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The Genus *Galanthus*: A Source of Bioactive Compounds

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1. Introduction

The Amaryllidaceae family is one of the 20 most important alkaloid-containing plant families (Zhong, 2005). It comprises about 1100 perennial bulbous species classified in 85 genera, distributed throughout the tropics and warm temperate regions of the world (Willis, 1988). The specific alkaloids produced by the amaryllidaceous plants have attracted considerable attention due to their interesting pharmacological activities. One of them, galanthamine, is a long acting, selective, reversible and competitive inhibitor of the acetylcholinesterase enzyme (Thomsen *et al.,* 1998), which is marketed as a hydrobromide salt under the name of Razadyne® (formerly Reminyl®) and Nivalin® for the treatment of Alzheimer's disease, poliomyelitis and other neurological diseases (Heinrich and Teoh, 2004). After its discovery in *Galanthus woronowii* by Proskurina and co-authors in 1955 (Proskurina *et al.,* 1955), the pharmacological properties of galanthamine soon attracted the attention of the pharmaceutical industry. It was first produced by Sopharma (Bulgaria) under the name of Nivalin® from *G. nivalis* in the early 1960s, but due to the small plant size and variability of galanthamine content, this species was soon replaced by other plant sources (Berkov *et al.,* 2009*b*).

The genus *Galanthus* (Snowdrop; Greek *gála* "milk", *ánthos* "flower") comprises about 19 species (World Checklist of Selected Plant Families), and to our knowledge 11 have been investigated for their alkaloid content. Although the genus has only been partially studied, phytochemical work has revealed an exceptional diversity of alkaloid structures, many of them reported for the first time and with still unknown bioactivity. The present article provides a brief overview of the phytochemical studies within the genus *Galanthus*.

2. Geographical distribution, taxonomical aspects and ecology of *Galanthus*

The genus *Galanthus* L. is distributed around Europe, Asia Minor and the Caucasus region. The limits of its area of distribution are the Pyrenees in the west, the Caucasus and Iran in the east, and Sicily, the Peloponnese and Lebanon in the south. The northern distribution limit cannot be assessed due to human introduction and cultivation (Davis, 1999). Some

species are widespread, while others are restricted to small areas. *G. nivalis,* for example, is native to a large area of Europe, stretching from the Pyrenees to Italy, Northern Greece, Ukraine, and European Turkey, while *G. trojanus* is a rare plant in the wild, found in a single location (an area less than 10 km²) in western Turkey (Davis and Ozhatay, 2001). Turkey is the country where most species (14) are geographically concentrated (Ünver, 2007).

All species of *Galanthus* are perennial, herbaceous plants that grow from bulbs. They have two or three linear leaves and an erect, leafless scape. The scape bears a pair of bract-like spathe valves at the top, from which emerges a solitary, bell-shaped white flower, held on a slender pedicel. The flower of *Galanthus* consists of six tepals, the outer three being larger and more convex than the inner series. The inner flower segments are marked with a green, or greenish-yellow, bridge-shaped mark at the tip of each tepal. The ovary is three-celled, ripening into a three-celled capsule. Each whitish seed has a small, fleshy tail (elaiosome) containing substances attractive to ants, which distribute the seeds (Davis, 1999). The genus *Galanthus* is closely related to the genus *Leucojum* L. but its plants can be easily distinguished because *Leucojum* has flowers with six equal tepals, from 2 to 6-7 flowers per scape and several leaves (Meerow and Snijman, 1998).

Species of the genus *Galanthus* L. (Amaryllidaceae) are difficult to distinguish and classify because of a lack of clearly definable morphological characteristics and a high level of variability. The search for other useful systematic information has produced little consensus in the enumeration of the species, divisions within the genus and relationships among their various components (Davis and Barnet, 1997). Besides morphological features, cariological (Kamari, 1981), anatomical (Davis and Barnet, 1997) and DNA (Zonneveld *et al.,* 2003) methods have been used to clarify the taxonomy of the genus.

It is generally accepted that the genus *Galanthus* comprises 19 species, 6 varieties and 2 natural interspecies hybrids (World Cheklist of Selected Plant Families):

1. *Galanthus alpinus* Sosn., Vestn. Tiflissk. Bot. Sada 19: 26 (1911).
   Galanthus alpinus var. alpinus.
   Galanthus alpinus var. bortkewitschianus (Koss) A.P.Davis, Kew Bull. 51: 750 (1996).
2. *Galanthus angustifolius* Koss, Bot. Mater. Gerb. Bot. Inst. Komarova Akad. Nauk S.S.S.R. 14: 134 (1951).
3. *Galanthus cilicicus* Baker, Gard. Chron. 1897(1): 214 (1897).
4. *Galanthus elwesii* Hook.f., Bot. Mag. 101: t. 6166 (1875), nom. cons.
   Galanthus elwesii var. elwesii
   Galanthus elwesii var. monostictus P.D.Sell in P.D. Sell & G.Murrell, Fl. Great Britain Ireland 5: 363 (1996).
5. *Galanthus fosteri* Baker, Gard. Chron., III, 5: 458 (1889).
6. *Galanthus gracilis* Celak., Sitzungsber. Königl. Böhm. Ges. Wiss., Math.-Naturwiss. Cl. 1891(1): 195 (1891).
7. *Galanthus ikariae* Baker, Gard. Chron. 1893(1): 506 (1893).
8. *Galanthus koenenianus* Lobin, C.D.Brickell & A.P.Davis, Kew Bull. 48: 161 (1993).
9. *Galanthus krasnovii* Khokhr., Byull. Moskovsk. Obshch. Isp. Prir., Otd. Biol., n.s., 68(4): 140 (1963).
10. *Galanthus lagodechianus* Kem.-Nath., Zametki Sist. Geogr. Rast. 13: 6 (1947).
11. *Galanthus nivalis* L., Sp. Pl.: 288 (1753).
12. *Galanthus peshmenii* A.P.Davis & C.D.Brickell, New Plantsman 1: 17 (1994).

13. *Galanthus platyphyllus* Traub & Moldenke, Herbertia 14: 110 (1948).
14. *Galanthus plicatus* M.Bieb., Fl. Taur.-Caucas., Suppl.: 225 (1819).
15. *Galanthus reginae-olgae* Orph., Atti Congr. Int. Bot. Firenze 1874: 214 (1876).
    Galanthus reginae-olgae subsp. reginae-olgae.
    Galanthus reginae-olgae subsp. vernalis Kamari, Bot. Jahrb. Syst. 103: 116 (1982).
16. *Galanthus rizehensis* Stern, Snowdrops & Snowflakes: 37 (1956).
17. *Galanthus transcaucasicus* Fomin, Opred. Rast. Kavk. Kryma 1: 281 (1909).
18. *Galanthus trojanus* A.P.Davis & Özhatay, Bot. J. Linn. Soc. 137: 409 (2001).
19. *Galanthus woronowii* Losinsk. in V.L.Komarov (ed.), Fl. URSS 4: 749 (1935).
20. *Galanthus* × *allenii* Baker, (*G. alpinus* × *G. woronowii*) Gard. Chron., III, 9: 298 (1891).
21. *Galanthus* × *valentinei* Beck, (*G. plicatus* × *G. nivalis*) Wiener Ill. Gart.-Zeitung 19: 57 (1894).

The habitats of *Galanthus* species are varied, ranging from undisturbed broad-leaved or coniferous woodlands of, for example oak (*Quercus* spp.), beech (*Fagus orientalis*), maple (*Acer* spp.), pines (*Pinus* spp.), Cilician fir (*Abies cilicia*), and cedar of Lebanon (*Cedrus libani*), woodland edges, river banks, scrub, grassland, amongst large rocks, and pockets of soil on rocks and cliff faces. *G. peshmenii* can sometimes be found only 10 m from the sea-shore on Kastellorhizo, a typical hot and dry Aegean island. In contrast, *G. platyphyllus* is a plant of the subalpine to alpine zone, and occurs mainly at altitudes of 2,000 - 2,700 m in alpine grasslands and meadows above the tree-line and at the edges of high-altitude woodlands (Davis, 1999). Typically, the *Galanthus* species are winter-to-spring flowering plants, but some species, like *G. cilicicus*, *G. peshmenii* and *G. reginae-olgae*, flower in autumn.

G. nivalis and *G. elwesii* are two of the best known and most frequently cultivated bulbous plants. Their popularity is due to their beauty, longevity and because they flower when little else is in season. A vast number of cultivars and clones are available (Davis, 1999). Huge numbers of wild-collected bulbs are exported annually from Turkey. In the early 1980s onwards this trade increased, with many millions of *G. elwesii* bulbs being exported via the Netherlands. The large numbers of *Galanthus* bulbs coming into commerce caused great concern because it was uncertain whether the collection of bulbs in such high numbers was sustainable. For this reason, *Galanthus* was placed on Appendix II of CITES in 1990. The wild harvesting of *G. elwesii* bulbs is now carefully controlled and monitored, and export quotas are set each year. Some snowdrop species are threatened in their wild habitats, and in most countries it is now illegal to collect bulbs from the wild. Under CITES regulations, international trade in any quantity of *Galanthus*, whether bulbs or plants, live or dead, is illegal without a CITES permit. This applies to hybrids and named cultivars as well as species. CITES does, however, allow a limited trade in wild-collected bulbs of just three species (*G. nivalis*, *G, elwesii* and *G. woronowii*) from Turkey.

3. Biosynthesis and structural types of Amaryllidaceae alkaloids

A particular characteristic of the Amaryllidaceae plant family is a consistent presence of an exclusive group of isoquinoline alkaloids, which have been isolated from plants of all the genera of this family. As a result of extensive phytochemical studies, over 500 alkaloids have been isolated from the amaryllidaceous plants (Zhong, 2005). The Amaryllidaceae type alkaloids have been structurally classified into nine main subgroups, namely lycorine, crinine, haemanthamine, narciclasine, galanthamine, tazettine, homolycorine, montanine

and norbelladine (Bastida *et al.,* 2006). In the genus *Galanthus*, however, two new structural subgroups, graciline and plicamine type alkaloids, have been found (Ünver, 2007). The following new subgroups have also been reported: specific augustamine-type structures in *Crinum kirkii* (Machocho *et al.,* 2004), a carboline alkaloid in *Hippeastrum vittatum* (Youssef, 2001), mesembrane (*Sceletium*)-type compounds in *Narcissus pallidulus* and *N. triandrus* (Bastida *et al.,* 2006), and phtalideisoquinoline-, benzyltetrahydroisoquinoline- and aporphine-type alkaloids in *G. trojanus* (Kaya *et al.,* 2004*b,* 2011). Mesembrane-type compounds are typical of the genus *Sceletium* of the Aizoaceae, while phtalideisoquinoline-, benzyltetrahydroisoquinoline- and aporphine-type alkaloids are found in the Papaveraceae, both families being dicotyledonous. Tyramine-type protoalkaloids, which are biosynthesized in Poaceae, Cactaceae, some algae and fungi, have also been found in *Leucojum* and *Galanthus* species (Berkov *et al.,* 2009*a,* 2011).

Amaryllidaceae alkaloids are formed biogenetically by intramolecular oxidative coupling of norbelladines derived from the amino acids L-phenylalanine and L-tyrosine (Bastida *et al.,* 2006). The key intermediate metabolite is *O*-methylnorbelladine. *Ortho-para´* phenol oxidative coupling of *O*-methylnorbelladine results in the formation of a lycorine-type skeleton, from which homolycorine-type compounds proceed. The galanthamine-type skeleton originates from *para-ortho´* phenol oxidative coupling. *Para-para´* phenol oxidative coupling leads to the formation of crinine, haemanthamine, tazettine, narciclasine and montanine structures (Bastida *et al.,* 2006). In the present article, for the structures reported by different authors we have adopted the numbering system according to Bastida *et al.,* (2006, Fig. 1).

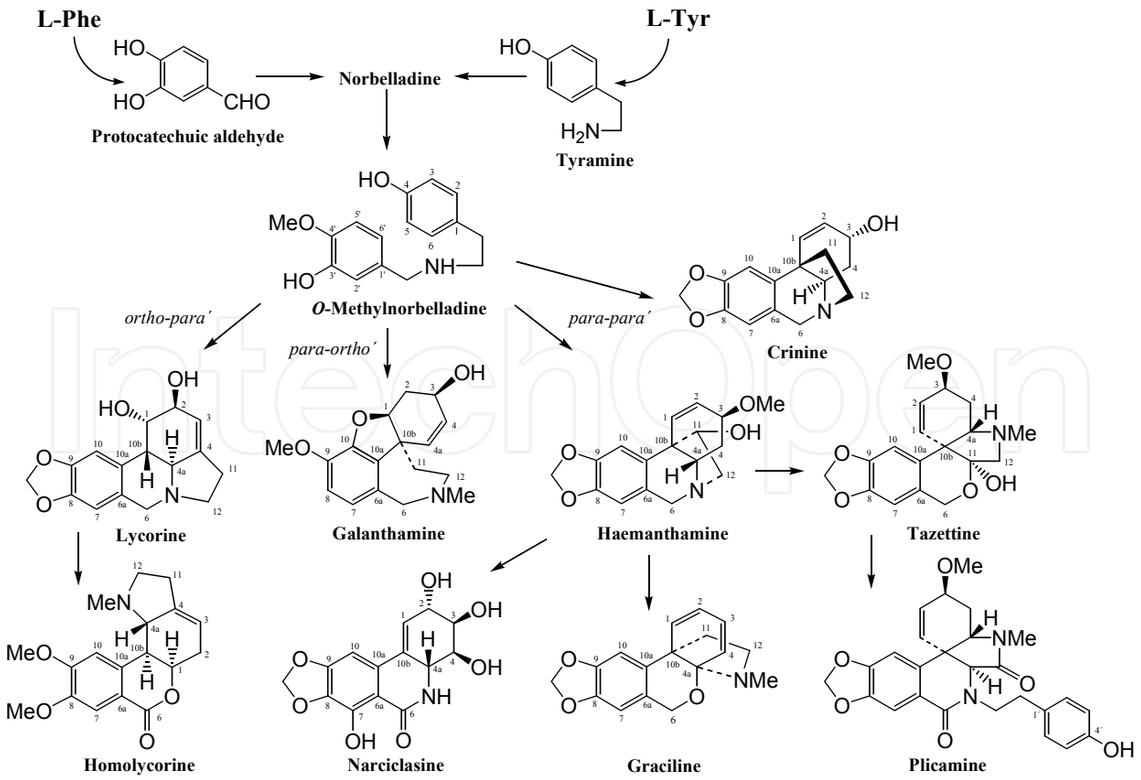


Fig. 1. Biosynthetic pathway of *Galanthus* alkaloids with representative compounds.

The biogenetic pathway of gracilines possibly originates from the 6-hydroxy derivatives of haemanthamine-type species (Noyan *et al.,* 1998), while plicamine-type alkaloids most probably proceed from tazettine-type compounds, considering their structural similarities (Ünver *et al.,* 1999*a*).

4. Distribution of alkaloids in the genus *Galanthus*

The phytochemical studies of the genus *Galanthus* started in the early fifties of the last century. Two of the first alkaloids reported for the genus were galanthine (Proskurina and Ordzhonikidze, 1953) and galanthamine (Proskurina *et al.,* 1955), which were isolated from *G. voronowii*. To the best of our knowledge, eleven species from the genus *Galanthus* have been phytochemically studied to date and ninety alkaloids have been found and classified in 11 structural types (Table 1, Fig.2).

Until recently, the distribution of alkaloids within the genus has been studied by classical phytochemical approaches. The collected biomass is extracted with alcohol, the neutral compounds removed at low pH and the alkaloids fractionated after basification of the extract. Individual alkaloids have been separated by column chromatography, preparative TLC, prep. HPLC, etc., and identified by spectroscopy, mainly 1D and 2D NMR. The GC-MS technique has proved to be very effective for rapid separation and identification of complex mixtures of Amaryllidaceae alkaloids obtained from low mass samples (Kreh *et al.,* 1995). Thus, the assessment of alkaloid distribution at species, populational and individual levels and the detection of new compounds have become much easier and faster (Berkov *et al.,* 2007*a*, 2009*c*, 2011).

An overview of the literature indicates that the genus *Galanthus* is a very rich source of novel compounds. Thirty-seven alkaloids (namely **12**, **22**, **26**, **29**, **34-39**, **46-49, 53, 56-58, 62, 67, 69-75, 77-86**) or *ca.* 40% of all identified compounds from the genus have been isolated for the first time from *Galanthus*. What is more, the biochemical evolution of the genus has led to the occurrence of two specific subgroups, namely graciline- and plicamine-type alkaloids.

The most studied species are *G. nivalis* and *G. elwesii*. Due to taxonomical changes over the years, the information on the alkaloids of *G. nivalis* is confusing. Thus, until 1966, only one *Galanthus* species had been recognized in Bulgaria, namely *G. nivalis* L. (Jordanov, 1964). This taxon was subsequently separated into *G. nivalis* L. and *G. elwesii* Hook. (Kozuharov, 1992). At present, it is unclear which plant species the alkaloids isolated in the early sixties from Bulgarian *G. nivalis* can be attributed to (Valkova, 1961; Bubeva-Ivanova and Pavlova, 1965). Kaya *et al.* (2004*b*) have reported five alkaloids for *G. nivalis* L. subsp. *silicicus* (Baker) Guttl.-Tann., a taxon regarded as a synonym of *G. silicicus* Baker by other authors (Davis and Barnett, 1997; Davis, 1999). A recent revelation has substantiated that *G. nivalis* subsp. *cilicicus* is identical to the newly introduced species, G. *trojanus* A. P. Davis and N. Özhatay, a plant species endemic to Northwestern Turkey (Davis and Özhatay, 2001).

Latvala *et al.,* (1995) isolated 18 alkaloids (6 new) from *G. elwesii* in addition to the already reported flexinine, elwesine, tazettine and haemanthamine (Boit and Ehmke, 1955; Boit and Döpke, 1961). The occurrence of elwesine (**26**) in the genus is particularly interesting. This compound displays a β-configuration of its 5,10b-ethano bridge, which is typical of the South African representatives of the family (Viladomat *et al.,* 1997). Although widely

accepted that *G. nivalis* was the industrial source of galanthamine (in Bulgaria) during the 1960s (Heinrich and Teoh, 2004), later studies on 32 Bulgarian populations of *G. nivalis* and *G. elwesii* indicate that the distribution of this important compound is limited to a few populations of *G. elwesii*, while just one population of *G. nivalis* has been found to contain galanthamine and only as a minor alkaloid (Sidjimova *et al.,* 2003; Berkov *et al.,* 2011). These studies, however, have also shown a great intra-species diversity of alkaloid synthesis in *G. nivalis* and *G. elwesii.* The populations displayed between 6 and 31 alkaloids in their alkaloid patterns and about 70 compounds have been detected in total. Many of them were left unidentified due to the lack of reference spectra, possibly indicating new structures. This biochemical diversity has led to the isolation of eight more new alkaloids from these well-studied species, after the collection of plant material from populations proven by GC-MS to be a rich source of unknown compounds (Berkov *et al.*, 2007*a*, 2009*c*). Interestingly, many of the *G. elwesii* populations have accumulated the tyramine-type protoalkaloids as major compounds (up to 99 % of all alkaloids). In addition to the tyramine chemotype, homolycorine, lycorine haemanthamine and galanthamine chemotypes have also been found in the studied populations of *G. elwesii*. A galanthamine chemotype population was also found for *G. nivalis*, but in contrast with *G. elwesii*, this *G. nivalis* population accumulated the 4,4a-dihydrogenated derivatives of galanthamine (**12**), lycoramine (**16)** and its isomer (**17**) (Berkov *et al.,* 2011).

As well as a high level of alkaloid diversity and the existence of different chemotypes among the species populations, *G. elwesii* and *G. nivalis* have also shown some important differences in their alkaloid patterns, at least in the studied Bulgarian populations. A study of sympatric populations, and 32 populations from both species showed that the alkaloid pattern of *G. nivalis* is dominated by compounds coming from a *para–para´* oxidative coupling of *O*-methylnorbelladine (haemanthamine- and tazettine-type alkaloids, Fig. 1). The conjugated and free lycorine-type alkaloids proceeding from an *ortho–para´* oxidative coupling were relatively less abundant. Homolycorine-type alkaloids were not detected in this plant species. In contrast to *G. nivalis*, the alkaloid pattern of *G. elwesii* was dominated mainly by compounds coming from *ortho–para´* oxidative coupling: free lycorine- and homolycorine-type alkaloids. The synthesis of *para–para´* oxidative products in *G. elwesii* is relatively weak (only haemanthamine- and no tazettine-type compounds, Berkov *et al.,* 2008, 2011). In total, 46 and 38 alkaloids have been identified in *G. elwesii* and *G. nivalis,* respectively.

In a study on sympatric *G. nivalis* and *G. elwesii* populations, it was found that the organs of the plants presented different alkaloid patterns (Berkov *et al.,* 2008). Thus, the predominant alkaloids of *G. nivalis* roots were found to belong to the lycorine and tazettine structural types, bulbs were dominated by tazettine, leaves by lycorine and flowers by haemanthamine-type alkaloids. The predominant alkaloids in *G. elwesii* roots, bulbs and leaves were those of the homolycorine type, whereas the flowers accumulated mainly tyramine-type compounds. To the best of our knowledge, no studies of the dynamics of the alkaloid patterns during ontogenesis have been reported for either of these two species or any other *Galanthus* species. Such studies, however, may contribute to the understanding of the chemoecological role of the alkaloids in the genus *Galanthus* and the Amaryllidaceae as a whole. A remarkably high number of alkaloids conjugated with 3-hydroxybutyryl moieties occur in *G. nivalis*. Co-existence of free and conjugated alkaloids in the plant implies that the latter may have a chemoecological role. Such conjugated alkaloids have rarely been reported for Amaryllidaceae plants.

Compound	*G. elwesii*	*G. nivalis*	*G. plicatus*	*G. gracilis*	*G. woronowii*	*G. caucasicus*	*G. ikariae*	*G. krasnovii*	*G. reginae-olgae*	*G. trojanus*	*G. rizehensis*
I. Tyramine type											
Tyramine (**1**)	+[1]	+[1]								+[25]	
Methyltyramine (**2**)	+[1]	+[1]									
Hordenine (**3**)	+[1,2]	+[1]	+[10]								
N-feruloyltyramine (**4**)	+[2]										
II. Norbelladine											
O-Methylnorbelladine (**5**)										+[25]	
III. Narciclasine type											
Ismine (**6**)	+[1]	+[1,7]	+[11]								
N-Formylismine (**7**)			+[12]								
Trisphaeridine (**8**)	+[1]	+[1]	+[13]								
5,6-Dihydrobicolorine (**9**)			+[13]	+[15]							
Arolycoricidine (**10**)										+[25]	+[27]
Narciprimine (**11**)											+[27]
IV. Galanthamine type											
Galanthamine (**12**)	+[1,2]	+[1]			+[19]	+[22]	+[4]	+[23]	+[24]		
3-Epigalanthamine (**13**)	+[1]										
Narwedine (**14**)	+[1,2]										
N-Demethylgalanthamine (**15**)	+[1,2]										
Lycoramine (**16**)	+[1]	+[1]									
3-Epilycoramine (**17**)	+[1]	+[1]									
Sanguinine (**18**)	+[2]										
N-Formylnorlgalanthamine (**19**)	+[1]										
Leucotamine (**20**)	+[1,2]										
O-Methylleucotamine (**21**)	+[2]										
Nivalidine (**22**)	+[3]	+[8]									
V. Haemanthamine type											
Buphanisine (**23**)	+[1,4]										
Vittatine/crinine (**24**)	+[1,5]								+[24]	+[26]	
Flexinine (**25**)	+[6]										
Elwesine (**26**)	+[6]										
Hamayne (**27**, 3-Epihydroxybulbispermine)	+[7]	+[7,9]					+[4]				
11-Hydroxyvittatine (**28**)	+[2]		+[10]							+[26]	
11-Hydroxyvittatine *N*-oxide (**29**)										+[25]	
Maritidine (**30**)	+[1]										
8-*O*-Demethylmaritidine (**31**)										+[25]	
Narcidine (**32**)										+[25]	
Haemanthamine (**33**)	+[1]	+[1]								+[25]	
11-*O*-(3′-Hydroxybutanoyl)hamayne (**34**)	+[1,7]	+[9]									
3,11-*O*-(3′,3′′-Dihydroxybutanoyl)hamayne (**35**)		+[9]									
3-*O*-(2′′-Butenoyl)-11-*O*-(3′-hydroxybutanoyl)hamayne (**36**)		+[9]									
3,11,3′-*O*-(3′, 3′′, 3′′′- Trihydroxybutanoyl)-hamayne (**37**)		+[9]									
3,3′-*O*-(3′,3′′-Dihydroxybutanoyl)hamayne (**38**)		+[7]									

Compound	*G. elwesii*	*G. nivalis*	*G. plicatus*	*G. gracilis*	*G. woronowii*	*G. caucasicus*	*G. ikariae*	*G. krasnovii*	*G. reginae-olgae*	*G. trojanus*	*G. rizehensis*
11,3′-*O*-(3′,3′′-Dihydroxybutanoyl)hamayne (**39**)		+[7]									
VI. Tazettine type											
11-Deoxytazettine (**40**)	+[1]	+[1]									
6-*O*-Methylpretazettine (**41**)	+[1]	+[1]									
Tazettine (**42**)	+[1]	+[7]	+[11]	+[15]	+[20]	+[22]	+[4]		+[24]		
Criwelline (**43**)		+[6]									
Macronine (**44**)		+[1]									
Epimacronine (**45**)		+[7]	+[11]	+[15]							
3-*O*-Demethyl-3-epimacronine (**46**)			+[13]								
3-*O*-Demethylmacronine (**47**)				+[13]							
3-*O*-(3′-Hydroxybutanoyl)tazettinol (**48**)			+[12]								
Isotazettinol (**49**)				+[13]							
VII. Lycorine type											
Anhydrolycorine (**50**)	+[1]	+[1]									
11,12-Dehydroanhydrolycorine (**51**)	+[1]	+[1]									
Caranine (**52**)		+[5]									
Galanthine (**53**)	+[1,2]	+[1]			+[21]	+[22]					
Lycorine (**54**)	+[1,2]	+[1,7]	+[14]	+[14]	+[21]	+[22]			+[24]	+[26]	
Incartine (**55**)	+[1]	+[1]									
2-*O*-(3′-Hydroxybutanoyl)lycorine (**56**)	+[1,7]	+[1]									
2?-*O*-(3′-Hydroxybutanoyl)lycorine isomer (**57**)		+[5]									
2-*O*-(3′-Acetoxybutanoyl)lycorine (**58**)		+[1,9]									
Ungeremine (**59**)		+[9]									
8-*O*-Demethylvasconine (**60**)		+[7]									
Nartazine (**61**)		+[6]									
8-*O*-Methyldihydrosternbergine *N*-oxide (**62**)										+[25]	
Dihydrolycorine (**63**)										+[25]	
VIII. Homolycorine type											
Homolycorine (**64**)	+[1]										
8-*O*-Demethylhomolycorine (**65**)	+[1,2]		+[15]	+[15]		+[22]	+[4]				
Masonine (**66**)	+[5]	+[6]									
2-Methoxy-8-*O*-demethylhomolycorine (**67**)	+[1,2]										
Hippeastrine (**68**)	+[1]	+[8]									
Galwesine (**69**)	+[1,2]										
8-*O*-Demethylgalwesine (**70**)	+[2]										
8-*O*-Demethyl-10b-hydroxygalwesine (**71**)	+[2]										
10b-Hydroxygalwesine (**72**)	+[2]										
Galasine (**73**)	+[2]										
2α-Hydroxyhomolycorine (**74**)	+[1]										
Galanthindole (**75**)			+[10]								
Neronine (**76**)									+[24]		
Galanthusine (**77**)						+[22]					
IX. Graciline type											
Graciline (**78**)				+[16]							
11-Acetoxygraciline (**79**)			+[16]								

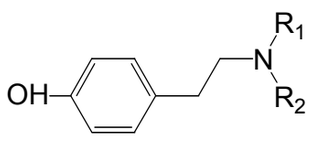
Compound	*G. elwesii*	*G. nivalis*	*G. plicatus*	*G. gracilis*	*G. woronowii*	*G. caucasicus*	*G. ikariae*	*G. krasnovii*	*G. reginae-olgae*	*G. trojanus*	*G. rizehensis*
3,4-Dihydro-3-hydroxygraciline (**80**)				+[12]							
3-Epi-3,4-dihydro-3-hydroxygraciline (**81**)				+[12]							
Digracine (**82**)				+[16]							
Gracilamine (**83**)				+[18]							
X. Plicamine type											
Plicamine (**84**)			+[17]								
Plicane (**85**)			+[12]								
Secoplicamine (**86**)			+[17]								
XI. Other											
Bulbocapnine (**87**)										+[26]	
Capnoidine (**88**)										+[26]	
Stylopine (**89**)										+[25]	
Protopine (**90**)										+[25]	

1) Berkov *et al.,* (2011); 2) Latvala *et al.,* (1995); 3) Bubeva-Ivanova and Pavlova (1965); 4) Sener *et al.,* (1998); 5) Berkov *et al.,* (2008); 6) Wildman, (1968); 7) Berkov *et al.,* (2009c); 8) Kalashnikov (1970); 9) Berkov *et al.,* (2007a); 10) Ünver *et al.,* (2003); 11) Akıneri and Günes (1998); 12) Ünver *et al.,* (2001); 13) Ünver *et al.,* (1999a); 14) Kaya *et al.,* (2004*a*); 15) Noyan (1999); 16) Noyan *et al.,* (1998); 17) Ünver *et al.,* (1999b); 18) Ünver and Kaya, (2005); 19) Proskurina *et al.,* (1955); 20) Yakovleva (1963); 21) Proskurina Ordzhonikidze (1953); 22) Tsakadze *et al.,* (1979); 23) Asoeva *et al.,* (1968); 24) Conforti *et al.,* (2010); 25) Kaya *et al.,* (2011); 26) Kaya *et al.,* (2004*b*); 27) Bozkurt *et al.,* (2010).

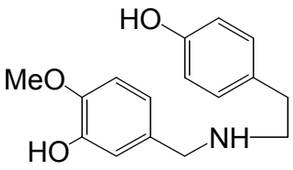
Table 1. Alkaloids reported in the genus *Galanthus*

Another two phytochemically interesting species from which a number of new alkaloids have been isolated are *G. gracilis* and *G. plicatus*. Phytochemical studies on *G. gracilis* resulted in the isolation of three novel monomeric alkaloids (**78**, **80**, **81**) and a dimeric compound (**82**) bearing a 10b,4a-ethanoiminodibenzo[b,d]pyrane skeleton, which represents a new subgroup of Amaryllidaceae alkaloids named gracilines (Fig. 1, Noyan *et al.,* 1998; Ünver *et al.,* 2001). An unusual pentacyclic dinitrogenous alkaloid, gracilamine (**83**), was also isolated from this species (Ünver and Kaya, 2005). Another new graciline-type alkaloid (**79**, Noyan *et al.,* 1998) has been isolated from *G. plicatus*, together with compounds **84**-**86** (Ünver et al., 1999*a*, 2001), representing a new subgroup of the Amaryllidaceae alkaloids where the oxygen atom at position 5 of a tazettine molecule is replaced by a nitrogen atom, conjugated with a 4-hydroxyphenethyl moiety. This new subgroup, named after the lead compound plicamine (**84**), was found later in another amaryllidaceous plant, *Cyrtanthus obliquus* (Brine *et al.,* 2002). Apart from plicamines, four new tazettine-type alkaloids (**46**-**49**) and a compound with a nonfused indole ring (**75**) have also been isolated in *G. plicatus* (Ünver *et al.,* 1999*b*, 2003). In total, 17 and 12 alkaloids have been reported for *G. plicatus* and *G. gracilis,* respectively (Table 1).

The other *Galanthus* species are relatively less studied. Four known alkaloids (**12**, **42**, **53**, and **54**), including galanthamine, have been reported for *G. woronovii* (Proskurina *et al.,* 1955; Proskurina and Ordzhonikidze, 1953; Yakovleva, 1963). A new compound, galanthusine (**78**),



1 $R_1=R_2=H$
2 $R_1=H$, $R_2=Me$
3 $R_1=R_2=Me$
4 $R_1=H$, $R_2=$ feruloyl



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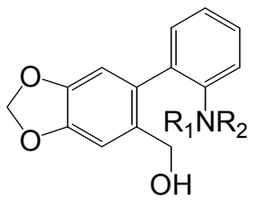
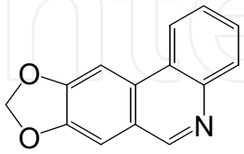


6 $R_1=H$, $R_2=Me$
7 $R_1=CHO$, $R_2=Me$



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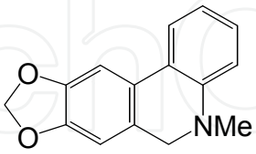

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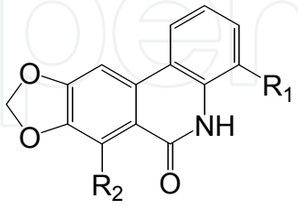
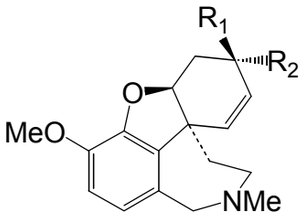
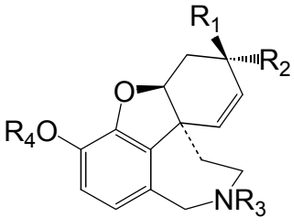


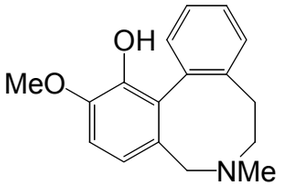
10 $R_1=OH$, $R_2=H$
11 $R_1=R_2=OH$



16 $R_1=OH$, $R_2=H$
17 $R_1=H$, $R_2=OH$



12 $R_1=OH$, $R_2=H$, $R_3=R_4=Me$
13 $R_1=H$, $R_2=OH$, $R_3=R_4=Me$
14 $R_1+R_2=O$, $R_3=R_4=Me$
15 $R_1=OH$, $R_2=R_3=H$, $R_4=Me$
18 $R_1=OH$, $R_2=H$, $R_3=Me$, $R_4=H$
19 $R_1=OH$, $R_2=H$, $R_3=CHO$, $R_4=Me$
20 $R_1=OCOCH_2CHOHMe$, $R_2=H$, $R_3=Me$, $R_4=H$
21 $R_1=OCOCH_2CHOHMe$, $R_2=H$, $R_3=R_4=Me$



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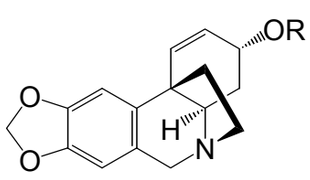
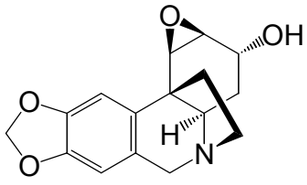


23 R=Me
24 R=H (crinine)



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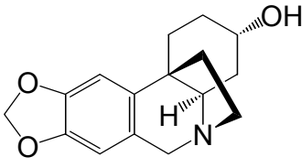

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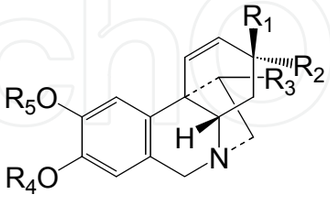
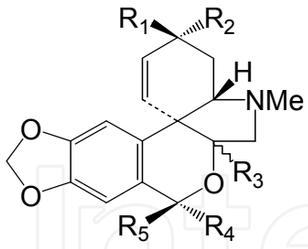
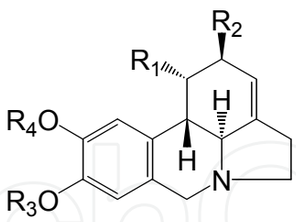


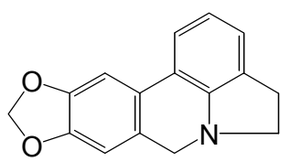
24 $R_1=OH$, $R_2=R_3=H$, $R_4+R_5=CH_2$(vittatine)
27 $R_1=H$, $R_2=R_3=OH$, $R_4+R_5=CH_2$
28 $R_1=OH$, $R_2=H$, $R_3=OH$, $R_4+R_5=CH_2$
30 $R_1=OH$, $R_2=R_3=H$, $R_4=R_5=Me$
31 $R_1=OH$, $R_2=R_3=R_4=H$, $R_5=Me$
32 $R_1=OMe$, $R_2=H$, $R_3=OH$, $R_4=H$, $R_5=Me$
33 $R_1=OMe$, $R_2=H$, $R_3=OH$, $R_4+R_5=CH_2$
34 $R_1=H$, $R_2=OH$, $R_3=OCOCH_2CHOHMe$, $R_4+R_5=CH_2$
35 $R_1=H$, $R_2=R_3=OCOCH_2CHOHMe$, $R_4+R_5=CH_2$
36 $R_1=H$, $R_2=OCOCH=CHMe$, $R_3=OCOCH_2CHOHMe$, $R_4+R_5=CH_2$
37 $R_1=H$, $R_2=OCOCH_2CH(Me)OCOCH_2CHOHMe$, $R_3=OCOCH_2CHOHMe$, $R_4+R_5=CH_2$
38 $R_1=H$, $R_2=OCOCH_2CH(Me)OCOCH_2CHOHMe$, $R_3=OH$, $R_4+R_5=CH_2$
39 $R_1=H$, $R_2=OH$, $R_3=OCOCH_2CH(Me)OCOCH_2CHOHMe$, $R_4+R_5=CH_2$



40 R_1=OMe, R_2=H, R_3=αH, R_4=R_5=H
41 R_1=OMe, R_2=H, R_3=βH, R_4=H, R_5=OMe
42 R_1=OMe, R_2=H, R_3=αOH, R_4=R_5
43 R_1=H, R_2=OMe, R_3=αOH, R_4=R_5=H
44 R_1=H, R_2=OMe, R_3=βH, R_4+R_5=O
45 R_1=OMe, R_2=H, R_3=βH, R_4+R_5=O
46 R_1=OH, R_2=H, R_3=βH, R_4+R_5=O
47 R_1=H, R_2=OH, R_3=βH, R_4+R_5=O
48 R_1=$OCOCH_2CHOHMe$, R_2=H, R_3=αOH, R_4=R_5=H
49 R_1=H, R_2=OH, R_3=αOH, R_4=R_5=H



52 R_1=OH, R_2=H, R_3+R_4=CH_2
53 R_1=OH, R_2=OMe, R_3=R_4=Me
54 R_1=R_2=OH, R_3+R_4=CH_2
56 R_1=OH, R_2=$OCOCH_2CHOHMe$, R_3+R_4=CH_2
58 R_1=OH, R_2=$OCOCH_2CHOAcMe$, R_3+R_4=CH_2



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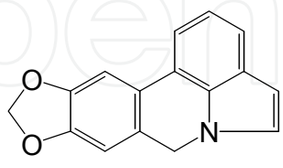

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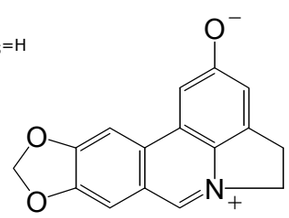

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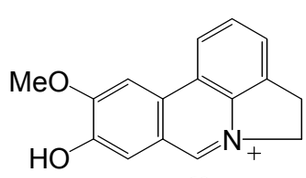

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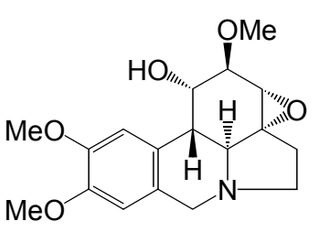

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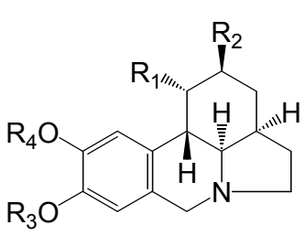
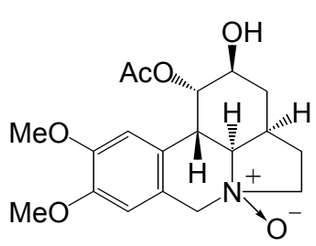


61 R_1=R_2=OAc, R_3+R_4=CH_2
63 R_1=R_2=OH, R_3+R_4=CH_2



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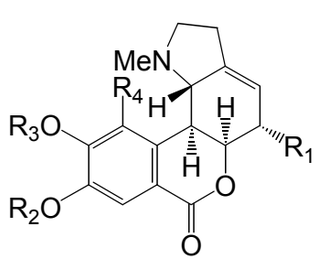
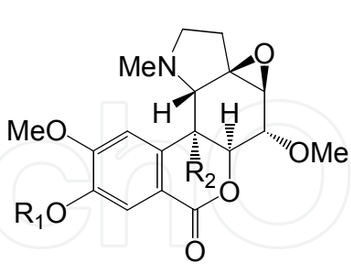
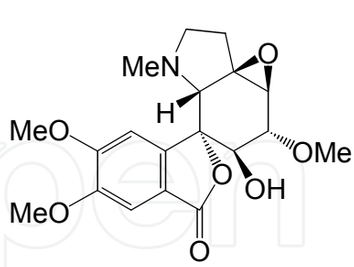


64 R_1=H, R_2=R_3=Me, R_4=H
65 R_1=R_2=H, R_3=Me, R_4=H
66 R_1=H, R_2+R_3=CH_2,R_4=H
67 R_1=OMe, R_2=H, R_3=Me, R_4=H
68 R_1=OH, R_2+R_3=CH_2, R_4=H
74 R_1=OH, R_2=R_3=Me, R_4=H
76 R_1=OH, R_2+R_3=CH_2, R_4=OMe



69 R_1=Me, R_2=H
70 R_1=R_2=H
71 R_1=H, R_2=OH
72 R_1=Me, R_2=OH



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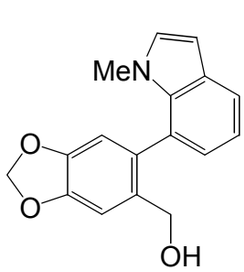

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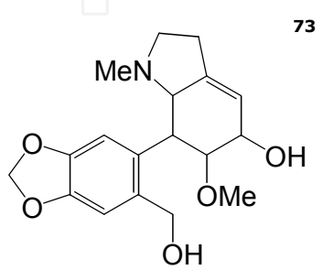

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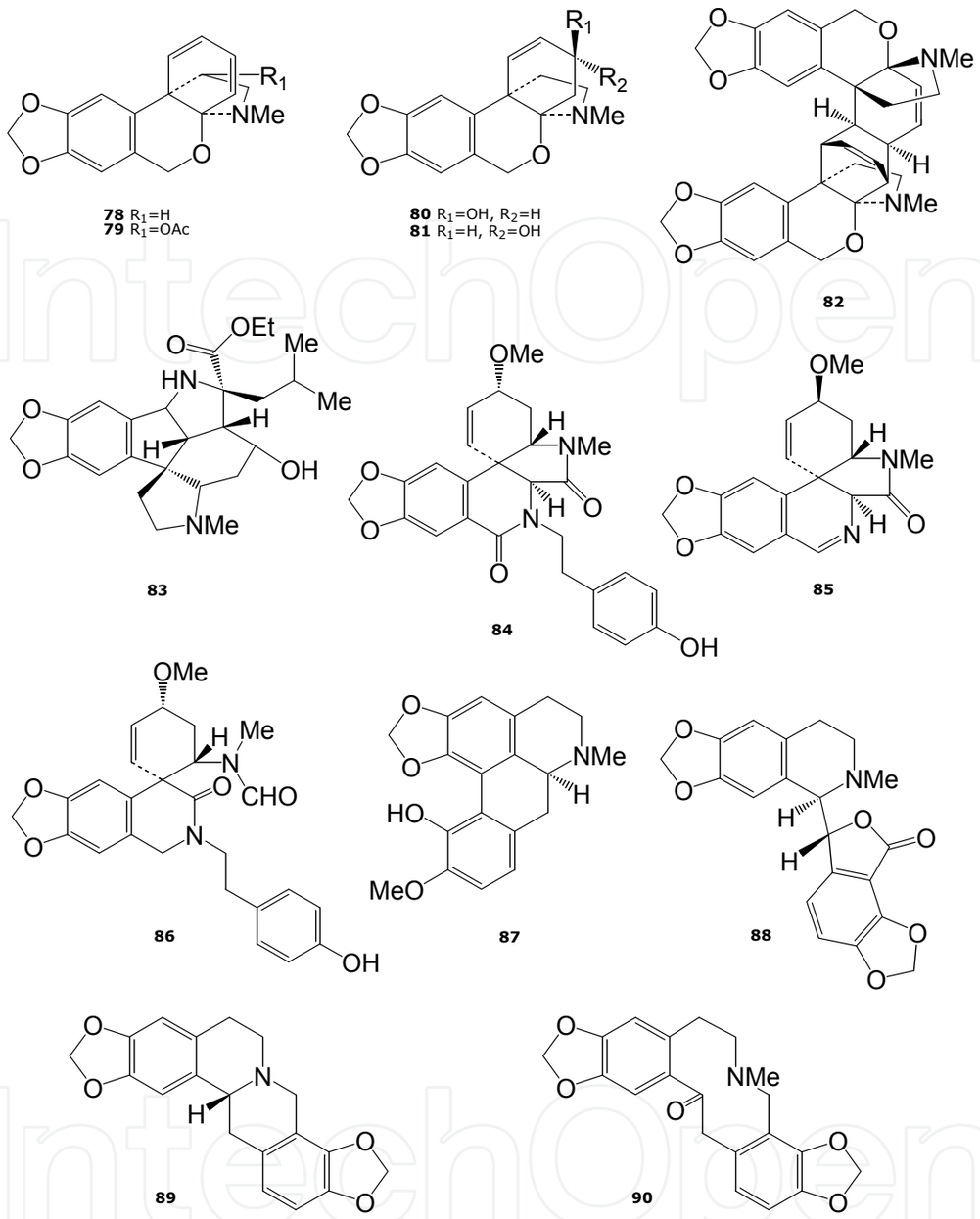

Fig. 2. Structures of the alkaloids found in the genus *Galanthus*

has been found in *G. caucasicus*, along with five known alkaloids (**12**, **42**, **53**, **54**, and **65;** Tsakadze *et al.,* 1979). Only galanthamine has been reported for *G. krasnovii* (Asoeva *et al.,* 1968). *G. ikariae* has furnished four known alkaloids (**12**, **27, 42**, and **65;** Sener *et al.,* 1998). A recent GC-MS report on *G. reginae-olgae* resulted in the identification of compounds **12**, **24**, **42**, and **66** (Conforti, *et al.,* 2010)**.** The presence of crinine (with the 5,10b-ethano bridge at the β-position) in this species, as well as in *G. elwesii*, as reported in our earlier GC-MS studies (Berkov *et al.,* 2004), is debatable because the absolute configuration of the 5,10b-ethano bridge cannot be established by GC-MS alone. Later phytochemical studies on *Galanthus* resulted in the isolation of crinane-3-ol derivatives with a *a*-configuration of their 5,10b-

ethano bridges, including vittatine (Kaya *et al.,* 2004*b*), which is the optical isomer of crinine, 11-hydroxyvittatine (Latvala *et al.,* 1995; Kaya *et al.,* 2004*b*); Ünver *et al.,* 2003) and hamayne (Berkov *et al.,* 2007*a*; 2009c). On the other hand, elwesine (**26**, 2,3-dihydrocrinine) and buphanisine (**23**) display a *β*-configuration of the 5,10b-ethano bridge (Wildman, 1968, Capo and Saa, 1989). Recently initiated phytochemical studies on *G. rizehensis* (Bozkurt *et al.,* 2010) have identified two narciclasine-type compounds, arolycoricidine (**10**) and narciprimine (**11**). An interesting example of biochemical convergence is the presence of bulbocapnine (**87**), capnoidine (**88**), stilopine (**89**) and protopine (**90**) in *G. trojanus* (studied as *G. nivalis* subsp. *silicicus* (Baker) Gottlieb-Tannenhain). Two new alkaloids, the *N*-oxides of 9-*O*-methyldihydrosternbergine (**62**) and 11-hydroxyvittatine (**29**), were also isolated, along with several known alkaloids **2, 5**, **10, 24, 28, 29, 31-33, 54, 62** and **63** (Kaya *et al.,* 2004*b*; Ünver 2007). Compounds **84-90** are benzyltetrahydroisoquinoline-, aporphine- and phthalide-type isoquinolines, found in dicotyledonous plants of the Fumariaceae and Papaveraceae families (Kametani and Honda 1985; MacLean, 1985).

5. Biological and pharmacological activities of the alkaloid found in *Galanthus*

Alkaloids are important for the well-being of the producing organism. One of their main functions is to provide a chemical defence against herbivores, predators or microorganisms (Wink, 2008). The biological roles of the numerous alkaloids found in the genus *Galanthus* remain largely unknown and only a few have been studied for their pharmacological activities.

Galanthamine-type

The most studied *Galanthus* alkaloid, galanthamine (**12**), is a long-acting, selective, reversible and competitive inhibitor of acetylcholinesterase (AChE) and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine. AChE is responsible for the degradation of acetylcholine at the neuromuscular junction, in peripheral and central cholinergic synapses. Galanthamine has the ability to cross the blood-brain barrier and to act within the central nervous system (Bastida *et al.,* 2006; Heinrich and Teoh, 2006). Owing to its AChE inhibitory activity, galanthamine is used and marketed under the name of Razadine®, formerly Reminyl®, in the USA, for the treatment of certain stages of Alzheimer's Disease (AD). According to data presented by the Alzheimer's Association in 2007, the prevalence of Alzheimer's disease will quadruple by 2050. Galanthamine hydrobromide has superior pharmacological profiles and higher tolerance as compared to the original AChE inhibitors, physostigmine or tacrine (Grutzendler and Morris, 2001).

Epigalanthamine (**13**), with a hydroxylgroup at *a*-position, and narwedine (**14**), with a keto group at C3, are also active AChE inhibitors, but about 130-times less than galanthamine (Thomsen *et al.,* 1998). The loss of the methyl group at the *N* atom, as in *N*-demethylgalanthamine (**15**), decreases the activity 10-fold. On the other hand, sanguinine (**18**), which has a hydroxylgroup at C9 instead of a methoxyl group, is *ca*. 10 times more active than galanthamine. Hydrogenation of the C4-C4a, as in lycoramine (**16**), results in a complete loss of AChE inhibitory activity (López *et al.,* 2002). It is suggested that in plants AChE inhibitors act as pesticides. The synthetic pesticides such as phosphoorganic compounds are non-reversible AChE inhibitors (Hougton *et al.,* 2006).

Tyramine-type

Compounds **1**-**4** can be attributed to the group of the phenolic amines that impact the hypothalamic-pituitary-adrenal axis (Vera-Avila *et al.,* 1996) due to their structural similarity to adrenaline (epinefrine). The consequent release of adrenocorticotropic hormone and cortisol results in sympathomimetic action with toxic effects in animals (Clement *et al.,* 1998). Hordenine (**3**) possesses diuretic, disinfectant and antihypotensive properties, and acts as a feeding repellent against grasshoppers (Dictionary of Natural Products).

Narciclasine-type

Trisphaeridine (**8**) has a high retroviral activity but a low therapeutic index. Ismine (**6**) shows a significant hypotensive effect on rats and cytotoxicity against Molt 4 lymphoid and LMTK fibroblastic cell lines (Bastida *et al.,* 2006). A recent study revealed that arolycoricidine (**10**) and narciprimine (**11**) were considerably effective in DNA topoisomerase reactions in a dose-dependent manner. Topoisomerase-interfering ability of these alkaloids partially correlated with cytostatic assays, using HeLa (cervix adenocarcinoma), MCF7 (breast adenocarcinoma) and A431 (skin epidermoid carcinoma) cells (Bozkurt *et al.,* 2010). Arolycoricidine showed inhibitory activity against African trypanosomes, (*Trypanosoma brucei rhodesiense)* at micromolar levels (Kaya *et al.,* 2011).

Haemanthamine type

Haemanthamine **(33)** has been shown to be a potent inducer of apoptosis in tumour cells at micromolar concentrations (McNulty *et al.,* 2007). This compound also possesses antimalarial activity against strains of chloroquine-sensitive *Plasmodium falciparum,* hypotensive effects and antiretroviral activity (Bastida *et al.,* 2006; Kaya *et al.,* 2011). Vittatine (**24**) and maritidine (**30)** have shown cytotoxic activity against HT29 colon adenocarcinoma, lung carcinoma and RXF393 renal cell carcinoma (Bastida *et al.,* 2006; Silva *et al.,* 2008). Antibacterial activity against Gram-positive *Staphylococcus aureus* and Gram-negative *E. coli* have been reported for vittatine (**24**) and 11-hydroxyvittatine (**28**) (Kornienko and Evidente, 2008). Data about the bioactivity of recently isolated compounds **34**-**39** is still lacking.

Tazettine-type

Moderate cytotoxic activity has been reported for tazettine (**42**), and epimacronine (**45**) (Weniger *et al.,* 1995). Tazettine, however, is an isolation artefact of chemically labile pretazettine, which is indeed present in plants. This compound has shown remarkable cytotoxicity against a number of tumor cell lines, being therapeutically effective against advanced Rauscher leucemia, Ehrlich ascites carcinoma, spontaneous AKR lymphocytic leukaemia, and Lewis lung carcinoma (Bastida *et al.,* 2006).

Lycorine-type

Lycorine (**54**), one of the most frequently occurring alkaloids in Amaryllidaceae plants, possesses a vast array of biological properties. It has been reported as a potent inhibitor of ascorbic acid synthesis, cell growth and division and organogenesis in higher plants, algae, and yeasts, inhibiting the cell cycle during the interphase (Bastida *et al.,* 2006). Additionally, lycorine exhibits antiviral (against poliovirus, vaccine smallpox virus and SARS-associated coronavirus), antifungal (*Saccharomyces cerevisiae, Candida albicans*), and anti-protozoan (*Trypanosoma brucei*) activities (McNulty *et al.,* 2009), and is more potent than indomethacin

as an anti-inflammatory agent (Citoglu *et al.,* 1998). Lycorine has also been shown to have insect antifeedant activity (Evidente *et al.,* 1986). As a potential chemotherapeutic drug, this compound has been studied as an antiproliferative agent against a number of cancer cell lines (Likhitwitayawuid *et al.,* 1993). The *in vitro* mode of action in a HL-60 leukemia cell line model is associated with suppressing tumor cell growth and reducing cell survival via cell cycle arrest and induction of apoptosis (Liu *et al.,* 2004). Further investigation showed that it is able to decrease tumor cell growth and increase survival rates with no observable adverse effects in treated animals (Liu *et al.,* 2007), thus being a good candidate for a therapeutic agent against leukaemia (Liu *et al.,* 2009).

Anhydrolycorine (**50**), in contrast to caranine (**52**), has shown a higher ability to inhibit ascorbic acid synthesis than lycorine (Evidente *et al.,* 1986). Analgesic and hypotensive effects have been reported for caranine and galanthine (**53**), the latter also being active against *Tripanosoma brucei rhodesiense* and *Plasmodium falciparum*. Some lycorine-type compounds such as caranine and ungeremine (**59**) have shown acetylcholinesterase inhibitory activity (Bastida *et al.,* 2006). Incartine was found to be cytotoxic and to weakly inhibit AChE (Berkov *et al.,* 2007).

Homolycorine-type

Cytotoxic activity has been demonstrated for homolycorine (**64**), 8-*O*-demethylhomolycorine (**65**), and hippeastrine (**68**). Homolycorine has shown high antiretroviral activity, while hippeastrine is active against *Herpes simplex* type 1. Homolycorine and 8-*O*-demethylhomolycorine have a hypotensive effect on normotensive rats. In addition, hippeastrine shows antifungal activity against *Candida albicans* and also possesses a weak insect antifeedant activity (Bastida *et al.,* 2006).

The bioactivity of the plicamine- and graciline-type alkaloids is largely unknown. Bulbocapline (**87**) and protopine (**90**) have been shown to act as inhibitors of acetylcholinesterase (Kim et al., 1999; Adsersen *et al.,* 2007) and dopamine biosynthesis (Shin *et al.,* 1998). Stylopine (**89**) suppresses the NO and PGE2 production in macrophages by inhibiting iNOS and COX-2 expression (Jang et al., 2004).

6. Conclusions

Although only some of the species of this phytochemically interesting genus have been studied, it has yielded a considerable number of new structures. Moreover, the high level of intraspecies diversity indicates that new compounds can be expected from already studied taxons. Only a few of the new alkaloids have been screened for their bio- and pharmacological activities, probably due to the small amounts isolated. Consequently, their synthesis or *in silico* studies will facilitate further bioactivity assessment.

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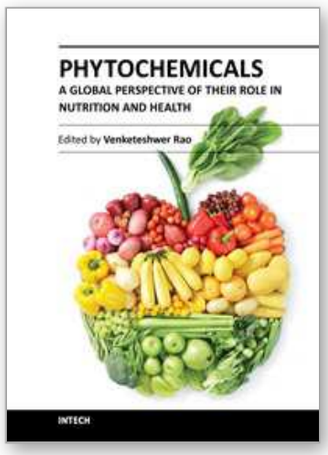

Phytochemicals - A Global Perspective of Their Role in Nutrition and Health

Edited by Dr Venketeshwer Rao

ISBN 978-953-51-0296-0
Hard cover, 538 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Strahil Berkov, Carles Codina and Jaume Bastida (2012). The Genus Galanthus: A Source of Bioactive Compounds, Phytochemicals - A Global Perspective of Their Role in Nutrition and Health, Dr Venketeshwer Rao (Ed.), ISBN: 978-953-51-0296-0, InTech, Available from: http://www.intechopen.com/books/phytochemicals-a-global-perspective-of-their-role-in-nutrition-and-health/the-genus-galanthus-a-source-of-bioactive-compounds

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