

Ammi Visnaga in treatment of urolithiasis and hypertriglyceridemia

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ABSTRACT

Ammi visnaga is a widely distributed Ancient Egyptian medicinal plant used for treatment of several diseases including urolithiasis (kidney stones). The active chemical constituents' khellin and visnagin obtained from the *A. visnaga* seeds have activity of antilithiogenic and pleiotropic. However, little is known about its activity on hypertriglyceridemia. The main aim of this review is to explore the use of *A. visnaga* in urolithiasis and to present a case of relevancy. We highlighted a case of a patient who has recurrent urethral stones and hypertriglyceridemia. The patient was treated with *A. visnaga* seeds, has recovered completely from ureteral stones and his high-density lipoprotein (HDL)-cholesterol low levels retained to normal after using of *A. visnaga* seeds for 10 days. The present case of *A. visnaga* seeds being local medicinal plant has shown the effect in treating urolithiasis with extended effect on raising HDL-cholesterol. These results may provide insights for *in vitro* studies for isolation of these biologically active compounds for potential in raising HDL-cholesterol. Whether or not the later effect can have clinical utility remains to be explored.

Key words: *Ammi visnaga*, high-density lipoprotein, khellin, ureteral stones, urolithiasis, visnagin

INTRODUCTION

Ammi visnaga with synonyms *Ammi daucoides* and *Daucus visnaga* is of family, Apiaceae/Umbelliferae. *A. visnaga* (Khella) is an annual herbaceous folk plant with bi-or tripinatisect linear segmented leaves and large compound umbels of white flowers grows wild in Mediterranean region especially in Egypt, Morocco and Islamic republic of Iran.^[1,2] The seeds of ovate, oblong fruit (2–2.5 cm) constitutes furanochromones having activity of hyperbilirubinemia,^[3] ripe fruit constitutes antilithiogenic activity and pleiotropic effect on urolithiasis, diuresis,^[4] antispasmodic^[5] and active component (60 µg/ml) having various cardiovascular beneficial effects.^[6] Due to these versatile effects, Ancient Egyptians traditionally used *A. visnaga* as a tea preparation for the treatment of urolithiasis and for analgesia.^[7] Furthermore, several studies had reported the importance of *A. visnaga* for the treatment of several diseases including

psoriasis,^[8] asthma,^[9] recovery of vitiligo,^[10] hypoglycemia^[11] and poisonous bites.^[12] Furthermore, preliminary evidence was observed that khellin might also increase high-density lipoprotein (HDL)-cholesterol level without effecting total cholesterol or triglycerides concentrations.^[13]

There are many conventional drugs including amiodarone, nifedipine, and cromolyn, have been developed from khella. Khella is sometimes confused with its less used relative, bishop's weed (*Ammi majus*). The two species have some common chemical constituents and pharmacological effects, but khella is more commonly used for cardiac and pulmonary conditions, and bishop's weed is more commonly used for dermatological conditions. Isolated khellin, a constituent of khella and bishop's weed, is used for angina pectoris; asthma; and in conjunction with phototherapy for vitiligo, psoriasis, and alopecia areata.

Pharmacological profile

Mechanism of action

The used parts of khella are the dried, ripe fruits. Khella has several constituents with known pharmacological activity, including visnadin, visnagin, and khellin. All of these

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constituents may have cardiovascular effects attributed to calcium channel blocking actions. Visnadin is the most active. It can inhibit vascular smooth muscle contraction and may dilate peripheral and coronary vessels and increase coronary circulation. Visnagin also has negative chronotropic and inotropic effects and reduces peripheral vascular resistance. The khellin constituent also acts as a vasodilator and has bronchodilatory activity. There is some preliminary evidence that khellin might also increase HDL-cholesterol levels without affecting total cholesterol or triglyceride concentrations.^[13]

A khella extract seems to have some antimicrobial activity. This might be attributable to both the khellin and visnagin constituents, which both seem to have antifungal, antibacterial, and antiviral activity. Researchers are interested in khella for use in psoriasis. The khellin constituent is structurally similar to the psoralen nucleus and might be useful as a photosensitizer in patients with psoriasis.^[6]

Ammi visnaga uses

Orally, khella is used as antispasmodic for colic and abdominal cramps, kidney stones, menstrual pain, and premenstrual syndrome.^[14] Khella is also used for respiratory conditions including asthma, bronchitis, cough, and whooping cough. It is also used for cardiovascular disorders including hypertension, cardiac arrhythmias, congestive heart failure, angina, atherosclerosis, and hypercholesterolemia. It is also used for liver and gall bladder disorders, diabetes, and as a diuretic. Topically, khella is used on the skin for vitiligo, psoriasis, patchy hair loss (alopecia areata), wound healing, inflammation conditions, and poisonous bites.^[15]

Dosing and administration

Orally khella is typically given as an extract standardized based on khellin content. Extracts are usually standardized to 12% khellin. A typical dose of khella is an amount that provides 20 mg of the khellin constituent per day. For angina, khella in an amount providing doses of 30–300 mg of the khellin constituent has also been used. Khella is sometimes used as a tea. The tea is usually prepared by pouring boiling water over powdered fruit, steeping 10–15 min, and straining.^[16]

Safety profile

Ammi visnaga is possibly unsafe when used orally in high doses. High doses of khella can cause increases in liver enzymes and possible liver damage. It is unlikely safe when used orally in pregnancy. The active constituent, khellin, has uterine stimulant activity; therefore is contraindicated in pregnancy.^[17] In lactation insufficient reliable information is available, however, it is advised to avoid using.

Possible adverse effects

Orally, prolonged use or use of high doses of khella can cause nausea, dizziness, constipation, lack of appetite, headache, itching, and insomnia. In some patients, khella can cause elevated liver transaminase (enzymes aspartate transaminase and alanine transaminase) and gamma-glutamyltransferase levels (alkaline phosphatase),^[6] probably due to the khellin constituent; which is known to affect liver enzymes. Liver dysfunction and jaundice are typically reversible when khella is discontinued. There is also some concern that khella might cause photosensitivity because of the constituents khellin and the furocoumarin. Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache, and sleeplessness.^[18]

Urolithiasis

Urolithiasis is a urological clinical condition commonly called as kidney stone disease with an average lifetime risk of stone formation in 5%–10% of the population.^[19] Several factors can promote the formation of kidney stones such as dehydration, consumption of foods containing high amount of calcium, uric acid, and some infectious diseases.^[20] Although patients with urolithiasis might be asymptomatic, many have pain and thus commonly present to the emergency department (ED).^[21] Khellin, a chemical obtained from *A. visnaga*, was used as a smooth muscle relaxant and has been thought to have pleiotropic effects on urolithiasis (smooth muscle relaxation, diuresis and the effects on urinary citrate).^[4]

The main constituent of kidney stones (80%) is calcium oxalate (Ca Ox). However, if the stone enlarges it causes ureteral obstruction (stones > 5 mm unlikely to pass spont) and produces symptoms of flank pain, burning micturition and hematuria requires emergency medical and surgical management. Although, medical and surgical treatments are widely used there were several disadvantages including reoccurrence of kidney stones and potential renal damage. Khellin may interfere with the citrate metabolism. Since Ca Ox urinary stones are the most common type of urinary stone (up to 80%) and citrate is a well-known inhibitor of Ca Ox crystallization^[22] Khan *et al.* reported that urinary citrate plays an important role in reducing recurrences of Ca Ox stones.^[11]

Therefore, traditional and alternative medications were other options to investigate. In this regard, we presented here a case of urolithiasis and hypertriglyceridemia treated with seeds of *A. visnaga*.

CASE REPORT

A 50-year-old man was referred to ED at King Abdullah University Hospital in Jordan from primary health center

with chief complaints of flank pain with dysuria for 3 h before admission. In detailed history, patient was known hypertensive since 10 years using only antihypertensive medication. He has a history of urolithiasis for the past 3 years and underwent regular medical treatment previously but not well-benefitted. At the time of admission to the ED, physical examination revealed tenderness on costovertebral angle was observed on both sides and burning micturition while passing the urine. He had a body temperature of 37.5°C and electrocardiogram remains normal. The clinical and laboratory findings were described in Table 1. Further, his hematological and electrolytic examinations showed normal. On ultrasound examination, it was observed two stones observed on right urethra (3–5 mm diameter) and one on the left kidney (3 mm diameter). Pain relief was provided in the ED and advised to have surgical removal of three stones.

Due to previous experience with surgeries and therapeutic treatment failures, preferred to search for other therapeutic options. In search of other alternatives, phyto-therapeutic option *A. visnaga* was considered and advised for the patient to use its seeds through boiling a tea spoon size (10 g) in 200 ml of water for 10 days twice daily. During follow-up, 2 days after initiation of the *A. visnaga* seed the patient was relieved from pain and no hematuria was observed. On day 5, the stone in kidney passed out through urine, further on day 7 and 8 the other two stones in the ureter were also passed out. On day 10 of ultrasound examination, no renal stones were observed and further the patient's lipid profile has showed improvement of HDL-cholesterol level from 32 to 56 mg/dL. There was no much improvement observed in other lipid parameters as cholesterol and low-density lipoprotein (LDL)-cholesterol and all other laboratory investigations were normal.

DISCUSSIONS

The case presented confirmed the importance of *A. visnaga* in treatment of urolithiasis with a beneficial effect in

improving HDL levels without effecting the triglycerides and LDL levels. In our case, the use of *A. visnaga* was able to relieve the pain and proven effective treatment toward urolithiasis by removing stones from kidney and urethras. Similar results were reported in other studies.^[12,14,15] The detailed mechanism of action of *A. visnaga* seeds was not yet elucidated. However, it may be due to the main compounds khellin and visnagin that can prevent cell damage caused by Ca Ox crystals in renal epithelial cells.^[13] Further, more than one mechanism has been proposed by various researchers. Hashim *et al.*^[19] described the action of *A. visnaga* to be attributed to its vasodilating and diuretic properties. Other researchers as Kilicaslan and Coskun^[20] explained it may be due to khellin interfere with the citrate metabolism in inhibiting the Ca Ox crystallization. Charafi *et al.*^[23] found that *A. visnaga* seeds were efficient in inhibiting the crystallization of Ca Ox. Furthermore, Khan *et al.*^[11] reported that urinary citrates are crucial in reducing recurrences of Ca Ox stones.

Some of the medical therapies have been reported to ease urolithiasis and studies highlighted the active metabolites of α -antagonists and calcium channel blockers benefit to enhance stone passage.^[21] In our case, the patient is using amlodipine 5 mg once daily for management of hypertension since 5 years and was suffering with recurrent urolithiasis from 3 years. In the present case, the calcium channel blocker has not shown any positive effect in preventing renal calculi passage. In addition, the chemical composition of the *A. visnaga* fruit attributes to have furanochromones derivatives as khellin and visnagin which reported to have anti-inflammatory and analgesic activity.^[24,25]

In our case, although the patient has urolithiasis, but laboratory investigations showed elevated levels of lipid profile of triglycerides and after using *A. visnaga* for 9 days the patient has showed increase in HDL-cholesterol levels, but also lowering effect on triglycerides. In Harvenget and Desager,^[13] placebo-controlled study, oral administration

Table 1: Patient clinical and laboratory data before initiation of “*Ammi visnaga*”

Patient clinical finding	Observations	Referral values	Comments
Blood pressure (mean value) (mmHg)	130/90	120/80	Patient using following medications since 5 years: *Amlodipine 5 mg tablet and enalapril 5 mg tablet both as once daily
Glycated hemoglobin (HbA _{1c}) (%)	6.1	5.3-7.5	Nondiabetic
Lipid profile tests (mg/dL)			
Total cholesterol	220	150-250	Normal
HDL	32	35-135	Low
LDL	154	62-130	High
Triglycerides	208	30-150	Very high
Urine analysis			
Creatinine (g/d)	1.8	1-1.5	High
Blood urea nitrogen (g/d)	20	6-17	High
Microalbumin (mg/L)	18	<20	Normal

HDL=High-density lipoprotein; LDL=Low-density lipoprotein

of 50 mg of khellin (*A. visnaga* compound) four times daily for 4 weeks showed significant increased levels of HDL-cholesterol concentration without affecting total cholesterol or triglycerides concentration. This supports that the khellin compound in *A. visnaga* can also be of value to raise HDL-cholesterol.

CONCLUSIONS

The present case of *A. visnaga* seeds being local medicinal plant has shown the effect in treating urolithiasis with extended effect on raising HDL-cholesterol. These results may provide insights for *in vitro* studies for isolation of these biologically active compounds for potential in raising HDL-cholesterol. Whether or not the later effect can have clinical utility remains to be explored.

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