

Ammi Visnaga L.

Subjects: Plant Sciences

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Ammi visnaga L. (*Visnaga daucoides* Gaertn., Family Apiaceae), also known as Khella Baldi or toothpick weed, is an annual or biennial herb indigenous to the Mediterranean region of North Africa, Asia, and Europe. Nowadays, it is used in modern medicine to treat many ailments such as renal colic and coronary insufficiency, and is used as an antioxidant, antifungal, and antibacterial, with a larvicidal effect on mosquito larvae.

Keywords: *Ammi visnaga* L. ; γ -pyrones ; khellin ; visnagin ; flavonoids ; essential oil ; muscle-relaxant

1. Introduction

Since prehistoric times, plants have been employed in the treatment of many illnesses. Ancient humans used plants for the treatment of diseases by trial and error. They also noticed that animals avoid some plants while consuming others, and they followed their ways in dealing with nontoxic plants. Over time, people in various civilizations used plants in a planned and studied way. The Ancient Egyptians, Greeks, Romans, Chinese, and Indians had their own *Planta Medica*, which was a part of their *materia medica*. Many of the drugs mentioned in the Ebers Papyrus are still used today, including *Ammi visnaga* L., a plant that was known in ancient times as Pharaoh's bread. Also, during the golden age of the Arabs, well-known physicians such as Avicenna, Al-Razy, Al-Antaki, and others mentioned many plants in their books, in an attempt to preserve, improve, and transmit the knowledge of ancient people [1]. This transferred knowledge is a cornerstone for modern pharmacognosy and phytochemistry.

Ammi visnaga L. is a short annual or biennial herb indigenous to the Mediterranean region of North Africa, Asia, and Europe [2][3]. In Egypt, the plant is widely distributed in the Delta region, and surrounds the Nile River, particularly in Assiut and Minia governorates [4]. It is also widely cultivated by many people and companies aiming to use its extracts or active components in the pharmaceutical industry. It has been recently discovered and added to the flora of Croatia at altitudes of 380–460 meters above sea level [5]. The plant is also distributed throughout North America (North Carolina, Pennsylvania, Oregon, Alabama, California, Florida, and Texas), the Atlantic islands, Argentina, Mexico, and Chile. In Asia, the plant is found in Iraq, Iran, and other western and southern countries. The plant, especially its fruit, has a wide range of applications either in traditional or modern medicine.

2. Chemical Review

The chemical constituents of *A. visnaga* are well known and have been reported by many researchers in numerous studies throughout the years. Previous studies have reported on various chemical constituents in *A. visnaga*, including γ -pyrones, coumarins flavonoids, and essential oils. The quality and quantity of these secondary metabolites depend on the part of the plant analysed, as well as the growing conditions and the addition of any bioregulators [6].

3. Pharmacological Review

3.1. Kidney Diseases

Ammi visnaga L. has been used in folk medicine by the Middle Eastern population since ancient times. The fruit decoction was used for the treatment of renal colic by the ancient Egyptians [7], as a treatment of kidney inflammation in Iraq [8] and Palestine [9], and in the treatment of urolithiasis and prostatic pain in Algeria [10]. Its use had spread to the extent that it was regarded as the most recommended species for the treatment of urinary tract infections [11]. Several studies have focused on the diuretic activity of *A. visnaga*; it has been shown to be effective in the treatment of nephrolithiasis and uremia [12]. Its use in the treatment of kidney disorders is commonly coupled with khellin and visnagin, i.e., the major γ -pyrones of *A. visnaga*. They have been shown to protect the renal epithelial cell damage from oxalate and calcium oxalate monohydrate crystals, and to prevent the oxalate formation that is associated with hyperoxaluria by increasing the urinary pH and citrate concentration, along with a decrease of urinary oxalates [13][14][15][16][17]. The pleiotropic effects of khellin

and visnagin on urolithiasis have been intensively studied by many researchers [18][19][20]. Bhagavathula reported that a patient suffering from recurrent urethral stones showed complete recovery after treatment with *A.visnaga* fruit for ten days [21]. Recently, an experiment was conducted in an approach aiming to further explain the mode of action of *A. visnaga* in inhibiting the nucleation and preventing the crystallization of kidney stone [22].

3.2. 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 [23], in addition to being an antiasthmatic and a vasodilator, as well as an effective muscle relaxant agent without affecting blood pressure [3][24]. 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 Ca^{2+} entry through L-type Ca^{2+} channels, and at high concentrations, it may also interfere with other sites involved in vascular smooth muscle contraction [25][26][27][28][29][30]. 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 [31][32][33].

3.3. Antidiabetic Activities

The use of *A. visnaga* as an antidiabetic agent is considered famous in many cultures, such as those of Palestine, Morocco, and the Sefrou region [7][34][35][36]. An aqueous extract of *A. visnaga* was shown to possess a significant hypoglycemic effect when given to both normal and streptozotocin diabetic rats [37]. Additionally, a decoction prepared from the fruits of the *A.visnaga* had the ability to reduce blood glucose levels by 51% in normoglycemic rats, compared to an oral hypoglycaemic agent (tolbutamide) [38].

3.4. Treatment of Vitiligo

Since 1982, khellin has been shown to be effective in both oral and topical photochemotherapy for the treatment of vitiligo. A study done by Orecchia indicated that treatment with a gel formulation of khellin based upon a water/2-propanolpropylene glycol (khellin-WPG) system combined with ultraviolet A (UVA) significantly improved the clinical outcome of patients with vitiligo by facilitating the availability of the drug in the skin [39]. The treatment was proven to be safe for both short- and long-term treatments [40]. Later on, an open clinical trial was conducted to investigate the efficacy and safety of treatment with khellin encapsulated in L-phenylalanine stabilized phosphatidylcholine liposomes in combination with ultraviolet A/ultraviolet B (UVA/UVB) light therapy (KPLUV) in 74 patients suffering from vitiligo. The treatment was shown to be highly effective, and did not cause any side effects [41]. Furthermore, the melanin biosynthesis inhibitory effects of khellin were investigated using a B16 melanoma cell line, and showed a potent inhibitory activity compared to arbutin, which was used as a positive control in the experiment [42]. Moreover, the additional value of combining blister roof transplantation (BRT) with khellin in liposomes and ultraviolet light (KLUV) in the treatment of recalcitrant vitiligo patches has been investigated; the results showed that almost 75% of the treated patients were extremely satisfied with the result [43].

3.5. Anti-inflammatory Effect

The anti-inflammatory effects of *A. visnaga* have been investigated, and it was shown that, depending on its visnagin content, it caused a decrease in mRNA expression and the release of TNF- α , IL-1 β , and IFN γ . In addition, visnagin reduced LPS-induced IL-6 and MCP-1 mRNA level, thus suggesting that the anti-inflammatory effect of visnagin may be due to the inhibition of transcription factors such as AP-1 and NF- κ B [44]. Moreover, Kwon et al. suggested that visnagin had a neuroprotective effect in terms of suppressing kainic acid-induced pathogenesis in the brain, and that these neuroprotective effects are associated with its anti-inflammatory effects [45].

3.6. Antimicrobial Effect

Several studies have reported on the antimicrobial effects of the different extracts of *A.visnaga*. The alkaloidal and sesquiterpene lactone fractions have shown activity against *Candida* species [46], while the ethanolic extracts of fruits showed a significant inhibition of the growth of *Mycobacterium tuberculosis* [47]. In addition, the fruit's aqueous extract inhibited the growth and aflatoxin production of *Aspergillus flavus* in a dose-dependent manner [48]. Additionally, remarkable activity was revealed for the aqueous and hydroalcoholic stem extracts of *A. visnaga* against *Streptococcus mutans*, *Streptococcus salivarius*, and *Streptococcus sanguis* [49]. In an approach aimed to evaluate the possibility of using *A. visnaga* extracts in pharmaceutical and food preservation systems, a study showed that the fruit ethanolic extract

was the most active extract against the Gram-positive bacteria *Enterococcus faecalis*. Moreover, the same extract revealed antimicrobial activity against the Gram-negative bacteria *Escherichia coli* and *Klebsiella pneumoniae* [50]. Several studies have focused on the antimicrobial effects of the essential oils of the *A. visnaga* L., showing their effectiveness against various microorganisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* strains [51][52][53][54]; however, they showed weak antifungal activities [55]. Razzaghi-Abyaneh identified components that strongly inhibited aflatoxin formation in toxigenic fungi, e.g., khellin, xanthotoxin, and bergapten [56].

3.7. Cytotoxic Activity

In recent years, focus has been directed to the discovery of new cytotoxic agents, and attempts have been made to investigate the cytotoxic activities of many medicinal plants, including *A. visnaga*. In 2004, khellin was isolated, and its cytotoxicity was evaluated against four human tumour cell lines: HT-29 (colorectal cancer), MCF-7 (breast cancer), HEP-2 (larynx cancer), and MKN-45 (gastric cancer). However, the results were not promising, and the substance did not show significant cytotoxic activity at the tested concentrations against the four cell lines [57]. On the other hand, khellin showed mild to moderate activity when tested against the hepatocarcinoma cell line (HepG2) [58]. An ethanolic extract of *A. visnaga* also showed inhibitory effects on both Hela (cervical cancer) and MCF7 cell lines [59]. The cytotoxic activity of isolated khellin and visnagin against four human cell lines, Hela (cervical carcinoma), Hep-G2 (liver carcinoma), HCT 116 (colon carcinoma), and MCF7 (breast carcinoma), was further investigated; the results revealed good cytotoxic activity of both γ -pyrones against the Hep-G2 cell line [60].

3.8. Antioxidant Activity

Very few studies have examined the antioxidant properties of *A. visnaga*. The free radical scavenging activity of the butanol extracts of the aerial parts of *A. visnaga* has been investigated, showing equivalent antioxidant activity, i.e., an IC_{50} equals to $8.77 \pm 0.2 \mu\text{g/mL}$, to the standard antioxidant rutin ($IC_{50} = 3.01 \pm 0.2 \mu\text{g/mL}$) [61]. Another study examined the antioxidant activity of essential oils isolated from the umbels of *A. visnaga*; however, the results showed only very weak activity [62].

3.9. Hair Loss

The topical application of *A. visnaga* for hair loss has been studied. A lotion for hair scalp composed of visnadin and other constituents led to an increase in arterial and arteriolar sphygmoc activity in the subpapillary plexus, leading to an improvement in local microcirculatory flow [63].

3.10. Antimutagenic Effect

In a study aiming to evaluate the antimutagenicity spectrum of *A. visnaga*, khellin showed inhibition to mutagenicity of promutagens benzo[a]pyrene, 2-aminofluorene, and 2-aminoanthracene in *Salmonella typhimurium* T98, while visnagin showed higher toxic activity. Meanwhile, the total extract from *A. visnaga* fruit showed higher inhibition potency than khellin alone against 2-aminoanthracene, 1-nitropyrene, and daunomycin. This was attributed to the presence of additional inhibitors such as coumarins, or to the synergistic effects with the accompanying compounds [64].

3.11. Cardiovascular Activity

It is well known that *A. visnaga* extract or its active principals exert a relaxant effect on smooth muscles, even those of coronary arteries. It was found that intravenous injection of visnagin lowered the blood pressure with no change in the heart rate. It was also found that samidin and khellol glycoside induced a positive inotropic effect on the heart, while visnadin in a concentration $60 \mu\text{g/mL}$ increased coronary blood flow in isolated guinea pig heart. On the other hand, it was found that khellin, samidin, dihydrosamidin, and visnadin effectively normalized the electrocardiogram of ischemic myocardia in a dog. It seems that khella extracts or active principals improve the blood supply to coronary smooth muscles, where it dilates the coronary arteries without affecting the heart rate. The administration of khellin by oral or intramuscular injection gave good results in treating angina pectoris, and is favored in case of coronary thrombosis. As a result, khellin in a concentration of 50 mg/mL can help prevent angina pectoris with no side effects, although it is weaker than glyceryl trinitrate [26][31][32][33].

3.12. Immunostimulatory Activity

A. visnaga total and protein extracts were found to have immunostimulatory effects. Extracts were tested using an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on splenocytes with or without stimulation by concanavalin-A (Con-A), a mitogenic agent used as a positive control. This could explain the traditional use of such a plant [65].

3.13. Other Reported Activities on Human

Gouda obtained results that suggested that *A. visnaga*, among other plants, might have analgesic activity [66]. Also, Bhagavathula et al. suggested that *A. visnaga* fruits have a significant effect on increasing HDL-cholesterol levels, highlighting the hypothesis that it could be used in treating hypertriglyceridemia [21].

3.14. Larvicidal and Insecticidal Activities

Many natural products isolated from plants could be used as alternative treatments with larvicidal and insecticidal activities. For this purpose, the larvicidal and insecticidal properties of *A. visnaga* were studied, and the toxicity of khellin was investigated against nymphs *Oncopeltus fasciatus* (Hemiptera) and the larvae of *Aedes aegypti* (Diptera), where it showed great activity [67]. Studying the acaricidal and ovicidal activity of khellin and visnagin against *Tetranychus urticae* showed that both khellin and visnagin were highly promising, and could be used for the development of new botanical acaricides from *A. visnaga* [68], as well as that they were both phytotoxic to model species lettuce (*Lactuca sativa*) and duckweed (*Lemna paucicostata*) [69]. The fruit extract was found to possess an inhibitory action on the lipid content in haemolymph of nymphs and adults [70], while the *n*-butanolic extract of *A. visnaga* was also shown to prevent the activity of Glutamic oxaloacetic transaminase (GOT) and Glutamic pyruvic transaminase (GPT) in haemolymph and fat bodies of last instar nymphs and newly-emerged adult females of the dangerous desert locust, *Schistocerca gregaria* [71].

3.15. Herbicidal Activity

A study done in Argentina found that the dichloromethane extract of *A. visnaga* had a significant herbicidal effect. Phytotoxicity fractionation was done, and the fraction that contained khellin and visnagin was found to be responsible for its significant herbicidal activity [69].

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