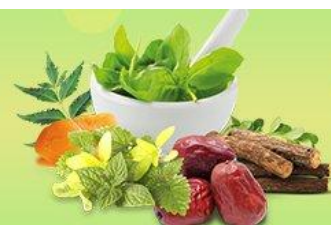


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Therapeutic potential of Ushaq (*Dorema ammoniacum* D. Don): A unique drug of Unani medicine

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Abstract

Ushaq (*Dorema ammoniacum* D. Don) is a well known and potent herbal drug used in various Traditional Medicines for its various beneficial effects in different ailment and diseases. It is commonly known as Gum Ammoniac. It consists of oleogum resin obtained by exudation from the stem of the flowering and fruiting plant of *Dorema ammoniacum* D. Don. The genus *Dorema* D. Don comprises 12 species and belongs to Apiaceae (*alt.* Umbelliferae) family. *Dorema ammoniacum* D. Don is one of them. It is used in Iranian, Indian and Western Medicine and is listed in the British pharmacopoeia as an antispasmodic and expectorant. The mentioned plant is utilized in the factories producing of glues and cosmetic industry. In Unani Medicine it is used as a potent drug for various ailments as mentioned by Avicenna and Razi in their treatises. This review article discusses the pharmacognosy, phytotherapy, phytochemical and biological studies of *Dorema ammoniacum* D. Don along with comprehensive review of based on Unani Medicine as well as recent scientific reports.

Keywords: Ushaq, *Dorema ammoniacum* D. Don, Unani Medicine, Oleogum resin

Introduction

Historically, plants, minerals and animals are the first and foremost source of therapeutic and healing and have been used since ancient times and in folklore for the treatment of human ailments and illnesses. The use of plants, minerals and animals as medicines has been described throughout history in the form of traditional medicines, remedies. The earliest records were depicted on clay tablets in cuneiform from Mesopotamia (2600 B.C.) which documented oils from *Cupressus sempervirens* (Cypress). The Ebers Papyrus (2900 B.C.) an Egyptian pharmaceutical record documents over 700 plant-based drugs. The Chinese Materia Medica (1100 B.C.) documented records of the uses of natural products of herbs. Dioscorides, (100 A.D.) a Greek physician recorded the collection, storage and the uses of medicinal herbs. During the Dark and Middle Ages the Arabs preserved the Greco-Roman knowledge and expanded the uses of their own resources, together with Chinese and Indian herbs unfamiliar to the Greco-Roman world. Avicenna, a Persian, physician, philosopher and pharmacist contributing much to the sciences of pharmacy and medicine through works such as the *Canon Medicinæ* [1]. He mentioned 719 single drugs of herbal, mineral and animal origin and 750 compound drugs [2]. The World Health Organization has estimated that more than 80% of the world's population in developing countries depends primarily on herbal medicine for basic healthcare needs [3]. There are over 80,000 plants that have medicinal uses throughout the world and usually a specific part of the plant is used for medical preparations such as tablets, infusions, extracts, tinctures, ointments, or creams. Currently, many of the commonly used drugs are of herbal origin and about 25% of the prescription drugs contain at least one herbal-derived active ingredient or synthetic compound, which mimics a plant-derived compound [4]. Ushaq (Gum Ammoniacum) is a well known and potent herbal drug used in various Traditional Medicines for its various beneficial effects in different ailment and diseases. Unani Medicine (one of the oldest traditional medicines) also known as Greco-Arab Medicine possesses a richest source and versatile treasure trove of medicinal plants. Ushaq (Gum Ammoniacum) is one of those herbal drugs mentioned in of Unani Medicine. The genus *Dorema* D. Don of the Apiaceae (*alt.* Umbelliferae) family comprises 12 species; *Dorema ammoniacum* D. Don is one of them mainly distributed in South-Western and Central Asia [5]. It is known as "Ushak, Ushuk, Kandari in Ayurveda [6, 7, 8, 9] and "Ushaq" or "Vasha" in Iranian Traditional Medicine and "Persian ammoniacum" in Greek and Latin medicinal literatures [10].

It is used in Iranian, Indian and Western Medicine and is listed in the British pharmacopoeia as an antispasmodic and expectorant [11]. The mentioned plant species in France are utilized in the factories producing of glues and cosmetic industry. Moreover, this plant has other varied uses such as food industry, confectionary products, paint industry, manufacturing, and production of the detergents and especially in production of special glues for jewellery [12].

Pharmacognosy

Taxonomic classification

Kingdom; *Plantae*, subkingdom; *Viridiplantae*, infrakingdom; *Streptophyta*, superdivision; *Embryophyta*, division; *Tracheophyta*, subdivision; *Spermatophytina*, class; *Magnoliopsida*, Superorder; *Asteranae*, order; *Apiales*, family; *Apiaceae*, genus; *Dorema*, species; *Dorema ammoniacum* [13].

Pharmacopoeial Name

Ayurvedic Medicine; Ushaka, Ushaka. *Unani Medicine*; Ushaq, Ushah, Kandal [14] *Iranian Traditional Medicine*; Ushaq or Vasha, Kandal, or Koma-kandal [10, 12].

Vernaculars

English: Gum Ammoniac, Ammoniac [9, 15-17] *Arabic*: Ushuq, Ushajj, Shajj, Wushaq, Lizaqz Zahab [6, 7, 8, 9] *Hindi*: Ushak, Ushuk, Kandar [6, 7, 8, 9] *Persian*: Usham, Usha, Usha Kalyani [6, 8, 9] *Urdu*: Ushaq [9]

Etymology

Dioscorides, (100 A.D.) a Greek physician is the first person who has mentioned it as a medicinal plant. Dioscorides observed and noted that this plant grows and found in abundant form near the temple of God Amon (God of ancient Egyptian/Greek/Roman era) and therefore he named it as Ammoniacon and the present medical name "Ammoniacom" is a modified name of that ancient "Ammoniacon" name given by Dioscorides [6].

Geographical Distribution and Habitat

Dorema ammoniacum D. Don. is a perennial monocarpic plant grows to height about 1–3 m and in spring and early summer contains a milky juice. It is one of the most important endemic medicinal plants in its family which grows in the arid and semi-arid areas in the regions of Iran and some of the Asian countries such as Turkmenistan, Afghanistan, Pakistan and India [11]. It is mainly distributed in South-Western and Central Asia [5] Persia, Southern Siberia [14].

Parts Used: Oleogum resin [9] *Mizaj* (Temperament): Hot 2⁰ Dry 1⁰ [6, 8-20] *Miqdar-e-Khorakh* (Dosage): 2-4grams [6, 9, 18] *Muzir* (Side Effect): Harmful for Stomach and Kidney [6, 19, 20] *Musleh* (Corrective): Anisoon for Stomach and Zoofa for Kidney [6, 19, 20] *Badal* (Substitute): Moom, Sakbinaj, Jaosheer [6, 8, 19, 20] *Murakkabat* (Compound Formulations): Zimade Ushaq [9]

Morphological description and characteristics, Identification and Standardization; Ammoniacum occurs into two forms; 1-Tears and 2-Lumps [21].

Tear Ammoniacum; Composed of separate, small, rounded to ovoid or irregular masses varying from about 0.5-3 cm in

diameter, hard and brittle, but soften when warmed; surface dull, pale yellow, darkens with age, fractured surface milky-white to pale brownish-yellow, opaque with a waxy lustre.

Lump Ammoniacum: Composed of tears and larger pieces of the gum-resin agglutinated together with a bluish, resinous substance and frequently mixed with varying amounts of extraneous materials [21].

Odour and Taste: The resin has a balsamic resinous odour and a bitter, unpleasant, somewhat acrid taste [9, 16, 21].

Solubility: Partially soluble in water giving turbid solution and slightly soluble in 10% HCL giving a light yellow solution, both solutions show very light blue fluorescence in UV 366nm; completely soluble in 10% H₂SO₄ giving brown colour solution; partially soluble in ethyl acetate, chloroform and alcohol giving a turbid solution which give blue fluorescence in UV 366nm; insoluble in n-hexane and petroleum ether (60-80 °C) [9].

Identification tests: Following tests are the mentioned in The Unani Pharmacopoeia of India

1. Take 1.0 gm of drug and triturate with water, and to one part of the white emulsion thus obtained, add a few drop of a solution of chlorinated soda; a deep orange colour develops.
2. Add a few drops of ferric chloride solution to the other part of the white emulsion. A transient faint violet colour develops.
3. Ushaq complies with the test for freedom from umbiferone when tested as follows: Boil 0.2 gm of drug powder for a few minutes with 2 ml of HCl and the dilute with equal volume of water, filter, make the filter alkaline with dilute ammonia solution and observe it under UV light; the solution should not show blue fluorescence [9].

Standardization: On the basis of identification, purity and strength the following standard values have been mentioned in The Unani Pharmacopoeia of India: [9].

Parameter	Percentage (%)	
Foreign matter	not more than	2
Total ash	not more than	13
Acid-insoluble ash	not more than	5
Water-soluble ash	not more than	2
Alcohol-soluble extractive	Not less than	68
Water-soluble extractive	Not less than	14
Moisture content	Not less than	3.69
Total phenolics	Not less than	0.9

TLC behaviour of ethanolic extract; [9]

Solvent system	Spray/reagent treatment	No. of spots	R _f value
n-hexane : Ethyl acetate : Metanol (3.5: 1.5: 0.2)	On spraying with 5% alcoholic ferric chloride solution	6	0.10
			0.40
			0.50
			0.64
			0.76
			0.90

Actions and uses (Afaal wa Istemalaat) mentioned in Unani Medicine

Actions: Muhallil Warm and Riyah [6, 8, 18, 19, 20, 22, 23]

Mulayyin [6, 8, 18, 22] Jazibe- Rutoobat [6, 8, 19] Mushile-Balgham [6, 19, 50, 22] Mukhrije and Musqite- Janeen [6, 8, 18, 19, 20, 22] Mudirre- Baul and Haiz [18, 22] Mumbite- Lahm [18, 19, 22] Jali [6, 19] Qatile- Habbul Quru [22] Munashshif [6] Daf-e-Ta'affun [9]

Avicenna (Ibne Sina) mentioned it as a potent Anti inflammatory (*Muhallil*) Desiccant (*Mujaffif*), Deobstruent (*Mufattih*), Laxative (*Mulayyin*) and Absorbive (*Jazib*) drug that does not produces irritation. A potent Diuretic (*Mudirr*) which sometimes causes Haematuria, Emmenagogue (*Mudirr Haiz*), Abortifacient and has Vermicide effect (Qatile Kirm) [24].

Therapeutic uses: Warm and Sudade Kabid and Tihal [6, 18, 19, 20, 22] [5, 9, 30, 86, 87] Waj'ul Mafasil and ThajjureMafasil [6, 8, 18, 19, 20, 22] Irqunnisa [18, 19, 20, 22] Niqras [18, 22] Wajul Zuhar [19, 20, 22] Khunnaq [8, 18-20] Usre Tanaffus and Rabu [6, 9, 18-20, 22] Sara, Falij and Khadar [6, 8, 18-20, 22] Bayaze Chashm and Jarbul Ajfaan [8, 18-20] Warne Khusia [8, 18] Khanazeer [6, 9, 19, 20, 22] Istisqa [6, 20] Husate Kulliyya wa Masana [6, 20] Qurooh [8, 18, 22] Kalaf wa Bahaq [6, 19, 20] Sa'fa [6]

Avicenna described therapeutic uses of Ushaq in various diseases; [24]

1. Awram wa Busoor (swelling/tumor and vesiculopustular eruption); in the form of Tila wa Zimad (paint/poultice and Paste/stupe) with vinegar.
2. Jarahat wa Qurooh (wound and ulceration); its absorptive and desiccant effect destroy the slough and grow new flesh thus promote healing.
3. Alaat Mafasil (joint diseases); sciatica, joint pain and diseases used with honey or Barle water orally and locally if applied with Honey and Zuffat in the form of Zimad. It resolves Tahjjur Mafasil (ossification of joints). Galen mentioned that its potent laxative effect resolve nodular swelling, inflammation of joints and spleen.
4. Azae tanaffus wa Sadr (respiratory organ and chest); asthma dypnoea and platypnoea if taken with honey and barle water in the form of Laooq.
5. Azae Giza (digestive organ); Izm wa Salabat Tihal wa Kabid (enlargement of Spleen and Liver) and Istisqa (ascites) if taken orally in syrup form and applied locally with vinegar.
6. Azae Nafz (excretory organ); acts as a potent diuretic (sometimes causes haematuria), emmenagogue and abortifacient and has vermicide effect.

Therapeutic uses mentioned by *Razi*, *Ibne Baitar* and *Hakeem Najmul Ghani* in their Treatises; [6, 8, 22]

GIT: Relieves constipation prevents obstruction and occlusion in the liver and spleen. *Powder*; resolves inflammation of spleen and liver. *Zimad*; resolves inflammation and bloating of stomach, swelling and enlargement of Spleen. It resolves ascites and decreases fluid in ascites if given orally or applied externally on abdomen. It Acts as laxative and purgative, if given in larger doses.

Nervous system: it has a beneficial effect on nervous diseases like paralysis, epilepsy, facial palsy and tremor and parasthesia.

Musculoskeletal system: it resolves inflammation of joints,

inflammation of synovial membrane and gout, if applied externally on them and prevents and resolves (Tahajjur mafasil) stiffening and fusion of joints.

Respiratory system: expectorate and expel out the thick sputum from lungs and relieves breathlessness and asthma if taken orally and applied externally on chest in the form of Zimad. Gargle with water eliminates phlegm from palate and inflammatory condition of throat.

Urinary system: it acts as a lithotryptic and excretes it out if taken orally and applied externally on lower abdomen. Acts as strong diuretic sometimes produces haematuria.

Skin and cosmatopathlogy: it resolves Melasma (*Kalaf*), Pityriasis (*Bahaq*) and Kerion of scalp if applied on them with olive oil.

Eye diseases: it resolves corneal scar and ulceration, palpbiral papulaovesicular eruption and ulceration, and relieves in itching and excessive lacrimation and watering.

Ulcer and swelling: it acts as detergent and absorbent and antiseptic and clears the slough material and promotes healing by grooving new tissue.

Ethnomedicinal Uses and Therapeutics:

Action Mentioned in Ethnomedicine: Expectorant [16, 17, 21, 25, 26] Stimulant [16, 17, 24] Anti-spasmodic [16, 25] Irritant [16]

Therapeutic uses Mentioned in Ethnomedicine: Respiratory troubles [17] Catarrh [16, 17] Asthma [16, 17] Bronchitis [16, 17] Cancer [17] Enlargement of Liver and Spleen [16]

Phytochemical studies

Major Chemical Constituents: Ushaq gum consists of volatile oil, resin and gum [9]. It contains; volatile oil 0.1-1.0; resin 65-70; gum, c. 20; moisture, 2-12; ash, 1.0; and insoluble residue 3.5% along with theses salicylic, valeric and butyric acids are present [16]. The main constituent of resin is a phenolic substance, ammosesinol, other constituents are dshamirone, doremin, doremine A, ammodoremin. [9, 10, 25]. The volatile oil contains various terpinoids with ferulene as major component. It does not contain umbelliferone [9].

Chemical Composition of the Essential Oils from different parts of the plant

Flower oil: Hydrodistillation of the dried flowers of *D. ammoniacum* D.Don afforded yellowish oil with pleasant aroma, yield 0.09% (w/w). Thirty components comprising 95.4% of the oil were identified. δ -cadinene (11.58%), α -himachalene (7.71%), α - Pinene (6.37%), liguloxide (6.15%) and α - guaiene(6.14%) were identified as the major components of the flower oil [26].

Fruit oil: The hydrodistillation of *D. ammoniacum* fruits gave yellow oil in 0.09% (w/w) yield, based on the dry weight of the fruit. Twenty-nine components were identified representing 95.1% of the total oil. The major constituents of the oil were (*Z*)-ocimenone (22.3%), (*E*)-ocimenone (18.1%) and \square -cyclocitral (9.9%) [11].

Leave oil: The leave oil of this species contains sesquiterpene rich oil (90.2%) which contained high amounts of α -gurjunene (49.5%) and β -gurjunene (19.0% as found in a previous study on the essential oil of *D. ammoniacum* leaves [16, 10].

Aerial parts oil; Thirty-four compounds representing 90.3% of the oil were identified as a result of GC and GC/MS analysis of the aerial parts essential oil [10].

Stem oil; Hydrodistillation of the dried stems of *D. ammoniacum* D. Don afforded pale-yellow colored oil with pleasant aroma, yield 0.08% (w/w). Twenty-one components comprising 93.37% of the stem oil were identified. δ -cadinene (16.24%), liguloxide (8.69%), δ -amorphene (8.43%), α – selinene (7.21%), β - selinene (6.62%) and α - himachalene (6.41%) were identified as the major components of the stem oil [26].

Root oil; Hydrodistillation of the dried roots of *D. ammoniacum* D. Don afforded pale- yellow colored oil with pleasant aroma, yield 0.08% (w/w). Twelve components comprising 90.30% of the oil were identified. 3-n-butyl phthalide (62.49%), benzyl butanoate (6.57%) and liguloxide (5.15%) were identified as the major components of the root oil [26].

Biomedical studies

- 1. Cytotoxic Activity:** Morteza Yousefzadi *et al* evaluated *In vitro* cytotoxic activity of the essential oil from dried Ripe fruits of *D. ammoniacum* in four cancer and normal cell line by MTT assay based on cell viability. In the work they demonstrated, for the first time, the potent cytotoxicity activity of *D. ammoniacum* against four cancers and normal cell line [27]. In another study the effects of methanolic crude extracts oleogumresin of *Dorema ammoniacum* D. Don on RS322N (rad52) of the yeast strains of *Saccharomyces cerevisiae* were Investigated and it was observed that, oleogumresin of *Dorema ammoniacum* is a potential cytotoxic agent [28]
- 2. Antimicrobial activity:** Antimicrobial activity reported by Crude extracts of *Dorema ammoniacum* which inhibited the growth of 12 microorganisms and exhibited significant antimicrobial activity. On the basis of anti microbial properties the investigators justified and supported folkloric use in the treatment of some diseases as broad-spectrum antimicrobial agents [25, 29]. In another study the antimicrobial assay of the essential oil of *Dorema ammoniacum* D. Don. Fruit done by the disc diffusion method and the MIC values indicated that the oil exhibited moderate to high antimicrobial activity, especially against *B. subtilis* and *S. epidermidis* with MIC value of 3.75 mg ml⁻¹ [11].
- 3. Antifungal Activity:** Ushaq has been found having antifungal properties and activity on *Candida albicans*, *Aspergillus niger* and *Saccharomyces cerevisiae* as it is appeared by summarizing various research reports published during last 22 years, i.e. from 1985 to 2007 on plants having antifungal properties against phytopathogenic fungi [29, 30]. M. Rajani *et al* also found that the Dichloromethane: methanol extract of ammoniacum gum exhibited antifungal activity against *Aspergillus niger* [25].

- 4. Antibacterial activity:** Dichloromethane: methanol extract of ammoniacum gum exhibited a broad spectrum antimicrobial activity against ten out of the 14 microorganisms tested. It inhibited the growth of all the seven Gram-positive bacteria tested while growth of only one Gram-negative bacterium (*B. bronchiseptica*) was inhibited. In agar plate method, with the broad range of concentrations of 100–400mg/ml of the extract, the growth of all the microorganisms, except *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *C. albicans*, was inhibited. The extract of ammoniacum gum has excellent antimicrobial activity, and provides a scientific basis for the traditional use of ammoniacum gum for bronchitis, respiratory infections, fever, cold and flu (BHP, 1983) [25].
- 5. Anticonvulsant activity:** An aqueous solution of *Dorema ammoniacum* gum extract was prepared and investigated for anticonvulsant activity on PTZ-induced seizures. In this study, *Dorema ammoniacum* gum extract produced a statistically significant reduction in seizures' duration and an increase in the latency period of seizures induced by PTZ in the mouse model. This effect was appeared in all doses used. No death was recorded even at highest dose of DAG used (1000 mg/kg). This anticonvulsant activity could be due to the involvement of the GABAergic pathway. This suggested that the gum aqueous solution is relatively safe and non-toxic in mice even at the highest dose used in this study. Hence supports the traditional use of the plant in the treatment of convulsive disorders [31].
- 6. AChE inhibitory activity:** AChE inhibitory activity study of a dichloromethane extract of gum ammoniacum of *Dorema ammoniacum* D. Don. was carried out by H.-R. Adhami *et al.* [32] The dichloromethane extract of gum ammoniacum was fractionated and four active compounds were isolated and their structures characterized. The AChE inhibitory activities of the dichloromethane determined for the first time in a microplate assay. Compounds 1, 2, and 4 showed only low activities, while compound 3 was about 10 times more active. They concluded that compounds contributing to the AChE inhibition of this drug. Due to these results, the use of this drug in improving cognitive functions seems plausible. Dshamirone turned out to be the most active compound with an IC50 value for AChE inhibitory activity of 23.5 μ M, whereas the other substances showed weak activity [32].
- 7. Antioxidant:** M.R. Delnavazi *et al.* [10] Evaluated Antioxidant activities of essential oils and extracts of *Dorema ammoniacum* roots and aerial parts by DPPH free radical scavenging assay and FRAP assay. 2,2-Diphenyl-1-picryl-hydrazyl (DPPH) method was used to assess the free radical-scavenging potential of the essential oils and extracts. The reducing powers of the extracts were determined using ferric reducing antioxidant power (FRAP) method. In DPPH assay, ethyl acetate and chloroform extracts of the roots along with the ethyl acetate extract of the aerial parts were found to have the highest free radical-scavenging activity, Ethyl acetate extracts of both plant samples also exhibited the highest ferric reducing power in FRAP assay [10].

8. Anti-inflammatory and Analgesic activities: Anti-inflammatory and analgesic activities of the aqueous solution of *D.ammoniacum* gum in animal models were observed by Shojaii *et al* 2017^[33]. Using carrageenan-induced rat paw edema, acetic acid-induced writhing test and formalin test. They have found significant analgesic effect ($P<0.05$) in acute as well as chronic phases of formalin test. Acetic acid-induced writhing test showed significant analgesic effects in the animals in 30 min after acetic acid injection. The study showed anti-inflammatory activity in a dose-dependent manner in the carrageenan-induced edema in mice. Anti-inflammatory activity of DAG was comparable to indomethacin in dose 500 mg/kg.^[33]

Conclusion

Ushaq (*Dorema ammoniacum* D. Don) is one of the important drug used in Unani medicine from centuries.it is found in the classical literature, that it is widely used in GIT and Hepatobiliary, respiratoty, skin and Musculoskeletal diseases as potent Anti inflammatory, Deobstruent, Laxative, Absorbtive and Desiccant. The recent studies on new parameters have explored the plant as Antioxidant, Anti-inflammatory and Analgesic, Antimicrobial, Anticonvulsant, AChE inhibitor and Cytotoxic pharmacological activities and hence supports its therapeutic value of centuries.

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