-DAs are a highly specific class of compounds among C_{19}-DAs featuring a δ-lactonized C ring. In recent years, only four lactone-type C_{19}-DAs have been reported (Fig. 5), that

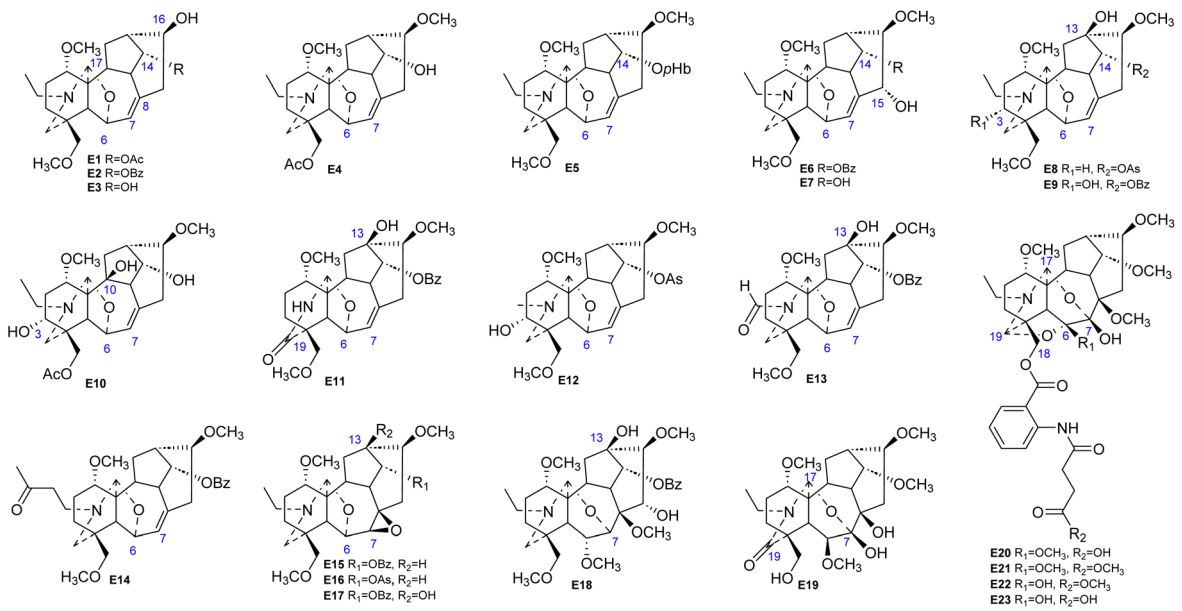

Fig. 6 Structures of franchetine-type C_{19}-DAs.

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is, 6β-methoxy,9β-dihydroxylheteratisine (**D1**), isolated from *A. heterophyllum*,[39] and rotundifosines A–C (**D2–D4**), isolated from *A. rotundifolium*.[40]

2.5. Franchetine-type C_{19}-DAs (E)

In the last ten years, 23 new franchetine-type DAs (**E1–E23**) have been reported. All DAs of this type were isolated from *Aconitum* plants, except grandifline B (**E19**), which was isolated from *D. grandiflorum*.[41] Typically, franchetine-type DAs are defined as DAs with a *N*-C-17–*O*-C-6 *N*,*O*-mixed acetal group, and these DAs generally have a $\Delta^{7,8}$ group (Fig. 6).[19,25,42–48] Three compounds, namely, 7,8-epoxy-franchetine (**E15**), acotarine B (**E16**), and flavumoline (**E17**), have a 7,8-epoxy group[42,45,48] and are likely derived from lycoctonine-type C_{19}-DAs. In addition, szechenyianine D (**E18**)[12] and grandifline B (**E19**)[41] possess *N*-C-17–*O*-C-7 *N*,*O*-mixed acetal groups, and aconicumines A-D (**E20–E23**) have *N*-C-17–*O*-C-7 and *N*-C-19–*O*-C-6 *N*,*O*-mixed acetal groups, but these two types of structures remain to be further confirmed by single-crystal X-ray diffraction experiments.[49]

2.6. Seco-type C_{19}-DAs (F)

Seco-type DAs (**F**) refer to 7,17-seco-type, 4,19-seco-type, 8,15-seco-type, and 15,16-seco-type C_{19}-DAs. Four 7,17-seco-type DAs, namely, hemaconitine A (**F1**) from *A. hemsleyanum* var. *circinatum*,[26] szechenyianine C (**F2**) from *A. szechenyianum*,[50] brunodelphinine D (**F3**) from *D. brunonianum*,[51] and brunodelphinine B (**F4**) from *D. brunonianum*,[51] have been reported in recent years (Fig. 7). Brunodelphinine B (**F4**) also possesses an open C ring, whose C-13–C-14 bond is also broken, forming an extra COOH-14 group, representing a novel class of seco-type DAs. Reported in 2015,[52] *N*-formyl-4,19-secopacinine (**F5**) from *D. elatum* is a 4,19-secotype DA whose C-4–C-19 bond is broken to form a new aldehyde group, CHO-19, which might be formed by Grob cleavage of a lycoctonine-type C_{19}-DA with an OH-3 group. An analog, *N*-formyl-4,19-secoyunnadelphinine (**F6**), was also isolated from *D. elatum*.[53] The 8,15-seco-type C_{19}-DAs nagarines A (**F7**) and B (**F8**) were isolated from *A. nagarum* by our group and possess an open D ring formed by breaking the C-8–C-15 bond.[54] These two compounds are also characterized by a lack of an oxygenated substituent at C-14. Stylosines A (**F9**) and B (**F10**) from *A. stylosum* are novel 15,16-seco-type C_{19}-DAs reported in 2020. These DAs are formed by cleaving the C-15–C-16 bond, and a new γ-lactone group is formed. Notably, nagarine A (**F7**) was also isolated from *A. stylosum*, suggesting that these two types of compounds may share similar biosynthetic pathways.[55] Kusnezosines A–C (**F11–F13**) are novel 15,16-seco-type C_{19}-DAs isolated from *A. kusnezoffii* var. *gibbiferum*. Their C-15–C-16 bond was opened, forming a new six-membered inner ester D ring.[56] The analog austroyunnanine D (**F14**) was isolated from *A. austroyunnanense*.[46]

2.7. Rearranged-type C_{19}-DAs (G)

Acoseptine-type DAs, whose C-17–C-7 bond is rearranged to a C-17–C-8 bond, was first discovered in *A. septentrionale* in 1999 by Usmanova *et al.* Acoseptine-type DAs usually contain a 7-keto substitution.[57] To date, only 10 acoseptine-type DAs have been reported. Pachycentine A (**G1**),[10] an acoseptine-type DA that lacks an oxygenated substituent at C-16 (Fig. 8), was isolated from *D. pachycentrum* by our group. In addition, two acoseptine-type compounds containing an *o*-aminobenzone moiety at C-18 DAs acosinomonines A–B (**G2–G3**) were isolated from *A. sinomontanum*.[58] The first vilmoraconitine-type DA, vilmoraconitine, which possesses a high-strain cyclopropane ring formed by the linkage of the C-8–C-10 bond, was isolated from *A. vilmorinianum* by Tan *et al.* Two analogs, vilmorines B (**G4**) and C (**G5**, vilmorrianine E[59]), were isolated from the same plant by our group.[60] A *N*-oxide derivative, episcopine A (**G6**), was isolated from *A. episcopale*.[61] Vilmotenitine-type DA was established by our group and is formed by the breakage of the C-8–C-9 bond on the basis of vilmoraconitine-type DA, thus generating a 6/6/6 framework. Thus far, only three vilmoraconitine-type DAs have been reported, namely, vilmotenitines A (**G7**) and B (**G8**), which were isolated from *A. vilmorinianum* var. *patentipilum*,[62] and nagarumine C (**G9**), which was isolated from *A. nagarum*.[63]

2.8. Grandiflodine-type C_{19}-DAs (H)

Grandiflodine B (**H1**), in which the *N*-C-19 bond is broken and a *N*-C-7 bond is formed, was isolated from *D. grandiflorum* by Chen *et al.*[64] Its structure suggests that it may be formed by Grob

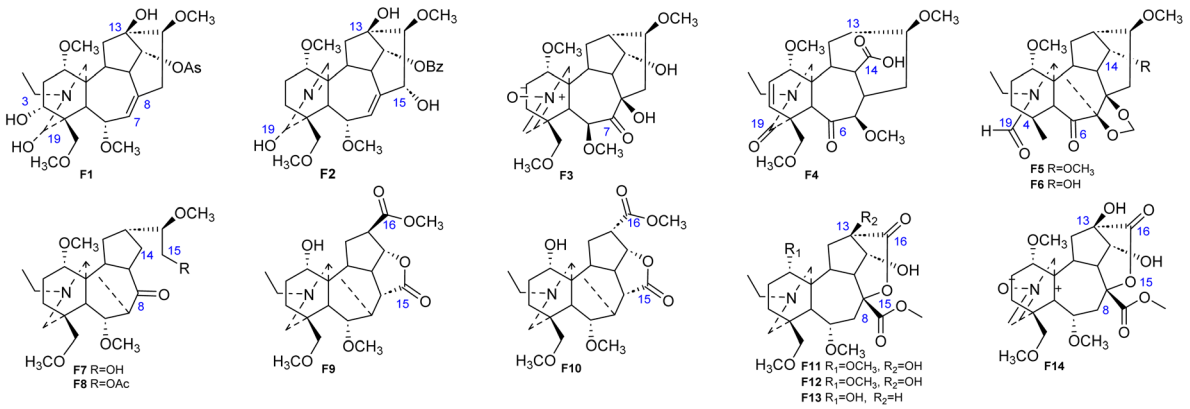

Fig. 7 The structures of seco-type C_{19}-DAs.

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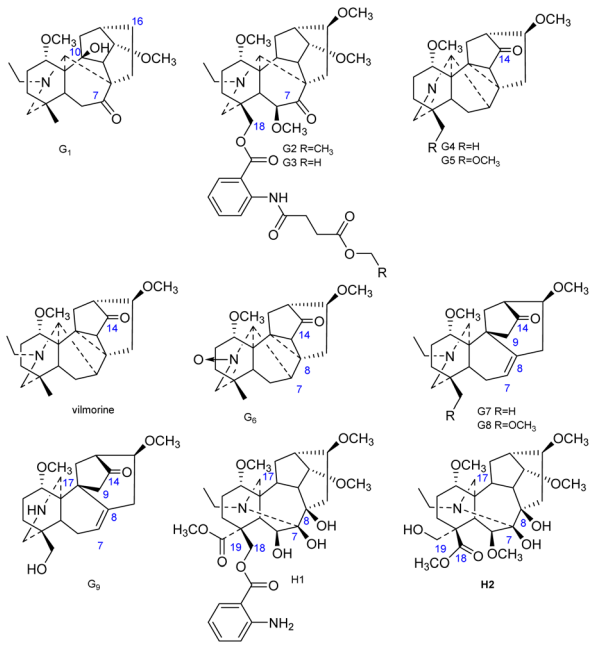

Fig. 8 Structures of rearranged-type and grandiflodine-type C_{19}-DAs.

cleavage of lycoctonine-type C_{19}-DAs with OH-19 substitution, resulting in the cleavage of *N*-C-19 and C-17–C-7 bonds, followed by oxidation and acetalization. An analog, gyalanutine A (**H2**), was isolated from *D. gyalanum*.[65]

3. Distribution

As shown in Table 1, the distribution of C_{19}-DAs is highly concentrated, in that all of the reported C_{19}-DAs were isolated from plants of the genera *Aconitum* and *Delphinium* in the Ranunculaceae family. In general, alkaloids with more complex and specialized structures have a narrower distribution in higher plants. Consistent with this pattern, C_{19}-DAs have a more complex skeletal ring system and also a narrower distribution than C_{20}-DAs do.[66]

The distributions of various subtypes of C_{19}-DAs exhibit strong regularity. Aconitine-type C_{19}-DAs have been reported mainly from *Aconitum* plants only approximately 10 aconitine-type DAs have been obtained from *Delphinium* plants. Conversely, lycoctonine-type C_{19}-DAs have been reported mainly from the genus *Delphinium*, and only approximately nine lycoctonine-type C_{19}-DAs have been isolated from the genus *Aconitum*. Therefore, aconitine-type and lycoctonine-type C_{19}-DAs can be considered characteristic DA components of *Aconitum* and *Delphinium*, respectively. According to systematic taxonomy and molecular biology, *Delphinium* plants are more evolved than *Aconitum* plants are.[67] In general, among metabolites with identical chemical structural skeletons, those with a higher the degree of oxidation are considered more evolved. The degree of oxidation of the lycoctonine-type C_{19}-DAs was greater than that of the aconitine-type compounds. The distribution of these two kinds of compounds supported the view that *Delphinium* plants are more evolved than *Aconitum* plants in terms of taxonomy. The number of other types of C_{19}-DAs was relatively small, but the regularity of their distribution was still apparent. In general, pyro-type, lactone-type, franchetine-type and seco-type C_{19}-DAs are distributed mainly in *Aconitum* plants and rarely in *Delphinium* plants. Currently, only two grandiflodine-type DAs are known, both isolated from *Delphinium*.

Table 1 The distributions of C_{19}-DAs

Family	Geneus	A	B	C	D	E	F	G	H
Ranunculaceae	*Aconitum*	182	9	2	4	22	10	8	0
	Delphinium	10	99	0	0	1	4	1	2

4. Biological activity

4.1. Anti-tumor activity

A series of natural C_{19}-DAs exhibit significant antitumor effects. Three recently characterized C_{19}-DAs, brunonianines D–F (**A85**, **A86**, and **B102**), discovered in the Chinese Tibetan medicine *D. brunonianum*, exhibited significant inhibitory effects on the proliferation of the ovarian cancer cell line Skov-3,[68] with IC_{50} values of 2.57, 8.05, and 5.85 μM, respectively. Among these DAs, brunonianine D (**A85**) had stronger activity than the positive control drug HCPT (IC_{50} = 3.06 μM) and also significantly inhibited tumor growth in a Skov-3 tumor load mouse model with little negative impact on healthy tissues. Studies have shown that brunonianine D (**A85**) exerts its antitumor effects by inhibiting cell migration, invasion and proliferation and by inducing cell apoptosis by activating the Bax/Bcl-2/caspase-3 signaling pathway.[68] The pyro-type DA nagaconitine C (**A40**) discovered in the medicinal plant *A. nagarum* var. *heterotrichum* in Yunnan, China, was also able to significantly inhibit the growth of Skov-3, with an IC_{50} value of 43.78 μM, whereas the IC_{50} value of cisplatin as the positive control drug was 11.58 μM.[38]

Several lipo class of C_{19}-DAs, which are defined as C_{19}-DAs that contain fatty acid ester groups (such as oleic acid and linoleic acid), have shown broad-spectrum tumor cytotoxicity *in vitro*.[69] Lipojesaconitine (**A47**) from *A. japonicum* subsp. *subcuneatum* in Japan[33] significantly inhibited the growth of four human tumor cell lines (A549, MDA-MB-231, MCF-7, and KB) (Table 2), with IC_{50} values between 6.0 and 7.3 μM. However, its cytotoxicity against the multidrug-resistant KB-VIN cell line was relatively weak (IC_{50} = 18.6 μM), indicating that lipojesaconitine was likely exported by P-glycoprotein. Similarly, the lipoalkaloid sinchiangensin A (**A104**), obtained from *A. sinchiangense*, and the known compound lipodeoxyaconitine also exhibited significant inhibitory activity against various tumor cell lines, with IC_{50} values comparable to that of cisplatin. Lipo DAs may be selective inhibitors of topoisomerase IIα.[70] Notably, compared with other ester C_{19}-DAs, lipoalkaloids are less toxic;[71] thus, they have unique advantages and great potential as antitumor drug lead compounds.[72,73]

Three aconitine-type C_{19}-DAs, 6-demethoxyhypaconine (**A11**), carmichaeline K (**A61**) and 8-*O*-ethyloyldeoxyaconine

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Table 2 IC_{50} values (μM) of C_{19}-DAs against tumor cells

Name	A-549	MDA-MB-231	H460	HeLa	HepG2	HL-60	SMCC-7721	MCF-7	KB	KB-VIN	SW480	Ref.
Lipojesaconitine (**A47**)	7.3	6.0						6.7	6.0	18.6		33
Sinchiangensine A (**A104**)	12.8					9.2	9.6	11.8			18.8	29
Lipodeoxyaconitine	10.1					3.2	12.4	9.7			7.4	29
6-*O*-Acetyl-16-demethyldelsolin (**B32**)							37.4	33.1				75
6-Demethoxyhypaconine (**A11**)	18.2		22.8									74
Carmichaeline K (**A61**)	21.3		22.3									74
8-*O*-Ethy-benzoyldeoxyaconine (**A62**)	12.6		12.8									74
14α-Benzoyloxy-13β,15α-dihydroxy-1α,6α,8β,16β,18-pentamethoxy-19-oxoaconitan (**A170**)	18.7			19.7	17.6							76

(**A62**), which were isolated from the TCM *A. carmichaelii*, moderately inhibited the proliferation of A549 and H460 tumor cells, with IC_{50} values ranging from 12.6 to 22.8 μM.[74] Network pharmacology analysis revealed that these DAs may inhibit tumor cell growth and promote apoptosis by regulating the PI3K-AKT signaling pathway, interleukin signaling pathway and MAPK signaling pathway. The IC_{50} values of 6-*O*-acetyl-16-demethyldelsolin (**B32**), isolated from *D. grandiflorum*, for the inhibition of SMCC-7721 and MCF-7 cell proliferation were 37.4 and 33.1 μM, respectively.[75] The aconitine-type DA **A170**, isolated from *A. austroyunnanense*, also inhibited the proliferation of A49, HeLa and HepG2 cells.[76]

In addition, Hu *et al.* reported that nagarumine E (**E12**) found in *A. nagarum*[47] exhibited cytotoxicity against five gastric cancer cell lines (GES-1, AGS, HGC-27, MKN-45 and MGC-803), with IC_{50} values of 16.1, 15.2, 14.7, 14.3 and 13.8 μM, respectively. Austroyunnanine D (**F14**), isolated from *A. austroyunnanense*, showed cytotoxicity against three gastric cancer cell lines, with IC_{50} values of 17.6 μM (MGC-803), 14.3 μM (BGC-823) and 15.8 μM (SGC-7901).[46]

4.2. Anti-inflammatory activity

The medicinal plants of the genera *Aconitum* and *Delphinium* are widely used in TCMs to treat inflammatory diseases, suggesting that they may be rich in active anti-inflammatory components. Some recently discovered C_{19}-DAs have shown significant anti-inflammatory activity *in vitro*. For example, two aconitine-type DAs, szechenyianines A (**A185**) and B (**A165**), and one seco-type DA, szechenyianine C (**F2**) discovered in the medicinal plant *A. szechenyianum*, which is widely distributed in western China, effectively reduced NO production in polysaccharide (LPS)-induced RAW 264.7 cells, with IC_{50} values of 36.6 μM, 3.3 μM and 7.5 μM, respectively (Table 3).[50] Notably, the activities of **A165** and **F2** were greater than that of the positive control dexamethasone (IC_{50}, 8.3 μM). The results showed that the presence of the N → O group might enhance anti-inflammatory activity.

The 11 novel lycaconitine-type C_{19}-DAs kamaonensines A–K (**B44**, **B7**, **B88**, **B82**, **B83**, **B67**, **B84**, **B68**, **B71**, **B69**, **B89**) isolated from *D. kamaonense* inhibited LPS-induced NO production, with IC_{50} values ranging from 0.9–85.5 μM.[77,78] In particular, kamaonensine E (**B83**) exhibited a greater ability to inhibit NO production than did the positive control (IC_{50} = 0.9 μM). Network pharmacology analysis predicted that these compounds might exert anti-inflammatory effects by regulating related proteins in the MAPK signaling pathway, such as MAPK8, MAPK14 and HSP90α. In addition, the molecular docking results revealed that compounds containing amide and methylenedioxy groups may have stronger anti-inflammatory effects. The novel franchetine-type DAs aconicumines A (**E20**) and C (**E22**), discovered in the medicinal plant *A. taipeicum* endemic to the Taibai Mountains in China,[49] and the novel scaffold compound grandiflodine B (**H1**), discovered in *D. grandiflorum*, also have NO production inhibitory effects.[64] Zhou *et al.* isolated four known franchetine-type DAs, *i.e.*, franchetine, kongboendine, leueandine and vilmorisine, from the roots of *A. sinoaxillare* and synthesized 14 analogs, all of which have been tested for their anti-inflammatory activities *in vitro*.[79]. The results showed that franchetine, kongboendine and two of the analog compounds had stronger inhibitory effects on NO

Table 3 Inhibitory effect of C_{19}-DAs on NO production in LPS-stimulated RAW264.7 cell (IC_{50}, μM)

Name	IC_{50}	Ref.	Name	IC_{50}	Ref.
Szechenyianine A (**A185**)	36.6	64	Kamaonensine H (**B68**)	16.0	78
Szechenyianine B (**A165**)	3.3	64	Kamaonensine J (**B69**)	18.1	78
Kamaonensine A (**B44**)	12.2	77	Kamaonensine I (**B71**)	17.4	78
Kamaonensine B (**B7**)	2.7	77	Kamaonensine K (**B89**)	2.2	78
Kamaonensine C (**B88**)	27.7	77	Aconicumine A (**E20**)	19.7	49
Kamaonensine D (**B82**)	12.2	77	Aconicumine C (**E22**)	97.4	49
Kamaonensine E (**B83**)	0.9	77	Szechenyianine C (**F2**)	7.5	64
Kamaonensine F (**B84**)	12.4	77	Grandiflodine B (**H1**)	72.7	81
Kamaonensine G (**B67**)	11.8	77			

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production than did the positive control celecoxib. Structure–activity relationship studies revealed that the *in vitro* anti-inflammatory activity of franchetine-type DAs was closely related to their C-14 ester group: when this group was substituted with linear-chain fatty acids, the chain length was positively correlated with the anti-inflammatory activity of the resulting compound; aromatic acyl group substitution produced greater activity than heterocyclic ring and cycloparaffin moieties, and methoxy substitution on the aromatic ring enhanced the anti-inflammatory activity. Further studies revealed that franchetine inhibited the expression of the inflammatory proteins iNOS and COX-2. The anti-inflammatory effect of franchetine might be based on the inhibition of the TLR4-MyD88/NF-κB/MAPK signaling pathway, thereby inhibiting the expression of NO, ROS, TNF-α, and inflammatory factors or mediators such as IL-6, IL-1β, iNOS, and COX-2. In addition, franchetine has low toxicity in mice (LD_{50} > 20 mg kg^{-1}), indicating its potential for development as a drug. C_{19}-DAs also inhibit the production of other proinflammatory factors. For example, the 8,15-seco-type DAs nagarines A (**F7**) and B (**F8**), isolated from *A. nagarum*,[54] and the aconitine-type DAs taronenines A (**A33**), B (**A30**) and D (**A27**), isolated from *A. taronense*,[80] can inhibit LPS-induced IL-6 production in RAW 264.7 cells, with IC_{50} values ranging from 25.4–29.6 μg mL^{-1}. The 15,16-seco-type DAs stylosines A (**F9**) and B (**F10**) significantly inhibited the LPS-induced inflammatory cytokines IL-1β, COX-2 and TNF-α in RAW 264.7 macrophages *in vitro*, and no cytotoxicity was detected at the test concentration (0.1 mg mL^{-1}).[80]

4.3. Analgesic effects

The medicinal plants of the genus *Aconitum*, represented by Aconite Radix, are widely used in TCM to treat various types of pain, including rheumatic joint pain, neuralgia, and trauma. C_{19}-DAs are considered the main analgesic active component of *Aconitum* plants. The aconitine-type DA bulletaconitine A, discovered in *A. bulletanum*, has been used clinically in China for more than 30 years to treat common chronic pain, osteoarthritis and other diseases.[82] Some natural C_{19}-DAs reported recently also have significant analgesic effects. Shi *et al.* used a mouse acetic acid-induced writhing response model to screen the analgesic activity of a series of C_{19}-DA arabinosides isolated from Aconite Radix.[24] The results showed that at a dose of 1.0 mg kg^{-1}, the aconicarmichosides E–F (**A106–A107**) and H–J (**A114**, **A111**, **A116**) exhibited significant analgesic effects compared with the blank control against the acetic acid-induced writhing response in mice, with an inhibition rate of more than 65.6%. In contrast, aconicarmichosides K (**A108**) and L (**A110**) only showed weak activity at high doses, with inhibition rates of less than 20%. Structure–activity relationship studies revealed that the analgesic activities and structures of these compounds were closely related. In particular, methoxylation at the C-1 position significantly reduced the activity. In addition, the configuration of the arabinoside moiety also affects the activity of the compounds. The new C_{19}-DA grandiflonine G (**B91**) and several known compounds isolated from *D. grandiflorum* were also tested for their analgesic activity *via* an acetic acid-induced mouse model.[83] The results revealed that deoxylapaconitine, a known aconitine-type DA, exhibited significant analgesic activity, with an ED_{50} of 0.35 mg kg^{-1} and a therapeutic index (TI) of 46.22, which were better than the corresponding values of the reference drug aconitine (ED_{50} = 3.5 mg kg^{-1}, TI = 3.34), highlighting deoxylapaconitine as a candidate substance for the development of new analgesic drugs. However, the new compound, grandiflonine G (**B91**), showed only a weak analgesic effect at a dose of 10 mg kg^{-1}.

Hu *et al.* used an acetic acid-induced abdominal contraction assay in mice to evaluate the analgesic effects of a series of new C_{19}-DAs discovered in *Aconitum* plants in Southwest China and reported that new compounds, including episcopine A (**G6**), isolated from *A. episcopale* (ID_{50} = 66.1 μM kg^{-1}),[61] pseudostapine A (**A73**) (ID_{50} = 83.2 μM kg^{-1}) and pseudostapine B (**A74**) (ID_{50} = 71.0 μM kg^{-1}), found in *A. pseudostapfianum*,[13] austroyunnanine B (**A124**), isolated from *A. austroyunnanense* (ID_{50} = 48.0 μM kg^{-1}),[17] and nagarumine C (**G9**), isolated from *A. nagarum* (76.0 μM kg^{-1}),[63] presented greater analgesic activity than the positive controls aspirin (ID_{50} = 135.0 μM kg^{-1}) and acetaminophen (ID_{50} = 127.7 μM kg^{-1}).

In addition, franchetine, a known C_{19}-DA component isolated from *A. sinoaxillare*, exhibited a significant analgesic effect in a mouse writhing model, with an ED_{50} of 2.15 mg kg^{-1}, and significantly increased the latency of foot licking in the hot plate experiment. These findings suggest that franchetine has central analgesic effects.[79] Whole-cell patch clamp experiments revealed that franchetine inhibited NaV1.7 and NaV1.8 channel currents in a state-dependent manner, with inhibition rates of 30.07% and 45.73% (resting state) and 59.15% and 65.49% (semiactive state), respectively. Molecular docking studies revealed that the carbonyl group of franchetine interacts with the amino acid residues Trp-1567, Ser-1568 and Arg-1620 through hydrogen bonds, which may be critical for the inhibition of NaV1.7 activity. Rearranged C_{19}-DA acosinomonine B (**G3**), found in *A. sinomontanum*, has a significant inhibitory effect on capsaicin-mediated activation of TRPV1 channels at 10 μM, with an inhibition rate of 31.78%, and may become the lead structure of analgesic drugs.[58] In addition, the aconitine-type DAs pendulumines A–F (**A55–A59**, **A171**), isolated from *A. pendulum*, also exhibited analgesic activity in a thermal avoidance response experiment in the roundworm *Pristionchus pacificus*.[84]

4.4. Biocontrol effects

Plants of the genera *Aconitum* and *Delphinium* have been applied as pesticides, indicating that their main components, DAs, may have biocontrol effects and could be used as a source of botanical pesticides. Feed repellents are a type of insecticide that controls the number of pests by interfering with the appetite center of the pests, making them develop a sense of disgust for food, reduce or stop feeding, and finally die of starvation. Zhou *et al.* discovered a series of novel C_{19}-DAs from *Aconitum* and *Delphinium* with significant antifeeding effects on *Spodoptera exigua* larvae.[43] With the exception of rockidine C (**E5**), which is a franchetine-type DA, these DAs were all

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aconitine-type DAs, and the EC_{50} values of many of the tested compounds were <1 mg cm^{-2} (Table 5).[43] Zhou *et al.* reported that chasmanthinine, a known component of aconitine-type DA with a cinnamoyl group, exhibited the best antifeedant activity and could be used as a lead compound for further study.[18] In addition, the aconitine-type DA pubescensine (**A41**), isolated from *A. soongaricum* var. *pubescens*, had a significant antifeedant effect on *Pieris rapae* larvae, with an EC_{50} of 0.03 mg cm^{-2}.[59] Furthermore, the study revealed that aconitine-type C_{19}-DAs had strong antifeedant activity, whereas napelline-type C_{20}-DAs had only weak activity. The above studies show that C_{19}-DAs can be used as a potential resource to develop new antifeedant agents, providing a new strategy for the green control of agricultural pests. In addition, 13-hydroxypatentine (**A88**), isolated from *A. pendulum*, had a moderate contact effect on two-spotted spider mites, *Tetranychus urticae*, with an LC_{50} of 0.86 mg mL^{-1}.[85] Acoapetaldine A (**A133**), isolated from *A. apetalum*, showed moderate anti-TMV (tobacco mosaic virus) activity, with an inhibition rate of 61.27% at 50 μg mL^{-1}, comparable to that of the positive control ningnamycin (55.12%).[75]

4.5. Antipathogenic effects

Some C_{19}-DAs have been reported to have antipathogenic effects on microorganisms including bacteria, fungi and viruses. The aconitine-type DA sinchiangensine A (**A104**), discovered in *A. sinchiangense*, showed strong antibacterial activity against *S. aureus*, with an MIC of 0.147 μM,[29] and had an inhibitory effect on *E. coli*, with an MIC of 2.55 μM, which was greater than that of the positive control drug berberine hydrochloride (MIC values of were 0.67 μM and 1.34 μM against *S. aureus* and *E. coli*, respectively). The MIC values of the 15,16-seco-type DAs stylosines A (**F9**) and B (**F10**) against *S. aureus* were 2.0 mg mL^{-1} and 32.0 μg mL^{-1}, respectively.[55] Acoapetaludines D (**A129**) and E (**A130**), isolated from *A. apetalum*, showed weak inhibitory activity against *Helicobacter pylori*, with MICs of 100 μg mL^{-1} and 50 μg mL^{-1}, respectively.[86] Ajacisines D–E (**B24–B25**), isolated from *D. ajacis*, showed moderate antirespiratory syncytial virus (RSV) activity, with IC_{50} values of 75.2 μM and 35.1 μM, respectively,[30] while the IC_{50} value of the positive control drug ribavirin was 3.1 μM, indicating that C_{19}-DAs may be a natural resource against RSV. The IC_{50} value of grandiflodine B (**H1**) from *D. grandiflorum* for the growth and proliferation of RSV was 75.3 μM.[64]

4.6. Cholinesterase inhibition

Alzheimer's disease (AD) is a neurodegenerative disease associated with a decrease in acetylcholine (ACh) levels in the brain. AChE and BChE are enzymes that decompose ACh. Inhibition of the activity of these enzymes can increase the level of ACh in the brain, thereby improving cognitive ability. Therefore, the discovery of natural cholinesterase inhibitors is important. Some C_{19}-DAs have been reported to have cholinesterase inhibitory activity (Table 4). Among these aconitine-type DAs, jadwarine A (**A23**) showed relatively good activity, with IC_{50} values of 9.2 and 19.6 μM for the inhibition of AChE and BChE, respectively.[28] In addition, the lycaconitine-type DA swatinine C (**B63**) and 6β-methoxy,9β-dihydroxyheteratisine (**D1**) also exhibit significant cholinesterase inhibitory activity.[88]

4.7. Neuroprotective effects

Zhou *et al.* discovered five novel aconitine-type C_{19}-DAs, apetalrines A–E (**A157–A161**), from *A. apetalum*, synthesized 20 derivatives of apetalrine B (**A158**),[89] and used a H_2O_2-induced SH-SY5Y cell injury model to evaluate the neuroprotective effects of these compounds. Under low-cytotoxicity conditions, 50 μM apetalrine B (**A158**) protected against H_2O_2-induced SH-SY5Y cells and had the greatest protective effect, with the protection rate reaching 77.4%. Further studies revealed that this compound could significantly reduce H_2O_2-induced intracellular ROS levels and regulate the expression of apoptosis-related proteins such as PARP, Bcl-2, Bax, and caspase-3, thereby reducing cell apoptosis and exerting neuroprotective effects. These components can be used as lead compounds to develop therapeutics for Alzheimer's disease.

4.8. Toxicity

C_{19}-DAs, represented by diester aconitine-type DAs such as aconitine and yunaconitine, are also known for their strong cardiotoxicity and neurotoxicity,[90] which severely limit the use of *Aconitum* plants as medicinal materials;[91] thus, the toxicity of these newly discovered DAs must also be assessed. Peng *et al.* assessed the cardiotoxicity of seven aconitine-type C_{19}-DA monoesters isolated from *A. carmichaelii*, including a novel compound, 1-*epi*-hokbusine A (**A8**), and 6 known compounds, in H9c2 rat cardiomyocytes and zebrafish.[92] All the C_{19}-DAs monoesters showed cardiotoxicity. Among these compounds,

Table 4 Inhibitory effects of C_{19}-DAs against AChE and BchE (IC_{50}, μM)

Name	AChE	BChE	Type of inhibition	Ref.
Uncinatine B (**A145**)	188.1	—	—	11
Uncinatine C (**A75**)	94.3	—	—	11
Uncinatine D (**A76**)	367.0	—	—	11
Hemsleyaline (**A50**)	471.0	—	—	87
1β-Hydroxy,14β-acetyl condelphine (**A17**)	19.8	31.5	Non competitive	28
Jadwarine A (**A23**)	9.2	19.6	Competitive	28
Jadwarine B (**A126**)	16.8	34.7	Non competitive	28
Swatinine C (**B63**)	3.7	12.2	Competitive	88
6β-Methoxy,9β-dihydroxylheteratisine (**D1**)	5.4	8.6	Non competitive	39

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Table 5 Antifeedant activities of the compounds against *Spodoptera exigua*

Name	EC_{50} (mg cm^{-2})	Ref.
Rockidine A (**A65**)	4.03	43
Rockidine B (**A66**)	0.32	43
Leucostosine A (**A64**)	19.77	94
Leucostosine B (**A139**)	1.54	94
Apetaldine A (**A137**)	0.45	18
Apetaldine B (**A136**)	0.94	18
Apetaldine C (**A138**)	1.18	18
Apetaldine D (**A135**)	0.64	18
Apetaldine E (**A148**)	0.28	18
Apetaldine F (**A127**)	0.68	18
Apetaldine G (**A191**)	9.23	18
Rockidine C (**E5**)	0.79	43

the known compounds 14-benzoylmesaconine and (−)-(Ab)-14α-benzoyloxy-*N*-ethyl-1α,8β,15α-trihydroxy-6α,16β,18-trimethoxyaconitane at 50 μM decreased the survival rate of H9c2 cells to 46.73% and 48.80%, respectively. In zebrafish experiments, 14-benzoylmesaconine and (−)-(Ab)-14α-benzoyloxy-*N*-ethyl-1α,8β,15α-trihydroxy-6α,16β,18-trimethoxyaconitane significantly affected embryo morphology, leading to pericardial edema and yolk sac edema and significantly increasing embryonic malformation rate and heart rate. Liu *et al.* evaluated the H9c2 cytotoxicity of compounds isolated from *A. carmichaelii*,[93] including four novel aconitine-type DAs and seven known compounds. The results revealed that compound **A12** (8β,14α-dibenzoyloxy-13β,15α-dihydroxy-1α,6α,16β,18-tetramethoxy-*N* methylaconitane)[93] and seven known compounds exhibited significant toxicity to H9c2 cells, with two known compounds with OBu-8 substituents being the most toxic. Further studies revealed that C_{19}-DAs exhibited strong cardiotoxicity by increasing the intracellular Ca^{2+} concentration, affecting the cell membrane potential and inducing mitochondria-mediated cell apoptosis. The above studies on the toxicity of C_{19}-DAs not only help to develop DA drug lead compounds with high efficiency and low toxicity but also promote the safe use and quality control of related TCMs.

5. Conclusion

In the past ten years, 354 natural C_{19}-DAs have been reported, including 192 aconitine-type C_{19}-DAs (**A**), 108 lycoctonine-type C_{19}-DAs (**B**), two pyro-type C_{19}-DAs (**C**), four lactone-type C_{19}-DAs (**D**), 23 franchetine-type C_{19}-DAs (**E**), 14 seco-type C_{19}-DAs (**F**), nine rearranged-type C_{19}-DAs (**G**), and two grandiflodine-type C_{19}-DAs (**H**). C_{19}-DAs are distributed only in *Aconitum* and *Delphinium* plants and show highly regular distribution patterns, which may be leveraged for the discovery and mining of corresponding bioactive natural products. Natural C_{19}-DAs and their derivatives generated *via* structural modifications exhibit a wide range of biological activities, including antitumor, anti-inflammatory, analgesic, biocontrol, antipathogenic, neuroprotective, and cholinesterase inhibitory effects. Structural modifications of these natural compounds can be carried out in the future to improve their efficacy. In summary, the rich diversity of the structures and biological activities of C_{19}-DAs indicates the great potential of this type of compound for drug development, especially for antitumor, anti-inflammatory and analgesic drugs, which merits further investigation.

Although C_{19}-DAs have attracted considerable interest, some deficiencies and research potential remain. First, most of the biological activities of C_{19}-DAs have been investigated *via in vitro* chemical and cellular models, and little *in vivo* research has been performed. Few studies have focused on the toxicity, side effects, and clinical efficacy of C_{19}-DAs, which hinders their application and promotion. Second, studies on the structure–activity relationships (SARs) and action mechanisms of these newly discovered components are still lacking, especially for those subtypes of C_{19}-DAs with a smaller quantity, such as pyro-, lactone-, rearranged-, and grandiflodine-types. Therefore, these areas should be addressed in the future.

Author contributions

Min Yan: writing – original draft, resources, visualization. Xijing Wang: writing – review and editing. Haiwen Wang: supervision. Tianpeng Yin: resources, supervision, writing – review and editing, funding acquisition.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

All relevant data are within the manuscript and its additional files.

Supplementary information (SI), which includes a table that lists the detailed information of natural C_{19}-diterpenoid alkaloids reported in the past ten years, is available. See DOI: **https://doi.org/10.1039/d5ra02226f**.

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