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Review

Chemical Structure and Biological Activities of Secondary Metabolites from *Salicornia europaea* L.

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Abstract: *Salicornia europaea* L. is a halophyte that grows in salt marshes and muddy seashores, which is widely used both as traditional medicine and as an edible vegetable. This salt-tolerant plant is a source of diverse secondary metabolites with several therapeutic properties, including antioxidant, antidiabetic, cytotoxic, anti-inflammatory, and anti-obesity effects. Therefore, this review summarizes the chemical structure and biological activities of secondary metabolites isolated from *Salicornia europaea* L.

Keywords: *Salicornia europaea* L.; halophyte; phytochemicals; secondary metabolites

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1. Introduction

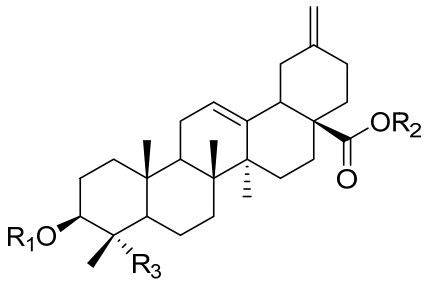
Salicornia europaea L., also known as *Salicornia herbacea* L., is a halophyte belonging to the Chenopodiaceae subfamily with many common names including glasswort, sea beans, sea asparagus, and samphire [1]. As implied by its names, this edible plant tolerates up to 3% salinity [2] and grows in salt marshes and muddy seashores in temperate and subtropical regions worldwide, including the western and southern coasts of Korea [3]. In Asia, *S. europaea* has been traditionally used as a traditional medicine for constipation, nephropathy, hepatitis, diarrhea, obesity, and diabetes, among other disorders [4,5]. Moreover, in addition to using *S. europaea* for glass making, its aerial parts are used in salads, pickles, fermented food, and salt substitutes [6,7]. Therefore, due to the many health benefits of *S. europaea*, several studies proposed the development of this halophyte as a functional food and medicinal plant. Importantly, *S. europaea* crude extracts reportedly possess several therapeutic properties. For instance, the presence of immunomodulatory compounds in crude extracts was demonstrated via RAW 264.7 macrophage cell line assays [8]. Moreover, the antioxidant activity of *S. europaea* was measured via the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, hydroxyl radical scavenging, and reactive oxygen species (ROS) generation assays [9]. The antihyperglycemic and antihyperlipidemic activities of this plant were also demonstrated in mice fed with a high-fat diet [10] and another study reported that a polysaccharide extract from this plant exhibited anti-inflammatory activity in vitro and in vivo [11].

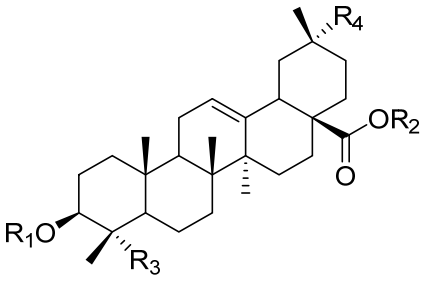
In addition to the many studies that have characterized the bioactivity of crude *S. europaea* extracts or individual fractions, many bioactive secondary metabolites have been isolated from this plant. Therefore, this review sought to systematically classify the secondary metabolites isolated from *S. europaea* according to their chemistry and summarize their biological activities. Most of the biological activities of the secondary metabolites discussed herein were taken from separate studies. Many studies generally classify glasswort-like

species as *S. europaea* due to the difficulties of taxonomic identification of the genus *Salicornia.* Therefore, it is worth noting that this manuscript is by no means a comprehensive review of all *S. europaea* studies, and instead focuses on representative examples.

2. Oleanane Triterpenoid Saponins

Triterpenoid saponins are abundant in plants and possess a variety of biological activities, including antifungal, antiviral, antioxidant, antiglycation, and anticancer properties [12–15]. More than twenty oleanane-type triterpenoid saponins, including 30-noroleanane triterpenoid saponins, have so far been isolated from *S. europaea* (Figure 1).





	R_1	R_2	R_3
1	GlcUA	Glc	CHO
2	GlcUA	Glc	CH_2OH
12	Y	H	CHO
13	Y	H	CH_3
14	Glc-(1-2)-[Xyl-(1-3)]-GlcUA	Glc	CH_3
15	H	H	CH_3
16	GlcUA	H	CH_3
17	GlcUA	Glc	CH_3
18	X	Glc	CH_3

	R_1	R_2	R_3	R_4
3	GlcUA	H	CHO	CH_3
4	GlcUA	Glc	CHO	CH_3
5	H	Glc	CH_3	CH_2OH
6	H	Glc	CH_3	CH_3
7	X	Glc	CH_3	CH_3
8	GlcUA	H	CH_3	CH_3
9	X	H	CH_3	CH_3
10	H	H	CH_3	CH_3
11	H	H	CHO	CH_3
19	Glc	H	CH_3	CH_3
20	GlcUA	Glc	CH_3	CH_3
21	GlcUA	Glc	CH_3	CH_2OH

Glc: β-D-glucopyranosyl
GlcUA: β-D-glucuronic acid
Xyl: β-D-xylopyranosyl
X: β-D-glucuronopyranoside methyl ester
Y: β-D-glucuronopyranoside butyl ester

Figure 1. Chemical structures of oleanane triterpenoid saponins isolated from *Salicornia europaea* (**1**–**21**).

In 2012, a new 30-noroleanane triterpenoid saponin, 3*β*-hydroxy-23-oxo-30-noroleana-12,20(29)-diene-28-oic acid 3-*O*-*β*-D-glucuronopyranosyl-28-*O*-*β*-D-glucopyranoside (**1**), and three known triterpenoid saponins (**2**–**4**) were also isolated from an *n*-BuOH fraction of an *S. europaea* extract [5]. The known compounds were identified as 30-norhederagenin 3-*O*-*β*-D-glucuronopyranosyl-28-*O*-*β*-D-glucopyranoside (**2**), gypsogenin 3-*O*-*β*-D-glucuronopyranoside (**3**), and gypsogenin 3-*O*-*β*-D-glucuronopyranosyl-28-*O*-*β*-D-glucopyranoside (**4**). The antioxidant activities of compounds **1**–**4** have been evaluated by measuring their 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical and peroxynitrite ($ONOO^-$) scavenging activities. All four compounds were found to be potent scavengers for both authentic peroxynitrite and peroxynitrite produced by morpholinosydnonimine (SIN-1) (IC_{50} between <<1 and 21.9 μM). Notably, compound **2** had the lowest IC_{50} values (<<1 μM) for both authentic $ONOO^-$ and $ONOO^-$ produced by SIN-1, but displayed no significant DPPH radical scavenging activity. Compound **1** also possesses a potent antifungal activity against *Colletotrichum gloeosporioides* [16]. Compound **1** has been previously isolated from *Salicornia*

bigelovii. Compound **3** has been isolated from the flowering plant *Gypsophila pacifica* and exhibited promising hepatoprotective activity [17]. This triterpenoid saponin has also been isolated from fruits of *Acanthopanax senticosus* and showed pancreatic lipase inhibitory activity (Table 1) [18].

In the same year, Yin et al. reported the isolation and structural elucidation of 3*β*,29-dihydroxyolean-12-en-28-oic acid 28-*O*-*β*-D-glucopyranosyl ester (**5**), a new oleanane triterpenoid saponin, along with four previously identified compounds: oleanolic acid 28-*O*-*β*-D-glucopyranoside (**6**), chikusetsusaponin IVa methyl ester (**7**), calenduloside E (**8**), and calenduloside E 6′-methyl ester (**9**) [19]. The plant sample in question was collected in Jiangsu Province, China, along the Yellow Sea shore. Although the biological activity of **5** has not yet been described, the bioactivities of compounds **6**–**9** have been studied extensively. Compound **6**, isolated from *Drypetes paxii* reportedly exhibits antibacterial activity [20], and an isolate from the plant *Aralia cordata* has been reported to possess anti-inflammatory effects [21]. A synthesized version of compound **6** also displayed potent *α*-glucosidase and *α*-amylase inhibitory activities [22]. The reported biological effects of compound **7** include anticancer [23–25], antifungal [16], and anti-inflammatory [26] activities. Compound **8** exhibited potent spermicidal [27] and anticancer activities [23,28]. Compounds **7** and **8** have been isolated from *Gardenia jasminoides* roots [23], whereas compound **9** has been isolated from *Salicornia bigelovii*, *Acanthopanax sessiliflorus*, and *Ilex rotunda*, and were reported to possess cytotoxic activity [29,30] and a moderate anticlotting effect [31].

In 2014, Zhao et al. identified two known oleanane-type terpenoid saponins, oleanolic acid (**10**) and gypsogenin (**11**), along with two new 30-noroleanane triterpenoid saponins, salbige A (**12**) and B (**13**), in a *S. europaea* methanol extract [32]. Interestingly, the *S. europaea* analyzed in this study was collected from the salt lake of Xinjiang Province in China, which is thousands of kilometers from the nearest ocean. Compounds **12** and **13** displayed potent anti-proliferative activities against A549 cancer cells in the aforementioned study, with IC_{50} values of 52.35 and 79.39 μM, respectively. The biological activities of compound **10**, which is one of the most abundant and well-known triterpenoid saponins, included antioxidant, antitumor, anti-inflammatory, antidiabetic, antimicrobial, hepatoprotective, antihypertensive, antiparasitic [33], and antiviral [34] activities. This versatile pentacyclic triterpenoid is abundant and conspicuous in plants of the Oleaceae family, including the olive plant, and have been identified in a wide range of plants including *Achyranthes aspera*, *Aspilia africana*, *Lantana camara*, *Ocimum sanctum*, *Vitis vinifera*, *Flaveria trinervia*, *Syzygium aromaticum*, and *Miconia albicans* [33]. Synthetically prepared compound **11** exhibited antimicrobial, antiproliferative, and apoptotic effects [35].

Table 1. Reported biological activities of compounds **1**–**21**.

No.	Biological Activities [1]														
	Antioxidant			Antidiabetic	Cytotoxic							Antibacterial/ Antifungal		Anti-Inflammatory	Others
	DPPH IC_{50} (μM)	Authentic $ONOO^-$ IC_{50} (μM)	SIN-1 IC_{50} (μM)	α-Glucosidase inhibitory IC_{50} (μM)	A2780 IC_{50} (μM)	HEY IC_{50} (μM)	HeLa IC_{50} (μM)	MCF-7 IC_{50} (μM)	A549 IC_{50} (μM)	A354-S2 IC_{50} (μM)	HepG2 IC_{50} (μM)	Antibacterial	Antifungal		
1	$>>5 \times 10^2$	4.9	6.6										O		
2	3.9×10^2	<<1	<<1												
3	$>>5 \times 10^2$	21.9	20.4												Pancreatic lipase inhibitory, hepatoprotective
4	$>>5 \times 10^2$	7.1	1.4												
5															
6				251.7	47.4	28.2						O		O	α-Amylase inhibitory
7					7.4	7.9	17.7	44.1	47.2	33.2			O	O	
8							5.4	56.0	97.5	29.9					Spermicidal
9							20.7	13.3	9.6	25.1					Anticlotting
10		O		O				O				O		O	Hepatoprotective, antihypertensive, antiparasitic, antiviral
11							22.5	9.0				O			
12									52.4						
13									79.4						
14															
15				9			27.8		48.8		51.9	O			Anti-HIV-1 protease, fibrillogenesis inhibitory
16				O											
17															
18								O					O		
19				O											PTP1B inhibitory
20				O										O	Antiviral, antithrombotic, insulinotropic, anti-obesity
21															

[1] Qualitative bioassay study reported without quantitative data was marked with O.

In 2018, Lyu et al. reported the isolation of five more 30-noroleanane triterpenoid saponins from whole *S. europaea* plants, including the previously undescribed compound salieuropaea A (3-*O*-*β*-glucopyranosyl-(1→2)-[*β*-xylopyranosyl-(l→3)]-*β*-glucuronopyranosyl 30-noroleanolic acid 28-*O*-*β*-glucopyranosyl ester, **14**) [36]. The other isolated 30-noroleanane triterpenoid saponins were identified as akebonic acid (**15**), boussingoside A_1 (**16**), boussingoside A_2 (**17**), and 3-*O*-[*β*-D-glucuronopyranosyl-6′-*O*-methyl ester]-30-norolean-12,20(29)-dien-28-*O*-[*β*-D-glucopyranosyl] ester (**18**). Nine oleanane triterpenoid saponins (**5**–**10** and **19**–**21**), including oleanolic acid 3-*O*-*β*-D-glucopyranoside (**19**), chikusetsusaponin IVa (**20**), and zygophyloside K (**21**), were also isolated and structurally characterized in this study. The plant sample was collected from Jiangsu Province, China. Although the biological activities of compounds **14** and **17** have not been described yet, compound **15** was reported to exhibit anti-HIV-1 protease activity [37], antibacterial activity [38], an inhibitory effect on Aβ42-induced fibrillogenesis [39], an α-glucosidase inhibitory effect, and moderate in vitro cytotoxic activity against human cancer cell lines [40]. Compound **15** has been isolated mostly from the flowering plant family Lardizabalaceae, such as *Stauntonia obovatifoliola*, *Akebia quinata*, and *Akebia trifoliata* [37–40]. Compound **16**, which was previously isolated from the Colombian climbing plant *Boussingaultia baselloides*, was found to exhibit hypoglycemic activity in rats [41]. Compound **18** has displayed cytotoxic activity towards the SK-N-SH and HL60 cell lines [42], as well as a potent inhibitory activity against *Colletotrichum gloeosporioides* [16]. Thiyagarajan et al. reported that vitalboside A (**19**) isolated from *Syzygium cumini* could be a potent therapeutic agent to manage obesity and diabetes due to its inhibitory effect on PTP1B and partial agonism of the peroxisome proliferator-activated receptor γ [43]. Compound **20** has been reported to possess antiviral [44], antithrombotic [45], insulinotropic [46], anti-inflammatory [47], and anti-obesity [48] activities. The presence of compound **20** has been reported in other plants, including *Alternanthera philoxeroides* [44], *Ilex paraguariensis* [45], and *Dolichos lablab* seeds [48]. No studies have been reported regarding the bioactivity of compound **21**.

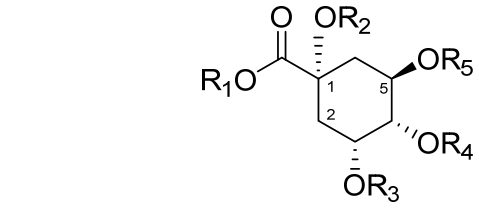
3. Caffeoylquinic Acid Derivatives

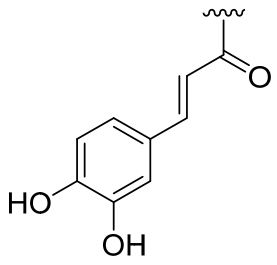
Caffeoylquinic acid (CQA) derivatives have been reported in many plants including coffee beans, and their various biological activities include antioxidant, antibacterial, anticancer, and antihistaminic effects [49] (Figure 2).

In 2005, Chung et al. isolated and determined the structure of a new natural chlorogenic acid derivative, tungtungmadic acid (3-caffeoyl-4-dihydrocaffeoyl quinic acid, **22**) [50]. The plant materials were collected from Busan, in the southern coast of Korea. In this study, tungtungmadic acid displayed a strong antioxidant activity in both DPPH free radical scavenging and iron-induced liver microsomal lipid peroxidation inhibitory assays, with IC_{50} values of 5.1 and 9.3 μM, respectively (Table 2). Studies have also reported that compound **22** can protect plasmid DNA from hydroxyl radical-induced strand breakage. Several other studies on the biological activities of compound **22** have been conducted since its isolation. For instance, compound **22** has also been reported to provide protection against carbon tetrachloride ($CC1_4$)-induced hepatic fibrosis and *tert*-butyl hydroperoxide (*t*-BHP)-induced hepatotoxicity [50,51]. Moreover, this compound possesses anti-inflammatory properties [52], inhibits tumor cell invasion [53], and prevents high-glucose-induced lipid accumulation in human HepG2 cells [54]. Interestingly, the occurrence of compound **22** has not been reported in other sources (Table 2).

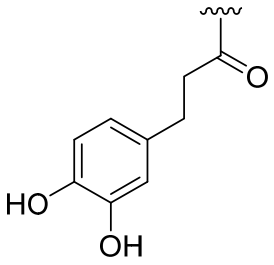
In 2011, Kim et al. reported the isolation of compound **22** and four other caffeoylquinic acid derivatives from *S. europaea* collected from Younggwang, southwestern coast of Korea [6]. The four known compounds were identified as 3,5-dicaffeoylquinic acid (**23**), methyl 3,5-dicaffeoylquinate (**24**), 3,4-dicaffeoylquinic acid (**25**), and the novel compound methyl 4-caffeoyl-3-dihydrocaffeoylquinate (salicornate, **26**). Importantly, all of these dicaffeoylquinic acid derivatives (**22**–**26**) were found to possess significant antioxidant activities, as demonstrated by measurements of both DPPH radical scavenging and cholesteryl ester hydroperoxide (CE-OOH) formation inhibiting activities. Dicaffeoylquinic acids (**23**, **25**)

derived from *Youngia japonica*, a biannual medicinal herb, also exhibited antibacterial activities [55]. Similarly, a dicaffeoylquinic acid methyl ester form (**24**) isolated from the aerial parts of *Ageratina adenophora* exhibited antibacterial activity against *Salmonella enterica* [56]. Moreover, extracts from the edible plant *Centella asiatica* exhibited neuroprotective activity in in vitro models of Aβ toxicity, which includes compounds **23** and **25** [57]. An independent study in 2012 also demonstrated the neuroprotective activity of compounds **23**–**25**, which were isolated from *Ilex latifolia* [58]. Furthermore, compounds **23**–**25** could be used to treat diabetes and diabetic complications, and were identified in other plant sources including *Artemisia capillaris*, *Gynura divaricata*, and *Artemisia iwayomogi* [59–61]. Compound **23** was also found in *Laggera alata*, *Artemisia capillaris*, *Helichrysum populifolium*, and *Erycibe obtusifolia* and was reported to possess antithrombotic activity [62], anti-inflammatory effects [63], hepatoprotective and antiviral activity [64–67], and cytotoxic activity [68]. Similarly, compound **24** exhibits a range of bioactivities, including anti-inflammatory [63,69,70], antitumor [71,72], and anti-melanogenic [73] effects. Compound **25** has been found to possess antithrombotic [62], antihyperlipidemic [74], and antiviral [65–67] activities. Interestingly, compound **25** was also found in the fruits of *Pandanus tectorius*, a mangrove plant [74].





Caffeoyl (Caf)



Dihydrocaffeoyl (DCaf)

	R_1	R_2	R_3	R_4	R_5
22	H	H	Caf	DCaf	H
23	H	H	Caf	H	Caf
24	CH_3	H	Caf	H	Caf
25	H	H	Caf	Caf	H
26	CH_3	H	DCaf	Caf	H
27	H	H	Caf	H	DCaf
28	H	H	H	DCaf	DCaf
29	H	Caf	Caf	H	H
30	H	H	DCaf	H	DCaf
31	H	H	Caf	H	H
32	CH_3	H	Caf	H	H
33	CH_3	H	Caf	H	DCaf
34	CH_3	H	Caf	DCaf	H
35	CH_3	H	DCaf	H	DCaf

Figure 2. Chemical structures of caffeoylquinic acids isolated from *Salicornia europaea* (**22**–**35**).

Table 2. Reported biological activities of compounds **22**–**35**.

No.	Biological Activities [1]						
	Antioxidant	**Antidiabetic**	**Cytotoxic**	**Antibacterial**	**Anti-Inflammatory**	**Anti-HMGB1**	**Others**
	DPPH Scavenging IC_{50} (μM)						
22	5.1		O		O		Hepatoprotective, lipogenesis inhibitory
23	6.1	O		O	O	O	Neuroprotective, antithrombotic, hepatoprotective, antiviral,
24	O	O	O	O	O	X	Neuroprotective, anti-melanogenic
25	3.4	O	O	O			Neuroprotective, antithrombotic, antihyperlipidemic, antiviral
26	O						
27	O					O	
28						X	
29	9.2		O			O	
30						O	
31	O						Influenza A neuraminidase inhibitory, neuroprotective
32	O						
33	O						
34	O						
35	O						

[1] Qualitative bioassay study reported without quantitative data was marked with O.

In 2015, two new (**27**, **28**) and four known caffeoylated quinic acids (**23**, **24**, **29**, **30**) were isolated from *S. europaea*, and their potential to alleviate high mobility group box 1 (HMGB1)-mediated vascular barrier disruption was evaluated in vitro and in vivo [75]. In this study, farm-raised plant material was obtained from Shinan, which is located on the southern coast of Korea. The new compounds were identified as 3-*O*-caffeoyl-5-*O*-dihydrocaffeoyl quinic acid (**27**) and 4,5-di-*O*-dihydrocaffeoyl quinic acid (**28**), along with the known compounds 1,3-di-*O*-caffeoyl quinic acid (**29**) and 3,5-di-*O*-dihydrocaffeoyl quinic acid (**30**). According to this study, compounds **23**, **27**, **29**, and **30** showed vascular protective activities against inflammatory responses induced by HMGB1 in both cellular and animal models. Compound **29** has also been reported to possess antioxidant and cytoprotective effects [76]. This study also showed that the positions of two caffeoyl groups were closely related to their activity. Among the di-*O*-caffeoylquinic acid compounds, entities with adjacent caffeoyl moieties exhibited better performance than their non-adjacent configured counterparts.

In 2016, Cho et al. reported the isolation of three known (**27**, **31**, **32**) and three new caffeoylquinic acid derivatives (**33**–**35**) from methanol extracts of *S. europaea* collected from Younggwang, in the southwestern coast of Korea [77]. The known compounds included 3-caffeoylquinic acid (**31**) and 3-caffeoylquinic acid methyl ester (**32**), and the new compounds were established as 3-caffeoyl-5-dihydrocaffeoylquinic acid methyl ester (**33**), 3-caffeoyl-4-dihydrocaffeoylquinic acid methyl ester (**34**), and 3,5-di-dihydrocaffeoylquinic acid methyl ester (**35**). In this study, all six compounds scavenged DPPH radicals and inhibited CE-OOH formation. The dicaffeoylquinic acid derivatives (**27**, **33**–**35**), which have two catechol groups, showed higher activities than the mono-caffeoylquinic acid derivatives (**31**, **32**) and caffeic acid did. Additionally, compound **31** extracted from leaves of *Moringa oleifera* reportedly possesses moderate influenza A neuraminidase inhibitory activity [78]. This compound also exerts neuroprotective properties via the inhibition of pro-inflammatory responses in activated microglia [79].

4. Flavonoids and Flavanones

Flavonoids and flavonoid glycosides have also been isolated from *S. europaea* (Figure 3). In 1982, Arakawa et al. reported the isolation and structural elucidation of 2′-hydroxy-6,7-methylenedioxyisoflavone (**36**), (−)-(2*S*)-2′-hydroxy-6,7-methylenedioxyflavanone (**37**), and 2′,7-dihydroxy-6-methoxyisoflavone (**38**) from a methanol extract of *S. europaea* [80]. The plants for this study were collected from lake Notoro, which is a coastal lagoon by the northern shore of Hokkaido, Japan.

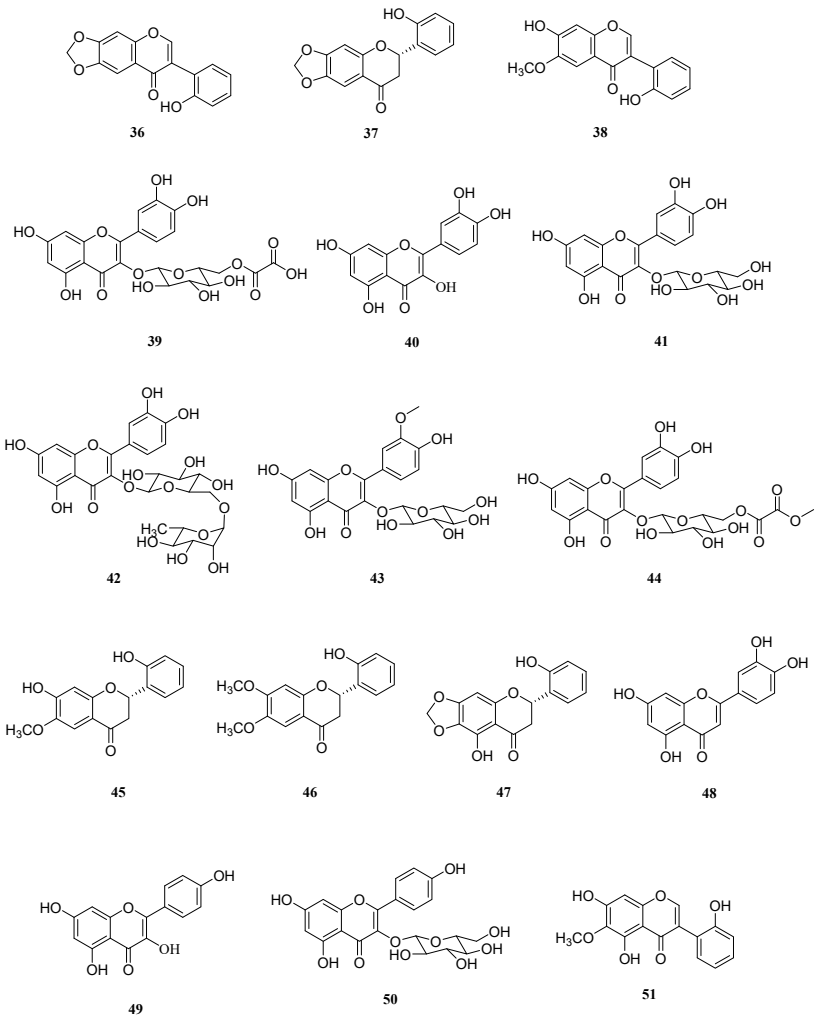


Figure 3. Chemical structures of flavonoids isolated from *Salicornia europaea* (**36**–**51**).

Three years later, Geslin et al. isolated quercetin 3-*O*-(6″-*O*-malonyl)-*β*-D-glucoside (**39**), quercetin (**40**), quercetin 3-*O*-*β*-D-glucopyranoside (**41**), rutin (**42**), and isorhamnetin 3-*O*-*β*-D-glucopyranoside (**43**) from *S. europaea* collected from Loire-Atlantique, by the Bay of Biscay, France [81]. A cherry blossom derived compound (**39**) reportedly acted as a potent suppressor of the production of advanced glycation end products (AGEs) and fibroblast apoptosis by AGEs [82]. This quercetin isolated from the leaves of *Corchorus olitorius* or the fruit peel of *Sicana odorifera* acted as an antioxidative agent [83,84]. A broad range of biological effects has been reported for compounds **40**–**42**, including anti-inflammatory, antidiabetic, cardiovascular protection, and anticancer effects [85–87]. Compound **43**, isolated from *S. europaea*, has been reported to be a potential agent for the prevention and/or treatment of diabetes [88] and a chemo preventive agent for cancer [89], as well as an anti-oxidant [90] and anti-obesity agent (Table 3) [91].

Table 3. Reported biological activities of compounds **36**–**51**.

No.	Biological Activities [1]					
	Antioxidant	**Antidiabetic**	**Cytotoxic**	**Anti-Inflammatory**	**Anti-HMGB1**	**Others**
		AGE Production Inhibitory IC_{50} (μM)				
36						
37						
38						
39	O	65.4				
40	O	105.9	O	O		Cardiovascular protection
41	O	64.6	O	O		Cardiovascular protection
42	O	O	O	O		Cardiovascular protection
43	O	O	O			anti-obesity
44	O					
45					O	
46					O	
47					O	Antiglycation
48	O		O	O		Antiapoptotic, cardioprotective
49	O	73.4	O	O		Neuroprotective, cardioprotective
50	O	227.5	O	O		Neuroprotective, cardioprotective
51	O			O		Antifungal, estrogenic

[1] Qualitative bioassay study reported without quantitative data was marked with O.

Kim and Park isolated compounds **41** and **43** in 2004 from plant samples collected from Muan-gun, southwestern coast of Korea, and demonstrated that the antioxidant activities of compounds **41** and **42** were similar to those of compound **40** [92]. However, the activity of compound **43**, which contains a methoxy group on the flavonoid B ring, was lower than the activity of compound **40**.

In 2011, Kim et al. reported the isolation and antioxidant activities of a novel flavonoid glycoside, isoquercitrin 6″-*O*-methyloxalate (**44**), along with the known compounds **41** and **43** [6]. Compounds **41** and **44**, which have no substitutions on their B rings, exhibited significant antioxidant activities, whereas the antioxidant activity of compound **43** was comparatively less potent. These results agreed with previous reports that the catechol group of the B ring plays an important role in determining the antioxidant activities of flavonoids [93,94].

In 2015, two new flavanones and one known flavanone (**45**–**47**) were isolated by Tuan et al. from an ethyl acetate extract of farm-raised *S. europaea* [95]. The isolated compounds were identified as 2*S*-2′,7-dihydroxy-6-methoxyflavanone (**45**), 2*S*-2′-hydroxy-6,7-dimethoxy-flavanone (**46**), and 2*S*-5,2′-dihydroxy-6,7-methylenedioxyflavanone (**47**). The authors assessed the suppressive activities of compounds **45**–**47** against HMGB1 and found that they inhibited both LPS-stimulated HMGB1 secretion in vitro and cecal ligation and puncture (CLP)-induced HMGB1 secretion in vivo. Moreover, compound **47**, which was previously isolated from *Iris* spp., also exhibited promising antiglycation activity [96].

Three flavonoids (**48**–**50**) that are widely known for their pharmacological activities have been isolated from *S. europaea*, in addition to compounds **40**–**43** [36]. Luteolin (**48**) has been found to display antioxidant, antitumor, anti-inflammatory, antiapoptotic, and cardioprotective activities [97]. This well-known flavonoid is one of the most intensely studied plant-derived metabolites, which is abundant in carrots, cabbage, tea, and apples. Kaempferol (**49**) is a hydroxyl group regioisomer of compound **48**. Compound **50** is a glucoside derivative of **49**. The biological activities of kaempferol (**49**) and kaempferol-3-*O*-*β*-D-glucoside (**50**) include anti-inflammatory, antioxidant, neuroprotective, cardioprotective, antidiabetic, and anticancer properties [98,99]. Compound **50**, also known as astragalin, is found in a wide range of medicinal plants such as wild garlic, tea, Chinese bittersweet, and sundew [99].

Irilin B (**51**) was recently identified and isolated from *S. europaea* via antioxidant activity-guided isolation and purification [100]. Compound **51** exhibits a good antioxidant and anti-neuroinflammatory potential. Moreover, compound **51** derived from *Chenopodium procerum*, an African medicinal plant, reportedly displayed antifungal activity against the plant pathogenic fungus *Cladosporium cucumerinum* [101]. Interestingly, another study reported the estrogenic activity of this compound from *Iris songarica* [102].

5. Chromones

Chromones are benzoannelated γ-pyrone heterocycles that are widely found in nature, particularly in plants (Figure 4). Several pharmacological properties of chromones, including their anti-allergic, anti-inflammatory, antidiabetic, antitumor, and antimicrobial effects, have been identified thus far [103,104].

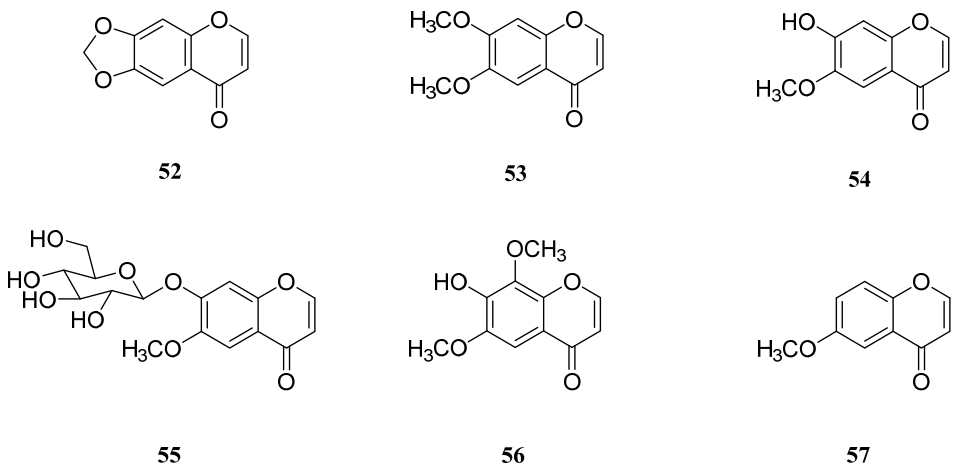


Figure 4. Chemical structures of chromones isolated from *Salicornia europaea* (**52**–**57**).

In 1978, two new naturally occurring 2,3-unsubstituted chromones, 6,7-methylenedioxychromone (**52**) and 6,7-dimethoxychromone (**53**), were isolated from the leaves and stems of *S. europaea* collected from the Notoro lakeside in Japan [105].

Five years later, Arakawa et al. identified and characterized the chromones 7-hydroxy-6-methoxychromone (**54**) and 7-*O*-*β*-D-glucopyranosyl-6-methoxychromone (**55**) from a methanol extract of *S. europaea*, neither of which had been previously identified in natural sources [106].

Most recently, Tuan et al. isolated a new naturally occurring chromone, 7-hydroxy-6,8-dimethoxychromone (**56**) along with compound **53** and 6-methoxychromanone (**57**) from farm-raised *S. europaea* [95]. In this study, compounds **53**, **56**, and **57** inhibited the release of HMGB1, which resulted in improved survival rates of CLP murine models. However, bioactivity study of these chromes are relatively unexplored, as shown in Table 4.

Table 4. Reported biological activities of compounds **52**–**57**.

No.	Biological Activity [1]
	Anti-HMGB1
52	
53	O
54	
55	
56	O
57	O

[1] Qualitative bioassay study reported without quantitative data was marked with O.

6. Sterols

Sterols are part of the vast isoprenoid family of compounds and are essential for all eukaryotes [107]. Five sterols have been isolated from *S. europaea*, including β-sitosterol (**58**), stigmasterol (**59**), ergosterol (**60**), β-daucosterol (**61**), and cerevisterol (**62**) (Figure 5).

In 2004, Lee et al. isolated and identified compounds **58** and **59** [108]. In this study, plant samples were collected from Mokpo, on the southwestern coast of Korea. Compound **58** has been shown to possess anti-inflammatory, anticancer, hypocholesterolemic, immunomodulatory, antioxidant, neuroprotective, and antidiabetic effects (Table 5) [109]. Moreover, this compound is among the predominant phytosterols in the human diet, along with campesterol and stigmasterol. Furthermore, compound **59** displays anti-osteoarthritic, anti-hypercholesterolemic, cytotoxic, antitumor, hypoglycemic, antioxidant, antimutagenic, and anti-inflammatory properties (Table 5) [110]. This compound was first isolated from *Physostigma venenosum*, a poisonous native tropical plant, but has thereafter been identified in other medicinal plants such as *Croton sublyratus*, *Ficus hirta*, *Eclipta alba*, *Eclipta prostrate*, and *Parkia speciosa*. Wang et al. isolated compounds **59** and **60** from *S. europaea* collected from Jiangsu Province, China [111], whereas Lyu et al. isolated compounds **58**, **59**, **61**, and **62** from the same plant species collected from a different location in Jiangsu Province [36]. Compounds **60** and **62** derived from the edible mushroom *Cantharellus cibarius* have been found to possess potent NF-κB inhibitory activities (Table 5) [112]. However, compound **62** isolated from *Agaricus blazei*, also known as almond mushroom, has been reported to exert cytotoxic effects [113]. This compound was also isolated from another mushroom genus *Trametes* and was found to exhibit antimicrobial effects, as well as antibiotic resistance modifying activity [114]. Compound **61** exhibits immunoregulatory [115], anti-inflammatory [116], and anticancer properties [117], and reportedly promotes the proliferation of neural stem cells (Table 5) [118].

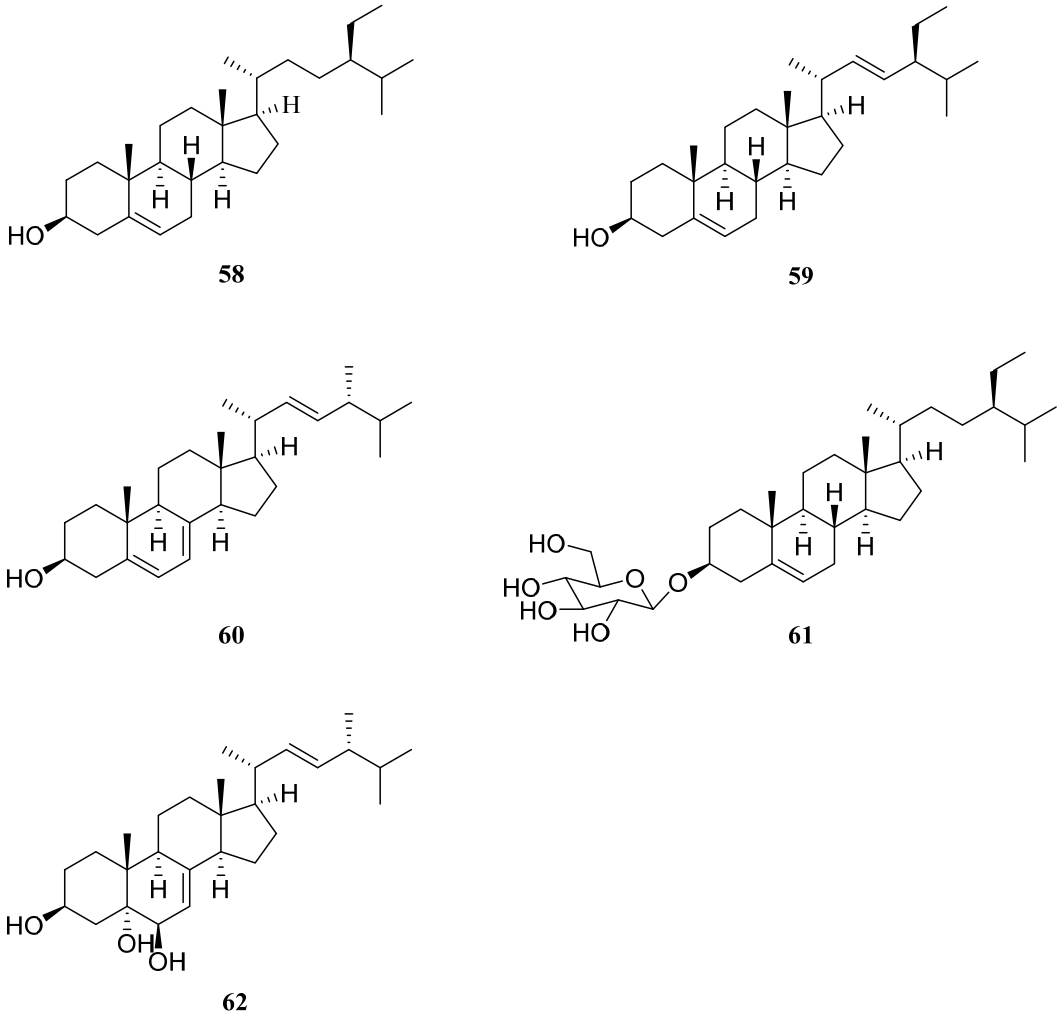


Figure 5. Chemical structures of sterols isolated from *Salicornia europaea* (**58**–**62**).

Table 5. Reported biological activities of compounds **58**–**62**.

No.	Biological Activities [1]					
	Antioxidant	**Antidiabetic**	**Cytotoxic**	**Anti-Inflammatory**	**Anticancer**	**Others**
		AGE Production Inhibitory				
58	O	O		O	O	Hypocholesterolemic, immunodulatory, neuroprotective
60	O		O	O		Anti-osteoarthritic, anti-hypercholesterolemic, antitumor, hypolgycemic, antimuatiogenic
61				O	O	Immunoregulatory, proliferation of neural stem cell
62						Antimicrobial, antibiotic

[1] Qualitative bioassay study reported without quantitative data was marked with O.

7. Lignans

Lignans are broadly distributed in the plant kingdom and possess significant pharmacological properties, including anti-inflammatory, antitumor, immunosuppressive, cardioprotective, antioxidant, and antiviral activities [119] (Figure 6).

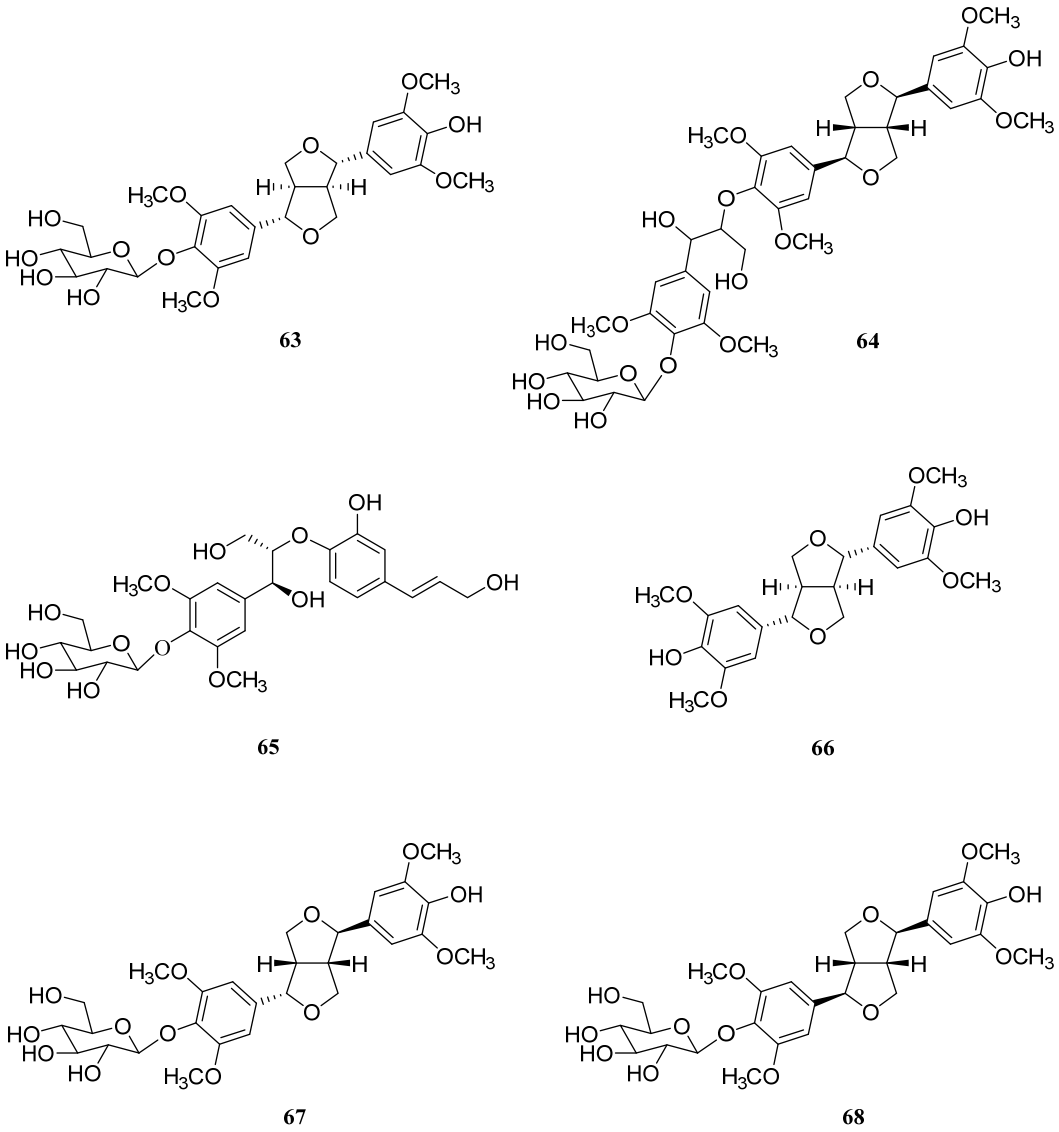


Figure 6. Chemical structures of sterols isolated from *Salicornia europaea* (**63**–**68**).

In 2011, Wang et al. reported the isolation and identification of syringaresinol 4-*O*-*β*-D-glucopyranoside (**63**), erythro-1-(4-*O*-*β*-D-glucopyranosyl-3,5-dimethoxyphenyl)-2-syringaresinoxyl-propane-1,3-diol (**64**), and longifloroside B (**65**) from *S. europaea* [120]. Although the bioactivities of compounds **64** and **65** have not been described yet, compound **63** has been shown to possess several potent biological activities, including DPPH radical scavenging activity (Table 6) [121], antiestrogenic activity against MCF-7 cells [122], and antitumor activity against the A549 cancer cell line [123]. Compound **63** was found in the stem bark of *Albizzia julibrissin* [121], the Thai medicinal plant *Capparis flavicans* [122], and leaves from the *Fatsia japonica* plant [123]. This compound also has been found to modulate lipid and glucose metabolism in HepG2 cells and C2C12 myotubes (Table 6) [124].

Table 6. Reported biological activities of compounds **63**–**68**.

No.	Biological Activities [1]		
	Antioxidant	**Anti-Inflammatory**	**Others**
	DPPH Scavenging IC_{50} (μM)		
63	10.5	O	Antiestrogenic, antitumor
64		O	
65		O	
66	19.5	O	Antiplatelet, nitric oxide inhibition, P-glycoprotein inhibition
67		O	NQO1-inducing
68	O	O	Anticholinergic, anti-neuroinflammatory, anti-amnesic

[1] Qualitative bioassay study reported without quantitative data was marked with O.

In addition to compounds **64** and **65**, Lyu et al. isolated lignans, (−)-syringaresinol (**66**) and episyringaresinol-4′′-*O*-*β*-D-glucopyranoside (**67**) from *S. europaea* [36]. Compound **66** has been found to possess antiplatelet aggregation [125], DPPH radical scavenging, nitric oxide (NO) inhibition [126], and P-glycoprotein inhibition [127] activities. Recently, the cosmeceutical potential of the compound was demonstrated with a series of *in-vitro* experiments showing antiphotoaging properties [128]. This compound was also discovered in Formosan *Zanthoxylum simulans* [125], *Wikstroemia indica* roots [126], and *Sasa borealis* whole plant extracts [127], respectively. Moreover, tortoside A (**67**) extracted from the Asian medicinal plant *Millettia pulchra* exhibited a moderate NQO1-inducing effect (Table 6) [129].

Recently, Karthivashan et al. identified and isolated acanthoside B (**68**) from *S. europaea* and reported that is possessed antioxidative, anticholinergic, anti-neuroinflammatory, and anti-amnesic properties [130].

8. Aliphatic Compounds

Seven aliphatic compounds have been isolated from *S. europaea*: stearic acid (**69**), γ-linolenic acid (**70**), (3*Z*,6*Z*,9*Z*)-tricosa-3,6,9-triene (**71**), linoleic acid (**72**), hexadecanoic acid (**73**), 1-octadecanol (**74**), and 1-octacosanol (**75**) [36,111] (Figure 7). Compounds **69** and **73** are saturated fatty acids, compounds **70** and **72** are omega-6 polyunsaturated fatty acids, compound **71** is a polyunsaturated linear hydrocarbon, and compounds **74** and **75** are aliphatic alcohols. Wang et al. isolated compounds **69**–**72** and investigated their antioxidant and antiproliferative activities towards HepG2 and A549 cells. Interestingly, none of these compounds displayed a strong antioxidant activity except for compound **72**, which exerted a potent antiproliferative effect against both HepG2 and A549 cells (EC_{50} values of 65.35 ± 1.22 μM and 83.23 ± 3.26 μM, respectively). Compound **72**, an essential omega-6 fatty acid, also exhibits anti-inflammatory activity and has been used to treat rheumatoid arthritis, eczema, premenstrual syndrome, and diabetic neuropathy (Table 7) [131].

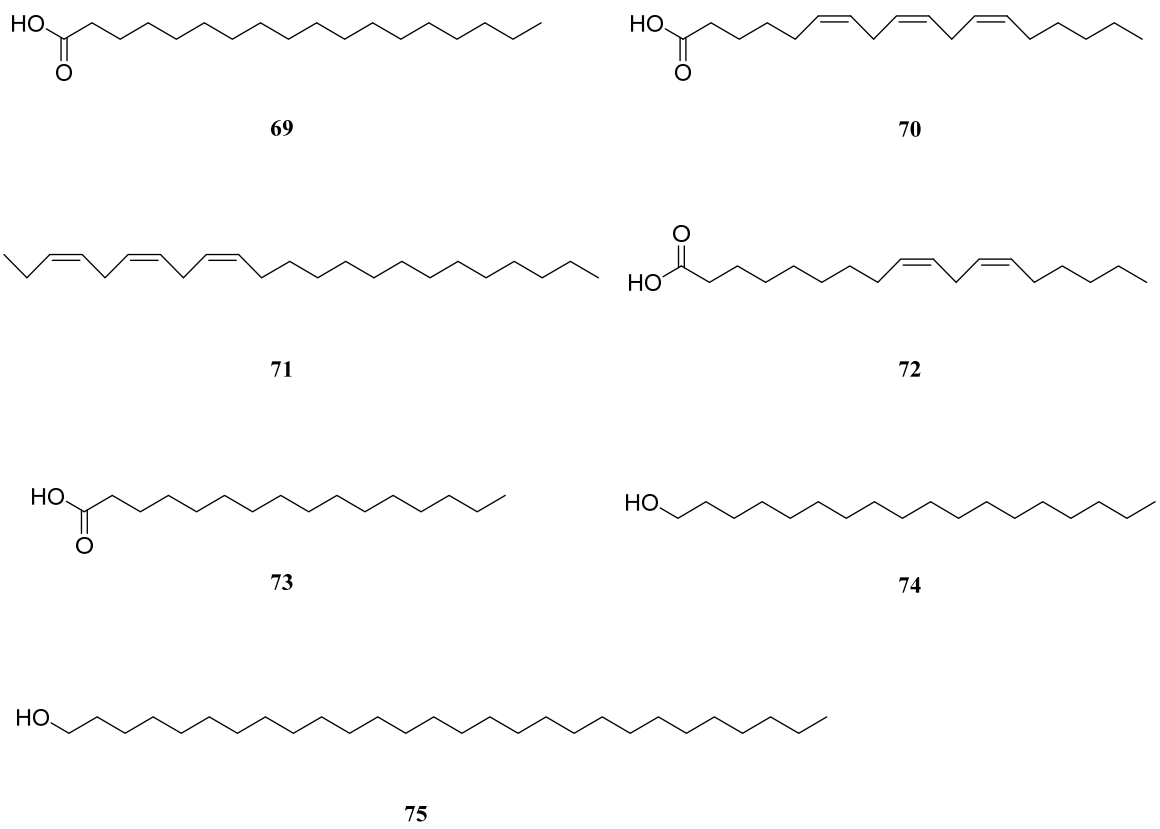


Figure 7. Chemical structures of aliphatic compounds isolated from *Salicornia europaea* (**69**–**75**).

Table 7. Reported biological activities of compounds **69**–**74**.

No.	Biological Activities [1]			
	Antioxidant	**Cytotoxic**		**Others**
		HepG2 EC_{50} (μM)	**A549 EC_{50} (μM)**	
69	O	O		Antiproliferative
70	O	O		Antiproliferative
71	O	O		Antiproliferative
72	O	65.4	83.2	Antiproliferative
73				
74				
74				Antiaggregatory, cytoprotective, antiparkinsonian

[1] Qualitative bioassay study reported without quantitative data was marked with O.

Compounds **73**–**75** have been isolated from *S. europaea* [36]. Compound **75** exhibits several pharmacological activities, including lipid-lowering, antiaggregatory, cytoprotective [132], and antiparkinsonian effects [133]. Compound **75**, 1-octacosanol, has also been reported to alleviate stress and restore stress-affected sleep in mice [134].

9. Others

In addition to the oleanane triterpenoid saponins, caffeoylquinic acid derivatives, flavonoids, chromones, sterols, lignans, and aliphatic compounds mentioned above, several other compounds have been isolated from *S. europaea* (Figure 8).

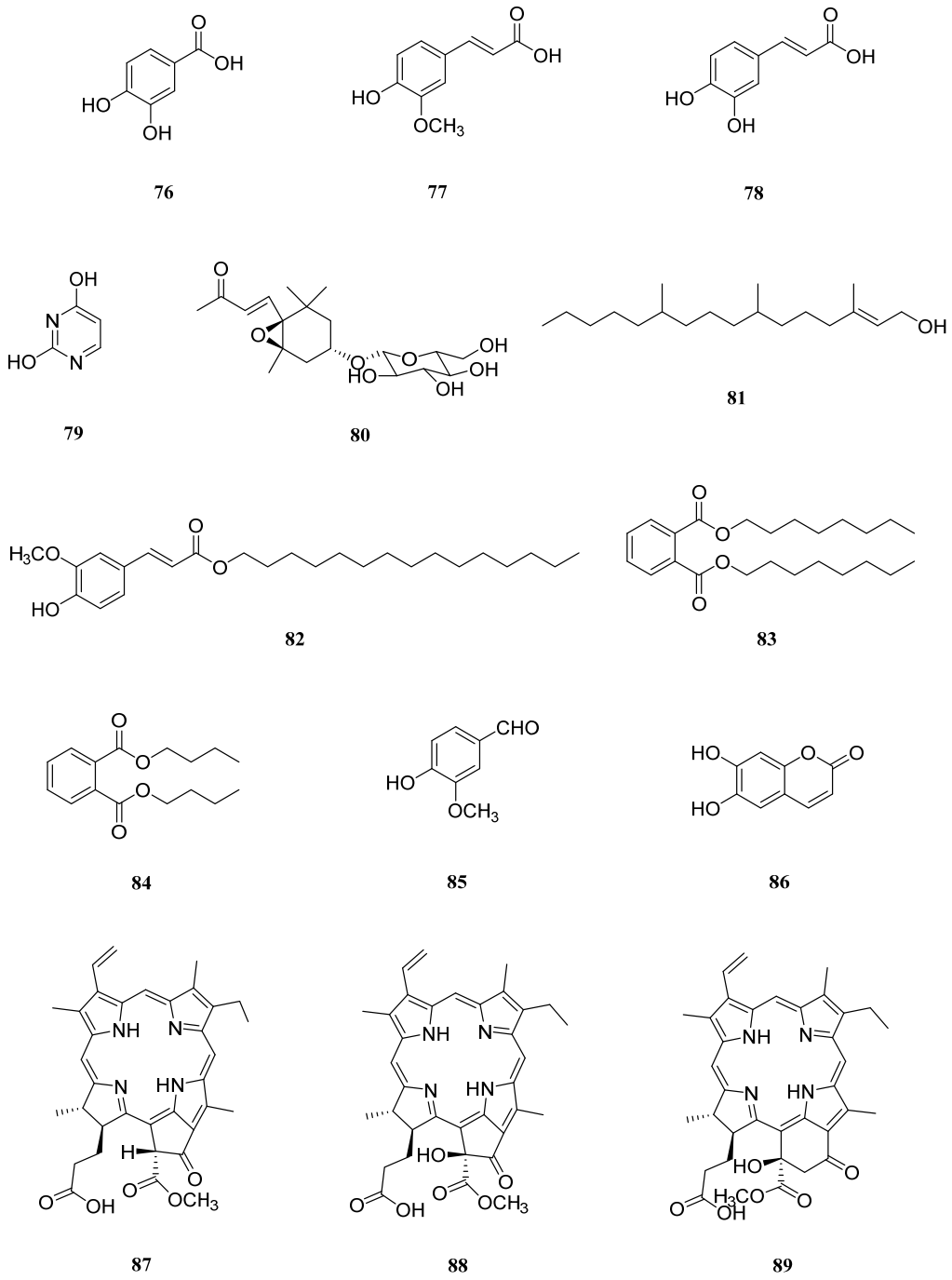


Figure 8. Chemical structures of isolates from *Salicornia europaea* (**76**–**89**).

In 2007, Oh et al. conducted antioxidant assay-guided isolation and identified three phenolic compounds, protocatechuic acid (**76**), ferulic acid (**77**), and caffeic (**78**) acid, in *S. europaea* harvested from an abandoned salt farm in Haenam, southwestern coast of Korea (Table 8) [135]. Compounds **76**–**78** displayed significant DPPH, superoxide, and hydroxyl radical scavenging activities in this study. In addition to their antioxidant activities, compounds **76**–**78** exhibited a vast spectrum of other potent bioactivities. The reported pharmacological activities of compound **76** include antibacterial, antidiabetic, anticancer, anti-ulcer, antiaging, antifibrotic, antiviral, and anti-inflammatory effects [136]. Catechol benzoic acid (protocatechuic acid, **76**) is commonly found in grains and vegetables such as bran, brown rice, plums, and onion [136]. Compound **77** displays cholesterol-lowering, antimicrobial, anti-inflammatory, and anticancer activities, along with inhibitory effects

against thrombosis and atherosclerosis (Table 8) [137]. This phenolic acid is abundant in plants and is usually found as an ester-linked form with polysaccharides from spinach, sugar beet, and bamboo. Compound **78** has been found to possess antibacterial, antiviral, anti-inflammatory, anti-atherosclerotic, immunostimulatory, antidiabetic, cardioprotective, antiproliferative, hepatoprotective, anticancer, antihepatocarcinoma, and antioxidant activities [138]. Caffeic acid (**78**) is a precursor of caffeine and is produced by a wide range of plants including olives, coffee beans, fruits, and potatoes (Table 8) [138].

Table 8. Reported biological activities of compounds **76–89**.

No.	Biological Activities [1]							
	Antioxidant		Antidiabetic	Cytotoxic		Anti-Inflammatory	Antibacterial	Others
	DPPH Scavenging IC_{50} (μM)	Superoxide Radical Scavenging IC_{50} (μM)	AGE Production Inhibitory IC_{50} (μM)	HepG2 EC_{50} (μM)	A549 EC_{50} (μM)			
76	O	O	O			O	O	Anticancer, anti-ulcerantiaging, antifibrotic, antiviral
77	O	O				O		Anti-microbial, anticancer
78	O	O	O			O	O	Antiviral, anti-atherosclerotic, immunostimulatory, cardioprotective, antiproliferative, hepatoprotective, anticancer, antihepatocarcinoma
79								
80						O		
81	O			78.5		O		Antimicrobial, apoptosis- and autophagy-modulating, anxiolytic, anticonvulsant, immunomodulatory, antinociceptive
82	27.6	38.6		56.3	48.9			
83		O			O		O	Melanogenesis-inhibitory
84								Antimicrobial, α-glucosidase inhibition, cathepsin B inhibition
85		O						Antidepressant
86		O			O			Hepatoprotective, acetylcholinesterase, hypouricemic, antifungal, immunomoudlatory, antithyroid, anti-P-388 murine leukemia cell, hypoglycemic, hypolipidemic, antiaging
87				17.6	6.2			
88					O			Anti-plasmodial
89	O							

[1] Qualitative bioassay study reported without quantitative data was marked with O.

Uracil (**79**) and icariside B2 (**80**) have also been isolated from *S. europaea* [108,120]. Compound **80** extracted from the Chinese desert-dwelling annual plant *Corispermum mongolicum* reportedly exhibits anti-inflammatory activity [139].

Moreover, in addition to phytol (**81**), dioctyl phthalate (**83**), dibutyl phthalate (**84**), vanillic aldehyde (**85**), and scopoletin (**86**), Wang et al. isolated a new compound, pentadecyl ferulate (**82**), from *S. europaea* collected from Jiangsu Province in China and elucidated its structure [111]. The antioxidant and antiproliferative activities of the isolated compounds were then investigated in this study. Compound **82** showed strong DPPH and superoxide radical scavenging activities (IC_{50} values of 27.6 ± 1.89 μM and 38.6 ± 2.23 μM, respectively) and inhibited the growth of both HepG2 and A549 cancer cells (EC_{50} values of 56 ± 2.32 μM and 48 ± 1.89 μM, respectively). Moreover, compound **81** exhibited selective antiproliferative activity against HepG2 cells (EC_{50} value of 78 ± 3.45 μM).

Compound **81** has also been reported to exert other biological functions, such as antimicrobial, cytotoxic, antioxidant, apoptosis- and autophagy-modulating, anxiolytic, anticonvulsant, immunomodulatory, antinociceptive, and anti-inflammatory activities [140]. However, phytol (**81**) is found in most plants as part of the chlorophyll molecule. Compound **83** has been shown to possess antibacterial [141], melanogenesis-inhibitory [142], and antioxidant activities, and reportedly exerts cytotoxic effects against the EACC cancer cell line [143]. This phthalate was isolated from a marine alga *Sargassum wightii*, *Nigella glandulifera* seeds, and the water hyacinth *Eichhornia crassipes*. Compound **84** exhibits antimicrobial [144–146], α-glucosidase inhibition [147], and cathepsin B inhibition activities [148]. Interestingly, dibutyl phthalate (**84**) was isolated from plants and bacterial sources such as *Ipomoea carnea*, *Begonia malabarica*, and *Streptomyces albidoflavus*, as well as *Streptomyces melanosporofaciens* and *Pseudomonas* sp. [144–148]. However, the debates about the origin of the phthalate should be considered whether the phthalates are natural products or accumulated contaminants.

Compound **85**, also known as vanillin, displays potent antimicrobial [149,150], antioxidant [151], and antidepressant activities [152]. A variety of pharmacological effects have been observed for scopoletin (**86**), which features a coumarin scaffold, as well as hepatoprotective [153], PC3 cell proliferation inhibitory [154], antioxidant [155], acetylcholinesterase inhibitory [156], hypouricemic [157], antifungal synergistic [158], immunomodulatory [159], antithyroid [160], anti-P-388 murine leukemia cell [161], hypoglycemic, hypolipidemic [162], and antiaging activities [163].

The pheophorbide compounds **87**–**89**, which are derivatives of chlorophyll a, have been isolated from a methanol extract of *S. europaea* [32]. Pheophorbide A (**87**) exhibits a strong antiproliferative activity against A549 and HepG2 cancer cell lines with IC_{50} values of 6.15 and 17.56 μM, respectively. (13^2S)-Hydro-pheophorbide-lactone A (**89**) has been shown to possess a weak antioxidant activity, with a ferric reducing/antioxidant power (FRAP) value of 79.58 ± 1.69 mM/100 g and a DPPH scavenging rate of 75.33 ± 1.61%.

Compound **87** also possesses antitumor [164–166], photodynamic [167–169], and anti-inflammatory activities [170]. (13^2S)-Hydroxy-pheophorbide A (**88**) exhibits potent photocytotoxicity, but its cytotoxic activity was reportedly lower than that of compound **87** [164,165]. However, compound **88** has a better anti-plasmodial performance than that of compound **87** [171]. The presence of a hydroxyl group at C-13 in compound **88** is the only structural difference between compounds **87** and **88.** Therefore, the hydroxyl substitution at the C-13 position might be responsible for the differences in the activities of these compounds.

In addition to the above-described compounds, *S. europaea* seeds have been reported to possess a wide range of fatty acids including compounds **69–73 [172]**.

10. Conclusions

Salicornia europaea is a popular salt-tolerant plant that has been traditionally used both as a functional food and vegetable seasoning; however, this plant is also known to produce

compounds with therapeutic potential. Therefore, this plant is among the most widely recognized halophytes and is farmed in some regions to meet consumer demand.

This review discussed the chemistry and biological activities of *S. europaea* secondary metabolites reported from 1978 to October 2019. To the best of our knowledge, eighty-nine metabolites have been isolated, including oleanane triterpenoid saponins, caffeoylquinic acid derivatives, flavonoids, chromones, sterols, lignans, and aliphatic compounds. The diverse biological/pharmacological activities of the isolated compounds were also described in this review. Most of the compounds were obtained in small quantities ranges from 0.1 to 10 ppm (Table 9). Only a handful of the isolates were obtained over hundreds of ppm, including **1**, **39**, and **41** (123, 700, and 467 ppm, respectively). However, attention to the direct comparison of the yields is required as these high yields have resulted from dried plant material extraction.

Table 9. Yield of the compounds.

Compound No.	Yield [2] (ppm)	Note [1] and Reference No.	Compound No.	YieldN [2] (ppm)	Note [1] and Reference No.	Compound No.	Yield [2] (ppm)	Note [1] and Reference No.
1	123.9	Dried [16]	**31**	0.2		**61**	0.2	Wet [36]
2	N.A.		**32**	0.3		**62**	0.12	
3	N.A.		**33**	1.3	Wet [77]	**63**	0.2	
4	N.A.		**34**	0.2		**64**	0.2	Wet [120]
5	0.1		**35**	0.4		**65**	0.3	
6	0.2		**36**	1.6		**66**	N.A.	
7	0.1	Wet [19]	**37**	0.9	Wet [80]	**67**	0.2	Wet [36]
8	0.1		**38**	0.4		**68**	3.8	Wet [130]
9	0.1		**39**	700		**69**	0.3	
10	0.6		**40**	93.3		**70**	0.5	Wet [111]
11	0.5	Wet [32]	**41**	466.7	Dried [81]	**71**	0.6	
12	0.3		**42**	33.3		**72**	0.2	
13	0.4		**43**	41.7		**73**	0.1	
14	0.1		**44**	0.5	Wet [6]	**74**	0.1	Wet [36]
15	0.1		**45**	0.9		**75**	0.1	
16	0.1		**46**	0.6	Dried [95]	**76**	1.54	
17	0.1	Wet [36]	**47**	0.7		**77**	8.54	Dried [135]
18	0.1		**48**	0.1		**78**	6.87	
19	0.2		**49**	0.3	Wet [36]	**79**	1.3	Dried [108]
20	0.1		**50**	0.1		**80**	0.9	Wet [120]
21	0.1		**51**	N.A.		**81**	0.2	
22	8	Dried [50]	**52**	0.3		**82**	1.2	
23	6.2		**53**	0.4	Wet [105]	**83**	0.3	
24	0.1	Wet [6]	**54**	0.5		**84**	0.2	Wet [111]
25	0.4		**55**	0.3		**85**	0.5	
26	0.6		**56**	0.4		**86**	0.2	
27	16.3		**57**	0.4	Dried [95]	**87**	1.1	
28	1.4	Dried [75]	**58**	20.7		**88**	0.6	Wet [32]
29	12.8		**59**	9.7	Dried [108]	**89**	0.9	
30	1.7		**60**	0.3	Wet [111]			

[1] Plant material status before extraction. Dried or Wet. [2] data Not Available (N.A.).

Most of the plant samples discussed herein were collected from East Asia, including Korea, Japan, and China, where this plant has been historically used as food and for its therapeutic properties. Nonetheless, research on this plant is not strictly limited to Asia, but includes some regions of Europe as well. Moreover, the study of secondary metabolites from the genus *Salicornia* encompasses other temperate and subtropical regions worldwide, including America and Africa.

Previous studies on *S. europaea* have mainly focused on the identification of its secondary metabolites but often fail to provide other details. Specifically, most studies provide

only basic descriptions of the collection sites and dates. However, the unique characteristics of this plant, including its seasonal color change, jointed segments, and scale-like stout leaves allow for its easy identification, which facilitates the isolation and identification of the enormous repertoire of secondary metabolites from this plant compared to that of other halophytes.

This review provides important insights that may facilitate the future study of the chemical profiles of this plant. For example, tungtungmadic acid (**22**) was exclusively isolated from the plant *S. europaea* and would be a good marker to identify this plant. Moreover, the chemical profile patterns of other secondary metabolites would provide useful references for chemists to identify and study this plant species. Therefore, we expect that future biochemical analyses of *S. europaea* and other halophytes will lead to the discovery of novel bioactive natural products.

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