Review Article

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CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL ACTIVITIES OF *AMMI MAJUS* AND *AMMI VISNAGA*. A REVIEW

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Abstract

Ammi species belong to the family Umbellifereae, contained bioactive compounds (mainly coumarins and flavonoids) of important biological activities. *Ammi majus* fruit contained amorphous glucoside 1%, tannin 0.45%, oleoresin 4.76%, acrid oil 3.2%, fixed oil 12.92%, proteins 13.83% and cellulose 22.4%. However , the major constituents of *Ammi majus* are the furanocoumarins, which included xanthotoxin (methoxsalen, 8-methoxypsoralen , ammoidin , up to 1.15%), imperatorin (ammidin, up to 0.75%) and bergapten (heraclin, majudin, 5-methoxypsoralen , up to 1.88%) , marmesin 0.25% , isoimperatorin 0.01%, heraclenin 0.07% and isopimpinellin 0.01%. *Ammi visnaga* contained γ-pyrones (furanochromone up to 4%), the principal compounds being khellin (0.3–1.2%), visnagin (0.05–0.30%), khellinol, ammiol, khellol and khellinin. *Ammi visnaga* also contained fixed oils (up to 18%) and coumarins (0.2–0.5%), the main one being the pyranocoumarin visnadin (0.3%). The previous pharmacological studies showed that *Ammi majus* was used effectively in the treatment of psoriasis, vitiligo and tinea versicolor. Its furocoumarins have bactericidal, fungicidal, insecticidal, larvicidal, moluscicidal, nematicidal, ovicidal, viricidal and herbicidal activities. *Ammi visnaga* was also used effectively for the treatment of vitiligo. It exerted a wide range of antibacterial activity and induced smooth muscle relaxant effects especially vascular smooth muscle. The present review will highlight the chemical constituents and the pharmacological and therapeutic effects of *Ammi majus* and *Ammi visnaga*.

Keywords: *Ammi majus, Ammi visnaga*, Furanocoumarins, Flavonoids, Vitiligo, Psoriasis.

Introduction

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavors, fragrances, colors, biopesticides and food additives. Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. *Ammi* species , belong to the family Umbellifereae , contained bioactive compounds (mainly coumarins and flavonoids) of important biological activities. *Ammi majus* is indigenous to Egypt and it grows in the Nile Valley, especially in Behira and Fayoom. It is also found in the basin of the Mediterranean Sea, West Africa, in some regions of Iran and the mountains of Kohaz. *Ammi visnaga* is distributed in North Africa, Europe, Eastern Mediterranean region, South western Asia,

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North America, Argentina, Chile, Mexico, and Atlantic Islands . In Iraq, *Ammi majus* usually found in fields and gardens and by the side of channels, often as weed of cultivation. It is collected from Kut, Baghdad, Hawija and many other areas, while *Ammi visnaga* is distributed in Erbil, Mousl, Baghdad, Sulaimania and Kirkuk in north of Iraq[1-3].

The dried ripe fruits of *Ammi majus* were used traditionally for the treatment of skin disorders, psoriasis and vitiligo. It was used as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of leprosy, kidney stones, and urinary tract infections[4-9]. While, *Ammi visnaga* was used traditionally in the treatment of mild anginal symptoms, as supportive treatment for mild obstruction of the respiratory tract in asthma, bronchial asthma or spastic bronchitis, and postoperative treatment of conditions associated with the presence of urinary calculi. It was also used for the treatment of gastrointestinal cramps, as diuretic, for painful menstruation and as an emmenagogue to regulate menstruation[10]. The aim of this study is to highlight the chemical constituents and the pharmacological and therapeutic effects of *Ammi majus* and *Ammi visnaga*

I-Ammi majus

Synonym: *Apium ammi*

Common names : English : Bishop's weed, Greater Ammi; Arabic: Khella shaitani , Khella bariah

Traditional use: The fruits were used for the treatment of skin disorders, psoriasis and vitiligo. It was also used as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of leprosy, kidney stones, and urinary tract infections[4-9].

Physicochemical properties[11]: moisture content : (loss on drying at 105^{o}C) - 5.25% w/w , total ash content of powdered drug - 7.00% w/w , water soluble ash - 5.35% w/w , and acid insoluble ash - 0.86 % w/w . Extractive value in different solvents %: Acetone - 6.00 w/w, absolute alcohol - 3.50 w/w, chloroform - 1.75 w/w, methanol - 7.85 w/w, petroleum ether (60-80) - 1.20 w/w, and water - 17.35 w/w.

Chemical constituents

Ammi majus fruits contained amorphous glucoside 1%, tannin 0.45%, oleoresin 4.76%, acrid oil 3.2%, fixed oil 12.92%, proteins 13.83% and cellulose 22.4%[3]. The major constituents of *Ammi majus* are the furanocoumarins, which included xanthotoxins (methoxsalen, 8-methoxypsoralen , ammoidin , up to 1.15%), imperatorin (ammidin, up to 0.75%) and bergaptens (heraclin, majudin, 5-methoxypsoralen , up to 1.88%) , marmesin 0.25% , isoimperatorin ,0.01%, heraclenin 0.07% and isopimpinellin 0.01%[12-21]. Selim and Ouf isolated two coumarins from the aerial parts of the Egyptian *Ammi majus* L. , 6- hydroxy-7-methoxy-4 methyl coumarin and 6-hydroxy-7-methoxy coumarin[9]. The presence of nonfurocoumarin, umbelliprenin, glycosides of quercetin, luteolin were reported in *Ammi majus* fruits[20-21].

Abdul – Jalil *et al* identified two flavonoids from *Ammi majus* fruit , quercetin and kaempferol . They found that the amount of kaempferol (0.045 %) was higher than quercetin(0.036 %).[22] The essential oil extracted from fruits contained high boiling hydrocarbons 1.34%, dipiperitone 10% , unsaturated cyclic terpeniole 15% and a mixture of furocoumarins 60%.[23]

Hussain *et al* investigated the fatty acids constituents of *Ammi majus* oil . A total of 18 different components were identified and quantified. Methyl ester of linoleic acid was found in high concentration 9.00%, followed by methyl ester of oleic acid 5.60%, palmitic acid 3.98% and linolenic acids 1.42% . The concentration of the rest identified fatty acids (hexanoic acid, carylic acid capric acid, lauric acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, stearic acid, elaidic acid, arachidic acid, behenic acid, tricosnoic acid, tetracosanoic acid) were less than 1%.[24]

Pharmacological effects

Effects on psoriasis , vitiligo and tinea versicolor

Numerous studies have assessed the efficacy of Fructus *Ammi majus* andxanthotoxin for the treatment of vitiligo, psoriasis, and hypopigmentation tinea versicolor. [6-8, 25-35]

Experimentation with *Ammi majus* extracts was started in Egypt by El Mofti.[8, 25] This followed by the work of Sidi and Bourgeois who used *Ammi majus* Linn, in six patients with vitiligo, five men and one woman. Their ages were from 30 to 50 years. *Ammi majus* Linn was used (a) by oral administration, (b) by local topical application at

the affected sites followed by sun or ultraviolet lamp exposure, or, (c) by a combination of (a) and (b). Three of patients were subjected to the combined treatment, two only to topical treatment and one to treatment by mouth for 5 months, and then to the combined treatment. The repigmentation appeared in all patients as pigmented minute macules with hair follicles in their center. These macules were distributed over the leukodermic plaques and increased progressively in size until they joined, forming larger islands. This was particularly distinct in the lesions on the trunk and on the extremities. On the face the repigmentation developed more rapidly and appeared to be progressing more from the periphery towards the center.[30]

Many clinical trials were carried out to investigate the efficacy of *Ammi majus* in vitiligo , Patient with leukodermis took oral *Ammi majus* powderd fruits with exposing the affected patches to direct sunlight for 1 hour developed symptoms of itching, redness, oedema, vesiculation and oozing in the leukodermic patches. Within few days , the affected skin gradually started to display deep brown pigmentation.[5]

In two small group of patients (eight patients each) with leukoderma treated with oral(0.05 g of *Ammi majus* three time daily) or liniment 1 g/100 ml, applied to the skin, with daily exposure of leukodermic areas to the sun for 0.5 hour or to UV light for 2 minutes, gradually increasing to 10 minutes , the leukodermic skin areas were inflamed and vesiculated, and the leukodermic areas began to show normal pigmentation.[7]

However *Ammi majus* and its furanocoumarins constituents showed good results in many other clinical studies , 70% of the patients treated with an oral dose of 0.6 mg/kg bw of xanthotoxin 2 hours before exposure to sunlight three times per week with calcipotriol ointment in a randomized double-blind study, showed significant improvement.[31]

Xanthotoxin with exposure to either UV-A or UV-B radiation for the treatment of plaque psoriasis in 100 patients appeared effective in reducing the number of plaques.[32] Oral administration of 0.6 mg/kg bw of xanthotoxin with two UV-A radiation dosage regimens was used for treatment of patients with moderate–severe chronic plaque psoriasis. 42% of patients were clear 1 year after treatment and the treatment regimens were well tolerated.[33] Many other similar results were obtained in assessment of *Ammi majus* and its furanocoumarins in the treatment of psoriasis, vitiligo and tinea versicolor by many authors. [7, 28, 34-35]

Other pharmacological effects

Furocoumarins have bactericidal, fungicidal, insecticidal, larvicidal, moluscicidal, nematicidal, ovicidal, viricidal and herbicidal activities.[3, 36] *Ammi majus* coumarins were evaluated for antiviral effects against two mammalian viruses, HSV-1 and VSV. The antiviral activity was determined by means of the end titration technique that depends on the ability of plant extract dilutions to inhibit the produced cytopathogenic effect**.** *Ammi majus* coumarins exerted antiviral activity against vesicular stomatitis virus (VSV) in a concentration-dependent manner at complete non-toxic concentration range 10-100 µg/ml**.** *Ammi majus* coumarins found to have no reliable antiviral activity against herpes simplex virus (HSV).[9] A dose of 400 mg/kg body weight of a hot aqueous extract and 15.0 mg/kg bw of petroleum ether extract of the *Ammi majus* fruits daily for six days reduced the *Schistosoma mansoni* worm burden in mice by 49.3–72.3%.[18] Mustafa and Al-Khazraji investigated the effects of the extracts *Ammi majus* against larval stage of *Culex pipiens* molestus Forskal. *Ammi majus* L. caused high mortality to the larvae after 7 days of treatment.[37] Acetone and 95% ethanol extract of *Ammi majus* inhibited the growth of the *Neurospora crassa* fungi *in vitro*.[38] *Ammi majus* coumarins were evaluated for anti-inflammatory activity by the carrageenan induced rat paw edema method. They possessed anti-inflammatory effects at a dose of 0.01 mg/100 g. [9]

Contraindications and adverse effects

A. majus L. 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. The fruits are also contraindicated in pregnancy, nursing, tuberculosis, liver and kidney diseases, human immunodeficiency virus (HIV) infections and other autoimmune diseases. [9,39-40]

Patients, after the first exposures, developed bullous reactions of more or less severe but in constant degree similar to burns, nervousness and insomnia,

nausea and gastric burning.[30] However , itching, edema, hypotension, vertigo, depression, painful blistering, burning and peeling of the skin, pruritus, freckling, hypopigmentation, rash, cheilitis and erythema were also recorded with xanthotoxin therapy.[39] Phototoxic dermatitis and allergic rhinitis and contact urticaria due to exposure to the fruits were recorded.[41-42] There are also reports of toxicosis by photosensitizing furocoumarins contained in *Ammi majus* seeds in many animal species. In a herd of pigs suffered simultaneous intoxications by ergot alkaloids from *Claviceps purpurea* sclerotia and furocoumarins from *Ammi majus* seeds. Nervous signs were first observed 5-7 days after the initiation of feeding. These signs were followed by cutaneous irritation. Snout ulcers, eyelid edema, and conjunctivitis were recorded in several piglets. Ten days after the start of feeding, 8 abortions were observed. Many of the sows that were nursing piglets developed udder edema and teat cracking. Dermal lesions were observed in most of the animals with unpigmented areas in the skin. Examination of impurities in the suspected wheat indicated the presence of 2.2% of *A. majus* seeds and 0.14% of *C.purpurea* sclerotia. The quantitative analysis indicated the presence of 3.2 g xanthotoxin and 0.65 g bergaptene/100 g *Ammi majus* seeds and 0.73 g ergot alkaloids (expressed as ergonovine) per 100g, of *C. purpurea*.[18, 42-44]

Dosage

Fructus *Ammi majus* was used as 0.02–0.04 g daily orally in divided doses, xanthotoxin 0.25–0.7 mg/kg bw. [4,6,8, 28-29]

II-Ammi visnaga

Synonyms : *Daucus visnaga* L., *Selinum visnaga* E.H.L. Krause, *Sium visnaga* Stokes, *Visnaga daucoides* Gaertn [45-47]

Common names : English: Pick-tooth, Tooth pick, Bishop's weed , Arabic: Khella , Khella baladi

Traditional uses : The fruits of *Ammi visnaga* were uses in the treatment of mild anginal symptoms. As supportive treatment of mild obstruction of the respiratory tract in asthma, bronchial asthma or spastic bronchitis, and postoperative treatment of conditions associated with the presence of urinary calculi. Treatment of gastrointestinal cramps and painful menstruation . Internally as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of vertigo, diabetes and kidney stones.[10]

Physico-chemical constants[10, 46]: loss in weight on drying at 105^0C: 4.60% , total ash: 9.4% , acid insoluble ash: 0.6% , and water soluble ash: 2.9% . Extractive value in different solvents (%): petroleum ether: 3.40, chloroform ($60\text{-}80^0$C): 6.10 , absolute ethanol: 11.10 and ethanolic water extract: 19.50.

Chemical constituents

Ammi visnaga contained γ-pyrones (furanochromone up to 4%), the principal compounds being khellin (0.3–1.2%) , visnagin (0.05–0.30%), khellinol, ammiol, khellol and khellinin . *Ammi visnag*a also contained fixed oils (up to 18%) and coumarins (0.2–0.5%), the main one being the pyranocoumarin visnadin (0.3%).[46-50] The hydrodistillation of *Ammi visnaga* yielded 1.3 % of yellowish oil. Twenty one components were identified representing 97.3% of the essential oil. These compound included 2,2- dimethylbutanoic acid (30.1%), isobutyl isobutyrate (14.0 %), croweacin (12.2%), linalool (12.1%), bornyl acetate (7.3%), thymol (6.0%), α-thujene (1.5%), 3-methylpentenol(2.5%), β-myrcene (0.1%) , methylbutyl 2-methylbutaoate (1.2%), α-isophorone (3.8%), 2-nonyne (1.2%) , hexenyl isobutanoate (1.6%) , endo-fenchyl acetate (0.2%) , geranyl acetate (1.2%) , lavandulyl acetate (1.2%), citronellyl propionate (0.6%) neryl isobutanoate (0.1%), lavandulyl 2- methylbutanoate (0.1%), and α –damascone(0.1%) , Z,E)-farnesal (trace).[51]

Eleven flavonols have been isolated from the aerial parts of *Ammi visnaga* L. from which four aglycones, four monoglycosides, two diglycosides and one triglycoside. The flavonoid aglycones were distributed into one hydroxylated (quercetin) and three methoxylated (rhamnetin, isorhamnetin and rhamnazin). The monoglycosides included three 3-O-glucosides respectively linked to rhamnetin , isorhamnetin and rhamnazin and one 7-O-glucoside of isorhamnetin . The two diglycosides were 3-O-rutin of quercetin and isorhamnetin while the single trioside was quercetin 7,3,3'-O-triglucoside.[49 ,52-54]

Pharmacokinetic studies

The plasma concentration of visnagin after oral dose reached the maximum level of 3270.72 ng/mL at 0.33 h and decreased to below limit of quantitation (1.0 ng/mL) after 12 h. For intravenous administration, the maximum concentration of

visnagin was 1635.76 ng/mL at 0 h. Visnagin at a dose of 10 mg/kg (in 2% ethanol and 10% PEG 200) was completely absorbed (oral bioavailability, F=100.71%). The half-lives of 0.79 and 0.61 was recorded in oral and intravenous administration respectively . The volume of distribution (Vd) of visnagin was 0.86 L, which is suggestive of the distribution into extracellular fluids in the body.[55]

Pharmacological effects

Antimicrobial effects

The antimicrobial effects of the ethanolic and aqueous extract of *Ammi visnaga* were tested against eight pathogenic microorganisms *Staphylococcus aureus*, *Leuconostic mesontroide*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Candida tropicans* and *C. albicans***.** The most active extract against Gram-positive bacteria was ethanol extract with a minimal inhibitory concentration (MIC) value of (5mg/ml) against *Enterococcus faecalis*. In addition, the same extract exerted antimicrobial activity against the Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae* with an MIC value of 12.5mg/ml. In yeast a high concentration of extract was needed to cause inhibition.[56]

The essential oil of *Ammi visnaga* was tested against *Escherichia coli ATCC 25922*, *Escherichia coli, Staphylococcus aureus ATCC 43300, Staphylococcus aureus, Pseudomonas aeruginosa* ATCC 27853, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, and *Morganella morganii*. The essential oil exhibited the best antibacterial activity against *Escherichia coli ATCC 25922, Escherichia coli, Staphylococcus aureus ATCC 43300* and *Pseudomonas aeruginosa* ATCC 27853 , the diameter of the inhibitory zones were 29 , 25, 25 , 25 mm respectively[51]. Ethanol extract of *Ammi visnaga* fruits (at a dilution of 1:40) inhibited the growth of *Mycobacterium tuberculosis* H37RVTMC 102[57]. An aqueous extract of the fruits, 2–10 mg/ml inhibited growth and aflatoxin production of *Aspergillus flavus* , the effects were dose-dependent[58]. The aqueous and hydroalcoholic extract of seed and stem of *Ammi visnaga* showed a good antibacterial activity against *Streptococcus mutans*, *Streptococcus salivarius* and *Streptococcus sanguis* oral pathogens[59].

Cardiovascular effects

Ammi visnaga induced relaxation of smooth muscle, including that of the ureter and coronary arteries, in a variety of animal species[60]**.** Durate *et al* found that visnadine caused nonspecific inhibition of vascular smooth muscle. It was selectively inhibited the contractile response in the rat isolated aortic ring and portal vein segment. On the other hand, intravenous administration of visnagin decreased blood pressure with no significant changes on the heart rate[61-63]. A chloroform, and methanol extract (1mg/ml) of the fruits inhibited the potassium chloride induced contractions of the rabbit guinea-pig aorta in vitro[64-66]. Visnadin, 60.0 µg/ml or 120.0 µg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% respectively[66]**.** Samidin and khellol glucoside induced positive inotropic effects on heart[67].

In coronary vasospasm and myocardial ischaemia induced in dogs by daily intramuscular injections of vasopressin , visnadin, dihydrosamidin, khellin and samidin effectively normalized the electrocardiogram when given in a dose of 4.7 mg/kg bw per day intramuscularly for 7 days[67]. Immediately after the rapid intravenous administration of 20-30 mg of khellin to the dogs , the blood pressure drops to about 50 mm Hg., the heart beats considerably slower, and the respiration is momentarily arrested. The entire effect lasts for only a short time, within a minute or two[68]. According to the results obtained by different researchers, khella seems to improve blood supply to smooth muscles and makes myocardial metabolism more efficient. It dilated the coronary vessels, and increased the capacity of the heart without increasing the heart rate or affecting blood pressure[69].

A clinical trial of khellin in 38 cases of angina pectoris and in 8 cases of coronary thrombosis was performed . Continuous treatment, by the oral or intramuscular routes or by both , gave favourable results in 35 out of 38 cases of angina pectoris. Continuously administration of khellin for several weeks to eight patients after coronary thrombosis appeared favourable[67].

A clinical study was carried out on 20 non-obese, normolipaemic male subjects to determine the effects of orally administered 50 mg khellin four times daily for 4 weeks on the plasma lipids. Plasma total cholesterol and triglyceride remained

unchanged, but high-density-lipoprotein cholesterol concentration was significantly elevated during the treatment and till one week after cessation of treatment[70]. In a comparison with glyceryl trinitrate, khellin (3 ml. containing 150 mg. of khellin , alcoholic extract standardized to contain 50 mg/ml) was used in twelve patients for prevention of angina of effort and the electrocardiographic changes that may accompany it . Khellin was less potent but longer acting than glyceryl trinitrate , and it did not cause any unpleasant side effects[71].

Treatment of vitiligo

A double-blind, placebo-controlled study of 60 people indicated that the combination of oral khellin (which is the main constituent of *Ammi visnaga*) and natural sun exposure caused repigmentation in 76.6% of the treatment group, in comparison, no improvement was seen in the control group receiving sunlight plus placebo[72]. A subsequent placebo-controlled study of 36 patients of vitiligo , showed that a topical khellin gel plus UVA caused repigmentation in 86.1% of the treated cases, as opposed to 66.6% in the placebo group[73].

Smooth muscle relaxant effects

Durate et al found that visnadine caused nonspecific inhibition of vascular smooth muscle. It was selectively inhibited the contractile response in the rat isolated aortic ring and portal vein segment[61-63]. Aqueous extract of *Ammi visnaga* seeds induced relaxant effect on contractibility of small intestine of rabbit[74]. *Ammi visnaga* induced relaxation of smooth muscle, including that of the ureter and coronary arteries, in a variety of animal species[60]. Khella's antispasmodic properties are also useful to treat asthma attacks. During the 1950′s, research into khella's usefulness as an asthma treatment led to the creation of many asthma medications containing khellin and visnagin[69].

Prevention of urolithiasis

Ammi visnaga was investigated for the preventive effect of kidney stone formation. In cell culture experiments, it was found that *Ammi visnaga* and its compounds (khellin and visnagin) protected cell damage from calcium oxalyate crystals. In addition, *Ammi visnaga* and its compounds prevented calcium oxalyate crystals formation in stone forming rats by increasing the urinary pH and citrate concentration along with a decrease of urinary oxalate. The calcium oxalyate crystals deposition in the rat kidneys was significantly decreased in the group of rats receiving *Ammi visnaga* and its compounds[55].

Antioxidant effects

The antioxidant activity of the butanolic extract of *Ammi visnaga* was determined by 2,2-Diphenyl-1-picryl-hydrazyl (DPPH) method . The butanolic extract of *Ammi visnaga* was markedly quenched the DDPPH radical by 78.7 % at a concentration of 200 ug/ml[75].

Contraindications and adverse effects

To minimize photosensitivity, the exposure to sun or other sources of ultraviolet light should be avoided during treatment with *Ammi visnaga* and its components. Long term use or overdose of the drug can lead to queasiness , dizziness , loss of appetite , headache , sleep disorders and with very high dosage (corresponding to over 100 mg khellin) , it caused reversible elevation in the levels of liver enzymes[76-77]. Ethanolic extract of *Ammi visnaga* was free from mutagenic effect, it also inhibit the mutagenic effects of ethyl methanesulfonate , 2-amino-anthracene , and benzopyrene in *S. typhimurium*[78].

Dosage

Average daily dose: Fructus *Ammi Visnaga* 0.05–0.15 g.[1, 46]

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