



## **BIOLOGICAL EVIDENCES OF LYCORINE: A REVIEW**

Khaled Rashed

*Department of Pharmacognosy, National Research Centre, 33 El Bohouth st.-Dokki, Giza, P.O.12622, EGYPT*

### **ABSTRACT**

Lycorine, a natural alkaloid extracted from the Amaryllidaceae family. It is extracted from the bulb of the *Lycoris radiate*. lycorine has a variety of pharmacological activities including anti-tumor, anti-virus, anti-inflammatory, anti-malaria, inhibition of acetylcholinesterase activity. It has been reported that lycorine and its derivatives have significant inhibitory effects on leukemia, lymphoma, melanoma, esophageal cancer, breast cancer, ovarian cancer, prostate cancer. So far, the existing evidence showed that Lycorine has stronger therapeutic effect on tumor cells than normal cells.

**Keywords:** Lycorine, chemical compounds, plants, bioactivities

## INTRODUCTION

Alkaloids constitute a diverse class of plant secondary metabolites with varied chemical structures and biological activities. In the context of their taxonomic distribution, family Amaryllidaceae, commonly known as the Amaryllis or Daffodil family, is one of the twenty most important alkaloid-containing families in the plant kingdom [1]. Amaryllidaceae plants are currently appreciated as a plentiful source of unique bioactive alkaloids. Among them, lycorine is one of the major pyrrolophenanthridine alkaloids commonly isolated from different species of this family [1]. From a chemical point of view, Amaryllidaceae alkaloids are classified into nine main structural classes, comprising belladine, lycorine, homolycorine, crinine, haemanthamine, tazettine, galanthamine, montanine, and narciclasine types, in addition to other minor groups, such as cherylline, ismine, plicamine, phenanthridine, phenanthridone, and mesembrine alkaloids. Lycorine-type alkaloids, which exhibit a unique pyrrolophenanthridine skeleton, represent the most common alkaloidal group, of which lycorine is the major alkaloid commonly found in the leaves and bulbs of all Amaryllidaceae plants [2]. This alkaloid was firstly isolated in 1877 from *Narcissus pseudonarcissus* L. and its structure was elucidated by Nagakawa [3]. Over the past decades, lycorine has attracted a special interest owing to its outstanding biological properties, including among others, analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiprotozoal, as well as wide-ranging cytotoxic effects against numerous tumor cell lines, e.g., leukemia, cervical cancer, and prostate cancer [4]. This review was undertaken to highlight the biological aspects of this promising Amaryllidaceae alkaloid, lycorine.

### **Biological Activities:**

#### **Anticholinesterase effect:**

Amaryllidaceae alkaloids are widely known for their acetyl cholinesterase (AChE) and butyryl cholinesterase (BuChE) inhibitory potential; however, lycorine exhibits no or very weak AChE inhibitory actions with an IC<sub>50</sub> of 213±1µM [5, 6]

#### **Antioxidant, hepatoprotective, and metabolic effects:**

Lycorine showed significant DPPH scavenging effects [7]. It also exerted protective effects on human erythrocytes against oxidative damage induced by 2-amidinopropane due to its antioxidant nature [8]. Lately, lycorine has been shown to exhibit significant hepatoprotective effects against CCl<sub>4</sub>-induced oxidative stress in Swiss albino mice at 5 mg/kg that were also comparable to Silymarin. It effectively normalized the increased generation of lipid peroxidation products and reduced the elevated levels of malondialdehyde, glucose, urea, bilirubin, and hepatic marker enzymes. It also restored both the levels of glutathione and vitamin C and the activities of superoxide dismutase, catalase, glutathione-S-transferase, and glutathione reductase. Moreover, the histological and ultra-structural observations have evidenced the protective effects of lycorine on hepatocytes against CCl<sub>4</sub>-induced oxidative damage without disturbing their cellular metabolic functions [9-11].

### **Immunological activity:**

Lycorine has been patented as an immunosuppressor and can be useful in suppression of the immune systems of mammals for the treatment of autoimmune diseases, complex immune syndromes, allergic and rheumatic conditions, as well as for prophylaxis against transplant rejections [12, 13].

### **Anti-inflammatory activity:**

Lycorine exerts good anti-arthritis potential when tested in various animal models [14-16]. It successfully blocks rat paw edema induced by carrageenan with an ED<sub>50</sub> of 0.514 mg/kg. It also efficiently reduces the cytotoxicity of calprotectin, a pro-inflammatory factor contributing to the development of inflammation leading to tissue destruction in severe inflammatory diseases [17]. Moreover, lycorine blocks lipopolysaccharide (LPS)-induced production of pro-inflammatory mediators and also decreases LPS-induced mortality in mice [16].

### **Inhibition of ascorbic acid biosynthesis:**

Lycorine has been proved to be an inhibitor of ascorbic acid biosynthesis both in vitro and in vivo [17]. It powerfully inhibits the in vivo conversion of galactono-gamma-lactone to ascorbic acid [18]. At a dose of 50 µM, lycorine was found to significantly inhibit ascorbic acid biosynthesis, and the effect continued even when the alkaloid was removed from the incubation medium. Further studies showed that lycorine selectively inhibits the activity of L-galactono-gamma-lactone dehydrogenase, but does not affect the activities of ascorbate peroxidase, ascorbate free radical reductase, and dehydroascorbate reductase [18].

### **Antiviral activity:**

Preliminary evaluation of the antiviral effects of lycorine and its derivatives indicated their possible in vitro/in vivo activities against Flaviviridae, Bunyaviridae, and Japanese encephalitis [19]. It is reported that lycorine inhibited flaviviruses mainly through suppression of viral RNA synthesis.

### **Effects on sexual functions:**

Application of lycorine to the testes and ovaries of immature rats inhibited cell division in the spermatogonia or primary spermatocytes. No spermatid cells were also found in the tested animals, whereas follicles were found to be smaller and less in number in rat's ovaries [20].

### **Antimalarial activity:**

Lycorine exhibited a dose-dependent antimalarial activity when tested against *Plasmodium falciparum* (T9.96) and *P. falciparum* (K1) at four doses (0.04, 0.2, 1.0, and 5.0 µg/ml) with IC<sub>50</sub> values of 1.026 and 0.379 µg/ml, respectively [21].

### **Antibacterial activity:**

Lycorine displayed no significant inhibitory actions against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* using the agar disc diffusion technique [22].

### **Anti-parasitic activity:**

The cytotoxicity of lycorine in *Trichomonas vaginalis* was found to be different in comparison with its

activities against a variety of tumor cell lines mentioned before. For instance, lycorine arrests the parasite cell cycle but fails to fulfill the criteria for apoptosis or apoptosis-like death. However, some similarities to paraptotic cell death described for multicellular organisms were observed [23]. Lycorine was found to strongly inhibit the activities of nucleoside triphosphate diphosphohydrolase (NTPDase) and ecto-50-nucleotidase in the 24 h-treated *Trichomonas* parasites, while the transcript levels of NTPDase A or B were not altered by lycorine [23].

### **Cytotoxic and antitumor activities:**

Lycorine was the first identified cytostatic compound from Amaryllidaceae [24]. After that, has been intensively investigated in various preclinical models of human cancers both in vitro and in vivo. In general, lycorine is recognized as a low micromolar antiproliferative agent against a wide range of multidrug-resistant and apoptosis-resistant tumor cells [25, 26], showing a selective cytotoxicity via mitochondrial pathways and induction of apoptosis. Lycorine was found to down-regulate Mcl-1 in human leukemia cells [27]. The apoptotic effect of lycorine involves cell cycle regulation in HL60 and KM3 cell lines, cytochrome-c release, and caspase activation [27]. It was also reported that lycorine can decrease HDAC enzymatic activities in K562 cells and up-regulate the expression of p53 and its target gene product p21, thus inhibits the proliferation of K562 cells [28].

### **CONCLUSION**

This review showed the importance of lycorine as a medicinal compound.

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