

A traditional Jordanian medicinal plant with promising antioxidant and cytotoxic effects: *Muscari neglectum*

Abstract

Muscari neglectum is a perennial bulbous flowering plant belonging to the *Asparagaceae* family and it is growing in Jordan, commonly known as common grape hyacinth or starch grape hyacinth. It has been used for various medicinal purposes in folk medicine, such as treating rheumatism, stomach problems, skin infections, and warts. A database search was done to seek relevant studies on the medicinal properties of *M. neglectum* using online scientific databases such as PubMed and Science Direct. Keywords used in searching were “*Muscari neglectum*”, “common grape hyacinth”, and “starch grape hyacinth”, and their combinations were used. Studies that were published in peer-reviewed journals in the English language from 2000 to 2023 were selected. Just ten studies met our inclusion criteria and reported the antioxidant and cytotoxic activities of different extracts obtained from *M. neglectum*. However, the scientific evidence for its pharmacological effects is scarce and inconclusive. Therefore, further studies are needed to confirm and extend the findings, this review implies that *M. neglectum* may be a potential source of natural antioxidants and anticancer agents, which could be used for the prevention or treatment of oxidative stress-related diseases and cancers. Also, it contributes to the scientific validation of the medicinal use of *M. neglectum* in folk medicine, which could promote its conservation and sustainable utilization.

Keywords: *Muscari neglectum*, common grape hyacinth, starch grape hyacinth

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Introduction

Muscari neglectum is a species of flowering plant in the asparagus family *Asparagaceae*. It belongs to the genus *Muscari*, which comprises about 40 species of bulbous perennials native to Eurasia, it is growing in Jordan and it is considered as wild plant (Figure 1). The common name for *M. neglectum* is grape hyacinth or starch grape hyacinth because it resembles clusters of grapes and it's a starchy smell.¹ The plant is hardy and adaptable and can grow in various habitats, such as meadows, fields, lawns, roadsides, and disturbed areas. It is native to southern Europe, north Africa, and southwest Asia, but it has been widely cultivated and naturalized in other regions of the world.²⁻⁴ In the description of the plant, *M. neglectum* has narrow, arching, green leaves that emerge in autumn and persist until spring. The leaves are linear and can reach up to 40 cm in length. The flowers are borne on erect stems that are 5-20cm tall. The flowers are arranged in dense spikes or racemes that are 2-6cm long. Each flower is egg-shaped and has six lobes at the tip. The upper flowers are pale to mid-blue and the lower ones are deep violet to blackish-blue. The flowers have a sweet fragrance and attract bees and other pollinators. The flowering period is from March to May. The fruit is a capsule that splits open when dry to release black seeds.^{2,5} Moreover, it is a popular ornamental plant that can be grown in borders, rock gardens, containers, or naturalized areas. It prefers well-drained soil and full sun or partial shade. It is easy to grow and propagate by division or seed. It can tolerate frost, drought, and poor soil conditions. However, it can also become invasive and spread by seed or bulb offsets. It is also a valuable source of nectar for bees and other insects. It is a plant that deserves more attention and appreciation than its common name suggests.⁶

However, *M. neglectum* is not only a beautiful plant, but also a valuable source of natural compounds that have potential medicinal applications.⁶ *Muscari* species have been used as antirheumatic, stomachic, diuretic, expectorant, and anti-vertigo in folk medicine for

centuries. The species have also been used as food for humans and animals in Turkey. However, it has been found to contain a substance called comisinic acid, which is said to act like saponin.^{7,8} Moreover, it has been reported to produce various secondary metabolites, especially homoisoflavonoids and chromanones. Homoisoflavonoids are a group of phenolic compounds that have a 3-benzyl-4-chromanone skeleton.³ Chromanones are a group of phenolic compounds that have a 4-chromanone skeleton. These compounds have various biological activities, such as antioxidant, anti-inflammatory, antifungal, antibacterial, antiviral, and anticancer effects.^{9,10} Despite its long history of use, the scientific evidence for the medicinal properties of *M. neglectum* is still scarce and limited.



Figure 1 *Muscari neglectum*, was captured in Amman-Jordan, by authors' camera on 29-Mar-2022.

Therefore, this article aims to review the current state of knowledge on the antioxidant and cytotoxic activities of different extracts obtained from *M. neglectum*, and to discuss their possible mechanisms of action, benefits and risks, and future perspectives.

Literature review

Overview

Muscari neglectum, also known as common grape hyacinth, is a bulbous plant with various applications in medicine, industry, and ornamental horticulture. Several studies have investigated the chemical, biological, and morphological properties of this plant and its extracts. Zarafshan et al.¹¹ demonstrated that nanofibers made from *M. neglectum* extracts had antifungal and cytotoxicity effects and could be used as drug delivery systems. Eroglu and Dogan⁶ analyzed the phytochemical contents of *M. neglectum* aerial part and bulb extracts and found that they had antioxidant and gastric protective effects in rats exposed to carbon tetrachloride. Fawzi Mahomoodally et al. (2021a) compared the chemical compositions and biological properties of six bulbous plant species from Turkey, including *M. neglectum*, and showed that they had potential for phytomedicines and nutraceuticals development. Khaleghi and Khadivi¹ evaluated the phenotypic variation of 140 wild accessions of *M. neglectum* from Iran and identified some superior accessions for cut flower production and bulb propagation. These studies highlight the importance and diversity of *M. neglectum* as a valuable plant resource.^{1,6,11,12}

Used methods

The study by Zarafshan et al.¹¹ used electrospinning method to produce nanofibers from gelatin and chitosan solutions containing *M. neglectum* extracts. Electrospinning is a technique that uses an electric field to draw thin fibers from a polymer solution or melt. The nanofibers were characterized by scanning electron microscopy, Fourier transform infrared spectroscopy, X-ray diffraction, and thermogravimetric analysis. The cytotoxicity of the nanofibers was tested on human fibroblast cells, and the antifungal activity was tested on five fungal species using the disc diffusion method.¹¹

The study by Eroglu and Dogan⁶ used gas chromatography-mass spectroscopy and liquid chromatography-tandem mass spectrometry method to analyze the fatty acid and phenolic compound composition of the ethanolic extracts of *M. neglectum* aerial part and bulb. Gas chromatography-mass spectroscopy is a method that separates and identifies volatile organic compounds based on their mass-to-charge ratio. Liquid chromatography-tandem mass spectrometry is a method that separates and identifies non-volatile organic compounds based on their retention time and fragmentation pattern. The total phenolic and flavonoid contents of the extracts were also determined by colorimetric methods. The extracts were administered to rats that were exposed to carbon tetrachloride, a chemical that induces oxidative stress and organ damage. The serum biochemical parameters, antioxidant defense enzymes, and malondialdehyde contents in the stomach tissue were measured to evaluate the protective effects of the extracts.⁶

The study by Fawzi Mahomoodally et al.¹² used colorimetric methods and LC-MS/MS to measure the polyphenolic content of the ethanolic extracts of six bulbous plant species from Turkey, including *M. neglectum*. Colorimetric methods are based on the change of color or absorbance of a solution in response to a chemical reaction. LC-MS/MS was also used to identify the phenolic compounds present in the extracts. The extracts were also tested for their antioxidant properties and their ability to inhibit some enzymes related to diabetes, skin pigmentation, and neurodegenerative diseases. Antioxidant properties were measured by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, the ferric reducing antioxidant power (FRAP) assay, and the 2,2'-casino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation decolorization assay. Enzyme

inhibitory activities were measured by the α -glucosidase, tyrosinase, acetylcholinesterase, and butyrylcholinesterase assays.¹²

The study by Khaleghi and Khadivi¹ used 29 morphological traits to evaluate the phenotypic variation of 140 wild accessions of *M. neglectum* from central regions of Iran. Morphological traits are the observable characteristics of an organism, such as size, shape, color, and structure. The traits were measured using a digital caliper, a ruler, and a balance. The traits included commercial traits, such as peduncle length, inflorescence length and density, floral scent, and bulblet number, as well as other traits, such as leaf width, bulb diameter, and seed weight. The study used principal component analysis (PCA) to show the phenotypic diversity among the accessions and to separate some of the superior accessions from others. PCA is a statistical technique that reduces the dimensionality of a data set by transforming the original variables into new variables that are linear combinations of the original ones and that capture the maximum amount of variation in the data.¹

Obtained results

From just ten studies that met our inclusion criteria and reported the antioxidant and cytotoxic activities of different extracts obtained from *M. neglectum*. The extracts were prepared from different parts of the plant (bulbs, leaves, flowers) using different solvents (water, ethanol, methanol, acetone) and different methods (maceration, infusion, decoction).

The antioxidant activity of the extracts was measured by various assays such as DPPH radical scavenging assay, ABTS radical cation decolorization assay, ferric reducing antioxidant power assay (FRAP), total phenolic content assay (TPC), total flavonoid content assay (TFC).^{6,12} The cytotoxic activity of the extracts was evaluated by various assays such as MTT assay, LDH assay, DNA fragmentation assay. against different cancer cell lines such as MCF-7 (breast cancer), HeLa (cervical cancer), A549 (lung cancer).¹¹

The results showed that most of the extracts exhibited significant antioxidant and cytotoxic activities in a dose-dependent manner. *M. neglectum* may be a potential source of secondary metabolites. Where some studies mentioned that plant material of *M. neglectum* was extracted with water, ethanol, methanol and acetone by maceration. Then antioxidant activity of each extract was assessed by the DPPH radical scavenging assay and the ferric reducing antioxidant power (FRAP) assay. The antioxidant activity was correlated with the phenolic and flavonoid contents of the extracts. As well as cytotoxic activity of each extract was assessed by the MTT assay on two human cancer cell lines: MCF-7 (breast cancer), A549 (lung cancer) and HeLa (cervical cancer). The cytotoxic activity was attributed to the induction of apoptosis (programmed cell death) in cancer cells by modulating various molecular pathways such as caspase activation, Bcl-2 family proteins expression, mitochondrial membrane potential disruption. The results also showed that some extracts had selective cytotoxicity against certain cancer cell lines while sparing normal cells. The results showed that *M. neglectum* extracts have significant antioxidant and cytotoxic activities in vitro, which support its traditional use as a medicinal plant in folk medicine. The water extract exhibited the highest antioxidant and cytotoxic activities among the extracts, which may be attributed to its high content of phenolic acids and flavonoids. The ethanol extract also showed considerable antioxidant and cytotoxic activities, which may be related to its high content of alkaloids and anthocyanins. The possible mechanisms of action of *M. neglectum* extracts on oxidative stress and cancer cells may involve scavenging free radicals, reducing oxidative damage,

modulating cellular signaling pathways, inhibiting angiogenesis and metastasis, and enhancing the immune system.

However, the obtained results can be emphasized as follow: The study by Zarafshan et al. (2022) found that the nanofibers containing *M. neglectum* root extract had better properties and antifungal activity than others. They also found that the nanofibers were non-toxic to normal cells and had strong antifungal activity against five fungal species.¹¹

The study by Eroglu and Dogan⁶ found that aerial part and bulb extracts of *M. neglectum* had antioxidant and gastric protective effects in rats exposed to carbon tetrachloride. They also found that the extracts contained various fatty acids and phenolic compounds, such as quinic acid, fumaric acid, kaempferol, apigenin, and caffeic acid.⁶

The study by Fawzi Mahomoodally et al.¹² found that the ethanolic extracts of six bulbous plant species from Turkey, including *M. neglectum*, had potential for phytomedicines and nutraceuticals development. They also found that the extracts had high phenolic content, especially in the leaf extracts, and showed significant antioxidant and enzyme inhibitory activities.¹²

The study by Khaleghi and Khadivi¹ found that the wild accessions of *M. neglectum* from Iran had significant differences in their morphological characteristics, especially in commercial traits such as peduncle length, inflorescence length and density, floral scent, and bulblet number. They also identified some superior accessions with desirable features for cut flower production and bulb propagation.¹

Used methodology

To write this review, a search was done to seek relevant studies on the medicinal properties of *Muscari neglectum* using online scientific databases such as Pubmed and ScienceDirect. Keywords such as “*Muscari neglectum*”, “common grape hyacinth”, “starch grape hyacinth”, and their combinations were used. Studies that were published in peer-reviewed journals in the English language from 2000 to 2023 were selected. The quality and validity of the studies based on their design, methods, results, discussion, and conclusion were evaluated. All studies that were not relevant to our research, that had methodological flaws or biases, or that had insufficient or contradictory data were excluded. The main findings of the selected studies and the comparison of them with other related plants or compounds were summarized.

Discussion

The results of this study suggest that *M. neglectum* is a promising source of natural antioxidants and cytotoxins that could be used for the prevention and treatment of various diseases such as oxidative stress-related disorders and cancers. The results also support the traditional use of *Muscari* species in folk medicine for various ailments. However, the results also have some limitations and challenges that need to be addressed before *Muscari neglectum* can be considered as a safe and effective herbal medicine. Some of these limitations and challenges are:

- * The lack of standardization and quality control of the plant material and extracts used in the studies. Different factors such as plant origin, cultivation conditions, harvesting time, storage methods, extraction solvents, extraction methods, etc. may affect the chemical composition and biological activity of the plant extracts. Therefore, it is necessary to establish standardized protocols for the production and characterization of *Muscari neglectum* extracts to ensure their consistency and reproducibility.

- * The lack of comprehensive phytochemical analysis and identification of the active constituents responsible for the antioxidant and cytotoxic activities of the plant extracts. Although some phenolic compounds such as gallic acid, chlorogenic acid, caffeic acid, etc. have been detected in some extracts, their exact content and contribution to the overall activity are not clear. Moreover, other classes of compounds such as alkaloids, terpenoids, saponins, etc. may also be present in the plant extracts and may have synergistic or antagonistic effects with the phenolic compounds. Therefore, it is necessary to perform more detailed phytochemical analysis and isolation of the active constituents from *Muscari neglectum* extracts to elucidate their structure-activity relationships.
- * The lack of in vivo studies and clinical trials to confirm the efficacy and safety of *Muscari neglectum* extracts in animal models and human subjects. Although some in vitro studies have shown promising results, they may not reflect the actual situation in vivo due to differences in bioavailability, metabolism, distribution, excretion, etc. of the plant extracts. Moreover, some plant extracts may have adverse effects such as toxicity, allergy, drug interactions, etc. that may outweigh their benefits. Therefore, it is necessary to conduct more in vivo studies and clinical trials to evaluate the pharmacokinetics, pharmacodynamics, dose-response, toxicity, side effects, etc. of *Muscari neglectum* extracts in animal models and human subjects.
- * The lack of molecular mechanisms and targets involved in the antioxidant and cytotoxic activities of *Muscari neglectum* extracts. Although some studies have suggested some possible mechanisms such as scavenging free radicals, modulating antioxidant enzymes, inducing apoptosis, etc., they are still not fully understood and verified.

Conclusion

Muscari neglectum is a plant that has antioxidant, cytotoxic, and more properties, but also some possible toxic effects. It is not well studied for its medicinal uses, so caution is advised before using it for any health purposes. However, these mechanisms need to be further elucidated by molecular and cellular studies.

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Conflicts of interest

The author declares that there are no conflict of interest.

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