Egyptian Herbal Monograph

Volume 2

Pharmacopoeial wild medicinal plants

Egyptian Drug Authority (EDA)

2023

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***Ammi majus* L.** خلة شيطاني / خلة بري

1. Names & Synonyms (1 - 3)

***Ammi majus* L.**

Family: Umbelliferae (Apiaceae).

Syns. *Apium ammi* Crantz.

Arabic: Khella sheitaani خلة شيطاني/ Khella barri خلة برى

English: Bishop's weed, Amee.

2. Geographical distribution (1 - 3)

Nile region, Oases of the Western Desert, Mediterranean region as well as Sinai Peninsula.

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

The fruits and leaves.

4. Major chemical constituents

- **Furanocoumarins:** Xanthotoxin (known as methoxsalen, 8-methoxypsoralen and ammoidin), imperatorin (ammidin) isoimperatorin, bergapten (known as heraclin, majudin and 5-methoxypsoralen), marmesin, heraclenin, pimpinellin, isopimpinellin, majurin, saxalin, pabulenol, marmesinin and xanthotoxol (4, 5).
- **Other coumarins:** Umbelliprenin, 6- hydroxy-7-methoxy-4 methyl coumarin, 6-hydroxy-7-methoxy coumarin (6) and umbelliferone (7).
- **Flavonoids**:
  - **Fruits:** Quercetin, isoquercetin, quercetin-7-O-glucoside, kaempferol, kaempferol-7-O-glucoside and luteolin glycosides (8, 9).
  - **Leaves:** Quercetin and its glycosides, isorhamnetin-3-O-glucoside, isorhamnetin-3-O-rutinoside, and luteolin glycosides (10).

- **Aerial parts**: Acetylated flavonol triglycosides (kaempferol and isorhamnetin 3-O-[2"-(4"'-acetylrhamnosyl) -6"-glucosyl] glucosides) and glycosides (isorhamnetin-3-O-rutinoside, kaempferol-3-O-glucoside and isorhamnetin-3-O-glucoside (11).

- **Fatty acids:** Linoleic, oleic, palmitic and linolenic acids as main fatty acids, in addition to hexanoic, carylic capric, lauric, myristic, pentadecanoic, margaric, stearic, elaidic, arachidic, behenic, tricosnoic and tetracosanoic acids as minors (5, 12).

- **Essential oil**

  - **Fruits:** The major identified monoterpenes are carvone, 1,8-cineole, α- terpinyl acetate, *trans*-pinocarveol and citronellal, while the major sesquiterpenes are globulol and nerolidol. Non-terpenic volatiles included high boiling hydrocarbons and bergapten (13).

- **Diterpenes:**

  - **Aerial parts:** Ammi majanes, phytol, isophytol and isoelemicin (14).

- **Other constituents**: Vitamin E, resin, mucilage (7), tannin, oleoresin, acrid oil, fixed oil, proteins (4), oleanolic acid, mannitol (15) and furoquinoline alkaloids (14, 16).

5. Medicinal uses

Well-established use (17-21)

Vitiligo

Traditional use (6, 21)

A. For skin disorders (Psoriasis, Vitiligo and Leprosy)
B. As emmenagogue
C. For Urinary Tract Disorders:

- Diuretic.
- Lithotriptic agent (to break up renal stones).
- Urinary tract infections.

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

6. Herbal preparations correlated to medicinal use (17-21)

1. Powdered dried fruits
2. Decoction

7. Posology and method of administration correlated to medicinal use

Average daily dose: 0.02–0.04 g in divided doses (17-21).
Method of administration: Oral use.

8. Contraindications (4, 17, 19 - 21)

- Hypersensitivity to active substances and to other plants of the same family.
- Diseases associated with photosensitivity.
- Cataract.
- Invasive squamous-cell cancer and known sensitivity to xanthotoxin (psoralens).
- Tuberculosis.
- Liver and kidney diseases.
- Human immunodeficiency virus (HIV) infections and other autoimmune diseases.
- Children under the age of 12 years.

9. Special warnings and precautions for use (21)

- Care should be taken where there is a familial history of sunlight allergy or chronic infections.

- Avoid direct and indirect sunlight for up to 8 hours after oral and 12–48 hours after following oral therapy, sunglasses must be worn for 24 hours.

- Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard and carrots (19).

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

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

- The toxicity of *A. majus* fruits may be increased when the fruits are administered with other photosensitizing agents such as coal tar, dithranol, griseofulvin, nalidixic acid, phenothiazines, sulfanilamides, tetracyclines and thiazides (19-21).

- Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard and carrots (19, 21).

11. Fertility, pregnancy and lactation (4)

- The fruits are contraindicated in pregnancy and nursing mothers (21).
- 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.
- 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. 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 (4, 19, 21, 22).

14. Overdose

- Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache, allergic symptoms and sleeplessness (21, 23).
- Clinical treatment requires management by a physician (21).

15. Relevant biological activities

Toxicology

- Chronic toxicity in the form of a decrease in the red blood cell count and haemoglobin A concentration was observed in mice after administration of 100.0 mg/kg bw of a 95% ethanol extract of the fruits in drinking water (21).
- Toxicities by photosensitizing furanocoumarins contained in *A. majus* fruits are reports in many animal species (4, 21).

Treatment of vitiligo, psoriasis and hypopigmentation tinea versicolor

Numerous clinical trials have assessed the efficacy of *A. majus* fruits and xanthotoxin for the treatment of vitiligo, psoriasis and hypopigmentation and tinea versicolor (4):

-- Experimentation with *A. majus* extracts for the treatment of leucodermia was started in Egypt by El Mofti (24, 25).

-- *A. majus* Linn was used in six patients with vitiligo, five men and one woman. Their ages were from 30 to 50 years. *A. majus* 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 re-pigmentation appeared in all patients as pigmented minute macules with hair follicles in their center (22).

-- The powdered fruits of *A. majus* was administered orally to leukodermic patients, who then exposed the affected patches to direct sunlight for 1 hour. The patients

subsequently developed symptoms of itching, redness, oedema, vesiculation and oozing in the leukodermic patches. A few days later the affected skin gradually started to display deep brown pigmentation (26).

-- In two small groups of patients (eight patients each) with leukodermia treated with oral (0.05 g of *A. 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 (27).

-- *A. majus* and its furanocoumarins constituents (xanthotoxin) showed good results in many clinical studies for the treatment of psoriasis, vitiligo and tinea versicolor (28-32).

Antimicrobial activity

-- All crude extracts of *A. majus* fruits (methanol, hexane, chloroform, ethyl acetate and butanol extracts) displayed moderate antimicrobial activity against one Gram positive bacteria, *Staphylococcus aureus,* and three Gram negative bacteria, namely *Escherichia coli, Haemophilus influenzae* and *Proteus spp.* with growth inhibition zone of 0–15 mm (33).

-- *A. majus* coumarins were evaluated for their anti-viral activity by means of the end titration technique that depends on the ability of plant extract dilutions to inhibit the produced cytopathogenic effect and expressed as reduction factor of the viral titer. *A. 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. *A. majus* coumarins found to have no reliable antiviral activity against herpes simplex virus (HSV) (6).

-- Furanocoumarins from *A. majus* have bactericidal, fungicidal, insecticidal, larvicidal, moluscicidal, nematicidal, ovicidal, viricidal and herbicidal activities (34, 35).

Antihyperlipidemic, anti-inflammatory, analgesic and antipyretic activities

-- The evaluation of the antihyperlipidemic, anti-inflammatory, analgesic, and antipyretic activities of the alcoholic extract of the *A. majus* fruits on albino rats and mice was done. After 2 months of administration, both the doses (50 and 100 mg/kg body weight [bwt], respectively) resulted in a significant decrease in the concentrations of cholesterol, triglycerides, and low-density lipoprotein and increase in the concentration of high-density lipoprotein. The extract was found to inhibit the rat paw edema at both the doses, which means that it exerts a significant anti-inflammatory activity compared with control-untreated groups at the intervals of 30 and 60minutes post-treatment. The antipyretic effect of the extract was quite obvious;

it showed that 100 mg/kg bwt was more potent in lowering body temperature starting after 1 hour of treatment than the lower dose (50mg/kg bwt) (36).

--*A. 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 (6).

The efficacy and dose- response effect of *A. majus* alcoholic extract (2, 4, 8, 16, and 32 mg/rat) were assessed using formalin to induce paw edema in rats as a model of chronic inflammation. The tested extract and control were given orally before induction of inflammation. Paw edema was measured by using vernier caliper after 7 days for chronic inflammation. The result indicated that *A. majus* alcoholic extract significantly lower paw edema (p<0.05) compared to standard and control, while the dose 16mg/rat also lower the paw edema compared with other tested groups but less compared with the dose 32mg/rat. *A. majus* alcoholic extract possessed anti-inflammatory activity in animal's model of chronic inflammation and the effect increased with increasing the dose (37).

Antioxidant activity

-- Determined by 1,1-diphenyl-2-picrylhydrazyl (DPPH). The highest antioxidant activity was observed in case of chloroform crude extract which indicates the presence of polyphenolic compounds whereas the lowest activity corresponded to methanol crude extract (33).

16. Additional Information

The crystalline extracts of *A. majus* L. have been used and proved to be of remarkable specific effect in treating leueoderma. This has been shown in two previous papers on the subject (26, 27) and by other workers (22, 38). Experiments with this drug showed that a high percentage of cases of vitiligo promptly responded and completely recovered or greatly improved within relatively short periods—either during or immediately after treatment. *A. majus* L. has been 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).

The best results were obtained when all the crystalline constituents of *A. mujus* L., were given orally, and the areas painted and exposed to ultraviolet rays (22, 39).

17. Date of compilation/last revision

27/8/2023.

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