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Atrilal (*Ammi majus* linn): Phytopharmacological Review of an Important anti Vitiligo Unani Drug

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ABSTRACT

Atrilal (*Ammi majus* linn.) an important Unani antiviligo medicine belong to the family Umbelifereae. It was in used since ancient time for vitiligo and mentioned in many unani classical texts. The previous pharmacological studies showed that atrilal (*Ammi majus* linn) was used effectively in the treatment of vitiligo, psoriasis, tinea and many other skin diseases. The aim of the present review is to collect the information of Atrilal (*Ammi majus* linn.) available in Unani classical literature, phyto-chemical and pharmacological studies and Unani formulations in which it is used as an ingredient also make an effort to prove the strength of action of drug mentioned in Unani classical literature. Fourteen Unani books were referred and eighteen pharmacological studies were recognized. This information gives the research question and guidance for future research.

KEYWORDS: Atrilal, Unani medicine, Phytochemistry, pharmacology, *Ammi majus* Linn. Vitiligo, Baras

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INTRODUCTION

Unani system of medicine (USM), is one of the oldest forms of medicine known to mankind. It is still the most widely practiced form of medicine in many parts of the globe with different name. USM is presently practiced with different names e.g., *Tıbb Sunnatı* (Traditional Medicine), Eastern Medicine, Uyghur Medicine Islamic Medicine or Arab Medicine etc in Different part of globe. USM offers four kinds of treatment modalities, pharmacotherapy is one of them. In which single and compound formulation from herbo-mineral and Animal Source are used for treatment. USM formulary and pharmacopeia is richest and most deserving therapy has a lot of herbs in its repository^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24}. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs^{25,26,27,28,29,30,31,32,33}.

Atrilal (*Ammi majus* linn.) is an important Unani medicine. Iranian Unani scholar Imamuddin Mehmood Sheerazi (1515-1592) wrote a short book entitled *Risala-e-Atrilal* on the medicinal properties in Persian. In Indian subcontinent three manuscripts of risala-e-atrilal were traced, one each in Khuda Bakhsh Library Patna, State library Hyderabad and Nizamia tibia college library Hyderabad. Founder of Ibn Sina Academy, Aligarh Hakim Zillur Rehman has translated the same into urdu after critical comparison of all the copies available. According to him many Unani Scholars has mentioned Atrilal (*Ammi majus* linn.) in their treatises e.g. Zakariya Raazi (854-925 AD) in *Al Hawi al Kabir*, Majoosi (930-994 AD) in *Kamil-us sana*, Ibn Sina (980-1037) in *Al qanoon fit tib*, Ibn Baitar (1197-1248) in *Al-Jami-ul-Mufradat-al-Advia-wal-Aghzia*, Daood Antaki (1543-1599 AD) in *Tazkira-Ulul-Albab*, Nooruddin Mohammad Abdullah (1646 d.) in *Alfaz-ul-Advia*, Yousuf bin Umar Ghasaani (1295 d.) in *Al-Motamid-fil-Advia-tul-Mufrada*, Mohd Husain Alvi Sheerazi (1790 d) in *Makhzan-ul-Advia*, Najmul Ghani (1859-1932) in *Khazainul Advia*, Hakim Abdul Haleem (1906-1954) in *Mufradat-e-Azizi*, Hakim Abdul Hakim (19th Century) in *Bustan-ul Mufradat* and many others³⁴. Atrilal (*Ammi majus* linn.) is mentioned with different name in the above said text of unani medicine and names are mentioned in the list of common name. Unani System of Medicine offers successful treatment for various diseases especially the chronic ones. These include skin diseases like vitiligo, eczema, psoriasis where allopathic has minimal effects or causes some dangerous side effects.

Atrilal (*Ammi majus* Linn) is native of Egypt, it was imported to India. Due to its less availability, although it was in practice by many unani scholars, but many scholars of unani medicine have not mentioned this important drug of vitiligo in their text. There is a long list of text that has no description regarding the usefulness of atrilal for vitiligo. *Riyaz-ul-Advia*, *Jami-ul-mufradat* of

Hakim Sheikh Banda Hasan, *Mufradat-e-Azizi* of Hakim Abdul Haleem etc¹. Similarly, many pharmacopeias are also free from its description or its usefulness in vitiligo e.g. *Qarabadeen-e-shifai* of Hakim Muzaffar bin Mohd Husaiyani Shifai, *Qarabadeen Qadri* of Akbar Arzani. In *qarabadeen-e-Zakai* 15 formulations are mentioned for vitiligo only one formulation has atrilal as one of the ingredients. In *Qarabadeen Azam* more than 30 formulation has mentioned for vitiligo only one formulation of *Zimad* and one of *Majoon* has mentioned in which atrilal is One of the ingredient³⁴.

Many other important unani classical books on single drugs and compound formulations (qarabadeen=pharmacopeias) are free from its description because the physician's family kept this medicinal property in secret and not share with others and even not mentioned in the literature of that time. Because of this the drug atrilal even having a good quality in treating in vitiligo got neglected. A long list of unani classical literature that do not having any reference on this plant. Many unani pharmacopeias have mentioned formulation for vitiligo but they are free from Atrilal (*Ammi majus* Linn.).

MATERIAL & METHODS

Unani classical Literature was searched from recent to past available in different libraries of India, for phyto-chemical and pharmacological activities and computerized databases such as Medline, Pubmed, Ovid SP, Google Scholar and Science-direct were searched to identify all phyto-chemical, experimental and clinical trials carried out to prove the importance of Atrilal (*Ammi majus* Linn).

Botanical Description

Atrilal (*Ammi majus* Linn) belong to family Apiaceae³⁵. English name is Bishop's Weed/ Greater Ammi³⁵ other common names are *Juz-ush-Shaitani*, *Rijl-ul-Ghuraab*, *Greater Ammi*, *Hashishatul Baras*, *Khella Shaitani*, *Shaitani Barrah*, *Tukhm-e-Talal*, *Atrilaan*, *Rijal-ul-Ghuraab*, *Rikl ul-Uqab*, *Rijl –ul Aqaq*, *Rijl-az-Zaagh*, *Kaak Changa*, *Missi*³⁴.

Description & Habitate:

Atrilal (*Ammi majus* Linn.) is an erect, branching annual herb, up to 1.5 m in height, sometimes grown as a winter ornamental. Leaves are oblong, 6.20 cm long, broad ternate or pinnate: leaflets lanceolate, obtuse to acute; flowers are white in colour with loose compound umbels. Its fruits are oblong, 1.5 - 2.0 mm long and 1 mm or less broad³⁵. The plant is indigenous to Egypt and it grows in the Nile valley, especially in Behira and Fayoon³⁶. In India its successful farming was conducted in plane of northern India, Jammu and Kashmir^{34,36}. It is also found in the basin of

Mediterranean Sea, West Africa, in some regions of Iran and the mountain of Kohaz. Its seeds are used for medicinal purposes and collected during the month of June to October In Unani Medicine Atrilal means its seeds, but some time its leaves called *Barg-e-murad* are also used for their medicinal values. Seed's longevity is 1 to 3 year after than that losses their strength³⁴⁻³⁶. According to a survey among the traditional healers and herbalist in all regions of the west bank of Palestine, it was found that *Ammi majus* Linn. was recommended for treatment of urinary tract infections³⁷.



Figure:1. Flowers of atrilal (*Ammi majus* Linn.)



Figure:2. Leaves of atrilal (*Ammi majus* Linn.)

Temperament:

In regards to its temperament Unani scholars have different opinions. According to some scholar it is Hot and Dry in second degree of temperament³⁸⁻⁴¹; and some says it is Hot and Dry in third degree of temperament⁴⁰⁻⁴³. Author of *Muheet Azam* also said according to some unani scholars it is hot and dry in fourth degree of temperament^{41,43}.

Part used:

The seeds of the plant are used as medicine with the name of atrilal, sometimes it leaves also used as medicine with the name of *barg-e-atrilal*³⁸⁻⁴².

Action:

Unani scholars mentioned many actions in their treatises. All the actions mentioned are listed here in alphabetic order with English equivalent in brackets.

Daf-e-Baras (Vitiligo) & *Behaq* (Malesma)^{35,37-43}, *Jali* (Detergent)^{35,38,41-46}, *Kasir-e-Riyah* (carminative)^{35,38,41-44}, *Mohallil* (Resolvent)^{35,38,41-45}, *Mudir-e-Baul* (Diuretics)^{35,40-46}, *Mudir-e-Haiz* (Emmenagogue)^{35,40-41}, *Mufattit-e-Hisat* (Lithotriptic)^{40,43-45}, *Mujaffif* (Desiccant)^{41,45-47}, *Mulattif* (Demulscent)⁴⁰, *Mufatteh* (Dilator)^{41,43-46}, *Mukhrij-e-Balgham* (Phlegmagogue)^{41,43-44}, *Mulayyan*

(Laxative)³⁹, *Musakkin-e-Alam* (Analgesic)⁴⁷, *Musaqqit-e-Janeen* (Abortifacient)^{35,40-41,43-45}, *Qatil-e-Kirm-e-Shikam* (Vermicidal)^{35,40-43}.

Potent Action:

Dafe-Baras wa Behaq (Antivertigo & Anti-ptyriasis)^{34,42-43}.

Uses:

The indications in which the plant parts are recommended for therapeutic uses mentioned in Unani texts are arranged below:

- The decoction of seed is used as gargle for treatment of toothache³⁵. Seeds of fruits were used for the treatment of skin disorders, psoriasis and vitiligo^{35,38,40-41,43}.
- The following prescriptions are mentioned in unani classics for vitiligo and malesma. Powder of seeds with honey and lukewarm water beneficial for Baras wa Behaq.
- It is also useful with aaqarqarha (*Anacyclus pyrethrum* DC.) and honey. Atrilal (*Ammi majus* Linn.), zanjabeel (*Zingiber officinale* Roscoe), aaqarqarha (*Anacyclus pyrethrum* DC.), nisoot (*Convolvulus turpethum*), and honey are used for baras (vitiligo)^{38,40-41,43-44}.
- Seeds of atrilal (*Ammi majus* Linn.), seeds of shaqaiq al-qahaan, aaqarqarha (*Anacyclus pyrethrum* DC.), jundbedaster (castorium) with honey orally thereafter honey water is of use for vitiligo.
- Atrilal (*Ammi majus* Linn.), barg-e-suddab (*Ruta graveolens* Linn.) and skin of snake with wine are beneficial for vitiligo.
- Paste of atrilal seed (*Ammi majus* Linn.) with vinegar applied on the affected part also helpful for vitiligo³⁹⁻⁴⁰.
- Its leaf decoction orally is useful in dog's bite^{40-41,43}.
- Decoction of atrilal or with plain water orally is abortifacient^{40,43}.
- It is also used as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of leprosy, kidney stone and urinary tract infections^{35,38,40,43}.
- Powder of seed of atrilal (*Ammi majus* Linn) one part and one part of powder of barg-e-suddab (leaves of *Ruta graveolens* Linn.) and skin of snake taken with wine of grapes³⁹⁻⁴⁰.
- It was also advised for treatment of vitiligo after taking atrilal orally or locally at the site exposed the affected part of body to sunlight or sit in sun light for a period till the sweating start^{35,37,39}.
- Powder of seeds are beneficial in niqras (gout), waja-ul-mafasil (polyarthritis)^{38,40}.
- It is also beneficial in disease of spleen, stomach and liver⁴⁰.

Dose:

2-3 gram^{35,42}; 3-9 gm^{38-41,43-44}.

Substitute

In Unani classics it is also said that in case of non-availability of the drug substitute may be used. Baabchi (*Psoralea corylifolia* Linn.)^{34,42}, tukhm-e-karafs (*Apium graveolens* Linn.)^{40,42}, ajwain desi (*Trachyspermum ammi* (Linn.) Spragne)^{40,44} could be substitute for kidney diseases kateera (*Astragalus gummifer*)³⁹, kundush [*Schoenocaulon officinale* (Schl. & Cham.) A.Gray] and could be used⁴³⁻⁴⁷.

Corrective

Unani scholars were well aware regarding the adverse and side effects of many unani drugs. So, they described about the corrective measures in terms of drugs and alternative measure in their treatments. Sometimes they add a corrective drug (muslehat) in prescriptions to counter the toxicity of the main drug. Daarchini (*Cinnamomum zeylanicum* Blume)⁴⁰⁻⁴², zanjabeel (*Zingiber officinale* Roscoe)⁴⁰⁻⁴², filfil siyah (*Piper nigrum* Linn.)⁴⁰⁻⁴¹ asl (Honey)⁴² and for liver disorders. Sikanjabeen^{40-41,43-44} and Sharbat banafsha⁴⁰⁻⁴¹ and for kidney disorders kateera (*Astragalus gummifer*)^{40-41,43}.

Chemical Constituents:

Its seeds contained amorphous glucoside, tannin, oleoresin, acrid oil, fixed oil, proteins and cellulose. The major constituents are furanocoumarins which included xanthotoxins, imperatorin, and bergapten, marmesin, isoimperatorin, heraclenin and isopimpinellin. 6-hydroxy-7-methoxy coumarin, nonfurocoumarin, umbelliprenin, glycosides of quercetin, luteolin, kaempferol, linoleic acid, methyl ester of oleic acid, palmitic acid, linolenic acid were also found⁴⁹⁻⁶³.

Pharmacological studies:

Experimentation with *Ammi majus* Linn was started in Egypt in ancient period for its usefulness in vitiligo and other skin disorders^{34,64}. In clinical studies it was found that *Ammi majus* Linn. is effective in cases of vitiligo, psoriasis and hypopigmentation tinea versicolor orally and locally⁶⁴⁻⁷⁶. It also has bactericidal, fungicidal, insecticidal, larvicidal, molluscicidal, nematocidal, ovicidal, and herbicidal activities^{49,78}. It showed antiviral activity against vesicular stomatitis virus (VSV) and Herpes simplex virus (HSV)⁵⁰. Its hot aqueous extract and petroleum ether extract reduced the *Schistosoma mansoni* worm burden in mice⁵⁷. It also inhibited the growth of the *Neurospora crass* fungi *in-vitro*⁷⁹.

Antioxidant activity

Chloroform crude extract showed antioxidant activity in experimental study determined by the free radical scavenging by DPPH method⁸⁰⁻⁸¹.

Antimicrobial activity

Methanol and Chloroform crude extracts *A. majus* displayed antimicrobial activity against Gram positive bacteria, *Staphylococcus aureus* (*S. aureus*), and Gram-negative bacteria *Escherichia coli* (*E. coli*), *Haemophilus influenzae* (*H. influenzae*), and *Proteus spp* (*Proteus spp*)⁸⁰⁻⁸¹.

Cytotoxicity activity

Crude extracts of different solvent obtained from the seed of *A. majus* exhibited potent cytotoxicity activity by killing all the larvae in artemia lethality method (Artemia cysts) in dose dependent manner⁸⁰⁻⁸¹. Pyrano-coumarin from atrilal plant showed cytotoxicity activity towards HCT116 cell line⁸². 8-methoxypsoralen inhibited cell growth in several cancer cell lines. The BrdU assay in neuroblastoma and metastatic colon cancer cells by induction of apoptosis via intrinsic and extrinsic pathways. They were the most sensitive to the compound. 8-MOP reduced the phosphorylation of AKT308, decreased the expression of Bcl-2, increased the Bax protein level, and activated caspases -8, -9, and -3 in both cell lines⁸³. 4-hydro-7-hydroxy-8-methoxyfuroquinoline & 4-hydro-7-hydroxy-8-prenyloxyfuroquinoline showed antiproliferative and cytotoxic effects, with IC50 = 230.2 and 326.5 μ M against HepG-2 and MCF-7, respectively⁸⁴. Xanthotoxin from the seeds of *Ammi majus* found to decrease the osteoclast number, prevents bone loss, rescues bone microarchitecture, and restores bone strength in ovariectomized mice. In ovariectomy-mediated bone loss through the inhibition of receptor activator of nuclear factor- κ B ligand-mediated osteoclastogenesis in mice. It may be considered to be a new therapeutic candidate for treating osteoporosis⁸⁵.

Antibacterial activity

Crude extract showed antibacterial activity against standard bacterial strains⁸⁶.

Antihyperlipidemic

The alcoholic extract of the *A. majus* seed significantly decreases the concentrations of cholesterol, triglycerides and low-density lipoprotein and increase in the concentration of high-density lipoprotein⁸⁷.

Anti-inflammatory activity

The alcoholic extract of the *A. majus* seed showed anti-inflammatory activity by significantly inhibiting the rat paw edema in dose dependent manner⁸⁸.

Analgesic activity

The alcoholic extract of the *A. majus* seed showed analgesic effect⁸⁸.

Antipyretic activity

The alcoholic extract of the *A. majus* seed lower the body temperature after one hour of treatment⁸⁸.

Other pharmacological actions

It also has bactericidal, fungicidal, insecticidal, larvicidal, moluscicidal, nematocidal, ovicidal, and herbicidal activities^{49,79}. It showed antiviral activity against vesicular stomatitis virus (VSV) and Herpes simplex virus (HSV)⁵⁰. Its hot aqueous extract and petroleum ether extract reduced the *Schistosoma mansoni* worm burden in mice⁵⁷. It also inhibited the growth of the *Neurospora crass* fungi *in-vitro*⁸².

Antidiabetic activity

Various extract showed hypoglycaemic activity in allaxon induced diabetic in experimental model animals⁸³

Contraindicated and adverse effect:

It is contraindicated in diseases associated with photosensitivity, cataract, invasive squamous cell cancer, sensitivity to xanthotoxin, children under the age of 12, pregnancy, nursing, tuberculosis, liver and kidney diseases, human immune-deficiency virus infections and other autoimmune diseases^{43,50,82,92}.

Patient can develop bullous reactions of more or less severe, nervousness, insomnia, nausea and gastric burning even after first exposure⁷¹. Itching, edema, hypotension, vertigo, painful blistering, burning and peeling of the skin, pruritus, freckling, hypopigmentation, rash, cheilitis and erythema were also recorded with xanthotoxin therapy⁹⁰. Phototoxic dermatitis and allergic rhinitis and contact urticaria is also reported due to exposure to fruits^{90,93}.

Unani Formulations

The Unani System of Medicine prescribes elaborate formulation or pharmaceutical processing of drugs for achieving stability, palatability, absorption and assimilability and for enhancing efficacy and safety. This pharmaceutical processing is applied to both single preparations and compound preparations, majority being of the later type. Some famous compound formulations of atrilal (*Ammi majus*) mentioned in Unani classical literature as: *Zimaad-e-Baras*, *Sofoof-e-Baras*, *Majon Atrilal*⁹⁴⁻⁹⁵, *Dawa-e-Bars*⁹⁶, *Marham Atrilal*⁹⁷ etc.

CONCLUSION

Atrilal (*Ammi majus* Linn) is one of the oldest medicinal plants documented in *Eber's papyrus* of Egypt and used for vitiligo. In early era it was used by the scholars for de-pigmentation of skin and kept secrets with the family the procedure of its usefulness in skin disorders³⁴. It also comes in the picture the Unani scholars who were well aware about its photosensitivity reactions³⁴. As written by an Iranian Unani scholar Imamuddin Mehmood Sheerazi laid down a short book on this single unani medicine entitled *Risala-e-Atrilal* on the medicinal properties in Persian language. Hakim Zillur Rehman has translated the same into urdu and this translation were published from India, Pakistan and Iran. The drug atrilal is highly reactive medicine, it causes blistering on skin and Melanoprotective activity. In some animals their beeks were also changes the color after ingestion and expose to sunlight. So it may be concluded its temperament may be hot and dry in third degree due to its high reaction. Unani scholars i.e., Hakim Azam Khan, Hakim Najmul Ghani and Hakim Rafiquddin are among those who say it is hot and dry in third degree of temeperament⁴¹⁻⁴². Ministry of AYUSH Government of India classified different system of medicine for a particular disease and system according to their strength. Central council for Research in Unani Medicine (CCRUM) has classified it for skin disorders. CCRUM is working in this area since last half century and designed many unani coded formulations under the name of UNIM-001, UNIM-002, UNIM-003, UNIM-005, UNIM-044, UNIM-045, UNIM-046, UNIM-047, DA₆, BSL₆ etc. Council conducted many clinical studies and got good results in cases of vitiligo⁹⁸⁻¹⁰⁶. It is also recommended that council must take up atrilal (*Ammi majus* Linn.) and its compound formulation for vitiligo in future.

Many Phytochemical analyses of *Ammi majus* Linn. have active constituents imperatorin, bergaptens, marmesin, 8-methoxypsoralen Ammoidin (xanthotoxin) having depigmentation properties. Even it is native to Egypt, CCRUM is farming this plant in Aligarh and other regional centre. It is suggested that further research studies have been designed to reveal its unmasked potential in social stigmatic problem vitiligo.

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