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Review Article

MUSCARI ARMENIACUM LEICHTLIN (GRAPE HYACINTH): PHYTOCHEMISTRY AND BIOLOGICAL ACTIVITIES REVIEW

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ABSTRACT

This review focuses on the *Muscari armeniacum* Leichtlin (*Asparagaceae* Juss) biologically active substances composition presented in the aireal and underground parts and finding their possible therapeutic effects. The systematic review is dedicated to the composition of biologically active substances, including recent advances in the biological activity investigation, phytochemical studies, and biotechnology methods of plant material producing. Various electronic search engines such as Google, Google Scholar, scientific literature, publishing sites, and electronic databases such as PubMed, Wiley, Springer, and Science Direct had been searched and data obtained. Other online academic libraries such as E-library and specific ethnopharmacological literature had been searched systematically for more exhaustive information on the crude herbal drug. The chemical composition of *M. armeniacum* biologically active substances is established; it contains anthocyanins (delphinidin and cyanidin derivatives), homoisoflavonoids, polyhydroxylated pyrrolizidine alkaloids (hyacinthacines A_1, A_2, A_3, and B_3), oligoglycosides (muscarosides), and ribosome-inactivating proteins (musarmins). Recent physicochemical analytical procedures for components determination and hyacinthacines synthesis pathways are mentioned. Moreover, future prospects and trends in the research of this plant have been proposed. We have reviewed researches conducted on *M. armeniacum* especially in areas of its use in medicine, phytochemicals, biological activity, and developed analytical methods. *M. armeniacum* possesses antioxidant, antimutagenic activity, and specific glycosidase inhibitory activity; *M. armeniacum* can be used for the production of potential anticancer, antiviral, antidiabetic, and anti-obesity drugs. It should be noted that more pharmacognostic, pharmacological studies are needed for giving further information on the clinical practice and standardization procedures for the crude herbal drug.

Keywords: *Muscari armeniacum*, Hyacinthacine, Muscarosides, Musarmin, Homoisoflavonoids, Muscarinin A.

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INTRODUCTION

Muscari armeniacum Leichtlin (*Asparagaceae* Juss) is small flowering plant in the squill subfamily (*Scilloideae*), also known as *Hyacinthaceae* family with numerous medicinal plant representatives (*Ornithogalum* species [1], *Urginea indica* [2], etc.). *M. armeniacum* is a bulbous perennial with simple, basal leaves, and short flowering stems. It is also known as grape hyacinth, viper onion, garden grape-hyacinth, or Armenian grape hyacinth [3,4]. *M. armeniacum* plants bloom in middle spring (April or May in the Northern areas) for 3 or 4 weeks. Established bulbs leaf in the autumn. *M. armeniacum* is widespread in the meadows and woods of the Eastern Mediterranean, from Greece and Turkey to the Caucasus, including Armenia [5]. *M. armeniacum* is popular with plant growers due to its bright flowering and unusual appearance. Some varieties are used in landscape design. *M. armeniacum* is an excellent honey plant; its pleasant smell attracts many bees, butterflies, and bumblebees to the garden [6].

Bulbs of *M. armeniacum* are suitable for human consumption in Turkey [7]. Possessing a pleasant smell, *M. armeniacum* found application in perfumery and cosmetology. *M. armeniacum* is a non-pharmacopeial plant; it is not used in official medicine. The therapeutic properties of *M. armeniacum* are known in traditional medicine. The plant is used externally as a wound healing [8,9], antiseptic, an anesthetic for inflammatory processes of a dermatological nature, wounds, and burns [10]. Recent studies have shown that *M. armeniacum* can be used as perspective a medicinal plant in official medicine.

The aim of this research is a pharmacognostic review of *M. armeniacum* plants including the studying the literature for biological properties and phytochemical composition.

METHODS

Various electronic search engines such as Google, Google Scholar, scientific literature, publishing sites, and electronic databases such as PubMed, Wiley, Springer, and Science Direct had been searched and data obtained. Other online academic libraries such as E-library and specific ethnopharmacological literature had been searched systematically for more exhaustive information on the crude herbal drug.

RESULTS AND DISCUSSION

M. armeniacum (Fig. 1) is a perennial, shade-tolerant and light-loving plant that prefers moderate hydration. The height of the plants during flowering is 15–20 cm. The bulb is fleshy, ovate, rounded, 2–3.5 cm in diameter, and covered with light scales. Leaves are basal, linear, belt-like, strong 10–17 cm long, and 0.5–2.5 cm wide. At the beginning of the growing season, up to seven leaves are produced from one bulb. Depending on the type and variety of basal leaves can be formed in spring or autumn. Stem is inflorescence shoot; it is bare, usually single (in some cases two stems appear). At the top of the stem, a dense, many-flowered, racemose inflorescence (simple raceme) 2–8 cm long is formed. The flowers are small 0.5–0.8 cm, actinomorphic, fragrant, on short pedicels, tightly pressed to each other. The shape of the buds resembles a jug or barrel with six short teeth, bent outwards. Miniature flowers sit tightly on the stem; dark blue perianth has white teeth. Androecium consists of 6 stamens located in 2 circles, attached by threads to the middle of the perianth tube and hidden in it. The gynoecium is represented by a pestle with an upper three-celled ovary, with one filiform column and a capitate. Nonacetolysed pollen grains with granulate ornamentation of the sulcus membrane have the following dimensions: Long axis is 28.08±1.24; short axis – 18.81±1.05; it's ratio - 1.49 [11]. Fruits are sincarp, winged, angular, three-nest box, dorsoventrally open. Seeds are round, black, smooth, net-wrinkled, remain viable for about 1 year. Seeds are formed only in the lower part of the inflorescence since apical flowers are barren [10]. The chromosome number (CN) is 2n=18 (Turkey, Greek populations); in general, CNs are 2n=18, 36 [12]. Polyploid *M. armeniacum* plants (2n=4x=36) were obtained by colchicine-induced chromosome reduplication [13].

M. armeniacum plants contain different groups of biologically active substances: Flavonoids, mucilages, saponins, and alkaloids among them [14-16].

The blue color of *M. armeniacum* flowers is associated with the content of anthocyanins. *p*-Coumaric acid is one of the acyl groups of muscarinin A, delphinidin-3-(6-*p*-coumaroylglucoside)-5-(4-rhamnosyl-6-malonylglucoside) (Fig. 2) [19]. P450 (MaP450) gene plays a role in the anthocyanin biosynthetic pathway; as flavonoid 3’5’-hydroxylase enzyme (F3’5’H), associated with this gene, provides the expression of blue or purple color in Muscari species flowers [20]. Furthermore, MaAN2 (R2R3-MYB family AN2 subgroup) take part in anthocyanin biosynthesis [21].

Studies of anthocyanins profile in various species of *Muscari* (also in *M. armeniacum*) were conducted by several groups of researchers. *M. armeniacum* is a popular ornamental perennial plant that is famous for its blue flowers, but there are cultivars with white, violet-blue, purple, and red-purple flowers [23,24]. This colors are formed by a mixture of anthocyanins: Cyanidin, cyanidin-3-O-caffeoyl-rutinoside, cyanidin-3-O-(p-coumaroyl)-lucoside-5-O-malonyl-glucoside, malvidin-3-O-glucoside, delphinidin-3-O-glucoside, pelargonidin-3-O-ferulylglucoside-5-O-arabinoside, pelargonidin-3-O-sinapyl-glucoside-5-O-glucoside, pelargonidin-C-O-caffeoyl-sophoroside-5-O-arabinoside, pelargonidin-3-O-sinapyl-glucoside-5-O-arabinoside, and petunidin-3-O-glucoside. *M. armeniacum* contains delphinidin and cyanidin derivatives [25-27]. Anthocyanins are known for their antioxidant abilities and widely represented in the plant world [28,29].

The isolation and structural clarification of homoisoflavonoids (3-benzylidene-4-chromanones with –OH or $–OCH_3$ groups in the 3’- and 4’- positions) was reported in *M. armeniacum* (Fig. 3) [30,31]. Homoisoflavonoids possess strong antioxidant activity [32] and the potential antimutagenic effect [33].

Fig. 1: *Muscari armeniacum* Leichtlin in flowering phase [17] with floral diagram [18] (1) and asleep bulbs [5] (2)

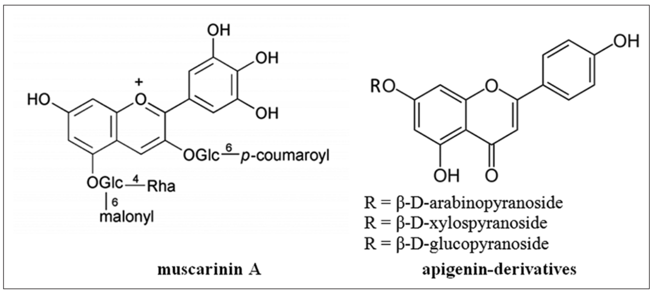

Fig. 2: Structure of muscarinin A [22] and apigenin-derivatives [14] from *Muscari armeniacum*

M. armeniacum flowers give off a floral, fruity, and slightly peach-like odor. 2-phenylethanol and 2-(4-methoxyphenyl)-ethanol are the main constituents of the corresponding odor concentrate. In the vacuum headspace concentrate of the *M. armeniacum* flowers such compounds as: Acetophenone (2%), 2-phenylethanol (20%), 1-phenylethanol (1%), 4-hydroxylinalool (3%), 2-(4-methoxyphenyl)-ethanol (31%), (E,E)-α-farnesene (2%), 1-phenylethyl benzoate (3%), and 2-phenylethyl benzoate (2%) were identified [34].

Analysis of nonstructural carbohydrates by high-performance anion-exchange chromatography with pulsed amperometric detection in *M. armeniacum* bulbs collected in the Netherlands was conducted in Cornell University (Ithaca, NY, USA). Concentrations of glucose were 0.6±0.1 mg/g, fructose - 4.4±0.4 mg/g, sucrose - 16±2 mg/g, starch - 244±1 mg/g, and fructan - 362±21 mg/g [35]. In the bulbs of *M. armeniacum* (known as *Muscari szovitsianum* Baker), water-soluble polysaccharide was determined, it was a neutral glucofructan containing glucose and fructose (in ratio 26:1) [36].

The content of biologically active and reserve substances in the aerial and underground parts of *M. armeniacum* was investigated by researchers from the Central Siberian Botanical Garden of the Siberian Branch of the Russian Academy of Sciences (Russia). The starch, sugar, ascorbic acid, saponins, protopectins, pectins, and catechins have been established in *M. armeniacum* bulbs, located in the forest-steppe zone of Western Siberia during the growing season (2007, 2009–2011). Flavonols were found in the leaves (1.8–2.2%). It was established that at the pre-winter period the amount of sugar in the bulbs decreases by 2–4 times as compared with spring, and the amount of starch increases by 1.5–2 times. In May, the content of ascorbic acid in the upper-ground organs is increased by 5–10 times, sugar - 1.5 times, and catechins - 2 times than in the underground organs. It is noted that the bulbs contain 2–3 times more, and the leaves 5–6 times more protopectins than pectins. It is noted in bulbs there are 2–3 times more protopectins compared with pectins and 5–6 times more in leaves. In the aerial and underground parts of *M. armeniacum* the content of reserve and biologically active substances depend on the seasonal and individual factors [37].

Hyacinthacines A_1, A_2, A_3, and B_3 (Fig. 4), polyhydroxylated pyrrolizidine alkaloids, have been isolated from the bulbs of *M. armeniacum*. They possess glycosidase inhibitory activity of rat intestine lactase (IC_{50}=4.4-μM), L-fucosidase (IC_{50}=46 μM), and amyloglucosidase (IC_{50}=25 μM) [38-41]. Hyacinthacines A_1, A_2, A_3, and B_3 can be obtained by various synthetic pathways [42-60].

M. armeniacum contains oligoglycosides, named muscarosides (A12, B13, G3, J6, K7, L8, and M9). They have spirocyclic nortriterpenoid aglycone that belongs to the eucosterol group (Fig. 5). The glycone moieties are presented by 4–6 units of arabinose, glucose, rhamnose, or apiose [61,62].

Musarmins (MUs) isoforms 1, 2, and 3, ribosome-inactivating protein ([RIP]; EC 3.2.2.22) [63] have been isolated from the bulbs of *M. armeniacum* by ion-exchange chromatography and gel filtration. MUs are single-chain proteins that were established by electrophoresis. Mass spectrometry showed Mr values of 28,708 (MU 1), 30,003 (MU 2), and 27,626 (MU 3). MUs inhibited strongly protein synthesis of mammalian ribosomes (IC50 is 0.14–0.24 nM) but did not inhibit protein synthesis of HeLa cells and plant cell-free systems. As opposed to other RIPs, MUs are located only in bulbs, and they are not induced in leaves. Hence, in plants these proteins may play a non-vital role; for example, as protective and anti-pathogens agents solely in some stages of the cycle in plant life [64]. The production of recombinant MU 1 was performed by bacterial expression [65].

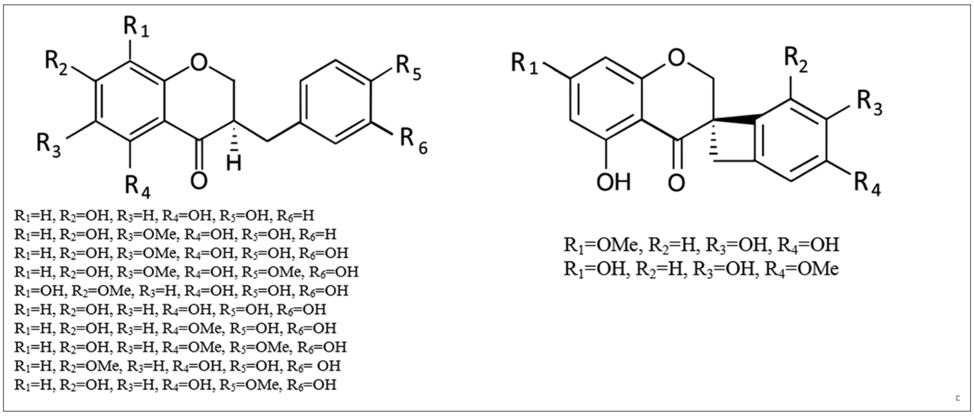

Fig. 3: Structures of homoisoflavonoids (3-benzylidene-4-chromanones) in *Muscari armeniacum* [14]

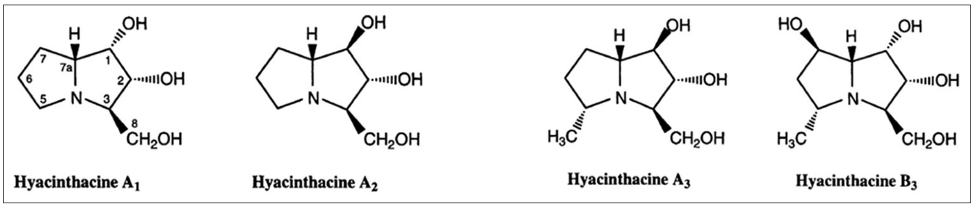

Fig. 4: Structures of polyhydroxylated pyrrolizidine isolated from *Muscari armeniacum*

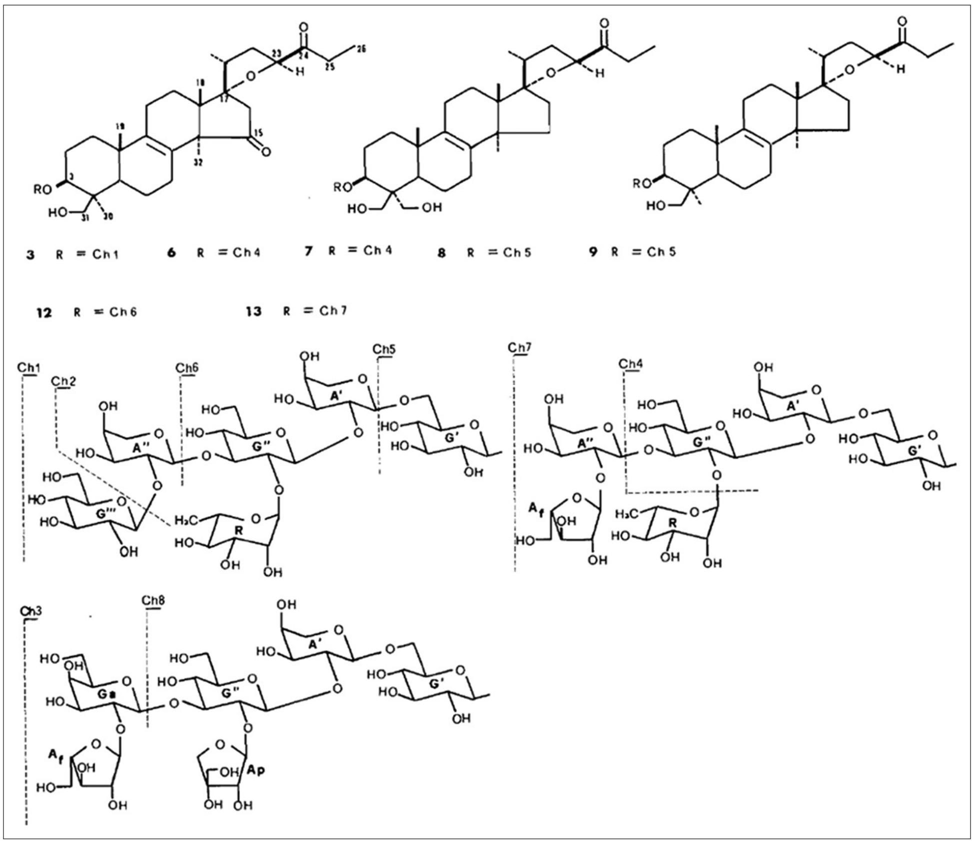

Fig. 5: Structures of muscarosides isolated from *Muscari armeniacum* [61]

Biotechnology (*in vitro* tissue culture) helps to clone material of *Muscari* and produce plants in volume [66]. *M. armeniacum* is also a good model for producing callus cultures with efficient genetic transformation system [67,68]; an efficient system for transgenic plants production of *M. armeniacum* through *Agrobacterium*-mediated transformation was developed [69]. The action of four potentially selective substances for transformed cells, antibiotics (geneticin, kanamycin, and hygromycin), bialaphos, antibiotics for eliminating *Agrobacterium* (cefotaxime and carbenicillin) on somatic embryogenesis, and growth of *M. armeniacum* ("Blue Pearl") calli was evaluated [68]. Furthermore, the system of plant regeneration from *M. armeniacum* leaf explants through somatic embryogenesis was presented [70], as well as *in vitro* propagation (regeneration) systems for this plant [71,72]. Plantlet regeneration Muscari species ("Blue Pearl") from protoplasts was successfully performed [73]. In *M. armeniacum* ("Early Giant") the influence of scale position, scaling time, leaf part, and leaf cutting time on growth and bulblet formation were studied [74,75].

Grape hyacinth bulbs were the object for investigation of gummosis hormonal regulation. The study focused primarily on the gums chemical composition (homogenous polysaccharides) [76]. Effects of plant hormones (gibberellic acid, benzyladenine, abscisic acid, and indole-3-acetic acid) were studied on inflorescence stalk and leaves growth of *M. armeniacum* [77] as well as cold forcing [78]. Plants freezing hardiness is an important aspect for landscape planting; *M. armeniacum* was resistant with median lethal dose temperature (LT_{50})<−9°C [79].

In Manisa Celal Bayar University (Manisa, Turkey), the *M. armeniacum* anatomical features growing in west Anatolia have been investigated. Superficial transverse sections, transverse cross-sections and of leaves, scapes, and roots were prepared for identification of anatomical features of plants (*M. armeniacum* and *Muscari neglectum*) collected from nine different spreading locations. Obtained indications help to differentiate the species anatomically; differences and similarities were determined. It was shown that the scapes and roots of species are similar anatomically as for leaves have several differences [80].

CONCLUSION

M. armeniacum has a wide range of biologically active substances. Thanks to the homoisoflavonoids content, crude herbal drug can demonstrate antioxidant, antimutagenic activity and can be used for cancer prevention.

Hyacinthacine alkaloids have specific glycosidase inhibitory activities; they have been identified as potential anticancer, antiviral, antidiabetic, and antiobesity drugs [81].

It should be noted that there is a need for further research. It is necessary to study the pharmacological profile of specific chemical compounds in order to check the *M. armeniacum* water extracts indication in traditional medicine; and an assessment of possible action mechanisms should be made. The present review focusing on the traditional uses, phytochemistry, biology, and pharmacological properties of *M. armeniacum* gave the preliminary information for additional studies on this plant. The results of the investigation can be used for further development of procedures for routine quality control and pharmacopeial monographs for crude herbal drugs.

AUTHORS' CONTRIBUTIONS

I declare that this work was done by the author named in this article.

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CONFLICTS OF INTEREST

None.

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