Egyptian Herbal Monograph

Volume 2

Pharmacopoeial wild medicinal plants

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***Ammi visnaga* L.** خلة بلدي

1. Names & Synonyms (1 - 3)

***Ammi visnaga* L.**

Family: Umbelliferae (Apiaceae)

Syn. *Daucus visnaga* L.

Arabic: Khella baladi خلة بلدى , Khella خلة, Gazar sheitani جزر شيطاني, Kammon habashi كمون حبشي

English: Pick-tooth , Tooth pick and Bishop's weed (3)

2. Geographical distribution (1 - 3)

Confined to the Nile valley and Mediterranean region.

3. Parts used for medicinal purpose (1 - 3)

The fruits and leaves.

4. Major chemical constituents

- **Furanochromone derivatives (*Y*-Pyrones):** Khellin, visnagin, khellinol, ammiol, visammiol, khellol, khellinin, khellinone, visnaginone (4) and visamminol.
- **Coumarins**:
- Pyranocoumarins/visnagans mainly as samidin, dihydrosamidin and visnadin (4), and furanocoumarins mainly as xanthotoxin, ammoidin, bergapten, and psoralen (5-12).
- **Flavonoids:** Quercetin, kaempferol, rhamnocitrin, rhamnetin and rhamnazin. Flavonoidal glycosides include quercetin-3-O-glucoside, kaempferol-3-O-glucoside and isorhamnetin 3-O-glucoside as well as rhamnetin-3-O-glucoside, isorhamnetin-3-O-glucoside, rhamnazin-3-O-glucoside, isorhamnetin-7-O-glucoside, quercetin-7,3,3'-O-triglucoside, quercetin-3-O-rutinoside, kaempferol-3-rutinoside and isorhamnetin-3-O-rutinoside. *A. visnaga* is also considered a rich source of flavonoidal sulfates including quercetin 3-sulfate, rhamnocitrin 3-sulfate, rhamnetin, and isorhamnetin-3-sulfate (13).

- **Essential Oil:** Major oxygenated monoterpenes were linalool and thymol, while monoterpene hydrocarbons were α-thujene, α-pinène, β-pinene, and β-myrcene (13). Major nonterpene derivatives were isoamyl 2-methylbutyrate, isoamyl isobutyrate, isobutyl 2-methylbutyrate, 2-methylbutyl 2-methylbutyrate, 2-methylbutyl isobutyrate, and isoamyl isovalerate (14, 15).
- **Sterols and Fatty acids:** β-Sitosterol and β-sitosterol-glucoside (16), in addition to palmitic, palmitoleic, stearic, petroselinic, linoleic, linolinic, arachidic and tetracosanoic acids (13).

5. Medicinal uses

Well-established use (17)

A. Muscle relaxant.
B. Dilate coronary vessels and the ureter.

Traditional use (13, 18, 19)

C. For mild anginal symptoms.
D. For Urinary Tract Disorders:

- Diuretic
- Renal colic
- In postoperative treatment of conditions associated with the presence of urinary calculi.
- Lithotriptic agent (to break up renal stones).

E. Supportive treatment for mild obstruction of the respiratory tract in asthma or spastic bronchitis.
F. For skin disorders (psoriasis and vitiligo).
G. As emmenagogue to regulate menstruation.
H. Treatment of gastrointestinal cramps and painful menstruation.

***A. visnaga* is a traditional medicinal plant for use in the specified indications exclusively based upon long-standing use.**

6. Herbal preparations correlated to medicinal use

1. Powdered dried fruits
2. Decoction

7. Posology and method of administration correlated to medicinal use

Average daily dose from *A. visnaga* fruit: 0.05 to 0.15 g in divided doses(20).

Method of administration: Oral use.

8. Contraindications

- Hypersensitivity to active substances and to other plants of the same family.

9. Special warnings and precautions for use

- If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.

- During treatment with *A. visnaga* and its constituents, the exposure to sun or other sources of ultraviolet light should be avoided, in order to minimize photosensitivity (21).

- Khella has been associated with the development of severe ophthalmologic changes, particularly pigmentary retinopathy. Patients receiving khella or its extracts should be monitored for ophthalmologic changes (22, 25).

- Intake of *A. visnaga* is not recommended at all along with blood thinners such as coumadin, heart drugs called calcium channel blockers or other drugs that lower blood pressure (18).

- Monitoring of blood glucose level should be done regularly.

10. Interactions with other medicinal products and other forms of interaction

None reported

11. Fertility, pregnancy and lactation

- *A. visnaga* should be avoided during pregnancy (19).

- Safety during lactation has not been established. In the absence of sufficient data, the use during lactation is not recommended.

- No fertility data available.

12. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

13. Undesirable effects

- If adverse reactions occur, a doctor or a pharmacist should be consulted.
- Side effects like pseudoallergic reactions, reversible cholestatic jaundice and elevated activities of liver transaminases and γ-glutamyltransferase have been observed with the use of *A. visnaga* or its constituents (21).

14. Overdose

- 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 (21, 24).

15. Relevant biological Activities

Kidney diseases

- Evaluation whether oral administration of an aqueous extract prepared from the fruits of *A. visnaga* could prevent crystal deposition in stone-forming rats was done. Hyperoxaluria was induced in male Sprague-Dawley rats by giving 0.75% ethylene glycol (EG) and 1% ammonium chloride (NH_4Cl) via the drinking water. The Khella extract (KE; 125, 250 or 500 mg/kg) was orally administered for 14 days. The histopathological examination of the kidneys revealed that KE significantly reduced the incidence of calcium oxalate crystal deposition. In addition, KE significantly increased urinary excretion of citrate along with a decrease of oxalate excretion (25).

- The effect of *A. visnaga* and its two major constituents (khellin and visnagin) on renal epithelial injury was evaluated using LLC-PK1 and Madin-Darby-canine kidney cells. It was found that *A. visnaga* extract as well as khellin and visnagin could prevent renal epithelial cell damage caused by oxalate and calcium oxalate monohydrate and could therefore play a potential role in the prevention of stone formation associated with hyperoxaluria (26).

- The effect of *A. visnaga* fruits was investigated in animal model for urolithiasis. When oxalate nephrolithiasis was induced by 3% glycolic acid given for 4 weeks, it was found that daily oral treatment with *A. visnaga* (500 mg/kg) could inhibit the formation of kidney stones by lowering the deposition of calculi in kidney. The prophylactic effect of *A. visnaga* was attributed to its diuretic activity (27).

- The inhibitory effect of *A. visnaga* extract (aqueous extract of whole plant and its fruits) was studied on the oxalocalcic crystallization in human urine. Even this study revealed the efficacy of extracts of the *A. visnaga* fruits in inhibiting the crystallization of calcium oxalate. Further, it was found that the extracts reduced oxalate calcium crystallization and specially monohydrate oxalate calcium (28).

Antispasmodic and vasodilating effects

- The vasodilating properties of *A. visnaga* have been investigated by several researches:

- It has been established as a bronchodilator and coronary medication in the treatment of angina pectoris due to its peripheral and coronary vasodilator activity (29).

- In addition to being an antiasthmatic and a vasodilator, as well as an effective muscle relaxant agent without affecting blood pressure (30, 31).

- The vasodilating properties of *A. visnaga* are associated with its two major γ-pyrones, khellin and visnagin, along with the pyranocoumarin, visnadin. Both khellin and visnadin have been proven to possess calcium antagonistic activity, which, in turn, yields vasodilating activities. Visnadin has been shown to possess both peripheral and coronary vasodilator activities, and is thus used for the treatment of angina pectoris. It preferentially inhibits the contractile responses mediated by Ca2+ entry through L-type Ca2+ channels, and at high concentrations, it may also interfere with other sites involved in vascular smooth muscle contraction (32-37).

- The vasodilating effect of visnagin is a result of inhibiting the vascular smooth muscle contractility at multiple sites, and weakly inhibiting the hydrolytic activity of the cyclic nucleotide phosphodiesterase (PDE) isozymes (38- 40).

Smooth muscle relaxant effects (41)

- 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 (33, 38, 40).

- Aqueous extract of *A. visnaga* fruits induced relaxant effect on contractibility of small intestine of rabbit (42).

- *A. visnaga* induced relaxation of smooth muscle, including that of the ureter and coronary arteries, in a variety of animal species (43).

Antimicrobial effects (41)

- The antimicrobial effects of the ethanolic and aqueous extract of *A. visnaga* were tested against eight pathogenic microorganisms. 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 (44).

- The essential oil of *A. visnaga* was tested against *Escherichia coli* ATCC 25922 and different other types of bacteria. The essential oil exhibited the best antibacterial activity against *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 43300 *and*

Pseudomonas aeruginosa ATCC 27853, the diameter of the inhibitory zones were 29, 25, 25 and 25 mm; respectively (45).

- An aqueous extract of the fruits of *A. visnaga* (2–10 mg/ml) inhibited growth and aflatoxin production of *Aspergillus flavus*. The effects were dose-dependent (46).

- The aqueous and hydroalcoholic extract of the fruits and stem of *A. visnaga* showed a good antibacterial activity against *Streptococcus mutans, Streptococcus salivarius and Streptococcus sanguis* oral pathogens (47).

- The 95% ethanol extract of the fruits exhibited antibacterial activity, inhibiting the growth of *Mycobacterium tuberculosis* H37RVTMC 102 even in a very low concentration (dilution of 1:40). Similarly, 50% acetone, 50% aqueous or 95% ethanol extract of *A. visnaga* inhibited fungal growth (*Neurospora crassa*) *in vitro* (18).

Cardiovascular effects (41)

- A chloroform, and methanol extract (1mg/ml) of the fruits inhibited the potassium chloride induced contractions of the rabbit and guinea-pig aorta *in vitro* (32, 48, 49).

- Visnadin, 60.0 µg/ml or 120.0 µg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% respectively (49).

- Samidin and khellol glucoside induced positive inotropic effects on heart (50).

- 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/day intramuscularly for 7 days (50).

- 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 (51).

- 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 (43).

- 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 favorable results in 35 out of 38 cases of angina pectoris. Continuous administration of khellin for several weeks to eight patients after coronary thrombosis appeared favorable (50).

- 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 (52).

- 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 (53).

Melanoprotective activity (13)

- A study on 60 people revealed that the combination of *A. visnaga* and natural sun exposure caused re-pigmentation in 76.6% of the treatment receiving group (54).

- A subsequent placebo-controlled study on 36 patients of vitiligo revealed that a topical *A. visnaga* gel plus UVA caused re-pigmentation in 86.1% of the treated cases compared to 66.6% in the placebo group (55).

-In a study on 28 patients with vitiligo, a new photo-chemotherapeutic course of therapy using *A. visnaga*, a furanochromone (as photosensitizer) and ultraviolet A (UVA) irradiation was used. More than 70% re-pigmentation was achieved in 41% of the patients who received 100 to 200 treatments (56).

-A pilot study was conducted on 33 patients to evaluate the effectiveness of local khellin and UVA (KUVA) and systemic psoralens and UVA (PUVA) therapy for vitiligo and to compare them in terms of the degree of re-pigmentation, duration of treatment, number of procedures, total UVA dose and side effects. The results revealed that local KUVA effectively induced re-pigmentation of vitiligo-affected skin areas to an extent comparable to a degree comparable to that achieved when using systemic PUVA, provided that treatment duration is long enough (57).

- In a study on 19 patients with vitiligo disease, who did not respond to khellin in liposomes and ultraviolet light (KLUV) treatment for no less than a year were treated with Blister Roof Transplantation (BRT) followed by KLUV. Around 75% of the patients were satisfied with the cosmetic results and more than 75% re-pigmentation of the vitiligo areas was noted in 47% of the patients (58).

Hypoglycemic activity

-The effect of the aqueous extract of *A. visnaga* on blood glucose levels was investigated in fasting normal and streptozotocin (STZ) induced diabetic rats after single and repeated oral administration. The aqueous extract of *A. visnaga* at a dose of 20 mg/kg significantly reduced blood glucose in normal rats six hours after a single oral administration ($p < 0.005$) and nine days after repeated oral administration ($p<0.05$). This hypoglycaemic effect is more pronounced in STZ diabetic rats ($p<0.001$). These findings suggest that the aqueous extract of *A. visnaga* possess significant hypoglycemic effect in both normal and STZ diabetic rats (59).

-An aqueous extract of *A. visnaga* was shown to possess a significant hypoglycemic effect when given to both normal and streptozotocin diabetic rats. Additionally, a decoction prepared from the fruits of the *A. visnaga* had the ability to reduce blood glucose level by 51% in normoglycemic rats, compared to an oral hypoglycemic agent (Tolbutamide®) (13).

Antioxidant effects

- The antioxidant activity of the butanol extract of *A. visnaga* was determined by 2,2-Diphenyl-1picryl-hydrazyl (DPPH) method. The butanol extract of *A. visnaga* was markedly quenched the DDPPH radical by 78.7 % at a concentration of 200 g/ml (60).

Neuroprotective activity

- Visnagin which is an active principle of was investigated for neuroprotective effect against kainic acid (KA) -induced neuronal cell death. Visnagin administration (100 mg/kg, p.o. or i.p.) not only inhibited microglial and astroglial activation but also attenuated the inflammatory marker expressions concomitantly, suggesting that visnagin exerts its neuroprotective effects via an anti-inflammatory mechanism in KA model (61).

16. Additional information

Worldwide, many pharmaceutical products are containing *A. visnaga* extract as active principal (13).

17. Date of compilation/last revision

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