Research Signpost
Trivandrum
Kerala, India

Recent Advances in Pharmaceutical Sciences VII, 2017: 69-82 ISBN: 978-81-308-0573-3
Editors: Diego Muñoz-Torrero, Montserrat Riu and Carles Feliu

5. Research in natural products: Amaryllidaceae ornamental plants as sources of bioactive compounds

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Abstract. Amaryllidaceae plants are known for their ornamental flowers all over the word, but they also have a medicinal value owing to their exclusive group of alkaloids. The Amaryllidaceae alkaloids have a wide range of important biological activities, notably anti-tumoral, anti-parasitic, and acetylcholinesterase inhibition. This review focuses on the chemical characteristics of Amaryllidaceae plants and alkaloids, as well as the different methodologies applied in their study, including promising new docking studies.

Introduction

Amaryllidaceae plants are known for their outstanding attractive flowers (Figure 1), and are widely used and cultivated for ornamental purposes. For example, *Narcissus* species are extensively cultivated and exported for

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ornamental use in the UK and the Netherlands, as are *Lycoris* species in China and Japan, while *Crinum* species are appreciated for their lily-like flowers [1].

Figure 1. *Hymenocallis* spp. (Amaryllidaceae) from Venezuela

Amaryllidaceae plants also have a long history of use for medicinal purposes. The specific type of alkaloids they contain, named Amaryllidaceae alkaloids, display a wide range of biological activities such as antiviral, antimalarial, anticancer and anticholinesterasic [2].

1. Amaryllidaceae family characteristics

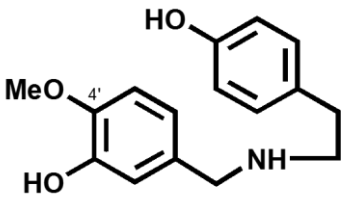
The Amaryllidaceae family, of the order Asparagales, consists of bulbous flowering plants, and is divided in three subfamilies (Agapanthoideae, Allioideae and Amaryllidoideae) previously considered as three separate families. The term "Amaryllidaceae", whether referring to plants or alkaloids, is ubiquitous in the phytochemical and pharmaceutical literature on the subfamily Amaryllidoideae [1, 3]. The monocotyledonous Amaryllidoideae subfamily comprises around 1000 species in 60 genera with a pantropical distribution, above all in three geographic locations: Andean South America, Southern Africa and the Mediterranean coast. Amaryllidoideae plants have a high capacity for adaptation. Those of the genera *Leptochiton* and *Paramongaia* survive in areas with a very arid

climate, since bulbs can remain latent for long periods, while *Hippeastrum* and *Hymenocallis* thrive in humid woods [4].

The medicinal use of Amaryllidaceae plants goes back to the Classical period, when Hippocrates and Dioscorides were already using *Narcissus* oil to treat illnesses thought to be linked to uterine tumours. References to *Narcissus* usage against cancer are also found in Pliny the Elder and the Bible. Today Amaryllidaceae plants are still extensively used in traditional medicine in several countries. For example, *Ammocharis* is cooked and used as an enema for blood cleansing or to cure open wounds; bulbs of *Brunsvigia* are applied as antiseptic dressing on fresh wounds and their decoctions treat coughs, colds, and liver diseases; *Clivia* species are used to treat snakebites and wounds, and to facilitate birth; *Crinum* species are applied as a powerful emetic, to treat tumours (Asia and America) and colds, wash wounds and haemorrhoids, as a gynecological remedy (South Africa) and a rubefacient in the treatment of rheumatism (India) [5].

2. Amaryllidaceae alkaloids

Virtually exclusive to the Amaryllidoideae subfamily, the Amaryllidaceae alkaloids have anti-viral, anti-parasitic, anti-cancer and anti- cholinesterasic



O-methylnorbelladine

ortho-para'	*para-para'*	*para-ortho'*
types	**types**	**types**
lycorine homolycorine	crinine haemanthamine tazettine narciclasine montanine	galanthamine

Figure 2. Three options of cyclization of the precursor *O*-methylnorbelladine and the resulting alkaloid types.

activities, which are probably the origin of many of the traditional medicinal uses of Amaryllidaceae plants. Although structurally diverse, Amaryllidaceae alkaloids are biogenetically related and can be classified into nine basic skeleton groups: norbelladine-, lycorine-, homolycorine-, crinine-, haemanthamine-, narciclasine-, tazettine-, montanine-, and galanthamine-types. However, there are exceptions like graciline or plicamine, which cannot be classified in any of these classical groups, and a new plicamine-type alkaloid was recently identified in *Narcissus broussonetii* [6].

All Amaryllidaceae alkaloids derive from the amino acids L-phenylalanine and L-tyrosine, from which the common precursor *O*-methylnorbellamine is synthesized. A final cyclisation step with different phenol oxidative couplings leads to a diversification of structures (Figure 2) [7].

3. Study of the genus *Narcissus*

The genus *Narcissus* comprises more than one hundred wild species and is mainly distributed around the Mediterranean Sea, including south-western Europe, North Africa, Italy and the Balkans. This genus has an ornamental value, and its easy hybridization has allowed numerous cultivars to be developed.

The traditional medicinal uses of this genus are well documented. The Bible mentions the treatment of symptoms that could now be defined as cancer with *Narcissus poeticus*. Chinese, North African and Arabian medicine continues using this treatment. Today, it is known that *N. poeticus* contains 0.012% of the anteneoplasic agent narciclasine [8].

The first isolated Amaryllidaceae alkaloid was lycorine, from *Narcissus pseudonarcissus* by Gerrard in 1877 [9]. Since then, numerous Amaryllidaceae alkaloids have been isolated in more than 40 wild species and over 100 cultivars. The most common alkaloids in *Narcissus* species are lycorine- and homolycorine-types; notably, they do not contain crinine-type alkaloids, as they synthesise alkaloids with the 5,10b-ethano bridge in an α, not β position [8].

Amaryllidaceae alkaloids isolated in the genus *Narcissus* were reviewed by Bastida et al. (2006) [8], and others have been identified by the same group since then [6, 7, 10, 11, 12, 13, 14].

4. Amaryllidaceae plants in traditional medicine in South Africa

Folk medicine still plays a crucial role in the healthcare of a great part of the population in South Africa. It has been estimated that around 27 million South Africans consult traditional healers. Contrary to popular belief, this practice is not restricted to poor and uneducated people, whose access to western medicine is limited by cost or distance, but extends to all sectors of the society [15, 16].

The use of Amaryllidaceae plants in traditional South African medicine by indigenous people has a long history, and some applications were also adopted by early European colonists. Today several concoctions, decoctions, extracts and herbal preparations of Amaryllidaceae species can be found in local traditional medicinal markets. For example, *Apodolirion buchananii* is taken for stomach disorders and *Brunsvigia* species are used against infertility in [16]. Since the application of Amaryllidaceae plants to wounds is widespread, it was suspected that they had antibacterial properties. Indeed, several Amaryllidaceae alkaloids have been isolated and identified in these plants and their antibacterial [17], antifungal [18] antiviral [19], anti-inflammatorial and antiparasitic [18] activities have been determined.

5. Amaryllidaceae alkaloids from Amaryllidaceae plants in Ibero-America

Ibero-America, together with South Africa, is a centre of diversification of the Amarylloideae subfamily. While many species remain unexplored, knowledge of Ibero-American Amaryllidaceae plants has advanced considerably in recent years. For example, the novel alkaloid phaedranamine was identified together with 7 known alkaloids in *Phaedranassa dubia* (Colombia) [20]. *Zephyranthes concolor* (Mexico) was studied for the first time in 2011 and 6 Amaryllidaceae alkaloids were identified [21]. Wild Amaryllidaceae species (*Habranthus jamesonii*, *Phycella herbertiana*, *Rhodophiala mendocina*, and *Zephyranthes filifolia*) from the Argentinian Andes were analysed for their alkaloid composition for the first time in 2011, revealing the presence of galanthamine and good acetylcholinesterase activity [22]. The alkaloid composition of the Colombian endemic species *Caliphruria subedentata*, one of only four species of the infrequent genus *Caliphruria*, was analysed by GC-MS and 18 alkaloids were identified, in addition to six others isolated with classical phytochemical methods [23]. The new alkaloid 1-epidemethylbowdensine

was reported for the first time in *Crinum erubescens* collected in Costa Rica [24].

Hippeastrum is a well-known ornamental genus from South America with around 70 species, 34 of them found in Brazil, which according to nrDNA ITS sequences is the area of origin of the genus [25]. In a review focusing on the chemistry and biological activity of Amaryllidaceae alkaloids in the genus *Hippeastrum*, de Andrade et al. (2012) [25] include several new Amaryllidaceae alkaloids they identified for the first time, notably 2α,7-dimethoxyhomolycorine and candimine in *Hippeastrum morelianum* [26], and 11β-hydroxygalanthamine in *Hippeastrum papilio* [27]. Other new alkaloids have been identified for the first time in the Brazilian species *Hippeastrum aulicum* and *H. calyptratum* (aulicine, 3-*O*-methylepimacowine, 11-oxohaemanthamine and 7-methoxy-*O*-methyllycorenine) [28], and *H. breviflorum* (9-*O*-demethyllycosinine B) [29]. Recently, more new Amaryllidaceae alkaloids have been identified in *H. papilio* (hippapiline, papiline, 3-*O*-demethyl-3-*O*-(3-hydroxybutanoyl)-haemanthamine) [30].

In Argentina, the genus *Hippeastrum* comprises nine widely distributed and poorly studied species, some of them used in traditional medicine by the Toba indigenous community. *H. argentinum* has recently been studied in terms of alkaloid composition and biological activity and two new alkaloids were identified (4-*O*-methylnangustine and 7-hydroxyclivonine). Furthermore, promising docking studies activities are being carried out [31].

6. Study of galanthamine-producing species

Galanthamine is an Amaryllidaceae alkaloid sold as a drug under the commercial name of Reminyl® in Europe and Razadine® in the USA for the palliative treatment of mild to moderate stages of Alzheimer's disease. Galanthamine can be obtained by chemical synthesis, but the yield is too low to be economically feasible. Instead, it is obtained from natural sources such as *Galanthus nivalis*, *Leucojum aestivum*, *Lycoris radiata* and different species of *Narcissus*. However, several problems, including unsuccessful cultivation or slow regeneration, make it difficult to meet the increasing pharmaceutical demands for this drug [14]. Another issue is the great chemodiversity in one of the main industrial sources of galanthamine, *Leucojum aestivum*. Balearic populations of this species have an alkaloid profile dominated by crinine-type

compounds, while in those close to the Danube River homolycorine-type alkaloids are dominant. In populations from east Bulgaria the main alkaloid is lycorine, and only populations in south Bulgaria were found to predominantly contain galathamine-type compounds. Thus, the content of galanthamine in *Leucojum aestivum* can range from 0.2 to 95% of total alkaloids [32].

More than 27,000 names of *Narcissus* ornamental cultivars have been registered in the International Daffodil Register and some intersectional cultivars have also been reported as potential sources of galanthamine. These cultivars present some advantages for alkaloid production, as they are less affected by planting depth and density, and large-scale cultivation has already been established for the ornamental plant industry [14]. In this context, 105 ornamental varieties of *Narcissus* were analysed by GC-MS for

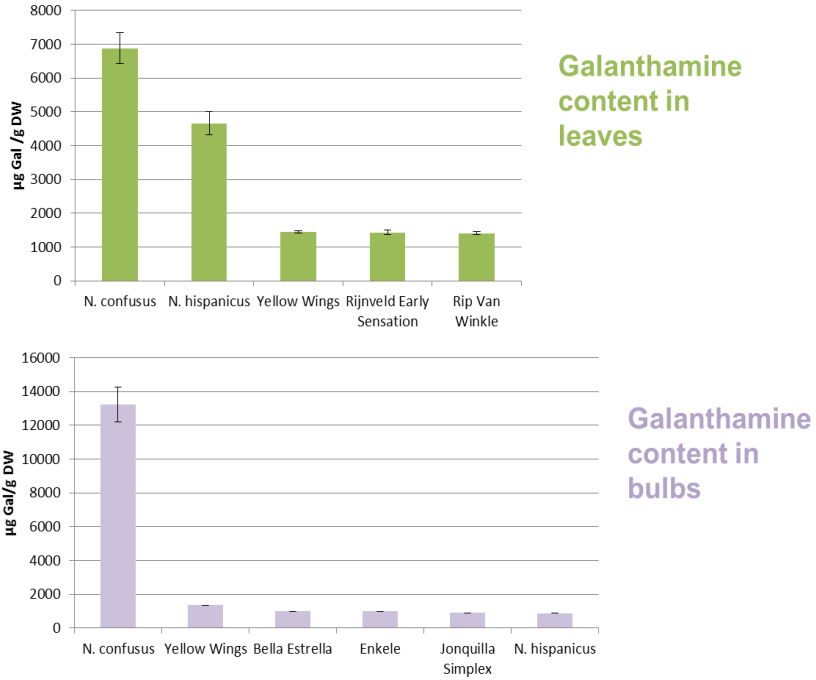


Figure 3. *Narcissus* varieties with highest galanthamine content

their galanthamine content and acetylcholinesterase inhibitory activity, distinguishing between bulbs and leaf tissues. The highest content of galanthamine was found in leaves from *N. hispanicus*, followed by the cultivars 'Rijnveld Early Sensation' and 'Rip van Winkle', and the bulbs of the cultivars 'Yellow Wings' and 'Bella Estrella', which could constitute promising new sources of this valuable metabolite (Figure 3) [14].

The total alkaloid composition of these varieties was also determined by GC-MS, comparing alkaloid mass spectra and the Kovats Retention Index with those of authentic standards previously isolated and identified by spectroscopic methods by our group in other Amaryllidaceae plants. Also, a k-means cluster analysis was performed with ornamental varieties according to the alkaloid composition of leaves and bulbs separately, obtaining 5 clusters of cultivars in each tissue. A correspondence analysis was performed to detect a possible relationship between those clusters according to the alkaloid composition and horticultural divisions of *Narcissus* ornamental varieties [7].

7. Pharmacological activity

7.1. Antitumoral

Antitumoral activity was one of the first biological effects attributed to Amaryllidaceae plants. In the early 1980s, several reports on cytotoxic and antineoplastic activities of certain Amaryllidaceae alkaloids appeared, but it was in 1995 when a significant number of Amaryllidaceae alkaloids with different skeleton types were evaluated for their cytotoxicity against a panel of human and murine cell lines. While almost all Amaryllidaceae alkaloids tested were active against fibroblastic LMTK murine cells, pretazettine was the most active against human tumoral Molt4 lymphoid cells, but with no activity against human tumoral hepatoma cells, HepG2. Conversely, lycorenine was the most active against HepG2 cells, and almost inactive against Molt4 cells [33]. Since then, other Amaryllidaceae alkaloids have proved active against other cell lines [34, 35, 36]. Selective apoptosis-inducing effects have been observed in Amaryllidaceae alkaloids of different structural types, leading to structure-activity studies (SAR). For example, an α-ethanobridge and a free hydroxyl at the C-11 position are required for the potent apoptosis induced by crinane- and lycorine-type Amaryllidaceae alkaloids in tumor cells [37, 38, 39]. The

phenanthridinones, exemplified by narciclasine and pancratistatine, have recently attracted considerable interest owing to their potent cell line-specific anticancer activities and minimal effect on normal cells, and a clinical candidate is earmarked for commercialisation in the next decade. Their mechanism is thought to be based on the initiation of cell death via the apoptotic pathway [40].

7.2. Antiparasitic

Antiparasitic properties have been found in some Amaryllidaceae alkaloids. For example, lycorine, augustine and crinamine are the principal antimalarial constituents of *Crinum amabile*, especially augustine, which inhibited both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Haemanthamine, haemanthidine, 3-epihydroxybulbispermine, galanthine and pancracine are also particularly active against these parasites, some even more so than the standards currently used for treatment [41].

In relation to Chagas disease and Sleeping Sickness, haemanthidine, pancracine, 3-*O*-acetylsanguinine and 1,2-*O*-diacetyllycorine showed biological activity against *Trypanosoma cruzi* and *Trypanosoma brucei-rhodesiense* [20]. The activity of alkaloids isolated in *Phaedranassa dubia* was evaluated against a range of parasitic protozoa, and ungeremine showed the best activity against *T. brucei-rhodesiense*, *T. cruzi* and *P. falciparum* [20]. Compounds from *Galanthus trojanus* also demonstrated antiparasitic properties, protopine being especially promising for its high selectivity and potency against *T. brucei-rhodesiense* and *P. falciparum* K1, which is a drug-resistant strain [42]. Also, the ethanolic extract of *Narcissus broussonetii* demonstrated significant activity against *T. cruzi* [6].

7.3. Acetylcholinesterase inhibition

Inhibition of the acetylcholinesterase enzyme is one of the most important biological activities of certain Amaryllidaceae alkaloids. Galanthamine is currently the only Amaryllidaceae alkaloid commercially sold for the treatment of mild-to-moderate stages of Alzheimer's disease, owing to its capacity to inhibit the enzyme acetylcholinesterase in the brain and, at same time, interact with nicotinic receptors. Thus, the levels of acetylcholine in the brain, which decline in people with Alzheimer's disease, can be maintained [1, 43]. Inhibition of acetylcholinesterase activity has

been reported in other Amaryllidaceae alkaloids, including sanguinine, montanine, 11-hydroxygalanthamine, epinorgalanthamine, and assoanine [44, 45, 46], and some of them, such as sanguinine, are even more potent than galanthamine. However, the extra hydroxyl group of sanguinine, available for the interaction with acetylcholinesterase, makes the molecule more hydrophilic, thus reducing its ability to cross the blood-brain barrier [47]. Also, natural *N*-alkylated galanthamine derivatives such as *N*-allylnorgalanthamine and *N*-(14-methylallyl)norgalanthamine demonstrate a higher inhibition of acetylcholinesterase than galanthamine [48].

7.4. Docking studies

Docking is the use of computational methods to predict the preferred conformation of one molecule to another when they form a stable complex [49]. Docking studies performed with several Amaryllidaceae alkaloids and acetylcholinesterase and butyrylcholinesterase enzymes have revealed, for example, that not only galanthamine-type alkaloids could be useful for the treatment of Alzheimer's disease. Tazettine-type alkaloids should also be considered owing to the high selectivity of 3-epimacronine derivatives for binding the enzyme locus [50]. Docking and molecular dynamics simulation studies have recently shown butyrylcholinesterase inhibitory

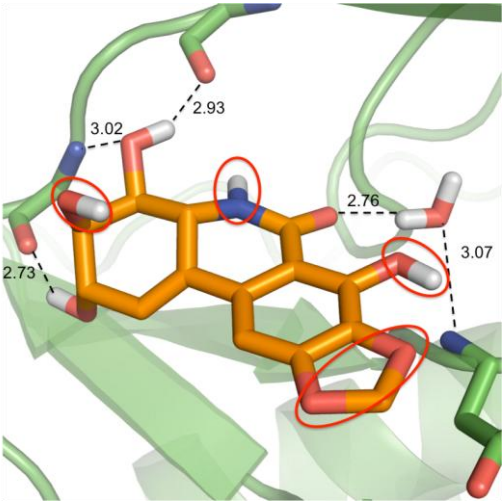


Figure 4. Putative binding mode of narciclasine in GSK-3β enzyme.

activity in 7- hydroxyclivonine, which interacts at the same binding site of the enzyme as galanthamine with very similar amino acids (Ortiz et al., 2016). Perspectives for the future include research into glycogen synthase kinase 3β (GSK3β) as a new therapeutic target for Amaryllidaceae alkaloids. This enzyme is involved in several cellular processes, including some proteins involved in Alzheimer's disease. Furthermore, there is a growing interest in GSK3β from unicellular parasites, due to their prominent role in the regulation of circadian rhythms of parasites, which are responsible, for example, for the circadian fever caused by *P. falciparum*, (Figure 4) [51].

8. Conclusion

Amaryllidaceae plants are outstanding, economically important plants, not only for their ornamental value, but also as medicinal plants and sources of drugs and new therapeutic targets. Due to their considerable biodiversification, they are found in almost all the continents: Europe, Asia, Africa and America. Their use in traditional medicine remains important in certain areas, and is supported by numerous scientific studies that have demonstrated the bioactivity of these plants, caused by their content of a particular and exclusive type of alkaloids, named Amaryllidaceae alkaloids.

Acknowledgements

The authors, members of the group 2014 SGR920, are grateful to Dr. A. Marín, Dr. M. A. Molins, Dr. A. Linares, Dr. M. Feliz and Dr. O. Jáuregui from the Scientific and Technological Services of the University of Barcelona.

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