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Phytochemical Constituents and Pharmacological Activities of *Eryngium* L. (Apiaceae)

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Abstract: *Eryngium* L. is the largest and arguably the most taxonomically complex genus of the family Apiaceae. The genus has approximately 250 species throughout the world, with the center of diversity in South America. Some *Eryngium* species are cultivated as ornamental, vegetable, or medicinal crops for folk uses. With increasing chemical and biological investigations, *Eryngium* has shown its potential as pharmaceutical crops. This review focuses on phytochemistry and pharmacological activities of 127 compounds isolated and identified from 23 species of *Eryngium*, particularly non-essential oil compounds such as terpenoids, triterpenoid saponins, flavonoids, coumarins, polyacetylenes, and steroids. *Eryngium* extracts or isolates have shown *in vitro* bioactivitities such as cytotoxicity against various human tumor cell lines, anti-inflammatory, anti-snake and scorpion venoms, antibacterial, antifungal, and antimalarial, antioxidant, and antihyperglycemic effects. *In vivo* studies through various animal models have also shown promising results. However, chemical constituents and their bioactivities of most species of this highly diversified genus have not been investigated. The molecular mechanism of bioactivities (particularly cytotoxicity and anti-snake and scorpion venoms) of *Eryngium* isolates remains elusive. Also, anti-tumor activity of polyhydroxylated triterpenoid saponins isolated from *Eryngium* needed to be furthur explored.

Keywords: *Eryngium* L., ethnobotany, phytochemistry, triterpenoid saponins, flavonoids, polyacetylenes, cytotoxicity, anti-inflammatory activity, anti-snake and scorpion venoms effects.

INTRODUCTION

Eryngium L. consists of approximately 250 species in Eurasia, North Africa, North and South America, and Australia [1, 2]. It is the largest and arguably the most taxonomically complex genus of the family Apiaceae [3]. Some species are rare or endangered, e.g., *E. alpinum* L., *E. aristulatum* Jeps. var. *parishii* (J.M. Coult. & Rose) Mathias & Constance, *E. constancei* Sheikh, *E. cuneifolium* Small, *E. viviparum* [4-7]. Wolff's (1913) treatment of *Eryngium* is the most comprehensive and predominant: two groups were recognized within the genus *Eryngium*: "Species gerontogeae" representing 12 sections from the Old World (Africa, Europe, and Asia) and "Species americanae and australienses" including 22 sections from the New World (Americas and Australia) [8]. Based on morphology, Wörz (2005) proposed five subgenera within *Eryngium*: subg. *Eryngium*, subg. *Fruticosa*, subg. *Monocotyloidea*, subg. *Semiaquatica*, and subg. *Foetida* with the subg. *Eryngium* occurring in Europe, Western Asia and North Africa, the other four subgenera mostly in the New World and in Australia [2, 9]. However, Wörz's classification is not supported by phylogenic data. Recent infrageneric relationship analysis of Calviño *et al*. (2007) using sequence data from the chloroplast DNA trnQ-trnK 5'-exon and nuclear ribosomal DNA ITS regions of 118 species support Wolff's two-group classification [3]. Calviño *et al*. (2007) recognized two subgenera within the genus: subg. *Eryngium* and subg. *Monocotyloidea* [3].

Like many other members of the celery or carrot family, *Eryngium* has been used as ornamental, vegetable, or medicinal plants. Some species, such as *E. foetidum* L., *E. maritimum* L., *E. planum* L., *E. dichotomum* Desf., *E. campestre* L. and *E. creticum* Lam. have been used as food or in traditional medicine locally or worldwide [10]. *E. foetidum* and *E. caucasicum* Trautv. are cultivated as leaf vegetable crops in Asia and Africa [11, 12]. The fruits of *E. foetidum* were taken as food in Nigeria. The plant is indigenous to Tropical America and the West Indies where it is used as medicine and food some having domesticated the plant in their kitchen gardens and orchards. It has become naturalized and often is cultivated across South Asia, the Pacific islands, Tropical Africa and the warmer southern parts of Europe [13].

Some species have been used in folk medicine. *E. campestre* is a well-known plant of the Apiaceae family and is used in Turkish folk medicine. Infusions of the aerial and root parts are used as an antitussive, diuretic, appetizer, stimulant, and aphrodisiac [14-16]. *E. creticum* has been used in folk medicine in Jordan as a remedy for scorpion stings in the rural areas and as a hypoglycemic agent [17]. *E. elegans* Cham. & Schltdl. was reported to be used for diuretic uses in Argentina [18], and *E. foetidum* for the treatment of several anti-inflammatory disorders in China [19].

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Several *Eryngium* species are used as medicine by various tribes of Native Americans. Whole plants of *E. alismifolium* are used for diarrhea; roots of *E. aquaticum* are used as emetic and gastrointestinal infusion, antidote for poisons, tapeworms and pinworms, diuretic, and venereal diseases; and roots of *E. yuccifolium* Michx. are used as snakebite and toothache remedy as well as for neuralgia, bladder and kidney troubles; roots of *E. yuccifolium* var. *synchaetum* are used for human and animal sickness such as digestive problems, diarrhea, headache, body soreness, and snakebites [20]. Some recent bioactivity investigations have confirmed some traditional medicinal uses. Ethanol extracts of *E. billardieri* Delar., *E. campestre, E. creticum, E. davisii, E. foetidum, E. isauricum, E. kotschyi, E. maritimum,* and *E. trisectum* showed apparent anti-inflammatory and antinociceptive activity [21-23]. The fresh leaf extract of *E. creticum* gave a higher percentage inhibition of the haemolytic activity of the scorpion venom compared with the dried leaf extract, but extracts of both fresh and dried roots of *E. creticum* gave 100% inhibition of the snake and scorpion venoms [24]. Also, some species (i.e., *E. caucasicum*) showed antioxidant activity [25, 26].

To date, terpenoids, triterpenoid saponins, flavonoids, coumarins, polyacetylenes, steroids, and essential oils have been reported in the genus *Erygnium*. However, most species of *Eryngium* have not been extensively investigated in chemical constituents. Existing phytochemical investigations indicated the presence of essential oils (primarily sesquiterpenes and monoterpenes) in *E. bourgatii* Gouan (*E. amethystinum* Lam.), *E. billardieri, E. bourgatii* Gouan, *E. bungei* Boiss., *E. caeruleum* M. Bieb., *E. campestre, E. corniculatum, E. creticum, E. foetidum, E. giganteum* M. Bieb., *E. glaciale* Boiss., *E. palmatum* Vis. et Pančić, *E. paludosum* (Moore et Betche) Michael, *E. paniculatum* Cav. & Domb. ex Delar., *E. rosulatum* Michael, *E. serbicum* Pančić, *E. vesiculosum* Labill., and *E. yuccifolium* [25, 27-48]. Other classes of compounds isolated from *Eryngium* include flavonoids from *E. campestre, E. giganteum, E. macrocalyx* Schrenk, *E. maritimum, E. octophyllum* Eug. Kor., and *E. yuccifolium* [10, 49-54], coumarins from *E. campestre* and *E. ilicifolium* Lam. [55-57], sterols from *E. foetidum* and *E. agavifolim* [21], a rosmarinic acid derivative from *E. alpinum* L. [13], lactone from *E. carlinae* Delar. [58], and triterpenoid glycosides from *E. bourgatii, E. bromeliifolium* Delar., *E. campestre, E. giganteum, E. macrocalyx, E. maritimum, E. octophyllum, E. planum,* and *E. yuccifolium* [10, 14, 15, 59-66]. The main saponins from this genus belong to polyhydroxylated triterpenoid glycosides with ester functions. This class of saponin has been found in various groups of plants such as *Aesculus chinensis* L. (Hippocastanaceae) [67-71], *Pittosporum tobira* (Thunb.) Ait. (Pittosporaceae) [72], *Sanicula elata* var. *chinensis* Makino (Apiaceae) [73], and *Harpullia austro-caledonica* Baill. (Sapindaceae) [74]. This type of saponin has been shown to possess anti-inflammatory property [71, 75, 76], anti-HIV-1 protease activity [68], and cytotoxicity for tumor cells [72, 77-79]. Recently, we isolated and identified 25 new polyhydroxylated triterpenoid saponins from North American *Aesculus pavia* L. [77, 80]. The saponins with two acyl groups at C-21 and C-22 had cytotoxic activity against 60 cell lines from nine different human cancers [77, 81].

This review focuses on phytochemistry and pharmacological activities of 127 compounds isolated and identified from *Eryngium*, particularly non-essential oil compounds such as terpenoids, triterpenoid saponins, flavonoids, coumarins, polyacetylenes, and steroids. This involves 23 species belonging to 9-11 sections of *Eryngium* in both Old and New Worlds (Table **1**).

PHYTOCHEMISTRY

Of 250 species of the genus *Eryngium*, only 23 species have been more or less investigated phytochemically. To date, at least 127 compounds, primarily phenolic compounds and terpenoids have been isolated and identified from these species, including triterpenoid saponins, monoterpene, sesquiterpenes, triterpenoids, flavonoids, coumarins, steroids, acetylenes, and other classes of compounds. A summary of the compounds isolated from *Eryngium* species is carried in Tables **2** and **3**.

Triterpenoid Glycosides

The genus *Eryngium* is known to contain triterpenoid saponins as the main components. To date, 25 saponins have been isolated from this genus. The most of *Eryngium* saponins belong to polyhydroxylated oleanene triterpenoid saponins (Table **2**). This class of saponins has been found in a wide range of plants belonging to different families, such as *Aesculus* L. (Hippocastanaceae) [100], *Pittosporum tobira* (Thunb.) Ait. (Pittosporaceae), and *Harpullia austro-caledonica* Baill. (Sapindaceae) [10]. In the family Apiaceae, *Hydrocotyle* L., *Hacquetia* Neck ex DC., *Steganotaenia* Hochst, and *Sanicula* L. have already indicated the present of polyhydroxylated triterpenoid saponins [14].

Recently, three detailed phytochemical investigation on the roots of *E. campestre* [14, 15] and the whole plant of *E. yuccifolium* [10] resulted in the isolation and structural elucidation of 19 new polyhydroxylated oleanene triterpenoid saponins, named 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl-22-*O*-β,β-dimethylacryloyl-A_1-barrigenol (**1**), 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl-22-*O*-angeloyl-R_1-barrigenol (**2**), 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl-21-*O*-acetyl-22-*O*-angeloyl-R_1-barrigenol (**3**), 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl-21-*O*-acetyl-22-*O*-β,β-dimethylacryloyl-R_1-barrigenol (**4**), 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucuronopyranosyl-22-*O*-angeloyl-28-*O*-acetyl-R_1-barrigenol (**5**), 3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucuronopyranosyl-22-*O*-angeloyl-R_1-barrigenol (**6**), 3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucuronopyranosyl-22-*O*-β,β-dimethylacryloyl-A_1-barrigenol (**7**), eryngiosides A-L (**8**-**19**), together with two know saponins 21β-angeloyloxy-3β-[β-D-glucopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyloxyol-ean-12-ene-15α, 16α, 22α, 28-tetrol (**20**) and sanitriculasaponin III (**21**).

Four triterpenoids R_1-barrigenol (**28**), A_1-barrigenol (**29**), barringtogenol C (**31**), and 3β, 16α, 22α, 28-tetrahydroxyolean-12-ene derivatives were recognized to be the aglycones of polyhydroxylated *Eryngium* saponins with acyl functions at C-21 and C-22 positions. The *Eryngium* saponins resemble that of *Aesculus* species, but there were

Table 1. List of *Eryngium* Species Included in this Review.

Section	Species	Reference
OLD WORLD		
Section Alpina	*E. alpinum* L.	[13]
	E. giganteum M. Bieb. (synonyms: *E. asperifolium* F. Delar., *E. glaucum* Hoffm.)	[13, 46, 54]
Section Campestria	*E. bourgatii* Gouan (synonyms: *E. alpinum* Lapeyr., *E. amethystinum* Lam., *E. pallescens* Mill., *E. planum* Lapeyr., *E. tounefortii* Bubani)	[13, 46, 82-84]
	E. campestre L. (synonyms: *E. latifolium* Hoffm. & Link ex Willk & Lange, *E. officinale* Garsault, *E. trifidum* L.)	[14, 15, 45, 50, 52, 55, 85]
Section Dryophylla	*E. ilicifolium* Lam.	[56]
	E. octophyllum Korovin (synonyms: *E. mirandum* Bobrov)	[51, 66]
Section Halobia	*E. macrocalyx* Schrenk (synonym: *E. incognitum* Paviov)	[65, 86, 87]
	E. maritimum L. (synonym: *E. marinum Garsault*)	[46, 49, 63, 88]
Section Palmito	*E. serbicum* Pančić	[82]
Section Plana	*E. caucasicum* Trautv. (synonyms: *E. biebersteinianum* Nevski)	[66, 89]
	E. creticum Lam. (synonyms: *E. cyaneum* Sm., *E. syriacum* Lam.)	[25, 90, 91]
	E. dichotomum Desf.	[53, 92]
	E. planum L. (synonyms: *E. E. armatum* Csató ex Simonk., *E. caeruleum* M. Bieb., *E. dalla-torrei* M. Hiroe, *E. intermedium* Weinm.), *E. latifolium* Gilib., *E. planifolium* Pall., *E. planum* Lindl., *E. planum* var. *armatum* Csató ex Simonk., *E. pumilum* Gilib., *E. pusillum* Gilib.)	[13, 46, 86, 93-98]
	E. variifolium Coss.	[13, 46]
	E. spinalba L. (synonyms: *E. rigidum* Lam., *E. leucacanthum* St.-Lag.)	[13]
Section (unknown)	*E. tripartitum* Desf.	[13]
NEW WORLD		
Section Areata	*E. agavifolium* Griseb.	[13]
Section Foetida	*E. foetidum* L. (synonyms: *E. antihystericum* Rottler, *E. antihystericum* Rottb.)	[21, 59, 99]
Section (unknown)	*E. bromeliifolium* Delar.	[60-62]
Section Panniculata	*E. eburneum* Decne. (synonyms: *E. bracteosum* (DC.) Griseb., *E. paniculatum* var. *bracteosum* DC.)	[13]
	E. pandanifolium Cham. & Schltdl. (synonyms: *E. decaisneanum* Urb., *E. oligodon* (DC.) Griseb., *E. pandanifolium* var. *atrocephalum* Kuntze), *E. paniculatum* var. *oligodon* DC.)	[13]
	E. paniculatum Cav. & Domb. Ex Delar. (synonyms: *E. paniculatum* var. *chinense* DC., *E. paniculatum* f. *junior* Urb., *E. paniculatum* var. *litorale* G. Kunkel, *E. subulatum* Vell.)	[47]
	E. yuccifolium Michx.	[10, 13, 27]

various differences between both saponins in aglycons and sugar components. Especially, all saponins identified from *E. campestre* are interesting structurally because the acylation by a *β*,*β*-dimethylacrylic acid or angeloyl at the C-22 position is rare among triterpenoid saponins [14]. *Eryngium* saponins from *E. yuccifolium* are characterized as an angeloyl (Ang) attached to C-21 or C-22, and an angeloyl (Ang)/acetyl (Ac) group to the C-21/22 positions. The saponins structurally based on three aglycones of R_1-barrigenol (**28**), A1-barrigenol (**29**), barringtogenol C (**31**) with the hydroxyl group at C-15 and/or C-21 contained one oligosaccharide chain with a glucuronopyranosyl unit attached to C-3 position of the aglycones. This oligosaccharide chain had a rhamnopyranosyl or an arabinopyranosyl unit attached to the glucuronopyranosyl unit. The saponins possessed the aglycone of 3*β*, 16*α*, 22*α*, 28-tetrahydroxyolean-12-ene without a hydroxyl group at C-15 and C-21 linked a trisaccharide chain of glucoses and galacoses to the C-3 position. However, these saponins were identified bearing none of acyl functions at C-21 and C-22. It was believed that at least one angeloyl moiety at either C-21 or C-22 positions of *Eryngium* saponins by a recent structure–activity relationship (SAR) investigation makes significant contribution to the cytotoxicities, but the type and number of sugar moiety at C-3 may decrease their cytotoxicities [101].

Some other classes of triterpenoid saponins were also reported in *Eryngium* species. 3-*O*-*β*-D-glucopyranosyl oleanolic acid 28-*O*-*β*-D-xylopyranoside (**22**) and 3-*O*-[*β*-D-glucopyranosyl-(1→2)-[*β*-D-fucopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→4)-*β*-D-glucopyranosyl]-olean-12-en-

Table 2. Major Non-Essential oil Compounds Isolated and Identified from *Eryngium*

No.	Compound Name	Botanical Source	Reference
	Triterpenoid Saponins		
1	3-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucuronopyranosyl-22-O-*β*,*β*-dimethylacryloyl-A_1-barrigenol	*E. campestre*	[15]
2	3-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucuronopyranosyl-22-*O*-angeloyl-R_1-barrigenol	*E. campestre*	[15]
3	3-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucuronopyranosyl-21-*O*-acetyl-22-*O*-angeloyl-R_1-barrigenol	*E. campestre*	[15]
4	3-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucuronopyranosyl-21-*O*-acetyl-22-O-*β*,*β*-dimethylacryloyl-R_1-barrigenol	*E. campestre*	[15]
5	3-*O*-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucuronopyranosyl-22-*O*-angeloyl-28-*O*-acetyl-R_1-barrigenol	*E. campestre*	[15]
6	3-*O*-*β*-D-glucopyranosyl-(1→2)-[*α*-L-rhamnopyranosyl-(1→4)]-*β*-D-glucuronopyranosyl-22-*O*-angeloyl-R_1-barrigenol	*E. campestre*	[14]
7	3-*O*-*β*-D-glucopyranosyl-(1→2)-[*α*-L-rhamnopyranosyl-(1→4)]-*β*-D-glucuronopyranosyl-22-*O*-*β*,*β*-dimethylacryloyl-A_1-barrigenol	*E. campestre*	[14]
8	eryngiosides A	*E. yuccifolium*	[10]
9	eryngiosides B	*E. yuccifolium*	[10]
10	eryngiosides C	*E. yuccifolium*	[10]
11	eryngiosides D	*E. yuccifolium*	[10]
12	eryngiosides E	*E. yuccifolium*	[10]
13	eryngiosides F	*E. yuccifolium*	[10]
14	eryngiosides G	*E. yuccifolium*	[10]
15	eryngiosides H	*E. yuccifolium*	[10]
16	eryngiosides I	*E. yuccifolium*	[10]
17	eryngiosides J	*E. yuccifolium*	[10]
18	eryngiosides K	*E. yuccifolium*	[10]
19	eryngiosides L	*E. yuccifolium*	[10]
20	21*β*-angeloyloxy-3*β*-[*β*-D-glucopyranosyl-(1→2)]-[*β*-D-xylopyranosyl-(1→3)]-*β*-D-glucuronopyranosyloxyolean-12-ene-15*α*, 16*α*, 22*α*, 28-tetrol	*E. yuccifolium*	[10]
21	saniculasaponin III	*E. yuccifolium*	[10]
22	3-*O*-*β*-D-glucopyranosyl oleanolic acid 28-*O*-*β*-D-xylopyranoside	*E. bromeliifolium*	[60]
23	3-*O*-[*β*-D-glucopyranosyl-(1→2)-[*β*-D-fucopyranosyl-(1→3)]-*α*-L-rhamnopyranosyl-(1→4)-*β*-D-glucopyranosyl]-olean-12-en-23,28-diol	*E. foetidum*	[59]
24	betulinic acid 3-*O*-*β*-D-glucopyranoside	*E. bromeliifolium*	[62]
25	betulinic acid-3-*O*-*β*-D-glucopyranosyl(1→6)-*β*-D-glucopyranoside	*E. bromeliifolium*	[61]
	Triterpenoids		
26	betulinic acid	*E. bromeliifolium*	[64]
27	oleanolic acid	*E. macrocalyx* (*E. incognitum*)	[65, 87]

Table 2. Contd….

No.	Compound Name	Botanical Source	Reference
28	R_1-barringenol	*E. maritimum* *E. planum* *E. caucasicum* (*E. biebersteini-anum*) *E. octophyllum*	[63, 66, 95]
29	A_1-barringenol	*E. maritimum* *E. planum* *E. caucasicum* (*E. biebersteini-anum*) *E. octophyllum*	[63, 66, 95]
30	22-(2-methyl-2-butenoate)-olean-12-ene-3,15,16,22,28-pentol	*E. macrocalyx*	[65]
31	barringtogenol C	*E. maritimum* *E. planum*	[63, 95]
32	erynginol A	*E. planum*	[95]
33	22α-hydroxyerythrodiol	*E. maritimum*	[63]
	Sesquiterpenes		
34	eryng-9-en-15-al	*E. creticum*	[25]
35	15-hydroxy-*α*-muurolene	*E. giganteum*	[46]
36	15-oxy-*α*-muurolene	*E. giganteum*	[46]
37	15-*nor*-*α*-muurolene	*E. giganteum*	[46]
38	(+)-ledol	*E. giganteum*	[46]
39	(+)-spathulenol	*E. giganteum*	[46]
40	germacrene D	*E. giganteum*	[46]
41	trans-*β*-farnesene	*E. giganteum*	[46]
	Monoterpenes		
42	3-(*β*-D-glucopyranosyloxymethyl)-2,4,4-trimethyl-2,5-cyclohexadien-1-one	*E. campestre* *E. creticum*	[45, 91]
43	3-(*β*-D-glucopyranosyloxymethyl)-2,4,4-trimethyl-2-cyclohexen-1-one	*E. campestre*	[45]
44	5-[(*β*-D-glucopyranosyloxy)methyl]-4-hydroxy-4-[(1*E*,3*S*)-3-hydroxy-1-butenyl]-3,5-dimethyl-2-cyclohexen-1-one,	*E. dichotomum*	[53]
45	isoferulyl senecioate	*E. variifolium*	[46]
46	(-)-2,4,4-trimethyl-3-formyl-2,5-cyclohexadienyl angelate	*E. paniculatum*	[47]
47	*O*-[2-angeloyloxymethyl-*cis*-crotonoyl]-ferulol	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
48	*O*-[2-angeloyloxymethyl-*cis*-crotonoyl]-isoferulol	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
49	*O*-[2-(2-methyl-butyryloxymethyl)-*cis*-crotonoyl]-ferulol	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
50	*O*-[2-(2-methyl-butyryloxymethyl)-*cis*-crotonoyl]-isoferulol	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]

Table 2. Contd….

No.	Compound Name	Botanical Source	Reference
51	*O*-[2-isovaleryloxymethyl)-*cis*-crotonoyl]-isoferulol	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
	Flavonoids		
52	quercetin	*E. creticum*	[91]
53	quercitrin	*E. campestre*	[52]
54	isoquercitrin	*E. campestre* *E. maritimum* *E. giganteum*	[49, 52, 54]
55	rutin	*E. campestre* *E. octophyllum*	[51, 52]
56	luteolin 7-*O*-*β*-D-glucopyranoside	*E. campestre*	[52]
57	astragalin	*E. campestre* *E. maritimum*	[49, 52, 54]
58	kaempferol 7-*O*-*α*-L-rhamnopyranoside	*E. campestre*	[52]
59	kaempferol 3-*β*-D-glucopyranosyl-7-*O*-*α*-L-rhamnopyranoside	*E. maritimum* *E. macrocalyx*	[49, 51]
60	kaempferol 3,7-di-*O*-*α*-L-rhamnopyranoside	*E. campestre* *E. planum* *E. giganteum*	[52, 54, 97, 98]
61	kaempferol-3-*O*-(6-*O*-*β*-D-glucopyranosyl)-*β*-D-galactopyranoside	*E. planum*	[96]
62	kaempferol 3-*O*-*β*-D-(2′-*p*-*E*-hydroxycinnamoyl) -glucopyranoside	*E. campestre*	[50]
63	kaempferol 3-*O*-*β*-D-(2′-*p*-*Z*-hydroxycinnamoyl)- glucopyranoside	*E. campestre*	[50]
64	kaempferol-3-*O*-(2-*O*-*trans*-*p*-methoxycoumaroyl-6-*O*-*trans*-*p*-coumaroyl)-*β*-D-glucopyranoside	*E. yuccifolium*	[10]
65	kaempferol-3-*O*-(2,6-di-*O*-*trans*-*p*-coumaroyl)-*β*-D-glucopyranoside	*E. yuccifolium*	[10]
66	naringenine 7-*O*-*α*-L-rhamnopyranosyl-(1→2)-*O*-*β*-D-glucopyranoside	*E. dichotomum*	[53]
	Coumarins		
67	umbelliferon	*E. biebersteinianum*	[89]
68	scopoletin	*E. bourgatii*	[84]
69	6,7-dimethoxycoumarin	*E. creticum*	[90]
70	bergaptin	*E. biebersteinianum*	[89]
71	decursinol	*E. biebersteinianum*	[89]
72	prantschimgin	*E. ilicifolium*	[56]
73	deltoin	*E. creticum*	[56, 91]
74	(+)-marmesin	*E. creticum* *E. ilicifolium*	[56, 91]
75	aegelinol benzoate	*E. campestre*	[55]

Table 2. Contd….

No.	Compound Name	Botanical Source	Reference
76	agasyllin	*E. campestre*	[55]
77	grandivittin	*E. biebersteinianum*	[55, 89]
78	aegelinol	*E. campestre*	[55]
	Phenolics		
79	1-*β*-D-Glucopyranosyloxy-3-methoxy-5-hydroxybenzene	*E. creticum*	[91]
80	3,4-dihydroxyphenyl caffeate	*E. yuccifolium*	[10]
81	(4-*β*-D-glucopyranosyloxy)-3-hydroxyphenyl caffeate	*E. yuccifolium*	[10]
82	R-(+)-rosmarinic acid	*E. alpinum*	[13]
83	R-(+)-3'-*O*-*β*-D-glucopyranosyl rosmarinic acid	*E. alpinum* *E. bourgatii* (*E. amethystinum*) *E. maritimum* *E. campestre*	[13]
84	caffeic acid	*E. yuccifolium*	[10]
85	chlorogenic acid	*E. alpinum*	[13]
	Steroids		
86	*β*-sitosterol	*E. foetidum*	[21, 91, 99]
87	*β*-sitosterol 3-*O*-*β*-D-glucopyranoside	*E. creticum*	[91]
88	stigmasterol	*E. foetidum*	[21, 92, 99]
89	stigmasterol 3-*O*-*β*-D-glucopyranoside	*E. dichotomum*	[92]
90	campesterol	*E. foetidum*	[21]
91	brassicasterol	*E. foetidum* *E. agavifolium*	[21, Supporting Data I]
92	3*α*-cholesterol	*E. foetidum*	[21]
93	(-)-clerosterol	*E. foetidum*	[21]
94	Δ^5-avenosterol	*E. foetidum*	[21]
95	Δ^5-avenasterol	*E. foetidum*	[21]
96	$\Delta^{5,24}$-stigmastadienol	*E. foetidum*	[21]
	Acetylenes		
97	falcarinone	*E. yuccifolium* *E. bourgatii*	[27, 83, 84]
98	falcarinolone	*E. bourgatii*	[84]
99	falcarinol	*E. yuccifolium* *E. bourgatii*	[27, 84]
100	yuccifolol	*E. yuccifolium*	[27]
101	1,8-heptadecadiene-4,6-diyne-3,9-diol	*E. yuccifolium*	[27]
102	(8*E*)-1,8-Heptadecadiene-4,6-diyne-3,10-diol	*E. agavifolium*	[Supporting Data I]
103	(*Z*)-15-hydroxy-9,16-Heptadecadiene-11,13-diyn-8-one	*E. agavifolium*	[Supporting Data I]]
104	(*E*)-15-hydroxy-9,16-Heptadecadiene-11,13-diyn-8-one	*E. agavifolium*	[Supporting Data I]
105	(*Z*)-6-pentyl-2-[2-oxobutin-(3)-yliden]tetrahydropyran	*E. bourgatii*	[83, 84]
106	(*E*)-6-pentyl-2-[2-oxobutin-(3)-yliden]tetrahydropyran	*E. bourgatii*	[84]

Table 3. Other non-Essential oil Compounds Isolated and Identified from *Eryngium*

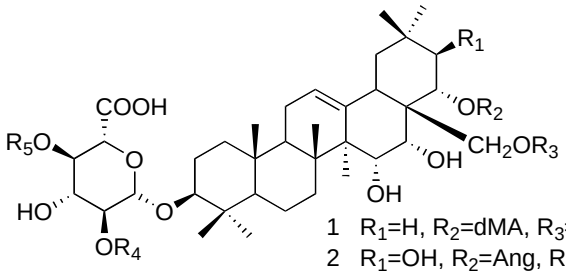
No.	Name	Botanical Source	Reference
107	2,3,4-trimethylbenzaldehyde	*E. varrifolium* *E. bourgatii* (*E. amethystinum*) *E. serbicum*	[46, 82]
108	2,3,6-trimethylbenzaldehyde	*E. varrifolium* *E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
109	*cis*-chrysanthenyl acetate	*E. planum*	[46]
110	*cis*-chrysanthenyl hexanoate	*E. planum*	[93]
111	*cis*-chrysanthenyl octanoate	*E. planum*	[93]
112	2-angeloyloxymethyl-*cis*-crotonic acid methyl ester	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
113	2-(2-methyl-butyryloxymethyl)-*cis*-crotonic acid methylester	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
114	2-isovaleryloxymethyl-*cis*-crotonic acid methylester	*E. bourgatii* (*E. amethystinum*) *E. serbicum*	[82]
115	10-hentriacontanone	*E. maritimum*	[46]
116	eicosa-8,11-dien-18-ol-2-one	*E. creticum*	[25]
117	hexadecanoic acid	*E. agavifolium*	[Supporting Data I]
118	(9*Z*,11*Z*)-9,11-octadecadienoic acid, methyl ester	*E. agavifolium*	[Supporting Data I]
119	(7*Z*)-7-hexadecen-1-ol, 1-acetate	*E. agavifolium*	[Supporting Data I]
120	1-kestose	*E. planum*	[94]
121	sucrose	*E. dichotomum*	[53, 94]
122	2-*O*-methyl-*α*-D-fructofuranose	*E. dichotomum*	[53]
123	D-glucose	*E. planum*	[94]
124	D-furanose	*E. dichotomum*	[53, 94]
125	D-mannitol	*E. dichotomum* *E. creticum* *E. campestre* *E. caeruleum* *E. macrocalyx*	[53, 91] [85] [86]
126	D-galactitol	*E. creticum*	[91]
127	piperidine-2-carboxylic acid	*E. maritimum*	[88]

23,28-diol (**23**) were isolated and identified from *E. bromeliifolium* [60] and *E. foetidum* [59]. Two glucopyranosyl glycosides of betulinic acid with monosaccharide (**24**) and disaccharide unit (**25**) attached to C-3 were also obtained from *E. bromeliifolium* [61, 62].

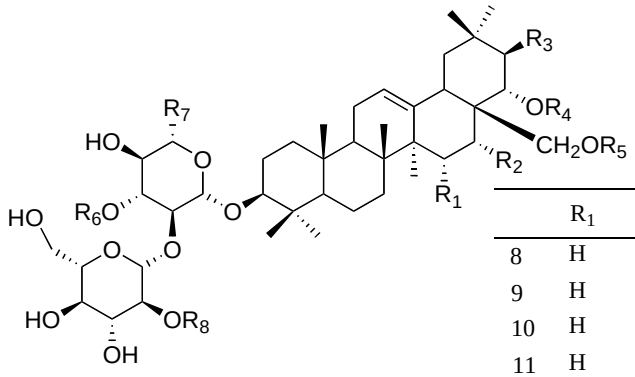
Terpenoids

Triterpenoids

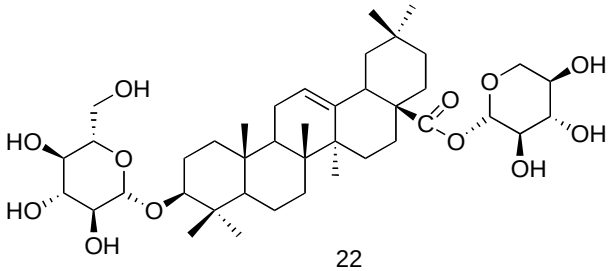
A total of 8 triterpenoids were isolated and identified from the acid and alkaline hydrolysates of *Eryngium* saponin in a few early investigations (Table **2**). All belong to pentacyclic triterpenoids, which are classified as two series of olean-12-ene and lupine. It is noted that olean-12-ene derivatives are characterized by having multiple hydroxyl groups at C-3, 15, 16, 21, 22, and 28 positions, rarely at C-29 position. These triterpenoids included betulinic acid (**26**) from *E. bromeliifolium* [64], oleanolic acid (**27**) from *E. macrocalyx* (*E. incognitum*) roots [65, 87], R_1-barringenol (**28**) and A_1-barringenol (**29**) from the aerial flowering plant parts of *E. maritimum* [63], *E. planum* leaves and roots [95], and the underground parts of *E. caucasicum* (*E. biebersteinianum*) and *E. octophyllum* [66], 22-(2-methyl-2-butenoate)-olean-12-ene-3,15,16,22,28-pentol (**30**) from *E. macrocalyx* [65], erynginol A (**32**) from *E. planum* leaves [95], barringtogenol C (**31**) and 22α-hydroxyerythrodiol (**33**) from *E. maritimum*



1 R_1=H, R_2=dMA, R_3=H, R_4=α-L-rhamnopyranosyl, R_5=H
2 R_1=OH, R_2=Ang, R_3=H, R_4=α-L-rhamnopyranosyl, R_5=H
3 R_1=OAc, R_2=Ang, R_3=H, R_4=α-L-rhamnopyranosyl, R_5=H
4 R_1=OAc, R_2=dMA, R_3=H, R_4=α-L-rhamnopyranosyl, R_5=H
5 R_1=OH, R_2=Ang, R_3=Ac, R_4=α-L-rhamnopyranosyl, R_5=H
6 R_1=OH, R_2=Ang, R_3=H, R_4=β-D-glucopyranosyl, R_5=α-L-rhamnopyranosyl
7 R_1=H, R_2=dMA, R_3=H, R_4=β-D-glucopyranosyl, R_5=α-L-rhamnopyranosyl



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
8	H	OH	H	Glc	H	H	CH_2OH	Glc
9	H	OH	H	Glc	H	H	CH_2OH	Gal
10	H	=O	H	Glc	H	H	CH_2OH	Glc
11	H	OH	H	H	Glc	H	CH_2OH	Glc
12	OH	OH	OH	Ang	H	Xyl	COOH	H
13	H	OH	OH	Ang	H	Xyl	COOH	H
20	OH	OH	O-Ang	H	H	Ara	COOH	H
14	OH	OH	O-Ang	H	H	Xyl	COOH	H
15	OH	OH	H	Ang	H	Ara	COOH	H
16	OH	OH	H	Ang	H	Xyl	COOH	H
17	OH	OH	O-Ang	Ac	H	Ara	COOH	H
21	OH	OH	O-Ang	Ac	H	Xyl	COOH	H
18	H	OH	O-Ang	Ac	H	Ara	COOH	H
19	H	OH	O-Ang	Ac	H	Xyl	COOH	H



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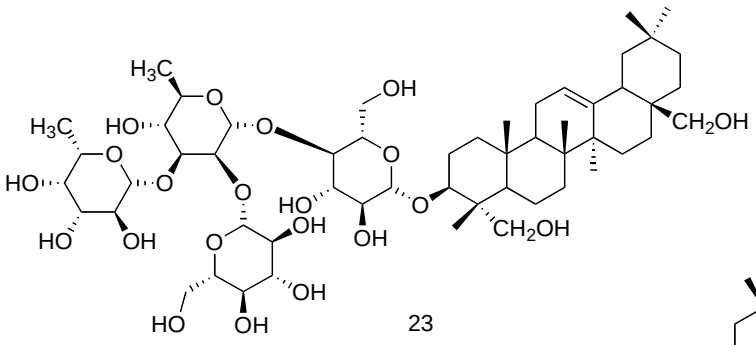
[63]. Barringtogenol C (**31**) was also identified being a major component from *E. planum* leaves [95].

Sesquiterpenes

Four perhydronaphthaline derivatives (Table **2**) substituted with one n-propyl were isolated and identified from the hexane/ether extracts of the aerial parts of *E. creticum* growing in Sinai, Egypt [25] and the etheral extracts of the seeds of *E. giganteum* [46]. The other four sesquiterpenes reported to naturally occur in various essential oils were isolated from the etheral extracts of the seeds of *E. giganteum* [46]. These sesquiterpenes are eryng-9-en-15-al (**34**), 15-hydroxy-α-muurolene (**35**), 15-oxy-α-muurolene (**36**), 15-*nor*-α-muurolene (**37**), (+)-ledol (**38**), (+)-spathulenol (**39**), germacrene-D (**40**), trans-β-farnesene (**41**).



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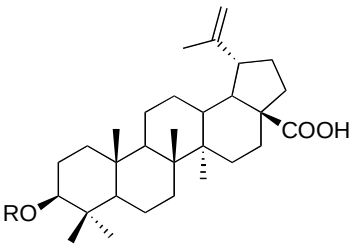
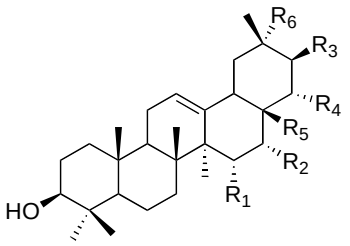
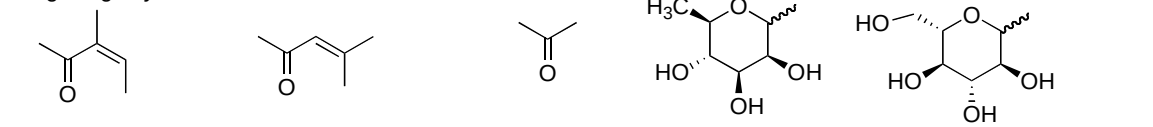


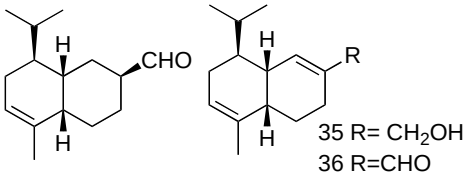
24 R=β-D-glucopyranosyl
25 R=β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl
26 R=H



27 R_1=H, R_2=H, R_3=H, R_4=H, R_5=COOH, R_6=CH_3
28 R_1=OH, R_2=OH, R_3=OH, R_4=OH, R_5=CH_2OH, R_6=CH_3
29 R_1=OH, R_2=OH, R_3=H, R_4=OH, R_5=CH_2OH, R_6=CH_3
30 R_1=OH, R_2=OH, R_3=H, R_4=Ang, R_5=CH_2OH, R_6=CH_3
31 R_1=H, R_2=OH, R_3=OH, R_4=OH, R_5=CH_2OH, R_6=CH_3
32 R_1=H, R_2=OH, R_3=OH, R_4=OH, R_5=CH_2OH, R_6=CH_2OH
33 R_1=H, R_2=H, R_3=H, R_4=OH, R_5=CH_2OH, R_6=CH_3

Ang=Angeloyl dMA=β,β-dimethylacryloyl Ac=Acetyl α-L-rhamnopyranosyl β-D-glucopyranosyl





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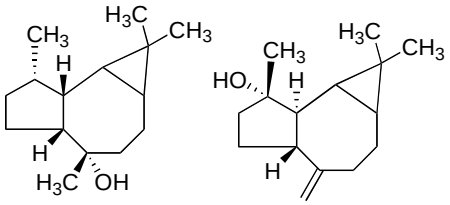
35 R= CH_2OH
36 R=CHO
37 R= H



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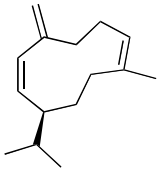

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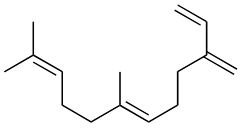

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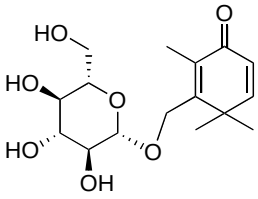

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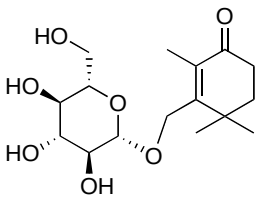

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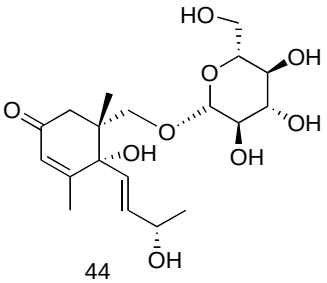

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Monoterpens

Three monoterpene glycosides of the cyclohexanone type and seven monoterpene aldehyde-esters were identified from seven *Eryngium* species (Table **2**). They are include 3-(β-D-glucopyranosyloxymethyl)-2,4,4-trimethyl-2,5-cyclohexadien-1-one (**42**) from *E. campestre* [45] and *E. creticum*, which grows wildly in Jordan [91], 3-(β-D-glucopyranosyloxymethyl)-2,4,4-trimethyl-2-cyclohexen-1-one (**43**) from *E. campestre* [45], 5-[(β-D-glucopyranosyloxy)methyl]-4-hydroxy-4-[(1*E*,3*S*)-3-hydroxy-1-butenyl]-3,5-dimethyl-2-cyclohexen-1-one (**44**) from the aerial parts of *E. dichotomum* from Tunisian [53], isoferulyl senecioate (**45**) from leaves of *E. variifolium* [46], (-)-2,4,4-trimethyl-3-formyl-2,5-cyclohexadienyl angelate (**46**) from seeds of *E. paniculatum* [47], *O*-[2-angeloyloxymethyl-*cis*-crotonoyl]-ferulol (**47**), *O*-[2-angeloyloxymethyl-*cis*-crotonoyl]-isoferulol (**48**), *O*-[2-(2-methyl-butyryloxymethy-l)-*cis*-crotonoyl]-ferulol (**49**), *O*-[2-(2-methyl-butyryloxymethyl)-*cis*-crotonoyl]-isoferulol (**50**), and *O*-[2-isovaleryloxy-

methyl-*cis*-crotonoyl]-isoferulol (**51**) from the roots of *E. bourgatii* (*E. amethystinum*) and *E. serbicum* [82].

Phenolic Compounds

Flavonoids

Flavonoids are also one of the main components of the genus *Eryngium*. A total of 15 flavonoids including flavonols (**52-65),** and flavanone (**66**) were isolated and identified from *Eryngium* species (Table **2**). The glycosides of quercetin (**52**) [91] and kaempferal with an oligosaccharide chain at C-3 or C-7, or two oligosaccharide chains at C-3 and C-7 are types of flavonol glycosides.

Chemical investigation on the aerial parts of *E. campestre* resulted in the isolation and structural determination of 8 flavonol glycosides [50, 52]. These compounds are quercitrin (**53**), isoquercitrin (**54**), rutin (**55**), astragalin (**57**), kaempferol 7-*O*-*α*-L-rhamnopyranoside (**58**), kaempferol 3,7-di-*O*-*α*-L-rhamnopyranoside (**60**), Kaempferol 3-*O*-*β*-D-(2'-*p*-*E*-hydroxycinnamoyl)-glucopyranoside (**62**), and kaempferol 3-*O*-*β*-D-(2'-*p*-*Z*-hydroxycinnamoyl)-glucopyranoside (**63**). Kaempferol 3-*β*-D-glucopyranosyl-7-*O*-*α*-L-rhamnopyranoside (**59**), astragalin, and isoquercitrin was identified as the major flavonoid constituents from the aerial parts of *E. maritimum* [49]. Three investigations led to the isolation and identification of two flavonoid glycosides Kaempferol-3-*O*-(6-*O*-*β*-D-glucopyranosyl)-*β*-D-galactopyr-anoside (**61**) and **60** from the leaves of *E. planum* [96-98]. A new compound, kaempferol-3-*O*-(2-*O*-*trans*-*p*-methoxycou-maroyl-6-*O*-*trans*-*p*-coumaroyl)-*β*-D-glucopyranoside (**64**), and a known flavonoid glycoside kaempferol-3-*O*-(2,6-di-*O*-*trans*-*p*-coumaroyl)-*β*-D-glucopyranoside (**65**) were recently isolated and identified from the whole plants of *E. yuccifolium* [10]. Additionally, Compound **55** was also found from the aerial parts of *E. octophyllum* [51], compound **59** from the aerial parts of *E. macrocalyx* [51], and compounds **54** and **60** from the leaves of *E. giganteum* [54].

Luteolin 7-*O*-*β*-D-glucopyranoside (**56**) and naringenine 7-*O*-*α*-L-rhamnopyranosyl-(1→2)-*O*-*β*-D-glucopyranoside (**66**) were also identified from *E. campestre* [52] and the aerial parts of *E. dichotomum* [53].

Coumarins

Simple coumarins and linear furanocoumarins were also found from *Eryngium* species (Table **2**). These coumarins are scopoletin (**68**) from the roots of *E. bourgatii* [84]; 6,7-dimethoxycoumarin (**69**), deltoin (**73**), and (+)-marmesin (**74**) from *E. creticum* [90, 91]; umbelliferon (**67**), bergaptin (**70**), decursinol (**71**), grandivittin (**77**) from *E. biebersteinianum* [89]; prantschimgin (**72**), deltoin, and (+)-marmesin from Et_2O extracts of *E. ilicifolium* [56]; and aegelinol benzoate (**75**), agasyllin (**76**), aegelinol (**78**), and grandivittin from the roots of *E. campestre* [55].

Other Phenolic Compounds

1-*β*-D-glucopyranosyloxy-3-methoxy-5-hydroxybenzene (**79**) was yielded from *E. creticum*, which grows wildly in Jordan [91]. Three phenolic compounds, including two new phenyl caffeates, 3,4-dihydroxyphenyl caffeate (**80**) and (4-*β*-D-glucopyranosyloxy)-3-hydroxyphenyl caffeate (**81**), together with known compound caffeic acid (**84**) were isolated and identified from *E. yuccifolium* [10].

In addition, the isolation of antioxidative substances from the root extracts of *E. alpinum* allowed the identification of R-(+)-3'-*O*-*β*-D-glucopyranosyl rosmarinic acid (**83**), a new rosmarinic acid derivative, together with two known compounds R-(+)-rosmarinic acid (**82**), and chlorogenic acid (**85**) [13]. Moreover, R-(+)-3'-*O*-*β*-D-glucopyranosyl rosmarinic acid (**83**) was found that is unstable in a $MeOH/H_2O$ (1/1, *v/v*) solution, of which one-third quantity was degraded after 11 h at room temperature. In the chemotaxonomic study analyzed by HPLC, R-(+)-rosmarinic acid and R-(+)-3'-*O*-*β*-D-glucopyranosyl rosmarinic acid were detected in all analyzed 13 *Eryngium* species, except *E. giganteum*, which was devoid of R-(+)-3'-*O*-*β*-D-glucopyranosyl rosmarinic acid, and distinct concentration variations of **83** were observed in *E. bourgatii* (*E. amethystinum*), *E. maritimum*, and *E. campestre* [13].

Steroids

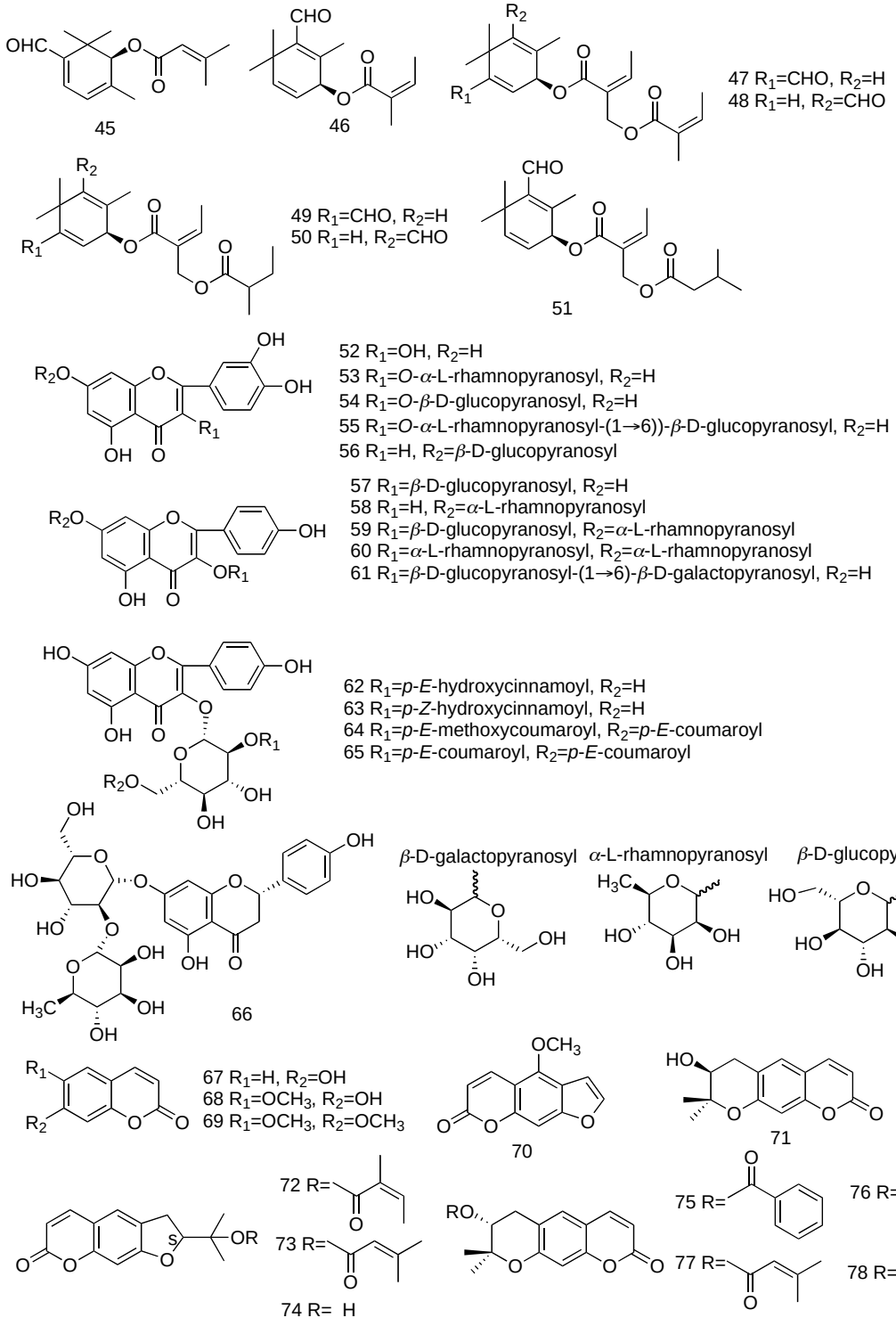
Eleven steroids have been identified from *Eryngium* species (Table **2**). These compounds include *β*-sitosterol (**86**), stigmasterol (**88**), campesterol (**90**), brassicasterol (**91**), 3*α*-cholesterol (**92**), (-)-clerosterol (**93**), $\triangle^5$-avenosterol (**94**), $\triangle^7$-avenasterol (**95**), and $\triangle^{5,24}$-stigmastadienol (**96**) from the hexane extracts of the leaves of *E. foetidum* [21, 99]. Brassicasterol (**91**) was also isolated and identified from the EtOH extract of the whole plant of *E. agavifolium* (Supporting Data **I**). A comparison study indicated that all of steroids in the leaves presented also in the stems with different quantities [99]. Stigmasterol, *β*-sitosterol, and their glycosides (**87** and **89**) were isolated and identified from the aerial parts of *E. dichotomum* grown in Tunisia [92] and *E. creticum* growing wildly in Jordan [91], respectively.

Acetylenes

Eryngium contains also polyacetylenes (Table **2**). Yuccifolol (nonadeca 1,11-diene 4,6,8-triyne 3,10-diol, **100**), a novel polyacetylene, was isolated and identified from the hexane/ether extracts of the aerial parts of *E. yuccifolium*, together with the known polyacetylenes, falcarinone (**97**), falcarinol (**99**) and heptadeca 1,8-diene 4,6-diyne 3,9-diol (**101**) [27]. (8*E*)-1,8-heptadecadiene-4,6-diyne-3,10-diol (**102**), (*Z*)-15-hydroxy-9,16-heptadecadiene-11,13-diyn-8-one (**103**), and (*E*)-15-hydroxy-9,16-heptadecadiene-11,13-diyn-8-one (**104**) were isolated from the EtOH extract of the whole plant of *E. agavifolium* (Supporting Data **I**). The roots of *E. bourgatii* afforded, in addition, to falcarinone, falcarinolone (**98**), and falcarinol, the *Z* and *E* isomers of 6-pentyl-2-[2-oxobutin-(3)-yliden]tetrahydropyran (**105** and **106**). The new *Z* isomer of 6-pentyl-2-[2-oxobutin-(3)-yliden]tetrahydropyran is unstable as it easily converts into the *E* isomer [83, 84].

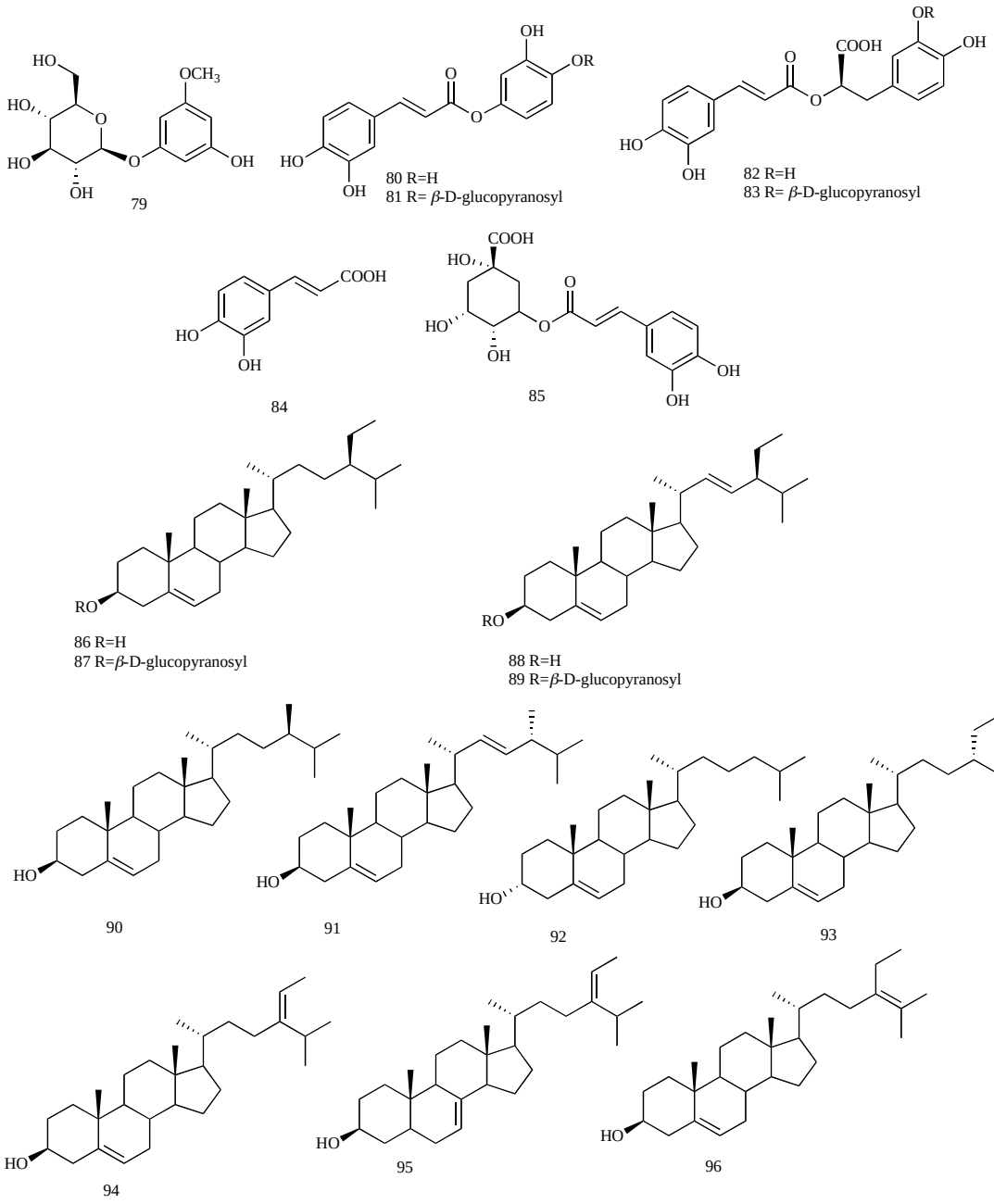
Miscellaneous

There are 18 other classes of compounds obtained from some species of *Eryngium* L. (Table **3**) These compounds include two trimethylbenzaldehydes (**107** and **108**) from the leaves of *E. varrifolium* [46], *E. bourgatii* (*E. amethystinum*) and *E. serbicum* [82], three *cis*-chrysanthenyl esters (**109-111**) from the flowers and seeds of *E. planum* [46, 93] , three 2-substituents derivatives of *cis*-crotonic acid methyl ester (**112-114**) from *E. bourgatii* (*E. amethystinum*) and *E. ser-*



bicum [82], two long-chain aliphatic ketones (**115** and **116**) from the leaves of *E. maritimum* [46] and *E. creticum* [25], and three long-chain aliphatic acids (**117**-**119**) from the EtOH extract of the whole plant of *E. agavifolium* (Supporting Data **I**). From a chemotaxonomic point of view, 10-hentriacontanone (**115**) appears to be a good chemical marker of *E. maritimum*. Analysis of several *E. maritimum* collections of different origins always showed the presence of this ketone. However, this metabolite has also been found in two other *Eryngium* species, namely *E. bourgatii* and *E. campestre* [46].

In addition, sucrose (**121**), furanose (**124**) and its 2-methyl analog (**122**) were found from the aerial parts of *E. dichotomum* in Tunisian [53]; D-glucose (**123**) and a nonreducible trisaccharide, 1-kestose (**120**), from *E. planum* roots [94]; two polyols, D-mannitol (**125**) and D-galactitol (**126**), from *E. dichotomum* [53], *E. creticum* [91], *E. campestre*



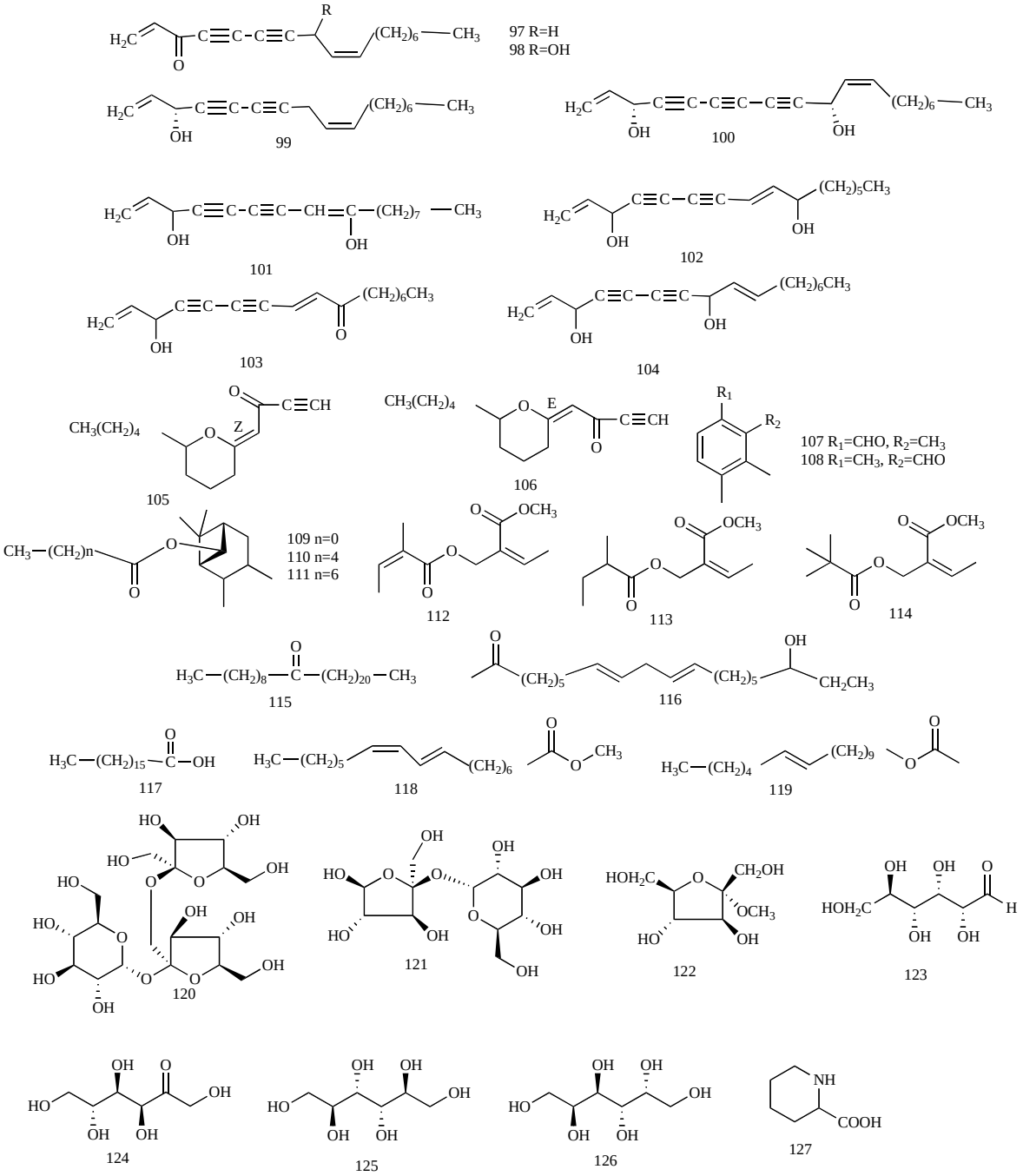
[85], *E. caeruleum* and *E. macrocalyx* [86]; and a piperidine-2-carboxylic acid (**127**) from *E. maritimum* [88].

BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES

The *in vitro* and *in vivo* biological activities of *Eryngium* extracts or isolates (including both essential oils and non-essential oil compounds) are summarized in Tables **4** and **5**.

Cytotoxicities

Eryngiosides A-C, E, F, H-J, L, 21β-angeloyloxy-3β-[β-D-glucopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyloxyolean-12-ene-15α, 16α, 22α, 28-tetrol (**20**), and Saniculasaponin III isolated from the whole plants of *E. yuccifolium* Michx [10] were evaluated for their ability to inhibit human DNA topoisomerase I (TOP1) and II (TOP2) activity and cytotoxicity against PANC-1, A549, PC-3, HL-60, and MRC-5 cell lines (Table **6**). None of eryngiosides demonstrated any TOP1 and TOP2 inhibitory activities. Three eryngiosides (eryngioside J, eryngioside L, and saniculasaponin III) showed moderate cytotoxicity against all cell lines after 48 h of incubation. The GI_{50} values vary from 3.54 μM to 16.02 μM. These eryngiosides were most effective against human lung cancer cell lines A-549 and normal cell lines MRC-5, and markedly inhibited the growth of pancreas cancer cell lines PANC-1. *Eryngium* saponin **20** also exhibited moderate cytotoxicity against A549, PC-3, HL-60, and MRC-5 cell lines with GI_{50} values of 7.34-9.38 μM while no toxicity against the human pancreas cancer cells PANC-1 [81]. Especial, Eryngioside H and I exhibited potent and highly selective inhibition against four



human tumor cells but almost no cytotoxicity against normal human cells (Figs. **1** and **2**, and see Supporting Data **II**). Compounds **1**-**4**, and **7** isolated from the roots of *E. campestre* showed a weak cytotoxic activity, with IC_{50} between 40 and 100 μg/mL, against HCT 116 and HT-29 human tumor cell lines by MTT assay [15].

Ethanol extracts from fruits of *E. planum* were shown to display highly significant in inducing apoptosis in two human leukemic cell lines C8166 (96%) and J45 (89%) after 24 h incubation in concentration of 300 μg/mL. Lower level of apoptotic cells was observed in HL-60 (49%) and ML-1 (42%). The tested human leukaemia cell lines included human acute myeloblastic leukaemia (ML-1), human acute T cell leukaemia (J-45.01), human eosinophilic leukaemia (EOL), human caucasian promyelocytic leukaemia (HL-60), human T cell leukaemia lymphoblast (1301), human T cell leukaemia (C-8166), human myeloma (U-266B1), human Caucasian normal B cell (WICL), and human T cell (H-9) [101].

Anti-Mutagenic Activity

An anti-mutagenic potential of *E. creticum* was evidenced on MNNG induced mutagenicity using rat hepatocytes. The study was focused on ethanolic extracts, while the extracts had no effect on cytotoxicity indicators such as necrosis and apoptosis. The effects obtained can be attributed

Table 4. Biological Activities of *Eryngium* as Revealed by *In Vitro* Studies

Bioactivties	Description	Bioactive Agents	Reference
Cytotoxicities	Exhibited moderate or weak cytotoxicities against human pancreas, prostate, lung, leukemic, colon cancer cell lines and normal human lung fibroblast cell line	Saponin Cmpounds	[15, 81, Supporting Data II]
	Ethanol extracts induced apoptosis in human leukemic cell lines	Ethanol Etracts	[101]
Anti-mutagenic Activity	Exhibited an anti-mutagenic potential on MNNG mutagenicity using rat hepatocytes	Ehanolic Etracts	[102]
Anti-inflammatory Activities	Extracts Inhibited cytokine-stimulated, iNOS-dependent synthesis of nitric oxide in murine endothelial cells, without affecting cell viability	Extracts	[103]
	Reduced myeloperoxidase activity strongly in the inflamed tissue of the acute model	Polar Sterols	[21]
Anti-snake and Scorpion Venoms Effects	Aqueous extracts of the leaves and roots inhibited the hemolytic activity of the snake and scorpion venoms	Aqueous Extracts	[24]
	Ethanol extracts of the leaves and roots enhanced RBC hemolysis on red blood cells	Ethanol Extracts	[24]
	Inhibited the contraction of isolated tracheal smooth musle of rabbits and	Aqueous Extract	[106]
Antibacterial, Antifungal, and Antimalarial Activities	Exhibited selective antibacterial activity against Salmonella species and the Erwinia genus of bacteria	Eryngial	[108, 109]
	Exhibited activity against parasitic trypanosomes, nematodes, fungi and bacteria in humans and other mammals	Eryngial	[109]
	Exhibited antifungal activity with MIC values of 0.16-0.32 μg/mL against several dermatophyte species	Volatile Extracts	[110]
	Showed antimycotic activity	Saponin Mixture Extracts	[111, 113, 114]
	Showed antimicrobial activities against 12 bacterial and yeast strains	Chloroformic Fractions	[112]
	Showed antiplasmodial activity against *Plasmodium falciparum* with IC_{50} of 25 μg/mL and *P. gallinaceum* which infects hickens	Extracts	[109]
Antioxidant Activities	Exhibited antioxidant activity in *in vitro* assays	Rosmarinic acid analogs Extracts	[13, 115-121]
	Exhibited different levels of antioxidant activity six *in vitro* assays at both flowering and non-flowering stage	Methanol Extracts	[26, 122]
	Exhibited weak radical scavenging activity, low total phenol content	Extracts	[112]
	Inhibited iron-fructose-phosphate-induced lipid peroxidation in lecithin liposome and linoleic acid emulsion systems	Ethanol Extracts	[123]
Other Activities	Exhibited the inhibition in the velvetleaf germination	(-)-2,4,4-trimethyl-3-formyl-2,5-cyclohexadienyl angelate	[47]
	Exhibited anthelmintic activity against *Strongyloides stercoralis*	Eryngial	[109]

to a direct antimutagenic activity and an increased recovery at the chromosomal level [102].

Anti-Inflammatory Activities

Extracts obtained from the root and aerial parts of various *Eryngium* species are used as folk remedy worldwide for the treatment of various inflammatory disorders. Recently, in a antiinflammatory activity screening on extracts of 121 plants typical for the traditional Mediterranean diet, *E. campestre* L. decreased nitric oxide and TNF-alpha synthesis in the murine endothelial cells of monocyte origin activated with LPS, decreased cytokine or LPS-stimulated iNOS mRNA levels in both cell types [103]. It has been reported that ethanol extracts either from the aerial parts or roots of 7 *Eryngium* species growing in Turkey showed remarkably anti-inflammatory and antinociceptive activity in mice. Especially, the aerial parts and roots of *E. maritimum* and *E. kotschyi* were found to possess most promising activities without including any apparent gastric damage [22]. More detailed research showed the antiinflammatory effect of *E. maritimum* may be produced by a sub-alkaline fraction [23]. Saponin mixtures isolated from *E. planum* prevented inflammatory responses when injected into rats at concentration of 0.5 mg/kg, but oral administration at same dose had no antiinflammatory effect [104].

The hexane extracts from the leaves of *E. foetidum* can reduce the edema, induced by 12-0-tetradecanoylphorbol acetate (TPA) in the mouse, in a similar proportion in acute

Table 5. Biological Activities of *Eryngium* as Revealed by *In Vivo* Studies

Bioactivities	Animal Model	Description	Bioactive Agents	Reference
Anti-inflammatory Activities	Mice	Inhibited carrageenan-induced hind paw oedema and TPA-induced ear oedema tests	Ethanol Extracts	[22]
	Mice	Showed antinociceptive activity in the p-benzoquinone-induced writhing test	Ethanol Extracts	[22]
	Mice	Reduced the auricular oedema in acute and chronic assay induced by 12-0-tetradecanoylphorbol acetate (TPA)	Polar Sterols	[21]
	Rats	Prevented inflammatory responses to s.c. injections of nucleic acid Na salt or ovalbumin into the hind-paw	Saponin Mixtures	[104]
	Rats	Inhibited the carrageenan-induced oedema in paw given orally	Decoctions	[105]
	Rats	Induced the number of abdominal writhing provoked by acetic acid as the pain stimulus	Decoctions	[105]
Anti- Scorpion Venoms Effects	Guinea pigs	prolonged the life from 20 min to 8 hr injected by Jordanian Leiurus quinquestriatus scorpion venom	Aqueous Extracts	[106, 107]
Antihyperglycemic Effects	Rats	Reduced blood glucose concentration given orally in normoglycemic and streptozotocin –induced models	Decoctions	[17]
	Rats	Exhibited substantial acute antihyperglycemic activities despite lacking any favorable *in vitro* effectiveness	Aqueous Extracts	[124]
	Rats	Showed no effected in the level of glucose of the normoglycemic and streptozotocin –induced diabetic, and normal models when given a single oral dose	Extracts	[109]
Other Activities	Rats	Exhibited anti-convulsant activity at a concentration of 110 g/250 mL induced by picrotoxin	Extracts	[109, 127]
	Rats	Enhanced the permeation of piroxicam across rat skin	Essential Oil	[125, 126]

and chronic assay. Myeloperoxidase activity was also strongly reduced in the acute, but not the chronic model. Although stigmasterol (**88**) yielded from the hexane extracts exerted a significant topical antiinflammatory activity, by itself it could not account for the overall effects observed for the total phytosterols [21]. Further study indicated that a polar sterol should be responsible for the so-called medicinal property of the plant [99]. Aadditionally, a decoction from the leaves of *E. foetidum* exhibited significantly dose-dependent anti-inflammatory activity by inhibiting the carrageenan-induced oedema in rat paw. However, oral administration was less active than topical administration. This decoction also potently decreased the number of abdominal writhings provoked by acetic acid as the pain stimulus [105].

Anti- Snake and Scorpion Venoms Effects

Traditionally, many *Eryngium* species were used to prevent and treat snake bites and scorpion stings [10]. Modern pharmacologic investigations are only limited to *E. creticum*. *E. creticum* has been used in folk medicine in Jordan as a remedy for scorpion stings in the rural areas and as a hypoglycemic agent [17]. Aqueous extracts of both fresh and dried roots as well as fresh leaves of *E. creticum* gave 100% or a higher percentage inhibition of the hemolytic activity of the snake and scorpion venoms. However, ethanol extract of the leaves and roots enhanced red blood cell (RBC) hemolysis rather than inhibiting venom activities on RBC [24]. Aqueous extract of the roots inhibited the contraction of isolated tracheal smooth musle of rabbits and guinea pigs caused by *Leiurus quinquestriatus* scorpion venom, and also prolonged the life of guinea pigs from 20 min to 8 h when injected by a Jordanian *L. quinquestriatus* scorpion venom [106, 107].

Antibacterial, Antifungal, and Antimalarial Activities

The aerial plant parts of *E. foetidum* exhibited selective antibacterial activity against Salmonella species and the Erwinia genus of bacteria [108, 109]. A fraction of the essential oil rich in eryngial is the subject of a US patent application for its effectiveness against parasitic trypanosomes, nematodes, fungi and bacteria in humans and other mammals [109]. The volatile extracts of *E. duriaei* subsp. *juresianum*

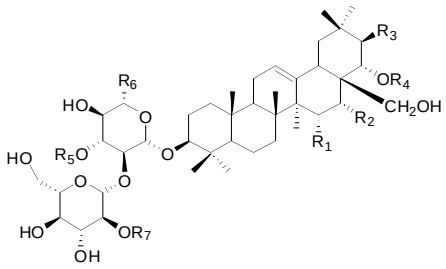


Table 6. Inhibitory Activity Against DNA Topoisomerases and Cytotoxicity Against Human Tumors of Some Oleanane-type Triterpenoids and Triterpenoid Glycosides

No.	Name	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Activity (IC_{50}) (μM)		Cytotoxicity (GI50) (μM)				
									TOP1	TOP2	A549	PC-3	HL-60	PANC-1	MRC-5
1	Eryngiioside J	OH	OH	O-Ang	Ac	Ara	COOH	H	(-)	(-)	4.3±0.34	5.08±0.38	7.36±0.28	11.45±0.75	5.61±1.27
2	Saniculasaponin III	OH	OH	O-Ang	Ac	Xyl	COOH	H	(-)	(-)	4.73±0.21	8.51±0.71	7.11±0.55	16.02±0.61	3.54±0.34
3	Eryngiioside L	H	OH	O-Ang	Ac	Xyl	COOH	H	(-)	(-)	8.35±2.89	11.32±1.60	8.41±1.84	13.0±1.27	8.71±1.45
4	21β-angeloyloxy-3β-[β-D-glucopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyloxy-olean-12-ene-15α, 16α, 22α, 28-tetrol	OH	OH	O-Ang	H	Ara	COOH	H	(-)	(-)	7.34±0.46	7.99±0.29	9.38±1.48	(-)	8.51±1.27
5	Eryngioside F	H	OH	OH	Ang	Xyl	COOH	H	(-)	(-)	(-)	(-)	(-)	(-)	(-)
6	Eryngioside E	OH	OH	OH	Ang	Xyl	COOH	H	(-)	(-)	(-)	(-)	(-)	(-)	(-)
7	Eryngioside H	OH	OH	H	Ang	Ara	COOH	H	(-)	(-)	1.0±0.15	2.12±0.11	3.65±1.00	12.71±2.19	5.61±0.71
8	Eryngioside I	OH	OH	H	Ang	Xyl	COOH	H	(-)	(-)	1.2±0.16	2.71±0.06	2.19±0.68	7.06±0.94	4.59±0.36
9	Eryngioside A	H	OH	H	Glc	H	CH_2OH	Glc	(-)	(-)	(-)	(-)	(-)	(-)	(-)
10	Eryngioside B	H	OH	H	Glc	H	CH_2OH	Gal	(-)	(-)	(-)	(-)	(-)	(-)	(-)
11	Eryngioside C	H	O	H	Glc	H	CH_2OH	Glc	(-)	(-)	(-)	(-)	(-)	(-)	(-)

Notes: *DNA Topoisomerase Inhibitory Activity:* For active compounds, IC_{50} (mean ± S.D.) refers to the concentration required to inhibit 50% of TOP1 activity. (-) indicates that the compound is inactive (negative at 312 μM or with IC_{50} >250 μM). *Cytotoxicity*: GI_{50} (mean ± S.D.) refers to the concentration required to have 50% cell-growth inhibition; (-) indicates that the compound is inactive at 25 μM

showed antifungal activity with MIC values of 0.16-0.32 μL/mL against several dermatophyte species (*Trichophyton mentagrophytes, T. rubrum, Epidermophyton floccosum; T. verrucosum, T. mentagrophytes var interdigitale, Microsporum canis* and *M. gypseum*) [110]. In an *in vitro* antimycotic activity screening against 8 phytopathogenic fungi, *E. creticum* showed more than 95% inhibition of spore germination in at least two fungi [111]. Two extracts from *E. maritimum* L. showed antimicrobial activities against 12 bacterial and yeast strains. The result indicated that chloroformic fractions were generally more active than methanolic ones [112]. A saponin mixture from dried leaves of *E. planum* also showed antimycotic effect [113, 114].

Despite the claims of traditional antimalarial use, *E. foetidum* showed lowly *in vitro* antiplasmodial activity against *Plasmodium falciparum* with IC_{50} of 25μg/mL. Interestingly, in the screening of the aqueous extract of the entire plant against various species of *Plasmodium*, activity was only reported against *P. gallinaceum* which infects chickens thereby suggesting another possible veterinary use [109].

Antioxidant Activities

There is currently an upsurge of interest in phytochemcals as new sources of natural antioxidants. In several *in vitro* antioxidant activity screening, many *Eryngium* species used as edible plants [115] and/or herbs in Thailand [116], Jordanian origin [117], Vietnamese [118], European [119], Sardinia [120], and Iran [121] have been demonstrated to have the antioxidant activity in tested models.

The roots of *E. alpinum* were shown to have highly antioxidant activity toward the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical in a TLC autographic assay. By further bioassay fractionation, compounds **82**, **83** and **85** were found to respond for the activity. Related to the activity of ascorbic acid, the antioxidant activity of **82** was almost one-fold higher than **83**, and similar to **84**. The results are consistent with published reports indicating that the position and/or the number of glycosyl groups present in the molecule plays a significant part in the antioxidant activity [13].

Methanol extracts of leaves and inflorescence of *E. caucasicum* at flowering stage, which was found recently as a new cultivated vegetable plant in home gardens in northern Iran, were investigated for their antioxidant activities employing six *in vitro* assay systems. Extracts exhibited different levels of antioxidant activity in all the models studied. Extracts showed very good scavenging activity of H_2O_2 with IC_{50} of 25.5 mg/mL for leaves and 177.2 mg/mL for inflorescence, respectively; IC_{50} for DPPH radical-scavenging

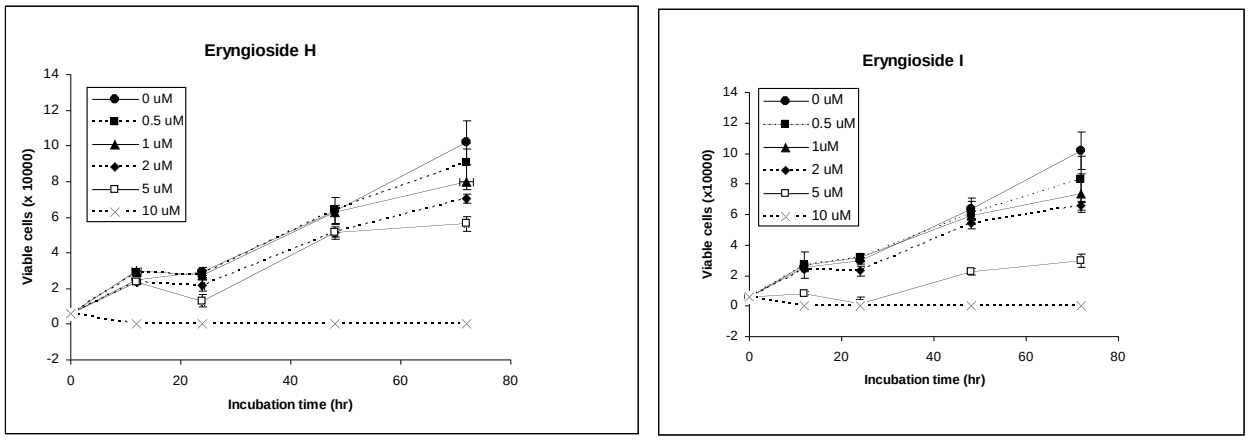


Fig. (1). Effects of Eryngioside H and I on the proliferation of human non-small cell lung cells (A549).

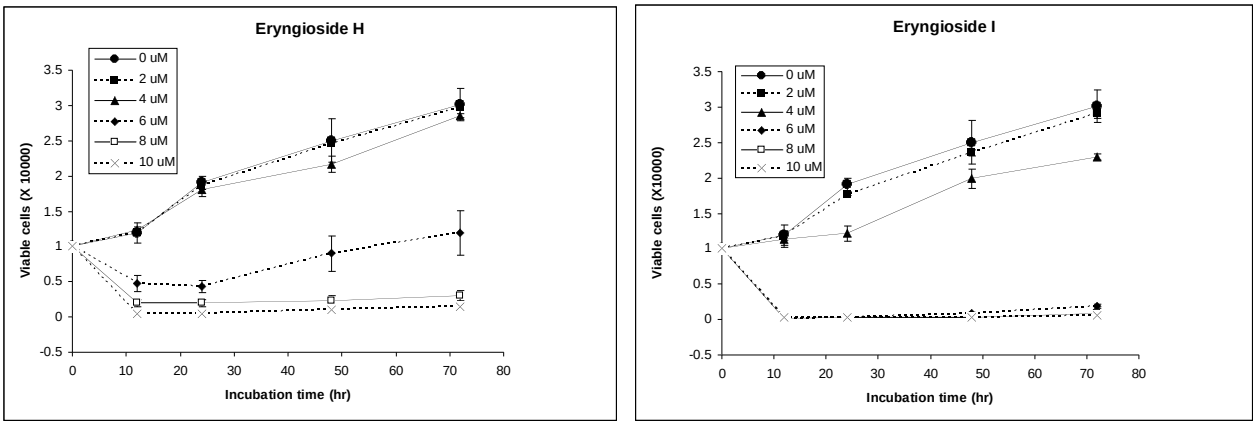


Fig. (2). Effects of Eryngioside H and I on the proliferation of human pancreatic cancer cells (PANC-1).

activity was 0.15 for leaves and 0.39 mg/mL for inflorescence; leaves extract exhibited better Fe^{2+} chelating ability (IC_{50} = 0.25 mg/mL) than that of EDTA (IC_{50} = 18 μg/mL) [26]. The research group also reported a good antioxidant activity of leaves of *E. caucasicum* at non-flowering stage using the same assay systems. However, these are so different from flowering stages. The leave extracts at non-flowering stage showed stronger NO scavenging and peroxidation inhibition, and very less scavenging activity of H_2O_2, reducing powers and Fe^{2+} chelating ability than leaves and inflorescence at flowering stage [122].

Eryngium maritimum exhibited weak radical scavenging activity (IC_{50} = 0.28 mg/mL), low total phenol content (16.4 mg/g), as well as relatively strong total antioxidant activities (from 32.7 to 48.6 mg/g) [112]. Ethanol extract of *E. billardieri* significantly inhibited iron-fructose-phosphate-induced lipid peroxidation in lecithin liposome and linoleic acid emulsion systems [123].

Antihyperglycemic Effects

A research indicated that an aqueous decoction from *E. creticum* caused significant reductions in blood glucose concentration when given orally in normoglycemic and streptozocin-hyperglycemic rats [17]. The aqueous extracts of *E. creticum* exhibited substantial acute antihyperglycemic activities in starch-treated rats, despite lacking any favorable *in vitro* effectiveness [124]. In a preliminary oral glucose-tolerance evaluation, a single (acute) oral dose of the leaf extract from *E. foetidum* did not cause significant reduction in the level of glucose of the models tested [109].

In addition, some other bioactivity and pharmacological properties of *Eryngium* also report. (-)-2,4,4-trimethyl-3-formyl-2,5-cyclohexadienyl angelate (**46**), only active compound isolated from the hexane extract of seeds from *E. paniculatum* was found to inhibit germination of velvetleaf [47]. The essential oil of *E. bungei* and *E. caeruleum* at the 5.0% concentration provided an almost 9.17-fold and 8.56-fold increase in permeability coefficients of piroxicam across rat skin [125, 126]. Pharmacological studies of the aerial plant parts of *E. foetidum* L. included also anthelmintic activity due to eryngial and anti-convulsant activity at a concentration of 110 g/250 mL induced by picrotoxin in the respective models [109, 127]. *Eryngium foetidum* is one of four plants used in a Japanese patent for having developed a skin-whitening agent [109].

CONCLUSIONS

Eryngium has been cultivated as ornamental, vegetable, and medicinal crops. However, phytochemistry and pharmacological properties of most of the 250 species remain unex-

plored. From the 23 species, at least 127 compounds have been isolated and identified. These are primarily non-essential oil compounds such as terpenoids, triterpenoid saponins, flavonoids, coumarins, polyacetylenes, and steroids. These 23 species represent nine to 11 sections of *Eryngium* in both Old and New Worlds. Initial data indicated that triterpenoid saponins, terpenoids, coumarins may be restricted to certain sections. Because the chemical investigations for the most of these species except *E. campestre* and *E. yuccifolium* are preliminary and incomplete, chemotaxonomical significance of these compounds will not be revealed until extensive investigations including more species.

Eryngium extracts or isolates have shown *in vitro* and *in vivo* activitities such as cytotoxicity against various human tumor cell lines, anti-inflammatory, anti-snake and scorpion venoms, antibacterial, antifungal, and antimalarial, antioxidant, and antihyperglycemic effects. There are no clinical data related to the numerous ethno medicinal uses. The molecular mechanisms of bioactivities (particularly cytotoxicity and anti-snake and scorpion venoms) of *Eryngium* isolates remain elusive. Also, chemical isolation and modification and animal tests of polyhydroxylated triterpenoid saponins may provide interesting lead for cancer drug development.

ABBREVIATIONS

A549	=	Human lung adenocarcinoma epithelial cell line
Ang	=	Angeloyl
Ac	=	Acetyl
dMA	=	*β*,*β*-dimethylacryloyl
DPPH	=	2,2-diphenyl-1-picrylhydrazyl
EDTA	=	Ethylenediaminetetraacetic acid
HL-60	=	Human promyelocytic leukemia cell line
HCT 116	=	Human colon adenocarcinoma epithelial cell line
HT-29	=	Human colon adenocarcinoma epithelial cell line
iNOS	=	Inducible nitric oxide synthase
LPS	=	Lipopolysaccharide
MNNG	=	N-methyl-N′-nitro-N-nitroso-guanidine
MRC-5	=	Human normal lung cell line
mRNA	=	Messenger ribonucleic acid
PANC-1	=	Human pancreatic carcinoma, epithelial-like cell line
PC-3	=	Human prostate adenocarcinoma epithelial cell line
RBC	=	Red blood cell
SAR	=	Structure–activity relationship
TOP1	=	DNA topoisomerase I
TOP2	=	DNA topoisomerase II
TNF	=	Tumor necrosis factor
TPA	=	12-O-tetradecanoylphorbol acetate

CONFLICT OF INTEREST

None Declared.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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