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Chemistry, Biology, and Medicinal Potential of Narciclasine and its Congeners

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1. Introduction

Ornamental flower growers know that placing a cut daffodil (aka narcissus) in a vase with other flowers has a negative effect on the quality of those flowers and significantly shortens their vase life. Furthermore, a common horticultural practice for the cultivation of narcissus flowers involves the introduction of cuts on the bulbs before immersing them into water. The mucilage that leaches out from the cuts is constantly removed by frequent changing of the water, and this leads to sprouting. These observations raise speculation that specific components in the mucilage of the narcissus bulbs may have powerful growth-inhibitory effects. Historical use of narcissus flowers, as well as at least 30 other plants of the Amaryllidaceae family, in folk medicine for the management of cancer[1] speaks volumes to validate this conjecture.

Indeed, powerful anticancer properties of *Narcissus poeticus* L. were already known to the Father of Medicine, Hippokrates of Kos (ca. B.C. 460−370), who recommended a pessary prepared from narcissus oil for the treatment of uterine tumors.[2] His successors, the ancient Greek physicians Pedanius Dioscorides (ca. A.D. 40−90) and Soranus of Ephesus (A.D. 98−138), continued using this therapy in the first and second centuries A.D.[3,4] In addition, the topical anticancer uses of extracts from this plant[5,6] as well as from *Narcissus pseudonarcissus*[7–9] were recorded in the first century A.D. by the Roman natural philosopher Gaius Plinius Secundus (A.D. 23−79), better known as Pliny the Elder.[10] Even the Bible provides multiple references to the Mediterranean *Narcissus tazetta* L., which has a long history of use against cancer.[11] The applications of narcissus oil in cancer management continued in the middle ages in Chinese, North African, Central American, and Arabian medicine.[1,12] The uses of other genera of the Amaryllidaceae family were also common; for example, *Hymenocallis caribaea* (L. emend Gawler) Herbert was utilized by early European medical practitioners for inflammatory tumors.[13]

More recently, the plants of Amaryllidaceae have been under intense scrutiny for the presence of the specific metabolites responsible for the medicinal properties associated with this plant family. The study began in 1877 with the isolation of alkaloid lycorine from *N. pseudonarcissus*,[14]

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Alexander Kornienko was born in the small Arctic town of Vorkuta, Russia, in 1971. He studied polymer chemistry at Mendeleev University in Moscow and then moved to the United States, where he received his Ph.D. in synthetic organic chemistry working with Professor Marc d'Alarcao at Tufts University in 1999. After a 2 year postdoctoral stay with Professor Stephen Hanessian at the University of Montreal, working on the synthesis of novel aminoglycoside antibiotics, he started his independent career as Assistant Professor of Chemistry at New Mexico Tech in 2001 and was promoted to Associate Professor in 2006. His research interests encompass broad areas of synthetic organic, biological, and medicinal chemistry. Projects in his laboratory include the development of practical syntheses of natural products and their analogues, discovery of novel synthetic methodology and rational design, and synthesis and biological evaluation of synthetic compound libraries based on natural product scaffolds.

Dr. Evidente is a professor of organic chemistry. He received his degree in Chemistry in 1975 from the University of Naples Federico II. He worked as a chemist of bioactive natural compounds at the University of Naples Federico II and from 1987 to 1989 at the University of Basilicata, Potenza. Dr. Evidente's research has been mainly devoted to the biosynthesis, biochemistry, chemistry, spectroscopy, and synthesis of bioactive metabolites (alkaloids, phytotoxins, plant growth regulators, antibiotics, mycotoxins, fungicides, phytoalexins, herbicides, proteins, and polysaccharides) produced by phytopathogenic fungi and bacteria and plants. In particular, the stereostructural determination and synthesis of bioactive metabolites and studies on structure−activity relationships and on their action modes were performed by using advanced spectroscopic and chemical methods. Prof. Evidente is a leader of national and international research projects on the isolation and structure determination of bioactive microbial and plant metabolites including lipo- and exopolysaccharides. Some of these have been used to correlate the tridimensional structure in solution with their roles in plant pathogenesis and as tools for the correct classification of the producer micro-organisms.

and since then, more than 100 alkaloids, exhibiting diverse biological activities, have been isolated from the Amaryllidaceae plants.

On the basis of the present scientific evidence, it is likely that isocarbostyril constituents of the Amaryllidaceae, such as narciclasine, pancratistatin, and their congeners, are the most important metabolites responsible for the therapeutic benefits of these plants in the folk medical treatment of cancer. Notably, *N. poeticus* L. used by the ancient Greek physicians, as was eluded before, is now known to contain some 0.12 g of narciclasine per kg of fresh bulbs.[15] Continuing along this intriguing path, the focus of the present review is a comprehensive literature survey and discussion of the chemistry and biology of these compounds as specifically relevant to their potential use in medicine. The examination of the synthetic organic chemistry, more specifically the total synthesis efforts inspired by the challenging chemical structures of narciclasine, pancratistatin, and their congeners, will be reduced to a minimum in view of the two very recent excellent reviews published on this subject.[16,17]

2. Plant Sources and Isolation Methods

2.1. Amaryllidaceae Plants in Traditional Medicine

Plants belonging to the Amaryllidaceae family are herbaceous perennials that grow from bulbs. The family consists of about 60 genera, whose 800 species are widely distributed in several countries around the world. They are also cultivated as ornamental plants for their beautiful flowers and for the production of volatile oil. Amaryllidaceae plants are extensively used in traditional medicine in different countries, and their pharmacological effects are frequently associated with several typical alkaloids that they synthesize. The therapeutic action of a range of wild plants, although not scientifically proven, has been discovered by indigenous people over centuries. Developing countries are often subject to shortages of funds, medical facilities, and newly developed medicine, which make them more dependent on their natural sources. Among these, various African, Asian, and Polynesian communities still use traditional remedies for primary health care.[18]

The majority of compounds found in the Amaryllidaceae family are alkaloids, which are uniquely associated with its members. The study of Amaryllidaceae alkaloids began in 1877 with the isolation of lycorine (**3**, Figure 1) from *N. pseudonarcissus*,[14] and the interest around this group of naturally occurring compounds has increased over time because of their effective antitumoral and antiviral activities. Lycorine is a pyrrolo[*de*]phenathridine ring type alkaloid extracted from different Amaryllidaceae genera, whose structure was elucidated by Nagakawa et al. in 1956.[19] However, because of increasing attention attracted by lycorine in the last few decades and, in particular, the ability of **3** to inhibit ascorbic acid synthesis in vivo,[20] the chemical and biological aspects of this interesting alkaloid are being further investigated.[21]

Hundreds of new alkaloids isolated from different parts and in different vegetative phases of ca. 150 species belonging to 36 genera can be grouped into 12 distinct ring types (Table 1). The structures of a representative alkaloid of each ring type are shown in Figures 1, 2, 3, and 7.[22] The advances made in the isolation as well as chemical and biological characterizations of such alkaloids have been extensively reviewed.[5,14,21–28]

The initially discovered analgesic activity exhibited by the Amaryllidaceae alkaloids generated a lot of interest, and it was attributed to their resemblance to morphine and codeine skeletons. In this respect, the alkaloids of the pyrrolo[*de*]phenanthridine group are considered more promising than the alkaloids of galanthamine and 5,10b-ethanophenathridine