Chemistry, biological activities and toxic effects of alkaloidal constituents of genus Delphinium - A mini review

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ABSTRACT

The genus Delphinium is one of the essential members of the family Ranunculaceae. These species grow wild in North America, Europe, and Asia. They have demonstrated antioxidant, antimicrobial, and cytotoxic activities. Diterpenoid alkaloids are their main constituents and seem to be responsible for medicinal and toxic properties. The primary purpose of this paper is to review the therapeutic benefits of Delphinium species, chemical composition, and its medicinal uses, in addition to the reported toxic effects of these plants influencing different animals and humans.

Introduction

The genus Delphinium sp. (larkspur) belongs to the family Ranunculaceae. This genus consists of approximately 356 species commonly spread in the northern hemisphere, North America, Europe, and Asia; however, 113 species are generally grown in China (1,2). The Delphinium genus encompasses diterpenoid alkaloids with a variety of medicinal uses (3,4). Ewan (1945) and Warnock (1995, 1997) were the first and second researchers who published the Delphinium genus' two synopses. So far, 427 alkaloids have been detected based on Yin et al studies (1,2). The toxicity of larkspurs has been attributed to two types of toxic alkaloids: 1) N-methylsuccinimidoanthranoyllycoctonine (MSAL) type that is toxic and 2) a less toxic type called methylenedioxy lycoctonine (MDL) (5, 6). However, tall larkspur species have high levels of MSAL-type alkaloids, namely methyllycaconitine (7), which have been declared responsible for the toxicity of these species.

Additionally, they are 20 times more toxic than MDL-type alkaloids (6). Several factors are known to influence the alkaloid content of larkspur and its toxicity: plant species, stage of plant growth, plant part, and environment (8). Cook et al identified two distinct chemotypes of D. ramosum and concluded botanical classification alone was not suitable for estimating the relative risk of toxicity in populations like D. ramosum. These two chemotypes will probably differ in their toxic potential and finally pose different risks of toxicity when grazed by livestock species. Knowledge in this area has important implications in grazing management decisions on D. ramosum infested...
rangelands and exhibits that botanical classification alone is not a helpful indicator of relative risk of toxicity (9). We suggest that some other factors, such as factors mentioned earlier in the text, play essential roles in plant poisoning. The Delphinium sp. alkaloid components have been found to inhibit the formation of action potential in muscle, decreasing synaptic functionality, and block neuromuscular transmission probably by antagonizing nicotinic receptors, suggesting a possible mechanism for poisonous effects of these chemical toxins (10). Apart from these poisoning activities of Delphinium sp., this genus has some medicinal uses such as antimicrobial, anti-inflammatory, antineoplastic, and antifeedant, as well as cholinesterase inhibition effects (2,11-13). Additionally, the medicinal uses of this genus showed diverse pharmacological potentials, including antiarrhythmic, arrhythmogenic, neurotropic, analgesic, anti-inflammatory, muscular relaxant, hypotensive, local anesthetic, psychotropic, and spasmyloytic activities. Its alkaloids are divided into two groups according to their diverse effects, varying from poisonous (e.g., aconitine) to therapeutic (e.g., lappaconitine) (14,15). On the other hand, it has been traditionally observed that the aqueous extracts of the roots of this species are beneficial for treating fungal infections, epilepsy, paralysis, cholera, jaundice, and cardiac diseases (16-18). The main goal of this review is to provide an updated overview of the literature on the medicinal uses of different Delphinium sp., their alkaloidal components, and the therapeutic benefits in addition to numerous toxic effects of the plant influencing animals and humans.

Materials and Methods
Records identified through databases of PubMed, Scopus, Web of Science, Cochrane Library, and Embase electronic databases up to June 2021, using keywords: Delphinium, larkspur, alkaloid, pharmacological, pharmaceutical, and biological were included in the study. This study summarizes the findings of alkaloidal content and pharmacological studies. We also checked review articles for additional studies. The references of articles selected were also reviewed for potentially eligible ones. Reviews, records not relevant, without pharmacological data, not accessible, or not eligible with reasons were excluded from the study. Two independent authors without knowledge of existing scores examined the selected studies based on the above criteria to resolve discrepancies.

Results
Botany
The Ranunculaceae family comprises 59 genera and 2500 shrubs, herbs, or woody climbers, generally known as the crowfoot or buttercup family. This family is found all over the world. In addition, several members of this family are in tropical and subtropical areas except in the Montane region (19).

The Delphinium genus is a prolific source of complex biologically active molecules, mostly nortriterpenoid and diterpenoid alkaloids. This genus consists of 370 species distributed all over the world in northern temperate areas. Munz (1967 & 1968) recorded 244 species from Asia, with a diversity center in the Eastern Himalayas and South-West China that 150 species live (19).

The Delphinium leaves are 5-15 cm in diameter, rounded shape, segregated into 3-5 mainly obviated parts, divided into 2-3 mm wide teeth or oblong lobes. Flowers’ characteristics are bisexual, regular, and approximately 2.5 cm long, with a 1.4-1.5 cm spur and upper outer petals of 1.2 cm. The upper inner petals are white, provided the other petals are blue. The perianth is simple or splits into a calyx and a corolla. It has several free stamens. In arranged flowers, the carpels, in most cases, are numerous. The fruit is an eteroio of achenes, follicles, or a berry. It has a squamulose leaf bud at the crown part. Some flowers are scattered, seeds are light blue, small, and endospermic (19). The herb has a blackish-brown rhizome, 1 cm to 2 cm wide and 3 cm to 6.5 cm long at the crown in length, very hard with conical shape and externally covered by a suberised metaderm, with numerous small circular scars that are the residues of lateral roots. The parenchymatic cells of the root part consist of the starch grains that occur in groups. These have no calcium oxalate, fibers, or cork cells (19).

Traditional application
There are minimal data on traditional uses of the genus Delphinium in the literature, and a few species of Delphinium have traditionally medicinal benefits. However, we present available published papers that show the applications of this genus in traditional medicine (Table 1). D. denudatum, known as Jadwar, is an herbal plant generally grown at high altitude habitats in the western Himalayas. Aqueous extract of the roots of this species is beneficial for treating fungal infections, epilepsy, paralysis, cholera, jaundice, and cardiac diseases (16-18).

Additionally, D. denudatum root is an invigorating supplementation and therapeutic approach for treating rheumatism, syphilis, toothache, and an antidote against aconite poisoning and snakebite (20,21). The indigenous traditional healers involved in the conventional Unani medical care system prescribe this species to treat epilepsy (22). In this medicinal system, the root extract of D. denudatum is a drug with effects on the central nervous system (CNS) as a sedative, analgesic, brain tonic, and therapy for tremors, hysteria, atony, numbness, paralysis, morphine addiction (23). Various extracts of Delphinium are used as a vomiting agent, relieving epileptic symptoms and tremors of tetanus and treating rabies in Turkish traditional medicine (24). Roots and flowers of Indian species of Delphinium sp. have been
applied as insecticides, anti-maggot in wounds, cardiac and respiratory depressants, stimulants, and treatment for patients with diarrhea and dysentery (22,25). Mongolian traditional healers have used the decoctions of some species of the *Delphinium* genus as antipyretics in cases of relieving toothache, infectious fever, and diarrhea therapy due to defects in the biliary system (26). In Chinese traditional medicine, *D. albocoeruleum* Maxim has reduced inflammation, fever, and pain. This species is a perennial plant grown at an altitude of 3600–4700 m in the Northwest areas of China (1). *D. anthriscifolium* var. *majus* is a traditional Chinese remedy with therapeutic effects on clearing heat, detoxification, healing cough, and treating phlegm (27). In Tibetan folk medicine, the aerial portions of *D. caeruleum*, known as Daimusa, have been revealed to have therapeutic potential against inflammation, diarrhea, and edema (28).

Another Chinese folk medicinal herb is *D. tianshanicum* W.T. Wang, distributed in the Xinjiang of China, which has beneficial effects on relieving pain and treating rheumatoid arthritis (29). The other Chinese medicinal plant is *D. trifoliatum*, whose root extracts treat rheumatism and neuralgia (30). In Nepal’s traditional medical system, roots and leaves extracts or juices of *D. scabriflorum* are used to treat rheumatism, reducing fever, and wound healing (28).

Table 1. Traditional uses of different *Delphinium* species in the traditional system

| Delphinium species | Traditional uses | Used part | Regional traditional system |
|--------------------|-----------------|----------|-----------------------------|
| *D. albocoeruleum* Maxim | Anti-inflammation, reducing fever, and analgesic | Whole herb | Chinese traditional medicine |
| *D. anthriscifolium* var. *Majus* | Clearing heat, detoxification, healing cough, and treating phlegm | Whole herb | Chinese traditional medicine |
| *D. tianshanicum* W.T. Wang | Relieving pain and treating rheumatoid arthrits | Whole herb | Chinese traditional medicine |
| *D. trifoliatum* | Treating rheumatism and neuralgia | Root extracts | Chinese traditional medicine |
| *D. caeruleum* | Anti-inflammation, diarrhea, and edema | Aerial parts | Tibetan traditional medicine |
| *D. scabriflorum* | Treating rheumatism, reducing fever, and wound healing | Roots and the juice of the leaves | Nepal’s traditional medicine |
| *D. denudatum* | Sedative, analgesic, brain and nerve tonic, tremors, hysteria, atony, numbness, paralysis, morphine addiction, and epilepsy | Root extract | Unani medical care system |
| Turkish species of *Delphinium* | To treat vomiting, relieving epileptic symptoms and tremors of tetanus, and treating rabies | Various extracts | Turkish traditional medicine |
| Indian species of *Delphinium* | Insecticides, anti-maggot in wounds, cardiac and respiratory depressants, stimulants, and treating diarrhea and dysentery | Roots and flowers | Indian Traditional medicine |
| Mongolian species of *Delphinium* | Therapy for infectious fever, diarrhea due to defects in the biliary system, and relieving toothache | Decoctions | Mongolian traditional medicine |

Alkaloidal distribution of *Delphinium* sp.

As mentioned earlier, the genus *Delphinium* has valuable, healthy properties, generally attributable to its chemical components. The main chemical components of this genus are diterpenoid alkaloids (36). Cook et al measured the levels of alkaloids in vegetative and floral tissues and pollen and nectar in *D. barbeyi* and *D. nuttallianum* species. Interestingly, they found that the alkaloid contents of nectar were considerably low compared to other tissues and proposed that these decreased levels could help plant compatibility via reducing harmful effects on the activity

Table 1. Traditional uses of different Delphinium species in the traditional system
of pollinators. They also discovered that fruits, flowers, and anthers had significant alkaloids in both species (37). This is inconsistent with optimal defense theory and may suggest that the latter tissues are the most heavily defended because they contain high concentrations of poisonous MSAL and MDL alkaloids, which protect them from herbivorous insects and mammals (38,39). Then, they assessed the alkaloid content of vegetative and reproductive tissues in *D. nuttallianum* at various phases of plant growth to uncover the effect of plant growth on alkaloid levels during a growing season. They observed high levels of alkaloids in reproductive tissues compared to vegetative ones with no remarkable variation in alkaloid contents of the plant during maturity stages across the growing season, suggesting the impact of the plant's life history on alkaloid allocation in its different parts (40). These alkaloid contents are useful to evaluate the chemical taxonomic diversity and classification of different species of larkspurs (41). Xue et al isolated 18 aconitine-type C19-diterpenoid alkaloids from the whole plant of *D. pseudoaemulans*, of which tianshanisine E, sharwuphinine B, potanisine A, lycoctonine, delbruline, isodelpheline, delavaines A–B, and shawurennines A–B, have been described previously, and no pseudophenines A–D, pseudorenines A–B, and pseudonidines A–B were found later. They performed an MTT assay to assess the effects of these compounds on cellular viability and consequently found that none of their compounds had cytotoxic potentials (42). Batbayar et al also isolated 14 norditerpenoid alkaloids from the aerial parts of 4 distinct species of *Delphinium*, including *D. dissectum* Huth, *D. excelsum* Reichenb., *D. grandiflorum* L., and *D. triste* Fisch. Eleven out of 14 alkaloids were previously reported, but 3 new ones have also been isolated from *D. dissectum* Huth and *D. excelsum* Reichenb. Known compounds were delavaine A/B, deoxylycoctonine, methyllycaconitine, delcaroline, delectinine, delterine, delcosine, deltatsine, grandiflorine, macrocentridine, and 14-dehydrodelcosine, but new cases were 10-hydroxymethyllycaconitine, 18-O-methyldelterine, and 10-hydroxynudicaulidine (26). In another phytochemical study, six alkaloids from *D. elatum* cv. Pacific Giant were isolated and identified. These C19-norditerpenoid alkaloids included: N-formyl-4,19-secoyunnadelphinine, anhweidelphinine, browniine, desacctylnudicauline, methyllycaconitine, and nudicauline, which all had been discovered in previous studies. They confirmed three new norditerpenoid alkaloids, tianshanisine E, isotalatizidine hydrate, and dihydropentagynine. Additionally, the structures of their compounds by interpreting spectral data (47). One year later, they reported that the extracts obtained from aerial parts of *D. trifoliatum* had three previously unknown C20-diterpenoid alkaloids, including trifoliolasine D-F. Additionally, the structures of all three alkaloids were estimated using spectroscopic and X-ray crystallographic techniques (30). Fang Sun and Michael Benn examined the alkaloid content of *D. zaitil*, and found seven norditerpenoid alkaloids in seed extracts of the plant. Six out of 7 isolated alkaloids were anhweidelphinine, brownine, desacctylnudicauline, lycoctonine, methyllycaconitine, and nudicauline, which all had been discovered in previous studies. They found that the seventh was an unknown compound and named it “Zalliline” (48). The phytoconstituents of the whole plant of *D. majus* have been reported by Chen and coworkers. Fifteen known alkaloids and three new C19-diterpenoid alkaloids, majusines A–C, and six new C20-diterpenoid alkaloids, majusimines A-D and majusidine A-B, were isolated from this plant (14). A study by Pradeep Man Shrestha and Alfred Katz indicated that chloroform-based extractions obtained from the roots of *D. cabriflorum* led to the isolation of a
new diterpenoid alkaloid, named 13-(2-methylbutyryl)azitine, together with 11 previously found alkaloids (31). Chemical investigation of the extracts from aerial parts of D. nordhagenii has resulted in the isolation of four norditerpenoid alkaloids, including nordenhagenine A-C, and lycoctonine (49). There are two different alkaloid isolates from the species D. anthriscifolium var. majus, anathriscifolones A and B, which both have a lycoctonine skeleton from the whole plant of this species (27). Another study on D. anthriscifolium was performed by Shan, et al. to evaluate the alkaloid content of the species. They found that the whole plant of D. anthriscifolium contained five C18-diterpenoid alkaloids such as anathriscifolite A, anathriscifolite B, deoxydecelorine, anathriscifolcine A, and anathriscifolcine G (50). Aerial parts of D. uralense have been described to have alkaloids methyllycaconitine and delcorine, as well as a norditerpenoid alkaloid, which was called Uraline (51). Using chromatographic techniques and spectroscopic method, to isolate the phytoconstituents and structures of compounds from D. grandiflorum were performed. The results showed that the roots of the plant encompass 5 diterpenoid alkaloids such as methyllycaconitine, lycoctonine, delavaine A, delsemene A, and deljadaine (52). Zhan, et al designed a study to determine the chemical composition of D. caeruleum. Their data demonstrated the presence of 10 diterpenoid alkaloids in the extracts of the plant, including lycoctonine, caeruodelphinine A, talidine A-C, tatsienine-V, d-magnoflorine, vakhmatine, delatisine, and a propionate derivative (28). Kurbanov et al revealed that the aerial parts of D. leptocarpum during flowering season possessed a new alkaloid compound with a formula of C_{21}H_{29}N_{2}O_{5} that was called leptanine (53). The genus D. delavayi Franch has been described to contain several diterpenoid alkaloid compounds; however, deltalone with formula C_{27}H_{41}N_{5}O_{9} is a major C19-diterpenoid alkaloid isolated from the root extracts of Delphinium sp. (54). Another typical C19-diterpenoid alkaloid, called bonvalotidine A, was also isolated from D. bonvalotii Franch. Its structure was determined using the crystallographic method (54). D. formosum roots collected from Trabzon, Turkey, were studied by Utsukarci et al to determine the plant’s alkaloid content. After different extraction steps, 7 norditerpenoid alkaloids (methyllycaconitine, avadharihine, antranolllycaconitine, delsemene A/B, brownine and lycoctonine) were isolated from root extracts of the plant (55). The name and chemical class of alkaloids isolated from Delphinium sp. are mentioned briefly in Table 2.

### Table 2. Name and the chemical class of alkaloids isolated from Delphinium sp.

| Alkaloid constituents name | Chemical class | Delphinium sp. | Ref. |
|----------------------------|----------------|----------------|-----|
| Tianshansine E, shawurhinine B, potanisine A, lycoctonine, delbruline, isondelpheline, delavaines A–B, shawureines A–B pseudophenines A–D, pseudoreines A–B, and pseudonidines A–B | 18 aconitine-type C19-diterpenoid alkaloids | D. pseudoaemulans | (42) |
| Delavaine A/B, deoxylycoctonine, methyllycaconitine, delcaroline, delectine, delterine, delcosine, delfatsine, grandiflorine, macrocentridine, and 14-dehydrodelcosine, hydroxyethyllycaconitine, 18-O-methyldeletine and 1-O-hydroxyundecalidin | 14 norditerpenoid alkaloids | D. dissection Huth, D. excelsum Reichenb., D. grandiflorum L., and D. triste Fisch | (26) |
| N-formyl-4,19-secopacine, iminosindelpheline, imindelpheline, iminopacine, 6-dehydroeladine, and elapacine | C19-norditerpenoid alkaloids | D. elatum cv. Pacific Giant | (43) |
| Trichodelphinines A–E and trichodelphine F | Hetitsane-type C20-diterpenoid and one delnudine-type C20-diterpenoid alkaloids | D. trichophorum Franch | (44) |
| 1β-hydroxy,14β-acetyl condelphine, jadwarine-A, jadwarine-B, isotalatizidine hydrate and dihydropentagynine | Norditerpenoid alkaloids | D. denudatum | (45) |
| Elapacigine, N-deethyl-N-formylpacamine, N-deethyl-N-formylpacamine, and N-formyl-4,19-secoyunnadelphin | C19-diterpenoid alkaloids | D. elatum cv. Pacific Giant | (46) |
| - | C19 and C20-diterpenoid alkaloids | D. alboaculearem Maxim | (1) |
| Tianshansine, tianshamine, and tianshanidine | C19-diterpenoid alkaloids | D. tianshanicum | (29) |
| Trifololinas A–C | Norditerpenoid alkaloids | D. trifoliatum | (47) |
| Trifololinas D–F | C20-diterpenoid alkaloids | D. trifoliatum | (30) |
| Anhweidelphine, brownini, desacetylindicauline, lycoctonine, methyllycaconitine indicauline, and Zalline | Nordterpenoid alkaloid | D. Zalli | (48) |
| Majusines A–C, majusimes A-D and majusidine A and B | C19 and C20-diterpenoid alkaloids | D. majus | (14) |
| 13-(2-methylbutyryl)azitine , together with 11 previously found alkaloids | Diterpenoid alkaloid | D. cabriflorum | (31) |
| Nordhagenine A–C, and lycoctonine | Nordterpenoid alkaloids | D. nordhagenii | (49) |

Chemical classification of Delphinium alkaloids

Based on a dictionary of natural products published
in June 2018, the main bioactive compounds found in Delphinium species were alkaloids divided into four major structural types, including C18-dinorditerpenoid, C19-norditerpenoid, C20-diterpenoid, and miscellaneous alkaloids. There are a few C-18 alkaloid diterpenes in Delphinium sp. which lack C-18 compared to the C-19 aconitine ring system and vary mostly in oxidation pattern of C-1, 3, 4, 6, 7, 8, 9, 14, and 16 and alkylation of the nitrogen atom. C-19 alkaloids differ mainly with C-18 alkaloids in an excess methyl group (C-18) on C-4. C-19 alkaloids vary in oxidation pattern at 1, 3, 6, 7, 8, 9, 14, 15, 16, and 18 or double bonds, especially at Δ7,8,9,14,15,16, and 18 or double bonds, especially at Δ

The majority of C-19 diterpene alkaloids are based on the aconitine ring system. A few alkaloids belong to 13,14-seco or 7,17-seco aconitine. 13, 14-Seco types form 13, 14-δ-lactone or tetrahydropyran ring, and 7,13, 14-secoaconitines usually have a double bond at C-7 (57). A few others have rearranged the framework and differed with aconitine in C8–C17 bridge instead of the C7–C17 bridge. The third major group is the C20 alkaloids, which are around 116 alkaloids in Delphinium sp. They are mainly based on atidane structure (Atisines or Atidines) derived from atisane tetracyclic diterpenes with additional 19,20-pentazene ring. Other variations are Denudated by the formation of C-7 to C-20 bond; Hedinines with C-14 to C-20 bond; Hetalines or Hetalines with C-14 to C-20, and C-6 to C-20 bonds (17 cases); Yakognavines or N.19 secobetisanes with caved N, C-19 bond and with C-14 to C-20, and C-6 to C-20 bonds (15 cases); Staphisagrinines with dimeric C-20 diterpene units. Napelline types are different C-20 alkaloids derived from Ent-kaurane tetracyclic diterpene with N to C-20, N to C-19, and C-7 to C-20 bonds, rare and reported in a few numbers in Delphinium sp. Minor alkaloids are from aporphine, benzylisoquinoline, or antranilic derivatives. A rare and undescribed alkaloid is also reported from D. caeruleum with 2-Methyl-4(3,6,7-trimethoxy-2-naphthalenyl)-2-azabicyclo[2.2.1]heptan-3-one structure (71,72). The alkaloids classification of these terpenoids are shown in Figure 1.

### Extraction and purification of the alkaloids

Alkaloids are alkaline and are present in salt form with organic acids in the plant. After the extraction of alkaloids, the salt is replaced by inorganic acid salt. Acid extraction methods usually use 0.1% to 3% sulfuric acid or hydrochloric acid to pH 3, followed by washing with chloroform to remove nonalkaloidal nonpolar components like fats, chlorophylls, and terpenoids. It becomes basic to pH 9, and alkaloidal material is extracted with CHCl3 (57). For purification, mostly alkaloid fraction is submitted on silica gel or alumina column using chloroform: methanol with increasing polarity. In a gradient system, fractions rich in alkaloids are submitted on a silica gel column chromatography (CC) with chloroform: methanol or hexane: ethyl acetate. Finally, subfractions are purified by repeated recrystallization, PTLC on alumina plate with hexane: ethyl acetate or Silica gel PTLC or CC using hexane: ethyl acetate: diethylamine in optimized ratio. For example, Gabbasov et al loaded alkaloid fraction of D. flexuosum over silica gel CC with benzene: methanol from 0.5% to 2% followed by silica gel CC using tetrachloride carbon: isopropanol from 0.5 to 1.5% (57). Chen et al isolated crude alkaloids of D. majus by CC over a silica gel column using cyclohexane: acetone with increasing polarity. In different ratios, fractions were purified on a silica gel CC using cyclohexane: acetone or CHCl3–CH3OH (57). Reina et al isolated five diterpenoid alkaloids from D. cardiopetalum by GC over alumina eluting with a gradient system of hexane: ethyl acetate. Preparative alumina TLC purification methods using hexane: ethyl acetate (4:1) six times (8). He et al isolated three C19-diterpenoid alkaloids from D. bonvalotii by repeated CC of alkaloid fraction on silica gel H using cyclohexane: acetone (5:1 to 1:1) followed by PTLC on silica gel plates by petroleum: acetonitrile.
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(75:25:2)] (22). Weda et al separated six norditerpenoid alkaloids from *D. elatum* by CC on silica gel eluting with a gradient system of hexane; diethyl ether saturated with 28% ammonia. They purified subfractions by repeated CC with chloroform: methanol (0–10%) saturated with 28% ammonia (43). Yang et al separated alkaloids from *D. ajacis* by silica gel column chromatography with chloroform: methanol (100:0, 100:1, 100:2, 100:3, 100:4, 100:5, 100:6) followed by HPLC on an ODA column using acetonitrile: water with different ratios (7).

**Biological activity of alkaloids isolated from Delphinium sp.**

As mentioned before, alkaloid compounds are the most investigated and discovered chemical components of *Delphinium* sp. Diterpenoid alkaloids isolated from the plant of *Delphinium* species are mainly C18, C19, and C20 diterpenoids. Medicinal chemists have received considerable attention for their diverse pharmacological potentials, including antiarrhythmic, arrhythmogenic, neurotropic, analgesic, anti-inflammatory, muscular relaxant, hypotensive, local anesthetic, and psychotopic spasmylytic activities. These researchers have subdivided these alkaloids into two groups according to their diverse effects, varying from poisonous (e.g., aconitine) to therapeutic (e.g., lappaconitine) (14,15). Interestingly, several reports on the antiproliferative properties of the diterpenoid alkaloids against cancer cells have appeared in recent years (58-62). *D. staphisagria* seeds have been observed to have pediculicide, vermin-destroying, and parasiticidal properties (63). Antibacterial activities of the plant have been repeatedly proven in several studies. Methanolic extracts of aerial parts of *D. uncinatum* have been highlighted against gram positive bacterial strains (*Bacillus cereus* and *Staphylococcus aureus*) with higher efficiency against *B. cereus*, *E. coli*, and *S. aureus* (64). *D. brunonianum* Royle, a plant indigenous to Afghanistan, has previously been reported as an antibacterial herb that affects *S. aureus*, *E. coli*, *B. subtilis*, and *P. aeruginosa* strains (65). Suresh et al synthesized silver nanoparticles (AgNPs) from water extracts of *D. denudatum* roots. Subsequently, they provided evidence to declare that these green synthesized AgNPs had antibacterial properties against four strains of bacteria such as *S. aureus*, *B. cereus*, *E.
coli, and P. aeruginosa, together with destroying effect on Aedes aegypti larvae (66). 8-Acetylheterophyllisine, vilmoreinone, panicutine are three diterpenoid alkaloids that revealed potential antifungal properties against four types of disease-caused by fungi (16). A study by Kolar et al revealed different phenolics, flavonoids, and alkaloid components in the roots, stems, and leaves of D. malabaricum. Furthermore, the authors have highlighted that the root had higher antioxidant activity than the other parts of the plant, which might be attributed to alkaloids (67). Alhalil and colleagues did another antifungal study of the aerial parts of Delphinium species. It was reported that isolated diterpenoid alkaloids including Hydrodavisine, Delcarpum, Delphitidine, and Peregrine from D. Peregrinum eriocarpum revealed antifungal activity (68). Kolak et al isolated eight norditerpene alkaloids from the root extracts of D. linearilobum. Further experiments clarified that all the diterpenoid alkaloids possess radical scavenging capacity (24). There are multiple pieces of evidence suggesting the effects of Delphinium isolates on CNS. Four studies performed by Raza et al indicated anticonvulsant activities of the root extracts obtained from D. denudatum. In 2001, they carried out an experiment to derive ethanolic and aqueous extracts of dried roots of D. denudatum, and reported that ethanolic extract showed weaker dose-dependent anticonvulsant activity on epileptic seizures; however, aqueous extract of the roots significantly displayed anticonvulsant property. Accordingly, they proposed further studies to affirm these anticonvulsant effects and description of underlying mechanism (69). Based on these results, the study implied a remarkable inhibiting effect of this fraction on sustained repetitive firing in hippocampal neurons similar to phenytoin. Moreover, further investigations unraveled the interaction of aqueous fraction with both inactive and resting state of the Na+ channels compared to phenytoin. This anticonvulsant drug binds to the sodium channel during an inactive state (70). Afterward, they tried to conduct a study to purify aqueous fraction of D. denudatum roots, so-called FS-1 subfraction, and assessing the effect of this subfraction on mouse models of induced seizure. According to their obtained data, FS-1 subfraction had compounds that significantly decreased the onset of seizure in mice, suggesting the strong anticonvulsant property of the compounds in FS-1 subfraction extracted from D. denudatum roots (71). Two years later, they investigated the effect of FS 1 subfraction of D. denudatum on SRF (sustained repetitive firing) in cultured neonatal rat hippocampal pyramidal neurons in vitro compared to phenytoin. Interestingly, they could prove that FS-1 subfraction had compounds, which have suppressing effects on SRF of their tested neurons similar to phenytoin and could act as a potent antiepileptic agent (18). Isotalatazidine hydrate isolated from the aerial parts of D. denudatum has been unraveled to block AChE competitively and BChE enzymes, implying this isolate is an efficient cholinesterase inhibitor a therapeutic agent for Alzheimer disease (72). The other activity of D. denudatum on CNS was observed in Abid et al. They identified that hydroalcoholic isolates extracted from D. denudatum root and Amaranthus spinosus leaves could have potential antianxiety activities in experimental rats. However, the results showed that A. spinosus was more potent than D. denudatum (73). Some studies have shown that D. denudatum extracts may act against morphine-induced tolerance and dependence symptoms via reducing morphine withdrawal syndrome signs could be an alternative therapy for morphine de-addiction (74-76).

Hair loss is a complication that has been proven to be treated by using seed extracts of D. staphisagria; however, the underlying mechanism was not known until Kopral and Bostancıoğlu reported that water and vinegar extract of D. staphisagria seeds could promote the hair growth by increasing the proliferation of human keratinocyte cells and inducing the angiogenesis in-vitro (77). The anti-inflammatory activity of isolated compounds from the root extract of D. tatsienense was examined by Yin et al. The isolated compounds comprising vakognavine-type C20-DA tatsiadiene C and lycaconitine-type C19-DAs tatsiadienes A and B were observed to display the inhibitory activity on NO production in vitro experiments. Although they had not remarkable inhibitory activities (78). The cytotoxic activity of herbaceous plant D. aemulans was checked. The isolated diterpene alkaloids showed significant cytotoxic activity in comparison with the positive control group (79). Table 3 lists the medicinal applications of Delphinium species.

Toxic activity of alkaloids isolated from Delphinium species
Ample evidence indicates the poisoning and toxic effects of Delphinium sp. to different mammalians (8,9,80). A vast body of literature implies that the toxic effects of different species of this genus mainly occur due to their alkaloid components. Pfister et al showed that young D. glaucescens leads to death loss in grazing cattle due to the high alkaloid compounds in these plants (80). Gardner and Pfister reported that the toxic alkaloids were isolated from D. nuttallianum, D. andersonii, and D. geyeri in North America, including methyllycaconitine, nudicauline, and geyerline compounds (7). They also asserted that toxic alkaloid concentrations ≥ 3 mg/g could risk death to grazing cattle, and all their investigated plants contained more than 3 mg/g of poisonous alkaloid content (81). Pfister et al suggested that the cattle should be returned to the area when alkaloid concentrations decreased to 3 mg/g during pod shatter (38). Manners et al examined 14 different norditerpenoid alkaloids of Delphinium sp. related to cattle intoxication. They reported that the tertiary nitrogen atom, the esterified anthranilic acid, and variation in C-14 functionality of the poisonous alkaloids are the key factors in toxic effects (82). Delphinium
Table 3. Medicinal application of different Delphinium species

| Delphinium species | Biological activity | Used part/ constituents | Affected in vitro/in vivo model | Ref. |
|--------------------|---------------------|-------------------------|---------------------------------|------|
| D. Staphisagria    | Pediculicide, vermin-destroying, and parasitical | Seed extracts | Lice, parasites, and vermins | (63) |
| D. uncinatum       | Antibacterial       | Methanolic extracts of aerial parts | Gram-positive bacterial strains (B. cereus and S. aureus) and gram-negative bacterial strains (E. coli and K. pneumonia); Higher efficiency against B. cereus, E. coli, and S. aureus | (64) |
| D. brunonianum Royle | Antibacterial     | Herba                  | S. aureus, E. coli, B. subtilis, and P. aeruginosa strains | (65) |
| D. denudatum       | Antibacterial and insecticide | Silver nanoparticles (AgNPs) synthesized from water extracts roots | S. aureus, B. cereus, E. coli, and P. aeruginosa. Aedes aegypti larvae | (66) |
| D. staphisagria    | Parasiticidal      | Flavonoid compounds isolated from the aerial parts | Trypanosoma cruzi | (63) |
| D. denudatum       | Antifungal         | diterpenoid alkaloids: 8-acetylhetophyllisine, vilmorrianone, panicutine | Disease caused by fungi | (16) |
| D. Peregrinum eriocarpum | Antifungal activity | diterpenoid alkaloids including Hydrodavisine, Delcarpum, Delphitisine, and Peregrine | in vitro | (68) |
| D. malabaricum     | Antioxidant activity | Phenolics, flavonoids, and alkaloid components in the roots, stems, and leaves of the plant | DPPH free radical-scavenging assay and Ferric reducing antioxidant power assay (FRAP assay) | (67) |
| D. linearilobum    | Antioxidant activity | Norditerpene alkaloids from the root extracts | DPPH free radical-scavenging assay | (24) |
| D. denudatum       | Anticonvulsant     | Ethanolic and aqueous extracts of dried roots | CF-1 mice and neonatal rat hippocampal pyramidal neurons | (71) |
| D. denudatum       | Cholinesterase inhibitor | Isotalatazidine hydrate isolated from the aerial parts | In vitro enzyme inhibition assay | (72) |
| D. denudatum       | Antianxiety        | Hydroalcoholic isolates of root extract | Rat | (73) |
| D. denudatum       | Morphone-induced tolerance and dependence symptoms and by reducing morphine withdrawal syndrome | Root extract | Mice | (74-76) |
| D. staphisagria    | Promote the hair growth | Seed extract | Human keratinocyte cells | (77) |
| D. tatsienense     | Anti-inflammatory   | vakognavine-type C2D-DA tatsiedine C and lycacovine-type C19-DAs tatsiedines A and B | LPS-stimulated RAW 264.7 macrophages | (78) |
| D. aemulans        | Cytotoxic activity  | Aerial part extract | | (79) |

alkaloids inhibit muscular action potential formation, decrease synaptic functionality and block neuromuscular transmission probably by antagonizing nicotinic receptors (10). On the contrary, Raza et al reported that the isolated subfractions from these plants with anticonvulsant activity were safe at the doses lower than 100 mg/kg with no significant change in behavior and neurotoxic activities (83). Some studies have introduced different ways of noninvasive samples collection from poisoned animals and suggested developing immunological techniques such as enzyme-linked immunosorbent assays (ELISA) to diagnose the animals intoxicated by alkaloid components of Delphinium sp. (84,85). Here (Figure 2), we summarized Delphinium sp. toxic effects in animals and humans.

In cattle, Welch et al conducted a study using Hereford steers administered with different doses of D. barbeyi. According to their data, the toxic effects of methyllycaconitine occurred when the serum levels of this alkaloid reached 355 ng/mL. They suggested that the consumption of 1.25 kg-day of D. barbeyi by a 500-kg steer did not lead to severe intoxication (86). On the other hand, the poisonous impacts of D. barbeyi appear to be also age-dependent. A study revealed that this species’ oral consumption of yearling Angus steers had more significant toxic effects than two years of animals (87).

Moreover, the susceptibility of cattle to standardized amounts of D. barbeyi seems to be also sex-dependent. Yearling Angus heifers are more susceptible to Delphinium sp. alkaloids than steers and bulls (88). The cattle that consume D. andersonii during the growing season are
generally at risk of death. Yearling heifers consume more than mature cattle and are more susceptible to plant intoxication (89). Toxicokinetics studies of *D. andersonii* with alkaloid constituents include MLA, geyerline, nudicauline, and 16-deacetylgeyerline in Angus steer, showed severe toxicities occur about 18 hours after consumption (90). Therefore, the animals are better to examined for at least 36 hours after the first consumption.

The MSAL-type alkaloids in *Delphinium* sp. were more toxic to cattle and mice 24 hours after treatment; thus, this type of alkaloid might be responsible for the lethal effects of the plant (91). However, non-MSAL-containing plants have a shallow risk for poisoning cattle, and consuming more than 70% of non MSAL containing diet was required to poison the cattle (92). Welch et al claimed decreased ratio of MDL- to MSAL-type alkaloids in cattle intoxication; however, less poisonous MDL-type alkaloids could lead to the more severe toxicity of the MSAL-type alkaloids. Therefore, estimating the concentrations of MSAL-type alkaloids and the total alkaloids is required to assess the relative toxicity of tall larkspurs (5,6). Pfister et al also affirmed that MDL-type alkaloids have a prominent role in poisoning properties of *Delphinium* sp. and may potentiate cattle intoxication (93). Green et al examined the alkaloid content of *D. nuttallianum* and *D. andersonii*. This alkaloid profile did not influence the kinetic parameters. However, they suggested examining the types and concentration of these chemical compounds are necessary to determine the risk of plant intoxication in cattle (94). Interestingly, administering an anticholinesterase inhibitor, physostigmine, to grazing cattle could rapidly reverse the toxic effects of larkspurs (95). Results of a previous investigation have established that MSAL-type alkaloids increase heart rate in cattle, but physostigmine and another anticholinesterase inhibitor, neostigmine, could reverse adverse effects of these alkaloids on cardiac function (96).

In 1991, Olsen and Sisson designed a study to establish an appropriate laboratory animal model in mice, hamsters, rats, and sheep. They found that mice were the best model to measure the toxicity of larkspur because these animals showed high susceptibility, immediate response time, and needed small doses for delivering the response (97). MLA is an MSAL-type diterpenoid alkaloid with toxic effects in larkspurs. There is an investigation of the clinical impacts of MLA intoxication and its excretion in mice. The results showed that MLA is immediately distributed in the body and excreted. It could cause CNS-related disorders such as convulsions, abnormal muscle contraction, and dyspnea (98).

*Delphinium barbeyi* plants have high concentrations of norditerpenoid alkaloids deltalone 14-O-acetyldictyocarpine (14-OAD), which both are MDL-type alkaloids compounds. As previously described in the case of cattle, consumption of MDL-type alkaloids in addition to MSAL-types exerts an additive adverse effect on MSAL-type alkaloid intoxication in mice (99). However, *Delphinium* sp. containing MSAL-type alkaloids has more toxic effects on mice and cattle, suggesting more severe death by consuming these plants (91). Some species of *Delphinium* have various harmful effects on different animals. For example, *D. stachydeum* exerts lower toxic effects on mice than *D. barbeyi* and *D. occidentale* because this species has only MDL-type alkaloids. However, it severely affects the heart rate and time of exercise in cattle compared with *D. occidentale* (100).

In the case of toxicity reported in sheep and goats, *Toxicoscordion venenosum* is a species of the Melanthiaceae family that cause toxicosis-related symptoms such as cardiovascular failure and muscle weakness in sheep. However, the study results affirmed that co-treatment of *Delphinium* sp. with this species could not exert additive toxic effects in these animals. This suggests that sheep are resistant to acute poisoning with *Delphinium* species (101). There appear to be some reasons for the difference in susceptibility between sheep, goats, and cattle to larkspur. One probable description could originate from variations in the toxicokinetics of the toxic alkaloids. For example, cattle absorb more poisonous alkaloids, and these chemicals are more bioavailable in cattle than the sheep and goats. High concentrations in the neuromuscular junctions cause an increased blocking of the nicotinic acetylcholine receptors (nAChR) and worsening the toxic effects. The other cause for this difference may arise from the lower binding affinity of the poisonous alkaloids for nAChRs in sheep compared to cattle (102). A study by Welch et al. indicated that the oral consumption of *D. barbeyi* by the goat is more effective in eliciting toxicities than the injection of its alkaloid extracts such as deltalone and MLA to the animal. A possible reason for this
effect may form flip-flop kinetics of deltaline and MLA contained in the plant, the kinetic that leads to a slower absorption rate of alkaloids than the rate of elimination (103).

Delphinium sp. toxic effect on humans is rare; Tomassoni et al in 1996 reported the first case of a teenager with ventricular tachycardia and convulsion, who consumed 1 gram of Delphinium root (104). The other case was a 13-year-old girl poisoned by drinking about 250 mL of D. peregrinum solution to treat migraine. She had clinical symptoms, including confusion, low respiration rate (eight breaths per minute), areflexia, and headache (105).

Conclusion
Diterpenoid alkaloids are the most investigated and the major chemical components of Delphinium species and are possibly responsible for both toxic and medicinal effects of this genus. Although phytochemical, biological, and toxicological studies on the alkaloidal extract, fractions, and chemical constituents of Delphinium sp. have attracted considerable interest, some points need more explanation. First, the biological activity of most of the isolated alkaloids wasn’t evaluated. Second, all of the biological activities of the isolated alkaloids were investigated by using in vitro tests and rarely have done in vivo animal models or on their pharmacological mechanisms. To date, there is no clinical trial examining the effects of safer doses of the plant or its isolated compounds on humans, and this lack of information does not allow us to fully comprehend the beneficial medicinal impacts of this genus and comparing its various species together. Accordingly, further preclinical and clinical experiments are required to thoroughly understand all aspects of the toxic and medical influences of the plant.

Limitation of the study
It is a short narrative review describing phytochemistry and biological data of Delphinium sp., which does not cover all of the data extracted so far about them. On the other hand, there are about 365 Delphinium species worldwide, but the natural compounds of only 87 species and 10 varietal have been investigated in the last decades. The natural chemical constituents of many of Delphinium species remain unexploited. Most of the medicinal activities of the Delphinium-derived constituents were also discovered by applying in vitro tests, and there is not many studies in animal models.

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Authors’ contributions
Supervision, conceptualization, and methodology: GM; investigation and original draft preparation: LM; writing-review and editing: LM, MPM, ASA, and KF.

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The authors declare that they have no conflict of interest.

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