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A Review on the Chemical and Biological Properties of the Amaryllidaceae Alkaloid, Narciprimine (1968-2020)

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Abstract

Amaryllidaceae occupies a prominent position among the most important alkaloid-rich plant families in the globe. Plants of this family show an exceptional ability to produce a myriad of structurally diverse alkaloids with noteworthy pharmacological and therapeutic potential. Of these alkaloids, narciprimine is a rare weakly basic phenanthridone alkaloid that was identified from some species belonging to the genera *Cyrtanthus*, *Galanthus*, *Lycoris*, *Narcissus*, and *Zephyranthes*. This alkaloid has attracted a lot of scientific attention in recent years thanks to its biological properties, including cytotoxic, anticancer, and anticholinesterase activities. Hence, this review affords a comprehensive focus on the chemical, spectral, and biological attributes of narciprimine; providing a future perspective for possible research on this valued Amaryllidaceae alkaloid.

Key words

Amaryllidaceae alkaloids, Anticholinesterase, Cytotoxicity, Narciprimine, Phenanthridone.

1. Introduction

Alkaloids are a group of biologically active plant constituents with powerful applications in medicine, food, and other fields of human life. Among different alkaloid-producing plant families, the family Amaryllidaceae (the Amaryllis or Daffodil family) has been described as a natural treasure of a wide array of tyrosine-derived alkaloids that are commonly known as "Amaryllidaceae alkaloids" [1]. This monocotyledonous plant family comprises more than 1600 perennial bulbous species in 75 genera that are grouped mainly into 15 tribes and 4 subfamilies, of which the subfamily Amaryllidoideae is an exclusive source of the so-called "Amaryllidaceae alkaloids" [2,3]. Different Amaryllidaceae plants have been noted since ancient times for their economic and horticultural value, while several species within this family are extensively used in traditional herbal medicine to cure a variety of ailments [4]. To date, the great phytochemical attention paid to various Amaryllidaceae species has resulted in the identification of more than 600 structurally diverse alkaloids with specific scarce skeleton types that also act as distinctive chemotaxonomic markers of Amaryllidaceae plants, particularly those of the subfamily Amaryllidoideae [5]. Most of the Amaryllidaceae alkaloids described so far are tertiary monomer bases, whereas some *N*-oxides, quaternary, glycosylated, and dimeric alkaloids have also been reported [5]. According to their ring systems, Amaryllidaceae alkaloids are generally classified into nine major types, encompassing norbelladine, lycorine, homolycorine, galanthamine, tazettine,crinine, haemanthamine, narciclasine, and montanine types. Other minor skeleton types, represented by some fewer representatives of the cherylline, phenanthridine, phenanthridone, ismine, plicamine, and sceletium types, have been also described [3,5]. A large body of literature has also shown the broad biological spectrum of various Amaryllidaceae alkaloids, including among others, cytostatic, anticancer, analgesic, anti-inflammatory, anticholinesterase, CVS, and CNS effects, in addition to their wide antiviral, antibacterial, antifungal, and anti-parasitic potential. Moreover, some alkaloids from the Amaryllidaceae have recently revealed potent inhibitory activities against glycogen synthase kinase-3β, which was identified as a potential therapeutic target in Alzheimer's disease, bipolar disorder, strokes, cancer, and diabetes [1,5,6]. Among different alkaloids obtained from Amaryllidaceae plants, the narciclasine or isocarbostyril-type includes a group of hydroxylated phenanthridones or benzoisoquinolinones that uniquely exhibit an amide group in ring B, e.g. narciclasine, pancratistatin, and lycoricidine. Several alkaloids belonging to this class have recently received great attention owing to their efficacy against several incurable diseases, mostly as interesting anticancer drug candidates [1,5,6]. The phenanthridone alkaloid, narciprimine (Figure 1) is a rare narciclasine-related metabolite, which was isolated from the bulbs of some *Cyrtanthus*, *Galanthus*, *Lycoris*, *Narcissus*, and *Zephyranthes* species [1,7–12]. This alkaloid was reported to exhibit anticholinesterase effects in addition to anti-proliferative and apoptosis-enhancing activities against some cancer cell lines [6,11,13]. Therefore, the current review highlights different chemical, spectral, and biological features of narciprimine; providing future research insights for the potential pharmaceutical application of this promising alkaloid.

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2. Biosynthesis of narciprimine

Narciprimine, also known as arolycoricidinol, was reported as a typical member of a group of about 33 biosynthetically related phenanthridine and phenanthridone/isocarbostiryl Amaryllidaceae alkaloids [5]. Generally, narciclasine-type alkaloids, exemplified by narciprimine, are biogenetically generated via an intramolecular para-para' oxidative phenolic coupling of the main precursor, 4'-*O*-methylnorbelladine forming the haemanthamine-type skeleton, which is subsequently rearranged to give narciprimine (Figure 1). 4'-*O*-Methylnorbelladine is obtained by the condensation of protocatechuic aldehyde and tyramine, previously derived from the amino acids L-phenylalanine and L-tyrosine, respectively [5,8,14].

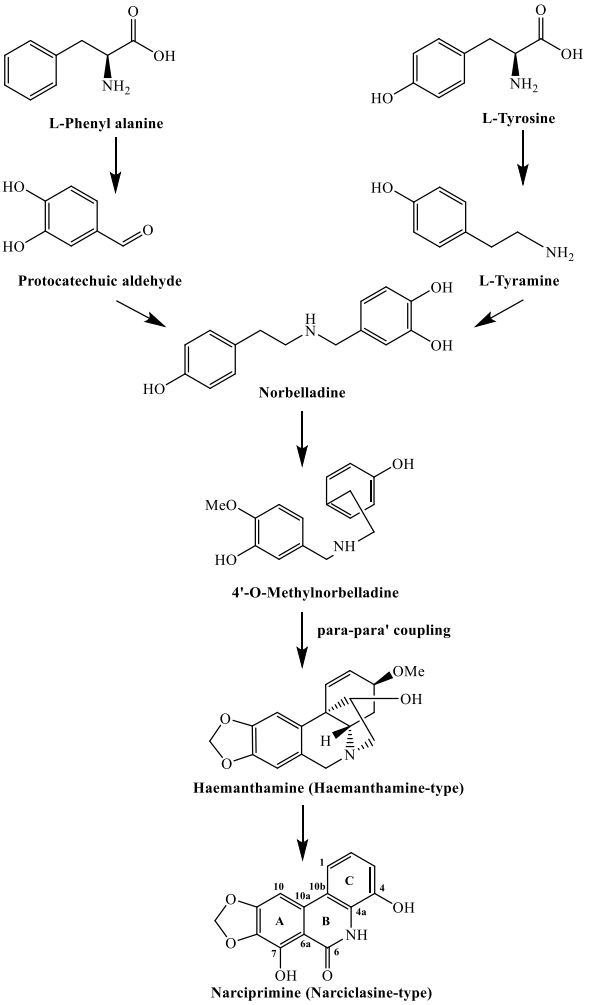

Figure 1: The biosynthetic pathway of narciprimine.

3. Plant sources of narciprimine

The first isolation of narciprimine was from the bulbs of *Narcissus incomparabilis* Mill var. *helios* in 1968 [15]. Later, it was obtained from other genera within the family, including *Zephyranthes* [*Z. tubispatha* (L'Hér.) Herb. (syn. *Habranthus tubispathus* (L'Hér.) Traub)] and *Lycoris* (*L. sanguinea* Maxim.), native to the Americas and Asia, respectively [1,9,12]. This rare alkaloid has also been recently reported from the bulbs of the African Amaryllidaceous plant, *Cyrtanthus contractus* N.E.Br., in addition to the flowers of *Galanthus rizehensis* Stern. and the bulbs of *Narcissus tazetta* var. *chinensis* Roem. endemic to Asia [10,11,16]. Lately, it has also been found in the crude extracts of *Narcissus pseudonarcissus* L. and *Galanthus* sp. [7].

4. Physical, chemical, and chromatographic aspects

Narciprimine is 4,7-dihydroxy-[1,3]dioxolo-[4,5-j]phenanthridin-6(5*H*)-one with a molecular weight of 271.0493 g/mol, in agreement with the molecular formula $C_{14}H_9NO_5$ (Figure 1). It is commonly isolated in the form of white powder and crystallized from analytically pure acetic acid or acetone as fine yellowish-white needles that melt at 310–315 °C and show strong yellow-green fluorescence [7,10,15]. Although the structure of narciprimine is related to several Amaryllidaceae alkaloids, this compound displays no basic properties as its nitrogen is amidic in nature. In this context, it was found that narciprimine shows no solubility in dilute mineral acids, but it is freely soluble in sodium hydroxide [15]. Narciprimine is sometimes isolated after several chromatographic purification steps of the acidic chloroform or ethyl acetate fractions obtained from the acidified total ethanolic extracts (pH= 4) of Amaryllidaceae plants, confirming its weakly basic characters [9]. This alkaloid gives a deep red-violet color with ferric chloride solution owing to its phenolic hydroxyl groups [15]. During thin-layer chromatographic (TLC) analysis, narciprimine reacts readily with Dragendorff's reagent to give the distinctive bright orange coloration associated with alkaloids [10]. Various solvent systems can be applied for TLC analysis and chromatographic separation of narciprimine on silica gel, e.g. $CHCl_3$–MeOH (19:1) [R_f = 0.45] and EtOAc–EtOH–H_2O (10:2:1) [R_f = 0.75] [7,15].

5. Spectral analysis of narciprimine

UV spectroscopic analysis of narciprimine in ethanol reveals several significant absorption maxima whose wavelength shift in alkaline media is attributed to the presence of phenolic hydroxyl groups.

The UV spectrum shows characteristic absorption bands (λ_{max}) at 353, 337, 322, 295, 274, 257, and 233 nm [15]. FT-IR analysis of narciprimine using NaCl provides a number of representative peaks [υ_{max} (cm^{-1})], including those evident for the amide and phenolic groups of its skeleton, as follows: 3458, 3290, 3100 (OH and NH groups); 2965, 2914, 1675 (lactam group); 1608 (phenyl); 1503, 1480, 1363, 1312, 1260, 1200, 1114, 1035 (C–O); 933 cm^{-1} (methylenedioxy group) [10,15].

Electron impact high-resolution mass spectrometry (EI-HRMS) of narciprimine displays a molecular ion peak $[M]^+$at *m/z* 271.0493 (100%), in harmony with the molecular formula $C_{14}H_9NO_5$ [10]. Other distinctive peaks also arise at *m/z* 242 (17%), 213 (36%), 185 (38%), 157 (22%), 129 (7%), and 102 (11%) [9,12]. ^{1}H-NMR analysis of narciprimine (500 MHz, DMSO-d_6) exhibits a decisive spectrum that accounts for its nine protons at δ_H: 13.75 (1H, s, chelated ArOH), 10.92 (1H, s, NH), 10.45 (1H, s, another ArOH), 7.89 (1H, dd, *J*= 8.1, 0.9 Hz, H-1), 7.70 (1H, s, H-10), 7.26 (1H, dd, *J*= 8.1, 8.0 Hz, H-2), 7.11 (1H, dd, *J*= 8.1, 0.9 Hz, H-3), and 6.20 (2H, s, OCH_2O) [10,11,15].

The ^{13}C-NMR spectrum of narciprimine (100 MHz, DMSO-d_6) displays characteristic resonances at δ_C: 164.94 (C=O), 153.65 (C-9), 144.38 (C-4), 144.90 (C-7), 132.31 (C-8), 107.09 (C-6a), 123.91 (C-4a), 123.13 (C-2), 119.39 (C-10b), 113.51 (C-1), 113.71 (C-3), 131.94 (C-10a), 102.29 (OCH_2O), and 93.64 (C-10) [10]. Moreover, the structure of this rare alkaloid is also confirmed through high-field 2D NMR correlations as depicted in Table 1 and the data were modified according to Nair et al., 2011 [10].

Table 1: Various 2D NMR correlations of narciprimine (DMSO-d_6).

H	COSY	NOESY	HMQC	HMBC
1	H-2, H-3	H-2, H-10	113.51, d	C-2, C-3, C-10a
2	H-1, H-3	H-1, H-3	123.13, d	C-4, C-10b
3	H-1, H-2	H-2	113.71, d	C-1, C-2, C-4a
4	–	–	144.38, s	–
4a	–	–	123.91, s	–
6	–	–	164.94, s	–
6a	–	–	107.09, s	–
7	–	–	144.90, s	–
8	–	–	132.31, s	–
9	–	–	153.56, s	–
10	–	H-1, OCH_2O	93.64, d	C-6a, C-8, C-9, C-10a, C-10b
10a	–	–	131.94, s	–
10b	–	–	119.93, s	–
OCH_2O	–	H-10	102.29, t	C-8, C-9
ArOH	–	–	–	–

6. Biological activities of narciprimine

6.1. Anticancer and cytotoxic activities

Many research studies depending on different bioassay methods have considered the anticancer potential of narciprimine, which was observed to be mediated by different mechanisms of action. In this regard, the plasmid relaxation and minicircle DNA decatenation assays were applied to explore the effects of narciprimine on both DNA topoisomerase I and II that act as important targets for several chemotherapeutic agents and play a vital role in the growth of cancer cells, respectively. The obtained findings revealed that narciprimine was active against both enzymes in a dose-dependent manner (0.1–0.25 µg/µL), with the highest activity was obtained at 0.25 µg/µL [6,11]. It was also found that the topoisomerase-opposing potential of narciprimine was associated to some extent with its anti-proliferative activity against different cell lines ($IC_{50} \geq 30$ µM), such as HeLa (cervix adenocarcinoma), MCF-7 (breast adenocarcinoma), and A431 (skin epidermoid carcinoma) cells using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay [11].

In another recent study, the apoptosis-inducing capacity of narciprimine was evaluated against many tumor cell lines, comprising acute lymphoblastic leukemia (CEM), malignant melanoma (G-361), breast adenocarcinoma (MCF-7), cervical adenocarcinoma (HeLa), and chronic myelogenous leukemia (K562), in comparison with the normal human fibroblast (BJ) cell line. Among different cells, narciprimine exhibited moderate cytotoxicity towards CEM cells (IC_{50}= 13.3 µM), with weak inhibitory effects against the other cell types (IC_{50} > 50 µM), which was attributed to its planar phenanthridone pharmacophore; however, it showed non-selective actions against the normal BJ cells (IC_{50} = 7.9 µM). Additionally, the amount of apoptotic cells was determined by a flow cytometry test that showed a dose-dependent decrease in the number of both G1 and S cells and a rise in the proportion of G2/M phase cells in narciprimine-treated cells at concentrations exceeding 20 µM; highlighting the specific aptitude of narciprimine to disrupt cell cycle and to induce apoptosis in CEM cells [13].

6.2. Anticholinesterase inhibitory activity

Alkaloids from the Amaryllidaceae family are well-known for their ability to suppress acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), particularly the precious alkaloid galanthamine, which is therefore often selected as a positive standard in most investigations and is widely used in the drug market for the treatment of Alzheimer's disease [3]. Narciprimine has been also recently shown to display a moderate inhibitory action on AChE, with an IC_{50} value of 78.9 µM using Ellman's colorimetric assay [17].

7. Conclusion and future perspective

Narciprimine is a rare narciclasine-type Amaryllidaceae alkaloid displaying weakly basic properties due to the amidic nitrogen atom of its phenanthridone skeleton. This alkaloid is biosynthesized from the main precursor, 4'-*O*-methylnorbelladine and was isolated from some genera within the Amaryllidaceae, namely *Cyrtanthus*, *Galanthus*, *Lycoris*, *Narcissus*, and *Zephyranthes*. To date, the physical, chemical, and spectral properties of narciprimine have been adequately described, while from a biological point of view, only the cytotoxic and anticholinesterase potential of this alkaloid have been reported so far, indicating the considerable gaps in the current biological data on that promising molecule. Consequently, future studies should comprehensively explore the detailed pharmacological and biological properties of narciprimine as well as its semisynthetic derivatives, together with the underlying mechanisms of actions, which would hopefully allow a reasonable application of such interesting Amaryllidaceae alkaloid in the pharmaceutical field.

Conflict of interest

The authors declare that there is no conflict of interest regarding this review.

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