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Review Article

Ammi visnaga (L.) Lam.: An overview of phytochemistry and biological functionalities

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ABSTRACT

Ammi visnaga (L.) Lam., (Apiaceae), known as" Bachnikha" or "Khella" in Morocco, is one of the oldest and most important medicinal herbs native to the Mediterranean region of Asia, Europe, and North Africa. Several studies have reported its importance as a diuretic, antiasthmatic, antipsoriasis, antioxidant, antifungal, antibacterial, vasodilator, and smooth muscle relaxant. These promising and valuable pharmacological effects result from a variety of important natural compounds constituting groups in the plant structure, *e.g.*, γ-pyrones, coumarins, chromones, polyphenols, alkaloids, reducing compounds, cardiac glycosides, catechols, sterols, terpenes, quinones, mucilage, essential oil, C-heterosides, and O-heterosides. Within this framework, the current review was prepared for the first time to cover the phytochemical constituents and various pharmacological and therapeutic impacts of *A. visnaga* (L.) Lam., aiming to enrich Moroccan traditional knowledge.

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1. Introduction

Traditional medication has been utilized for a very long time for well-being improvement as well as the treatment and prevention of physical and mental diseases all through the world, including different regions of China, India, South America, and Africa. Even today, herbs are considered the primary source of active components with related-health properties which are used by 85% of the world population (Fitzgerald et al., 2020).

Among the medicinal plants used in the Mediterranean basin, different species of some of the most important plant families involving Lamiaceae, Asteraceae, and Apiaceae represent the most widespread and the highest frequency (María de Cortes, 2016). Herbal medicine has a positive effect on human health in treating many conditions and diseases such as hypertension, toothache, arthritis, rheumatism, headache (Boy et al., 2018), gastrointestinal disorders, various inflammatory diseases as well as bacterial and fungal infections (Algieri et al., 2016; Ez zoubi et al., 2020). Evidence for the effectiveness of herbal drugs has been obtained using extracts from aromatic and medicinal plants including essential oils, alcoholic, hydrolyzed and other solvent-based extracts along with fruit juices and extracts obtained from resins. The plant constituents represent a potential source of active ingredients that could be used for drug discovery (Ambrosio et al., 2023; Barazorda-Ccahuana et al., 2023; Garza-Cadena et al., 2023).

Ammi visnaga (L.) Lam. (syn. *Daucus visnaga* L., *Visnaga daucoides* Gaertn.) known in Moroccan local languages as "*Bachnikha*" is one of the oldest and most important medicinal herbs native to the Mediterranean region of Asia, Europe, and North Africa (Khalil et al., 2020). It belongs to the Apiaceae family and contains many bioactive compounds with considerable biological

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activities that explain its use as a medicinal plant (Mohammadhosseini et al., 2019; Ogunlakin and Sonibare, 2022; Kazeminia et al., 2022). Robust evidences have reported the importance of *A. visnaga* (L.) Lam. as a diuretic, anti-asthmatic, anti-psoriasis, vasodilator, and potent smooth muscle relaxant (Koriem et al., 2019). In addition, it is used against the crystallization of calcium oxalate (CaOx) in the kidneys and for its ability to mitigate severe pain caused by kidney stones (Kachkoul et al., 2018). *Khella* has been traditionally used to alleviate stomach cramps, liver disorders, dysmenorrhea, and gall bladder inflammation (Al-Snafi and Al-Snafi, 2013). This herbal species is also used to treat panel respiratory problems, including bronchitis, cough and whooping cough, as well as cardiovascular illnesses like heart failure, hypertension, cardiac arrhythmias, hypercholesterolemia, and atherosclerosis (Amin et al., 2015). It has been found that *A. visnaga* (L.) Lam., is effective in treating vitiligo, and problems caused by poisonous insect bites, whereas its constituents are used in several conventional medications, including amiodarone, nifedipine, and cromolyn (Bhagavathula et al., 2015). In a recent review, Khalil et al. (2020) summarized the medicinal potentialities of *A. visnaga* (L.) Lam. While, it does not yet reveal all its capabilities which requires a literature update.

Within this framework, the current review was prepared for the first time to highlight the phytochemical composition and various pharmacological and therapeutic effects of *A. visnaga* (L.) Lam., in addition to enrich the Moroccan traditional knowledge on the use and health benefits of *A. visnaga* (L.) Lam.

2. Methodology

All papers used in the preparation of the present review were gathered via different scientific engines, such as Google scholar, Science Direct, MDPI, Web of Science, and PubMed using the following keywords, *Ammi visnaga* (L.) Lam., phytochemistry, biological functionalities, beneficial effects of *A. visnaga* (L.) Lam. The articles were selected on the basis of their scientific soundness and significance. Studies exploring the beneficial properties of *A. visnaga* were integrated and the article search was restricted to studies published in the English language. This review was prepared during the winter 2022.

3. General description of *A. visnaga* (L) Lam.

3.1. Habitat

A. visnaga (L.) Lam. originates from a temperate Mediterranean climate and is widely distributed in North Africa, Europe, North America, the Atlantic Islands, the Eastern Mediterranean region and South-Western Asia (Ahmed et al., 2021).

3.2. Common names

A. visnaga (L.) Lam. is a flowering plant that is traditionally known by numerous names depending on the different areas of cultivation. It is well-known as "*Bisnaga*", "*Toothpick weed*", and "*Khella*" (Hashim et al., 2014) as well as "*Ammi*", "*Tooth-pick Ammi*", "*False Queen Anne's Lace*", "*Honey plant*", "*Tooth-pick fruit*", "*Green Mist*", "*Spanish carrot*", and "*Lace flower*" (Shah et al., 2018). Other common names for *A. visnaga* in Arabic nations are "*Khella baladi*", "*Khellah*", "*Khellakl*", "*Chellah*", "*Kella*", "*Gazar sheitani*", "*Kammon habashi*", "*Bizer*", "*Al-Khilla*", "*Kulla*", "*Swak*", and "*Al-Nabi*" (Shah et al., 2018; Khalil et al., 2020), while "*Bechnikha*" is the most used name in Morocco. In Turkey, it is known as "*Kilir*", "*Hiltan* and *disotu*", while in England it is known as "*Pick tooth*" and "*Toothpick*"; In France, it is called "*Herbe aux cure-dents*", while in Germany it is named "*Zahnstocherkraut*". The name "*Tabellaout*" is a Berber word for this species (Khalil et al., 2020).

3.3. Plant characteristics and morphology

A. visnaga (L.) Lam. is an annual or biennial plant that grows upright from a taproot to a height of approximately 1.5 m (Fig. 1). The root is fattened in the same way as in the carrot. The leaves are triangular, 5-20 cm long, dissected, and pinnately divided, with terminal divisions ranging from linear to filiform. The stems are firm, upright, and densely branched. The inflorescence is a compound umbel with white flowers, very swollen at the base; it eventually becomes woody and is used as a *toothpick*. The flowers are tetracyclic pentamerous with radial symmetry, an inferior ovary, and five stamens formed of two connected carpels. The fruit has a compressed oval-shaped structure with two mericarps and a length of approximately 3 mm, similar to caraway (Amin et al., 2015; Shah et al., 2018).

4. Phytochemistry

A. visnaga (L.) Lam. contains several groups of biochemical compounds pharmacologically active, including γ-pyrones, coumarins, chromones, polyphenols, alkaloids, cardiac glycosides (Zaher et al., 2019), catechols, sterols, terpenes, quinones, and mucilage (Table 1). The chemical density of *A. visnaga* (L.) Lam. is highly related to the stage of plant growth and the part analyzed (Feirouz and Salima, 2014), along with the growing conditions and effects of some external factors, such as the use of biostimulants (Sellami et al., 2013; Talaat et al., 2014; Gad et al., 2022).

4.1. γ-Pyrones (Furanochromone derivatives)

A delve into the phytochemistry of *A. visnaga* (L.) Lam. revealed that khellin (28.3%) and visnagin (25.6%) were the most abundant bioactive compounds belonging to the γ-pyrones family (Furanochromone derivatives) (Fig. 2) (Alaatabi et al., 2020). Other notable γ-pyrones include khellinin, cimifugin, khellol, khellinol, visamminol, visnaginol, ammiol, pimolin, and prim-*O*-glucosylcimifugin, as well as cimifugin 3-methyl-butanoate and cimifugin 2-methyl-butanoate (Fig. 2) (Sellami et al., 2013).

Table 1
Phytochemical contents of different parts of *A. visnaga* L.

Country	Part of plant	Extraction method	Identification method	Bioactive compounds	Reference
γ-Pyrones (Furanochromones)					
Iraq	Whole plant	Soxhlet method	GC-MS	Khellin (28.4%) and visnagin (25.6%)	(Alaatabi et al., 2020)
Tunisia	Umbels	Soxhlet method (Al-zaidi and Khorsheed, 2021).	HPLC-ESI/IT/MS	Khellin, cimifugin, khellol, khellinol, visamminol, visnaginol, pimolin, prim-O-glucosylcimifugin, cimifugin 3-methyl-butanoate, and cimifugin 2-methyl-butanoat	(Sellami et al., 2013)
Morocco	Umbels	Maceration and soxhlet methods	HPLC/UV-ESI-MS	Ammiol, ammiol glucoside	(El Karkouri et al., 2020)
Pyranocoumarins					
Austria	Fruits	Sonication	Acquity UPC2 SFC	Visnadin (0.14%), samidin (0.16%), and dihydrosamidin (0.08%)	(Winderl et al., 2016)
Egypt	Aerial parts	Percolation	Chromatography/NMR, UV, MS and IR spectra	*cis*-khellactone-3′-β-glucopyranoside	(Ashour et al., 2013)
	Fruits	Soxhlet extraction	HPLC-NMR	Khellol glucoside	(Badr et al., 2015)
Tunisia	Umbels	Soxhlet extraction	HPLC-ESI/IT/MS	Dimidin	(Sellami et al., 2013)
Furanocoumarins					
Iraq	Whole plant	Soxhlet extraction	GC-MS	Edulisin III and (*Z*)-cnidimine	(Alaatabi et al., 2020)
Tunisia	Umbels	Soxhlet extraction	HPLC-ESI/IT/MS	Isoimpinellin, heraclenin, and biakangelicol	(Sellami et al., 2013)
Chromones					
Tunisia	Umbels	Soxhlet extraction	HPLC-ESI/IT/MS	Noreugenin 7-*O*-β-D-glucoside, maritimin, and noreugenin	(Sellami et al., 2013)
Egypt	Aerial parts	Percolation	Chromatography/NMR, UV, MS and IR spectra	Norkhellol	(Ashour et al., 2013)
Phenolic compounds					
Iraq	Seeds	Soxhlet extraction	HPLC (SYKAM)	Quercetin, kaempferol, rutin, apigenin, caffeic acid, and ferulic acid	(Al-zaidi and Khorsheed, 2021)
Morocco	Umbels	Maceration/ soxhlet extraction	HPLC/UV-ESI-MS	Rhamnetin, rhamnetin glucoside, kaempferol glucoside, rhamnazine glucoside, kaempferol rhamnoside, rhamnetin rutinoside, kaempferol rutinoside, rhamnazine rutinoside, chrysoeriol, chrysoeriol, apiine, diosmetine rutinoside, biochanin A, and biochanin a 7-*O*-ß-D-glucoside	(El Karkouri et al., 2020)
Algeria	Aerial parts	Maceration	Chromatography-NMR/ UV/MS	Isorhamnetin, isorhamnetin-3-*O*-glucoside, isorhamnetin-7-*O*-glucoside, quercetin-7,3,3′-*O*-triglucoside, and isorhamnetin-3-*O*-rutinoside	(Bencheraiet et al., 2011)
Czech republic	Seeds	Fex 50 (IKA-Werke) extractor	HPLC-MS/ELISA	Formononetin, coumestrol, genistein, daidzein, 6,7,40-trihydroxyisoflavone, prunetin, daidzin, isofomononetin, sissotrin, and genistin	(Abdulmanea et al., 2012)

4.2. Coumarins

Coumarins constitute a remarkable group of *A. visnaga* (L.) Lam. chemical ingredients (Fig. 3) that are further classified into furanocoumarins and pyranocoumarins. Furanocoumarins are represented mainly by edulisin III (5.6%), and (*Z*)-cnidimine (5.2%) (Alaatabi et al., 2020), followed by isoimpinellin, geraclenin and viakangelicol (Sellami et al., 2013). Visnadin (0.1%), samidin (0.1%), dihydrosamidin (0.08%), dimidin (Sellami et al., 2013), and khellol glucoside are members of the pyranocoumarins (Badr et al., 2015)

Fig. 1. The photograph of an *Ammi visnaga* L. sample

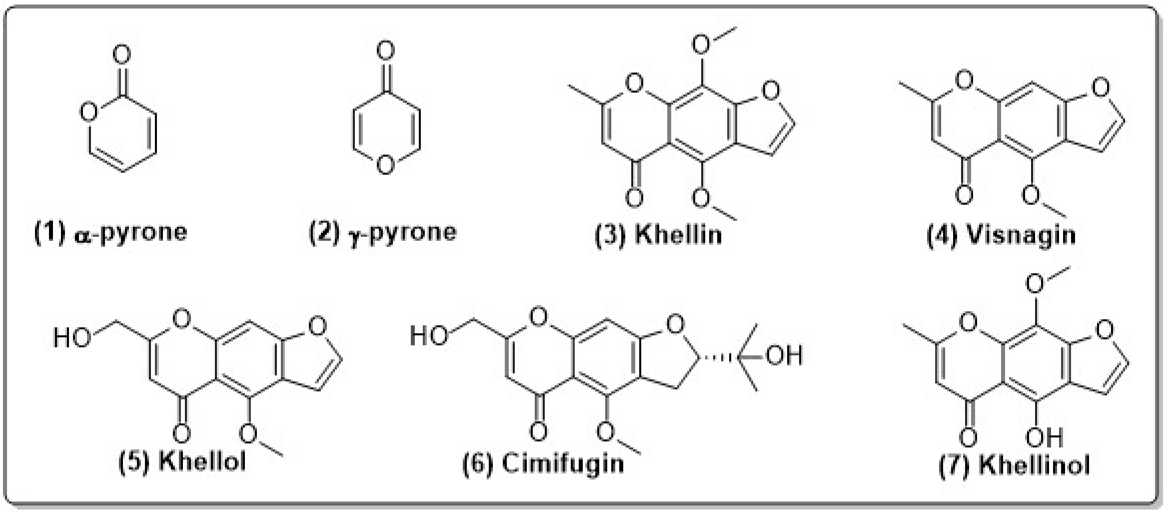

Fig. 2. Structures of the most abundant γ-pyrones found in *Ammi visnaga* (L.) Lam.

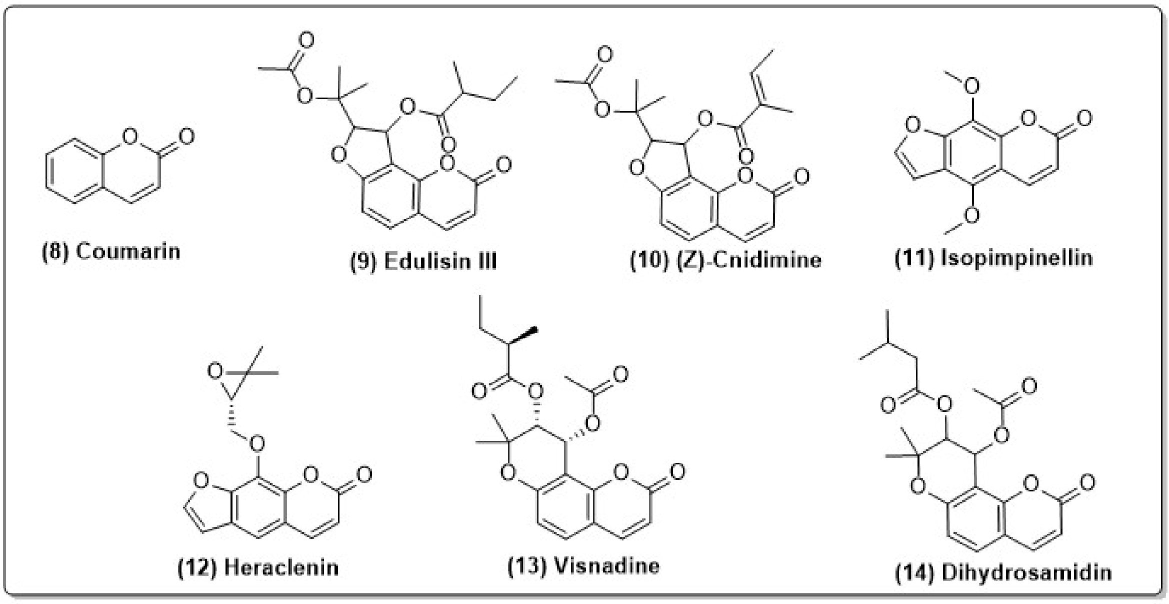

Fig. 3. Structure of coumarins detected in *A. visnaga* (L.) Lam.

4.3. Chromones

A. visnaga (L.) Lam. contains a broad spectrum of bioactive compounds such as chromones (Fig. 4), which are represented by noreugenin 7-*O*-β-D-glucoside, maritimin, and noreugenin, as previously described by (Sellami et al., 2013). Chromones have been shown to be useful in treating neurological and mental diseases as well as allergies, cancer, infections, inflammation, and oxidative damage in a range of *in vitro*, *in vivo*, and clinical studies (Kuroda et al., 2009; Nam et al., 2010; Silva et al., 2016; Hiruy et al., 2021).

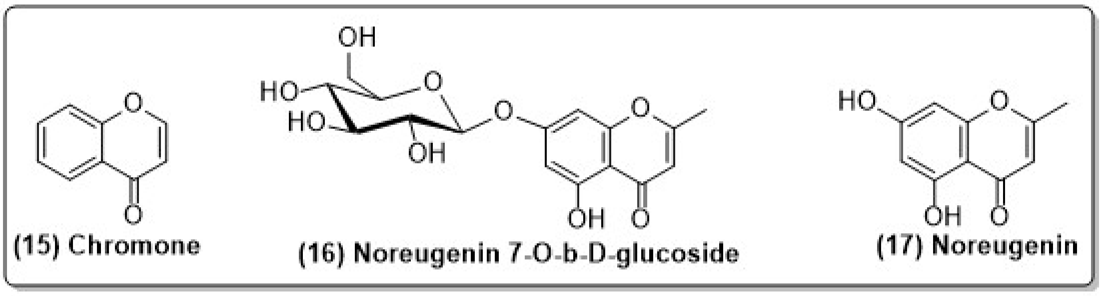

Fig. 4. Chromones found and characterized in *A. visnaga* (L.) Lam.

4.4. Phenolic compounds

Phenolic compounds constitute an important group of biologically active molecules identified in *A. visnaga* (L.) Lam. They mostly belong to the flavonoid class, which is further subdivided into flavones, flavonols, and isoflavones (Fig. 5). The bulk of the flavonoids found in *A. visnaga* (L.) Lam. are flavonols, including quercetin, kaempferol (Al-zaidi and Khorsheed, 2021), rhamnazine, rhamnetin (El Karkouri et al., 2020), and isorhamnetin (Bencheraiet et al., 2011), as well as their conjugated forms either with glucose or rutinose, such as rhamnetin glucoside, kaempferol glucoside, rhamnazine glucoside, and kampferol rhamnoside (Fig. 4) (El Karkouri et al., 2020). These compounds are among the most frequently conjugated with glucose,in addition to isorhamnetin-3-*O*-glucoside, isorhamnetin-7-*O*-glucoside, and quercetin-7,3,3′-*O*-triglucoside (Bencheraiet et al., 2011). Compounds conjugated with rutinose comprise rhamnetin rutinoside, kampferol rutinoside, rhamnazine rutinoside (El Karkouri et al., 2020), and isorhamnetin-3-*O*-rutinoside (Bencheraiet et al., 2011). Flavones are another important class of flavonoids, which are identified in *A. visnaga* (L.) Lam., including chrysoeriol, chrysoeriol glucoside, apiine, and diosmetine rutinoside, (El Karkouri et al., 2020) as well as rutin, and apigenin (Al-zaidi and Khorsheed, 2021). *A. visnaga* (L.) Lam., is also a rich source of isoflavones represented by formononetin, coumestrol, genistein, daidzein, 6,7,40-trihydroxyisoflavone, prunetin, isofomononetin, sissotrin, genistin, daidzin (Abdulmanea et al., 2012), biochanin A, and biochanin A 7-*O*-β-D-glucoside (El Karkouri et al., 2020). It is also worth noting the presence of simple and catechic tannins, other phenolic components that are widely present in the aqueous extract of the umbels and

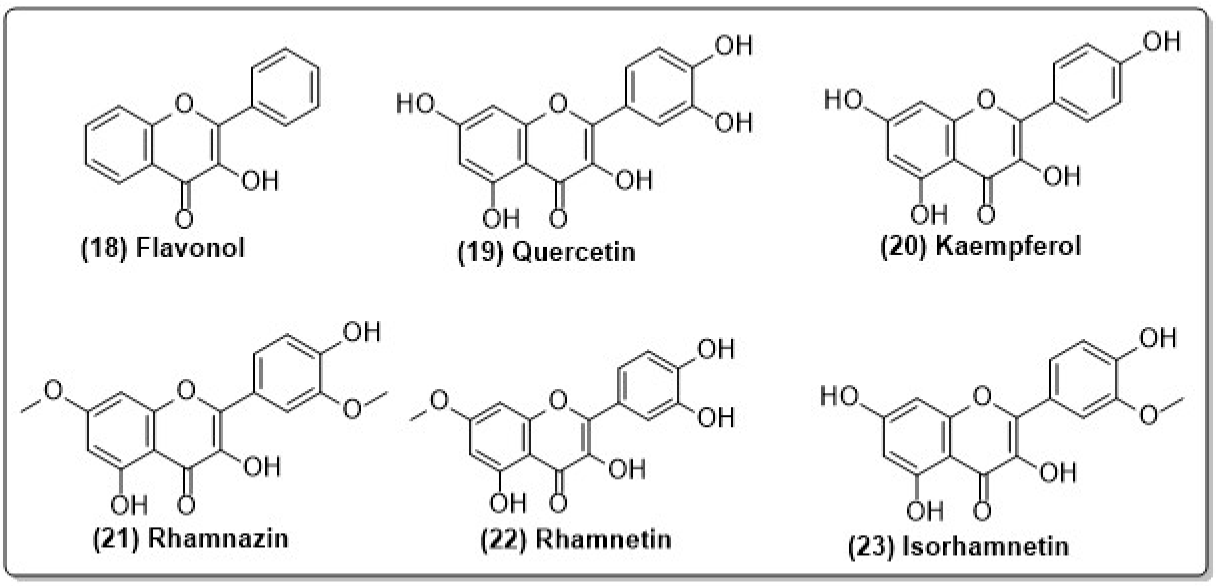

Fig. 5. Structures of flavonols found in *A. visnaga* (L.) Lam.

seeds of *A. visnaga* (L.) Lam. (Soro et al., 2015; Zaher et al., 2019). Furthermore, the presence of phenolic acids like caffeic and ferulic acid has been reported.

4.5. Essential oil composition

A. visnaga (L.) Lam. is also a source of essential oil (EO) (Table 2). The umbel hydrodistillation yielded 0.13% from material sampled in Morocco (Soro et al., 2015), whereas for plants collected in Algeria, the yield of essential oil in the aerial parts was 0.4% (Feirouz and Salima, 2014), however, the populations from Tunisia exhibited a content of 0.2% (v/w) in the fruits (Khadhri et al., 2011). The variability of EO yield as well as the chemical composition are dependent on the geographic origin, vegetative phase of the plant, plant part, and environmental and growth conditions (Gad et al., 2022). These factors may cause the activation or inactivation of certain enzyme groups, resulting in the up- or downregulation of specific biosynthetic pathways (Khalil et al., 2020). The delve into phytochemistry of Moroccan samples revealed 39 compounds with a predominance of abietadiene, linalool, 2-methylbutyrate isoamyle, abietol, isovalerate isopentyle, lavandulyl isovalerate, butyrate amyle, manool, germacrene D, and propanoate neryle with a proportion of 91.7% (Soro et al., 2015). In populations from Algeria, the main components among the 34 identified, were 2-methylbutyl-2-methylbutyrate, linalool, limonene, and isoamyl isovalerate (Keddad et al., 2016). In Egyptian populations, several different components were identified, such as 2,2-dimethylbutanoic acid, isobutyl isobutyrate, α-isophorone, fenchyl acetate, linalool, thymol, and croweacin, which contribute to the total EO composition (Talaat et al., 2014). According to Khadhri et al. (2011), 41 components were identified in *A. visnaga* (L.) Lam. flowers collected in Tunisia, where isoamyl methyl-2butyrate, linalool and isobutyrate amyl were identified as the main EO components.
Fatty acids were found in *A. visnaga* (L.) Lam. seed oils in both saturated and unsaturated forms. CG/MS analysis allowed the identification of 15 fatty acids, including oleic (13.3%), linoleic (11.3%), palmitic (7.8%), and stearic (1.8%) acids in high concentrations (Ullah, 2012). Other fatty acids, such as lauric, myristic, pentadecanoic, palmitolic, margaric, heptadecanoic, arachidic, heneicosanoic, behenic, tricosanoic (Ullah, 2012), and tetracosanoic acid (Ashour et al., 2013), were less than 1%.

4.6. Miscellaneous

Other classes of chemical compounds were found in various parts of *A. visnaga* (L.) Lam., including proteins (Amin et al., 2015), alkaloids, sterols, triterpenes, cardiac glycosides, C-heterosides, and O-heterosides, in addition to a small proportion of mucilage (Table 3) (Zaher et al., 2019; El Karkouri et al., 2020). Finally, the lack of tannins, saponins, narcotics, carotenoids, anthocyanins and leucoanthocyanin, anthracene derivatives, genin C-heterosides, free anthraquinones, and combined anthraquinones is noteworthy (Zaher et al., 2019; El Karkouri et al., 2020).

5. Ethnobotanical reports

Herbal medicine has a positive effect on human health in treating many conditions and diseases. *A. visnaga* (L.) Lam. is one of the oldest and most important medicinal herbs (Khalil et al., 2020) containing a large number of bioactive compounds with considerable biological activities that explain its use as a medicinal plant. Several studies have reported the importance of *A. visnaga* L. (Table 4).

6. Biological, pharmacological and medical activities of *A. visnaga* (L.) Lam.

6.1. Antimicrobial activity

Microbial strains gained resistance, which permits their persistence in different environments and could be more pathogenic. Natural products are a promising source of natural agents with considerable antimicrobial properties. Several studies have investigated the antimicrobial potential of different extracts of *A. visnaga* (L.) Lam. against bacterial and fungal strains (Amin et al., 2015).
The in vitro antibacterial and antifungal activity of essential oils of *A. visnaga* (L.) Lam. at doses of 30, 50, and 70 µL has being investigated, showing the best antibacterial activity against *Escherichia coli, Bacillus subtilus*, *Salmonella* spp., *Pseudomonas aeruginosa* and *Klebsiella pneumoniea*, with a high inhibition zone diameter (32, 31, 30 and 20 mm, respectively) (Feirouz and Salima, 2014) when compared with Ampicillin at a dose of 10 µg/mL (Khalfallah et al., 2011). However, antifungal activity was not expressed much (Feirouz and Salima, 2014).
It has been reported that the methanol extract of *A. visnaga* (L.) Lam. exhibited remarkable antibacterial effects against Gram-positive and Gram-negative bacteria (Amin et al., 2015). The authors found that the minimum inhibitory concentrations (MIC) for *S. aureus, E. coli,* and *P. aeruginosa* were 0.3, 2.7, and 5.5 mg/mL, respectively. Similarly, the ethanol seed extract at doses varying between 12.5 and 50 mg/mL was effective against a range of microorganisms causing gastrointestinal and respiratory infections, including *Escherichia coli, Salmonella enterica (S. typhi), Proteus vulgaris, Staphylococcus aureus, Klebsiella pneumoniae, Shigella dysentery* (Moalim et al., 2018), and *Campylobacter spp* (Mahmood, 2019).
Within this framework, *A. visnaga* (L.) Lam. contains numerous biologically active compounds that can be useful in overcoming the existing problems relating to drugresistance. Imane et al. reported that the methanol extract at a dose of 10 mg/mL possessed high antimicrobial activity against five strains of *Bacillus cereus*, a crucial pathogenic bacteria causing food spoilage (poisoning), with an inhibition zone (IZ) varying in the range of 12 to 21 mm. In addition, at a concentration of 10 mg/mL, the extract was more effective in swarming motility and biofilm formation. Therefore, it is possible to use *A. visnaga* (L.) Lam. extracts in the food industry as a natural preservative (Imane et al., 2016). The aqueous extract *A. visnaga* (L.)

Table 2
Essential oil composition of different parts of *A. visnaga* L.

Country	Part of plant	Extraction method	Identification method	Bioactive compounds	references
Iraq	Seeds	Hydrodistillation (HD)-Clevenger	GLC	α-Pinene (20.5%), linalool (15.8%), sabinene (14.9%), limonene (19.8%), terpene (7.9%), and myrcene (5.9%)	(Al-zaidi and Khorsheed, 2021)
Algeria	Umbels		GC-MS and GC-FID	2-Methylbutyl-2-methylbutyrate (16.7-27.4%), linalool (24.8-41.2%), limonene (6.8-9.9%), isoamylisovalerate (7.3-7.4%), α-terpinene (1-2%), *p*-cymene (0.3-0.6%), *trans*-linalool oxide (0.9-1.1%), 2,4(10)-thujadiene (0.2%), 1,8-cineole (0.1%), α-terpineol (0.2%), hotrienol (0.2%), β-bourbonene (0.4%), and citronellyl valerate (0.8%)	(Keddad et al., 2016)
	Fresh aerial parts		GC-MS	Isobutyl isobutyrate (14%), linalool (12.1%), 2,2-dimethylbutanoic acid (30.1%), thymol (6%), bornyl acetate (7.3%), croweacin (12.2%), α-isophorone (3.8%), 3-methylpentenol (2.5%), α-thujene (1.5%), methylbutyl 2-methylbutanoate (1.2%), 2-nonyne (1.2%), hexenyl isobutanoate (1.6%), geranyl acetate (1.2%), and lavandulyl acetate (1.2%)	(Khalfallah et al., 2011)
	Fresh aerial parts (fructification period)			2-Methylbutyl, 2-methyl butanouate (10.2-28.5%), isoamyl isobutyrate (1.8-6.7%), and iso-valerate acid, 2-methyl butyl ester (1.3-3.4%)	(Feirouz and Salima, 2014a)
	Fresh aerial parts (full flowering period)			β-Linalool (2.8-3.4%), spiro (2.5) octane-3,3-dimethyl -2-(1-buten-3-on-1-yl) (4.9-13.6%)	
	Fresh aerial parts (full flowering period)			Verticiol (5.9-9.8%), floriffone(1.71%), linalool isobutyrate (2.2%), and butanoic acid decyl ester (5.8%)	
Tunisia	Fruits			Linalool (23.6-32%), isoamyl 2-methyl butyrate (24.2-36%), isopentyl isovalerate (10-14.8%), (*Z*)-farnestyl acetate (2.5-4.2%), α-bisabolol (0.2-0.5%), spathulenol (0.3-0.6%), (*E*)-nerolidol (0.2-3%), β-sesquiphellandrene (0.3-1.6%), lavandulyl 2-methyl-butyrate (0.8-2.2%), lavandulyl isovalerate (0.4-3.4%), linalyl valerate (1-1.5%), germancrene D (0.8-1.6%), α-humulene (0.1-0.5%), trans-bergamoptene (0.2%), lavandyl isobutyrate (0.3-2.9%), dodecanal (1.8%), β-elemene (0.1%), β-bourbonene (1.4%), α-terpinol (0.3%), ipsedienol (0.5%), amyl isovalerate (1%), γ-terpinene (0.5%), 2-methyl butyl-2-methyl butyrate (0.6%), α-terpinene (0.2%), isobutyl isovalerate (0.9%), pentyl-proanoate (1.5%), myrcene (1.2%), butyl isobutyrate (3.0%), β-pinene (0.9%), α-pinene (1.0%), sabinene (0.7%), and α-thujene (0.3%).	(Khadhri et al., 2011)
	Roots			Nonane (4.5%), heptanal (4.8%), α-pinene (10.7%), octanal ((9.6%), limonene (14%), linalool (6%), (*E*)-non-2-enal (7.1%), spathulenol (1.1%), and *endo*-frenchyl acetate (26.9%)	(Sellami et al., 2011)

Table 2 Continued

Country	Part of plant	Extraction method	Identification method	Bioactive compounds	references
Tunisia	Stems	Hydrodistillation (HD)-Clevenger	GC-MS	Nonane (37.6%), oct-1-en-3-ol (1.9%), 2-pentyl furan (2.4%), phenylacetaldhehyde (2.7%), γ-terpinene (1.5%), dec-4-yne (1.7%), isoamyl 2-methylbutanoate (34.2%), nonanal (5.9%), isopentyl 3-meethylbutanoate (10.2%), lavandulyl 2-methylbutanoate (2.9%), citronellol 2-methylpropanoare (1.9%), and (*Z*,*E*)-farnesyl acetate(6.5%)	(Sellami et al., 2011)
	Leaves			Nonane (46%), 2-pentyl furan (2.4%), (*E*)-β-farnesene (1.3%), germacrene D (5.2%), (*E*)-β-ionone (1.8%), 2,6,10-trimethylundeca-5,9-dienal (7.6%), bicyclogermacrene (1.6%), lavandulyl 3-methylbutanoate (6.9%), lavandulyl 2-methylbutanoate (6%), δ-cadinene (2.3%), spathulenol (0.5%), caryophyllene oxide (0.7%), 14-oxy-α-muurolene (0.8%), and 6,10,14-trimethylpentadecanone (3%)	
Morocco	Umbels			Abietadiene (53.4%), linalol (19.2%), 2-methylbutyrate isoamyl (5.3%), isovalerate isopentyle (2.5%), lavandulyl isovalerate (2.2%), amyl butyrate (2.0%), manool (1.5%), germacrene D (1.4%), abietol (2.8%), and neryl propionate (1.0%)	(Soro et al., 2015)

Table 3
Fatty acids and sterols composition of different parts of *A. visnaga* L.

Country	Part of plant	Extraction method	Identification method	Fatty acids	references
Pakistan	seeds	Soxhlet method	GC-MS	Lauric acid, myristic acid, pentadecanoic acid, palmitic acid, palmitolic acid, margaric acid, heptadecanoic acid, stearic acid, oleic acid, linoleic acid, arachidic acid, heneicosanoic acid, behenic acid, and tricosanoic acid	(Ullah, 2012)
Egypt	Aerial parts	Percolation	Chromatography/ NMR, UV, MS and IR spectra	Tetracosanoic acid, ß-sitosterol, and ß-sitosterol glucoside	(Ashour et al., 2013)

Table 4
Diverse uses of *A. visnaga* L. in the folk medicine.

Plant part used	Mode of preparation	Diseases or symptoms treated in humans	References
Dry umbel	herbal tea: boiling spoon size of about 10 g of the herb in 200 mL of water	Urolithiasis and hypertriglyceridemia	(Bhagavathula et al., 2015)
	Decoction	Elevation of HDL-cholesterol level	(Jan, 2016)
	A lotion for hair scalp cure kidney pain	Hair Loss hypoglycaemic effect	(Abousamra et al., 2016; Ahmed et al., 2022)
Fruit	Decoction	Renal colic	(Sayed, 1980)
		kidney inflammation	(Al-douri, 2000)
		Urolithiasis and prostatic pain	(Said et al., 2002)

Table 4 Continued

Plant part used	Mode of preparation	Diseases or symptoms treated in humans	References
Fruit	Decoction	Hypertension, depression, leukoderma, allergic rhinitis and rash	(Abdul-Jalil et al., 2010; Ghareeb et al., 2011)
Fruit		Toothpicks	(Koriem et al., 2019)
Seeds	Orally administrated	Diuretic properties	(Al-Snafi, 2015)
	10 g in 200 mL of water vasodilation	Hypolipidemiceffect: Elevation of HDL-cholesterol level	(Bhagavathula et al., 2015)

Lam. at a concentration of 40% was also effective against seven tested dermatophytic fungi, including *Candida albicans, Candida tropicalis, Epidermophyton floccosum*, *Trichophyton rubrum, Trichophyton verrucosum,* and *Microsporum canis,* and showed the highest growth inhibition (70%) against *Trichophyton mentagrophytes*, which is the most common fungus causing tinea infections in humans and dermatophytosis in zoonotic skin disease (Sabry et al., 2014). In addition, the *A. visnaga* seed extract at a dose of 40% showed high antifungal activity against many dangerous phytopathogenic fungi such as: *Aspergillus flavus, Alternaria alternata*, *Cochliobolous spicifer*, *Stachybotrys atra* var. *microspora*, and *Ulocladium botrytis* (Sabry et al., 2014).

6.2. Anti-gastric acid secretory action

Only a few studies have examined the antipeptic ulcer properties of *A. visnaga* (L.) Lam. The main study conducted by Jan (2014) showed that *A. visnaga* (L.) Lam. methanol extract applied at a dose of 500 mg/kg body weight reduced the volume of gastric secretion, free acidity, and total acidity in rabbits by 48%, 37%, and 46%, respectively, when compared with the values of carbachol at a concentration of 600 µg/kg (control group). Moreover, when compared with effect of the verapamil (10 mg/Kg), a well-known calcium channel blocker and the Cimetidine (2,5 mg/Kg), a standard anti-ulcer drug, the extract acted very similarly (Jan, 2012; Jan et al., 2015). *A. visnaga* (L.) Lam. extract had no effect on kidney (assessed by serum creatinine and blood urea) and liver functions (assessed by serum bilirubin, SGPT and alkaline phosphatase) after sustained 45 days of administration, proving that *A. visnaga* (L.) Lam. extract may be beneficial in case of hyperacidic secretory conditions and peptic ulcer disease without adverse effects on liver and kidneys (Jan, 2014; Jan et al., 2015).

6.3. Neuroprotective effect

The main component of *A. visnaga* (L.) Lam. named visnagin had a significant neuroprotective effect on kainic acid (KA)-induced neuronal cell death (Kwon et al., 2010). The administration of visnagin at a dose of (100 mg/kg), attenuated OX-42 (microglia marker) and GFAP (astrocyte marker) expression but also inhibited the pro-inflammatory cytokine production (IL-1β, TNF-α, IL-6, and COX-2) increased by KA (Kwon et al., 2010; Lee et al., 2010).

6.4. Antioxidant activity

Free radicals are the key factors in the development of various diseases, including cancer, cardiovascular disease, neurological difficulties, ulcerative colitis, aging, and atherosclerosis (Taha, 2018). Controlling reactive oxygen species (ROS) production constitutes a strategic approach to avoid the development of illnesses in which ROS are involved. Natural products are important sources of bioactive compounds well known for their ability to neutralize ROS effects (Taha, 2018). *A. visnaga* (L.) Lam. is widely studied for its antioxidant activity, as evaluated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. It was found that the ethyl acetate fraction of the hydromethanolic extract obtained from umbels had the most powerful radical scavenging capacity (IC_{50} = 8.7 µg/mL) when compared to the standard antioxidant substances such as BHA (IC_{50} = 10.9 µg/mL) and ascorbic acid (IC_{50} = 8.8 µg/mL) (El Karkouri et al., 2020). Similarly, another study confirmed the effectiveness of the *A. visnaga* (L.) Lam. shoot's methanolic extract, which had the higher free radical scavenging activity (IC_{50} = 6.0 µg/mL) compared to the trolox standard (IC = 1.5 µg/mL) (Amin et al., 2015; Imane et al., 2016). Additionally, remarkable antioxidant activity was revealed for the *A. visnaga* (L.) Lam butanolic extract (IC_{50} = 8.8 µg/mL) (Bencheraiet et al., 2011). Antioxidant activity was shown to be dependent on the type of the extract, *i.e.*, ethanol, water, and acetone used at the same concentrations (Imane et al., 2016). The antioxidant ability of each extract was highly correlated with the total polyphenolic content (Imane et al., 2016; El Karkouri et al., 2020). *A. visnaga* (L.) Lam., improved the antioxidant defense system by increasing the antioxidant enzymatic activities of superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH-Px), while the malondialdehyde (MDA) concentration was decreased (Kamal et al., 2022). These findings imply that *A. visnaga* (L.) Lam. may be a good source of natural antioxidant molecules for protecting against free radical-related illnesses.

6.5. Cancer related activity

Cancer treatments with official cytostatic drugs are generally associated with several side effects limiting their usage. To reduce these adverse effects, plants and their derivative products as complementary and parallel therapies, could become suitable alternatives. In this context, *A. visnaga* (L.) Lam. could be placed among the most promising plants because of its chemical composition consisting mainly of furanochromone derivatives. Aydoğmuş-Öztürk et al. (2019) found that visnagin exhibited 80.93% inhibitory activity against HT-144 (human malignant melanoma) cell line at a dose of 100 µg/mL, where the percentage of apoptosis was 25.88%, suggesting that the antitumor effect of visnagin is due to the induction of apoptosis by increasing the intracellular production of reactive oxygen species (ROS) in the apoptotic pathway. Another study revealed that khellin and visnagin were effective on four human cancer cell lines, including HeLa (cervical carcinoma), Hep-G2 (liver carcinoma), HCT 116 (colon carcinoma), and MCF7 (breast carcinoma), where the highest cytotoxic activities were shown against Hep-G2 cell line with an IC_{50} = 10.9 µg/mL at visnagin and khellin concentration of 13.3 µg/mL, while the IC_{50} of standard drug used (Doxorubicin) do not exceed 5.3µg/mL (Beltagy and Beltagy, 2015).
Ethanol extract of *A. visnaga* (L.) Lam. has an inhibitory effect on the cell growth of MCF-7 (human breast adenocarcinoma), and Hela (human cervical cancer) cell lines with IC_{50} values of 2000 µg /mL, and 570 µg/mL, respectively (Pakfetrat et al., 2015). However, the methanol extract had no effect against HeLa cells, but exhibited a remarkable antitumor activity against MCF7 (breast carcinoma cell line) when compared with the ethanol extract with the IC_{50} values ranging from 88 µg/mL to 97 µg/mL (Beltagy and Beltagy, 2015).
However, some synthesized benzofurans derived from naturally occurring visnagin sources showed strong to moderate cytotoxic effects against liver HEPG2 cancer cell line compared to values of IC_{50} of 5-fluorouracil (5/FU) and doxorubicin (DOX), known anticancer agents. The visnagin was the most active *A. visnaga* (L.) Lam. Agent, inducing a significant growth inhibition, in a dose-dependent manner with an IC_{50} = 0.0054 µM when compared to 5-FU and DOX (El-Nakkady et al., 2012). Furthermore, DOX causes cumulative and dose-dependent cardiotoxicity, resulting in increased risks of mortality among cancer patients and thus limiting its wide clinical applications. Some recent studies have showed the protective effect of visnagin against DOX-induced cardiotoxicity through the inhibition of mitochondrial malate dehydrogenase (MDH2), a key enzyme in the citric acid cycle, which can rescue cardiac performance and circulatory defects (Kim and Choi, 2021; Rawat et al., 2021). Within this framework, the combination of khellin and visnagin could be useful for the treatment of cancer on the basis of future research.

6.6. Cardioprotective activity

Visnagin is known to lower blood pressure without altering heart rate by blocking Ca^{2+} channels and hence inhibiting vasoconstriction (Ghareeb et al., 2011). Also, visnagin along with khellin and visnadin, demonstrated peripheral and coronary vasodilator properties and was used to treat angina pectoris due to the non-specific inhibition of vascular smooth muscle contractility (Fu et al., 2020). Furthermore, visnadin efficiently normalized the electrocardiogram of ischemic myocardia in dogs and showed an enhanced coronary blood flow in isolated Guinea pig hearts at doses of 60 and 120 g/mL by 46% and 57%, respectively (Vanachayangkul et al., 2011; Al-Snafi and Al-Snafi, 2013; Hashim et al., 2014a; Khalil et al., 2020; Ahmed et al., 2021). However, the protective effect of visnagin on myocardial ischemia/reperfusion injury has not been confirmed until the study conducted by Fu et al. (2020) found that intravenous visnagin injection had a protective effect on myocardial ischemia/reperfusion (MIR) damage, which can significantly reduce the size of the myocardial infarct region after 24 hours of reperfusion; meanwhile, visnagin can reduce cardiac dysfunction and inhibit myocardial fibrosis after 4 weeks of reperfusion as compared with control group treated with saline (3mL/kg) (Fu et al., 2020). In addition, apoptosis was inhibited and the number of autophagosomes increased, indicating that the protective mechanism of visnagin may be linked with autophagy and inhibition of apoptosis in the ischemic area after myocardial IR injury (Fu et al., 2020).

6.7. Kidney diseases

Urolithiasis is a recurrent disease characterized by the calculi's presence in the urinary tract. Urinary calculi contain a significant amount of CaOx, which is found mostly in its stable crystalline state and is the most prevalent in clinical calculations as calcium oxalate monohydrate (Kachkoul et al., 2018).
A. visnaga (L.) Lam. has been used for a long time to treat urolithiasis. It contains a broad spectrum of bioactive compounds like *khelline, visnagine, and visnadine.*, which could be responsible for its beneficial properties (Hashim et al., 2014; Bhagavathula et al., 2015; Kachkoul et al., 2018; Ahmed et al., 2022). Kachkoul et al. (2018) showed that the methanol extract of *A. visnaga* (L.) Lam. seeds inhibited 67.94% to 73.25% the CaOx's crystallization for 67.94% to 73.25% at concentrations of 0.25-2 g/L, respectively.
In addition to the finding that *A. visnaga* (L.) Lam. seeds were efficient in inhibiting the crystallization of CaOx, the action of *A. visnaga* (L.) Lam. may be due to its vasodilation and diuretic properties (Vanachayangkul et al., 2011; Hashim et al., 2014) as well as the ability of khellin to mediate citrate metabolism in inhibiting CaOx crystallization (Kilicaslan and Coskun, 2012). Bioactive compounds of *A. visnaga* (L.) Lam. act synergistically to prevent damage to renal epithelial cells by CaOx crystals (Hashim et al., 2014; Khalil et al., 2020; Ahmed et al., 2021). Furthermore, it was found that oral administration of Khella extract (KE; 125, 250, or 500 mg/kg) have sustained the incidence of CaOx crystal deposition by increasing urinary citrate excretion and urine pH, suggesting a mechanism that may interfere with citrate reabsorption (Vanachayangkul et al., 2011).

6.8. Anti-inflammatory Effect

Very few studies have examined the anti-inflammatory properties of *A. visnaga* (L.) Lam. Visnagin at concentration of 100μM attenuated significantly LPS-induced mRNA expression and release of pro-inflammatory cytokines, such as TNF-α, IL-1β, IFNγ and IL-6, as well as the CC chemokine-MCP-1, further leading to a considerable increase in the expression of anti-inflammatory cytokines (IL 10) (Lee et al., 2010). These results suggest for the first time that the anti-inflammatory effect of visnagin may be due to the inhibition of AP-1 and NF-κB transcription factors. Another study reported that khellin exhibited a more potent anti-inflammatory effect than visnagin, while some of its synthetic derivatives administered at a dose of 20 mg/kg exhibited better effects than diclofenac sodium, a well-known anti-inflammatory drug (Abu-Hashem and Youssef, 2011).

6.9. Analgesic activity

Pain is a very unpleasant physical sensation caused by injury, illness, or other stimuli. The eddy's plate method was used for screening the analgesic activity of fifteen plant aqueous extracts of *A. visnaga* (L.) Lam. exhibiting the best properties at a dose of 300 mg/kg, which was justified by comparison with the negative (normal saline) and positive control (diclofenac sodium 1 mg/kg) (Gouda et al., 2014). The obtained activity is attributed to khellin and visnagin, which have already been reported for their analgesic activity (Abu-Hashem and Youssef, 2011).

6.10. Hypolipidemic effect

The hypolipidemic effect of *A. visnaga* (L.) Lam. has been assessed by several experiments. A study conducted by Bhagavathula et *al*. suggested that after continuous use of *A. visnaga* (L.) Lam. seeds (10 g in 200 mL of water) for 10 days twice a day, the patients exhibited an improved HDL-cholesterol level ranging from 32 to 56 mg/dL (normal values 35-135 mg/dL), and remarkable decrease of triglycerides, total cholesterol and low-density lipoprotein (LDL)-cholesterol. Another study also showed that the elevation of HDL-cholesterol level was obtained during the treatment and one week after treatment cessation, due to effect of khellin in dose of 50 mg administrated four times a day for 4 weeks) (Al-Snafi, 2015). Furthermore, the complexation of khellin with MβCD (methyl-β-cyclodextrin) both improved the dissolution and the bioavailability of the bioactive ingredient (kellin) and lowered serum triglycerides and the total cholesterol levels in diabetic rats (Abousamra et al., 2016). Thus, *A. visnaga* (L.) Lam. extract and its individual compounds could be considered as antidiabetic and antiobesity drugs in the future.

6.11. Larvicidal and acaricidal activities

The use of synthetic insecticides faces several serious problems today; therefore, many active components isolated from plants such as *A. visnaga* (L.) Lam. can be used as an alternative source of larvicidal and insecticide activities. Maleck et *al*. reported for the first time the efficiency of khellin against insect vectors for human diseases. In their study, khellin was used against *Oncopeltus fasciatus (*Hemiptera: Lygaidae*)*, a *Phytomonas* vector responsible for many plant diseases. The khellin was used at 100 μg/nymph, resulting in 50% nymph mortality and 80% adult mortality, whereas the treated group showed 90% to 100% inhibition of egg hatching at concentrations of 10 and 100 μg/nymphs, respectively.
In addition, *A. visnaga* (L.) Lam. compounds were known to be effective against *Aedes aegypti* (Diptera: Culicidae), which is responsible for dengue fever and resistant to the pyrethroid insecticide and acaricide. Khellin used at 50 μg/mL has shown 46,6% larval toxicity on the L3 larval stage, while L4 and Pupae stages were not affected (Maleck et al., 2013). *A. visnaga* was found to be effective against *Culex quinquefasciatus*, a vector of avian malaria, and arboviruses, including Zika virus and West Nile virus (Pavela, 2016).
The acaricidal and ovicidal efficacy of the methanol extract obtained from *A. visnaga* (L.) Lam. seeds on *Tetranychus urticae* showed that khellin was highly toxic for adults, with LD_{50} (for 72 h) estimated as 10 g cm^{-2}, compared to the extract and visnagin with LD50 equal to 17 and 98 g cm^{-2}, respectively (Jan, 2016). The case of direct application of the methanol extract on infested plants, the concentration of 10 mg mL^{-1} exhibited the highest reduction, observed at 98.5% on day 10 after application. The *A. visnaga* (L.) Lam. extract and two tested furanochromenes inhibited the development of eggs and caused their mortality, where LD_{50} was estimated at 13.3, 0.5 and 1.8 g cm^{-2}, for the MeOH extract, visnagin, and khellin, respectively.

6.12. Bioherbicidal activity

The phytotoxic potential of medicinal plants against weeds constitutes a promising avenue for searching for effective and environmentally safe herbicides (Rob et al., 2020).The herbicidal activity of khellin and visnagin from a dichloromethane extract of *A. visnaga* showed that these compounds were phytotoxic to model species lettuce (*Lactuca sativa*) and duckweed (*Lemna paucicostata*), with IC_{50} values ranging from 110 to 175 μM; also tested compounds inhibited the growth and germination of a diverse groups of weeds including five grasses (*Lolium multiflorum, Echinocloa crus-galli, Digitaria sanguinalis, Setaria italica*, and *Panicum* sp.) and two broadleaf species (*Ipomea* sp. and *Abutilon theophrasti*) at 0.5 and 1 mM. Moreover, during greenhouse studies visnagin was the most active and its effect at 4 kg/ha was comparable to the bioherbicide - the pelargonic acid at the same rate (Travaini et al., 2016). Many studies have addressed the possible mechanisms of plant metabolites on seed germination, showing that some plant extracts or their compounds initiate damage of the embryo cell membranes, could affect the DNA structure and mitosis cycle, and affect the amylase activity in the endosperm, and to influence other biochemical processes which delay or inhibit seed (Radhakrishnan et al., 2018).

7. Concluding remarks

A. visnaga (L.) Lam. is a wealthy natural product well-known in traditional medicine for its multiple biological properties, including antimicrobial, antigastric acid secretory, neuroprotective, antioxidant, anticancer, cardioprotective, anti-inflammatory, analgesic, hypolipidemic, bioherbicidal, and larvicidal activities. Different analytic techniques were used to delve into the phytochemistry of this plant showing the presence of a broad spectrum of bioactive compounds, which are highly associated with its biological functionalities. The most abundant pharmacologically active compounds were khellin, visnagin, and visnadin. All phytochemicals found in *A. visnaga* (L.) Lam. acted synergistically to provide several properties, as mentioned above. Furthermore, there is a real need for future studies to explore the positive impact of the combination of the plant with chemical drugs and other targets, such as the regulation of gut microbiota.

Data availability

The data used to support the findings of this study are included within the article.

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Conflicts of interest

The authors declare that there is no conflict of interest.

Abbreviations

CAT: Catalase; COX-2: Cyclooxygenase-2; DNA: Deoxyribonulceic acid; ELISA: Enzyme-linked immunoassay; EO: Essential oil; GC-FID: Gas chromatography flame ionization detection; GC-MS: Gas chromatography-mass spectrometry; GFAP: Glial fibrillary acidic protein; GSH-Px: Glutathione peroxidase; HCT 116: Colon carcinoma; HDL: High density lipoprotein; Hep-G2: Liver carcinoama; HEPG2: Hepatoblastoma cell line; HPLC-ESI/IT/MS: High pressure liquid chromatography-electrospray ionization tandem mass spectrometry; HPLC-NMR: High pressure liquid chromatography nuclear magnetic resonance; HPLC/UV-ESI-MS: High pressure liquid chromatography/ultraviolet-electrospray ionization tandem mass spectrometry; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; IR: Infrared; KA: Kainic acid; MCF7: Breast carcinoma; MDA: Malonadehyede deshydrogenase; MIC: Minimal inhibition concentration; MIR: Myocardial ischemia/reperfusion; mRNA: Messenger RNA; MS: Mass spectrometry; NMR: Nuclear magnetic resonance; ROS: Reactive oxygen species; SGPT: Serum glutamate pyruvate transaminase; SOD: Superoxyde dismutase; TNF-α: Tumour necrosis factor-alpha; UV: Ultraviolet visible spectrophotometry.

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