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A Comprehensive Review on Pharmacognostical and Pharmacological Characters of *Anchusa azurea*

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Abstract

Anchusa azurea (Syn. *Anchusa italica*) belong to the Boraginaceae family and were distributed in the temperate, especially in Mediterranean regions. Chemical studies showed that *A. azurea* contains mainly triterpenes and polyphenols. *A. azurea* possessed many pharmacological effects; these included anticancer, antioxidant and antiviral effects etc. The aim of this review article is to gather information about *A. azurea* which is currently scattered in form of various publications PubMed, Science Direct and Elsevier etc. Through this review article we tried to attract the attention of people for therapeutic potential of *A. azurea*. The present review comprises upto date information of traditional uses, phytochemistry and pharmacology of *A. azurea*. Some progress has been made, but still consistent efforts are required to explore the individual compounds isolated *A. azurea* to validate and understand its traditional uses and clinical practices. This review article provides preliminary information and gives a direction for the basic and clinical research on *A. azurea*.

Key words: *Anchusa azurea, A. italica,* Boraginaceae, Traditional uses, Phytochemistry, Pharmacology.

INTRODUCTION

Anchusa azurea Mill. (Figure 1) is a species of flowering plant known by the common name Italian bugloss.[1] It is belonging to the Boraginaceae family, which included a variety of shrubs, trees and herbs, totaling about 2000 species in 146 genera found worldwide while it is represented in wild Iraq by 26 genera and about 93 species.[2,3] *A. azurea* was used traditionally as stimulant, tonic, demulcent, in bilious complaints, fever, cough and asthma and as diuretic in bladder and kidney stones.[4-6] It was also used as diaphoretic, narcotic, hypnotic, antiarthritis, antirheumatic and cathartic.[7] The leaves of the plant were used as decoction in cold, sore throat and chest pain.[8] The lack of a comprehensive review on the phytochemistry and pharmacology of *A. azurea* prompted us to compile a review on the traditional uses, phytochemistry and pharmacology of *A. azurea*.

Nomenclature[1]

Anchusa azurea Mill. has a synonym, also it has some common names as shown in Table 1.

Classification

The collected plant species were classified and identified as *Anchusa azurea* Mill. from ESUH (Education Salahaddin University Herbarium). Table 2 shows the classification of the plant.[1]

Taxonomical features

Perennial, densely hispid, patent, rigid or soft, often tubercle-base hairs stems; 20-150 cm, erect. Leaves 100-300 × 15-50 mm. Cymes many; pedicels 1-3 mm, up to l0 mm in fruit; bracts shorter than calyx. Calyx 6-8 mm, up to 18 mm in fruit, divided almost to the base into linear, acute lobes. Corolla violet or deep blue; tube 6-10 mm, slightly exceeding or shorter than calyx;

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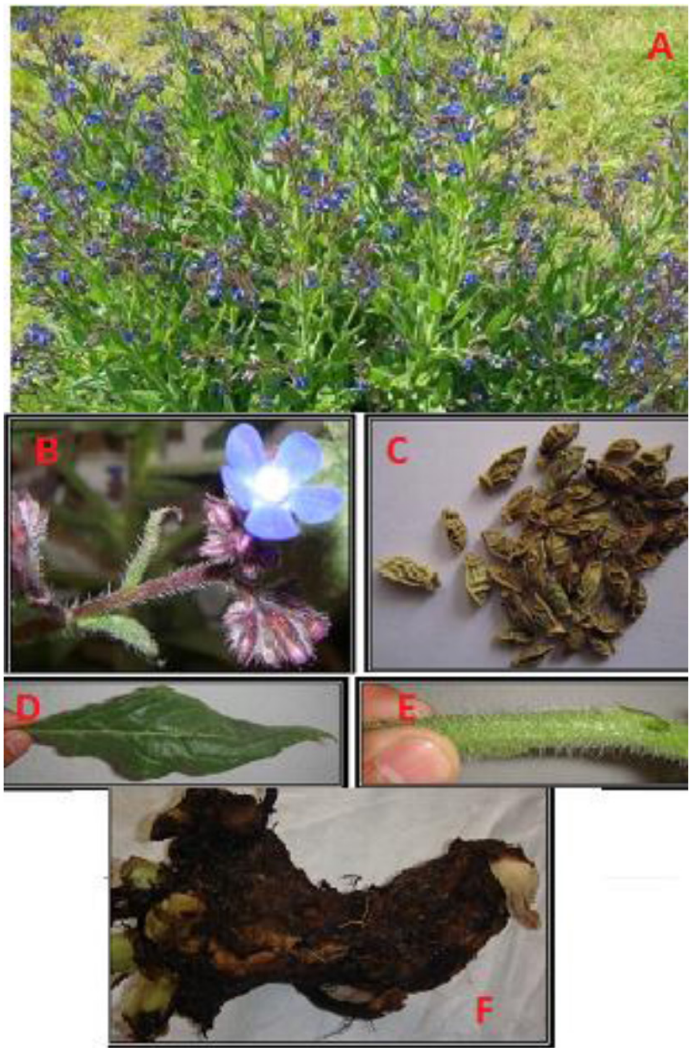


Figure 1: *Anchusa azurea* Mill different parts: (A) Aerial parts, (B) Flowers, (C) Seeds, (D) Leaf, (E) Stem and (F) Root.

Table 1: Nomenclatures of *Anchusa azurea* Mill.

Scientific name	*Anchusa azurea* Mill
Synonyms	*Anchusa italica* Retz.
Common names	Italian Bugloss, Large blue alkanet, Garden Anchusa
Kurdish names	Gormza, Kawlla Shina, Chizy
Arabic names	Lsan Al-thor, Ward Mawe
Plant Family	Boraginaceae (borage or Forget-me-not-family)
Species name derivation	*Anchusa* = comes from the greek word meaning [face make-up] since of a particular red due extracted from roots. Such a name was already by Aristofans and Xenofon, (400BC) for the name of a plant (Greek); *Italic* = Italian origin or related to Italy (Latin)

limb 10-15 mm in diameter; stamens inserted at top of tube, overlapping scales. Nutlets 7-10 × 2-3 mm, oblong or oblong-obovoid and erect.[9]

Distribution in the world

A. azurea is native throughout whole Europe, especially the southern and central parts (e.g. Italy, Greece, Hungary, France, Portugal, Spain, Ukraine and also Russia). It is also found in Western Asia (Iraq, Pakistan, Israel, Cyprus, Turkey, etc), Causcasus (e.g.: Azerbaijan. Soviet and Middle Asia: Kazakhstan etc.) and Tropical Asia (e.g.: Pakistan). It is believed to be originated from the Mediterranean areas from Portugal and east to the Caucasus.[9]

Table 2: Classification of *Anchusa azurea* Mill.

Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Lamiales
Family	Boraginaceae
Genus	*Anchusa*
Species	*azurea*

Distribution in Iraq

The plant is present in Iraq especially it is widely distributed in Kurdistan region like; Kirkuk District, Persian Foothill District, Mosul District, Upper Jazira District, Amadia District, Rawanduz District and Sulaimaniya District.[10]

Traditional uses

Anchusa species are used in folk medicine for wound healing and as a diuretic agent.[11] The whole plant is antitussive, depurative and diuretic. It is harvested when in flower and dried for later use. The dried and powdered herb is used as a poultice to treat inflammations. Use internally with caution, the plant contains the alkaloid cynoglossine which can have a paralyzing effect[12] and carcinogenic.[13]

Flowers used like tea, tonic to invalids and children; lowers pulsation. It is a substitute of *Anchusa officinalis*, used as a diaphoretic and diuretic.[10] nerves, vision, arthritis.[14] The recommended use for plant flowers and roots are antidiabetic, while the recorded literature uses are weight loss.[7] A red dye is obtained from the root; this was at one time used as a basis for some cosmetics.[12] The flowers are a good source of food for bees.[15] Many named forms been selected for their ornamental value. The plants tend to be short-lived perennials but they can he propagated by means of root cuttings.[16]

Edible uses

Raw flowers are an excellent and decorative additions to the salad bowl, or used as a garnish.[17] The tender young leaves and young flowering shoots can be cooked and eaten as a vegetable.[12] In Tunisia, the young leaves were used to be mixed with those of wild sorrel and eaten in soup.[18]

Phytochemistry

The seeds of *A. azurea* are rich sources of many unsaturated fatty acids like; linoleic acid, oleic acid, γ- linolenic acid, eicosenoic acid. Also, the plant is containing some other saturated fatty acids like; palmitic acid. The seeds of *A. azurea* contained 21 % (v/w) oil. The gamma-linolenic acid represented 13% (v/v) of the oil and 2.7% (v/w) of the seeds.[19]

Four new triterpene glycosides (saponins), named oleanazuroside 1 (1), oleanazuroside 2 (2), ursolazuroside 1 (3) and ursolazuroside 2 (4), together with the seven known compounds named (2α, 3β, 4α, 19α)- 2,3 19,23 -tetrahydroxyurs- 1 2-en-28-oic acid p-glucopyranosyl ester (=quercilicoside A; 5), kaempferol 3-0-glucopyranoside) (=astragalin; 6), quercetin 3-(fi-glucopyranoside) (=isoquercitrin; 7), quercetin 3-(a-rhamnopyranosyl-(1 6)-P-glucopyTanoside) (=rutin; 8), kaempferol (α-rhamnopyranosyl-(1 6)-p-glucopyranoside) (9), rosmarinic acid (10) and 3-(3,4-dihydroxyphenyl) lactic acid (11), were isolated from the methanolic extract of the aerial parts of *A. azurea*.[20]

European Food Safety Authority (EFSA) shows that the plant contains toxic pyrrolizidine alkaloids: lycopsamine and untoxicpyrrolizidine alkaloids: laburnine and acetyllaburnine.[21] The plant shows positive tests for alkaloids and tannins and it contained oil rich in Vitamin E. The flowers yield anthocyanins and the leaf, stem yield bornesitol.[4]

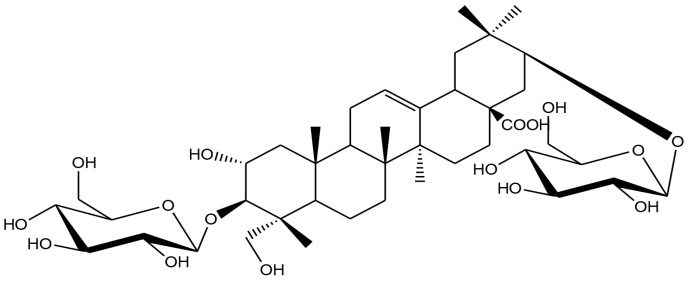
The total lipid content of *A. azurea* leaves was 0.93 g / 100 g. It contained 16.59% saturated fatty acids, 3.15% monounsaturated fatty acids and 4.85% polyunsaturated fatty acids. Oil contained the following compounds: capric acid (0.07%), undecanoic acid (0.01%), lauric acid (0.07%), tridecanoic acid (0.01%), myristic acid (0.35%), myristoleic acid (0.16%), pentadecanoic acid (0.12%), palmitic acid (10.45%), palmitoleic acid (0.14%), heptadecanoic acid (0.22%), stearic acid (1.67%), oleic acid (2.20%), linoleic acid (12.16%), γ-linolenic acid (1.46%), α-linolenic acid (64.74%), arachidic acid (1.64%), eicosenoic acid (0.17%), cis-8.11.14-eicostrienoic acid (1.69%), cis-11.14.17-eicosatrienoic acid, heneicosanoic acid (0.21%), behenic acid (1.25%), eruicic acid (0.07 %), tricosanoic acid (0.02%), lignoceric acid (0.72%) and nervonic acid (0.40%). However, Conforti *et al.* showed that *A. azurea* yield linoleic acid 2.57 % and linolenic acid 5.02 %. It also contained hydroalcoholic extracts 23.8 % and the total phenolics content (using Folin– Ciocalteau method) was 85.5 chlorogenic acid equivalents (mg/g).[22]

Peshawa *et al.*[23] characterized eleven fatty acids in triglycerides isolated from the seeds of traditional Kurdish medicinal plant *A. azurea* by GC-MS analysis, the main components were oleic, palmitic, palmitoleic, 11-eicosenoic, erucic and two ω-9 acids. Totally, eleven fatty acids were analyzed from the seeds of the studied plant using GC-MS analysis. The results showed that the plant seeds contain high percentage of elaidic acid (46.42%), palmitic acid (18.9%), linoleic acid (14.59%) and the other main fatty acids (FAs) are erucic acid (6.33%), 11-eicosenoic acid (5.02%), stearic acid (4.55%) and 6,9,12-octadecatrienoic acid (2.43%). The percentage of minor FAs is (0.78%) nervonic acid, (0.46%) myristic acid, (0.38%) palmitoleic acid and (0.14%) for 11-hexadecenoic acid. Major chemical constituents of *A. azurea* shown in Figure 2.

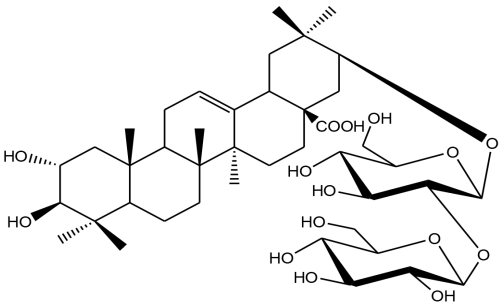
Pharmacological Reports

Antioxidant effects

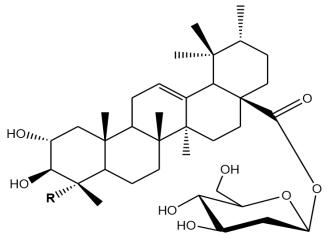
The radical-scavenging activities against 2,2-dipheny1-1-picrylhydrazyl (DPPH) of the butenolic extract and of the compound (8) and (10) were very strong.[20] The IC_{50} values of inhibition of Nitric Oxide (NO) production and cytotoxicity of *A. azurea* were 123 μg/ml and >1000 respectively. The IC_{50} value of free radical scavenging activity on DPPH of *A. azurea* was 84 μg/ml.[22]



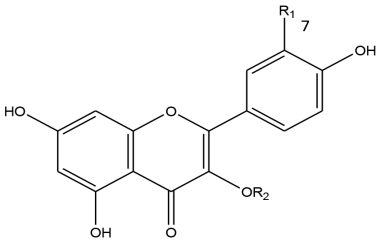
Oleanazuroside 1 (1)



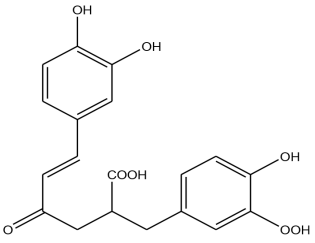
Oleanazuroside 2 (2)



R = Me = Ursolazuroside 1 (3)
R = CHO = Ursolazuroside 2 (4)
R = $HOCH_2$- = (2alpha ,3beta, 4alpha, 19alpha)- 2,3 19,23 -tetrahydroxyurs- 1 2-en-28-oic acid p-glucopyranosyl ester (=quercilicoside A; 5)



R_1= H, R_2 = Glc = Kaempferol 3-0-glucopyranoside) (=astragalin; 6)
R_1 = OH, R_2 = Glc = Quercetin 3-(fi-glucopyranoside) (=isoquercitrin; 7)
R_1 = OH, R_2 = Glc-Rha = Quercetin 3-(a-rhamnopyranosyl-(1➞6)-P-glucopyTanoside) (=rutin; 8)
R_1 = H, R_2 = Gla-Rha = Kaempferol (a-rhamnopyranosyl-(1 ➞6)-p-glucopyranoside) (9)



Rosmarinic acid (10)

Figure 2: Chemical constituents reported from *A. azurea*.

Anticancer effects

The cytotoxic activity of *A. azurea* against MCF-7, HepG2, WEHI and MDBK cell lines was evaluated. IC_{50} was more than 100 μg/ml against all evaluated cell lines.[23] *A. azurea* is one of the thirteen plants contained in the Abnormal Savda Munziq of Traditional Uighur formula (ASMq), which used for the treatment and prevention of cancers. The effects of ethanol extract of ASMq on cultured human hepatoma cells (HepG2) was carried out to explore the mechanism of its putative anticancer properties by using many experimental methods including the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) bromide, neutral red and lactate dehydrogenase (LDH) leakage, the incorporation of 3[H]-leucine and 3[H]-nucleosides into protein, DNA and RNA and quantifying the formation of malondialdehyde-thiobarbituric acid (MDA). ASMq ethanol extract significantly inhibited the growth of HepG2 and cell viability, increased the leakage of LDH after 48 hr or 72 hr' treatment in a concentration and time dependent manner (p <.05). Cellular protein, DNA and RNA synthesis were inhibited in a concentration and time dependent manner (P <.05). No significant MDA release in culture medium and no lipid peroxidation in cells were observed. According to the results, the cytotoxic effects of ASMq ethanol extract might be related to inhibition of cancer cell growth, alteration of cell membrane integrity and inhibition of cellular protein, DNA and RNA synthesis.[24]

Central nervous and endocrine effects

Oral administration of Abnormal Savda Munsiq (ASMq) which contained *Anchusa italica*, also found to exert a memory-enhancing effect in the chronic stressed mice induced by electric foot-shock. The memory improvement of the stressed mice was shown by an increase of the latency time in the step-through test and the decrease of the latency time in the Y-maze test. Treatment with ASMq induced significant decrease the serum levels of adrenocorticotropic hormone, corticosterone and β-endorphin as well as the brain and serum level of norepinephrine. Furthermore, ASMq was able to significantly reverse the chronic stress by decreasing the brain and serum levels of the monoamine neurotransmitters dopamine, 5-hydroxytryptamine and 3,4-Dihydroxyphenylalanine.[25]

Antiviral effects

The antiinfluenza virus activity of aqueous and alcoholic extract of *Anchusa italica* plant (2.5-80 μg/ml) was investigated on the viral infected Madin-Darbey -Canine Kidney cell monolayer. *A. azurea* extracts possessed higher antiviral properties when used one hour before infection compared to their usage after infection. However, the antiviral effect of alcoholic extract was more pronounced than that of the aqueous preparation. The antiviral activity of *A. azurea* was likely due to interference with viral replication and transcription; accordingly, *A. azurea* can be use such as amantadin for the treatment of influenza.[26]

Anti-inflammatory activity

The anti-inflammatory activity of different extracts from the aerial parts and the roots of *A. azurea* were investigated in rats using carrageenan-induced acute inflammation. The methanolic extract from the aerial parts, its *n*-butanol fraction and rosmarinic acid, which was isolated from the *n*-butanol fraction of the methanol extract, showed significant dose-dependent anti-inflammatory activity. During the acute phase of inflammation, the anti-inflammatory activity of rosmarinic acid was comparable to that of ibuprofen.[27] In another study, both the ethanol and aqueous extracts of *A. azurea* were found to be ineffective in anti-inflammatory and antinociceptive activity tests.[28]

CONCLUSION

In recent years, phytochemical investigation of herbal flora has received much attention of the scientists and pharmaceutical industries so as to know about novel herbal compounds which can be screened for their therapeutic potential to treat several health disorders without any side effects. This genus could be a promising source for the development of novel strategies to cure fatal maladies. Further consideration, standardization and clinical trials of pharmacological potential of *A. azurea* is essential for its recommendation as a medicine at safer level. The information summarized above will serve as a reference tool for the research groups working in the area of developing alternatives of synthetic drug. However, there is a need to evaluate the therapeutic potential on modern scientific lines through clinical trials, phytochemicals and pharmacological studies. Experimental studies have demonstrated its anticancer, neuroprotective, antimalarial, anthelmintic, antipyretic, antidepressant, antiulcer, antibacterial and antioxidant activities. The information congregated in this review will help researchers and industry persons to work in line to reconnoiter the potential of this plant and utilize it for the benefit of the society.

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CONFLICT OF INTEREST

None.

ABBREVIATIONS

Syn.: Synonym; **EFSA:** European Food Safety Authority; **GC-MS:** Gas chromatography mass spectroscopy; **DPPH:** 2,2-dipheny1-1-picrylhydrazyl; **IC:** Inhibitory concentration; **LDH:** Lactate dehydrogenase; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium; **HepG2:** Human hepatoma cells.

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