EGYPTIAN DRUG AUTHORITY

هيئة الدواء المصرية

Volume 2

# Herbal Monograph on Wild Medicinal Plants in Egypt

## (Pharmacopoeial Plants)



Version 1

# Monograph

on

# Wild Medicinal Plants

In Egypt

## *(Pharmacopoeial Plants)*

**Egyptian Drug Authority (EDA)**

**2021**

# Contents

# Acknowledgment

Under the patronage of **Prof. Dr. Tamer Mohamed Essam**- Chairman of Egyptian Drug Authority (EDA) and **Prof. Dr. Ayman Saad Nasr El-Din El-Khatib-** Vice president of EDA, **Prof. Dr. Hanan Amin Rizk** - Head of Central Administration of Pharmaceutical products- is honored to launch the monograph on wild medicinal plants - Pharmacopeial Plants- which is considered as continuation of the previous monograph on wild medicinal plants. EDA wishes to express sincere appreciation for the committee working group who contributed to the preparation of this monograph consisting of:

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Also; it is a great pleasure to thank all members of "General Committee of The Egyptian Pharmacopeia", the scientists and specialists in the different relevant fields who contributed in Egyptian pharmacopeia editions.

## Preface

Monographs on wild medicinal Plants in Egypt are comprehensive scientific references for drug regulatory authorities, manufacturers, research scientists and the general public. The monographs are designed to facilitate the appropriate use of medicinal plants and assist manufacturers in preparing the registration files for their products. The present monograph includes seven Pharmacopeial plants widely used in Egypt and for each sufficient scientific information are available. Therapeutic uses are categorized as well-established (those specified mainly in the Egyptian Pharmacopoeia; E.P. 1953-2005) and traditional (those described in Egyptian folk medicine). It is anticipated that this monograph will be revised again in the near future, in response to the update of Egyptian Pharmacopeia.

*Egyptian Drug Authority (EDA)*

*2021*

# Monograph on Wild Medicinal Plants in Egypt

## *Ammi majus* (L.) خلة شيطاني / خلة بري

### 1. Names & Synonyms (1 - 3)

*Ammi majus* (L.)
**Family:** Umbelliferae (Apiaceae)
**Arabic:** Khella sheitaani خلة شيطاني/ Khella barri خلة برى
**English:** Bishop's weed, Amee
**Syns.** *Apium ammi* Crantz.

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

**Diterpenes:**
**Aerial parts:** Ammi majanes, phytol, isophytol and isoelemicin were identified (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 (17-18)**

Vitiligo

**Traditional use (6, 17)**

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)

- Powdered dried fruits
- Decoction

## 7. Posology and method of administration correlated to medicinal use

**Oral**: Average daily dose: 0.02–0.04 g in divided doses (17).

## 8. Contraindications (4, 17)

- 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) (19).
- Tuberculosis.
- Liver and kidney diseases.
- Human immunodeficiency virus (HIV) infections and other autoimmune diseases (20).
- Children under the age of 12 years (21).

## 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

- Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard and carrots (19).
- 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, 20).

## 11. Fertility, pregnancy and lactation (4)

- The fruits are contraindicated in pregnancy and nursing mothers (21).
- No data were found about the plant effect on fertility.

## 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

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 (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

12/01/2021

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# Monograph on Medicinal Plants in Egypt

## *Ammi visnaga* (L.) خلة بلدي

### 1. Names & Synonyms (1 - 3)

*Ammi visnaga* (L.)

**Family:** Umbelliferae (Apiaceae)

**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)

**Syn.** *Daucus visnaga* L.

### 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 (Ɣ-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)**

d) For mild anginal symptoms.
e) 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).
f) Supportive treatment for mild obstruction of the respiratory tract in asthma or spastic bronchitis.
g) For skin disorders (psoriasis and vitiligo).
h) As emmenagogue to regulate menstruation.
i) 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

- Powdered dried fruits
- Decoction

## 7. Posology and method of administration correlated to medicinal use

***Oral:**

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

## 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 data were found about the plant effect on fertility.

## 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

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 µg/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

12/01/2021

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# Monograph on Medicinal Plants in Egypt

## *Citrullus colocynthis* (L.) حنظل - حنضل

### 1. Names & Synonyms (1-3)

***Citrullus colocynthis*** (L.)
**Family:** Cucurbitaceae
**Syns.** *Cucumis colocynthis*
*Colocynthis vulgaris*
**Arabic:** Hanzal حنظل - Handal **حنضل**
**English**: Colocynth, Bitter apple, Bitter gourd

### 2. Geographical distribution

Common in nearly all the phytogeographical regions of the country (3).

### 3. Parts used for medicinal purpose

Colocynth; Pulp of the peeled fruit (dried unripe, but fully grown fruits deprived of its seeds and hard outer part of pericarp) (4, 5); seeds, leaves, and roots are also used (2, 6).

### 4. Major chemical constituents (3)

- **Cucurbitacins and cucurbitacin glycosides** (7): Cucurbitacin A, B, C, D, E, I, J, K and L (8-13), 2-O-*β*-D-glucopyranosyl-cucurbitacin I, 2-O-*β*-D-glucopyranosyl-cucurbitacin L (14), colocynthein, colocynthetin (15), and Cucurbitane-type triterpenoid glycoside (saponin) (16) as colocynthosides A and B (11) are major constituents in the fruit.

- **Flavonoids**: Quercetin (leaf, stem, fruit, root), flavone-C-glucoside (Isovitexin), isoorientin and isoorientin 3′-O-methylether (fruit), C-*p*-hydroxybenzyl derivatives as 8-C-*p*-hydroxybenzylisovitexin, 6-C-*p*-hydroxybenzylvitexin, 8-C-*p*-hydroxybenzylisovitexin 4’-O-glucoside (aerial parts) (14, 17,18),

kaempferol (19), catechin, myricetin (19-21), isoscoparin and isosaponarin (14).

- **Phenolic acids**: Gallic acid (20), *p*-hydroxybenzoic acid, chlorogenic acid, caffeic acid, vanillic acid, *p*-coumaric acid, sinapic acid, and ferulic acid from fruit pulp (19), and 3-O-caffeoylquinic acid from the leaves (22).

- **Alkaloids**: Alkaloids from the whole fruit and pulp (13, 23- 26); choline from fruit pulp (24), 2-(nonan-8-one)-(1H)-4-quinolone and 2-(nonan-8-one) 4-methoxy-quinoline from the aerial parts (27).

- **Fatty acids**: Linoleic (dominant), oleic, palmitic, stearic, myristic, linolenic acids (17, 28-31) and arachidic acid from seeds (20).

- **Amino acids:** The dominant amino acids are arginine (in pulp), aspartic acid (in rind) and glutamic acid (in seeds) (32).

**Others**: (17)

- Protein: rich in lysine, leucine, sulfo-amino acids as methionine
- Vitamins: Vitamin B ( Thiamine, Riboflavin and Niacin)
- Minerals: Ca, Mg, Mn, K, P, Fe and Zn
- Tocopherols and Carotenes: $\alpha$-Tocopherol (20), $\gamma$-tocopherol and $\beta$-carotene from fruit seed oil (33).
- Volatile compounds (fruit pulp): 2-Methyl, 4-heptanone, 3-methyl, 2-heptanone, trimethylsilyl methanol and 1-propoxy pentane (34).

## 5. Medicinal uses

**a) Well-established**

**Oral**: Purgative (4-5).

**b) Traditional use**

**Externally**: Rheumatic disease (low back, knee and joints pain) (35-37).

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

## 6. Herbal preparations correlated to medicinal use

**a)** Oral dried fruits powder (4-5).

**b)** Topical Poultice (with warm cooking oils) (35-37).

## 7. Posology and method of administration correlated to medicinal use

a) **Oral:** 0.1 – 0.3g of dried fruits powder as purgative (4-5).
b) **Externally:** Poultice is made of colocynth with warm cooking oils to place it topically on the joint for rheumatic pain (35-37).

## 8. Contraindications

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

## 9. Special warnings and precautions for use

- Colocynth should be used under medical supervision and in proper dose as it is severely poisonous. It has a strongly irritating and painful effect on mucous membranes due to its content of cucurbitacin glycosides, out of which cucurbitacins are released in watery environments (38).
- **Diabetes**: Colocynth might lower blood sugar levels. Blood glucose levels should be regularly monitored in diabetics (39).
- **Surgery**: Colocynth might interfere with blood sugar control during and after surgery. Colocynth should be stopped at least 2 weeks before a scheduled surgery (39).
- Encouraging use of seeds (containing no saponin) instead of the whole fruit or pulp (40).

## 10. Interactions with other medicinal products and other forms of interaction (39)

**Digoxin**
Colocynth is a stimulant laxative which can decrease potassium levels in the body therefore can increase the risk of side effects of digoxin.

**Warfarin**
Colocynth can work as a laxative. In some people colocynth can cause diarrhea which can increase the effects of warfarin and increase the risk of bleeding.

**Diuretic drugs**
Colocynth is a laxative and can decrease potassium in the body. Diuretic drugs can also decrease potassium in the body. Taking colocynth along with diuretic drugs might decrease potassium in the body too much. Some diuretic drugs that can decrease potassium include chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, and others.

## 11. Fertility, pregnancy and lactation

Colocynth is not recommended in pregnancy and breast-feeding (39) <<see section 15. Relevant Biological properties >>.

Long term exposure to *C. colocynthis* L. may cause adverse effects on the reproductive system and fertility (41) <<see section 15. Relevant Biological properties >>.

## 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

Gastrointestinal disorders such as diarrhea, painful cramp (42), colitis (43, 44); intestinal damage (45); the dried fruit pulp is irritating to the eye and powdered colocynth pulp causes severe pain if it meets the nasal mucous membrane (46-47); leucocytosis (48-49).

## 14. Overdose

Vomiting, bloody diarrhea, colic, and kidney irritation follow the intake of toxic dosages (0.6 to 1 g), and then increased diuresis that progresses to anuria. Lethal dosages (starting at 2 g) lead to convulsions, paralysis and, if untreated, lead to death through circulatory collapse. The treatment for poisonings should proceed symptomatically following gastric lavage (38).
In case of poisoning, a dilute tannic acid solution should be taken, followed by large quantities of drinks that contain eggs (albuminous drinks) (39).

## 15. Relevant biological activities

**Analgesic, anti-inflammatory and antinociceptive**

-- Carrageenan-induced edema in a rat hind paw was carried out to evaluate the topical anti-inflammatory effect of the *C. colocynthis* (*CC*) fruit extract cream (2–8%) and the tissue levels of IL-6 and TNF-α were estimated by using a commercial ELISA kit. The topical antinociceptive activity of CC cream (2–8%) was evaluated in the rat formalin test. The study indicated that the topical application of *CC* cream possesses significant anti-inflammatory and antinociceptive activities in animal models, which were probably mediated by opioid receptors and the suppression of pro-inflammatory cytokines (TNF-α and IL-6) (50).

-- *C. colocynthis* aqueous extracts of plant different parts were screened for analgesic and anti-inflammatory activities using the acetic acid writhing test in mice and the

carrageenan-induced paw edema assay in rats, respectively. All extracts displayed analgesic and anti-inflammatory activities at different doses without inducing acute toxicity. Topic results were obtained with immature fruits followed by seeds. The stem and root extracts were shown to possess the less significant inhibitory activity against analgesic and anti-inflammatory models (51). Also, the same assessment was carried out on the immature fruit and seed organic extracts (petroleum ether, chloroform, ethyl acetate, acetone and finely methanol extract). All extracts displayed an important analgesic and anti-inflammatory activities at different doses without inducing any side effects. Experiment results provide scientific insight into the ancient practice of utilizing *CC* as analgesic and as anti-inflammatory agents (52).

-- The extract of the dried pulp of the plant fruits was studied for its effects through inhibition of inflammatory cytokines secreted in obesity conditions on male mice. The fed animals received 50 mg/kg of hydroalcoholic extract by gavage for 42 days. TNF-α, IL-6 and IL-10 in serum were assayed by ELISA technique after every two weeks. The extract dramatically decreased expression of TNF-α 44.83 (***$p < 0.001$), IL-6 30.23 (***$p < 0.001$) and marginally increased IL-10 5.31 (ns-$p > 0.05$) in obese mice. This study demonstrated that, although the extract did not show anti-obesity effects, it could have an anti-inflammatory effect through down regulation of obesity-associated pro-inflammatory cytokines (53).

-- The effect of ethanol extract of plant roots at dose of 20 ng/ml on inflammatory cytokine expression in inflamed cells and monocytes with LPS20 both cartilage cells/macrophage was examined. The results indicated that the ethanol extract of root can reduce expression levels of pro-inflammatory cytokines in inflamed cells caused by situation same osteoarthritis (54).

-- Sodium carboxymethyl cellulose (5%) topical gel formulations containing 3% of colocynth extract, hydrolyzed extract, or acetylated extract were studied for their release through cellophane membrane and their permeability through hairless mouse skin and also, for the *in vivo* anti-inflammatory activity of the different types of colocynth extract using the carrageenan induced paw edema model in albino rats in comparison with the commercial Voltarin Emulgel®. The acetylated extract gel showed comparatively rapid permeability through hairless mouse skin, with low release rate through cellophane membrane. The pharmacological screening revealed that the percent reduction of edema produced by colocynth extract was 45.39%, the hydrolyzed extract produced 54.11% inhibition and the acetylated extract produced 64.95%, while Voltarin Emulgel® produced 63.35%. This means that acetylated colocynth extract can be used as an effective local anti-inflammatory agent (55).

-- Fruit extracts in methanol were subjected to check anti-inflammatory activity against carrageenan induced paw edema, serotonin induced edema and prostaglandin E1-induced paw edema in albino rats. Extracts showed anti-inflammatory activity against all types of edema but the most significant results were seen against prostaglandin E1-induced paw edema (56).

**Toxicity**

-- The study was undertaken to determine the acute median lethal dose of the methanol extract of the fruit of *C. colocynthis* and to evaluate the toxic effects of this extract at a single daily oral dose (131mg/kg) in 50 Albino rats. Liver, kidney and bone marrow function test were assessed using standard techniques. The acute median lethal dose of the extract was found to be 1311.45 mg/kg. The plasma ALT, AST, urea, and creatinine levels were significantly affected, an indication that the extract is hepato-nephrotoxic. The results obtained for hematological parameters reflect that methanol extract with a dose of 131 mg/kg did not affect quantitatively but disrupted qualitatively some functions of the bone marrow. The study also showed that the intake of extract of ripe *C. colocynthis* fruit presented some adverse effects on the functions of the liver, kidney, and bone marrow in rats (57).

-- The toxic effects of *C. colocynthis* on male rabbits were investigated. Test animals were treated with 100 or 200 mg/kg/day of either pulp or seed extract. One month later, surviving animals were sacrificed and specimens of small intestine, kidney, and liver were prepared for morphological evaluation. No animals treated with 200 mg/kg/day of pulp extract survived. Animals treated with 100 mg/kg/day of pulp extract displayed sever lesions in the small intestine, kidney, and liver. Interestingly, animals treated with either 100 or 200 mg/kg/day of seed extract displayed only minor intestinal insult. In contrast to seed extract, pulp extract of *C. colocynthis* can be fatal to rabbits. Therefore, seed extract may be the preferred route for therapeutic application (45).

-- The toxic effect of alcoholic extract of *C. colocynthis* on rat Liver was investigated with a single daily dose of (50, 100, 200, 400 g/kg) administered intraperitoneally. The results indicated that there is a morphological change in liver cells including karyrrhexis, chromatolysis, and granulation of the cytoplasm. Additionally, collagen and reticular fibers were evident in liver parenchyma in high doses. *C. colocynthis* can have toxic effects on liver cells which may induce hepatocyte necrosis and liver fibrosis. These effects were dose dependent (58).

-- The acute toxicity studies of the methanolic extract of dried fruit pulp of *C. colocynthis* (Cucurbitaceae) in albino mice NMRI indicated the highly toxic nature of the colocynth. A very significant decrease in body weight of test animals was noted at $p < 0.05$. The $LD_{50}$ was calculated as 1000mg/kg body weight. Within four days of experimentation, mortality was 100%. Histopathological studies confirmed the toxic nature of extract. Gross changes in histology of heart, liver and kidneys were noted. Section of spleen did not exhibit any abnormality (59).

-- Ethanolic extract of plant fruits was investigated for its sub-chronic toxicity on Sprague Dawley (SD) rats, to develop safe doses, 30 male rats were used with 0, 12.5 and 25 mg/kg of the extract twice per week for 8 weeks. The raw extract of the fruits at dose of 12.5 mg and 25 mg/kg induced significant increase in level of creatinine and total protein and increased non-significantly levels of glucose and blood urea while

reduced level of triglycerides, total cholesterol, and high-density lipoprotein-cholesterol significantly when compared with control group. Histopathological examination revealed that kidney of rat treated with *C. colocynthis* at dose of 12.5 mg/ kg show interstitial chronic inflammatory cell infiltrate while kidney of SD-rat treated with *C. colocynthis* at dose of 25 mg/kg showed interstitial fibrosis stained with Mallory trichrome stain. While liver showed lytic necrosis replaced by leukocyte infiltration at dose of 12.5 mg/kg of raw extract and rat treated with 25 mg/ kg show interstitial fibrosis stained with Mallory trichrome stain. Raw extract of the fruits had adverse effect on liver and kidney while in improving lipid profile and hematology in a novel manner in SD rats at selected dosed (60).

**Case Presentations**

-- Four patients with colocynth intoxication are presented. The main clinical feature was acute rectorrhagia preceeded by mucosal diarrhea with tenesmus, which gradually progressed to bloody diarrhea and overt rectorrhagia within 3 to 4 hours. The only colonoscopic observation was mucosal erosion which was completely resolved in follow-up colonoscopy after 14 days.
The membranolytic activity of some *C. colocynthis* ingredients is responsible for the intestinal damage. Patients and herbalists should be acquainted with the proper use and side effects of the herb. Clinicians should also be aware of *C. colocynthis* as a probable cause of lower GI bleeding in patients with no other suggestive history, especially diabetics (40).

-- Three examples were reported of toxic acute colitis which occurred after ingestion of *C. colocynthis* for ritual purposes. The prominent clinical feature was dysenteric diarrhea; colonoscopic changes included congestion and hyperaemia of the mucosa with abundant exudates but no ulceration or pseudopolyp formation. A causal relationship between colonic injury and the intake of colocynth was supported by the following features: (1) the pharmacology of the colocynth extract ingested; (2) the temporal relationship between colocynth intake and clinical onset (eight to 12 h); (3) the rapid recovery within three to six days, with normal endoscopy at day 14; (4) the absence of other possible causes for the observed patterns, except in one case, in which a concomitant intestinal infection with *Clostridium perfringens* Type A was discovered; (5) the specific pathological features. Colonic biopsies taken 27, 44, and 72 h after colocynth intake showed: erosions with fibrino-purulent exudate, early fibrosis of the lamina propria, hyaline thickening of the superficial epithelial basal membrane. These pathological features completely disappeared within 14 days in all three cases (61).

**Pregnancy and Lactation**

In Ayurvedic medicine, the fruit pulp has a reputation of causing miscarriage, when administered to pregnant women (62) and colocynth has also been used for this purpose in Europe (49, 63). Such activity could arise indirectly from congestion in the pelvic region as a manifestation of the cathartic action (62). It should be added,

however, that on several occasions colocynth was ineffective as an abortive agent, even though it produced serious poisoning (63).

**Fertility**

-- An ethanolic extract of *C. colocynthis* seeds, administered at an oral dose of 200 mg/kg for 2 days, did not inhibit copper acetate induced ovulation in rabbits to such an extent that further research seemed warranted (64). Different extracts of *C. colocynthis* were screened for anti-implantation activity by feeding female rats with each extract from day 1 to day 7 of their pregnancy. Acetone and methanolic root extracts in doses of 150 mg/kg prevented implantation in 3 and 4 of 7 test animals, respectively, whereas 200 mg/kg of an ethanolic leaf extract and 150 mg/kg of a benzene leaf extract inhibited implantation in 4 of 6 rats (65). The spermatotoxicity was observed in mice treated with an alcoholic extract of *C. colocynthis* fruit in daily oral doses of 0.1 g/kg body weight for 3 months (48). Early textbooks claim that *C. colocynthis* is excreted into breast milk and should therefore not be given to nursing women (66-68).

The short and long effects of *C. colocynthis* L. (400 mg/kg/body weight) on the reproductive system after administration to female Sprague-Dawley rats were investigated. The rats were intraperitoneally injected in dose of 400 mg/kg/body weight. First group received treatment for 4 weeks and a second group received the same dose of treatment for a period of 12 weeks. Female rats were allowed mating with males after 10 days prior to the last administration dose. Several parameters were determined including: number of pregnant rats, body and reproductive organ weight, number of implantation sites, viable fetuses and resorption sites. The results indicate that long-term exposure of female rats to *C. colocynthis* L. causes adverse effects on the reproductive system and fertility (41).

## 16. Additional Information

Colocynth has a drastic purgative and irritant action and has been superseded by less toxic laxatives. It is used in homoeopathic medicine (69).

*C. colocynthis* has showed wide range of pharmacological activities including:

- Antidiabetic, hypoglycemic and antihyperglycaemic activities (30, 70-85).
- Peripheral neuropathy (86).
- Antioxidant activity (19, 87-90).
- Hair growth effect (91, 92).
- Anti-microbial activity (13, 25, 93-98).
- Anthelmintic activity (99-103).

- Cytotoxic activity (87, 104-106).
- Hypolipidemic effect /antihyperlipidemic (89, 107,108).
- Hepatoprotective effect (109-111).

## 17. Date of compilation/last revision

17/02/2021

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# Monograph on Medicinal Plants in Egypt

## *Datura stramonium* (L.) داتورا

## 1. Names & Synonyms (1 - 4)

*Datura stramonium* L.
Synonym: *Datura tatula* L.
Family: Solanaceae
Arabic: Datura داتورا , Tatura طاطورا
English: Thorn-apple, Devil's apple, Jimson Weed, Stramonium

## 2. Geographical distribution

Confined to Nile region (3).

## 3. Parts used for medicinal purpose

All parts possess medicinal value, though seeds and dried leaves with or without flowering tops are most widely used (2, 5-7).

## 4. Major chemical constituents

**Tropane alkaloids**:
The plant contains 0.2- 0.6% tropane alkaloids; the seeds contain more alkaloid than the leaves (8). The Major alkaloids are hyoscyamine and hyoscine (scopolamine) (9).
Other alkaloids are present in trace amount e.g. 3-(hydroxyacetoxy) tropane, 3-hydroxy-6-(2-methylbutyryloxy)tropane, 3α-tigloyloxy-6-hydroxytropane, 3,7-dihydroxy-6-tigloyloxytropane, 3-tigloyloxy-6- propionyloxytropane, 3-phenylacetoxy-6,7-epoxytropane, 3-phenylacetoxy-6-hydroxytropane, aponorscopolamine, 3α,6α-ditigloyloxytropane, 7-hydroxyhyoscyamine (10-14), 3-phenylacetoxy-6, 7-epoxynortropane, and 7-hydroxyapoatropine (15).

**Steroids**:
Datura lactones (withanolides): withastramonolide (16), withatatulin and several other with anolides (17).
Ergostane-type sterols (18), stigmasterol and campesterol (19).

**Essential oil:**

**Leaf oil**: The main constituent is phytol. Other main classes of compounds are diterpenes and oxygenated monoterpenes (9).

**Other Constituents:**

Phenolic acids: caffeic, *p*-coumaric, and ferulic acids; Flavonoids: chrysin, quercetin and their esters; Coumarins: umbelliferone, fraxetin, scopoletin, scopolin, umckalin; Major free amino acids: asparagines and glutamine; Fatty acids: daturic acid; Terpenes: hyoscyamilactol, daturaolone, daturadiol. *N-trans*-feruloyl tryptamine, tyramine, *N-trans*-ferulicacyl-tyramine; Coumarinolignoid: cleomiscosin A; Carbolines: 1-acetyl-7-hydrox-*β*-carboline, and 7-hydroxy-*β*-carbolinel-propionic acid (19, 20); saponin and tannins (21).

## 5. Medicinal uses

**Well-established (5)**

- Spasmolytic
- anti-asthmatic

**Traditional use**

- Rheumatic disease (7)

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

## 6. Herbal preparations

A) Powdered leaves (7) and seeds (4).

B) Fluid extract from leaves or seeds, tincture from leaves, powdered extract using the same amount of the stabilized standardized powdered drug (7).

C) Poultice (7).

## 7. Posology and method of administration correlated to medicinal use

**Oral**

Leaves:

A single dose of 50-100mg of stabilized powdered leaves (up to 3 times a day); maximum daily dose: 600mg in divided doses (4).

*Stabilized powdered leaves standardized to contain 0.23 to 0.27% of tropane alkaloids, calculated as hyoscyamine (22).

Seeds:
A single dose of 50mg of stabilized powdered seeds; maximum daily dose: 600mg in divided doses (4).
*Stabilized powdered seeds standardized to contain 0.4 to 0.6% of tropane alkaloids, calculated as hyoscyamine (4).

**Topical**
Leaves have been used as poultice (with some oil) for rheumatic pain (7).

Note: *D. stramonium* is to be dispensed by prescription only (a prescription drug). It is considered to be potentially harmful if not used under medical supervision.

## 8. Contraindications

- Hypersensitivity to active substances and to other plants of the same family.
- Congestive heart failure; acute pulmonary edema; Constipation; Down syndrome; Seizures; Esophageal reflux; Fever; Stomach ulcer; Stomach and intestinal infections; Hiatal hernia; Glaucoma; Rapid heartbeat (tachycardia); Toxic megacolon; Ulcerative colitis; Obstructive digestive tract disorders (as atony, paralytic ileus, and stenosis); Urinary retention; Enlarged prostate (prostatic hypertrophy) (4); thyrotoxicosis; Asthma; Acute haemorrhage; hepatic disease; myocardial ischemia; CNS disorders (as myasthenia gravis); hyperthyroidism; hypertension; renal disease (23).

## 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.
- Children, patients with urine retention or coronary sclerosis should not use *D. stramonium* (4).
- Rubbing skin and eyes after contact with this plant is dangerous (2).

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

*D. stramonium* will have an additive effect when taken with other anticholinergic medications; co-administration of *D. stramonium* with other anticholinergic drugs may increase the frequency and/or severity of anticholinergic side effects (such as dry mouth, constipation, drowsiness, and others).

**With drugs:**

- *D. stramonium* will have an additive effect when taken with other anticholinergic drugs (drying medications) as atropine, scopolamine, some antihistamines and antidepressants; Together with these medications might cause side effects as dry skin, dizziness, low blood pressure, fast heartbeat, and other serious side effects. (4, 24).
- Antacids: decrease action of Jimsonweed (23).
- Phenothiazines: *D. stramonium* decrease the action of Phenothiazines (23).

**With herbs:**

Aloe, Buckthorn, Cascara, Chinese Rhubarb, Senna: *Stramonium* increase action in case of chronic use or abuse (23).

## 11. Fertility, pregnancy and lactation

- The use should be avoided during pregnancy and lactation as atropine component crosses the placenta and excreted in breast milk (23).

- *D. stramonium* may cause impotence (23).

## 12. Effects on ability to drive and use machines

Not reported.

## 13. Undesirable effects (23)

- **Central nervous:** Headache, dizziness, confusion, anxiety, flushing, drowsiness, insomnia, weakness, involuntary movements, decreased sweating, increased/decreased body temperature, coma, seizures, death (plant ingestion).
- **Cardiovascular:** Hypotension, paradoxical bradycardia, angina, premature ventricular contractions, hypertension, tachycardia, ectopic ventricular beats.

- Blurred vision, photophobia, eye pain, pupil dilatation, nasal congestion.
- **Gastrointestinal:** Nausea, vomiting, anorexia, dry mouth, abdominal pain, constipation, abdominal distention, altered taste.
- **Genitourinary:** retention, hesitancy, impotence, dysuria.
- **Integumentary:** hypersensitivity reactions, rash, urticaria, contact dermatitis, dry skin, flushing.

## 14. Overdose (4, 25)

- The intake of very high dosages leads to central excitation (restlessness, compulsive speech, hallucination, delirium, manic episodes), followed by exhaustion and sleep. The four early warning symptoms of poisoning are skin reddening, dryness of the mouth, tachycardia and mydriasis. Accommodation disorders, heat build-up through decline in sweat secretion, miction disorders and severe constipation can occur as side effects, particularly with overdosages.

- *D. stramonium* acts as a narcotic in an oral dose of 1gm powdered leaves.

- Lethal dosages (for adults starting at 100 mg atropine, depending upon atropine content, 15 to 100 g of the leaf drug, 15 to 25 g of the seed drug, considerably less for children) carry with them the danger of asphyxiation.

- Treatment for poisoning include stomach emptying, temperature-lowering measures with wet cloths (no antipyretics), oxygen respiration for respiratory distress, intubation, parenteral physostigmine salts as antidote, diazepam for spasms and chlorpromazine for severe excitation.

## 15. Relevant biological activities

**Antimicrobial effect**

-- The antimicrobial activity of *D. stramonium* (leaf ethanolic extract) studied were assessed against pathogenic bacteria. The plant showed significant antibacterial activity against the tested pathogens (26-29).

-- Aerial parts (mainly stem and bark) of *D. stramonium's* aqueous and ethanolic extract were investigated for their antimicrobial effect on *Eschericia coli, Salmonella typhi, Staphylococcus aureus, Klebsiella pneumonia, Shigella and Neisseria gonorrhea*. The stem bark extract exhibited different inhibitory activities on the tested microorganisms. Ethanol extract exhibited the highest inhibitory activity against *K. pneumonia* followed by *S. aureus. S. typhi* showed the least activity. The aqueous

extract showed activity only on *S. aureus*, while *N. gonorrhea* was resistant to both extracts (30).

-- *D. stramonium* phytochemicals were investigated for their in-vitro activity against bacterial pathogens by disk diffusion method. *D. stramonium* leaf extracts exhibited a considerable antibacterial activity even at low concentrations. Of various fractions obtained from leaf, methanol extracts showed maximum inhibitory effect (31).

-- The antibacterial activity was detected by agar well diffusion method *against Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.* The zones of inhibitions obtained were recorded and analyzed against standard control of Ampicillin. The methanolic extract showed higher antibacterial activity against *E. coli* and least antibacterial activity of against *P. aeruginosa* (21).

-- The plant extracts were tested on Gram negative bacteria *Escherichia coli* and on Gram positive bacteria *Staphylococcus aureus*. Both tested strains showed resistance but for *E. coli* a higher inhibition was observed at all samples containing *D. stramonium* extract (32).

-- The antibacterial activity of aqueous extracts of different parts of *D. stramonium* (root, stem, leaf, seed and fruit coat) studied against five human pathogenic bacteria viz*. B. megaterium, B. cereus, E. coli, S. typhi and S. aureus*. The results indicated that aqueous extract of leaf were most effective against all the tested pathogens (33).

-- The antimicrobial activities of *in-vitro* grown callus and *D. stramonium* methanolic extracts of root, stem, leaves, fruits, were studied against *E. coli, S. aureus and P. aeruginosa.* The methanolic leaf extract exhibited better antimicrobial activity against *S. aureus, E. coli, P. aeruginosa*. In the metabolite rich fraction (flavonoids, phytosterols and alkaloids), greatest bactericidal activity was exhibited by flavonoids against *P. aeruginosa* (34).

-- The antibacterial activity of *D. stramonium* branches and leaves samples in three different solvents benzene, chloroform and ethanol was studied against *Enterobacter, Micrococcus luteus, Pseudomonas aeruginosa, E. coli, S. aureus and K. pneumonia*. All the solvent extracts showed significant antibacterial activity against tested pathogens. Comparative minimum inhibitory concentration of benzene, chloroform and ethanol extract determined that benzene extract was very effective against all bacterial strains (35).

-- The methanolic extract of *D. stramonium* was screened for antimicrobial assay against different bacterial. Standard antibiotic (Azithromycin) and methanol were used as a positive and negative respectively. Leaf extract showed strong antimicrobial

activity against bacterial species like *Bacillus thuringiensis, Pseudomonas aeruginosa, Agrobacterium tumefaciens and Klebsiella pneumoniae* (36).

--The fungicidal effects of the acetone extracts indicate the potential of *D. stramonium* seeds as natural source of antifungal agent. The MIC of *D. stramonium* extracts ranges from 1.25- 2.50mg/ml (37).

**Antiasthmatic activity**

-- In 12 asthmatic patients with mild airway obstruction we have measured the effect on specific airway resistance (sRaw) of inhaling the smoke of one *D. stramonium* cigarette. In 11 patients sRaw decreased substantially after the cigarette, the mean maximal decrease being 40% at the 30$^{th}$ minute. Minor side effects were observed in six patients after the cigarette (38).

-- The regular use of antiasthmatic cigarettes ever, cannot be recommended for the following reasons: (1) the duration of action seems rather short. This could therefore lead to repeated inhalations and tachyphylaxis might occur. The risk of addiction from overuse has also been suggested (2) the total composition of the smoke is not known. It may contain unwanted alkaloids, particles that may cause chronic mucosal inflammation, or even carcinogenic agents (38).

-- The exposure of *D. stramonium* to the fetus when a mother uses it for asthma will cause a continuous release of acetylcholine, resulting in the desensitizing of nicotinic receptors, which could ultimately result in permanent damage to the fetus (39).

**Anticholinergic activity**

The alkaloids found in *D. stramonium*, are organic esters used clinically as anticholinergic agents. The anticholinergic syndrome results from the inhibition of central and peripheral muscarinic neurotransmission (40 - 43).

**The antioxidant effect**

-- The antioxidant activity of methanolic extract of *D. stramonium* seeds was studied. The methanolic extract reduced the concentration of DPPH free radical with an efficacy near to that of standard antioxidant gallic acid, but less than butylated hydroxytoluene (BHT) (21).

-- The methanolic extract of *D. stramonium* seeds is a potential source of natural antioxidants and significantly inhibit free radicals dose-dependently. The difference in the antioxidant activity may be ascribed to their different group of phenolic and flavonoid compounds. The extract showed higher phenolic content contributes to the

higher antioxidant activity. Based on the results obtained, it can be concluded that the plant contains essential phytochemical constituents and possess antioxidant property (44).

**Anticancer activities**

-- The evaluation of the cytotoxic effect of aqueous extract of *D. stramonium* leaves extract on different human cancer cell lines *in-vitro*. Breast (MDA-MB231), head, neck (FaDu), and lung (A549) cancer cell lines were treated with 1 mg/ mL of *D. stramonium* aqueous extract for 24 and 48 hours. The results may suggest therapeutic potential of *D. stramonium* aqueous leaf extract for the treatment of different types of cancer (45).

-- *In-vitro* cytotoxic activity for breast cancer cell line (MCF7) was studied by MTT reagent assay method using the methanolic extract of *D. stramonium* seeds. The study do confirm that extracts exhibit cytotoxic effect on MCF-7 (44).

-- Experiment on the cytotoxicity of methanol extracts of *D. stramonium* seeds on human breast adenocarcinoma cells (MCF-7) showed increasing cytotoxicity with increasing concentrations of extract and the viable cells detected by MTT assay (46).

**Analgesic activity**

The analgesic effect of alcoholic extract of *D. stramonium* seeds extract was evaluated in acute and chronic pain using hot plate and formalin tests. The extracts when administrated intraperitoneally administrated to the animals, the extract alleviated the pain dose dependently ($ED_{50}$ values of 25 and 50mg/ kg in hot plate and formalin tests, respectively) (47).

**Organophosphate poisoning**

-- *D. stramonium* contains atropine and other anticholinergic compounds, it is a useful remedy for the central cholinergic symptoms of organophosphate (OP) poisoning. The seeds were heated in water to make 2mg/ml atropine solution and administrated to male rats as a single intraperitoneal injection 5min before the subcutaneous injection of 25mg/kg of Dichlorvos . Pretreatment with *D. stramonium* seed extract significantly increased survival in a rat model of severe OP (48).

**Antiepileptic effects**

-- According to Peredery and Persinger (2004), rats were continuously administrated once of three herbal treatments *S. lateriflora, G. sempervirens* and *D. stramonium* through water supply for 30 days, one week after the induction of status epilepticus by a single injection of lithium (3mEq/kg) and pilocarpine (30g/kg). The number of spontaneous seizures per day during a 15min observation interval was recorded for

each rat during the treatment period and during an additional 30 days when only tap water was given. Rats that received a weak solution of the three herbal fluid extracts displayed no seizures during treatment. However, when this treatment was removed, the rats displayed numbers of spontaneous seizures comparable to the controls (49).

**Antiinflammatory activity**

The ethanolic extract of *D. stramonium* leaves showed significant anti-inflammatory activity comparable to the standard drug Diclofenac sodium against carrageenan induced paw edema in rats. 39.43% inhibition of the edema was observed after 3 hours of oral administration of 200mg/kg extracts. Maximum activity was observed when the extract was administered in doses of 3-hours intervals (50).

**Wound healing activity**

The hydro-alcoholic extract of *D. stramonium* leaves was investigated for wound healing potential in rats. The leaves were dried, crushed and the hydro-alcoholic extract was obtained and turned to 10% ointment form. In the course of this study, 18 male wistar albino rats weighing approximately 150- 180g were used. Group 1 as negative control group, Group 2 as reference group were treated topically with Povidone-Iodine ointment USP, Group 3 as test control were treated with 10% *D. stramonium* ointment. Wound healing was monitored on days 4, 8, 12, 16 and histopathological evaluation was carried out on the samples. Leaf extract of *D. stramonium* promotes wound healing via bactericidal activity (51).

**Vibriocidal activity**

Water, ethanol and acetone extracts of *D. stramonium* leaves were tested for their vibriocidal activity. A simple *in-vitro* screening assay was employed for the standard strain of *Vibrio cholerae*, 12 isolates of *Vibrio cholerae* non-O1, and *Vibrio parahaemolyticus*. The extracts were investigated by using the disk diffusion method. The results indicated that *D. stramonium* served as broad-spectrum vibriocidal agents (52).

**Toxicity studies**

-- Due to *D. stramonium* anticholinergic activity, it has been reported as a drug of abuse and has been involved in the accidental poisoning of humans and animals. Symptoms of acute *D. stramonium* poisoning included dryness of the mouth and extreme thirst, dryness of the skin, pupil dilation and impaired vision, urinary retention, rapid heartbeat, confusion, restlessness, hallucinations, and loss of consciousness (53 - 55).

-- Two doses of 50 and 200 mg/kg of the leaves ethanolic extract were administered to the rats for five weeks. Parameters studied were the indices of liver and kidney

function and some biochemical and haematological parameters. Feed intake, final body weight, serum AST, ALT, billurubin, total protein, urea and the electrolyte studied were not affected by the extract administration. Serum creatinine levels were, however, significantly raised in the rats administered with the ethanolic extract at the dose of 200 mg/kg body weight. The biochemical and haematological parameters were also affected (56).

-- Ingestion of *D. stramonium* seeds at concentrations of 0.5% or more in the diet have reported to produce adverse physiological changes in rats (57).

-- The effects of acute, subacute and chronic administration of alkaloids atropine and scopolamine, the main active principle of *D. stromonium*, with toxic properties, were studied in male Albino Wistar rats. After acute *i.p.* administration of dose 100mg/kg of total alkaloids of the seeds of *D. stramonium*, there were no remarkable changes in general appearance and no deaths occurred in any experimental group. Twenty-four hours after administration of total alkaloids of seeds, a significant reduction in indices of liver, spleen, brain and kidney function and some biochemical and haematological parameters were observed. The red blood cells, hematocrit, hemoglobin and white blood cells were significantly higher in the treated groups than the control group. Subacute study for four weeks showed no resulting mortality or signs of toxicity. In chronic study, the synthetic alkaloids administered *i.p.* at daily doses of 4.2 mg/kg of atropine and 1.6 mg/kg of scopolamine, did not produce death. However, diarrhea and hypoactivity were observed. The relative weight of liver was significantly less than that of the control group (58).

Administration of scopolamine in drinking water to pregnant rabbits on days 10-14 of gestation led to fetal deformities of eye. These malformations were observed in all living fetuses present in six different animals (59).

--Various cases of toxic delirium and psychiatric symptoms have been reported after ingestion of *D. stramonium*. Careful consideration of the toxicity of the plant is required before its use. Its ingestion induces characteristic symptoms such as dry mouth, intense thirst, blurred vision, mydriasis and increased heart rate followed by hallucinations, delirium and loss of motor coordination leading to comma and ultimately to death by respiratory failure (55, 60 - 63).

## 16. Additional information:

- Store *D. stramonium* in airtight containers. Protect from moisture and light (22).

- The atropine component is well absorbed, metabolized by the liver, and excreted by the kidneys (23).
- *D. stramonium* has also been smoked in cigarettes or burnt in powder and the fumes inhaled but the irritation produced by the fumes may aggravate bronchitis (22).
- Toxicity varies from season to season and depends on the manner in which the plant is ingested *i.e.* chewed, drank as an extract or smoked (64).

## 17. Date of compilation/last revision

02/02/2021

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# Monograph on Wild Medicinal Plants in Egypt

## *Plantago afra* (L.) قاطونة

## 1. Names & Synonyms (1-3)

**Family:** Plantaginaceae

**Synonym:** *Plantago psyllium* L.

*Plantago parviflora* Desf.

**Arabic:** Qatoona قاطونة, Hab El-baragheet حب البراغيث

Seeds are known as Bizr qatoona بذر قاطونة

**English:** Flea-wort

## 2. Geographical distribution (1-3)

Desert east of the Nile including that of Sinai as well as the Red Sea and Gebel Elba

## 3. Parts used for medicinal purposes (1-3)

Ripe seeds

## 4. Major chemical constituents

**Polysaccharides:**
Mucilage (4) mainly composed of arabinoxylan (5).

**Phenylpropanoid glycosides**:
Acetoside (Verbascoside) and isoacetoside (isoverbascoside) (seeds) (6).

**Fatty acids:**
Tritriacontanoic acid (synonyms: psyllic acid, ceromelissic acid) (husk) (7, 8).

**Iridoids:** aucubin (seeds) (9).

## 5. Medicinal uses

**Well-established**

- Emollient, demulcent (10) and in chronic constipation (10, 11).
- Bulk-forming laxative to provide gentle relief of constipation (for the treatment of habitual constipation).
- In conditions where easy defecation with soft stool is desirable, *e.g.* in cases of painful defecation after rectal or anal surgery, fissures and haemorrhoids, following rectal examinations and pregnancy (9, 12, 13, 15).
- In conditions which need an increased daily intake of fiber, *e.g.* irritable bowel syndrome (12, 16).

**Traditional use (2, 17)**

- Emollient
- Bulk forming laxative for chronic constipation

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

## 6. Herbal preparations (2)

- Seeds
- Decoction of seeds

## 7. Posology and method of administration

Adults and children over 12 years of age: as laxative, 4-16g orally (11), 1-3 times daily depending of the individual response (13).

Children 6-12 years: as laxative, half of the adult dose (9).

**Duration of administration**

Continued use for 2 to 3 days is needed for maximum laxative benefit (13).

**Method of administration**: oral

A sufficient amount of liquid (water, milk, fruit juice or similar aqueous liquid) should always be taken *e.g.* 30 ml of water per 1 g of herbal substance (12). The medicinal product can be mixed with the liquid and then swallowed as quickly as possible after stirring briskly, and then adequate fluid intake has to be maintained (9). The effect starts 12 - 24 hours later (12).

## 8. Contraindications

- Hypersensitivity to active substances or to other plants of the same family.
- Patients who have difficulty in swallowing or any throat problems (9, 11, 18-19).
- Patients suffering from abnormal constrictions (12, 20) or inflammatory illness in the gastro-intestinal tract (20).

- In case of intestinal obstruction, potential or existing intestinal blockage (ileus) (12, 13, 20, 21).
- Patients with diseases of the esophagus and cardia (12).
- Paralysis of the intestine or megacolon (12).
- Patients experiencing a sudden change in bowel habits that has persisted for more than 2 weeks (9, 12).
- Patients with fecal impaction (12).
- Patients with undiagnosed rectal bleeding, or failure to defaecate following the use of another laxative product (9, 12, 13, 22).
- Diabetic patients who have difficulty managing their blood sugar level (9, 12, 13, 18-20, 22).

## 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.

- It should always be taken with sufficient fluid *e.g*. 30 ml of water per 1 g of herbal substance (12), as there is a risk of intestinal or esophageal obstruction and fecal impaction, especially if it is swallowed dry (12, 13, 20, 23).

- When taken with inadequate fluid amounts, bulk forming agents can cause obstruction of the throat and esophagus with choking and intestinal obstruction. Symptoms can be chest pain, vomiting, or difficulty in swallowing or breathing (12).

- It should not be taken immediately before going to bed (23).

- In patients who are confined to bed, do little physical exercise, debilitated patients or elderly patients, a medical examination may be necessary prior to treatment with the drug (12, 13).

- It should be taken at least half an hour after other medications to prevent delayed absorption of the latter (13).

- If taken with medicinal products known to inhibit peristaltic movement (*e.g*. opioids) a medical supervision is necessary in order to decrease the risk of gastrointestinal obstruction (ileus) (12).

- Treatment should be stopped and medical advice sought, in case of bleeding , or if no response occurs after ingesting the drug, or in cases of any irregularity of feces, (12, 13, 24); symptoms such as abdominal pain, nausea and vomiting can be signs of potential or existing intestinal blockage (ileus) (12).

- It is not recommended to be used for children under 6 years of age due to insufficient data on efficacy (12).

- Laxative bulk producers should be used before using other purgatives if change of nutrition is not successful (12).

- In patients with diabetes taking oral agents or insulin to achieve glycemic control, blood glucose levels should be monitored more closely when initiating or adjusting doses of the latter can lower blood glucose level and impair carbohydrate absorption (25).

- In the case of insulin dependent diabetics, if the product is taken together with meals, it may be necessary to reduce the insulin dose (26, 27).

- Bulking agents have been reported to diminish the absorption of concomitantly some administered medicines (13).

- Psyllium seed should be used concomitantly with thyroid hormones only under medical supervision. The dose of the thyroid hormones may have to be adjusted (12).

**Warning on hypersensitive reactions concerning powder formulations:**

- Allergic sensitization may occur due to inhalation of the airborne dust upon using the powder of Psyllium seeds or in individuals with continued occupational contact to powder (*i.e.* healthcare workers, caregivers). This sensitization usually leads to hypersensitivity reactions which could be serious (12). To minimize the potential allergic reaction, users should spoon the product from the container directly into a drinking glass and then add liquid (24) and the health professionals who frequently dispense powdered should avoid inhaling airborne dust while handling these products (13). It is recommended to assess clinically the possible sensitization of individuals at risk. In case of proven sensitization leading to hypersensitivity reactions, exposure to the product should be stopped immediately and avoided in the future (12).

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

- **Oral medicinal products (9, 12, 13, 21, 25, 26, 29-31):** Enteral absorption of concomitantly administered medicines may be delayed such as:
  - Minerals (*e.g.* calcium, magnesium, copper and zinc)
  - Vitamins (B 12)
  - Cardiac agents (beta-blockers, calcium channel blockers and cardiac glycosides)
  - Coumarin derivatives
  - Lithium salts
  - Carbamazepine

- **Antidiabetic agents:** If the product is taken together with meals in the case of insulin dependent diabetics it may be necessary to reduce the insulin dose (9, 12, 13, 21, 26, 27).

- **Thyroid hormones:** It should be used concomitantly with thyroid hormones only under medical supervision because the dose of the thyroid hormones may have to be adjusted (9, 12).

- **Peristaltic movement inhibitor agents:** In order to decrease the risk of gastrointestinal obstruction (ileus), it should only be used under medical supervision together with medicinal products known to inhibit the peristaltic movement (*e.g.* Morphinomimetics and Loperamide) (9, 12).

- **Sodium picosulfate:** Mild interactions (32).

- **Food:** It may decrease nutrient absorption (21).

- **Lab Test:** Psyllium may decrease blood glucose testing (theoretical), may decrease total cholesterol, LDL, HDL ratio test results and may cause a false increase in serum digoxin (21).

## 11. Fertility, pregnancy and lactation

It can be used during pregnancy and lactation (9, 33). A risk is not to be expected since the constituents of Psyllium seed are not absorbed and have no systemic effects (9).

No fertility data available (13).

## 12. Effects on ability to drive and use machines

Not relevant.

## 13. Undesirable effects

- Hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm and in some cases, anaphylaxis; cutaneous symptoms such as exanthema and/or pruritus have also been reported (9, 12, 13, 18-20, 34-36).

- Flatulence may occur with the use of the product, (9, 12, 13, 19, 21, 27). These side-effects may be reduced by gradually increasing fiber intake, starting at one dose per day and gradually increasing to three doses per day and may be reduced by decreasing the amount of Psyllium taken for a few days (13, 27) with generally disappears in the course of the treatment (9, 12).

- Abdominal distension and risk of intestinal or esophageal obstruction and fecal impaction may occur, particularly if swallowed with insufficient fluid. The frequency is not known (9, 12, 21).

- Nausea, vomiting, anorexia, diarrhea (21).

## 14. Overdose

Overdose may cause abdominal discomfort and flatulence, or even intestinal obstruction. Adequate fluid intake should be maintained, and management should be symptomatic (9, 12).

## 15. Relevant biological activities

**Laxative effect**

A preparation made from "*Plantago psyllium*" was administered (3 times 3.4 g daily) to 63 patients suffering from chronic functional constipation for a period of 20 days. The tolerance of the preparation was satisfactory in 55 patients (87%), including 49 (89%), who reported a favorable effect, i.e. problem-free defecation and regression or disappearance of meteorism. A statistically significant decline of serum cholesterol occurred. In 14 patients (25%) a weight loss of more than 1 kg was observed. The results concluded that the preparation can be considered suitable for the treatment and probably also the prevention of chronic functional constipation and as an adjuvant in the treatment of hyperlipoproteinaemia type II, in particular when associated with obesity (37).

--The therapeutic value of "Psyllium" for the treatment of constipation among others was discussed: 'There is a scientific basis for Psyllium working as a mild laxative. This evidence, combined with the available research in humans, suggests that Psyllium decreases the time necessary to pass bowel movements, increases the number of bowel movements per day and increases the amount of stool passes (38).

Psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight (39) and ameliorating chronic diarrhea (40).

The hypothesis that a gel-forming fraction of Psyllium escapes microbial fermentation and is responsible for the characteristics that enhance laxation were tested. Fifteen healthy adults consumed controlled diets for two 7-d periods, one of which included 8.8 g dietary fiber provided by 15 g/d of a Psyllium seed husk preparation. All stools were collected and evaluated and diet was monitored throughout. Psyllium significantly increased the apparent viscosity of an aqueous stool extract, stool moisture, and wet and dry stool weights. A very viscous fraction, not present in low-fiber stool and containing predominantly 2 sugars: xylose (64%) and arabinose (27%), the same two sugars that account for the majority (79%) of the carbohydrate in Psyllium. The results concluded that in contrast with other viscous fibers that are fermented completely in the colon, a component of Psyllium is not fermented. This gel provided lubrication that facilitated propulsion of colon contents and produced a stool that

was bulkier and moister than were stools resulting with use of comparable amounts of other bowel-regulating fiber sources (41).

Psyllium has been reported to increase stool frequency, weight and decrease stool consistency in constipated patients. These effects are not associated with significant changes in colorectal motility. The clinical parameters were not significantly affected by treatment with Psyllium although there was a significant decrease in transit time (42-46).

## 16. Additional information

It has lipid- and glucose-lowering effects (47-51).

## 17. Date of compilation/last revision

18/03/2021

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# Monograph on Wild Medicinal Plants in Egypt

*Senna alexandrina* Mill. سنا مكي

## 1. Names & Synonyms (1-3)

***Senna alexandrina* Mill.**

**Family:** Leguminosae (Caesalpinioideae)

**Arabic:** Sanna Mekki سنا مكى , Salamekki سلامكى

**English:** True Senna, Alexandrian Senna

**Synonyms:**

*Cassia acutifolia* Delile, *Cassia senna* L., *Cassia lanceolata* Forssk.

## 2. Geographical distribution

The Nile region, desert east of the Nile including that of Sinai as well as the Red Sea and Gebel Elba regions (3).

## 3. Parts used for medicinal purposes

Leaves and pods (3).

## 4. Major chemical constituents

**Anthraquinones**: Sennoside A and sennoside B , sennosides C and D (4), gluco aloe-emodin, rhein-8-monoglucoside, rhein 8-diglucoside, sennidin (5-7).

**Naphthalene glucoside:** 6-Hydroxymusicin glucoside (8).

**Flavonoids:** Mostly as mono- and di-*O*-glycosides of quercetin, kaempferol and isorhamnetin (5).

## 5. Medicinal uses

**Well-established uses**

Purgative (9) for short term use in occasional constipation (10).

**Traditional medicinal uses**

Stimulant laxative (11).

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

## 6. Herbal preparation correlated to medicinal use

- Liquid extract (alcoholic 30%) (12).
- Infusion (13).
- Decoction, dried extract, elixir, granules (pharmaceutical), oral solution, powder, rectal suppositories and tablets (14-15).
- The boiled tea of leaves, sweetened with black honey, is taken in the morning before breakfast for treatment of constipation (11).

## 7. Posology and method of administration correlated to medicinal use

**Adult oral dose:**

- **Powdered drug:** 0.5-3gm (12).
- **Liquid extract:** 0.5-3ml (12).
- **Senna preparations expressed in terms of total sennosides calculated as sennoside B:** The usual adult dose is 15 to 30 mg given by mouth once or twice daily (15).

**Children younger than 12 years of age:** under medical supervision (14).

- Children over 6 years of age: one-half the adult dose (15).
- Children aged 2 to 6 years: one-quarter the adult dose (15).
- Not to be used by children younger than 2 years of age (15).

**Elderly patients**: Should initially take half of the normal prescribing dose (13).

## 8. Contraindications

- Hypersensitivity to active substances and to other plants of the same family.
- Children younger than 2 years of age (13).
- It should not be used by persons with intestinal obstruction, ulcerative colitis, gastrointestinal bleeding, appendicitis, nausea, vomiting, congestive heart failure, or an acute condition in the abdomen caused by surgery (14).
- Patients with suspected stricture, inflammatory bowel disease, or impending obstruction should not receive a bowel stimulant, to reduce the risk of colonic perforation (15).
- Senna should not be given to patients with undiagnosed abdominal pain (15).
- Prolonged use should generally be avoided (15).

## 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.

- Hypersensitivity reactions manifesting as asthma and rhinoconjunctivitis have been reported in those manufacturing or dispensing Senna products (15).

- This herb should not be used for longer than 1-2 weeks without medical advice (14).
- Children younger than 12 years of age should not be used unless prescribed by a physician (14).

## 10. Interactions with other medicinal products and other forms of interaction (14)

- Cardiac glycosides (digoxin): Chronic use of Senna may potentiate cardiac glycosides.
- Disulfiram: Do not use Senna with disulfiram.
- Laxatives /stimulant laxative herbs: Avoid the concurrent use of Senna with other laxatives; additive effect can occur.
- Jimson weed (*Datura stramonium* L.): The action of Jimson weed is increased in cases of chronic use or abuse of Senna.

## 11. Fertility, pregnancy and lactation

The use of Senna should be avoided during pregnancy (13) and lactation due to its content of anthraquinones (16) which is distributed into breast milk (15).

No fertility data is 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

Senna may cause mild abdominal discomfort such as colic or cramps (15), nausea, vomiting, anorexia, cramping, diarrhea, flatulence, hypocalcemia, enteropathy, alkalosis and hypokalemia (14).

## 14. Overdose

Prolonged use or over dosage can result in diarrhoea with excessive loss of water and electrolytes, particularly potassium; there is also the possibility of developing an atonic non-functioning colon. Anthraquinone derivatives may colour the urine yellowish-brown at acid pH, and red at alkaline pH. Reversible melanosis coli has been reported following chronic use (15).

Prolonged use or abuse of Senna laxatives has been associated with reversible finger clubbing, hypokalaemia and tetany, hypertrophic osteoarthropathy, intermittent urinary excretion of aspartylglucosamine, hypogammaglobulinaemia, reversible cachexia, and hepatitis or hepatic failure (15).

## 15. Relevant biological activities

The laxative action and the laxative potency of Alaxandria and Tinnevelley senna in mice were studied using a standardized procedure. The results indicated that the laxative potency of various grades have been found to be reasonably uniform, the variations in potency not exceeding 25 per cent of the mean (17-18).

-- The effect of repeated administration of the doses of Alexandria or Tinnevelly senna on mice over many weeks were studied. Two sets of experiments were

conducted. In the first set of experiments no tolerance to either Tinnevelly or Alexandria senna developed. In the second set of experiments, 31 out of 40 mice survived the twenty-three-week period. It would therefore seem that mice may be used once a week for quantitative assay of laxative activity of senna and the repeated administration of the doses over many weeks did not cause any tolerance (19).

--Intravenous and intraperitoneal injection of Senna infusion produced negligible cathartic response compared to the same dose after oral administration (20).

-- The effect of repeated administration of the doses of Alexandria Senna on mice over many weeks was studied. It would therefore seem that mice may be used once a week for quantitative assay of laxative activity of Senna and the repeated administration of the doses over many weeks did not cause any tolerance (19).

--Purgative action of Senna depends on the amount of hydroxyanthraquinone existing in the plant (21-22) but the effect is not due to the presence of sennoside A and B only (23), rather a synergistic action of different components (24), because Senna extracts are more potent laxatives than the pure active principles (25). Oral Senna-pod extract reverses net absorption of water, sodium and chloride to net secretion, and increases potassium secretion and stimulates output of PGE2 into the colonic lumen (26). The purgative action of Senna has been attributed, in part, to the release of histamine in the gut (27).

-- Senna extract (SE) causes diarrhea and enhances gastrointestinal motility through digestive tract administration. Long-term gastric administration of SE induces inflammatory changes and cell damage in the whole gastrointestinal tract. The differential proteins screened from the colonic tissues of the model mice might mediate the enhancing effect of SE on gastrointestinal motility (28).

## 16. Additional information

Senna preparations may be used for bowel evacuation before investigational procedures or surgery, prior to X-ray examination or in mechanical preparation in the evening before elective colonic or rectal resection, as a colon cleansing, for elective colonoscopy (15, 29-32).

- The *β*-*O*-linked glycosides (e.g. sennosides and rhein 8-*O*-glucoside) are neither absorbed in the upper gut nor split by human digestive enzymes. They are converted by the bacteria of the large intestine into the ultimately active metabolite (rheinanthrone) (10, 33). The Aglycones are absorbed in the upper gut.

- Animal experiments with radio-labeled rheinanthrone administered directly into the caecum demonstrated absorption < 10%. In contact with oxygen, rheinanthrone is oxidised into rhein and sennidins, which can be found in the blood, mainly in the form of glucuronides and sulphates.

- After oral administration of sennosides, 3 - 6% of the metabolites are excreted in urine; some are excreted in bile (10). However, most of the sennosides (ca. 90%) are excreted in faeces as polymers (polyquinones) together with 2 - 6% of unchanged sennosides, sennidins, rheinanthrone and rhein. (10.)
- In human pharmacokinetic studies with Senna pods powder (20 mg sennosides), administered orally for 7 days, a maximum concentration of 100 ng rhein/ml was found in the blood, but an accumulation of rhein in blood was not observed. Small amounts of rhein pass into breast milk (10).

- Animal experiments demonstrated that placental passage of rhein is low.

## 17. Date of compilation/last revision

07/06/2021

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# Monograph on Wild Medicinal Plants in Egypt

## *Urginea maritima* (L.) Baker بصل العنصل

## 1. Names & Synonyms (1-3)

***Urginea maritima* (L.) Baker**

**Family:** Hyacinthaceae (Liliaceae)

**Arabic:** Basal Far'aon بصل فرعون , Onsol عنصل , Basal Onsol بصل عنصل , Ashkil اشقيل , Askil أسقيل , Askal أسقال (4)

**English:** Sea onion, Squill, Medicinal squill, White squill

**Synonyms**

*Scilla maritima* L., *Urginea scilla* (Steinh.), *Drimia maritima* (L.) Stearn (3)

## 2. Geographical distribution

Mediterranean coastal strip and Sinai (3)

## 3. Parts used for medicinal purposes

The dried fleshy scales of the bulbs of *U. maritima* (4) collected after withering of leaves; known as white squill (2) [Not to be confused with red squill used as rodenticide].

## 4. Major chemical constituents

**Cardiac glycosides "Bufadienolides" (bulb):**

- Scillaren A, proscillaridin A, scilliroside, scillaridin A, scilliglaucoside, scillipheoside, glucoscillipheoside, scillicyanoside, glucoscillaren A, scillarenin (5-7).

- Forty-one compounds were isolated from the Egyptian squill from which sixteen were glycosides; 16$\beta$-hydroxy-scillarenin, 16$\beta$ -*O*-acetyl-scillarenin, 12$\beta$ -hydroxy-5 $\alpha$-4,5-dihydro-scillirosidin, 16$\beta$ - hydroxy-5$\alpha$ -4,5-dihydro-scillirosidin, 16$\beta$ -*O*-

acetyl-5$\alpha$ -4,5- dihydro-scillirosidin, 12$\beta$-hydroxy-scillirubrosidin, 16$\beta$-*O*-acetyl-scillirubrosidin, 9-hydroxy-scilliphaeosidine, and 12$\beta$ -hydroxy-desacetyl-scillirosidin (8).

**Other constituents:**

Flavonoids (5) (vitexin, isovitexin, orientin, isoorientin, scoparin, vicenin-2, quercetin-3-monoglucoside, dihydroquercetin, dihydroquercetin-4'-monoglucoside), calcium oxalate (5,7,9), xanthoscillide (5), dihydro-benzofuran-type neolignan glucoside and free amino acids (L-azatidine-2-carboxilic acid was the predominant one) (7).

## 5. Medicinal uses

**Well-established uses (4)**

Expectorant.

**Traditional medicinal uses (2,10)**

Expectorant.

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

## 6. Herbal preparation correlated to medicinal use (11)

Infusion

Liquid extract (Alcoholic 70%)

Vinegar

Tincture

## 7. Posology and method of administration correlated to medicinal use (11)

Dried bulb powder 60-200mg as infusion three times daily; with maximum daily dose of 500mg (4)

Liquid Extract (12): 0.06-0.2 ml

Vinegar (12): 0.6-2.0 ml

Tincture (12): 0.3-2.0ml

## 8. Contraindications

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

- The drug and pure glycosides, among others, should not be administered in the presence of second- or third-degree atrioventricular block, hypercalcemia, hypokalemia, hypertrophic cardiomyopathy, carotid sinus syndrome, ventricular tachycardia, thoracic aortic aneurysm or Wolff-Parkinson-White (WPW) syndrome (13).

- It is not recommended for patients with impaired hepatic or renal function (11).

- It is not recommended for children under 12 years old (11).

- It is not recommended in stomach or bowel problems, as it can irritate the stomach and intestine (11).

## 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.

- Squill contains cardiac glycosides with a narrow therapeutic range, thus therapeutic doses may induce side effects in susceptible individuals (14).

-Contact with the juice of the fresh bulb can lead to skin inflammation (squill dermatitis) (14).

- Monitoring of blood glucose level should be done regularly when used for diabetics as squill had been used in traditional medicine for diabetes (2).

- Squill is to be dispensed by prescription only (a prescription drug). It is considered to be potentially harmful if not used under medical supervision.

## 10. Interactions with other medicinal products and other forms of interaction (14-16)

- Digoxin
- Calcium supplements
- Medications for inflammation (Corticosteroids)
- Quinidine
- Stimulant laxatives
- Water pills (Diuretic drugs)

## 11. Fertility, pregnancy and lactation

Squill must be avoided during pregnancy and lactation. It has been reported to be an abortifacient and to affect the menstrual cycle (11, 17).

## 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

These include gastric irritation or hypersensitivity reactions (urticaria/hives, flushing or dermatitis), salt and water retention, low potassium levels in blood and irregular pulse (14).

## 14. Overdose (13)

Overdosage can lead to cardiac rhythm disorders, life-threatening ventricular tachycardia, atrial tachycardia with atrioventricular block, stupor, vision disorders, depression, confusion, hallucinations and psychosis. Fatal dosages lead to cardiac arrest or asphyxiation.

## 15. Relevant biological activities

**Anti-asthmatic activity**

A preliminary evaluation of the efficacy and safety of an add-on Squill Oxymel treatment in patients with moderate to severe persistent asthma was done. In a 6-week, triple-blind, randomized, placebo-controlled trial, 60 patients with stable moderate to severe persistent asthma were randomly allocated to receive either 10 ml syrup of Squill Oxymel, simple oxymel, or a placebo 2 times a day, as an add-on to their routine treatment (inhaled corticosteroids and $\beta 2$ agonists). Spirometry and plethysmography were performed on patients to evaluate the effect of the treatment at baseline and end of intervention. The results showed significant improvement in spirometry parameters, especially FEV1 (1.54 ± .38 *vs.* 2.11 ± .49 l), in the Squill Oxymel group compared with the other groups. The increases in FEV1 liter, FEV1%, FEV1/FVC%, and MEF 25–75% during the intervention were significantly higher in the Squill Oxymel group than in the other groups ($p < .001$). However, the improvement of plethysmographic parameters showed no significant difference between the study groups ($p>.05$). The SGRQ scores (symptoms, activity, and total score) were significantly improved after intervention in both the Squill Oxymel and

the simple honey oxymel groups ($p < .001$), but not in the placebo group. Nausea and vomiting was reported in 5 patients in Squill Oxymel and simple oxymel groups. No other serious adverse event was observed. The results of the study showed preliminary evidence for the efficacy and safety of the add-on treatment of Squill Oxymel in patients with moderate to severe persistent asthma (18).

**Toxicity in human**

*U. maritima* led to death in 55 years-old woman who orally consumed two bulbs for arthritic pain. She was diagnosed with Hashimoto thyroiditis before ingestion of this plant and hypothyroidism may had associated with sever toxicity. Poisoning symptoms were similar to digitals included vomiting, seizure, significant hyperkalemia, ventricular arrhythmias, atrioventricular block (19).

## 16. Additional information

*U. maritima* is the oldest drug used by human for cardiac problems (7). The glycosides present in the squill have digitalis like cardiotonic properties due to their aglycones. Action is faster but shorter-lasting than that of digitalis glycosides (20). Ingestion of squill is poisonous mainly due to its cardiac glycosides content (19).

## 17. Date of compilation/last revision

20-05-2021

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# Annex

**Dry extract:** is a solid preparation obtained by evaporation of the solvent from a liquid/fluid extract. Dry extract can also be prepared by spray-drying with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. This may be further processed by compression or with use of a binding agent or granulation liquid to produce multiparticulate granules (1).

**Elixir**: are clear, flavored oral liquids containing one or more active ingreients dissolved in a vehicle that usually contains a high proportion of sucrose or a suitable polyhydric alcohol or alcohols and may also contain ethanol or a diluted ethanol (2).

**Liquid extract (1)**: is a liquid preparation of herbal materials obtained using water, alcohol or other extraction solvents. Common preparations include:

- **Decoction**: is a water-based herbal preparation made by boiling herbal materials with water, and is commonly utilized in various traditional medicine contexts. In some cases, aqueous ethanol or glycerol can also be used to prepare decoctions. However, decoctions may be prepared by a programmable decocting machine that processes the herbal material at a specific temperature for a specific duration and then dispenses the decoction in hermetically sealed plastic pouches of a specified single-dosage volume that can be refrigerated for subsequent reheating and consumption. The amounts of herbal material and solvent used, as well as the length of the decocting process, should be specified.
- **Infusion**: is a dilute solution prepared by steeping the herbal materials in boiling water for a short time. Infusions prepared in edible oil or vinegar are also available.
- **Tincture** : As a general rule, a "tincture" is an alcoholic or hydroalcoholic extract of a herbal material, typically made up of 1 part herbal material and 5–10 parts solvent (for example, ethanol, vinegar, or glycerin). Tinctures can be prepared by extracting herbal materials usually with ethanol of a suitable concentration. The ratio of water to alcohol should be recorded.

**Poultice:** a paste of plant part or drug applied to the sore or inflamed part of the body to supply moisture or to act as a local stimulant (3).

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