



Review Article

Eryngium creticum – ethnopharmacology, phytochemistry and pharmacological activity. A review



Małgorzata Kikowska^{a,*}, Marzena Dworacka^b, Izabela Kędziora^a, Barbara Thiem^a

^a Department of Pharmaceutical Botany and Plant Biotechnology, Poznan University of Medical Sciences, Poznan, Poland

^b Department of Pharmacology, Poznan University of Medical Sciences, Poznan, Poland

ARTICLE INFO

Article history:

Received 28 September 2015

Accepted 14 January 2016

Available online 28 March 2016

Keywords:

Eryngium creticum

Eryngo

Ethnopharmacology

Phytochemistry

Pharmacological activity

ABSTRACT

Eryngium creticum Lam. (*E. cyaneum* Sibth. & Sm., *E. syriacum* Lam.), Saniculoideae, Apiaceae is of great importance in the traditional Greco – Arab medicine. This study was carried out in order to contribute to the ethnopharmacological knowledge of this medicinal species. This review describes the botanical characterization and distribution, as well as critically assesses the phytochemical properties and biological activities of *E. creticum*, a species that has been used in traditional medicine for many decades. Possible trends and perspectives for future research of this plant are discussed, as well. *E. creticum* has been found to contain several chemical constituents, mostly sesquiterpenes, monoterpenes, aldehydes, coumarins, sitosterols and sugars. Eryngo with its bioactive compounds possesses a wild range of biological activities. It was reported that in traditional medicine *E. creticum* was applied mainly as the remedy for snake and scorpion bites. Some published studies have shown a broad spectrum of biological and pharmacological activities, including anti-snake and anti-scorpion venom, as well as antibacterial, antifungal and antileishmanial effects. Other have indicated antihyperglycemic, hypoglycemic and antioxidant activities of this species. The *in vitro* studies and *in vivo* models have provided a simple bioscientific explanation for its various ethnopharmacological uses.

© 2016 Sociedade Brasileira de Farmacognosia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

To promote traditional medicine and herbal therapeutics, there should be provided the knowledge of plant bioactive compounds playing an important role in human healthcare and the scientific confirmation of their traditional use. *Eryngium creticum* Lam., Apiaceae is an example of a species that has remained a wild edible plant and it is known mostly to gatherers. This article provides an overview of *E. creticum*, a traditional herbal remedy used mostly for snake and scorpion bites: the distribution pattern and botanical description of the species, the status of ethnopharmacology, phytochemistry and the laboratory data on the bioactivity. The current status of literature on eryngo has been reviewed.

In brief, this review presents the results of the investigations on *E. creticum* that have been conducted so far and points out the gaps in knowledge, which disclosure is necessary to understand the mechanism of action of the extracts used in a traditional medicine. Also it indicates the necessity to conduct in-depth examination of the correlation between the pharmacological effect and

the presence of the bioactive compounds responsible for the action. The review summarizes the phytochemical analysis and biological studies that may be helpful for researches to undertake further studies supporting the existing knowledge necessary to understand the action and may contribute to the discovery of new uses of this interesting species.

Botanical characteristics and distribution

Genus *Eryngium* L. comprises about 250 species and is distributed throughout temperate regions of every continent. The *Eryngium* species grow in Eurasia, North Africa, North and South America, and Australia. It is the most species-rich genus of the Apiaceae (Wolff, 1913; Wörz, 1999, 2004, 2005, 2006; Calvino et al., 2008; Wörz and Diekmann, 2010). Wolff (1913) grouped the species into 34 sections and numerous subsections. He also recognized two major informal groups: *Species gerontogae* and *Species americanae and australiensis*, the former representing twelve sections from the Old World, and the latter 22 sections from the Americas and Australia. *E. creticum* with *E. planum* and *E. caeruleum* belongs to Plana section (Wolff, 1913). A new subgeneric classification of the genus was presented by Wörz (2005). It recognizes five subgenera. The classification was based on morphology and did

* Corresponding author.

E-mail: kikowska@ump.edu.pl (M. Kikowska).

not reflect phylogeny or solve problems of infrageneric relationships (Wörz, 2005). The other paper dealt with the Balkan species. The classification of the Balkan species of *Eryngium* was based on conventional morphological characteristics. The basal leaves provided the main characteristics. Specialization, the high rate of endemism, sectional diversity, and distribution patterns suggest relatively old age of most Balkan *Eryngium* species. The topographical and climatic diversity resulted in isolation and some ecological adaptations. Exceptions to the old age species are probably the 3 widespread species including *E. creticum* which are migratory. Within the Circum-Mediterranean Plana section, *E. creticum* is the only Balkan species. The closest relative is the Caucasian *E. caeruleum* (Wörz, 2006). The study carried out by Calvino et al. (2008), based on phylogenetic analyses of DNA sequences from three non-coding chloroplast DNA loci and the nuclear ribosomal DNA internal transcribed spacer region, was useful in corroborating the monophyly of *Eryngium*, dividing it into redefined and monophyletic subgenera (*E. subgenus Eryngium* and *E. subgenus Monocotyloidea*), and identifying clades that shared several morphological, biogeographical and/or ecological traits (Calvino et al., 2008).

E. creticum Lam. (*E. cyaneum* Sibth. & Sm., *E. syriacum* Lam., eryngo, flat holly, blue sea holly) was described by Jean-Baptiste Pierre Antoine de Monet de Lamarck in 1798. It is known by several local names, but the most recognizable are: Qors Anneh used in Lebanon and Qarsa'na (Palestine). Eryngo is a species that belongs to Apiaceae family (Umbellifereae) and it can be found in the Eastern Mediterranean region, mostly in Lebanon, Palestine, Jordan and Syria. It grows at low altitudes, in sunny places. It is commonly found in fallow fields, roadsides, waste places, and, occasionally, even in the understory of olive groves. In Syria it was found in various environments, which indicates its adaptability and abiotic stress tolerance (Jawdat et al., 2010). The species is also found in the Alpine and sub-Alpine calcareous grasslands in the high mountains of northern and central Greece. The soils are usually deep and relatively rich in nutrients (Tutin et al., 1968; Wörz, 2006; Caballero et al., 2009).

The Hebrew name of *E. creticum* – Charchevina–Makchila, is based on the fact the plant grows in dry weather; the root name is H-R-V which means dry, while the second word means “turning blue”. Despite its name, Charchevina is actually listed in the Mishnah, the 2nd C. AD books of Jewish practices, as one of the Passover bitter herbs (Passachim 2: 6).

E. creticum is a spiny perennial, or sometimes biennial or annual, glaucous and globrous herb, reaching up to 50 cm in height and it has erect branched stems. Stem leaves are sessile and palmately divided into 3–8 prickly lobes. Winter rosette leaves are quickly withering, bluish, long petioled, not prickly, entire to dentate, or lobed. Inflorescences are repeatedly forked; umbels of 0.7–1 cm, head-like, with an involucre of 5 long, blue, spiny bracts 2–5 times as long as the head, spreading, linear, boat-shaped, prickly at base or along the long margin. Fruits are scaly-bristly, obscurely ribbed (Konig and Sims, 1806; Don, 1831; Muschler, 1912; Tutin et al., 1968; Mayer-Chissick and Lev, 2014).

It is cultivated for use as a vegetable, mainly in salads. Its young leaves are eaten fresh and thick roots are eaten raw or cooked (Mayer-Chissick and Lev, 2014). An ethnobotanical survey of wild edible plants of Cyprus (Paphos vine zone and Larnaca mixed farming zone) revealed that young stems and leaves of eryngo preserved in vinegar were eaten as appetizers with several kinds of food (Della et al., 2006). The freshly harvested, simple leaves on long stalks of *E. creticum* and deeply lobed leaves of *E. glomeratum* are made into pickles by Greek Orthodox monasteries in Cyprus (Lardos, 2012). In Lebanon, eryngo is consumed mainly when freshly gathered and prepared mainly raw as a salad. Most information shows that the plant is appetizing and it is described as bitter in taste. According to an ethnobotanical survey of edible plants in northeast Lebanon,

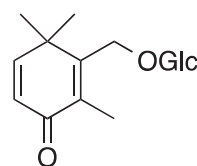
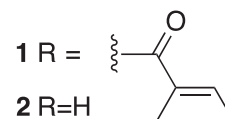
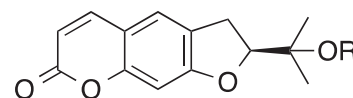
eryngo is consumed about three times a week (Jeambey et al., 2009).

Phytochemistry

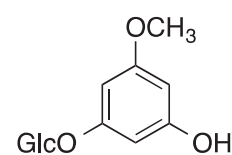
Unfortunately, the literature on phytochemistry of *E. creticum* is still scarce. There are some studies on the chemical composition of the essential oil. However, the knowledge about their non-volatile chemical constituents is limited.

The phytochemical screenings of aqueous, ethanolic, and methanolic extracts of *E. creticum* indicated the presence of different bioactive compounds, mainly sesquiterpenes, monoterpenes, aldehydes, coumarins, sitosterols, tannins, resins and sugars. On the other hand, screening for metal by means of spectroscopy showed that this plant contains metals such silver, zirconium, nickel, selenium, niobium and molybdenum, iron, calcium, manganese and copper (Al-Khalil, 1994; Ayoub et al., 2003; Celik et al., 2011; Farhan et al., 2012; Dammous et al., 2014; Dirani et al., 2014; Rammal et al., 2015; Erdem et al., 2015).

One of the first phytochemical investigations of the roots of *E. creticum*, which grows wildly in Jordan, led to the isolation and characterization of nine compounds: two coumarins – deltion (1) and marmesin (2), cyclic alcohol – quercitol, monoterpene glycoside 3-(β -D-glucopyranosylmethyl)-2,4,4-trimethyl-2,5-cyclohexadien-1-one (3), phloroglucinol glycoside (1-(β -D-glucopyranosyloxy-3-methoxy-5-hydroxy benzene)) (4), β -sitosterol and its glycoside (β -sitosterol- β -D-glucopyranose), and two sugars – mannitol and dulcitol (Al-Khalil, 1994).

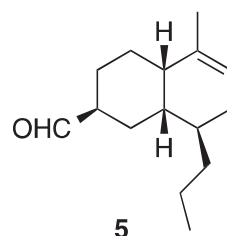


3

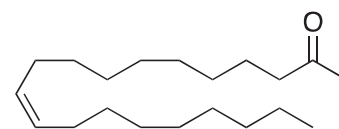


4

The unique 1-*n*-propyl-perhydronaphthalene 1,2,4a,5,6,7,8,8a-octahydro-4-methyl-1-propyl-naphthalene-7-carbaldehyde (eryng-9-en-15-al) (5), a compound which possesses an unusual sesquiterpene carbon skeleton, was isolated and identified, together with the new natural methyl ketone eicos-8,11-dien-18-ol-2-one (6), from the hexane: ether (1:1) extract of the aerial parts of *E. creticum* growing in Egypt. The structures of those compounds were established by conventional methods of analysis and confirmed by DEPT, COSY, HMQC and HMBC spectral analysis (Ayoub et al., 2003).



5



6

A report by Mahommadhosseini (2013) deals with the chemical composition of the volatile oil from stems of *E. creticum* from Iran. The oil was obtained using a modified Clevenger-type apparatus and the respective analyses were performed by means of GC and GC–MS. It was obtained as a clear yellowish liquid containing 0.18% (w/w). There were identified seventeen components constituting 91.4% of the oil composition. The major components of the oil were found to be bornyl acetate (28.4%), camphor (17.8%), α -pinene (12.1%), germacrene D (9.4%), borneol (8.6%) and α -thujene (4.2%). Based upon the chemical profile, the essential oil was mainly characterized by the presence of increased amounts of oxygenated monoterpenes (Mahommadhosseini, 2013).

The chemical composition of the essential oil was determined by direct thermal desorption (DTD)-GC/MS analyses. The result for essential oil yields of *E. creticum* growing in the Aegean region of Turkey was 0.21% (v/w). The oil was colorless, with a weak perfumery odor. The essential oil contains a mixture of several compounds, predominantly aldehydes and oxygenated monoterpenes. Hexanal ($52.90 \pm 2.70\%$), heptanal ($13.90 \pm 3.82\%$) and octane ($8.95 \pm 2.32\%$) were the major compounds. The percentage of other compounds ranged from 0.14 to 3.57% (Celik et al., 2011). To the best of our knowledge, it is not possible to calculate RI values lower than 800 using the mixture of C8–C32 alkanes. Moreover, the order of compounds listed in Table 1 is not correct because it is based on RI values and these are unreliable, e.g. neither of the first compounds can have RI below 600; RI of compounds with the same formula, e.g. monoterpene hydrocarbons (limonene, cymenes, pinene, camphene), cannot differ as greatly as reported; RI (retention indices) of a pair of homologous compounds such as hexanal (given RI = 816, proper RI = 800) and heptanal (given RI = 1140, proper RI = 900) should differ by ca. 100, and for nonanal (given RI = 1128) RI = 1100 etc. It is not possible to identify enantiomers using GC or GC–MS on non-chiral phase. The methodology and results reported in this article are not reliable.

The total phenolic (TPC; Folin-Ciocalteu method) and total flavonoid (TFC; aluminum chloride method) content in the leaves and stems of *E. creticum* was evaluated and expressed in mg of gallic acid or rutin equivalent per gram of dry weight. The amounts of TPC and TFC in the leaves were higher than in the stems. The ethanolic extracts of both leaves (TPC 253 ± 0.031 mg; TFC 729 ± 0.023 mg) and stems (TPC 230 ± 0.043 mg; TFC 258.9 ± 0.041 mg) of this plant were found to contain higher amounts of TPC and TFC than the aqueous extract (Farhan et al., 2012; Dammous et al., 2014). The latest studies this group of authors also showed a high content of phenolics and flavonoids in the methanolic extracts, which was much greater than in aqueous extracts, and the same of slightly lower than in ethanolic extracts, both in the leaves and stems of *E. creticum* (Rammal et al., 2015).

As it turns out, *E. creticum* contains various concentrations of elements and heavy metals. It was found that this taxon is a plant which did not show heavy metal tolerance. The results obtained using microwave digestion (X-ray fluorescence spectrometry) demonstrated also that the amount of elements differed between the leaves and stems of the studied plant. The level of these elements was higher in leaves than in stems and calcium was found at higher concentration ($321.06 \text{ mg kg}^{-1}$) in the leaves than in stems (46.43 mg kg^{-1}), compared to other elements. These results show that eryngo has good nutritional value (Farhan et al., 2012; Dammous et al., 2014).

Many factors such as the geographical origin may be responsible for the variation of the content of bioactive compounds in the plant material, and for this reason the place of *E. creticum* origin was pointed.

Traditional medicine

The plant is recognized as one of the varieties which can be used as the bitter herb required for the Passover meal. The Arabs of Israel, who are accustomed to eating various kinds of sea holly, used *E. creticum* in their traditional medicine. Because of its traditional use, the plant is of much scientific interest nowadays. It was reported that eryngo was applied as the remedy for snake and scorpion bites. The Arabs eat the leaves or smear the ground root to cure scorpion stings. Roots and seeds immersed in water have been drunk in order to treat kidney stones and infections, skin diseases and tumors. The seeds serve to cure stomach sores, cataract in the eyes, and to expel worms. The juice of the leaves is also used to treat diabetes. In Islamic medicine, *E. creticum* is used to treat a wide range of ailments; particularly its roots are used against edema, sinusitis, urinary infections, and inflammations. It has also been used to treat liver diseases, poisoning, anemia and infertility—a standard decoction was prepared from 50 g of whole plant in 1 l water and taken orally, three times per day until improvement occurs (Palevitch et al., 1985; Yaniv et al., 1987; Marles and Farnsworth, 1995; Abu-Rabia, 2005; Thiem and Wiatrowska, 2007; Aburjai et al., 2007; Saad et al., 2008; Jeambey et al., 2009; Saad and Said, 2011; Mayer-Chissick and Lev, 2014).

These traditional uses of eryngo need scientific *in vitro* and *in vivo* confirmation of its effects.

Biological and pharmacological activities

The results of a number of published studies show a broad spectrum of biological and pharmacological activities of *E. creticum* which are attributed to different parts and extracts of this plant, including anti-snake and anti-scorpion venom, antibacterial and antifungal, and antileishmanial effects (Table 1). Others include antihyperglycemic, hypoglycemic and antioxidant activities (Table 1).

Anti-snake and anti-scorpion venoms properties

Snake bites and scorpion stings are major health hazards that lead to suffering and high mortality of the victims. Thousands of injuries associated with such bites and stings of venomous animals have been the cause of innumerable cases of deaths worldwide (Oukkache et al., 2014). The plant remedies may be beneficial in the treatment of snake bites and scorpion stings and they may be regarded as an alternative to anti-venom. The plant mentioned in the literature of the Mediterranean region that used to treat snake and scorpion venoms was *E. creticum*. It was reported that an aqueous extract of the root was applied as the remedy for scorpion stings in the rural areas of Jordan (Yaniv et al., 1987).

When testing the efficiency of *E. creticum* aqueous extract, it was found to significantly prolong the life of guinea pigs from 20 min to 8 h when combined with *Leiurus quinquestriatus* scorpion venom (Jaghabir et al., 1989). The same extract combined with *Cerastes snake* venom prolonged the life span from 12 to 72 h (El-Saket, 1990).

In another study, the anti-venom activity of *E. creticum* aqueous extract was tested using isolated rabbit and guinea pig jejunum and trachea. The extract caused a dose-dependent inhibition of tracheal and jejuna contraction induced by *L. quinquestriatus* scorpion venom and inhibited spontaneous movements of the jejunum (Afifi et al., 1990).

The aqueous and ethanol extracts ($1.0 \mu\text{g ml}^{-1}$) of fresh and dried leaves and roots of *E. creticum* were tested for their inhibitory properties against snake and scorpion venoms (*Cerastes cerastes*, *Leiurus quinquestriatus*). The fresh leaf extract gave higher

Table 1
Pharmacological activity of *Eryngium creticum*.

Activity	Part of plant	Type of extract/compound	Experimental model	Effect	References
Anti-snake and anti-scorpion venoms properties	Roots	Aqueous extract	Guinea pigs treated with extract combined with <i>Leiurus quinquestriatus</i> venom	Prolongs the life of animals from 20 min to 8 h	Jaghabir et al. (1989)
	Roots	Aqueous extract	Guinea pigs treated with extract combined with <i>Cerastes cerastes</i> venom	Prolongs the life of animals from 12 to 72 h	El-Saket (1990)
	Roots and leaves	Aqueous extract	Isolated rabbit and guinea pig jejunum and trachea treated with extract combined with <i>Leiurus quinquestriatus</i> venom	Inhibits tracheal and jejuna contraction and inhibits spontaneous movements of the jejunum	Afifi et al. (1990)
Antibacterial and antifungal activity	Roots and leaves	Aqueous and methanolic extract	Sheep red blood cells treated with <i>Cerastes cerastes</i> and <i>Leiurus quinquestriatus</i> venoms	Inhibits haemolytic activity of snake and scorpion venoms	Alkofahi et al. (1997)
	Aerial parts	Aqueous and ethanolic extract	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumonia</i> , <i>Proteus vulgaris</i> and <i>Pseudomonas aeruginosa</i>	Antibacterial activity was low or moderate depending on tested strain	Ali-Shtayeh et al. (1998)
	Leaves, stems and roots	Aqueous and ethanolic extract	<i>Staphylococcus aureus</i> , <i>S. epidermidis</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> and <i>Enterococcus faecalis</i>	Antibacterial activity was low, moderate or significant depending on tested strain	Makki et al. (2015)
	Flowering plant	Essential oil	Methicillin-resistant <i>Staphylococcus aureus</i>	Antibacterial activity was lower with those of the reference	Celik et al. (2011)
	Leaves, roots and fruits	Aqueous and ethanolic extract	<i>Candida albicans</i>	Antibacterial activity was moderate in comparison with reference antibiotic	Ali-Shtayeh et al. (1998)
	Leaves	Aqueous extract	<i>Microsporum canis</i> , <i>Trichophyton mentagrophytes</i> and <i>T. violaceum</i>	Low mycelia inhibitory efficacy, inhibition of spore germination	Ali-Shtayeh and Abu Ghdeib (1999)
Antimalarial and antileishmanial activity	Aerial parts	Methanolic and dichloromethanolic extract	<i>Botrytis cinerea</i> , <i>Alternaria solani</i> , <i>Penicillium</i> sp., <i>Cladosporium</i> sp., <i>Fusarium oxysporum</i> f. sp. <i>melonis</i> , <i>Rhizoctonia solani</i> , <i>Verticillium dahlia</i> and <i>Phytophthora infestans</i>	Activity against promastigote cultures of <i>L. donovani</i> . No antimalarial activity	Fokialakis et al. (2007)
			<i>Plasmodium falciparum</i> and <i>Leishmania donovani</i> promastigotes		
Antioxidant activity	Leaves and stems	Aqueous and ethanolic extract	DPPH assay	A significant antioxidant activity	Dammous et al. (2014)
	Leaves and stems	Aqueous and ethanolic extract	H ₂ O ₂ test	A significant antioxidant activity	Farhan et al. (2012)
	Leaves and stems	Aqueous and ethanolic extracts	Ferrozine test	A significant antioxidant activity	Dammous et al. (2014)
	Leaves and stems	Aqueous, methanolic and ethyl acetate extract	DPPH assay	A significant antioxidant activity	Farhan et al. (2012)
	Whole plant	Ethanolic extract	Ferrozine test	A significant antioxidant activity	Dammous et al. (2014)
	Leaves and stems	Aqueous and ethanolic extract	Ferrozine test	A significant antioxidant activity	Rammal et al. (2013)
	Leaves and stems	Aqueous and ethanolic extract	VCEAC	A significant antioxidant activity	Hijazi et al. (2015)
Cytotoxicities	Leaves and stems	Aqueous and ethanolic extract	Iron-induced lipid peroxidation in rat liver homogenates	It moderately suppresses Fe ²⁺ -induced lipid peroxidation	Farhan et al. (2012)
	Aerial parts	Methanolic and dichlorometanolic extract	Monkey kidney fibroblast (Vero) cell line	Not cytotoxic up to conc. of 47.6 µg ml ⁻¹	Dammous et al. (2014)
	Leaves and stems	Aqueous, methanolic and ethyl acetate	MCF7 breast cancer cell line by the XTT	Inhibits growth of cells by and 68–72%	Ljubuncic et al. (2005)
Antimutagenic activity	Leaves, stems, roots and whole plants	Aqueous and ethanolic extract	HeLa cancer cells by Natural Red Assay	Inhibits cell viability up to 97%	Fokialakis et al. (2007)
	Aerial parts	Ethanolic extract	Rat hepatocyte primary cultures treated with <i>N</i> -methyl- <i>N</i> '-nitro- <i>N</i> -nitrosoguanidine	A direct antimutagenic activity and an increased recovery	Rammal et al. (2013)
Antihyperglycemic and hypoglycemic effects	Aerial parts	Aqueous decoction	Streptozotocin-induced diabetic rats	Significant reductions in blood glucose concentration when given orally	Dirani et al. (2014)
	Aerial parts	Aqueous extract	<i>In vitro</i> (according to Granfeld method) and <i>in vivo</i> enzymatic starch digestion	Lack of <i>in vitro</i> inhibitory activity	Khader et al., 2010
	Aerial parts	Aqueous extract	Bioassays of β-cell proliferation and insulin secretion as well as glucose diffusion	Highly significant proliferative efficacies; lack of any statistically substantial glucose diffusional hindrances into external solution across dialysis membrane	Jaghabir (1991)
					Kasabri et al. (2011)
					Kasabri et al. (2012)

percentage inhibition of the haemolytic activity of the scorpion venom *Leiurus quinquesteirtus*, as compared to the dried leaf extract. Extracts of both fresh and dried roots gave 100% inhibition of the snake and scorpion venom. However, ethanol extracts of the leaves and roots enhanced RBC haemolysis rather than inhibit venom activities on red blood cells (Alkofahi et al., 1997).

Unfortunately, the authors do not perform phytochemical analysis of the tested extracts and did not respond to the question about which group of secondary metabolites or which particular compound is responsible for the activity. However, it is known from the literature that the plant reputed active against snake bite venom is another species belonging to *Eryngium* genus: *E. yuccifolium* Michx, known in North America as 'rattlesnake master'. Dimethyl ether (veratrum aldehyde) present in this species, which was officially published in the US Pharmacopeia of 1820–1860, was identified to neutralize the effects of snake venoms (Mors et al., 2000).

Antibacterial and antifungal activities

There has been launched extensive research aimed at obtaining new antimicrobial medicines from different sources. Despite progress in the development of antibacterial agents and antifungal, the need to find new antimicrobial agents is still particularly urgent due to the development of multidrug resistant bacteria and fungi. The extracts and essential oil from *E. creticum* have been tested against different strains of bacteria and fungi (Ali-Shtayeh et al., 1998; Ali-Shtayeh and Abu Ghdeib, 1999; Abou-Jawdah et al., 2002; Celik et al., 2011; Makki et al., 2015; Erdem et al., 2015).

The *in vitro* antibacterial activity of *E. creticum* was investigated against five bacterial species (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa*) by the disc diffusion method. The aqueous extract (inhibition zone with diameter 7.0 mm) proved to be more effective against *K. pneumoniae* than the ethanolic extract (6.0 mm), while the ethanolic extract (8.0 mm) proved to be most effective against *P. vulgaris*. There were no differences between the effect of the aqueous and ethanolic extracts against *S. aureus* (9.1 mm), *E. coli* (6.0 mm) and *P. aeruginosa* (6.0 mm) (Ali-Shtayeh et al., 1998).

The antibacterial activity against these three mentioned species of bacteria (*S. aureus*, *E. coli*, *P. aeruginosa*) and the two new species (*Staphylococcus epidermidis*, *Enterococcus faecalis*) was also measured by broth microdilution method. According to the research the aqueous extracts were stronger than ethanolic extracts for the growth inhibition of both Gram-positive and Gram-negative strains. Gram-positive strains were generally more sensitive to the tested extracts (MIC = MBC = 5.0 mg ml⁻¹). The authors concluded that their studies have demonstrated that the extracts *E. creticum* have a promising antibacterial effect and the further phytochemical analysis on bioactive compounds responsible for this effect will be performed (Makki et al., 2015).

The *in vitro* anti-MRSA activity of the essential oil from *E. creticum* was assessed by the disc diffusion method using a panel of Gram-positive clinical isolates of nine methicillin-resistant *Staphylococcus aureus* strains. The antibacterial activity of the essential oil was lower (inhibition zones with diameters from 0 to 11 ± 1 mm) than that of the reference antibiotic vancomycin (from 15 ± 1 to 16 ± 1 mm) (Celik et al., 2011).

The *in vitro* antifungal activity of plant extracts was investigated against *Candida* with the disc diffusion method. Aqueous and ethanolic extracts of *E. creticum* did not differ in their activity against the tested microorganism (6.0 mm) (Ali-Shtayeh et al., 1998).

The aqueous extracts reduced colony growth of three dermatophytes: *Microsporum canis*, *Trichophyton mentagrophytes* and *T. violaceum* when tested by means of the agar dilution method. However, the inhibitory effect of extracts calculated as the

percentage mycelia inhibition of tinea capitis dermatophytes was moderately or low and varied from about 12.4 ± 4.26% (*M. canis*) to 56.6 ± 7.42% (*T. mentagrophytes*) inhibition, in comparison with the control treatment – reference antibiotic – Griseofulvin (Ali-Shtayeh and Abu Ghdeib, 1999).

Moreover, the petroleum and methanolic extracts were tested *in vitro* against eight plant pathogenic fungi: *Botrytis cinerea*, *Alternaria solani*, *Penicillium* sp., *Cladosporium* sp., *Fusarium oxysporum* f. sp. *melonis*, *Rhizoctonia solani*, *Verticillium dahlia* and *Phytophthora infestans*. The extracts had low efficacy of mycelial growth inhibition, whereas they showed inhibition of spore germination. *E. creticum* showed >95% inhibition of spore germination in at least two fungi: *B. cinerea* and *F. oxysporum* f. sp. *melonis*. The level of antimycotic activity determined by mycelia growth inhibition test varied, depending on the fungus and extract tested, from 33% to 98% for petroleum, and from 3% to 75% for methanolic extracts (Abou-Jawdah et al., 2002).

To conclude, little is known about the antimicrobial activity of *E. creticum*, but the experiments as referred to above showed a very wide spectrum of activity against many animal, human, and plant pathogens, including fungi, yeast, and bacteria.

Antimalarial and antileishmanial activities

Malaria and leishmaniasis are two of the most common parasitic diseases that infect a large human population over five continents. There is a rapid increase in the resistance of malaria parasites to antimalarial drugs. Most of the treatments available for parasitic diseases show limited efficacy and undesirable side effects.

The extracts of aerial parts of *E. creticum* from West Crete have been investigated for *in vitro* antiprotozoal activity. There was performed an evaluation of their activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* and *Leishmania donovani* promastigotes. The extracts were tested against promastigote cultures of *L. donovani*. IC₅₀ (the concentration causing 50% of cell deaths) was 35 µg ml⁻¹ and 38 µg ml⁻¹ for methanolic extract and dichloromethanolic extract, respectively. Plant extracts were also tested for antimalarial activity. However, the extracts of *E. creticum* (4, 20, and 100 µg ml⁻¹), as well as the other species from the same genus tested in the same experiment, namely *Eryngium campestre*, were not active against *P. falciparum* (Fokialakis et al., 2007).

Antioxidant activity

The beneficial effect of many herbal plants on human health may be due to their antioxidant properties. The ability of the bioactive compounds present in *E. creticum* (including phenolic acids and flavonoids) to act as efficient free radical scavengers, as well as their natural origin in contrast to synthetic antioxidants, is the main advantage.

There was a number of studies carried out in order to evaluate the antioxidant power of the extracts (aqueous, ethanolic/methanolic and ethyl acetate) from different parts of *E. creticum* (leaves, stems) using several methods (Ljubuncic et al., 2005; Farhan et al., 2012; Rammal et al., 2013; Dammous et al., 2014; Dirani et al., 2014; Hijazi et al., 2015).

Three *in vitro* antioxidant methods, namely DPPH radical scavenging method (DPPH assay), scavenging activity of hydrogen peroxide radical (H₂O₂ test) and chelating effects on ferrous ions (the Ferrozine test), were used by Farhan et al. (2012) and Dammous et al. (2014) to check the antioxidant activity of fresh leaves and stems of Lebanese *E. creticum*. Moreover, ABTS radical scavenging capacity assay was used to determine their total antioxidant activity (Farhan et al., 2012). The results showed significant antioxidant activity in both aqueous and ethanolic extracts, revealing that

E. creticum is a rich source of different antioxidant compounds (Farhan et al., 2012; Dammous et al., 2014). In DPPH assay, ethanolic extracts from both leaves and stems have higher antioxidant activity than aqueous extracts at different concentrations. The leaves possess higher free radical scavenging activity than the stems (Dammous et al., 2014). The free radical scavenging activity (H_2O_2 test) was enhanced with the increase in the concentration of the extract. The extracts from both the leaves and stems and from both the aqueous and ethanolic extracts of *E. creticum* were able to scavenge H_2O_2 in a concentration-dependent manner (Farhan et al., 2012; Dammous et al., 2014).

The chelating capacity (Ferrozine-test) of the extracts increases with concentration. Both extracts, the aqueous and ethanolic one, provide almost the same chelating activity (Dammous et al., 2014).

The antioxidant capacity of different extracts of *E. creticum* has been evaluated using two *in vitro* tests, the DPPH and iron chelating (spectrophotometric analysis). In the first experiment, the methanolic and aqueous extracts from both the leaves and stems have exerted an antioxidant power in DPPH radical scavenging activity, depending on the concentration. To confirm the results from DPPH method, the Iron-Ferrosine method was used. The results showed that the antioxidant activity of leaves was higher than that of stems, regardless of the concentration. The authors suggested that this activity was due to leaves containing more phenolic compounds, as compared to stems (Rammal et al., 2013). In the second experiment, the antioxidant activity was investigated depending on the different percentages of ethanol in the extracts (40%, 80%, 100%), extraction times (2 h, 4 h, 12 h) and extraction methods (maceration, reflux, microwave assisted extraction). The microwave assisted extraction was the most effective extraction technique. Generally, 80% ethanolic extracts possessed the highest DPPH scavenging activity and 40% ethanolic extracts had the highest iron chelating activity (Hijazi et al., 2015).

The total antioxidant capacity, expressed as vitamin C equivalent antioxidant capacity of fresh leaves and stems, was 79.00 ± 0.80 mg and 50.42 ± 0.50 VCE/100 g fresh weight, respectively (Farhan et al., 2012; Dammous et al., 2014).

The antioxidant potential of the extracts at different concentrations was tested by quantifying their ability to suppress the extent of iron-induced lipid peroxidation in rat liver homogenates. The extract efficacy IC_{50} was very low and the value of the maximum inhibition was moderate compared to other extracts. To conclude, the extracts of *E. creticum* can moderately suppress Fe^{2+} -induced lipid peroxidation (Ljubuncic et al., 2005).

All of these results showed that although *E. creticum* does not show strong antioxidant activity, it might be considered a good source of natural substances that may be employed in the treatment of different diseases associated with oxidative stress.

Cytotoxicity

The cytotoxicity of *E. creticum* extract obtained from a plant from West Crete was tested on a mammalian/monkey kidney fibroblast cell line. The aerial part extract at the concentration of $47.6 \mu\text{g ml}^{-1}$ was not cytotoxic to mammalian cells (Fokialakis et al., 2007).

The cytotoxicity of three extracts (aqueous, methanolic and ethyl acetate) from leaves and stems of fresh plants on the MCF7 breast cancer cell line by the XTT cell viability technique was studied. The results showed that the aqueous and ethyl acetate extracts of both leaves and stems (at the concentration of 2.5 mg ml^{-1}) did not show any cytotoxicity after 48 h of treatment on this cell line, while the methanolic extract of both studied parts inhibited the growth of MCF7 by 72% and 68%, respectively (Rammal et al., 2013).

The MTT and LDH assays are well-established methods (Bunel et al., 2014) to assess mitochondrial competence and cell membrane integrity, respectively. Using these assays, the authors found that the aqueous extract ($1.0 \mu\text{g ml}^{-1}$ – 1.0 mg ml^{-1}) of *E. creticum* did not suppress mitochondrial respiration or increase LDH leakage in PC12 and HepG2 cell cultures (Ljubuncic et al., 2005).

In the recent studies, the cell viability and cytotoxicity effect of aqueous and ethanolic extracts (leaves, stems, roots, and whole plant) of *E. creticum* in HeLa cancer cells were evaluated using the Natural Red Assay. The effect of inhibition was dose and time-dependent. The results showed that the aqueous extracts from leaves (150 , 200 and $250 \mu\text{g ml}^{-1}$) acting for 48 and 72 h (90% inhibition on HeLa cells) and from roots ($250 \mu\text{g ml}^{-1}$, 72 h, 90% inhibition) exerted anti-proliferative activity. On the other hand, the ethanolic extracts showed a significant effect at different concentrations and times of exposition (up to 97%) (Dirani et al., 2014).

Antimutagenic activity

In the study, the antimutagenic activity of ethanolic extract (the highest concentration applied was $120 \mu\text{g ml}^{-1}$) of *E. creticum* was tested in rat hepatocyte primary culture treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), a directly acting mutagen which methylates DNA. It was shown that MNNG induced a massive chromosomal damage to hepatocytes. Antimutagenicity testing was performed in three modes: pre-treatment, combined treatment and post-treatment of the primary cultures with plant extract and MNNG. Therefore, both the induction of metabolizing enzymes, direct interaction of plant constituents with the mutagen and increased recovery, *i.e.* enhanced repair of induced DNA damage, could be evaluated. The results of the investigation clearly indicated the inhibitory effect of the plant extract on MNNG-dependent mutagenicity, and this effect could be attributed to direct antimutagenic activity and increased recovery (Khader et al., 2010).

Antihyperglycemic and hypoglycemic effects

An aqueous decoction of *E. creticum* leaves is used in traditional medicine in Palestine and Jordan as anti-diabetic therapy (Yaniv et al., 1987; Kasabri et al., 2011, 2012).

Jaghahir et al. (1991) carried out an investigation of the hypoglycemic effect of *E. creticum*. The hypoglycemic activity of the aqueous decoction of aerial parts was tested in normoglycemic and hyperglycemic rats with streptozocin-induced diabetes. Drinking water for the animals was replaced with the plant extract and blood glucose concentration was measured after 1, 4, and 24 h. It was found, admittedly, that the extract of eryngo decreased glucose levels in both diabetic and non-diabetic animals and this change was statistically significant for the hyperglycaemic rats only. Nevertheless, it is not known if the rats had free access to food or were fasting within 24 h of the experiment which influences the interpretation of these results. Moreover, replacing water with the tested extract is not a method which gives us certainty that the active substance was really taken in by each animal. The authors suggested that *E. creticum* may have increased the peripheral utilization of glucose, but this interpretation seems to be uncertain regarding the very short period of observation (24 h) and the single dose of the extract used in the study (Jaghahir, 1991). However, we must note that replacing water with the tested extract is questionable, and to obtain reliable results of this experiment the extracts should have been applied intragastrically.

Kasabri et al. (2011) evaluated the effect of the aqueous extract (up to 50 mg ml^{-1}) from fresh aerial parts of Jordanian *E. creticum* on *in vitro* (according to Granfeld method) and *in vivo* enzymatic

starch digestion. *In vitro* enzymatic starch digestion with acarbose, an α -glucosidase-inhibitor, used as a control or with plant aqueous extract was assayed using α -amylase and α -amylglucosidase; while *in vivo* there were observed changes in glycaemia in rats treated with plant extract or with acarbose that were compared to the effects of starch feeding. The results demonstrated the lack of the effect of *E. creticum* extract on enzymatic starch digestion in comparison to the effect induced by acarbose, a reducing agent used widely in postprandial hyperglycaemia. Nevertheless, the aqueous extract from *E. creticum* significantly decreased glucose level during starch tolerance test. Although the *E. creticum*-treated rats did not demonstrate any decrease in overall glycemic excursion *versus* the control and the drug-treated animals, substantial improvements of glucose handling were evident at a later time – 90 and 135 min after corn starch ingestion. Unfortunately, oral administration of *E. creticum* extract had no marked improvement in glucose tolerance in the rats. Moreover, when glucose load was ingested by *E. creticum* rats, the corresponding glycemic incremental curves were not affected during the 165 min time course of the acute experiment. The authors suggest that the lack of *in vitro* inhibitory activity does not relate to the *in vivo* activity, because the intestinal luminal activation of effective entities precursors offers a valid justification for the acute *in vivo* outcomes. The contradicting effects ascribed to *E. creticum* do not necessarily role out any other potential pancreatic or extrapancreatic mode of action (Kasabri et al., 2011).

Next year, the same group of authors aimed at investigating the pancreatic and extrapancreatic effects of the aqueous extract from fresh aerial parts of Jordanian *E. creticum*. They recruited bioassays of β -cell proliferation and insulin secretion, as well as glucose diffusion, as possible models of action. The mouse insulinoma MIN6 β -cell line was the cellular model to examine the *in vitro* effects of *E. creticum* extract on pancreatic β -cell proliferation and insulin secretion. *E. creticum* extract was found to be significantly potentiating MIN6 glucose stimulated insulin secretion (GSIS). *E. creticum* evoking GSIS in MIN6 cells was shown to take place by modulating Ca^{2+} regulated exocytosis machinery. Moreover, *E. creticum* substantially augmented the β -cell proliferation in a dose-dependent manner ($0.001\text{--}1.0\text{ mg ml}^{-1}$). *E. creticum* aqueous extracts may offer a promising avenue for the potential treatment of β -cells demise in diabetes. Hence, intensive chronic testing of plants inducing the pancreatic β -cell expansion will allow the emergence of safe and efficient cell replacement therapies. The authors concluded that future directives may assess the use of *E. creticum* as a new potential source of functional food or nutraceuticals or active leads into diabetes type 2 pharmacotherapy (Kasabri et al., 2012).

Taking into consideration both papers published by Kasabri et al. (2011, 2012), the *in vivo* hypoglycaemic activity of *E. creticum* extract is uncertain, but further studies should be focused on anti-hyperglycemic effect documented *in vivo* and *in vitro* by glucose diffusional retardation effects. The results of present investigative study of Twaij and Al-Dujaili (2014) did not ultimately elucidate the main mode of action of *E. creticum* extract. It was found that the oral administration of aqueous extract from the aerial parts of *E. creticum* produced significant effect in rats, namely reduced postprandial (post-load) hyperglycaemia. Interestingly, the hypoglycemic effects of the aqueous extracts from *E. creticum* were confirmed only in normal and not in alloxan-induced diabetic animals which suggests its insulinotropic activity (Twaij and Al-Dujaili, 2014).

The traditional use of *E. creticum* in the treatment of diabetes is supported by laboratory results from these studies, suggesting the need to isolate and evaluate active constituents responsible for the exhibited biological activity.

Other activities

The methanolic extract of *E. creticum* was evaluated for their hormone sensitive lipase inhibitory potential, quantified by a colorimetric assay that measured the release of *p*-nitrophenol as HSL substrate and expressed as % inhibition of XO activity. Hormone-sensitive lipase (HSL), a neutral lipase, is a vital enzyme in lipid metabolism and general energy homeostasis in mammals. HSL is a component of the metabolic switch between glucose and FFAs as energy sources. The pivotal role of elevated plasma FFAs in the development of insulin resistance and type 2 diabetes have rendered HSL as a potential therapeutic target for this disease; lowering plasma FA levels and, thereby, reducing insulin resistance. The percentage of residual activity of HSL was determined for each extract by comparing the lipase activity of HSL with and without the extract. However, the extract showed weak activity (Bustanji et al., 2011).

Conclusion

This present review offers basic information on current knowledge for further studies of *E. creticum*. The *in vitro* studies and *in vivo* models have provided a simple bioscientific explanation for its various ethnopharmacological uses. Unfortunately, some of the studies appeared to be only partial and did not answer questions from selected research area. Other studies, particularly in the field of phytochemical analysis, remain unimplemented or their results are unreliable due to improperly constructed research methodology. Besides, the majority of the pharmacological studies were carried out using crude and poorly characterized extracts. Therefore, the authors of this article took *in vitro* cultures of *E. creticum* to amplify the plant material needed for in-depth studies of selected phytochemicals and selected biological activities.

Authors' contributions

MK contributed in the review of the scientific bibliography using the following publishers websites and electronic databases to collect information on the subject: Elsevier, Springer, PubMed, Medline, Google Scholar and Web of Science. Additionally, she analyzed published monographs theses, and proceedings of scientific congresses. JK drew all the chemical formulas. JK, MD and BT participated in the critical reading and final editing of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Abou-Jawdah, Y., Sobh, H., Salameh, A., 2002. Antimycotic activities of selected plant flora, growing wild in Lebanon, against phytopathogenic fungi. *J. Agric. Food Chem.* 50, 3208–3213.
- Abu-Rabia, A., 2005. Herbs as a food and medicine source in Israel. *Asian Pac. J. Cancer Prev.* 6, 101–107.
- Aburjai, T., Hudaib, M., Tayyem, R., Yousef, M., Qishawi, M., 2007. Ethnopharmacological survey of medicinal herbs in Jordan, the Ajloun Heights region. *J. Ethnopharmacol.* 110, 294–304.
- Affi, F.U., Al-Khalil, M., Aqel, M., Al-Muhteseb, M.H., Jaghabir, M., Saket, M., Muheid, A., 1990. Antagonistic effect of *Eryngium creticum* extract on scorpion venom *in vitro*. *J. Ethnopharmacol.* 29, 43–49.
- Al-Khalil, S., 1994. Phytochemistry of *Eryngium creticum*. *Alex. J. Pharm. Sci.* 8, 73–75.
- Alkofahi, A., Sallal, A.J., Disi, A.M., 1997. Effect of *Eryngium creticum* on haemolytic activities of snake and scorpion venoms. *Phytother. Res.* 11, 540–542.
- Ali-Shtayeh, M.S., Abu Ghdeib, S.I., 1999. Antifungal activity of plant extracts against dermatophytes. *Mycoses* 42, 665–672.
- Ali-Shtayeh, M.S., Yaghmour, R.M.-R., Faidi, Y.R., Salem, K., Al-Nuri, M.A., 1998. Antimicrobial activity of 20 plants used in folkloric medicine in the Palestinian area. *J. Ethnopharmacol.* 60, 265–271.

- Ayoub, N.A., Kubeczka, K.-H., Nawwar, M.A.M., 2003. An unique n-propyl sesquiterpene from *Eryngium creticum* L. (Apiaceae). *Pharmazie* 58, 674–676.
- Bunel, V., Ovedraogo, M., Nguyen, A.T., Stevigny, C., Duez, P., 2014. Methods applied to the *in vitro* primary toxicology testing of natural products: state of the art, strengths and limits. *Planta Med.* 80, 1210–1226.
- Bustanji, Y., Issa, A., Moulay, A., Hudaib, M., Tawaha, K., Mohammad, M., Hamed, S., Masri, I., Alali, F.Q., 2011. Hormone sensitive lipase inhibition by selected medicinal plants. *J. Med. Plants Res.* 5, 4405–4410.
- Caballero, R., Fernandez-Gonzalez, F., Badia, R.P., Molle, G., Roggero, P.P., Bagella, S., D'Ottavio, P., Papanastasis, V.P., Fotiadis, G., Sidiropoulou, A., Ispikoudis, I., 2009. Grazing systems and biodiversity in Mediterranean areas: Spain, Italy and Greece. *Pastos XXXIX*, 1–152.
- Calvino, C.I., Martinez, S.G., Downie, S.R., 2008. The evolutionary history of *Eryngium* (Apiaceae, Saniculoideae): rapid radiations, long distance dispersals, and hybridizations. *Mol. Phylogenet. Evol.* 46, 1129–1150.
- Celik, A., Ayddinlik, N., Arslan, I., 2011. Phytochemical constituents and inhibitory activity towards methicillin-resistant *Staphylococcus aureus* strains of *Eryngium* species (Apiaceae). *Chem. Biodivers.* 8, 454–459.
- Dammous, M., Farhan, H., Rammal, H., Hijazi, A., Bassal, A., Fayyad-Kazan, H., Makhour, Y., Badran, B., 2014. Chemical composition of Lebanese *Eryngium creticum* L. *Int. J. Sci.* 3, 40–53.
- Della, A., Paraskeva-Hadjichambi, D., Hadjichambis, A.Ch., 2006. An ethnobotanical survey of wild plants of Paphos and Larnaca countryside of Cyprus. *J. Ethnobiol. Ethnomed.*, <http://dx.doi.org/10.1186/1746-4269-2-34>.
- Dirani, Z., Makki, R., Rammal, H., Naserddine, S., Hijazi, A., Kazan, H.F., Nasser, M., Daher, A., Badran, B., 2014. The antioxidant and anti-tumor activities of the Lebanese *Eryngium creticum* L. *IJBPA* 3, 2199–2222.
- Don, G., 1831. A general system of gardening and botany: containing a complete enumeration and description of all plants hitherto known with their generic and specific characters, places of growth, time of flowering, mode of culture and their uses in medicine and domestic economy: preceded by introductions to the Linnaean and Natural Systems and a glossary of the terms used; founded upon Miller's Gardener's Dictionary and arranged according to the Natural System; in four volumes, Tom 3 (e-Book Google), pp. 176–177.
- El-Saket, M., 1990. Potency of Jordanian *Cerastes cerastes* snake venom and the effect of *E. creticum* on this potency. *Bull. Fac. Pharm. Cairo Univ.* 28, 53–55.
- Erdem, S.A., Nabavi, S.F., Orhan, I.E., Daglia, M., Izadi, M., Nabavi, S.M., 2015. Blessings in disguise: a review of phytochemical composition and antimicrobial activity of plants belonging to the genus *Eryngium*. *DARU J. Pharm. Sci.* 23 (53), 1–22.
- Farhan, H., Malli, F., Rammal, H., Hijazi, A., Bassal, A., Ajouz, N., Badran, B., 2012. Phytochemical screening and antioxidant activity of Lebanese *Eryngium creticum* L. *Asian Pac. J. Trop. Biomed.* 2, S1217–S1220.
- Fokialakis, N., Kalpoutzakis, E., Tekwani, B.L., Khan, S.I., Kobaisy, M., Saltsounis, A.L., Duke, S.O., 2007. Evaluation of the antimalarial and antileishmanial activity of plants from the Greek island of Crete. *J. Nat. Med.* 61, 38–45.
- Hijazi, A., Al Masri, D.S., Farhan, H., Nasser, M., Rammal, H., Annan, H., 2015. Effect of different ethanol concentrations, using different extraction techniques, on the antioxidant capacity of Lebanese *Eryngium creticum*. *J. Pharm. Chem. Biol. Sci.* 3, 262–271.
- Jaghabir, M., 1991. Hypoglycemic effects of *Eryngium creticum*. *Arch. Pharm. Res.* 14, 295–297.
- Jaghabir, M., Saket, M., Afifi, F., Khalis, S., Muheid, A., 1989. Potency of Jordan *Leiurus quinguistriatus* scorpion venom and the effect of *Eryngium creticum* on this potency. *Dirasat* 4, 172–178, Jordan University VI.
- Jawdat, D., Al-Faouy, H., Ayyoubi, Z., Al-Safadi, B., 2010. Molecular and ecological study of *Eryngium* species in Syria. *Biologia* 65, 796–804.
- Jeambey, Z., Johns, T., Talhouk, S., Batal, M., 2009. Perceived health and medicinal properties of six species of wild edible plants in north-east Lebanon. *Public Health Nutr.* 12, 1902–1911.
- Kasabri, V., Afifi, F.U., Hamdan, I., 2011. Evaluation of the acute antihyperglycemic effects of four selected indigenous plants from Jordan used in traditional medicine. *Pharm. Biol.* 49, 687–695.
- Kasabri, V., Abu-Dahab, R., Afifi, F.U., Naffa, R., Majdalawi, L., 2012. Modulation of pancreatic MIN6 insulin secretion and proliferation and extrapancreatic glucose absorption with *Achillea santolina*, *Eryngium creticum* and *Pistacia atlantica* extracts: *in vitro* evaluation. *J. Exp. Integr. Med.* 2, 245–254.
- Khader, M., Bresgen, N., Eckl, P.M., 2010. Antimutagenic effects of ethanolic extracts from selected Palestinian medicinal plants. *J. Ethnopharmacol.* 127, 319–324.
- Konig, Ch., Sims, J., 1806. Vegetable productions of the countries situated between the Terek and Kur. *Ann. Bot.*, 426–428.
- Lardos, A., 2012, May. Historical *iatriasophia* texts and modern plant usage in monasteries on Cyprus. A thesis. Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London.
- Ljubuncic, P., Azaizeh, H., Portnaya, I., Cogan, U., Said, O., Abu Saleh, K., Bomzon, A., 2005. Antioxidant activity and cytotoxicity of eight plants used in traditional Arab medicine in Israel. *J. Ethnopharmacol.* 99, 43–47.
- Makki, R., Dirani, Z.E., Rammal, H., Sweidan, A., Al Bazzal, A., Chok, A., 2015. Antibacterial activity of two Lebanese plants: *Eryngium creticum* and *Centranthus longiflorus*. *J. Nanomed. Nanotechnol.*, <http://dx.doi.org/10.4172/2157-7439.1000315>.
- Marles, R.J., Farnsworth, N.R., 1995. Antidiabetic plants and their active constituents. *Phytomedicine* 2, 137–189.
- Mayer-Chissick, U., Lev, E., 2014. Wild edible plants in Israel tradition versus cultivation. In: Yaniv, Z., Dunat, N. (Eds.), *Medicinal and Aromatic Plants of the Middle-East. Medicinal and Aromatic Plants of the World 2*. Springer, Dordrecht/Heidelberg/New York/London, <http://dx.doi.org/10.1007/978-94-017-9276-9>.
- Mahommadhosseini, M., 2013. Hydrodistilled volatile oil from stems of *Eryngium creticum* Lam. in the Marginal Brackish Regions of Semnan Province by using gas chromatography combined with mass spectrometry. *Asian J. Chem.* 25, 390.
- Mors, W.B., do Nascimento, M.C., Ruppelt Pereira, B.M., Alvares Pereira, N., 2000. Plant natural products active against snake bite – the molecular approach. *Phytochemistry* 55, 627–642.
- Muschler, R., 1912. A Manual Flora of Egypt. Friedlaender R and Sohn, pp. 44–45.
- Oukkache, N., El Jaoudi, R., Ghalim, N., Chgoury, F., Bouhaouala, B., Mdaghri, N.E., Sabatier, J.M., 2014. Evaluation of the lethal potency of scorpion and snake venoms and comparison between intraperitoneal and intravenous injection routes. *Toxins (Basel)* 12 (6), 1873–1881.
- Palevitch, D., Yaniv, Z., Dafni, A., Friedman, J., 1985. Ethnobotanical Survey of the Flora of Israel as a Source for Drugs. Ministry of Science, Jerusalem (Hebrew).
- Rammal, H., Farhan, H., Jamaledine, N., El Mestrah, M., Nasser, M., Hijazi, A., 2015. Effects of altitude on the chemical composition and on some biological properties of Lebanese *Eryngium creticum* L. *J. Chem. Pharm. Res.* 7, 887–893.
- Rammal, H., Farhan, H., Mohsen, H., Hijazi, A., Kobeissy, A., Daher, A., Badran, B., 2013. Antioxidant, cytotoxic properties and phytochemical screening of two Lebanese medicinal plants. *Int. Res. J. Pharm.* 4, 132–136.
- Saad, B., Azaizeh, H., Said, O., 2008. Arab herbal medicines. In: Preedy, V.R., Watson, R.R. (Eds.), *Botanical Medicine in Clinical Practice*. CAB International.
- Saad, B., Said, O., 2011. Greco-Arab and Islamic herbal medicine. In: *Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues*. John Wiley & Sons, Inc. Publication.
- Thiem, B., Wiatrowska, I., 2007. *Eryngium campestre* L. (field eryngo) and other species of *Eryngium* L. – little know medicinal plants. *Herba Pol.* 53, 93–102.
- Tutin, T.G., Burges, D.H., Valentine, S.M., Walters, S.M., Webb, D.A., 1968. *Flora Europaea: Rosaceae to Umbelliferae*. Cambridge University Press, pp. 321–322.
- Twaij, H.A., Al-Dujaili, E.A.S., 2014. Evaluation of the Anti-diabetic and Anti-ulcer Properties of Some Jordanian and Iraqi Medicinal Plants: A Screening Study. IBIMA Publishing. *JMED*, <http://dx.doi.org/10.5171/2014.539605>.
- Wolff, H., 1913. *Umbelliferae – Saniculoideae*. In: Engler, A. (Ed.), *Das Pflanzenreich*, IV. 228 (heft 61). Engelmann W., Berlin, pp. 106–271.
- Wörz, A., 1999. A taxonomic index of the species of *Eryngium* L. *Stuttgarter Beiträge zur Naturkunde A* 596, 1–48.
- Wörz, A., 2004. On the distribution and relationships of the South-West Asian species of *Eryngium* L. (Apiaceae – Saniculoideae). *Turk. J. Bot.* 28, 85–92.
- Wörz, A., 2005. A new subgeneric classification of the genus *Eryngium* L. (Apiaceae – Saniculoideae). *Bot. Jahrb. Syst.* 126, 253–259.
- Wörz, A., 2006. Systematics and distribution patterns of the Balkan species of *Eryngium* (Apiaceae, Saniculoideae). *Phytol. Balc.* 12, 221–230.
- Wörz, A., Diekmann, H., 2010. Classification and evolution of the genus *Eryngium* L. (Apiaceae – Saniculoideae): results of fruit anatomical and petal morphologies studies. *Plant Divers. Evol.* 128, 387–408.
- Yaniv, Z., Dafni, A., Friedman, J., Plevitch, D., 1987. Plants used for the treatment of diabetes in Israel. *J. Ethnopharmacol.* 19, 145–151.