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Review

Aatrilal (*Ammi majus* L.), an important drug of Unani system of medicine: A review

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ABSTRACT

Ethnopharmacological relevance: Ammi majus L. (*Aatrilal*) a member of the family Apiaceae, is native to Egypt and widely distributed in Europe, the Mediterranean, and West Asia. It has been used for the treatment of various dermatological disorders particularly vitiligo in the Unani system of Medicine for ages. In traditional medicine, fruits are used as an emmenagogue as well as a diuretic, blood purifier and to treat leprosy, urinary and digestive disorders.

Aim of the review: This paper aims to highlight the medicinal properties of *Aatrilal* in view of its temperament and phytoconstituents; to signify its potential in the treatment of vitiligo and other ailments as mentioned in Unani system of medicine and also to explore its phytochemistry, pharmacological and clinical studies.

Materials and methods: Aatrilal was explored in classical Unani literature for its temperament (*mizaj*), medicinal properties and therapeutic uses. Published works available on PubMed, Science Direct, and Google Scholar were referred to collect all the available information regarding its phytochemicals and pharmacological studies. All relevant articles up to 2020 were referred including 15 classical Unani books, 15 English books, 72 research, and 3 review papers. The plant's scientific names were validated using 'The Plant List' (www.theplantlist.org). Standard Unani Medical Terminology published by Central Council for Research in Unani Medicine in collaboration with the World Health Organization was used to describe the appropriate Unani terminologies. Glossary of Indian Medicinal Plants and different indexed journals were consulted for botanical and English names.

Results: Aatrilal has been used in traditional medicine for ages. Due to controversies in its identity, it was adulterated and substituted with many drugs. The real identity of *Aatrilal* is now established as the fruit of *A. majus* L. Despite having numerous pharmacological activities, it is considered the first-line drug for the treatment of vitiligo. It is a rich source of furanocoumarins (xanthotoxin, also known as 8-methoxypsoralen, bergapten, imperatorin, isopimpinellin) with other compounds viz. flavonoids, terpenoids, proteins, essential oil constituents, etc. It has been reported for anti-inflammatory, analgesic, antibacterial, antiviral, cytotoxic, and many other activities. Clinical trials have shown the therapeutic potential in vitiligo and other skin disorders.

Conclusion: Based on the available literature, it can be concluded that *Aatrilal* is a drug that has been effectively used in Unani system of medicine for centuries to treat the cases of vitiligo and other dermatological disorders. It has been studied extensively for its phytopharmacological properties. Raw extracts of *A. majus* form the crux of the main research. Many potentially bioactive compounds are included in the essential oil, but to our knowledge, no detailed studies of its biological activity are yet available. Therefore, our suggestion is to focus future research on essential oil and its ingredients.

Abbreviations: CPC, Centrifugal Partition Chromatography; DPPH, 2,2,1-diphenyl-1-picrylhydrazyl; GC-MS, Gas Chromatography-Mass Spectrometry; HSV, Herpes Simplex Virus; HDL, High-Density Lipoproteins; LDL, Low-Density Lipoprotein; MIC, Minimum Inhibitory Concentration; MBC, Minimum Bactericidal Concentration; MDA, Microbial Detection Array; NIUM, National Institute of Unani Medicine; SD rat, rat; UV-A, Ultra Violet-A; VSV, Vesicular Stomatitis Virus.

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1. Introduction

The Unani system of medicine, as the name suggests, owes its immediate origin to ancient Greece (Yūnān) and has been subsequently developed by Roman, Arabic, Spanish, Iranian and Indian physicians. Hence, the name Greco-Arab Medicine. It is a comprehensive medical system, which meticulously deals with the various states of health and disease. It provides promotive, preventive, curative, and rehabilitative healthcare. The Unani medicine has been transformed into medical science based on the framework of the teachings of Greek physician *Buqrat* (Hippocrates, 460-370 BC) and Roman physician *Jalinoos* (Galen, 129-210 AD) and developed into an elaborate medical system by Arab and Persian physicians such as *Al-Razi* (Rhazes, 850-925 AD), *Ibn Sina* (Avicenna, 980-1037 AD), *Al-Zahrawi* (Abulcasis, 936-1036 AD) and *Ibn Nafis* (1213-1288 AD) (Lone et al., 2012a,b; Makbul et al., 2018). It is primarily based on the Hippocratic doctrine of four humours viz. blood, phlegm, yellow bile, and black bile with their four temperamental qualities viz. hot and moist, cold and moist, hot and dry and cold and dry, respectively. According to the Unani principle, the human body is composed of seven basic principles viz. element, temperament, humours, organ, pneuma, faculties, and functions. The mere absence of any of the components threatens the very existence of life and derangement of which results in disease. Unani system of medicine believes that Medicatrix Naturae (*Ṭabī'at Mudabbira -i- Badan*) is the supreme power, which controls all the physiological functions of the body, provides resistance against the diseases, and helps in healing naturally. The fundamentals, diagnosis, and treatment modalities of the system are based on scientific principles and holistic concepts of health and healing. Its holistic approach takes into account the whole personality rather than taking a reductionist approach towards disease (Ibn abi Usaiba, 1990). Many of its theories and principles are different from that of Western medicine. It may or may not correlate with western medicine, but still, there is no doubt in the rational way of describing the concepts (Makbul et al., 2018).

The demand for Unani Medicine is increasing exponentially because of people's faith in its safety and efficacy. Since the beginning, this system has used medicine to beautify the skin, face, hair, eyes, and nails. It is the world's most ancient science of health care and healing, which works on four humours i.e., blood, phlegm, yellow bile, and black bile. When these humours are in equilibrium, a person glows with inner and outer beauty. Since skin and hair form an integral part of judging a human's beauty through outward demeanour, several single drugs, and compound cosmeceutical preparations are summarized in classical Unani literature and these cosmeceuticals are aimed at glamorizing human personality. Furthermore, several preparations regarding skin disorders like leucoderma, acne vulgaris, blemishes, and blackening of the skin, moles, and warts, etc. are also mentioned in the classics (Razi, 1991).

In the Unani system of medicine, a lot of single and composed drugs are used to alleviate diverse pathological states caused by abnormal blood e.g., Wild Fig (*Ficus hispida*), *Babchi* (*Psoralea corylifolia*), *Aatrilal* (*Ammi majus*), Globe-Thistle (*Echinops echinatus*), *Chaksu* (*Cassia absus*), *Chiraita* (*Swertia chirata*), China root (*Smilax china*), *Mundi* (*Sphaeranthus indicus*), etc. (Ghani, 2001). Unani physicians elaborately discussed the mechanism of action of these drugs, which are used to treat various dermatological disorders.

A. majus L. belongs to the family Apiaceae and has long been used for the treatment of vitiligo in various traditional systems of medicine (Ahmad et al., 2007). It is native to Egypt and widely distributed in Europe, the Mediterranean, and West Asia (Al-Hadhrami, 2016). Through UNESCO's effort for its medicinal and ornamental importance in India, it was introduced in Forest Research Institute, Dehradun in 1955 (Bradu and Atal, 1970). The experimental cultivation has been attempted in many parts of India, including Jammu, Dehradun, Mumbai, Chennai, Delhi, Aligarh, Punjab, and Himachal Pradesh (Cherian and Bhambri, 2010). The photosensitizing activity of furanocoumarins naturally occurring in *A. majus* fruits has been utilized to treat certain skin disorders such as leucoderma, psoriasis, vitiligo, and hypopigmentation in tinea versicolor (Staniszewska et al., 2003; Bartnik and Mazurek, 2016).

The manuscript's main objective is to explore the *Aatrilal* for its medicinal efficacy in various disorders especially vitiligo and other skin ailments in the light of its temperament and phytoconstituents. Moreover, no such type of review is available which focuses on the medicinal value in light of the Unani concept. This manuscript also highlights various tested prescriptions suggested by eminent Unani physicians and numerous scientific studies conducted on this drug. For a systematic and parallel presentation of this manuscript, it has been divided into two parts. One is the description of *Aatrilal* in Unani and other ancient literature and other concerns scientific works.

2. Methodology

A manual literature survey of classical Unani texts was conducted to collect the information available on "*Aatrilal*" for its temperament (*mizaj*), pharmacological actions, mechanism of action, and therapeutic uses. Besides, a comprehensive search of electronic databases like PubMed, Google Scholar, and Science Direct, was carried out to collect all the available information regarding its phytochemical, physicochemical, and pharmacological studies. All the relevant articles written in English up to 2020 were referred to, which include seventy-two research and three review papers. The period of the search ranged from March 2020 to January 2021. Urdu translation of the classical books such as *Al Hawi* of *Al-Razi* (850-925 AD), *Al Jami ul Mufradat Al Advia Wal Aghzia* of *Ibn al Baitar* (1197-1248 AD), *Muheet Azam* of *Hakeem Mohammad Azam Khan* (1806–1902 AD), *Khazainul Adwiya* of *Najmul Ghani*, (19th century), *Kitab ul Mansoori* of *Al-Razi* (850-925 AD) and *Tazkira Oolul Albab* (Arabic) of *Dawud al Antaki* (1541-1599 AD), *Tuhfat ul Momineen* (Persian) of *Momin Tonekaboni* (1669 AD), etc., were conferred. Standard Unani Medical Terminology published by Central Council for Research in Unani Medicine in collaboration with the World Health Organization was used to describe the appropriate Unani terminologies. Glossary of Indian Medicinal Plants and different indexed journals were consulted for botanical and English names. The keywords used were 'Unani Medicine', '*Ammi majus*', '*Aatrilal*', 'Bishop's weed', '*in vitro* study', '*in vivo* study' 'clinical trial', 'study on vitiligo', 'phytochemistry', 'adverse effect', and 'pharmacognostic study'. Boolean operators "AND" and "OR" were used appropriately. All the old traditional terms were written in Urdu along with equivalent terms in English. The scientific name and synonyms were validated using 'The Plant List' (www.theplantlist.org).

3. Results

3.1. Description of Aatrilal in Unani and other ancient literature

3.1.1. Vernaculars

Arabic: *Hiirz al Shayateen, Hasheeshatul Arz, Khilla bariah, Rijlul Ghurab, Rijulul Tair* (Antaki, 2008; Khan, 2012); Chinese: Da a mi qin (Akbar, 2020); English: Greater Ammi, Bishop's weed, Lady lace (Khare, 2007); French: Ammi Comum (Adham, 2015); Hindi: Kagchangi (Sheerazi, 1993); Persian: Golsefid (Sadat-Hosseini, 2017); Turkish: Qaz Abaghi, Kurdanotu (Sheerazi, 1993; Akbar, 2020).

3.1.2. Unani description

Aatrilal is a Berberi word that means '*Rijul ul Tair*' (leg of birds). It is known as '*Rijul ul Ghurab*' in Egypt and Damascus because its branches appear like crow's claw. *Aatrilal* is also called '*Atrilaan*' (Ibn al Baitar, 1999; Khan, 2012). *Dawud al-Antaki* described it under the heading of '*Atriyal*' (Antaki, 2008). Its generic name is Ami and the root word of Ami is Ammos (sand) because mostly plants of the Ami genus cultivated in sandy soil (Sheerazi, 1993).

Aatrilal was not a well-known drug in the era of Avicenna (980-1037 AD) hence its absence in the book *Al-Qanoon*. This drug's efficacy was first known to a tribe of Berbers (*Bani Abi Shoaib*) in the Middle West African desert. They kept this drug hidden from others and used it to treat vitiligo; transferred this knowledge to their offspring. However, the drug's existence couldn't be hidden for long and its efficacy in treating vitiligo and other skin disorders was generalized. Thereafter, it prevailed in Egypt, and from there it shot to fame in other countries. Egyptians described this drug in detail, they discussed its similarity with other drugs such as *Khilla bahria* (*Ammi visnaga*), and they also described its particular effectiveness in vitiligo (Sheerazi, 1993). Arab expert of *Ilmul Advia* (Pharmacology) *Ibn al Baitar* (1197-1248 AD) discussed it under the heading of its Berberian name "*Aatrilal*".

3.1.3. Resemblance with other species (drugs)

Due to the resemblance to many different drugs, *Aatrilal* has been a controversial drug. There are many different opinions about its identification. Many researchers took interest in studying its differences and similarities with other plants; it shows that drug is important and scarcely available. These similarities and differences are given below:

1. The twig, flower, fruit, and root of *Aatrilal* appear similar to *Shibbat* (*Anethum sowa* Kutz.) distinguishing feature is the flower's colour, *Shibbat* is yellow and *Aatrilal* is white (Ibn al Baitar, 1999; Antaki, 2008; Khan, 2012).
2. It is also similar to an herb known as *Karafs barri* (*Apium graveolens* L.) and *Khilla* (*A. visnaga* L.) in Egypt. The difference is that *Aatrilal* fruits are small in size and longitudinal in shape; hot, pungent, bitter, and cause irritation over the tongue. Instead of that, *Karafs barri* and *Khilla* do not have these characteristics (Sheerazi, 1993).
3. Hakim Sharif (18th century) described it as the fruit of a drug which is known as *Duqu* (*Peucedanum grande* CB Clarke) in Unani. *Ibn al Baitar* contradicted this and said that *Aatrilal* is a different drug (Ibn al Baitar, 1999).
4. Some learned people considered it as a fruit of *Ra'iul Abl.* Ibn Baitar denied their statement and wrote that Dioscorides's statement about *Ra'iul Abl* is that its twig is angular, flowers yellowish-brown, and leaves are big. Instead, *Aatrilal* does not have these features (Ibn al Baitar, 1999).

3.1.4. Temperament (Mizaj)

Temperament (*Mizaj*) is one of the principal fundamental concepts of the Unani system of medicine, and the temperament of drugs has remained central to the theory of drug action. The temperament of a human being and the drug serves as a conceptual framework to use the drug rationally, predict its effect on the body, and serve as an indicator of drug potency. A drug's temperament is defined specifically in terms of nature and extent of deviation in state of the body due to drug action, produced after administration of the drug. For example, a drug is hot or cold in nature when on administration, it tends to increase or decrease the state related to hot temperament or induce such effects in the body, which is attributable to increase heat or coldness respectively. The physicians have categorized the drugs into four groups concerning the effect on a moderate human body. A drug can be hot, cold, wet, or dry in 1, 2, 3, or 4th degrees as per the increasing intensity of action. That is why there is variability in the temperament of *Aatrilal*, proposed by different scholars (Kabeeruddin, 2007; Khazir et al., 2013). The temperament of *Aatrilal* is Hot and Dry in the second degree (Yusuf Bin Umar, 1909); Hot and Dry in third-degree (Ghani, 2001); Hot in fourth and Dry in third-degree (Antaki, 2008; Khan, 2012).

3.1.5. Action and uses (Af'a¯l aur Mawaqe istemal)

It has several pharmacological properties such as *Muḥallil* (Resolvent: an agent which resolves thick and viscous humours, thus resolve the inflammation and reduce swelling) (Antaki, 2008; Khan, 2012), *Mufattiḥ Sudad* (Deobstruent: an agent which dilates the blood vessels or dissolves thick/viscous matter to remove the obstruction) (Momin, 1855; Antaki, 2008), *Mulattif* (Demulcent: an agent which liquefies thick and viscous matter) (Khan, 2012), *Muqatte* (Disintegrator: an agent which dissolve and remove any unwanted collection of morbid matter) (Khan, 2012), *Kasir-i-riyah* (Carminative: an agent which expels the gases from the gastrointestinal tract) (Momin, 1855), *Mudir-i-fuzlat* (expel morbid matter) (Momin, 1855; Antaki, 2008), *Mudirr-i-Bawl wa Ḥayḍ* (Diuretic and Emmenagogue: an agent that increases the excretion of urine and which induce menstrual bleeding) (Khan, 2012), *Mukhri-j-i-balgham* (expectorant), *Qatil-i-Deedan* (Anthelmintic: an agent which kills the intestinal worms) (Khan, 2012), *Musqiṭ-i-Jani¯n* (Abortifacient: an agent which expels out the foetus by virtue of contracting the uterine muscles) (Momin, 1855; Antaki, 2008), *Munaqqi Gurda wa Masana* (to expel the morbid matter from kidney and urinary bladder) (Momin, 1855; Antaki, 2008) internally and *Mujaffif Qurooh* (Desiccant: an agent which constricts blood vessels and decreases exudation from them and thus helps in healing of wounds) (Momin, 1855; Antaki, 2008), *Ja¯li¯* (Detergent: an agent which clean the sticky matter from skin surface) (Khan, 2012) properties when applied externally.

Aatrilal when used either singularly or combined with other drugs is beneficial for *Bars wa Bahaq* (Vitiligo and Pityriasis) (Momin, 1855; Ibn al Baitar, 1999; Antaki, 2008; Khan, 2012). It heals wound if applied locally (Momin, 1855). *Aatrilal* with honey is found useful in *ila¯u¯s* (dynamic intestinal obstruction) (Momin, 1855; Antaki, 2008). *Aatrilal* fruits are burnt with lead and taken with honey in the treatment of urolithiasis (Momin, 1855; Antaki, 2008). *Aatrilal* is effective in treating splenic disorders. It also treats gastrointestinal ailments when mixed with astringent and tonic drugs (Khan, 2012). When used as a decoction, it is beneficial in back pain, hip, and joint pain, and if boiled with olive oil it is very useful for arthritis (Antaki, 2008).

3.1.6. Traditional uses

The fruit is used to treat leukoderma, leprosy, and other skin disorders (Ageel et al., 1987). Photochemotherapy was developed by El-Mofty while working in the Department of Dermatology, Cairo University Medical School, Egypt after his observations on the use of this plant in many patients with vitiligo who would apply juice from *A. majus* plant, to the affected areas and then lie in the sunlight (Bowers, 1999; Batanouny, 2005). The decoction of the fruit, when taken orally after intercourse, prevents implantation of the fertilized ovum; the decoction is also used as a gargle in the treatment of toothache (Bhambri et al., 2012). According to the Bedouins, they used *A. majus* to treat asthma, diabetes, digestive problems; this drug is also used as an antispasmodic, diuretic, and carminative agent (Batanouny, 2005; El-Fruiti et al., 2013). The ripe fruit is used for regulating menstruation, in the treatment of leprosy, kidney stones, and urinary tract infections. Chinese herbal medicine specifically uses the plant as a diuretic, carminative, and to treat angina pectoris and asthma. In Oman, *A. majus* is traditionally used for the treatment of mouth ulcers. The Egyptians used it for the treatment of leucoderma, melasma, and pityriasis alba (Al-Hadhrami et al., 2016).

3.1.7. Dose (Miqdar e khorak)

The dose of *Aatrilal* is 4.5 g but can be taken up to 10 g depending upon patients' age, temperament, and severity of the disease (Ibn al Baitar, 1999; Ghani, 2001; Antaki, 2008; Kabeeruddin, 2014). It can be used in various dosage forms such as infusion, decoction, and powder orally, while its paste is applied locally.

3.1.8. Adverse effects (Muzir)

According to Unani physicians, *Aatrilal* is difficult to digest and harmful to the liver in hot temperament person and kidney (Momin, 1855; Khan, 2012). Details of its adverse effects are not available in medical literature but experience has it that it upsets the stomach, causes malaise, vomiting and anorexia. Very often it is seen that its prolonged use led to weight loss and some patients experienced watery bowel

movements upon the use of the drug. Patients of vitiligo with gastric ulcers or acidity experience worsening of gastric symptoms after using this drug. Excessive use of this drug causes darkening of skin colour which gets normal after stopping drug use. Some parts or the entire body may feel itchy. In some patients, who get itching over the whole body with lesions, this drug is not much effective for them because their body develops resistance against it (Sheerazi, 1993).

3.1.9. Correctives (Muṣleḥ)

Gastric adverse effects can be avoided by the use of Cinnamon, Ginger, Black Pepper, and Ajowan while liver toxicity can be prevented by the use of *Sikanjabeen* (a liquid preparation made of lemon and vinegar), *Sharbat Banafsha* (Syrup of *Viola odorata* L.), *Dawaul Kurkum* (a type of confection prepared by Saffron as the main ingredient with other drugs); an adverse effect on kidney can be avoided with the use of gum tragacanth (Momin, 1855; Ghani, 2001; Nabi, 2007; Khan, 2012).

3.1.10. Substitute (Badal)

Some authors stated *Missi* (*Leea aequata* L.) for internal use and *Kundush* (*Dregea volubilis* (L.f) Benth.) as a paste to use in lieu as a substitute for *Aatrilal.* According to *Hakim Alvi Khan* (1669-1749 AD), *Babchi* (*Psoralea corylifolia* L.) an Indian drug is the nearest substitute in both internal and external use. *Tukhme Karafs* (Fruits of *Apium graveolens* L.) and *Tukhme Suddab* (Fruits of *Ruta graveolens* L.) can also be good alternatives for *Aatrilal* (Ghani, 2001; Khan, 2012).

3.1.11. Ethnopharmacological prescriptions of Aatrilal for vitiligo treatment

- *Aatrilal* 3.5 g and *Aqerqarha* 1 g (*Anacyclus pyrethrum* L.), after mixing with honey if taken orally along with exposure of the affected part to sunlight for one to 2 h was found to be very effective in vitiligo. It results in blister formation and secretion of a yellowish-white fluid from the blisters. The oral intake of the drug should be continued along with the application of any wound healing ointment locally till the wounds heal. It gives the best result if used in the summer season or under bright sunlight. But before starting this regime it is necessary to remove the morbid matters from the body (Morbid phlegm) which are responsible for the disease. It was also observed by the physicians that the white patches faded away quicker on muscular parts than on bony ones. The efficacy of the drug varies from patient to patient, some patients get cured in one or two doses while others got relief after multiple doses (Ibn al Baitar, 1999).
- *Dawud al-Antaki* (1541-1599 AD) mentioned that *Aatrilal* is a very effective prescription for chronic vitiligo in which the powder of *Aatrilal* fruits 3 g, *Zanjabeel* (*Zingiber officinale*) and *Turbud* (*Ipomoea turpethum*) 3.5 g each are taken and mixed with honey and ingested orally with hot water but it is ensured to expose hypopigmented areas to sunlight (Antaki, 2008).
- According to *Abdullah Hussaini*, *Aatrilal* should be grounded with vinegar and then applied to the affected part (Ghani, 2001).
- Another regime described by *Hakeem Shareef* (1722- 1807AD) in which one and half part of *Aatrilal* fruit, *Barg Suddab* (leaves of *Rutea graveolens* L.) and snake skin one part each are taken, then all the drugs are mixed, powdered and taken orally in the dose of 10.5 g for five days along with the *Sharbat Angoori* (Grape syrup). Patients are advised to expose to sunlight until perspiration (Khan, 2012).
- One more effective prescription has been mentioned by *Hakeem Shareef* in which he suggested that 10 g fine powder of *Aatrilal* fruits are mixed with honey to prepare a linctus and this should be consumed with lukewarm water, daily for 15 days. *Hakeem Azam Khan* and *Hakeem Ali Hussain Geelani* also mentioned this remedy with some differences in doses (Ibn al Baitar, 1999; Khan, 2012).
- According to *Hakeem Akbar Arzani* (1722 AD), powder of *Aatrilal*, *Aqerqerha* (*Anacyclus pyrethrum* DC.), *Post Bekh Kibr* (*Capparis spinosa* L.), *Sheetraj* (*Plumbago zeylanica* L.), each 7 g is taken and mixed with vinegar or honey, from which 5 g is taken orally daily along with exposure of affected area under sunlight (Khan, 2012).
- *Hakeem Azam khan* mentioned *Aatrilal* 14 g, *Aqerqerha* 3.5 g, *Gul Lala* (*Anemone coronaria* L.) 7 g, *Jund bed aster* (Castoreum, an animal origin drug) 2.5 g in powder form orally with exposure to sunlight is a good remedy for vitiligo (Khan, 2006).

3.1.12. Unani formulation and pharmaceutical products

Majoon Aatrilal (Anonymous, 1987; Khan, 2006) and *Dawae Bars* (Shareef, 2006) two pharmacopoeial preparations are used in the Unani system of medicine. Worldwide, many pharmaceutical products contain *A. majus* extract or active principle Xanthotoxin as marketed under the trade name 'Oxsoralen', 'Methoxsalen' or 'Meladinine' produced by many pharmaceutical companies in different dosage forms in various countries (Batanouny, 2005; Chopra, 2010); Suntan lotion (Chopra, 2010); Lukoskin ointment and oral liquid (an Ayurvedic proprietary) produced by Aimil pharmaceutical.

3.2. Description of Aatrilal in the scientific literature

3.2.1. Synonyms

Apium ammi Crantz, *Selinum ammoides* E.H.L. Krause, *Ammi boeberi* Hell. Ex Hoffm., *Ammi broussonetii* DC., *Aethusa ammi* Spreng., *Ammi cicutifolium* Willd. Ex Schult., *Ammi elatum* Salisb., *Ammi glaucifolium* L., *Daucus parsae* M. Hiroe, *Cuminum regium* Royle (theplantlist.org, 2020).

3.2.2. Plant description

A. majus is an annual plant of 0.9–1.5 m height with whitish tap-roots and an erect stem. Slender, glabrous with fine longitudinal striations; leaves alternate with long petiole, pinnately divided, lobes oblong, acutely serrulate; inflorescence a compound umbel, the involucral bracts generally divided and about 13 in number, bracteoles of the involucre about 8 in number, the primary ray of umbel sometimes 5 cm long; slender, secondary rays 2–5 cm long; flower whitish actinomorphic or zygomorphic, bisexual, pentamerous and bracteate; calyx teeth obsolete or small; petals obovate with an inflexed point, the exterior ones frequently longer; stamens epigynous; ovary inferior, two-celled, stigma capitate (Anonymous, 1987; Akhtar et al., 2010). The fruits are entire cremocarps (schizocarps) and separate mericarps. The pedicel is usually attached with fruit. They are glabrous, cylindrical to oblong-obovoid, 2.5–3.0 mm in length, and 1 mm or less wide in yellowish-brown colour. Stylopods at the fruit's tip are bifid with free ends curving along the dorsal sides. The mericarp's dorsal side is convex and consists of five prominent longitudinal yellow ridges that extend from base to apex and four dark brown furrows. The commissural surface with a central brown coloured line is almost flat, i.e., carpophore extending from apex base. The taste of the fruit is extremely pungent but slightly bitter, which causes a burning sensation on the tongue and has a characteristic terebinthinate odour (Anonymous, 1987; Gupta and Tandan, 2004; Akhtar et al., 2010).

3.2.3. Cultivation

It is grown as an annual crop in India, some private pharmaceutical companies of the northern part, as well as the Central Institute of Medicinal and Aromatic Plants, cultivate *Aatrilal* (Kokate and Purohit, 2012). The sowing date depends on the onset of significant rainfall, temperature, and humidity of a region. Heavy rainfall doesn't support its growth. In the early stages of crop growth, a mild cool climate and warm, dry weather at maturity are ideal (Bhambri et al., 2012). Well-drained, loamy soil rich in organic matter is good for this crop. Sulphur and Nitrogen nutrients enhance nitrate reductase activity and physiological changes which result in higher fruit yield (Ahmad et al., 2007, 2010). The fruit can be sown directly in the final site or fruitlings are transplanted. Before sowing the farmyard, manure and superphosphate are added to the soil. Fruits are sown in well-fertilized, porous,

and raised beds; germination begins within 10–12 days after sowing. Fruitlings are transplanted in the final site during October–November when fruitling attains an age of 50–60 days. Flowering ranges from January to February. Fruits are harvested during April–May when the fruits in most of the umbel turn light brown. After harvesting, the crop is threshed manually on the threshing floor and fruits are dried in shades (Bhattacharjee, 2004; Kokate and Purohit, 2012).

3.2.4. Microscopic features of fruit

The epicarp is made up of a single-layered epidermis, the outer wall in many epidermal cells is plain while in others, particularly on the ridges slightly protrudes out to form short papillae. These cells contain cruciferous and caryophyllaceous types of stomata. Each epidermal cell usually contains a single rosette of Calcium oxalate crystal, which varies in size. The inner mesocarp consists of few layers of slightly thickened (sclerenchymatous) yellowish-brown to reddish-brown cells. A solitary vitta is spread underneath any secondary ridge through the mesocarp. The walls of the vittae are lined with many polygonal, sinuous epithelial cells of variable sizes. The mesocarp cells are radially elongated to the outside of the vittae, comparatively longer than other mesocarp cells, which are typical of the genus. Underneath each primary ridge, the vascular strands run. The endocarp is single-layered, with narrow and tangentially elongated cells (Anonymous, 1987; Gupta and Tandan, 2004; Akhtar et al., 2010).

Plant and Flower Source: NIUM Herbal garden, Bengaluru, Karnataka, India.

Fruit Source: https://www.ehorticulture.com/tree-plants-fruits/medicinal-plants/ammi-majus-detail.html.

3.3. Phytochemistry

The main bioactive compounds of *A. majus* with a focus on their isolation and identification are listed in Table 1.

A. majus fruits contained proteins 13.83%, fixed oil 12.92%, oleoresin 4.76%, acrid oil 3.2%, amorphous glucoside 1% and tannin 0.45% (Anonymous, 1987; Al-Snafi, 2013).(see Fig. 1-6)

3.4. Pharmacology

Extracts and isolated compounds from *A. majus* have been extensively studied for their pharmacological properties. The main results of these *in vitro* and *in vivo* (preclinical) studies are listed in Table 2 and Table 3 respectively.

3.5. Clinical pharmacology

El-Mofty (1949), initiated experimentation with crystalline extract of *A. majus* in Egypt. Significant reduction in the leucodermic patches was observed on consumption and local application on the hypopigmented areas, this and many other researchers like El-Mofty (1948, 1952), Sidi and Bourgeois (1951), Kaminsky (1954) and Venkateswaran (1955) had reported the efficacy of *A. majus* in vitiligo.

Many clinical trials were performed to evaluate the efficacy of *A. majus* in vitiligo. Patient with leukoderma took oral *A. majus* powdered fruits with exposure of the affected patches to direct sunlight for 1 h manifested as redness, itching, oedema, vesiculation, and oozing in the leucodermic patches. The affected skin gradually began to exhibit dark brown pigmentation within a few days (Hakim, 1969).

A clinical trial was conducted at Ajmal Khan Tibbiya College (AKTC) Hospital, Aligarh on 88 vitiligo patients (38 males and 50 females) in the age group of 3–68 years. Two tablets (0.75 g each) of powdered *A. majus* fruits were given thrice daily after meals, while a lotion of whole fruit powder in vinegar (1:2) was applied locally over the vitiliginous area twice daily. After 90 min of morning dose, the affected area was exposed to sunlight for 15 min. The response was good at 12.5%, fair at 56.8%, while 30.7% reported no change (Saleem et al., 1976).

Salahuddin et al. (1978) investigated the effect of micro pulverized powder of *A. majus* fruits in tablet form in 91 patients (3–60 years of age) of vitiligo in a clinical trial at AKTC Hospital, Aligarh. The daily dose of the tablets (0.75 g) was adjusted according to the age of the patient. The powdered paste was also applied over vitiliginous patches followed by exposure to sunlight daily for 5–15 min. The duration of treatment varied from 3 to 15 days. The drug was found to be effective in 83.5% of patients. The rest of the patients did not show any improvement. However, an increase in hypopigmented area was not observed in any case (Husain et al., 1978).

The leukoderma patients treated with oral (0.05 g of *A. majus* thrice daily) or liniment 1g/100 ml, applied to the skin, with daily exposure of affected areas to the sun for 30 min or to UV light for 2 min and gradually increasing to 10 min in two small groups (eight patients in each group). The leucodermic skin areas were inflamed, vesiculated, and began to show normal pigmentation (Fahmy and Abu-Shady, 1984).

In an open clinical trial, the efficacy of ultra-micronized methoxy psoralen (0.25 mg/kg b. wt. of xanthotoxin) in 10-mg capsules was assessed in 53 patients (15 psoriases, 26 vitiligo, and 12 tineae versicolor) with exposure to UV-A light for varying periods. In 87% of psoriasis patients, the excellent response was observed after 30 treatments with xanthotoxin and UV-A, 85% of patients with vitiligo had acceptable repigmentation after 70 sittings, and 100% of patients with hypopigmentation tinea versicolor showed complete repigmentation after 12 sittings and this new preparation of xanthotoxin was well tolerated by the patients (El-Mofty et al., 1994).

Xanthotoxin with exposure to either UV-A or UV-B radiation in 100 patients of plaque psoriasis proved to help decrease the number of plaques. For the treatment of patients with moderate to severe chronic plaque psoriasis, oral administration of 0.6 mg/kg b. wt. of xanthotoxin with two UV-A radiation dose regimens were used. The result shows that after one year of therapy, 42% of patients were clear and the treatment regimens were well tolerated (Collins, 1996).

A randomized comparative trial assessed the efficacy of xanthotoxin with exposure to either UV-A or UV-B radiation in 100 patients with plaque psoriasis. The result observed that both the treatments were effective in reducing the number of plaques and there was no significant difference between the treatments (De Berker et al., 1997).

In a randomized double-blind study on 19 patients, 12 of the patients treated with an oral dose of 0.6 mg/kg body weight of xanthotoxin, 2 h before exposure to sunlight, three times per week with calcipotriol (a vitamin D3 analogue, may act either by 1,25-dihydroxy vitamin D3 receptors on melanocytes or by modifying defective calcium homeostasis). Ointment showed significant improvement (Parsad et al., 1998).

A comparative trial on 34 patients with plaque psoriasis assessed the efficacy of xanthotoxin administered by two different routes in combination with exposure to UV-A light. In both groups, patients were treated with the drug delivered either orally or in a water bath. Both treatments were effective; however, the bath treatments were more effective than oral and required less than half the dose of UV-A radiation with fewer side effects (Cooper et al., 2000).

In a randomized open multicentre clinical trial, 72 moderates to severe plaque psoriasis patients were evaluated. 36 patients receive 8-MOP (0.5–0.7 mg/kg orally) with UVA radiation and 38 patients taken bath PUVA (0.0001% 8-MOP in 150L bath) for 6 weeks. The result shows that both the treatment modalities were well tolerated and significantly reduced the median psoriasis area and Psoriasis Severity Index Score (Berneburg et al., 2013).

5-Methoxypsoralen has been employed for the treatment of psoriasis. In comparative clinical trials of parallel design, psoriasis clearance rates of >90% or >97% were observed in similar numbers of patients (60–77%) receiving oral PUVA 5-methoxypsoralen or oral PUVA 8-methoxypsoralen treatments (Rio, 2014). In several open clinical trials, patients with systemic lupus erythematosus have been treated with ECP using 8-MOP, showing a significant response to the treatment, with no or minor side effects (Rio et al., 2014).

Table 1
The main secondary metabolites detected and isolated from *A. majus* L.

Chemical Compound	Parts used	Types of extract	Analytical method	Reference
COUMARINS				
Xanthotoxin (8-Methoxysoralen)	Fruits	Chloroform extract	TLC-Spectrophotometric method	Karawya et al. (1970)
	Fruits	Successive extraction	Column Chromatography	Balbaa et al. (1972)
	Fruits	Methanol, petroleum ether, chloroform extract	GC-MS	Krolicka et al. (2001)
	Fruits	Extraction with water, ethanol, petroleum ether, methanol	TLC	Arab et al. (2008)
	Fruits	Supercritical extract	Supercritical Fluid Extraction	Pokrovskii et al. (2009)
	Fruits	Extraction in methanol and chloroform	HPLC	Harsahay et al. (2014)
	Fruits	Petroleum ether extract	CPC isolation of pure compound with HPLC/MS qualitative and quantitative assay	Bartnik and Mazurek (2016)
	Fruits	n-hexane extract	GC-MS	Sajadi Kaboodi et al. (2017)
Bergapten (5-Methoxysoralen)	Fruits	Chloroform extract	TLC-Spectrophotometric method	Karawya et al. (1970)
	Fruits	Successive extraction	Column Chromatography	Balbaa et al. (1972)
	Fruits	Methanol, petroleum ether, chloroform extract	GC-MS	Krolicka et al. (2001)
	Fruits	Extraction with water, ethanol, petroleum ether, methanol	TLC	Arab et al. (2008)
	Fruits	Supercritical extract	Supercritical Fluid Extraction	Pokrovskii et al. (2009)
	Fruit oil	Hydro-distillation	GC-MS	Akhtar et al. (2009)
	Fruits	Extraction in methanol + chloroform	HPLC	Harsahay et al. (2014)
	Fruits	n-hexane extract	GC-MS	Sajadi Kaboodi et al. (2017)
Isopimpinellin	Fruits	–	Column Chromatography	Abdel-Hay et al. (1966)
	Fruits	Methanol, petroleum ether, chloroform extract	GC-MS	Krolicka et al. (2001)
	Fruits	Supercritical extract	Supercritical Fluid Extraction	Pokrovskii et al. (2009)
	Fruits	Petroleum ether extract	CPC isolation of pure compound with HPLC/MS qualitative and quantitative assay	Bartnik and Mazurek (2016)
Psoralen	Fruits	Extraction in methanol and chloroform	HPLC	Harsahay et al. (2014)
Imperatorin	Fruits	Extraction with water, ethanol, petroleum ether and methanol	TLC	Arab et al. (2008)
	Fruits	Extraction in methanol and chloroform	HPLC	Harsahay et al. (2014)
Marmesin	Fruits	Successive extraction	Column Chromatography	Balbaa et al. (1972)
	Fruits	Extraction with water, ethanol, petroleum ether and methanol	TLC	Arab et al. (2008)
	Fruits	n-hexane extract	GC-MS	Sajadi Kaboodi et al. (2017)
6-hydroxy-7-methoxy-4methyl and 6-hydroxy-7-methoxy coumarin	Aerial parts	Methanol extract	Column Chromatography	Selim and Ouf (2012)
Ammirin	Fruits	–	Preparative Layer Chromatography	Abu-Mustafa et al. (1971)
Alloimperatorin	Fruits	–	Preparative Layer Chromatography	Abu-Mustafa et al. (1971)
Ammajin	Fruits	Successive extraction	Column Chromatography	Balbaa et al. (1972)
Pimpinellin	Fruits	n-hexane extract	GC-MS	Sajadi Kaboodi et al. (2017)
Umbeliferone	Fruit, Callus, Hairy root culture	Methanol, petroleum ether, chloroform extract	GC-MS	Krolicka et al. (2001)
Isoarnottinin, Scopoletin, Apiumetin, Lomatin, Ammirol, Dihydroxanthyletin	Whole plant	Methanol extract	Column Chromatography	Elgamal et al. (1993)
Pyrano coumarin (5-isobutylcoumarin-6-C-glucoside)	Aerial parts	Methanol extract	Column Chromatography	El-Sharkawy and Selim (2017)
Furanocoumarin (6,7,9-Trimethoxy-3-(8′-methoxy-2′-oxo-2H-chromen-3- yl)-2H-furo[3,2-g] chromen-2 (3H)-one)	Aerial parts	Methanol extract	Column Chromatography	El-Sharkawy and Selim (2017)
Pyrone coumarin (6-hydroxy-3-(2-hydroxypropyl)-7-methoxy-4 methyl coumarin)	Aerial parts	Methanol extract	Column Chromatography	El-Sharkawy and Selim (2017)

(*continued on next page*)

Table 1 (*continued*)

Chemical Compound	Parts used	Types of extract	Analytical method	Reference
Flavonoids				
Kaempferol	Fruits	85% methanol + 90% ethanol extract	TLC and HPLC	Abdul-Jalil et al. (2010)
Quercetin	Fruits	85% methanol + 90% ethanol extract	TLC and HPLC	Abdul-Jalil et al. (2010)
Isorhamnetin-3-O-rutinoside Kaempferol-3-O-glucoside Isorhamnetin-3-O-glucoside	Aerial parts	n-butanol extract	Silica gel column	Singab (1998)
Terpenoids				
Diterpenes: ammimajane, isoelemecin, phytol and isophytol	Aerial parts	Volatile fraction	Preparative TLC and Spectroscopy	Abraham et al. (1996)
Monoterpenes: carvone, 1,8-cineole, α-terpinyl acetate, trans-pinocarveol, citronellal	Fruit oil	Hydro-distillation	GC-MS	Akhtar et al. (2009)
Thymol, carvacrol, p-cymene, γ-terpenene	Fruit oil	n-hexane extract	GC-MS	Nayebi et al. (2013)
Sesquiterpenes: nerolidol, globulol	Fruit oil	Hydro-distillation	GC-MS	Akhtar et al. (2009)
Fatty acid				
Oleic acid, Palmitic acid, Elaidic acid	Fruits	After methylation process	GC-MS	Hussain et al. (2012),
	Fruits	n-hexane extract of the fruit	GC-MS	Sajadi Kaboodi et al. (2017)
Linoleic acid, Linolenic acid	Fruits	After methylation process n-hexane extract of the fruit	GC-MS	Hussain et al. (2012)
Ellagic acid	Fruits	Aqueous extract	HPTLC and UPLC-MS	Nazik et al. (2020)
Furoquinoline Alkaloid				
4-hydro-7-hydroxy-8-methoxyfuroquinoline, 4-hydro-7-hydroxy-8prenyloxyfuroquinoline	Whole plant	Methanol extract	Successive silica gel Column Chromatography with NMR Spectrometer	Mohammed and El-Sharkawy (2017)

Fig. 1. (1) Whole plant of *A. majus* L.

Fig. 2. (2) Twig of *A. majus* L.

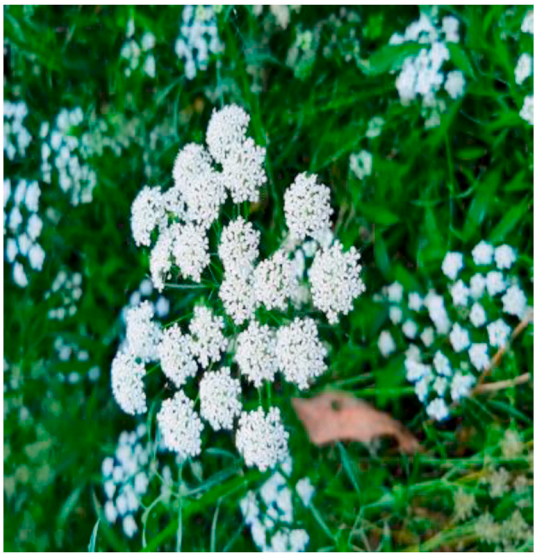

Fig. 3. (3) Inflorescence of *A. majus* L.

The effect of PUVA therapy (0.3–0.6 mg/kg orally 8-MOP and UVA radiation) on retinal electrophysiologic function was investigated using electroretinographic in Patients with vitiligo, psoriasis, or eczema for 6 months (mean number of sessions: 45 ± 11). After this, a complete ophthalmic examination was performed, and found no significant change in electroretinographic traces was observed; oral photochemotherapy seems safe for retinal electrophysiologic function (Shoeibi et al., 2016).

3.6. Adulteration

Aatrilal is in some cases, adulterated with the fruits of *A. visnaga*. These two drugs are easily identified by some chemical tests. The alcoholic extract of *Aatrilal* fruit turns blue when observed on Flame photometer but does not in the case of Khilla fruit (Batanouny, 1999). Another scientist, Rahman in 1944, extracted both the drugs with NaOH then one drop of extract of each drug was placed on Whatman filter

Fig. 4. (4) Flowers of *A. majus* L.

Fig. 5. (5) Fruits of *A. majus* L.

paper and observed under ultraviolet light after processing with concentrated hydrochloric acid. Consequently, khilla's extract showed a brownish dark violet colour while *Aatrilal's* extract showed a light violet colour (Sheerazi, 1993).

After boiling 0.05 g of *A. majus* fruit with 5 ml water for 1 min and straining, one or two drops to 1 ml of solution (1:1) of sodium hydroxide is added, no rose red colour is produced, while in *A. visnaga* a rose-red colour appears within 2 min of treatment (Batanouny, 1999).

In the transverse section of fruit, *A. majus* can be distinguished by the presence of four much prominent secondary ridges and the absence of lacuna in primary ridges, which is seen in *A. visnaga* (Qadri, 2014).

Scanning electron microscopy (SEM) inspection of dried powder sample shows quite different epicarp micro characters with different cuticle ornamentation patterns of the cells in the intercostal spaces. The polygonal area cells of the intercostal spaces in *A. visnaga* show outer walls as smooth or weak longitudinal striations and strongly striated with a cuticle ornamentation pattern resembling the helianthoid type of epidermis seen in the *A. majus* (Cappelletti, 1979). SEM studies reveal that in *A. majus* the epicarp surface ornamentation is torulose, while in *A. visnaga,* it is rugulate (Bagchi and Srivastava, 1989).

The active principle and therapeutic properties of *A. majus* are quite different. *A. visnaga* contains mainly khellin, visnagin, and used in the treatment of renal colic, mild anginal symptoms, treatment abdominal cramps, and as a specific bronchodilator (Khalil et al., 2020).

3.7. Toxicity, allergenic reactions and contraindications

Fruit powder shows some undesirable manifestations such as headache, nausea, vomiting, diarrhoea, gastric burning, and when given in very high doses, even nephritis and coma may occur (Sidi and Bourgeois, 1952). One case of phototoxic dermatitis was reported in a patient with vitiligo after ingestion of *A. majus*; another case of allergic rhinitis and contact urticaria surfaced due to exposure to the *A. majus* fruits (Ossenkoppele et al., 1991; Kiistala, 1999). Phototoxic reactions were also reported in subjects who handled the fruits and were subsequently exposed to sunlight. Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache, allergic symptoms, and sleeplessness. Other adverse reactions reported after treatment with its constituent xanthotoxin include itching, nausea, oedema, hypotension, nervousness, vertigo, depression, painful blistering, burning and peeling of the skin, pruritus, freckling, hypopigmentation, rash, cheilitis, and erythema (WHO Monograph on selected medicinal plants, 2007). Alouani et al. (2018) indicated that the adverse effect of *A. majus* on vitiligo patients was burning sensation, pain, itching, and erythema on vitiligo patches, and multiple bullae. Two other cases of phytophotodermatitis by using *A. majus* were reported in the literature (Alouani et al., 2018).

Fruits are contraindicated in pregnancy, nursing, tuberculosis, liver and kidney diseases, and human immunodeficiency virus (HIV) infections. Care should be taken where there is a familial history of allergy to the sunlight or chronic infections. Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard, and carrots (WHO Monograph on selected medicinal plants, 2007). Fruit of *A. majus* is contraindicated in diseases associated with photosensitivity, cataract, invasive squamous-cell cancer, known sensitivity to xanthotoxin (psoralens), and in children under the age of 12 years (Asadi-Samani et al., 2015).

4. Discussion

Unani system of Medicine is a treasure trove of the single (crude drugs when used one at a time is called single drug) and compound (formulation prepared by combining two or more drugs) drugs. Single drugs of all three origins viz. plant, mineral, and animal are used; however, plant origin drugs are predominantly used. Though many pharmacological properties characterize all the single drugs, each drug has some specific or main action due to the temperament or active principle. *Aatrilal* is an epitome of such a drug. After scrutinizing the Unani and conventional literature, it was noted that *Aatrilal* has a diverse range of pharmacological actions and its efficacy in treating dermatological disorders is noteworthy. Hence its consideration as a first-line drug for the treatment of vitiligo. Some tested prescriptions are mentioned in Unani literature with the full potential of treating vitiligo, and many clinical trials (El-Mofty et al., 1948, 1952, 1994; Sidi and Bourgeois, 1951; Saleem et al., 1976; Abu-Shady, 1984; Parsad et al., 1998) have been carried out on this drug. Therefore, it is mandatory to understand the Unani explanation of the mechanism of action of *Aatrilal* in vitiligo.

The concept of four humors, propounded by Hippocrates (460-377 BC), forms the basis of health and disease in the Unani system of medicine (Lone et al., 2012a,b). *Bars* (vitiligo) is a humoral disease whose occurrence is construed to the accumulation of excess morbid phlegm beneath the skin. According to most of the Unani physicians like *Rabban Tabri* (810-895 AD) in his famous book "Firdaus-ul-Hikmat, *Al-Rhazi* (850-925 AD) in Kitabul-Havi, *Jurjani* (11 century AD) in Zakheera Khawarizm Shahi, *Al-Majusi* (930-994 AD) in Kamilus Sana'ah, *Ibn Sina*

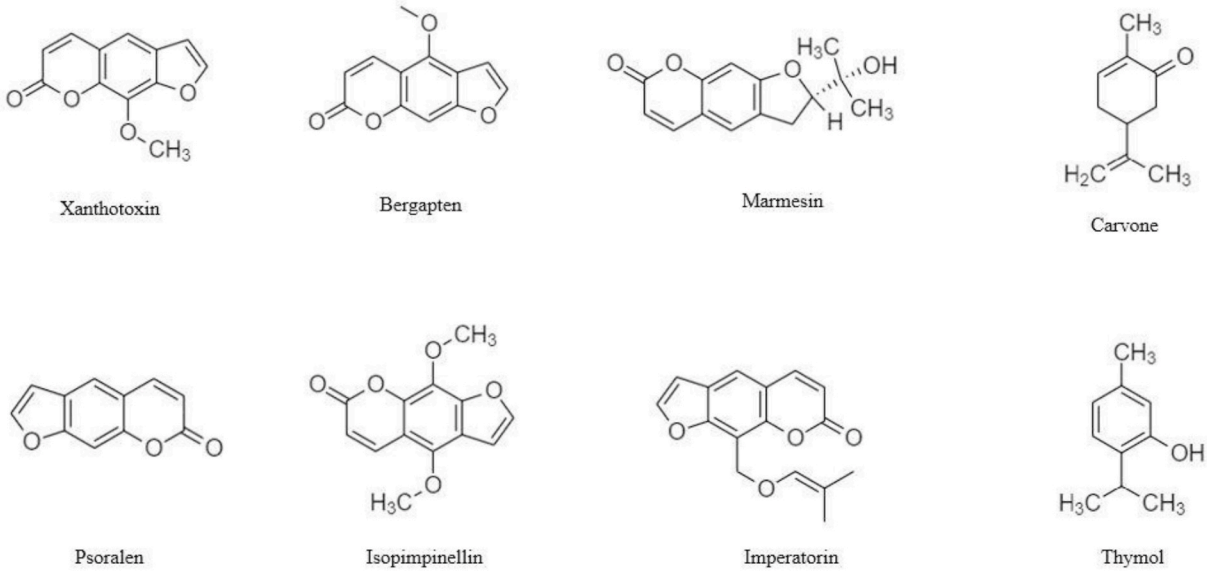

Fig. 6. Structures of key bioactive ingredients.

(980-1037 AD) in Al-Qanoon fit Tib, *Ibn Hubl Bhagdadi* (1122-1213 AD) in Kitabul Mukhtarat fit Tib, *Mohammad Aazam* (1813–1902 AD) in Rumooz-e-Aazam and *Akbar Arzani* (18th century AD) in Tibb-e-Akbar described that *Barṣ* occurs because of weakness/or malfunctioning of *Quwwate Mughayyira* (transformative faculty) and *Quwwate Mushabbiha* (resemblance faculty) the power that brings about changes in the nutrients so that these become the part of the body. This weakness may be because of *Fasad-ud-dam* (morbid blood) and *Burudat-ud-dam* (coldness of blood), or due to the collection of *Balghame ghaleez* (viscous phlegm) in the whole body or the affected parts. Under the influence of morbid humors, the incoming nutrients that reach the affected part through blood circulation lose their tendency to get converted into a similar form and colour of skin. These unaltered nutrients remain accumulated in the affected area, finally leading to the ailment's genesis (Monograph, 2006).

As per Unani doctrine, *Barṣ* is a chronic disease caused due to *sue mizaj barid* (altered cold temperament) therefore, based on the principle of *Ilaj bi'l-Ḍidd* (contrary therapy), the hallmark of Unani treatment methodology, the first-line treatment of *Barṣ* is *Tadeel Mizā̄j* (to restore the normal temperament). *Hakeem Azam Khan*, in his famous book "Ikseer Azam," has quoted the reference of various Unani physicians who have advocated for *tanqia badan* (removal of harmful matter from the body) to be the inception for the treatment along with *munḍij* (concoctive) and *mushil* (purgative)therapy. After completing this, *ma'jeen harra* (compound drugs having hot temperament) and the specific medicines for the *Barṣ* are advocated in systemic and topical application with exposure of the hypopigmented area to the sunlight. These drugs alleviate the excess *buroodat* (coldness) from the body and the site of the lesion and produce *hararat* (warmth) over the affected area. Consequently, the blood circulation of the affected part increases and restores the normal pigmentation of the skin. *Harul Mizāj Adwiya* (hot temperament drugs) possesses *Ja*$\bar{}$*li*$\bar{}$ (detergent), *Muḥammir* (rubefacient), *Muḥallil* (resolvent) and *Musakhkhin* (calorific) properties. *Aatrilal* is endowed with all such properties; besides, it also has *Mukhrij-i-Balgham* (expelling of phlegm) and *Mudirr-i-Bawl* (diuretic) actions, which help in the treatment of vitiligo (Sheerazi, 1993; Monograph, 2006).

As per scientific literature, vitiligo is an acquired idiopathic pigmentary disorder of skin and hair, in which melanocytes lose their function, resulting in the formation of white macules. Irrespective of its cause, there is the destruction of melanocytes resulting in depigmented lesions (Rio et al., 2014). It is a well-known fact that vitiligo can be treated effectively by medicinal plants along with sunlight exposure. *Aatrilal* (Fruits of A. majus) in Egypt and *Babchi* (Fruits of Psoralea corylifolia) in India were used to treat vitiligo by herbalists and traditional healers (Hussein et al., 2016). *A. majus* provides a huge number of compounds and is a rich source of furocoumarins, which are therapeutically very important and have various clinical applications. They can sensitize cells to visible light, sunlight, and ultraviolet light (Rio et al., 2014). Numerous clinical trials have assessed the efficacy of *A. majus* and its active principle xanthotoxin for the treatment of vitiligo, psoriasis, and hypopigmentation (Hussein et al., 2016). El-Mofty demonstrated the efficacy of 8-methoxy psoralen in the treatment of vitiligo (El-Mofty, 1952). Some other furocoumarins: bergapten, imperatorin, isopimpinellin, etc., which have photosensitizing action and psoralens, are still used in the PUVA photochemotherapy for vitiligo, psoriasis, and other skin disorders (Hönigsmann, 2013). The actual mechanism of action of these compounds is complicated to explain. However, psoralen and its related compounds are proven to induce repigmentation and have been described by El-Mofty (1948) based on his trial and observation. Psoralen reactivates the melanocytes in the vitiliginous patches and releases the inhibited tyrosine enzymes resulting in increased migration of active melanocytes from the surrounding normal epidermis. There is increase tolerance to UV or sunlight exposure, at which point further stimulation of the melanocytes occurs, which corrects the structural abnormalities of melanocytes in the vitiliginous skin (Ortonne, 1989).

In vitiligo, the quality of blood is altered due to excessive production of morbid phlegm and as per scientific literature either melanocytes are rendered incapable or their normal production is impaired. Melanin is the part of melancholic humor whereas phlegmatic humor especially phenylalanine and tyrosine (amino acids) are the precursor of melanin formation, which are converted by the process of *ihtiraq* (oxidation) into DOPA by *balghami khamir* i.e., tyrosinase enzyme. DOPA is further converted to Dopa quinone and after a series of reactions, a final product melanoprotein or melanin is formed (Ahmad, 1980). Hence, the alteration of quality and quantity of phlegmatic humor affects the production of black bile resulting in insufficient production of *saudain* (melanin). The Unani drugs which are used in vitiligo including *Aatrilal* are blood purifiers, detergent, laxative, resolvent, lenitive, diaphoretic, and diuretic. By these properties, they act as a digestive, appetizer, tonic to the stomach and liver, anti-septic and immune system booster. These drugs are *muaddil* (alterative), bring the quality and quantity of *akhlāt* (humors) or blood in equilibrium, normalize the blood composition and

Table 2
Preclinical (*In vitro*) studies of *A. majus* L.

Pharmacological activity		Tested organism	Plant part	Dosage form/ concentration	Model used	Standard control	Zone of inhibition	Outcome	Reference
Antimicrobial	**Antibacterial**	*S. aureus, E. coli* and *Proteus vulgaris*	Fruits	Extracted in sodium phosphate citrate buffer at pH (6.8)	Agar well diffusion assay	Chloramphenicol	12–14 mm	Found to be very effective against *S. aureus, E. coli* and *P. vulgaris*	Al Akeel et al. (2014)
	Antibacterial	*S. aureus*, *E. coli*, *Haemophilus influenzae* and *Proteus* spp.	Fruits	Methanol, chloroform, hexane, ethyl acetate, water, and butanol extract	Agar disc diffusion method	Amoxicillin	0–15 mm	Moderate activity against the bacterial strains at all concentrations except methanol and ethyl acetate crude extracts did not show any activity *against H. influenzae* and *Proteus* spp.	Al-Hadhrami and Hossain (2016)
	Antibacterial	*S. aureus,* and *E. coli*, *Haemophilus influenzae* and *Proteus* spp.	Leaves	Methanol, chloroform, hexane, ethyl acetate, water, and butanol extract	Agar disc diffusion method	Amoxicillin	0–20 mm	Moderate activity against the bacterial strains at all concentrations except for *H. influenza*	Al-Hadhrami et al. (2016)
	Antibacterial	*S. aureus* and *E. coli*	Fruits	Methanol extract/ (0.5–2%) concentration	Disk diffusion and Well diffusion method	–	9 to 2.3 ± 0.57 mm	Effect on gram+ was stronger than on Gram-	Sajadi Kaboodi et al. (2017)
	Antibacterial	Six Gram + bacteria	Fruits	Ethanol 80% and ethyl acetate extract	Disk diffusion and agar overlay bioautography method	Azithromycin	10–12 mm	Significant on *Streptococcus* species	Adham and Abdulah (2017)
	Antibiofilm	Six Gram + bacteria	Fruits	Ethanol 80% and ethyl acetate extract/0.5–62.5 mg/ml	Modified crystal violet assay method	–	–	Significant against *Staphylococcus* species	Adham and Abdulah (2017)
	Anti-viral	Mammalian viruses; HSV-1 and VSV	Aerial parts	Methanol extract	End titration technique	–	–	Significant against (VSV) in a concentration-dependent manner and no activity against HSV	Selim and Ouf (2012)
Larvicidal		*Culex pipiens molestus* F.	Fruits	Methanol extract/ 50–200 μg/ml	–	–	–	High mortality to the larvae after 7 days at 200 μg/ml concentration	Mustafa and Al-Khazraji (2008)
Anti-insect		*Tribolium castaneum*	Leaves	Methanolic extract	–	–	–	50% mortality during the 30 days and 79% after 45 days of treatment. The result was very significant $p < 0.05$	Hussein et al. (2016)
Cytotoxic		–	Leaves	Methanol, chloroform, hexane, ethyl acetate, water, and butanol extract	Brine shrimp lethality assay	–	–	Methanol extract has the highest cytotoxicity with an LC_{50} value of 45.75 mg/ml, and the lowest 570.02 mg/ml in butanol extract	Al-Hadhrami et al. (2016)
		–	Fruits	Crude extracts	Artemia lethality method	–	–	Chloroform extract has the highest cytotoxicity with an LC_{50} value of 46.168 mg/ml, and the lowest 652.38 mg/ml in water extract	Al-Hadhrami and Hossain (2016)
		–	Fruits	Methanol Extract/ 5–50 μg/ml	Lung adenocarcinoma (A549), human	–	–	Pyrone coumarin showed high	El-sharkawy and Selim (2017)

(*continued on next page*)

Table 2 (*continued*)

Pharmacological activity	Tested organism	Plant part	Dosage form/ concentration	Model used	Standard control	Zone of inhibition	Outcome	Reference
				colon carcinoma (HCT116), and human breast carcinoma (MCF-7) cell lines/MTT assay			cytotoxicity on different cell line	
Anti-proliferative	–	Fruits	8-methoxypsoralen (8-MOP)/ (1.56–400 μM)	BrdU assay in neuroblastoma (SK–N-AS) and metastatic colon cancer cells	–	–	Inhibit the growth by induction of apoptosis via intrinsic and extrinsic pathways	Bartnik et al. (2017)
Anti-oxidant	–	Fruits	Methanol, chloroform, hexane, ethyl acetate, water, and butanol extract	DPPH method	Gallic acid	–	The highest antioxidant activity was found in chloroform crude extract and the lowest was in methanol extract	Al-Hadhrami and Hossain (2016)

Table 3
Preclinical (*In vivo*) studies of *A. majus* L.

Pharmacological activity	Plant part	Dosage form	Dose	Model used	Standard control	Outcome	Reference
Analgesic	Fruits	Ethanolic extract	50 and 100 mg/kg b. wt.	Hot plate method in male albino mice	Tramadol/40 mg/ kg b. wt.	A dose of 100 mg/kg shows effective analgesic activity	Koriem et al. (2012)
Anti-inflammatory	Fruits	Ethanolic extract	50 and 100 mg/kg b. wt.	Carrageenan induced hind paw oedema in SD rats	Indomethacin/20 mg/kg b. wt.	Significant inhibition of the rat paw oedema at a dose of 100 mg/kg b. wt.	Koriem et al. (2012)
	Fruits	Alcoholic extract	2–32 mg/ Rat p.o.	Formalin induced chronic inflammation paw oedema in rats	Piroxicam/5 mg/ kg b. wt.	16, 32 mg/rat showed significant reduction in paw thickness ($p < 0.05$)	Mutlag (2012)
	Aerial parts	Methanol extract (6-hydroxy-7-methoxy-4 methyl coumarin; 6-hydroxy-7-methoxy coumarin)	0.01 mg/ 100 g b. wt.	Carrageenan induced paw oedema in rats	Indomethacin/ 0.1 g/kg b. wt.	Test compound has a significant reduction in rat paw oedema	Selim and Ouf (2012)
Antihyperlipidemic	Fruits	Ethanolic extract	50 and 100 mg/kg b. wt.	High fat diet induces hyperlipidaemia in SD rats	Atorvastatin/1 mg/kg twice a week	Significant decrease in the concentrations of cholesterol, LDL, triglycerides, and increase HDL	Koriem et al. (2012)
Antipyretic	Fruits	Alcoholic extract	50 and 100 mg/kg b. wt.	Brewer's yeast suspension in male SD rats	Paracetamol/50 mg/kg b. wt.	100 mg/kg b. wt. was more potent in lowering the body temperature after 1 and 2 h	Koriem et al. (2012)
Hepatoprotective	Fruits	Ethanolic extract	1–16mg/ rat	CCl_4 induced liver damage in rats	–	Significant hepatoprotective effects in a dose-dependent manner	Mutlag et al. (2011)
Nephroprotective	Fruits	Ethanolic extract	128 mg/kg	Gentamicin induced nephrotoxicity on a small group of rats	–	Serum creatinine and urea levels in the test drug treated group were lower than the group treated with gentamicin alone ($P < 0.05$)	Mutlag et al. (2012)

tone up the sluggish liver and kidney for its normal function (Ghani, 2001). Moreover, when applied locally in the form of a paste and exposed to direct sunlight, its *muhammir* (rubefacient) action kicks in and increases blood circulation. Furanocoumarins present in *Aatrilal* initiate the transformation of DOPA to melanin under the influence of UV light and psoralen stimulates the proliferation of melanocytes. The immunomodulating properties of *Aatrilal* prevent the destruction of melanocytes by the deranged immune system (Anonymous, 2003; Kiritikar and Basu, 2003). Based on the above explanation, it is now clear that the mechanism of action of Unani drugs is nearly similar as discussed in the scientific literature with the only difference in terms and concept.

Numerous clinical trials have been reported on vitiligo and other skin disorders, but most of them are either on the crude extract or a few well-known compounds and were carried out in the mid of 20th century. The long gap in the clinical trial of *Aatrilal* is palpable. This may be due to the availability of its better substitute, i.e., *Babchi*. Nevertheless, *A. majus* is also cultivated in India; therefore, it is necessary to research its other components. A well-designed comparative clinical trial and a safety study should be planned on both the drugs using crude extract and isolated compounds to develop a more efficacious and safer drug for the patients of vitiligo and other associated disorders.

Aatrilal has also been studied for several other pharmacological activities such as analgesic, anti-inflammatory, antipyretic, anti-hyperlipidemic, anti-microbial, anti-viral, insecticidal, antioxidant, larvicidal, hepatoprotective, and nephroprotective (Mustafa and Al-Khazraji, 2008; Mutlag et al., 2011, 2012; Koriem et al., 2012; Selim and Ouf, 2012; Al-Hadhrami and Hossain, 2016; Adham and Abdulah,

2017; Sajadi Kaboodi et al., 2017). Its methanol extract has shown a better antibacterial effect on gram-positive bacteria than gram-negative bacteria. This might be due to the structure of the plasma membrane and cell wall in the bacteria (gram-negative), limiting the entrance of the active ingredients of herbal extract into the cell (Sajadi Kaboodi et al., 2017). *A. majus* fruit's antibacterial effect is due to bioactive constituent's phenolic acid, terpenes, tannin, and flavonoids (Al-Hadhrami et al., 2016). The hypolipidemic activity may be attributed to the coumarin contents of the plants, which were reported to exhibit a lipid-lowering effect and significantly decrease total cholesterol level (Koriem et al., 2012). The anti-inflammatory and anti-nociceptive effect may be due to the influence on the inflammatory mediators and also on the pathway of prostaglandins synthesis, which may be due to the presence of coumarin compound (Koriem et al., 2012). The above phytochemical and pharmacological studies are testimony of the therapeutic potential of *A. majus* in diverse pathological states of the body.

5. Conclusion

The review tried to explore *Aatrilal* (*A. majus* L.) in Unani, other traditional literature, and scientific reports. Based on the information extracted above, it can be concluded that *Aatrilal* is a drug that has been effectively used in the Unani system of medicine for centuries to treat the cases of vitiligo and other dermatological disorders. Unani physicians suggested several tested prescriptions and formulation based on their experiences and observations, which are still found effective in the patients of vitiligo. Having a well-established concept of disease and line of treatment, the mechanism of action of *Aatrilal* relating to its physicochemical properties is justified. Its many other properties are validated by *in vitro* and *in vivo* pharmacological studies. Most of the studies conducted so far on the crude extract and isolated principles proved the multipotent action of *Aatrilal* together with its efficacy in vitiligo and other dermatological disorders. Many potentially bioactive compounds are included in the essential oil, but to our knowledge, no detailed studies of its biological activity are yet available. Therefore, our suggestion is to focus future research on essential oil and its ingredients. Furthermore, it is also suggested to attempt experimental and clinical studies on its tested prescriptions to ascertain the efficacy and safety in the patients of vitiligo.

Declaration of competing interest

There is no conflict of interest.

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