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Lycorine: A prospective natural lead for anticancer drug discovery

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ABSTRACT

Nature is the most abundant source for novel drug discovery. Lycorine is a natural alkaloid with immense therapeutic potential. Lycorine is active in a very low concentration and with high specificity against a number of cancers both in vivo and in vitro and against various drug-resistant cancer cells. This review summarized the therapeutic effect and the anticancer mechanisms of lycorine. At the same time, we have discussed the pharmacology and comparative structure-activity relationship for the anticancer activity of this compound. The researches outlined in this paper serve as a foundation to explain lycorine as an important lead compound for new generation anticancer drug design and provide the principle for the development of biological strategies to utilize lycorine in the treatment of cancers.

1. Introduction

Throughout the ages, organic compounds from terrestrial and marine organisms have been applied for the treatment of a wide spectrum of diseases. Particularly plants are the richest source and the basis of these traditional medicines. The history of using plants and plant-derived substances dates back to 2600 BCE [1]. Over the past fifty years, development of combinatorial chemistries and high-throughput screening methods has made these natural products and related structures extremely important elements of pharmacopeias [2,3]. As studied by Chin et al. [4], over 20 new drugs have been launched between 2000 and 2005, which were originated from natural sources. The search for anti-cancer agents from natural sources dated back to the 1950s with the discovery and development of the vinca alkaloids vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins which took almost 30 years for these drugs to came into clinical usage during 1990 [5]. Among 121 drugs prescribed currently for cancer treatment, 90 were derived from plants. These include vinca alkaloids (vinblastine, vincristine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivations (topotecan, irinotecan) and anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) [6,7]. Plants from traditional Chinese medicine are the rich host for novel drug discovery and these traditional medicines are being used for the treatment of ailments ranging from coughs and colds to parasitic infections and inflammation [8]. Amaryllidaceae family plant *Lycoris radiate* is an ornamental and Chinese medicinal plant [9]. Amaryllidaceae family plants are well known as an extensive source of pharmacologically active alkaloids [10–13], and lycorine was the first among these alkaloids to be isolated in 1877 from the plant *Narcissus pseudonarcissus* [14]. From then onwards, lycorine and its derivatives are drawing interest in the medicinal field due to their divergent chemical structures and strong biological effects **[**Fig. 1**]**.

This review will focus on the diverse pharmacological function and anticancer mechanism of lycorine and the associated pharmaco-chemical characteristics.

2. Sources and chemistry of lycorine

The pyrrolophenanthridine alkaloid lycorine is found in various Amaryllidaceae species. The Amaryllidaceae is a family of herbaceous, perennial and bulbous flowering plants. Compounds isolated from Amaryllidaceae plants are known for their medicinal properties over millenaries. Most frequently reported Amaryllidaceae species to contain lycorine include *Lycoris radiate*, *Leucojum aestivum*, *Hymenocallis littoralis*, *Hippeastrum equestre* [15], flowers of *Clivia nobilis* [16], *Ammocharis coranica*, *Brunsvigia radulosa*, *Crinum macowanii*, and *Leucojum aestivum* [17]. Lycorine can be obtained by asymmetric chemical synthesis or total synthesis strategies that are also applicable for generating other derivatives of lycorine [18,19]. Amaryllidaceae provides a great diversity of biologically potential alkaloids that have been shown to arise biosynthetically from a common intermediate, norbelladine. Norbelladine undergoes different cyclizations, rearrangements, elimination

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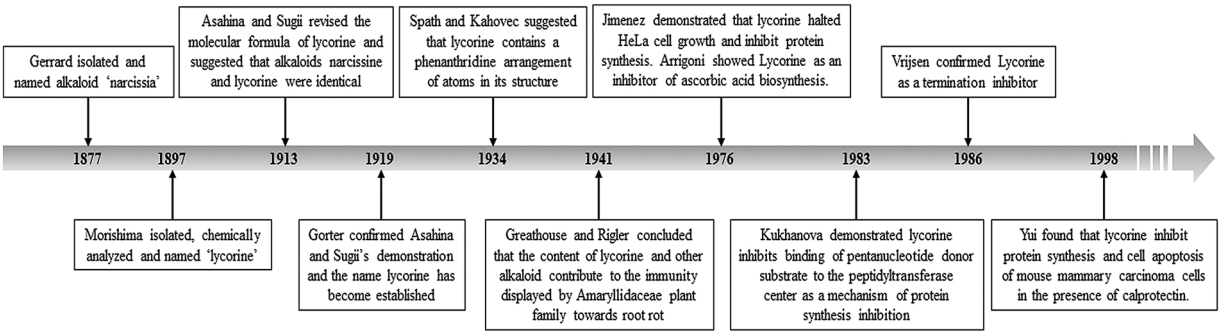
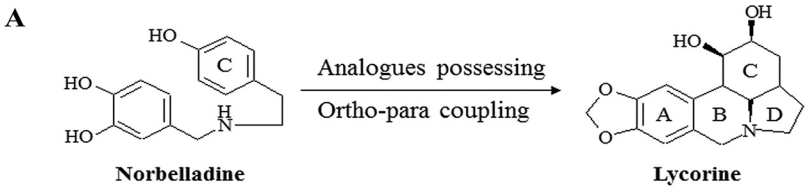


Fig. 1. Timeline for the history of lycorine. First isolated as narcissia from *Narcissus pseudo-narcissus* L., the alkaloid was later named as lycorine. Further research was performed to establish the molecular formula and general properties of this compound. After confirmation of the chemical properties by several studies, lycorine was investigated for it's in vitro properties which formed the foundation of our current knowledge of this pharmacologically potent alkaloid.



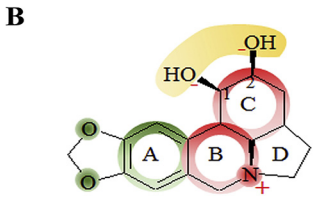


Fig. 2. Chemistry of lycorine. A. Synthesis of lycorine. Lycorine and lycorine like Amaryllidaceae alkaloids are generated from a common precursor norbelladine. Norbelladine undergoes analogs possessing of the −OH group of A-ring and ortho-para coupling of A and C-ring to produce lycorine. B. Structure-activity relationship of lycorine. The anticancer property of lycorine is largely depended on its structure. The red shades indicate the parts that lycorine requires absolutely to exert its activity. The green shades mean that these part can be changed with chemical modification while the yellow shades represent the part that can be replaced with only a few suitable groups.

and/or recyclization to provide a variety of skeletons [9,20,21]. Lycorine comprises analogs possessing and ortho-para coupling of a double bond in the C-ring **[**Fig. 2**A]** . The full chemical name of lycorine is 2,4,5,7,12b,12c-hexahydro-1H-(1,3) dioxole(4,5-*j*)-pyrrole(3,2,1de) phenanthridine-1-diol, the molecular formula $C_{16}H_{17}NO_4$ and the relative molecular mass 287.31. Lycorine is a colorless crystal with the melting point of 260–262 °C and it is immiscible to the wastewater and insoluble in ether and alcohol [22]. The biological activity of lycorine is firmly associated with its structure. For example, the anti-tumorigenic effect of lycorine is extensively attributed by its structure (discussed later in this article) and slight modification at certain group renders this compound either less active or inactive **[**Fig. 2**B]** . The structural parameters that provide a significant contribution to its activity include the presence of planarity of the molecule, olefin or dioxole ring, the function of hydroxyl groups and the presence of a positive charge on the nitrogen and the amine group [9,23,24].

3. Pharmacological functions of lycorine

3.1. Antiviral activity

The first reported activity of lycorine as an inhibitor of termination of protein synthesis was found in poliovirus-infected HeLa cells [25]. In subsequent studies lycorine showed moderate to potent antiviral activity and reduced viral titers of herpes simplex virus [26], retrovirus HIV-1 [27], severe acute respiratory syndrome associated coronavirus [28], poliovirus [29], West Nile Virus (WNV), dengue and yellow fever viruses [30], enterovirus 71 [31], influenza virus [32], hepatitis C virus [33] and adult zika virus vector *Aedes aegypti* [34,35]. Lycorine could not exert antiviral activity against alphavirus, Western equine encephalitis virus, rhabdovirus and vesicular stomatitis virus, suggesting a selective antiviral spectrum of this compound [30]. The antiviral effect of lycorine is due to the multiplication inhibition by blocking of viral polymerase activity or elongation of the viral polyprotein during protein synthesis [26,31]. Structure-activity analysis revealed that the free hydroxyl groups at C-1 and C-2, intact benzodioxole group at A-ring, the basic nitrogen, and the C3-C4 double bond are crucial for the anti-virus activity of lycorine [36].

3.2. Antibacterial effects

The main metabolite of lycorine degradation, ungeremine, and carbamate substitution at C-1 and C-2 of lycorine had stronger antibacterial activity toward fish bacterial pathogen *Flavobacterium columnare* isolates than lycorine itself [37,38]. Lycorine though shows almost no inhibitory activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* [39], a recent study by Bendaif and colleagues demonstrated the anti-bactericidal effect of lycorine in several bacterial strains, suggesting a preferential antibiotic property of lycorine [40].

3.3. Anti-parasitic properties

Lycorine was found to be the most potent alkaloids against *Plasmodium falciparum*, *Tribolium castaneumand*, and *Aphis gossypii* [14,41]. This compound abolishes the nucleoside triphosphate diphosphohydrolase (NTPDase) and ecto-5′-nucleotidase activities of *Trichomonas vaginalisin* [42], and also causes cell cycle arrest of this parasite [43]. Lycorine shows significant inhibition of DNA topoisomerase-I activity that is required for cell growth in parasites [44,45].