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REVIEW

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An overview of the chemical constituents from the genus *Delphinium* reported in the last four decades[†]

Tianpeng Yin, 🔟 ab Le Cai^{*b} and Zhongtao Ding 🔟 *b

Species of the genus *Delphinium* have been extensively used for different purposes by various civilizations worldwide since antiquity. Phytochemical investigations on *Delphinium* plants in the last four decades (1980–2019) have afforded a total of 453 new compounds, most of which are diterpenoid alkaloids. These constituents are of great research significance due to their novel structures and broad bioactivities. This review addresses, for the first time, the chemical constituents of *Delphinium* plants and the biological properties of these compounds to facilitate future research.

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1. Introduction

The genus *Delphinium* (Larkspur), an important member of the family Ranunculaceae, comprises approximately 365 species, which are distributed mainly in northern temperate regions, including in Asia, Europe, and North America.¹ There are also a few species growing in North Africa, such as *D. cossonianum* and *D. staphisagria* in Morocco,^{2,3} *D. macrocentrum* in Kenya,⁴ and *D. leroyi* in Ethiopia.⁵ Notably, among the 365 *Delphinium* species, 232 (200 endemic) have been found in China.⁶ *Delphinium* plants prefer cool and moist conditions and mainly grow in alpine-cold regions, such as the Hengduan Mountains region in Southwest China, which is the most important centre of diversity and speciation of this genus, as at least 167 *Delphinium* species have been found in this region.

Delphinium plants have been extensively used for different purposes by various civilizations worldwide since antiquity. *Delphinium* plants feature various coloured flowers ranging from white, yellow, and red to blue, and they have been cultivated as horticultural plants in Europe since the 17th century. Currently, *Delphinium* plants are one of the most famous and popular horticultural plants around the world, and thousands of ornamental varieties of *Delphinium* have been cultivated and applied widely in bonsai, gardens, and greenbelts. *Delphinium* flowers are also an important source of natural dyes; for

example, yellow dye for silk has been extracted from D. zalil flowers for a long period of time in Iran and India.⁷ In addition, Delphinium plants are traditionally used as herbal pesticides against lice and scorpions since the time of Dioscorides (in the 1st century A.D.), approximately two thousand years ago.⁸ During the battle at Waterloo, the British army also used the powders of D. staphisagra and D. peregrinum to prevent and kill lice.9 In China, there are five Delphinium species, namely, D. grandiflorum, D. albocoeruleum var. przewalskii, D. chefoense, D. korshinskyanum, and D. likiangense, that have been used to kill the larvae of mosquito, lice, and flies.6 Most importantly, for centuries, plants of this genus, mainly their tubers and roots, have been extensively used as herbal medicines-in Turkey to treat epilepsy, tetanus, rabies, and emesis; in Iran to treat disorders of the spleen, jaundice, a nd dropsy; and in Nepal to treat fever and wounds.^{7,8} In China, Delphinium plants have a long history as folk medicines for the treatment of many kinds of diseases, such as traumatic injury, rheumatism, enteritis, influenza, oedema, asthma, ringworm, scabies and other skin diseases, as well as stomach ache, migraine, tooth ache, neuralgia, and other kinds of pain. At least 18 species of Delphinium have been used medically in Chinese traditional medicine (TCM) because of their unique and proven therapeutic effects.6

Since the end of the 18th century, the chemical constituents in *Delphinium* plants have been investigated. Several earlier studies have attempted to isolate anthocyanin pigments from *Delphinium* flowers, and the first anthocyanin (delphinin) was identified from *D. consolida* in 1915 by Willstätter *et al.*¹⁰ At almost the same time, research on *Delphinium* alkaloids, mainly the diterpenoid alkaloid (DA) components, was also conducted.¹¹ The DAs in *Delphinium* plants have attracted the attention of scientists for a long time, and most studies on these plants have been devoted to the DA components. In addition, the nonalkaloidal constituents of *Delphinium* plants have also been

[&]quot;Zhuhai Key Laboratory of Fundamental and Applied Research in Traditional Chinese Medicine, Department of Bioengineering, Zhuhai Campus of Zunyi Medical University, Zhuhai 519041, China

^bFunctional Molecules Analysis and Biotransformation Key Laboratory of Universities in Yunnan Province, Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, Kunming 650091, China. E-mail: ztding@ynu.edu.cn; caile@ynu.edu.cn

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studied. To date, thousands of components with diverse chemical structures, including alkaloids, flavonoids and other phenolic compounds, fatty acids, terpenoids and steroids, have been isolated from *Delphinium* plants. These constituents offer novel structures and broad and impressive biological activities, including antioxidant, antiparasitic, antiphlogistic, antineoplastic, and immunoregulatory effects.

Several review articles and monographs regarding the distribution and physiological and NMR spectroscopic data of naturally occurring DAs, which have mainly been isolated from *Delphinium* and its sibling genera *Aconitum* and *Consolida*, have been published.¹²⁻¹⁵ However, to date, there has been no individual and comprehensive review of the chemical constituents of the *Delphinium* genus. Therefore, this review was prepared to summarize the structural features and biological activities of the chemical constituents from *Delphinium* species for the first time. The aim of this review is to provide a complete overview of the chemical constituents of the *Delphinium* genus reported in the last four decades (from 1980 to 2019), which will facilitate further research and exploitation of this genus.

2. Alkaloids

In addition to the genera *Aconitum* and *Consolida*, *Delphinium* is a genus in the Ranunculaceae family that is well known for its characteristic DA components.^{16,17} DAs are clearly the major constituents of *Delphinium* plants, and most of the published articles are devoted to DA components. In the past forty years, a large number of biologically active and structurally complex DAs have been isolated from various species of *Delphinium*. Table 1S[†] lists the names, plant sources, types, and the references of the new DAs isolated from *Delphinium* plants in the last four decades. Structurally, DAs are usually classified as C_{18^-} , C_{19^-} , or C_{20} -DAs, which can be further divided into several to dozens of subtypes. Fig. 1 shows the fourteen subtypes of DAs that have been found in *Delphinium* plants in the last four decades. Herein, the new DAs as well as other alkaloids isolated from *Delphinium* plants are summarized by category.

2.1 C₁₈-Diterpenoid alkaloids

The C_{18} -DAs, also called "bisnorditerpenoid alkaloids", are a small sub-group of DAs.¹⁸ Compared with C_{19} -DAs, C_{18} -DAs are distinguished by the absence of C-18, and their C-4 moiety is a methine or an oxygenated quaternary carbon. C_{18} -DAs can be classified into two subtypes based on whether an oxygencontaining functionality is attached at C-7, namely, lappaconitine-type compounds (A-2), which do not possess an oxygen-containing functionality at C-7, and ranaconitine-type compounds (A-1), which do have an oxygen-containing functionality at this position.

To the best of our knowledge, only 23 new C_{18} -DAs from *Delphinium* plant have been reported in the last four decades, and they were obtained from 7 different species (Fig. 2). Most of these compounds are ranaconitine-type C_{18} -DAs, with the exception of giraldine I (21) from *D. giraldii*,¹⁹ delphicrispuline (22) from *D. crispulum*,²⁰ and naviconine (23) from *D. naviculare*



Fig. 1 Subtypes of DAs covered in this review.

var. lasiocarpum,²¹ which are lappaconitine-type compounds. Sixteen ranaconitine-type C18-DAs possessing a 7,8-methylenedioxy group were reported, and these compounds are anthriscifolcones A and B (1 and 2) and anthriscifoltines A-G (3-9) from D. anthriscifolium var. majus,²²⁻²⁴ and anthriscifolcines A-G (10-16) from D. anthriscifolium var. savatieri.25,26 Most of them contain a 10-OH substituent, and the exceptions are alkaloids 10–11 and 16. Three of the ranaconitine-type C_{18} -DAs, namely, delboxine (18) from D. bonvalotii,²⁷ 14-demethyltuguaconitine (19) from D. stapeliosum,28 and tiantaishansine (20) from *D. tiantaishanense*,²⁹ contain a 3,4-epoxide unit. Giraldine I (21) was characterized by the lack of an oxygenated substituent at C-16.19 Alkaloids delphicrispuline (22) and naviconine (23) possess an anthranoyl group at C-18,20 and 23 features an N-CHO formamide group instead of an N-ethyl group.21

2.2 C₁₉-Diterpenoid alkaloids

The majority of naturally occurring DAs are C_{19} -DAs, and they are usually regarded as the representative type of DAs. In-depth investigations of C_{19} -DAs in chemical and pharmacological fields have been carried, and more information is available on



these compounds than on C_{18} - or C_{20} -DAs. According to their molecular skeletons, C_{19} -DAs can be divided into six types, namely, lycaconitines (B-1), aconitines (B-2), lactones (B-3), 7,17-seco derivatives (B-4), rearranged compounds (B-5), and pyro derivatives. In the last four decades, a total of 299 new C_{19} -DAs belonging to these five types have been isolated from *Delphinium* plants.

2.2.1 Lycaconitines. In *Delphinium* plants, lycaconitines are the most common type of C_{19} -DAs. A total of 232 new lycaconitine-type C_{19} -DAs were isolated from *Delphinium* plants in the last four decades. The lycaconitine-type C_{19} -DAs are characterized by the presence of an oxygenated group at C-7, and it is usually a 7-OH or a 7,8-methylenedioxy group. Based on the state of the *N*-atom, lycaconitine-type C_{19} -DAs can be further divided into four subtypes, namely, the *N*,*O*-mixed acetal sub-type, the amide sub-type, the imine and quaternary ammonium sub-type, and the amine sub-type.¹⁴



Fig. 3 Lycaconitines with mixed acetal unit from Delphinium plants.



Fig. 4 Amide lycaconitines from Delphinium plants.



Fig. 5 Imine lycaconitines from *Delphinium* plants.

		Ň	R1	R7	R ₄ (''' (''R ₃)			
			$\sum R_{\epsilon}$	R_2 O	Ē			
	R1	R ₂	R₃	R₄	R₅	R ₆	R ₇	R ₈
91	OMe	OMe	ОН	OMe	н	н	н	н
92	OMe	0	OMe	OMe	н	н	H	н
93	OMe	0	OMe	OMe	н	н	н	н
95	OH	н	OMe	OMe	OMe	н	он	он
96	OMe	н	OMe	OMe	OMe	н	н	ОН
97	OMe	н	OMe	OMe	OMe	н	OH	ОН
98	OAc	н	OMe	OMe	OMe	н	ОН	ОН
99 100	OMe	н	OMe	OMe	OMe	н ц	н	ОН
100	ONE	н	ONIE	OMe	H	н	н	ОН
102	OMe	н	ОН	OMe	OMe	н	н	н
103	OH	ОН	ОН	OMe	н	н	н	н
104	OMe	OMe	ОН	OMe	OMe	н	н	н
105	OMe	н	0	OMe	OMe	н	Н	н
105	OMe	н ОН		OMe	OMe	н	ОН	н
108	OMe	OAc	0	OMe	OMe	н	ОН	н
109	OMe	н	OAc	OMe	ОН	н	ОН	н
110	OMe	н	OMe	OMe	OH	н	OH	н
111	OMe	Н	ОН	OMe	OMe	н	н	н
112	OH	ОН	OMe	OH	OMe u	Н	н	н
114	OH	OMe	OH	OMe	OMe	н	н	н
115	OMe	0	OMe	OH	н	н	н	н
116	ОН	н	ОН	OMe	н	н	н	н
117	OMe	OAc	OMe	OH	н	Н	н	н
118 110	OMe	о н	OMe	OMe	H OMe	он ц	н	н
120	OMe	н	OAc	OMe	OMe	н	н	н
121	OH	ОН	OH	OMe	OMe	н	н	н
122	ОН	ОН	ОН	OMe	н	н	н	н
123	OMe	OH	ОН	OMe	OMe	н	н	н
124	OMe	OH	OMe	OMe	OMe	Н	OH	Н
125	OMe	0	ОП	OMe	н	н	ОН	н
127	OH	OMe	OH	OMe	н	н	н	н
128	OMe	0	OMe	ОН	OMe	н	н	н
129	OMe	н	OMe	OH	OMe	н	н	н
130	OMe	ОН	OMe	OH	н	Н	н	н
132	ОН	OAc	OMe	OMe	н	н	н	н
133	ОН	OMe	OH	OMe	он	н	н	н
134	OMe	OAc	OMe	ОН	н	н	ОН	н
135	OMe	OAc	OMe	OH	н	ОН	н	н
136	OMe	OAc	OMe	OMe	н	OH	н	н
137	OMe	OMe	OMe	OMe	п ОМе	н	н	н
139	OMe	OMe	OH	OMe	OH	н	ОН	н
140	OMe	0	OAc	OMe	н	н	н	н
141	OMe	OAc	OMeBu	OMe	н	н	OH	н
142	OMe	OAc	OiBu OB=	OMe	н	н	OH	н
143	OMe	OAC	OB2 OMe	OMe	н	н	Н	н
145	OMe	OMe	OMe	OMe	н	н	н	н
146	OMe	OAc	OMe	OAc	н	н	ОН	н
147	OMe	OH	OMe	OMe	н	н	н	н
148	OMe OM-	0	0	OMe OM-	Н	Н	Н	Н
149		n OAc	OMe		н	н	н	п
151	OMe	Н	OMe	OMe	н	н	н	н
152	OMe	OMe	OMe	OMe	н	н	OMe	н
153	0	0	ОН	OMe	н	н	н	н
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Fig. 6 Amine lycaconitines with 7,8-methylenedioxy group from *Delphinium* plants.

In the last four decades, only seven lycaconitine-type DAs (24–30) with an $N-C_{(19)}-O-C_{(1)}$ mixed acetal unit were found (Fig. 3). Among them, graciline (28) and 8-*O*-cinnamoylgraciline



(29) are characterized by the absence of an oxygenated group at C-16,³⁰ and alkaloid 29 features a cinnamoyl unit at C-8.² In addition, laxicymine (24) from *D. laxicymosum* var. *pilostachyum* has a rare 5-OH group,³¹ and grandifloricine (30) from *D. gran*-*diflorum* contains a ketone carbonyl at C-14 along with an *N*-(succinimido)anthranoyl group at C-18.³²

Twenty new amide lycaconitines were reported in the studied period (Fig. 4). Alkaloids **31–38** contain an *N*–C₍₁₉₎=O lactam group, which might be formed by the carbonylation of 19-OH.^{33–37} Budelphine (**36**) from *D. buschianum* possesses a rare 1,2-epoxy group.³⁶ There are 12 alkaloids (**39–50**) with an *N*–CHO formamide group formed from a C-21 aldehyde.^{4,38–45} Among these compounds, alkaloids **41–45** are DAs that have no oxygen-containing group at C-16.^{4,39–41} *N*-Formyl-4,19-secopacinine (**51**)⁴⁵ and *N*-formyl-4,19-secoyunnadelphinine (**52**)³⁸ from *D. elatum* contain another kind of formamide, which is formed from C-19 aldehydes.

Sixteen lycaconitine-type DAs with an imine group at C-19 were isolated from Delphinium plants (Fig. 5). Nine of these DAs (53-61) contain a 7,8-methylenedioxy group,^{29,45-51} and of these, caerunine (60) from D. caeruleum possesses a 9-OH group.⁵⁰ Another five imine DAs (64–68) contain a 7,8-diol group along with an anthranoyl group at C-18.7,37,52-54 In addition, orthocentrine (63) from D. orthocentrum possesses an 8-OMe moiety along with a 10-OH group.55 Eight quaternary ammonium bases, including pseudorenines A and B (69 and 70), and pseudophnines A-D (71, 73-74, and 76) from D. pseudoaemulans,48 and sharwuphinine B (72) from D. shawurense,56 naviculine (75) from D. naviculare var. lasiocarpum²¹ were reported, although these might be artefacts of the extraction and isolation procedure. Sharwuphinine A (76) from D. shawurense⁵⁷ and chrysotrichumine A (77) from D. chrysotrichum58 are both alkaloids with a nitrone group between C-17 and C-19.

A total of 177 new amine lycaconitine-type C_{19} -DAs have been reported, and they can be subdivided into three groups

according to their oxygenated substituents at C-7 and C-18, namely, the 7,8-methylenedioxy group, the 7-OH group, and the 7-OH/18-anthranoyl group.

Seventy-six new lycaconitine-type alkaloids with a 7,8methylenedioxy unit have been reported in the last four decades (Fig. 6). Among these alkaloids, eight (**79–86**) contain a $\Delta^{2,3}$ group, including siwanines A–D (**79–82**) from

OMe OMe OMe OF 'R -N OMe OF ŌAc 154 R1 = OMe; R2 = R3 = OH; R4 = H 165 R4 = OMe 167 R1 = R3 = H; R2 = R4 = OH 155 R₁ = OMe; R₂ = OH; R₃ = OAc; R₄ = H 168 R1 = OMe; R2 = H; R₂ = OBz; R₃ = Et 156 R₁ = OMe; R₂ = OH; R₃ = OBz; R₄ = H 166 R1 = O $R_3 = OH$: $R_4 = OBz$ 157 R₁ = R₂ = OMe; R₃ = OH; R₄ = H R₂ = OAc; R₃ = H 158 R₁ = R₃ = R₄ = OMe; R₂ = OH 159 R1 = OMe; R3 = O; R4 = H; R2 = OH 160 R₁ = R₂ = R₃ = OH; R₄ = H 164 R₃ = OCOH₂CH₂CO 161 R1 = OH; R3 = OAc; R4 = H; R2 = OMe 162 R1 = OH; R2 = OMe; R3 = OAc; R4 = H 163 R1 = !ÁOAc: R2 = OH: R3 = OAc: R4 = H 164 R1 = R2 = R4 = OMe ΌΗ \bar{R}_2 R R₂ R₃ R₄ R₅ Re R₇ ОН OMe OMe 169 OMe OMe н OH 170 ОН ОН OMe OMe OMe н OAc 171 OMe OMe OH н OMe OMe OH 172 ОН OMe OMe н OH OMe OH 173 OMe 0 OH н OMe OMe н 174 OBz н OMe OMe н н OH 175 OH н OMe н OMe ОН н 176 OH н OMe н OAc OMe н ОН н н 177 OMe н OH OMe OAc 178 OMe OMe OH OMe OMe н 179 OH OMe OMe н OAc OMe OMe 180 ОН OMe OMe н OMe OMe OMe 181 OMe н OMe O⊦ ОН OMe н 182 OH н ОН OMe н н OH 183 OH OMe OH н OH OMe н 184 OH н OH н OH н н 185 OMe OMe OH OMe OMe OH н OMe OMe 186 OMe OH н OH н 187 OH н OH н OAc OMe н 188 ОН OMe ОН н н OMe OMe OMe OMe OH OMe 189 н OBz н OMe OMe OH 190 н OiBu OMe н 191 OMe OMe ОН н OMeBu OMe н 192 OMe OMe OH н cis-OCr OMe н OMe ОН н н 193 OMe OMe OCn 194 OMe OMe OH н OMeBu OMe OMe 195 OH OMe OH н OAc OMe н 196 ОН ОН OMe н OMe OMe OH 197 OMe OMe ОН OMe ОН н OAc OMe 198 OMe OH н OAc OMe н 199 OMe OMe OH н OMe OMe н 200 OMe OH OH н OMe OMe н OMe 201 OMe OH н OiBu OMe OMe 202 OMe OMe OH н OH OMe OMe 203 OH αΟΜε OH н OF OMe OMe

Fig. 7 Amine lycaconitines with 7-OH group from Delphinium plants.

D. siwanense var. leptogen,⁵⁹ siwanine E and F (82 and 83) from D. siwanense,⁶⁰ deacetylswinanine A (85) from D. orthocentrum,⁵⁵ and tatsiensine (86) from *D. tatsienense*.⁶¹ Notably, iliensine A (90) from D. iliense features a 4-O-B-D-glucosecinnamate ester, making it the first example of a natural DA containing a glucose moiety.⁶² Pseudouridine B (87) from D. pseudoaemulans possesses a rare acetonyl group at C-19.48 The remaining alkaloids contain only common oxygenated groups, such as OH, =O, OMe, and OAc groups, while OMeBu (2-methylbutyryl) and OiBu (isobutyryl) groups are less common. In most cases, these oxygenated groups are located at C-1, C-6, C-14, and C-18. There are also a small number of alkaloids with oxygenated groups at C-5, C-9, and C-10. Most of them possess a 16-OMe group, and some have a 16-OH substituent; delretine (146) from D. retropilosum has a rare 16-OAc.63

Fifty new amine lycaconitines possessing a 7-OH group were reported in the past forty years (Fig. 7). Eleven alkaloids (**154– 164**) containing a $\Delta^{2,3}$ group were reported, ^{26,64–68} and among these, majusine D (**164**) from *D. majus* possesses a novel 3-(cyclononyloxy)propanoate ester group at C-14.⁶⁹ Alkaloids **192** and **193**, a pair of isomers from *D. cardiopetalum*, possess *cis*and *trans*-cinnamoyl groups at C-14, respectively.⁷⁰ Gracinine (**168**) from *D. gracile* has a hydroxyl group at C-10, which is an infrequently substituted position.⁷¹ Pergilone (**166**) and delphiperegrine (**165**) from *D. peregrinum* uniquely feature a methoxy group at C-7.⁷²

Fifty-two new DAs belonging to the 7-OH/18-anthranoyl group were reported (Fig. 8). These alkaloids are substituted with anthranilic acid derivatives at C-18. Amidogens are usually substituted by succinyl or methyl-succinyl groups or other amide side chains, which might be formed by the breakage of succinyl or methyl-succinyl groups. Ajanine (**208**) from *D. ajacis* possesses a 2-hydroxyl-2-methylbutyroyle ester chain at C-14,⁷³ and alpinine (**219**) from *D. alpinum* possesses a propionyl group at C-14.⁷⁴

2.2.2 Aconitines. Although aconitine-type C₁₉-DAs represent the most common naturally occurring DAs, the number of these DAs reported from Delphinium plants is much lower than the number of lycaconitine-type compounds. In the last four decades, only 62 new aconitine-type C₁₉-DAs from Delphinium plants were reported (Fig. 9). Several alkaloids possessed at least one uncommon substituent. For example, alkaloids 262, 263 and 264 possess $\Delta^{1,2}$, $\Delta^{2,3}$ and $\Delta^{5,6}$ groups,⁷⁵⁻⁷⁷ respectively, and alkaloids 256-260 possess an N-C(19)-O-C(1) mixed acetal unit.78-82 Staphisadrine (267) from D. staphisagria features an aldehyde at C-18,83 and peregrinine (261) from D. peregrinum var. elongatum has an N=C(19) imine.⁸² Alkaloids 261 and 262 contain a β-oriented OAc group at C-6.75,82 The other alkaloids mainly vary in the quantity, position and orientation of common oxygenated substituents, including OH, OMe and OAc. Most of the oxygenated substituents are located at C-1, C-6, C-8, C-16, and C-19. Alkaloids 269-270 and 266 have a hydroxyl group at C-10,75,84,85 which is a rare substitution pattern. Generally, aconitine-type DAs have a 16-OMe moiety, but cardiopetaline (290) from D. cardiopetalum and souline (297) from D. souliei are exceptions to this statement, as they lack this

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$\langle \rangle - R_7$	

	R1	R ₂	R3	R₄	R₅	R ₆	R ₈	R9	R ₇
204	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH ₂ CH(Me)COOMe
205	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH(Me)Et
206	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH(Me) ₂
207	OMe	OMe	ОН	OAc	OMe	Et	н	н	NHCOCH(Me)Et
208	OMe	OMe	ОН	OCOC(Me)(OH)Et	OMe	Et	н	н	NHCOMe
209	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH(Me)CH ₂ COOH
210	OMe	OMe	ОН	ОН	OMe	Et	н	ОН	NH ₂
211	OMe	OMe	ОН	OMe	OMe	Et	н	ОН	NH ₂
212	OMe	OMe	ОН	0	OMe	Et	н	н	NH ₂
213	ОН	OMe	ОН	ОН	OMe	Et	н	н	NH ₂
214	ОН	OMe	ОН	OMe	ОН	Et	н	н	NH2
215	ОН	OMe	ОН	OMe	OMe	Et	н	н	NH ₂
216	OMe	OMe	OH	OMe	OMe	Et	н	н	NHCOCH(Me)CH ₂ CONH ₂
217	OMe	OMe	OH	OMe	OMe	Et	н	н	NHCOCH ₂ CH(Me)CONH ₂
218	ОН	OMe	ОН	OH	OMe	Et	н	н	NHCOCH ₃
219	OMe	OMe	OFt	OCOEt	OMe	Ft	н	н	MeSuc
220	OMe	OMe	OH OH	OiBu	OMe	Ft	н	н	Suc
221	OMe	OMe	ОН	OiBu	OMe	Et	н	н	NHCOCH
222	OMe	OMe	ОН		OMe	Et	н	ц	Suc
222	OMe	OMe	ОН	OMe	н	Et	н	ц	MeSuc
223	OMe	OMo		OMeRu	OMo		п ц	н Ц	
224	OMe	OMo		OMeBu			п Ц	п ц	
225		OMo	OMo	OMe		E+	п ц	п ц	MoSuo
220	OMe	OMe		OMe		EL	п ц	п ц	
227	ONe	ONe	Olvie	Oivie	ONe		п 		
228	ONe	Olvie		Olbu	Olvie				
229	ONe	Olvie		Owebu	Olvie				
230	Oivie	Olvie	OH	OIBU	Olvie	EL	п	п	
231	OMe	OMe	OH	OH	OMe	Et	н	н	
232	OMe	OMe	OH	OIBU	OMe	Et	н	н	NHCOCH ₂ CH(Me)CONH ₂
233	Оме	OMe	OH	OMe	OAc	Et	н	н	MeSuc
234	OMe	OMe	OH	OMe	OMe	Et	UH 	н	MeSuc
235	OH	Oivie	OH	OMe	Olvie	Et	н	н	MeSuc
236	OMe	OMe	ОН	OH	OAc	Et	н	н	MeSuc
237	OMe	OMe	ОН	OAc	OAc	Et	н	н	MeSuc
238	ОМе	OMe	ОН	OMe	ОН	Et	н	н	MeSuc
239	OMe	OMe	ОН	OMe	н	Et	н	н	NHCOCH(Me)CH ₂ COOMe
240	OMe	OMe	ОН	OMe	н	Et	н	н	NHCOCH ₂ CH(Me)COOMe
241	OMe	OMe	ОН	OAc	OAc	Et	н	н	NHCOCH ₂ CH(Me)CONH ₂
242	OMe	OMe	ОН	OAc	OAc	Et	н	н	NHCOCH(Me)CH ₂ CONH ₂
243	OMe	OMe	ОН	OAc	OAc	Et	н	н	NHCOCH ₂ CH(Me)COOH
244	OMe	OMe	ОН	OH	OMe	Et	н	н	NHCOMe
245	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH(Me)CH ₂ COO(CH ₂) ₃ Me
246	OMe	ОН	OAc	OMe	OMe	Et	н	н	Suc
247	ОН	OMe	OMe	0	OMe	Et	н	н	MeSuc
248	OMe	OMe	ОН	OMe	OMe	Et	н	н	NHCOCH ₂ CH ₂ COOMe
249	OMe	OMe	ОН	0	OMe	Et	н	н	MeSuc
250	ОН	OMe	OMe	OMe	OMe	Et	н	н	NH ₂
251	OMe	OMe	OMe	OMe	OMe	Et	н	н	NH ₂
252	OMe	OMe	OH	OAc	OMe	Et	н	н	NHCOCH ₂ (Me)COOMe
253	OMe	OMe	OH	ОН	OMe	Et	н	н	MeSuc
254	OMe	OMe	OH	OMe	OMe	Et	н	н	NHCOCH(Me)CH ₂ COOMe
255	OMe	OMe	OH	OMe	OMe	н	н	н	NH ₂
254 255 7 OU	OMe OMe	OMe OMe	OH OH	OMe OMe	OMe OMe	Et H	н н	н н	NHCOCH(Me)CH ₂ COO NH ₂

Fig. 8 Lycaconitines with 7-OH/18-anthranoyl group from *Delphinium* plants.

group at C-16.^{81,86} Moreover, delstaphisine (**309**) from *D. staphisagria* has a 16-OH group,⁸⁷ and staphisadrinine (**291**) from *D. staphisagria* features a ketone carbonyl at C-16.⁸³

2.2.3 Lactone-, rearranged- and 7,17-seco-type compounds. The other types of C_{19} -DAs are rare (Fig. 10). Two new lactone-type C_{19} -DAs, namely, 8-acetylheterophyllisine (319) from *D*.



Aconitines from *Delphinium* plants Fig. 9

denudatum⁸⁸ and souline B (318) from D. souliei,⁸⁹ both featuring a hexanolactone C ring, were reported. In addition, two rearranged C_{19} -DAs, grandiflodine B (320) and yunnanenseine A (321), were isolated from D. grandiflorum and D. yunnanense, respectively.90,91 Yunnanenseine A (321) is a typical acoseptine-type rearranged C_{19} -DA in which its $C_{(7)}$ - $C_{(17)}$ bond was rearranged to a $C_{(8)}$ - $C_{(17)}$ bond, forming an additional ketone at C-7. Grandiflodine B (320) features an unusual lycoctonine-type C19-DA skeleton generated via cleavage of the N-C₍₁₉₎ and C₍₇₎-C₍₁₇₎ bonds and the construction of a $N-C_{(7)}$ bond. Leueandine (322) is the only 7,17-seco-type C₁₉-DA from a *Delphinium* plant, and it possesses a franchetinetype skeleton with a cinnamoyl group at C-14.92

2.3 C₂₀-Diterpenoid alkaloids

Although C₂₀-type DAs account for a relatively small proportion of DAs in terms of quantity, they are much more structurally diverse than C₁₉-type DAs. The skeletons of C₂₀-DAs are fairly complex, and more than 20 subtypes have been defined.⁹³ As listed in Table 1S,† approximately 89 new alkaloids belonging to seven of the subtypes of C₂₀-DAs were isolated from Delphinium plants in the last four decades.

Hetisine-type C₂₀-DAs (C-1), which are characterized by a heptacyclic system with an N-C₍₆₎ bond, constitute the majority of the new C20-DAs from Delphinium plants. A total of 56 new hetisines were obtained from the Delphinium species (Fig. 11 and 12). These alkaloids vary mainly in the variety, quantity, position and orientation of their oxygenated substituents, including

R ₃							
		R	X $\bar{\bar{R}}_2$				
	R1	R ₂	R₃	R₄	R₅	R ₆	R ₇
280	OMe	OAc	OMe	ОН	н	Et	OMe
281	ОН	βΟΗ	OMe	OAc	OMe	Et	OMe
282	ОН	OMe	OMe	ОН	ОН	Et	OMe
283	ОН	н	OMe	OH	н	Et	OMe
284	OMe	OAc	OMe	OAc	н	Et	OMe
285	OMe	OAc	OMe	OMe	н	Et	OMe
286	ОН	н	н	OH	н	Et	OMe
287	OMe	OMe	ОН	OH	н	Et	OMe
288	OAc	βOH	OAc	OH	н	Et	OMe
289	ОН	н	OAc	OAc	OMe	Et	OMe
290	ОН	н	ОН	OH	н	Et	Н
291	ОН	OMe	ОН	OH	OMe	Et	0
292	OMe	OAc	OMe	OBz	н	Et	OMe
293	OMe	0	OMe	OH	н	Et	OMe
294	OMe	OH	ОН	OH	н	Et	OMe
295	ОН	βOH	OMe	OH	н	Et	OMe
296	OMe	н	OMe	OH	н	Et	OMe
297	OMe	н	ОН	OH	н	Et	Н
298	ОН	н	ОН	OAc	н	Et	OMe
299	OMe	OAc	OMe	OMe	н	н	OMe
300	OMe	OAc	OMe	OH	н	Et	OMe
301	ОН	βΟΑς	ОН	OH	н	Et	OMe
302	ОН	βOMe	ОН	OAc	OH	Et	OMe
303	ОН	βOMe	ОН	OH	ОН	Et	OMe
304	OMe	βOMe	ОН	OH	ОН	Et	OMe
305	ОН	βΟΗ	ОН	OAc	н	Et	OMe
306	ОН	Н	ОН	OMe	OMe	Et	OMe
307	он	βΟΗ	OAc	OAc	OMe	Et	OMe
308	OAc	βΟΜε	OAc	OAc	OMe	Et	OMe
309	ОН	OMe	OAc	OAc	OMe	Et	OH
310	ОН	OMe	OAc	OAC	OH	Et	OMe
311	ОН	OMe	ОН	OAC	Olvie	Et	OMe
312	OH		OH	OH	OH	Et	Oivie
313	OH	BOINE	OAC	OAC	Olvie	ivie	Oivie
314	Olvie	Ome	OAC	OBZ	н	ivie	Olvie
315	OMe	H OMo		OAC	H OMa		OMe
316		Оме		CAC	OMe		OMe
317	рОН	н	OH	BOAC	Oivie	Εt	Oivie
(contd)							

Fig. 9 (contd.)

hydroxyl, acetyl, benzoyl, isobutyryl, 2-methylbutyryl, ketone and carbonyl groups. Anthriscifolmine J (330) from D. anthriscifolium var. savatieri features a unique 2-hydroxy-2-methylpropanoyloxy group at C-3 along with a formyloxy group at C-13,94 and grandiflodine A (324) from D. grandiflorum has a rare cyano group at C-18.90 14-Hydroxyhetisinone N-oxide (327) from D. gracile is a rare hetisine-type N-oxide,95 and delatisine (326) from D. elatum possesses an N-C(19)-O-C(2) mixed acetal unit.96 In addition, several structurally novel hetisine-type C20-DAs were reported. Anthriscifolsine A (325) from D. anthriscifolium var. majus features a seco C ring generated through unprecedented C(11)-C(12) bond cleavage in the hetisine skeleton.97 The N-C(17) bond in grandiflodine A (324) can be cleaved, forming an additional ketone carbonyl at C-17.90 Leptanine (323), which was isolated from D. *leptocarpum*, is a dimeric alkaloid consisting of a hetisine-type C₂₀-DA part and an indolinonepyrrole fragment. According to X-ray

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Fig. 10 Lactone-, 7,17-seco-, and rearranged-type DAs from *Delphinium* plants.

crystal structure analysis, the indolinonepyrrole fragment was bound to the hetisine-type C₂₀-DA part through an α -directed (relative to the indoline core) C₍₁₇₎-C_(3') covalent bond.⁹⁸

Vakognavine-type C_{20} -DAs (C-2) have an $N-C_{(19)}$ seco hetisine skeleton in addition to a formyl group at C-4. During the past forty years, 17 new vakognavines were isolated from 6 *Delphinium* species (Fig. 13). Generally, vakognavine-type C_{20} -DAs seldom have a $C_{(15)}=C_{(16)}$ bond, but anthriscifolmines G (393) and H (392) from *D. anthriscifolium* var. *savatieri* are exceptions to this statement.⁹⁹ In addition, anthriscifolmines E-H (390–393) feature a rare formyloxy group at C-11 along with a unique 2-hydroxy-2-methylpropanoyloxy group or a 2-methylpropanoyloxy group at C-13.⁹⁹

Atisine-type C₂₀-DAs (C-4) have always been regarded as the biosynthetic precursors of the other C₂₀-DAs, possess a relatively simple pentacyclic framework. Twelve atisines from seven *Delphinium* species were reported (Fig. 13). Structurally, isoazitine (**404**) and 13-(2-methylbutyryl)azitine (**406**) each possess an azomethine between *N* and C-19 or C-17^{,3,100} Uncinatine (**414**) from *D. uncinatum* bears an uncommon *N*-CH=CHOH group.¹⁰¹ Delphatisine A (**412**)¹⁰² and delphatisine D (**413**)⁵⁸ possess oxazolidine rings formed by a carbinolamine ether linkage between C-20 and C-17 or C-19, respectively. Delphatisines B (**411**) and C (**410**) feature a γ -lactone-fused oxazolidine ring.¹⁰³ The γ -lactone ring in honatisine (**403**) was open, forming an extra carboxylic acid group at C-22. In addition, a unique 1',3',5'-trimethyl-4'-oxocyclohexyloxy unit was substituted at C-24.¹⁰⁴

Other subtypes of C_{20} -DAs were also reported. Six new hetidine-type C_{20} -DAs (C-3), including anthriscifolmine I (396) from *D. anthriscifolium* var. *savatieri*,⁹⁴ carduchoron (398) and delcarduchol (399) from *D. carduchorum*,¹⁰⁵ macrocentrine (401) from *D. macrocentrum*,⁴ cardionidine (402) from *D. cardiopetalum*,¹⁰⁶ and 2-dehydrodeacetylheterophylloidine (400) from *D. pentagynum*,⁵² were acquired. Among these alkaloids, cardionidine (402) features an anhydride function in its B



Fig. 11 Hetisine type C₂₀-DAs from *Delphinium* plants.

ring.¹⁰⁶ Three denudatine-type DAs (C-5), including anthriscifolmines A (**416**) and B (**415**) from *D. anthriscifolium* var. *savatieri*, which possess a 16,17-epoxy group and a butyryl group at C-13,¹⁰⁷ and cordizine (**417**) from *D. corymbosum*, which possesses a CH₃-17β angular methyl group, were reported.¹⁰⁸ Moreover, a napelline-type C₂₀-DA (C-6), norsongoramine (**418**), with an N-C₍₁₉₎-O-C₍₁₎ mixed acetal unit was obtained from *D. tamarae*,¹⁰⁹ and a delnudine-type C₂₀-DA (C-7), trichodelphinine F (**419**), possessing a rare phenylacetyl group at C-2, was isolated from *D. trichophorum*.¹¹⁰

2.4 Other alkaloids

In addition to DAs, other types of alkaloids have also been isolated from *Delphinium* plants (Fig. 14). Several amide alkaloids from *Delphinium* plants have been reported. Five new acyl anilines, delamides A–E (**420–424**), which possessed an *O*-ester aniline bearing an amide side chain, were isolated from *D. brunonianum* by Zou *et al.*¹¹¹ Diaz *et al.* reported the isolation of three new anthranilic acid derivatives (**425–427**), also called dianthramides, from tissue cell cultures of *D. staphisagria.*¹¹² In addition, a novel lactam (**428**) possessing a 2-azabicyclo[2.2.1] heptane unit bearing a trimethoxy naphthalene ring, was isolated from *D. caeruleum.*¹¹³

Tetrahydroisoquinoline alkaloids are widely distributed in the Ranunculaceae family. While little attention has been paid to the isoquinoline alkaloids in *Delphinium* plants, a new benzyltetrahydrobenzylisoquinoline alkaloid, *O*methylroefractine *N*-oxide (**429**), was found in *D*. *fangshanense*.¹¹⁴

			-			6	0			
			ŀ	7 3	ΥĬ	R _t	5			
			F	R ₁₀	R	4				
	R1	R ₂	R3	R₄	R₅	R ₆	R ₇	R ₈	R9	R ₁₀
333	βOH	н	н	н	Н	н	Н	н	βOH	Н
334	н	αOiBu	н	н	αOAc	н	αOAc	αOBz	Н	βΟΜε
335	н	αOiBu	Н	н	Н	н	αOAc	αOAc	н	αOH
336	н	αOiBu	Н	н	Н	н	αOH	αOAc	н	αOH
337	н	αOiBu	н	н	н	н	αOH	αOH	н	αOH
338	н	αOAc	OAc	н	н	ОН	βΟΗ	βΟΗ	βOH	н
339	н	αOiBu	н	ОН	н	ОН	βΟΗ	Н	βOiBu	αOH
340	н	αΟΗ	н	н	н	н	aOH	βΟΑς	н	Н
341	н	aOAc	OBZ	н	H	н	βOH	0	н	BOH
342	н	н	н	н	aOiBu	н	βOAc	aOAc	н	BOH
343	н	н	н	н	aOiBu	н	βÜAC	aOH	н	βOH
344	н	н	0	ОН	н	н	н	aOiBu	н	н
345	н	н	0	п	н	н	н	aOiBu	н	н
346	н	н 	0	ОН	н	н	п		н	н
347	н	н	0	н	н	н	aOH	aOivieBu	H	н
340					aou aou		ROAC	п 	<i>а</i> Он	
349		рОн #OU			рОн		pOH	П *О:Ри		
250		иОн «Оч	п	п	п			«OiBu	п	п
250		иОн «ОЧ	п	п	п		αOA ο	«OMeBu	п	п
352		aON a	п ц		п	п ц				
254	п ц	0	п ц	п	п Ц	п Ц	aOA a	aOiRu		п
355	∩ ~0⊔	0 0087	п ц	ц	ц	п ц		ROH	п ц	⊓ ~∩⊔
356	цоп	uOB2	 	 	r∩i₽u			роп ц	ROH	ROH
357	8040	r∩MeBu		 	цови	 	αOΛο	40B7	роп	роп
358	BOAC			ц	н	н	aOAc	aOBz	н	ч
359	BOAc	aOH	OiBu	н	н	н	aOAc	aOBz	н	н
360	BOAc	αOH	OMeBu	н	н	н	aOAc	aOBz	н	н
361	<i>ро</i> , ю н	BOBz	OAc	н	н	н	aOH	aOAc	н	н
362	н	0	н	н	н	н	aOBz	BOH	BOH	н
363	н	0	н	н	н	н	αOBz	BOH	BOAc	н
364	н	0	н	н	н	OAc	н	αOH	н	н
365	н	н	н	н	αΟΗ	н	<i>α</i> -OH	αOH	н	н
366	н	н	ОН	н	Н	н	Н	н	BOAc	βOH
367	н	0	н	ОН	н	н	αOH	BOH	H	н
368	н	н	н	ОН	н	н	αOH	н	н	н
369	н	0	н	н	н	н	αOH	αOH	βOH	н
370	н	0	н	ОН	н	н	αOMeBu	βΟΗ	Н	н
371	н	0	н	ОН	н	н	αOH	, βOAc	н	н
372	н	0	βOAc	ОН	н	н	αOMeBu	βΟΗ	н	н
373	н	0	н	н	н	OAc	αOH	αOAc	н	н
374	н	ОН	н	ОН	н	н	н	βΟΗ	н	н
375	н	0	н	ОН	н	ОН	н	βOAc	н	н
376	н	0	н	ОН	н	н	н	βOH	н	н
377	н	н	н	н	αOH	н	αOAc	н	βΟΗ	н
378	βΟΑϲ	βΟΑϲ	н	н	н	н	н	βOAc	н	н

 R_8

Fig. 12 The hetisine type C₂₀-DAs from *Delphinium* plants.

3. Flavonoids

Delphinium, the flowers of which have petals of various colours, *i.e.*, white, red, violet and blue, are widely cultivated as one of the most famous horticultural plants in the world. The anthocyanidin pigments in the *Delphinium* flowers have attracted considerable attention for a long time. As early as 1915, Willstitter isolated the first anthocyanidin pigment, delphinin, from the reddish-purple petals of *D. consolida*.^{10,115} During the last

four decades, eight new anthocyanidins were reported from different cultivated varieties of *D. hybridum* (Fig. 14). Two new delphinin glycosides, violdelphin (**450**)¹¹⁶ and cyanodelphin (**443**),¹¹⁷ were isolated from the violet petals of *D. hybridum* cv "Blue Night" and the blue petals of *D. hybridum* cv "Blue Springs", respectively. Structurally, violdelphin (**450**) contains two *p*-hydroxybenzoic acid units and four hexose substituents in addition to the delphinin core, and cyanodelphin (**443**) contains four *p*-hydroxybenzoic acid units and seven glucose units in its



Fig. 13 The vakognavine-type, hetidine-type, atisine-type, denudatine-type C₂₀-DAs from *Delphinium* plants.

structure. In addition, six new acylated pelargonidin 3,7-glycosides (**444–449**) were isolated from the red petals of *D. hybridum* cv "Princess Caroline".¹¹⁸ These pelargonidin glycosides possess various acylated glucoses and rhamnoses at C-3 and C-7. Characteristically, glycosides **447** and **449** are acylated at the 3-glucose residue with malonic acid. In addition to anthocyanidins, *Delphinium* plants are also rich in flavonol glycosides. In 1973, Arazashvili *et al.* first reported the identification of two known flavonol glycosides from the leaves of *D. flexiosum* and *D. elisabethae.*¹¹⁹ Dozens of flavonols and their glycosides were isolated from *Delphinium* plants during the next forty years, including some common and widespread constituents, such as rutin, quercetin, kaempferol, and luteolin as well as



Fig. 14 The other alkaloids from *Delphinium* plants.

their glycosides.¹²⁰ Eleven new compounds have been reported from four *Delphinium* species, with the aglycones being kaempferol (**434–437** and **440**) and quercetin derivatives (**430–433** and **438–439**) (Fig. 15). The novelty of these flavonol glycosides is mainly determined by the type and position of the acyl groups on the carbohydrate chains. Structurally, flavonol glycosides **436–439** from *D. staphisagria* possess a 2-*O*-acetyl glucosyl group at C-7,¹²¹ while flavonol glycoside **440** from *D. formosum* has a 4,6-*O*-diacetyl glucosyl group.¹²² Compound **430**, a benzoylated quercetin glycoside, was isolated from *D. carolinianum*,¹²³ and compounds **431–435** are a series of tetraglycosides acylated by caffeic acid and cumaric acid.¹²⁴

4. Phenolics

A certain number of phenolic compounds, such as benzoic and phenylacetic acid derivatives, have been identified from *Delphinium* plants.¹²⁵⁻¹²⁷ However, most of these phenolic compounds are common, structurally simple and widely distributed in the plant kingdom; new structures are rarely discovered.



Fig. 15 Flavonoid glycosides from Delphinium plants.



Fig. 16 Phenolics and diterpenoid from *Delphinium* plants.

Only two new phenolic compounds, namely, 2,5,6-trihydroxypiperonylic acid methyl ester (**451**) from *D. venulosum*¹²⁸ and oxformasine (**452**) from *D. formosum*,¹²⁹ were reported during the studied period (Fig. 16). Oxformasine (**452**) represents the first benzoxepine derivative from *Delphinium* species.

5. Terpenoids

In contrast to the wide variety of DAs present in *Delphinium* plants, terpenoids are rare. To date, only one new non-alkaloidal diterpenoid, campylopin (**453**) from *D. campylocentrum*, has been reported¹³⁰ (Fig. 15). Campylopin (**453**) is the first naturally occurring hetidane-type diterpenoid, and it has great significance for the biosynthesis of diterpenoid alkaloids, as it implies a new biosynthetic pathway from atisane or hetidane-type C_{20} -diterpenes to hetidine-type C_{20} -diterpenoid alkaloids.¹³¹

6. Bioactivities

In the past forty years, compounds isolated from *Delphinium* plants, mainly DAs and flavonols, have been screened for their multiple biological activities, including antineoplastic, antimicrobial, anti-inflammatory, and insecticidal and antifeedant activities, as well as cholinesterase inhibition effects. Some of the tested compounds showed considerable activities. Herein,

 Table 1
 Cytotoxic activity of Delphinium alkaloids

			IC_{50} (μM)		
Plants	Alkaloids	Туре	MCF-7	A549	
D. chrysotrichum	Delphatisine C (410)	C-4	>50	2.36	
-	Delpheline	B-1	17.32	>50	
	Delbrunine	B-1	16.50	10.63	
	Etoposide	_	7.56	1.8	
D. honanense	Honatisine (403)	C-4	3.16	>50	
	Siwanine E	B-1	35.32	>50	
	Delcorinine	B-1	18.60	31.63	
	Uraphine	B-1	33.21	9.86	
	Nordhagenine A	B-1	17.38	9.62	
	Etoposide	_	7.53	1.82	
D. trichophorum	Trichodelphinine A (350)	C-1	—	27.62	
	Trichodelphinine B (351)	C-1	—	18.64	
	Trichodelphinine C (352)	C-1	_	48.08	
	Trichodelphinine D (353)	C-1	—	52.79	
	Trichodelphinine E (354)	C-1	_	12.03	
	Trichodelphinine F (419)	C-1	—	16.55	
	Doxorubicin	—	—	0.60	

the bioactivities of the compounds from the *Delphinium* plants are summarized.

6.1 Anticancer activity

A certain number of natural DAs have been reported to possess antiproliferative activities against various human cancer cell lines, indicating their great potential as new drugs for treating the corresponding cancers.133 New DAs along with known DAs from Delphinium plants have also been reported to have in vitro anticancer activities (Table 1). The atisine-type DA delphatisine C (410) from D. chrysotrichum showed significant cytotoxic activity against A549 cells (IC50, 2.36 µM),103 and its analogue honatisine (403) from D. honanense also displayed impressive cytotoxic activity against MCF-7 cells with an IC50 value of 3.16 μM, making it more effective than the positive control etoposide (IC₅₀, 7.53 µM).¹⁰⁴ The cytotoxic activities of five hetisine-type C20-DAs, trichodelphinines A-E (350-354), and one delnudinetype C₂₀-DA, trichodelphinine F (419), against A549 cells were tested.¹¹⁰ The most active compounds (351, 354 and 419) had low IC₅₀ values (18.64, 12.03 and 16.55 µM, respectively), and the other compounds showed moderate cytotoxicities against A549 cells. In addition, known lycaconitine-type C₁₉-DAs, including delpheline, delbrunine, siwanine E, delcorinine, uraphine, nordhagenine A, and delbrunine from D. chrysotrichum and D. honanense, also showed certain anticancer activities against A549 and MCF-7 cells with IC₅₀ values ranging from 9.62 to 35.32 µM.104

Although no detailed structure–activity relationship (SAR) study has yet been reported, it seems that C_{20} -DAs have shown more potential to be developed as antitumor drugs on account of their higher efficiency and lower toxicity.¹³ Especially, the hetisine-type C_{20} -DAs, which have exhibited selective antiproliferative activity on human lung cancer cell A549, deserve further studies to identify more potent antitumor DAs. On the other hand, *Delphinium* plants have rarely been utilized for the treatment of cancer in TCM. The research presented above suggests that *Delphinium* plants with abundant DAs have great potential as herbal drugs for treating cancer, but more research is required to confirm this.

6.2 ChE inhibition effects

The discovery of natural ChE inhibitors is an active research area in natural medicinal chemistry due to the involvement of cholinesterases in Alzheimer's disease and related dementias.¹³⁴ In the early 1990s, methyllycaconitine, one of the principal active constituents of *Delphinium* species, was found to be an effective ligand for neuronal nicotinic acetylcholine receptor (nAChR) subtypes, which attracted the attention of scientists to the screening of natural cholinesterase inhibitors from *Delphinium* species. Several *Delphinium* alkaloids have been reported to exhibit considerable ChE inhibitory effects (Table 2). The aconitine-type C₁₉-DAs 1β-hydroxy, 14β-acetylcondelphine (**31**7), jadwarine-A (**270**), jadwarine-B (**262**), and dihydropentagynine (**203**) from *D. denudatum* have been found to possess inhibitory effects of AChE and BChE with EC₅₀ values ranging from 9.2 to 34.7 μ M.⁷⁵ Ahmad *et al.* reported that an

			EC_{50} (μ M)		
Plants	Compounds	Туре	AChE	BChE	
D. denudatum	1β-hydroxy, 14β-acetyl condelphine (31 7)	B-2	19.8	31.5	
	Jadwarine-A (270)	B-2	9.2	19.6	
	Jadwarine-B (262)	B-2	16.8	34.7	
	Isotalatizidine hydrate	B-2	12.1	21.4	
	Dihydropentagynine (203)	B-1	11.2	22.2	
	Allanzanthane A	_	8.2	18	
	Galanthamine	_	10.1	20.6	
D. brunonianum	Delamide A (420)	Amide	9.7	>50	
	Rivastigmine	_	4.7	>10	

isotalatazidine hydrate crystal isolated from *D. denudatum* showed competitive inhibition of both AChE and BChE with IC₅₀ values of 12.13 μ M and 21.41 μ M, respectively.¹³⁵ In addition, the amide alkaloid delamide A (420) from *D. brunonianum* also showed highly selective AChE inhibitory activity (EC₅₀, 9.7 μ M) and was shown to be a mixed-type reversible inhibitor of AChE by kinetic analysis.¹¹¹

6.3 Insecticidal and antiparasitic activities

Delphinium plants have been used as natural insecticides since the time of Dioscorides. Previous studies have indicated that DAs might have evolved in nature to protect *Delphinium* and *Aconitum* plants against pests. Hence, searching for valuable natural insecticides from plants that are rich in DAs, which have been shown to be potent and selective ligands of the insect nicotinic receptor, is quite effective.^{136,137} A series of DAs from *Delphinium* plants have been shown to possess insecticidal and antifeedant activities. Ulubelen *et al.* tested the repellency of 8 new alkaloids along with 12 known alkaloids belonging to three subtypes of DAs from Turkish *Delphinium* species against *Tribolium casteneum* (Table 3).¹³⁸ Most of the tested new alkaloids (**280**, **285**, **299**, **331**, **368–369**, and **378**) had repellency class III values (40.1–60%) for a short period, and venuluson (**369**) gave the highest level of repellency (59.37%), suggesting it is a promising candidate for insecticide development.

Several investigations on the antifeedant activities of *Delphinium* alkaloids have been performed. The crude alkaloids of *D. cyphoplectrum* have slight antifeedant and insect repellent activities against the larvae of *Spodoptera littoralis*.¹³⁹ González-Coloma *et al.* tested the insect antifeedant activities of 21 DAs isolated from *Delphinium* species on *Spodoptera littoralis* and *Leptinotarsa decemlineata*. The antifeedant effects of the test compounds were structure- and species-dependent (EC₅₀ values ranging between 0.42–22.5 and 0.1–17.77 µg cm⁻² for *L. decemlineata* and *S. littoralis*, respectively). The most active antifeedants to *L. decemlineata* and *S. littoralis* were found be to

Plants	Alkaloids	Туре	Repellency (%)	Class
D. venulosum	Venulol (368)	C-1	31.25	II
	Venuluson (369)	C-1	56.25	III
	Venudelphine (378)	C-1	40.62	III
	Hetisine	C-1	59.12	III
	Hetisinone	C-1	37.50	II
D. gueneri	14-Methyl peregrine (285)	B-2	46.87	III
	N-Deethyl-14-O-methylperegrine (299)	B-2	40.62	III
	Peregrine (280)	B-2	53.12	III
	Peregrine alcohol	B-2	37.50	II
	Talatisamine	B-2	34.37	II
	14-Acetyneoline	B-2	53.12	III
D. albiflorum	Lycoctonine	B-1	46.87	III
D. davisii	18-Benzoyldavisinol (331)	C-1	46.87	III
	Karakoline	B-2	37.50	II
D. uncinatum	14-Acetylvirescenine	B-1	43.75	III
	Condelphine	B-2	40.62	III
D. formosum	14-Demethylajacine (244)	B-1	40.62	III
-	Delsemine B	B-1	37.50	II
	Delsoline	B-1	37.50	II
D. crispulum	Browniine	B-1	46.87	III
D. montanum	Gigactonine	B-1	43.75	III

Table 4 Antifeedant effects of Delphinium alkaloids to L. decemlineata and S. littoralis

			$EC_{50} (\mu g \ cm^{-2})$		
Plants	Alkaloids	Туре	L. decemlineata	S. littoralis	
D. cardiopetalum	Hetisinone	C-1	13.1	>50	
-	Cardiopetamine (362)	C-1	22.5	5.5	
	15-Acetyl-cardiopetamine (363)	C-1	12.9	>100	
	Cardiodine (329)	C-1	2.2	4.4	
D. gracile	Atisinium chloride	C-3	3.4	2.4	
D. stenocarpa	Ajaconine	C-3	5.1	8.2	
D. staphisagria	19-Oxodihydroatisine (408)	C-3	>50	0.1	
	Azitine	C-3	>50	1.1	
	Isoazitine (404)	C-3	6.9	4.1	
D. cardiopetalum	Karakoline	B-2	0.44	>50	
-	Cardiopetaline (259)	B-2	0.42	≈50	
	Cardiopetalidine (184)	B-1	>50	>50	
	14-Benzoylgadesine	B-1	>50	13.61	
D. montanum	8-O-Ethylaconine	B-2	>50	8.29	
	Neoline	B-2	≈50	≈50	
	Gigactonine	B-1	13.02	9.31	
	Delcosine	B-1	1.11	3.53	
	Methylicaconitine	B-1	2.78	17.77	
D. pentagynum	Gadenine	B-1	11.93	>50	

the cardiopetaline (**259**, EC₅₀, 0.42 µg cm⁻²) and 19-oxodihydroatisine (**408**, EC₅₀, 0.1 µg cm⁻²), respectively.^{140,141} Shawurensine (**209**) from *D. naviculare* var. *lasiocarpum* also showed considerably potent antifeedant activity with EC₅₀ values of 0.42 and 0.81 mg cm⁻² against the larvae of *Spodoptera exigua* in a choice test and no choice test, respectively.¹⁴² Generally, the antifeedant activities of C₂₀-DAs are lower than those of C₁₉-DAs, which might be attributed to the species- and structurerelated differences in the taste receptor binding to these two classes of DAs,¹⁴³ and this result suggest that further investigations on the antifeedant effects of these compounds should be concentrated on C₁₉-DAs.

Among the new flavonol glycosides that have been isolated from Delphinium plants, a series of compounds (431-437, 439 and 441-442) have demonstrated high antiparasitic activities.132,144,145 In some cases, the antitrypanosomatid activities of these flavonol glycosides against Trypanosoma cruzi were more potent than that of the reference drug benznidazole. For example, compound 436 showed higher trypanocidal activity $(IC_{50} = 6.5 \ \mu M)$ than benznidazole $(IC_{50} = 15.8 \ \mu M)$ against the epimastigote form of T. cruzi, and compound 432 exhibited higher trypanocidal activity (IC₅₀, 21.2 μ M) than benznidazole (IC₅₀, 23.3 μ M) against the amastigote form of *T. cruzi*. These compounds also showed impressive leishmanicidal activities against both the extra- and intracellular forms of three Leishmania species (Leishmania infantum, L. braziliensis and L. donovani), and among these compounds, 439 presented the highest antileishmanial activity. Notably, all of these tested flavonol glycosides showed low toxicity to the corresponding host cells, resulting in higher selectivity indices than the reference drugs, which highlights their potential in the treatment of leishmaniasis and Chagas disease (Table 4).

6.4 Antifungal and antiviral activity

Delphinium species have been used for the treatment of itches and other skin eruptions in folk medicine, which indicates that the plants may possess constituents with antifungal activities. The new lactone-type C_{19} -DA 8-acetylheterophyllisine (**319**) from *D. denudatum* showed antifungal activity against a number of human pathogenic fungi, including *Allescheria boydii*,



Fig. 17 The percentage of each type and sub-type of alkaloids from *Delphinium* species.

Aspergillus niger, Epidermophyton floccosum, and Pleurotus ostreatus, with MIC values of 100, 200, 250, and 150 μ g mL⁻¹, respectively.⁸⁸

Delphinium-derived DAs also showed antiviral activity. The new lycaconitine-type C₁₉-DAs ajacisines C–E (**212–214**), along with the known alkaloid isodelectine, which were isolated from *D. ajacis*, exhibited moderate to weak *in vitro* antiviral effects against respiratory syncytial virus (RSV) with IC₅₀ values of 75.2, 35.1, 10.1, and 50.2 μ M, respectively,¹⁴⁶ while the positive control (ribavirin) showed an IC₅₀ value of 3.1 μ M. The rearranged-type C₁₉-DA grandiflodine B (**21**), isolated from *D.* grandiflorum, also displayed a weak inhibitory effect on the growth of RSV with an IC₅₀ value of 75.3 μ M.⁹⁰

7. Conclusions

To the best of our knowledge, investigations on the chemical constituents of Delphinium in the last four decades have reported a total of 453 new compounds, including 429 alkaloids, 21 flavonoids, two phenolic compounds, and one diterpenoid. Among the 429 new alkaloids, 419 are DAs, including 23 C₁₈-DAs, 299 C19-DAs, and 97 C20-DAs, which cover fourteen subtypes of DAs (Fig. 17). In view of the chemical diversity described, the lycaconitine sub-type of C₁₉-DAs (B-1), with 230 new members, are the most abundant DAs in the Delphinium plants, as they accounted for the largest proportion of new compounds (55.37%), followed by aconitine-type C_{19} -DAs (B-2) with 64 new members (14.8%) and hetisine-type C_{20} -DAs (C-1) with 56 new members (13.37%). The other subtypes only account for only a small portion of compounds (less than 20%). Obviously, DAs, especially lycaconitine-type C₁₉-DAs, are characteristic components of the genus Delphinium, which is distinguished from the genus Aconitum by the large number of aonitine-type C19-DAs. Among these new compounds, several possess unprecedented structures, and their various biological activities, including anticancer activity, cholinesterase inhibition effects, insecticidal and antiparasitic activities, and antifungal and antiviral activities, have been reported. These findings underscore the large chemical and biological diversity among the chemical constituents of Delphinium plants, which could not only serve as a vast resource for drug discovery but also help elucidate the therapeutic effects of Delphinium-derived herbal drugs.

Although phytochemical and biological studies on the chemical constituents of *Delphinium* species have attracted considerable interest, some deficiencies remain. First, there are approximately 365 *Delphinium* species around the world, but the chemical constituents of only 87 species and 10 varietal have been studied in the last four decades. Among these species, *D. elatum*, *D. staphisagria*, *D. anthriscifolium* var. *savatieri*, *D. nuttallianum*, *D. anthriscifolium* var. *majus*, and *D. cardiopetalum* contributed relatively more new compounds than the other species. The biological constituents of other *Delphinium* species remain untapped. Hence, an extensive investigation of other species, especially species that are used medicinally, remains necessary. Second, all of the biological activities of the isolated compounds were investigated by using *in vitro* tests, namely,

chemical and cellular models, and there is little research confirming the biological activities of *Delphinium* compounds using *in vivo* animal models or on their pharmacological mechanisms. It is necessary to evaluate the biological activities of *Delphinium*-derived constituents using both *in vitro* and *in vivo* models, which will facilitate further research and exploitation of this genus.

Conflicts of interest

There are no conflicts to declare.

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