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CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF *ERYNGIUM CRETICUM*- A REVIEW

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Abstract:
The preliminary phytochemical analysis of Eryngium creticum showed that it contained alkaloids, tannins, resins, saponins, coumarin, phenols, terpenoids, flavonoids and carbohydrates. The previous pharmacological studies revealed that Eryngium creticum possessed antioxidant, antimicrobial, anti-inflammatory, antinociceptive, anticancer, antileishmanial and many other effects. The current review highlights the chemical constituents, pharmacological and therapeutic effects of Eryngium creticum.

Keywords: *Eryngium creticum, constituents, pharmacology, therapeutic.*

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INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-16]. The preliminary phytochemical analysis of *Eryngium creticum* showed that it contained alkaloids, tannins, resins, saponins, coumarin, phenols, terpenoids, flavonoids and carbohydrates. The previous pharmacological studies revealed that *Eryngium creticum* possessed antioxidant, antimicrobial, anti-inflammatory, antinociceptive, anticancer, anti-leishmanial and many other effects. The current review will discuss the chemical constituents, pharmacological and therapeutic effects of *Eryngium creticum*.

Synonyms:

Eryngium cyaneum Sm. and *Eryngium syriacum* Lam [17].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Tracheobionta, **Superdivision**: Spermatophyta, **Division**: Magnoliophyta, **Class**: Magnoliopsida, **Subclass**: Rosidae, **Order**: Apiales, **Family**: Apiaceae / Umbelliferae, **Genus**: *Eryngium*, **Species**: *Eryngium creticum* [18].

Common names:

Arabic: Shuk Al-Akrabati, Qurs'anna, Qursanna ekritiah**, English**: Eryngo, Snake root, Field Eryngo small-headed, Blue eryngo, Cretan eryngo; **French**: Panicaut de Crete; **Italian:** Calcatreppola di Creta [19].

Distribution:

Eryngium creticum is distributed in **North Africa** (Egypt), Asia (Iraq, Palestine, Lebanon, Syria, Jordan and Turkey) and **Europe** (Albania, Bulgaria, Greece, Macedonia, Montenegro and Slovenia) [20].

Description:

Eryngium 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 [21].

Traditional uses:

It was cultivated for the consumption as a leafy vegetable in salads. It was used medicinally as a diuretic and laxative. Roots and seeds were immersed in water are drunk by people to treat kidney stones, infections, skin diseases, and tumors as antidote for the treatment of the snakebite. It was also used for the treatment of liver diseases, poisoning, anemia and infertility [22-23].

Chemical constituents:

The preliminary phytochemical analysis showed that the plant contained alkaloids, tannins, resins, saponins, coumarin, phenols, terpenoids, flavonoids and carbohydrates [24-25].

The total alkaloids in the plant reached 0.57 ± 0.0058 wt %, humidity 79.16 ± 0.0078 wt %, total ash 18.10 ± 0.0015 wt %, total phenolic contents 8.57 ±0.006 - 17.68± 0.0043 µg/ml and total flavonoids contents 17.73± 0.012 - 20.19± 0.041 µg/ml [26].

The highest flavonoids contents was recorded in the ethanolic extract of leaves and stems, while the highest total phenolic content was recorded in the aqueous extract of both leaves and stems [24].

The essential oils yield of *Eryngium creticum* was 0.21% (v/w). The oils were colorless, with a weak perfumery odor. They contained Pentanal 0.97±3.18%, -Methylhexane 0.89±2.08 %, Pentan-1-ol 0.54±5.20%, 3,7-Dimethyloct-1-ene 0.51±3.9%, 2,4-Dimethylhexane 0.14±1.18%, 3-Ethylhexane 0.43±0.66%, 3,4-Dimethylhex-1-ene 2.90±2.84%, Octane 8.95±2.32%, Hexanal 52.90±2.70%, 6-Methylhepta-3,5-dien-2-one 2.13±2.74 %, (E)-Hex-2-enal 1.02±3.20%, Acetic acid 3.57±2.36%, Heptan-3-one 1.78±3.24%, Non-1-ene 0.27±2.72%, Heptan-2-one 2.01±3.42%, 2-Butylfuran 2.79±3.16%, 5-Methylhexan-2-one 0.50±3.44%, Nonane 0.56±2.7%, Heptanal 13.90±3.82%, CO_2 0.09±1.94%, Pentanoic acid 0.90±3.10% and (1R)-a-Pinene 2.51±3.58% [27].

The chemical analysis of volatile oil of the stems of *Eryngium creticum* growing wild in Iran, showed that the total oil contents was 0.18 w/w % with a clear yellowish colour. Seventeen components were identified 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 characterized by the presence of higher amounts of oxygenated monoterpenes [28].

Nine fatty acid derivatives were extracted from *Eryngium creticum*: Methyl tetradecanoate 32.56%, Methyl hexadecanoate 49.34 %, Methyl 9,12-octadecanoate 8.59 %, Methyl octadecanoate 13.89 %, Cyclohexyl nonyl oxalate 28.94 %, 1-Methylhexyl hexanoate 10.89 %, Allyl nonyl oxalate 4.23 %, 2-propyl tridecylsulphinate 2.93 % and Methyl 4-hydroxyl octadecanoate 5.84 % [26].

A sesquiterpene, 1-n-propyl-perhydronaphthaline 1,2,4a,5,6,7,8,8a-octahydro-4-methyl-1-propyl-naphthalene-7-carbaldehyde and a new natural methyl ketone eicos-8,11 -dien-18-ol-2-one were isolated from the hexane: ether extract of the aerial parts of *Eryngium creticum* [29].

Phytochemical investigations of the roots of Jordanian *Eryngium creticum*, showed the presence of nine compounds: two coumarins, deltion and marmesin, cyclic alcohol, quercitol, monoterpeneglycoside 3-(β-D-glucopyranosyloxymethyl)-2,4,4-trimethyl-2,5-cyclohexadien-1-one, phloroglucinol glycoside (1-(β-D-glu-copyranosyloxy-3-methoxy-5-hydroxy benzene)), β-sitosteroland and its glycoside (β-sitosterol-β-D-glucopyranose), and two sugars, mannitol and dulcitol [30].

Pharmacological effects:

Antidiabetic effect:

The hypoglycemic activity of an aquous decoction of arial parts of *Eryngium creticum* was tested in normoglycemic and streptozocin-hyperglycemic rats. Results indicate that those extract caused significant reductions in blood glucose concentrationin in normoglycemic rats (20%), and streptozocin-hyperglycemic rats (64.2%) when given orally [31].

The hypoglycemic effects of the aqueous extracts of *Eryngium creticum* aerial parts were examined in normal, glucose loaded and alloxan diabetic experimental animals. *Eryngium creticum* exhibited a potent and significant hypoglycemic effects in normal-fed, glucose loaded and and alloxan diabetic animals [32-34].

The pancreatic and extrapancreatic effects of of *Eryngium creticum* was studied using bioassays of β-cell proliferation and insulin secretion as well as glucose diffusion as possible modes of actions. Similar to L-alanine insulinotropic efficacy in MIN6 β-cell, glucose-stimulated Ca^{2+} regulated- insulin secretion was potentiated by crude aqueous extracts of *Eryngium creticum* (0.01 mg/ml). Comparable to glucagon-like peptide-1-enhanced β-cell proliferation in 2-day treatment wells, a dose dependent augmentation of bromodeoxyuridine incorporation was obtained with the *Eryngium creticum* crude aqueous extracts (0.1, 0.5 and 1 mg/ml) [35].

Anti-scorpion and snake and venoms:

Aqueous and ethanol extracts of the fresh and dried leaves and roots of *Eryngium creticum* were tested for their inhibitory effect against snake and scorpion venoms. The fresh leaf extract gave a higher percentage inhibition of the haemolytic activity of the scorpion venom *Leiurus quinquesteiartus* compared with the dried leaf extract. Extracts of both fresh and dried roots gave 100% inhibition of the snake and scorpion venoms. However, ethanol extracts of the leaves and roots enhanced RBC haemolysis rather than inhibiting venom activities on red blood cells [36].

Aqueous extract of *Eryngium creticum* in combination with Cerastes snake venom prolonged the life span from 12 to 72 h [37].

The aqueous extract of *Eryngium creticum* caused a dose dependent inhibition of rabbits tracheal and jejunal contraction induced by the *L. quinquestriatus* scorpion venom and inhibited the spontaneous movements of the jejunum [30, 38].

Antioxidant effect:

In estimation of antioxidant activity of *Eryngium creticum*, it appeared that the antioxidant activity of the aqueous extracts of the leaves and stems of *Eryngium creticum* was increased with increasing the concentration of the aqueous extract. This increase was reached 59 % and 35 % at the concentration of 0.5 mg/ml for the leaves and stems respectively. Studies on the same plant but from an altitude 300 m showed that the leaves and stems at the same concentration (0.5 mg/ml), exerted an antioxidant activity of 90 % and 75 % respectively. On the other hand, at a concentration of 0.5 mg/ml, the ethanolic extract showed an important antioxidant activity of both leaves (81 %) and stems (79 %). However, this antioxidant capacity was highest for the plant that grows at 300 m, it reached the 93 % for the leaves and 82 % for the stems. In addition, methanolic extract showed that both leaves and stems have exerted an important antioxidant activity reaching 90 % and 79 % respectively at a concentration of 0.5 mg/ml [24].

Antioxidant power of the Lebanese *Eryngium creticum* was determined by DPPH assay using different extraction techniques. The results indicated that the antioxidant effect was increased with the concentration, the highest antioxidant activity in all the extraction techniques was obtained at a concentration of 0.5 mg/ml [26, 39].

The *in vitro* antioxidant activity of the aqueous and ethanolic extracts from different parts (leaves, stems, roots, and the whole plant) of the fresh plant *Eryngium creticum* from the first and second harvest, were

performed using antioxidant DPPH radical scavenging and superoxide radical scavenging tests. The results showed that the 4 parts of the plant exerted antioxidant activity that may be due to their phenolic content. The antioxidant activity of the aqueous extract of leaves, stems and roots of *Eryngium creticum* was increased with increasing concentrations. It reached 77% , 89% and 70% at the concentration of 0.5 mg/ml of leaves, stems and roots, respectively, for the first harvest, while, it reached 73%, 59% and 34% at the same concentration of the leaves, stems and roots respectively for the second harvest. The aqueous extract of the whole plant showed an antioxidant activity of 72% at the same concentration for the first harvest and 49% for the second. The ethanolic extract showed an antioxidant activity of 93%, 82% and 44% for leaves, stems and roots, respectively, at a concentration of 0.5 mg/ml for the first harvest, whilst for the second harvest, the antioxidant activity was 56%, 65% and 61% at the same concentration for the leaves, stems and roots, respectively [40].

The antioxidant effect of three extracts (aqueous, methanolic and ethyl acetate) from fresh leaves and stems of *Eryngium creticum* was studied. The results showed that both leaves and stems extracts of the plant exerted an antioxidant activity correlated to their phenolic content [41]. The consumption of 100 g of fresh *Eryngium creticum* leaves and stems provided antioxidants activity equivalent to (78.50±0.80) and (50.42±0.50) mg of vitamin C, respectively [25].

Antimicrobial effect:

The antibacterial activity of the Aqueous and ethanolic extracts of *Eryngium creticum* leaves and stems was studied against three Gram positive bacteria (*Staphylococcus epidermidis* CIP 444, *Staphylococcus aureus* ATCC 25923, and *Enterococcus faecalis* ATCC 29212) and two Gram negative strains (*Escherichia coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853). Aqueous extracts from *Eryngium creticum* showed stronger antibacterial activity than the ethanolic extracts against both Gram positive and Gram negative strains. Among these strains, Gram positive ones were more sensitive, with *Staphylococcus epidermidis* being the most inhibited with MIC=MBC=5 mg/ml for the leaves aqueous extract, in particular in the first harvest period. During the second period, however, the activity decreases, to show equal concentrations (MIC = MBC = 27.9 mg/ml). Whereas the stem aqueous extract, during the first harvest period, exhibited a considerable activity with MIC=26 mg/ml and MBC=53 mg/ml [42].

The antibacterial activity of *Eryngium creticum* was tested against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris* and *Pseudomonas aeruginosa* using disc diffusion method. The aqueous was more effective against *K. pneumoniae* than the ethanolic extract, while the ethanolic extract was more effective against *P. vulgaris*. However, against *S. aureus, E. coli* and *P. aeruginosa*, there were no differences between the effect of the aqueous and ethanolic extracts [43].

The essential oils of *Eryngium creticum* were tested for their inhibitory activity against nine different methicillin-resistant *Staphylococcus aureus* (MRSA) strains by agar disc diffusion method. Three strains showed zone of inhibition 9-11mm, four strains 5-7mm and 2 strains resisted *Eryngium creticum* essential oils [27].

The antifungal effect *Eryngium creticum* aqueous extracts (15 micrograms/ml medium) was investigated against *M. canis, T. mentagrophytes* and *T. violaceum*. The percentage of mycelial inhibition was 12.4±4.26, 56.6±7.41 and 38.8±7.98% for the three fungi, respectively [44].

Anti-inflammatory and antinociceptive effects:

Ethanolic and aqueous extracts obtained from either aerial parts or roots of eight Eryngium species growing in Turkey, were evaluated for their *in vivo* anti-inflammatory and antinociceptive activities, using p-benzoquinone-induced writhing test for estimation of antinociceptive activity, and carrageenan-induced hind paw oedema and TPA-induced ear oedema tests for anti-inflammatory activity. Ethanolic extracts either from the aerial parts or roots of *Eryngium creticum* showed apparent anti-inflammatory and antinociceptive activity [45].

The anti-inflammatory activity of extracts prepared using different solvents from leaves and stems of *Eryngium creticum* was evaluated by measuring the viability of the RAW264.7 macrophage cell line after 24 hours treatment with increasing concentrations (5, 25, 50, 100, and 200 µg/ml) of these extracts. The cell viability (XTT test) showed that aqueous extracts of the leaves and stems of *Eryngium creticum* increased the number of macrophages (RAW 264.7) with increasing concentrations of the extract from 5 to 200 µg/ml compared to control [24].

Anticancer effect:

Ethanolic extracts of *Eryngium creticum* were tested against N-methyl-N-nitro-N-nitrosoguanidine (MNNG), a directly acting mutagen. Primary cultures of rat hepatocytes were used and the plant ethanolic extracts were applied along with MNNG in three protocols: pre-treatment, combined treatment and post-treatment. The results indicated an inhibitory effect of the plant extracts on MNNG mutagenicity, while the extracts had no effect on cytotoxicity indicators such as necrosis and apoptosis [46].

The cytotoxic effects of three extracts (aqueous, methanolic and ethyl acetate) from fresh leaves and stems of *Eryngium creticum*, were studied on MCF7 breast cancer cell line using XTT cell viability technique. The results showed that the aqueous and ethyl acetate extracts of both leaves and stems of the plant inhibited the growth of cancer cell line from 68 % to 72 % [41].

The anticancer activity of the extracts prepared from leaves and stems of *Eryngium creticum* by different solvents was evaluated by measurement of cell viability in MCF-7 cell line and MDA-MB-468 cells after treatment for 24 and 48 hours with increasing concentrations (5, 25, 50, 100, and 200 µg/ml) of these extracts. After 24 hours treatment with the aqueous extract from leaves and stems of *Eryngium creticum* with increasing concentrations, caused partial inhibition of the proliferation of cancer cells MCF-7 and MDA. Leaves extracts induced a maximal inhibition of the cell line MCF-7 at a concentration of 200 µg/ml. For the MDA cell line, the maximum inhibition of the proliferation was occurred at low concentrations (50 and 100 µg/ml). On the other hand aqueous extracts from stems of *Eryngium creticum* did not exert an antiproliferative effect at all used concentrations. After 24 h treatment with ethanolic extract, it was noted that both leaves and stems of the plant did not exert antiproliferative effect of the MCF-7 cell line at all concentrations. Leaves ethanolic extract at the concentration of 200 µg/ml decreased the number of MDA cells by 6%. Stems extracts showed a partial inhibition of the proliferation at the concentrations 25 and 100 µg/ml by 18 % and 6 % respectively. The methanolic extract of the leaves at the concentration of 200 µg/ml induced significant decrease in the number of MCF-7 and MDA cells by 62 % and 48 % respectively. While, all concentrations of stems except 25 µg/ml induced antiproliferative activity by decreasing the number of MCF-7 cells. The most important concentration was 5 µg/ml which decreased the number of MCF-7 by 28 %. For the MDA cells, methanolic extract of stems was only decreased the number of cells at the concentration 5 µg/ml. After 48 hours treatment with the three extracts from leaves and stems of *Eryngium creticum*, the number of treated cells was lower than the control for both MCF-7 and MDA cell lines. The most important decrease was noted for the concentration of 200 µg/ml of both leaves and stems for all extracts [24].

The anti-proliferative and cytotoxic activities of the aqueous and ethanolic extracts from different parts (leaves, stems, roots, and the whole plant) of the fresh plant *Eryngium creticum* from the first and second harvest, were performed using cytotoxic and cell viability (Neutral red assay on HeLa cells), and apoptotic activity (DNA fragmentation assay on HeLa cells). The results showed that the 4 parts of this plant inhibited the viability of HeLa cell line in a time-dependent (0–72 h) and dose-dependent (0–250 µM) manner. The ethanolic extracts from leaves of the second harvest were the most potent (at 48 h) with an IC_{50} value of ≤ 47.24 µg/ml [40].

Antileishmanial activity:

Antileishmanial activity of *Eryngium creticum* extract was tested *in vitro* on a culture of *Leishmania donovani* promastigotes. IC_{50} of dichloromethane extract of the aerial parts of *Eryngium creticum* against *Leishmania donovani* was 38µg/ml, while IC_{50} of methanolic extract of the aerial parts of *Eryngium creticum* was 35µg/ml [47].

LD_{50} and toxicity:

LD_{50} of *Eryngium creticum* aerial parts aqueous extract was 2400mg/kg in mice, equivalent to 23.8g crude, and 24.7 of the leaves extract. However, in therapeutic doses, the extracts had no significant changes in the spontaneous motor activity and rectal temperature. They did not produce any other changes in behaviour, food and water intake and the morphology of viscera [32, 48].

CONCLUSION:

The current paper reviewed the chemical constituent, pharmacological and therapeutic effects of *Eryngium creticum* to be utilize in the medical practice as a result of its safety and effectiveness.

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