Review

Secondary Metabolites and Biological Activity of Invasive Macroalgae of Southern Europe

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Abstract: In this review a brief description of the invasive phenomena associated with algae and its consequences on the ecosystem are presented. Three examples of invasive algae of Southern Europe, belonging to Rodophyta, Chlorophyta, and Phaeophyta, were selected, and a brief description of each genus is presented. A full description of their secondary metabolites and biological activity is given and a summary of the biological activity of extracts is also included. In Asparagopsis we encounter mainly halogenated compounds. From Caulerpa, several terpenoids and alkaloids were isolated, while in Sargassum, meroterpenoids prevail.

Keywords: invasive species; Asparagopsis sp.; Caulerpa sp.; Sargassum sp.; chemistry and biological activity

1. Introduction

Alien species are plants, animals, or microbes that have been introduced and spread into new host regions, establishing populations that can become invasive if they interfere with the host ecosystem. These invasive species become established in natural or seminatural ecosystems, increasing in abundance and distribution and threatening biological diversity. They compete with native species, and usually have high reproductive rates assisted either by the lack of predators in the new environment or by the tolerance of a different range of environmental conditions. As a consequence, they are difficult to contain, harm biodiversity, and change the new host ecosystem [1].

Alien macroalgae are particularly likely to become invasive: their high reproductive rates, their production of toxic metabolites, and/or their perennial status make them more competitive than the native species, increasing the probability that they will become invasive. Several of these species periodically become a major problem, clogging waterways, fouling nets, and changing nutrient regimes in areas around fisheries, desalination facilities, and aquaculture systems [1]. They impact on local economies, such as fishery [2] and tourism.

The mechanism of invasion by macroalgae thus begins with transport (by means of fouling, ballast waters, or aquaculture), proceeds by establishment of the species (through biotic and abiotic factors), and ends with its spread and impact [3–7]. Management of this update problem requires adequate measures [8] and control procedures, such as mechanical means, biological control, and/or chemical remedies [9].

With global warming there is a general increase of the tendency of invasive episodes, this being a situation of concern especially for Southern Europe. The Mediterranean coast and Atlantic areas near Gibraltar are key points in the dynamics and spread of these phenomena. As an example, in 2016, several beaches in Gibraltar were interdicted by Dictyota invasions with direct impact on local
tourism, and remediation and management costs. However, macroalgae have underlying potential. Their commercial use as a source of nutraceuticals, food additives, biofuel, antifouling agents, or pharmaceuticals could be a way to exploit these phenomena in a more profitable way [4,10].

Thus, knowledge of the chemistry of these macroalgae is by no means out of date, as recent papers on the activity of algal extracts well document. Knowledge of their secondary metabolites and this review are also a starting point to the understanding of the chemistry of these species. There is a need, however, to fully characterize these invasive species in their new environment in order to make the most of their existence, and perform a strict correlation between metabolite and activity.

In this review we chose three genera of invasive species of the Mediterranean—Asparagopsis, Caulerpa, and Sargassum—as examples of the chemistry of red, green, and brown algae, respectively. Two of them—Asparagopsis and Caulerpa—are already signaled by the International Union for Conservation of Nature (IUCN) Centre for Mediterranean Cooperation [1].

The secondary metabolites of the chosen genus are presented and, when possible, the studied biological activities are given. Reference to their study as invasive specimens is also provided. A list of papers on the biological activity of extracts is also given. This review covers the literature up to 2017.

2. Structural Characterization and Biological Activity

In this paper a chemical and biological activity summary of three different genera of invasive species of Southern Europe is presented. The structural identification of the mentioned metabolites relies on the usual techniques such as NMR, IR, MS, and chemical transformations for the less recent publications. Although some of the studies include biological activities of the isolated metabolites, most of the papers only mention isolation and characterization.

2.1. Asparagopsis

Asparagopsis is a red seaweed genus of the family Bonnemaisoniaceae that has a diplohaplontic life cycle and a heteromorphic tetrasporophyte known as the “Falkenbergia” stage [11] Currently, only two species of this genus are accepted, A. armata and A. taxiformis, the former being endemic to the southern hemisphere and the latter being widely distributed in the tropics and sub-tropics [12]. Recently, a study of the lineages of this genus by DNA sequence was published [13].

Both species of this genus are native to Western Australia. A. armata is nowadays distributed throughout Europe in both the Atlantic and the Mediterranean basin, where it is highly invasive. A. taxiformis is invasive around the Indo-Pacific region, including Japan and Hawaii, and is currently widespread throughout the Mediterranean and along the Atlantic coast of Europe. While A. armata was probably introduced by maritime transport, A. taxiformis was probably introduced by oyster aquaculture [1].

Asparagopsis has been known to produce halogenated low-molecular-weight compounds [14–21].

We can also find reports on the presence of sterols in A. armata including 22-dehydrocholesterol, cholesterol, desmosterol, brassicasterol, 25-hydroxycholesterol, 25-hydroxy-24-methylcholesterol, fucosterol, β-sitosterol, liagosterol, and the hydroxylated sterols 1–4 represented in Figure 1 [22–24].

![Figure 1. Hydroxylated sterols from A. armata.](image-url)
A more recent study consists of the identification of the two brominated cyclopentenones 5 and 6 from A. taxiformis (Figure 2) [25].

![Brominated cyclopentenones from A. taxiformis.](image1)

Ecotoxicological activities of 5 and 6 against a marine bioluminescent bacterium (Vibrio fischeri) were used as an assessment of their role in the environment, revealing high toxicities for both compounds (EC$_{50}$ effective concentration, 0.16 µM for 5 and 6). Additionally, both compounds were evaluated in antibacterial, antifungal, and cytotoxicity assays. Compounds 5 and 6 exhibited mild antibacterial activities against the human pathogen Acinetobacter baumannii.

2.2. Caulerpa

Green algae of the genus Caulerpa Lamouroux represent the single genus in the family Caulerpaceae, which consists of approximately 60 species worldwide, generally distributed in shallow-water tropical and subtropical marine habitats. One of its species, Caulerpa racemosa, also known as “sea grapes”, is an edible marine green seaweed widely distributed throughout the South China Sea.

C. racemosa var. cylindrica is native to SouthWestern Australia, and is invasive in the Mediterranean [26–28] where its introduction is still speculative. Maritime traffic and aquarium trade are the most likely vectors. It can still be found in aquarium stores and is sold by internet retailers. C. taxiformis was accidentally introduced into the Mediterranean from a public aquarium in Monaco. Since then, it has spread rapidly due to its natural vegetative dispersal mechanism, its lack of natural grazers, and the ease of dispersion by boats, anchors, fishing nets, and aquaria [1].

2.2. Caulerpa

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We can find several reports on the chemistry of Caulerpa sp. These include the isolation of three squalene derivatives from C. prolifera [29] and fatty acids and sterols from C. chemnitzia, C. faridii, C. manorensis, C. racemosa, and C. taxiformis, including cholesterol, 24-methylcholesterol, 24-methyl-cholesta-7,22-diene-3β-ol, 4,24-dimethyl-cholesta-5,22-diene-3β-ol, and β-sitosterol [30].

From C. racemosa, fucosterol and the oxygenated sterols 7–10 in Figure 3 were isolated, together with both C-24 epimers of saringosterol 2 [30,31].

![Oxygenated sterols from C. racemosa.](image2)

From C. racemosa, several varied metabolites were obtained by Yang et al. [31]. These include trans-phytol, trans-phytylacetate, α-tocopherolquinone, and the metabolites 11–17 in Figure 4.
The enzyme inhibitory activities of all the compounds were evaluated in vitro against PTP1B (protein tyrosine phosphatase 1B) and related PTPs (protein phosphatases) (TCPTP (T-cell PTP), CDC25B (cell division cycle 25 homolog B), LAR (leukocyte antigen-related phosphatase), SHP-1 (src homology phosphatase-1), and SHP-2 (src homology phosphatase-2)). Compounds 14, trans-phytol, trans-phytylacetate, \( \alpha \)-tocopherolquinone, 16, and 17 and the sterols 7, 8, and 24R sarinogosterol 2 and 10 exhibited different levels of PTP1B inhibitory activity with IC\(_{50}\) (inhibitory concentration) values ranging from 2.30 to 50.02 \( \mu \)M. Of these compounds, 14, \( \alpha \)-tocopherolquinone, and 7 showed the most potent inhibitory activities towards PTP1B with IC\(_{50}\) values of 2.30, 3.85, and 3.80 \( \mu \)M, respectively. More importantly, the potent PTP1B inhibitors 14, \( \alpha \)-tocopherolquinone, and 7 also displayed high selectivity over the highly homologous TCPTP and other PTPs. The neuroprotective effects of the compounds against A\( \beta \)25–35 (amyloid \( \beta \)-peptide fragment 25–35)-induced cell damage in SH-SY5Y (neuroblastoma cell line) cells, a widely used neuroblastoma cell line for study of neurodegenerative disease, were also investigated. Compounds 17, 7, and 8 exhibited significant neuroprotective effects against A\( \beta \)25–35-induced SH-SY5Y cell damage with 11.31–15.98% increases in cell viability at 10 \( \mu \)M. In addition, the cytotoxic activities of the isolated compounds were tested against the human cancer cell lines A-549 (human lung carcinoma) and HL-60 (promyelocytic leukemia cells). Only the mixture
of 11 and 12, 16, and α-tocopherolquinone exhibited moderate cytotoxicity against HL-60, and α-tocopherolquinone exhibited weak cytotoxicity against A-549 [31].

From C. racemosa we can find two prenylated p-xylens [32] 18 and 19 and racemosins A 20 and B 21 [33] (Figure 5).

![Figure 5. Metabolites from C. racemosa.](image)

From C. prolifera [34], caulerpin 22 was isolated (Figure 6).

![Figure 6. Metabolite from C. prolifera.](image)

In vitro bioassays, the compounds 18 and 19 exhibited a broad spectrum of antifungal activity against Candida glabrata, Trichophyton rubrum, and Cryptococcus neoformans with MIC$_{80}$ (minimum inhibitory concentration) values between 4 and 64 μg/mL when compared to amphotericin B (MIC$_{80}$ values of 2.0, 1.0, and 4.0 μg/mL, respectively) as a positive control and showed no growth inhibition activity against the tumor cells HL60 and A549 [32].

The biological activity of compounds 20–22 was tested in a neuroprotective bioassay using Aβ25–35-induced neurotoxicity in SH-SY5Y cells. Compound 22 showed significant neuroprotection (14.6% increase in cell viability) at the concentration of 10 μM, while compounds 20 and 21 showed moderate/weak neuroprotective activity with 5.5% and 8.1% increase in cell viability (10 μM), respectively, when compared to EGCG (epigallocatechin gallate), 16.57% increase at 10 μM) as the positive control [33].

On the terpenoid constituents of this genus we can find reports on monoterpenes [35,36]; the sesquiterpenes 23–39 (Figure 7, Table 1), isolated from several species [35–39]; the diterpene 40 from C. trifaria [40]; and the diterpenes 41–54 from C. brownii [41,42] (Figure 8).
Table 1. Sesquiterpenes from *Caulerpa* sp.

| Species                 | Compounds | Biological Activity                                      |
|-------------------------|-----------|----------------------------------------------------------|
| *C. ashmeadii* [39]     | 34–39     | Feeding preference, antimicrobial, ichthyotoxicity       |
| *C. bikinensis* [38]    | 30–32     | Feeding deterrents                                       |
| *C. flexilis var. muelleri* [35] | 29, 33   |                                                         |
| *C. prolifera* [37]     | 25        | -                                                        |
| *C. taxifolia* [36]     | 26–28     | -                                                        |

![Figure 7. Sesquiterpenes from *Caulerpa* sp.](image)

38 \( R = C_{18}H_{31}O \)
39 \( R = C_{17}H_{29}O \)
Figure 8. Diterpenes from *Caulerpa* sp.
A study [39] on the feeding preference by herbivorous fishes on several species of caulerpa led to isolation of 34–39 from C. ashamadii. Compounds 34 and 36–39, along with the alkaloid caulerpin 22, were tested for field feeding preference, antimicrobial activity (against the marine fungus Lagenidium callinctes, and the bacteria Vibrio leignathi, V. phosphoreum, and SK13 (Gram-positive spore-forming bacteria requiring Mn for growth)), and ichthyotoxicity. All compounds except compounds 38 and 39 showed antimicrobial activity toward at least one marine bacterium. Compounds 36 and 37 also showed activity toward all three bacteria. All metabolites, except the fatty esters 38 and 39 and caulerpin 22, were toxic to damselfish within 1.5 h. Compounds 36 and 37 again showed the highest degree of biological activity in this assay.

From C. bikinensis, compounds 30–32 were isolated and tested as feeding deterrents [38]. The diacetate 30 and the dialdehyde 31 were found to be toxic to the Pacific damselfish Pomacentrus phillipinus at the 10 and 5 µg/mL levels. Feeding deterrence effects were reliably produced from 30 and 31 when tested at 1000 ppm levels against similar herbivorous fishes. The cytotoxicities of these compounds against the fertilized egg of the Pacific sea urchin Lytechinus pinctus were also measured. Again, 30 and 31 showed ED50 (effective dose) values of 2 and 1 µg/mL. The activities noted for these metabolites reinforce their likely roles in nature as agents of chemical defense.

From C. flexis var. muelleri, compounds 29 and 33 were isolated. No absolute configuration was determined for 33 [35].

From C. prolifera, 25 was isolated and its absolute configuration determined as S [37].

A study of C. taxifolia from Cap Martin, Côte d’Azur, at the time considered an invasive species, allowed the isolation of compounds 24–28, for which no absolute configurations were determined. The proposed configurations were based on biosynthetic considerations [36].

From a larger study on algae of the order Caulerpales, diterpene 43 was isolated from C. brownii. [41]. Compound 43 had already been tested for biological activities. It showed antibacterial activity towards the pathogenic bacteria Staphylococcus aureus and Bacillus subtilis. It was also tested against marine bacteria and was found to be inhibitory towards Vibrio harveyi and V. leignathi. It is also active against E. coli and V. anguillarum [41]. Handley reported the isolation of diterpenes 41–54 from branched and unbranched specimens of C. brownii and compound 50 was reported for the first time as a natural product [42].

From C. trifaria, diterpene 40 was isolated and the depicted configuration is proposed [40].

2.3. Sargassum

Sargassum is a genus of brown seaweeds with tropical and subtropical distribution, existing in all oceans. It is a large genus, comprising over 350 species. Some of its species are used in food in Japan and Korea, such as S. fusiforme and S. muticum. Due to air vesicles, S. natans and S. fluitans form large floating masses. S. muticum is invasive in the Mediterranean [43,44] and in Western Europe [45], and seems to have been introduced by the business of oyster culture [46].

A recent review on the therapeutic potential and health benefits of these species has been published [47].

We can find several reports on the isolation of sterols (Figure 9) from Sargassum sp.

From S. asperifolium [48], saringosterol 2 and 60 were isolated.

From S. carophyllum [49], 61 and 62 were isolated, together with fucosterol, 24-ethylcholesta-4, 24(28)-dien-3,6-dione, 56, 57, 9, and 10. All compounds were tested for bioactivity of inducing morphological deformation of P. oryzae mycelia, and cytotoxic activity against several cultured cancer cell lines (P388 (mouse lymphocytic leukemia), HL-60, MCF-7 (breast adenocarcinoma), HCT-8 (human ilececal cancer), 1A9 (human ovarian cancer), HOS (human bone tumor), PC3 (human prostate cancer)).

The data showed that all the steroids exhibited activities causing morphological abnormality of P. oryzae mycelia. Fucosterol and 24-ethylcholesta-4,24(28)-dien-3,6-dione exhibited significant cytotoxicity toward P388 cancer cells, whereas 61 and 56 showed mild activity against the growth of HL-60 cancer cells. In the antitumor screen using a panel of human cell lines only the epoxy sterol
showed some cytotoxicity against several human cell lines. Compounds 62, 9, and 10 were also evaluated for HIV (Human immunodeficiency virus) growth inhibition activity in H9 lymphocytes. The EC$_{50}$ and IC$_{50}$ values for 9 were 0.500 and 0.975 mg/mL, whereas 62 and 10 were inactive.

From *S. fusiforme*, fucosterol [50,51], both C-24 epimers of saringosterol 2 [51] and 55–59 were isolated [51]. Fucosterol was shown to possess antidepressant and anticonvulsional effects [50]. Compounds 55–59, fucosterol, and both C-24 epimers of saringosterol 2 were tested as LXR (liver X receptor) agonists: 24S-saringosterol 2 acted as a selective LXR$\beta$ agonist and was found to be potentially useful as a natural cholesterol lowering agent [51].

Figure 9. Sterols from *Sargassum* sp.
X receptor) agonists: 24S-saringosterol 2 acted as a selective LXRβ agonist and was found to be potentially useful as a natural cholesterol lowering agent [51].

From *S. oligocystum* [52], cholesterol, 22-dehydrocholesterol, fucosterol, both C-24 epimers of saringosterol 2, and 55, 56 and 58 were isolated.

From *S. thunbergii* [53], 63 was isolated, together with 3, and 64−66. Compound 63 exhibited significant inhibitory activity against human PTP1B with an IC₅₀ value of 2.24 µg/mL.

From the genus Sargassum we can also find reports on the isolation of quinones and hydroquinones, chromenes, and varied structures.

Quinones and hydroquinones

We can find several reports on the isolation of quinones and hydroquinones from *Sargassum* sp. [54−65]. Their structures are in Figure 10 and occurrences are in Table 2.

![Figure 10. Cont.](image-url)
Figure 10. Quinones and hydroquinones from *Sargassum* sp.

From *S. elegans*, 68, 69, and 72 were isolated by electrochemistry-guided fractioning and their antioxidant potential was evaluated [54].

From *S. fallax* [55], 67–71 were isolated. Sargaquinone 67 was isolated as a mixture with sargaquinoic acid 68. Both 68 and 69 were found to display moderate antitumor activity when tested against P388 cells. They displayed only weak activity against *Bacillus subtilis*. 
From *S. herophyllum* [56], 67, 69, and 72 were isolated. They displayed moderate antiplasmodial activity against *P. falciparum*.

**Table 2.** Quinones and hydroquinones from *Sargassum* sp.

| Species                  | Compounds | Biological Activity                                      |
|--------------------------|-----------|--------------------------------------------------------|
| *S. elegans* [54]        | 68, 69, 72| Antioxidants                                           |
| *S. fallax* [55]         | 67–71     | Antitumour against P388                               |
| *S. herophyllum* [56]    | 67, 69, 72| Antiplasmodial activity                                |
| *S. michranthum* [57]   | 73–76     | Antioxidants, radical scavenging, inhibitory effect on lipid peroxidation, antiproliferative against 26-L5, cytotoxicity |
| *S. paradoxum* [58]     | 67–71, 77–83 | Antibacterial                                      |
| *S. sagamium* var. yezoense [59] | 68, 69, 80, 84 | -                                           |
| *S. sagamium* [64, 65]  | 68        | Anticholinesterase activity, proapoptotic, and anti-inflammatory |
| *S. serratifolium* [60] | 68, 80    | -                                                      |
| *S. siliguaster* [61]   | 96, 97    | Radical scavenging                                    |
| *S. thunbergii* [62, 63]| 68, 69    | Osteoblastogenesis-enhancing abilities                 |
| *S. tortile* [66]       | 67, 89–95 | -                                                      |
| *S. yezoense* [67, 68]  | 68, 69, 85–88 | Transcriptional activity of PPARs (Peroxisome proliferator-activated receptors), antidiabetic potential |

From *S. michranthum* [57], 73–76 were isolated. Compounds 74–76 displayed strong antioxidant activity, such as an inhibitory effect on NADPH-dependent lipid peroxidation in rat liver microsomes and radical-scavenging effect on DPPH (1,1-diphenyl-2-picrylhydrazyl). The inhibitory effect on lipid peroxidation was shown to be the same or stronger than that of the positive control, α-tocopherol. The authors identify the absence or presence of an unsaturated cis carbon–carbon double bond in the long-chain fatty acid ester moiety of 75 and 76 as responsible for the large difference in the inhibitory activity. Both compounds were found to have moderate radical-reducing effect on DPPH at a dose of each sample of 100 mg/mL. Based on these preliminary results, the author suggest that the hydroquinone moiety of 74 must participate in antioxidant activity, while in compounds 75 and 76, hydrolysis of their ester group occurs first, and the resulting 74 may owe this activity. Antiproliferative activity of 74–76 against Colon 26-L5 cell was also evaluated. Compounds 74 and 76 showed relatively strong cytotoxic activity while moderate activity in the case of 75 was observed.

From *S. paradoxum* [58], 67–71 together with 77–83 were identified by HPLC-NMR and HPLC-MS. Some of the compounds were isolated by bioguided fractioning and tested for their biological activity. Compared to the antibiotic ampicillin, the isolated compounds were far less potent against *S. aureus* and *S. pyogenes*. However, compounds 69, 71, 80, and 260 were more potent against *P. aeruginosa* than ampicillin. There was no difference in activity between compounds with the hydroquinone or the p-benzoquinone moieties. The activity observed for sargaquinone 67, the simplest of the meroditerpenoids isolated, suggests that the unsubstituted meroditerpenoid skeleton is responsible for the activity against *P. aeruginosa*. The addition of an alcohol group at position 12′ or 20′ (70, 77, 78, 82, and 83) appears to reduce the activity against *P. aeruginosa*, but increases the activity against *S. pyogenes*. Finally, incorporation of a carboxylic acid at position C-20′ (69 and 68) gives rise to activity against *S. aureus* and *S. aureus* MRSA Methicillin-resistant *Staphylococcus aureus*.

From *S. sagamium* var. *yezoense* [59], 68, 69, 80, and 84 were isolated and from *S. sagamium*, 68 was isolated [64]. Its anticholinesterase activity and potential in Alzheimer’s disease is described [64]. The proapoptotic [65] and anti-inflammatory activities [69] of 68 are also documented.
From *S. serratifolium* [60], 68 and 80 were isolated and from *S. siliquastrum* [61], 96 and 97 were isolated. Compound 96 showed radical-scavenging activity in DPPH assays.

From *S. thunbergii* [62,63], sargaquinoic acid 68 and sargahydroquinoic acid 69 were isolated. Since *S. thunbergii* was shown to inhibit adipogenesis in pre-adipocytes while enhancing osteoblast differentiation of pre-osteoblasts, and 68 and 69 were isolated in a bioguided study, the authors suggest that these two compounds possess osteoblastogenesis-enhancing abilities [63].

From *S. tortile* [66], 67 and 89–95 were isolated. Compounds 68 and 69 were also isolated from *S. yezoense* [67]. Their effect on the transcriptional activity of PPARs (Peroxisome proliferator-activated receptors) was studied. The authors suggest that both compounds could be possible candidates for the treatment of type-2 diabetes and dyslipidemia.

From *S. yezoense* [68], 85–88 were also isolated. Their antidiabetic potential was also evaluated.

### 2.4. Chromenes

We can also find reports on the isolation of chromenes [58,60,62,64,65,70–77]. Their structures are in Figure 11 and occurrences are in Table 3.

| Species          | Compounds | Biological Activity                                          |
|------------------|-----------|-------------------------------------------------------------|
| *S. paradoxum*   | 98        | Anti-inflammatory, antioxidant activity, inhibition of butylcholine esterase |
| *S. serratifolium* | 99        | Anti-inflammatory, antioxidant activity, inhibition of butylcholine esterase |
| *S. siliquastrum* | 100–120   | Anti-inflammatory, antioxidant, radical-scavenging activity, inhibition of butylcholine esterase |
| *S. sagagianum*  | 125       | Proapoptotic activity, anticholinesterase activity           |
| *S. thunbergii*  | 121,122,125 | Radical scavenging                                         |
| *S. tortile*     | 123,124,126 | Larval attractants                                           |
| *S. yezoense*    | 127       | Anti-inflammatory, antioxidant activity, inhibition of butylcholine esterase |

**Figure 11.** Cont.
Figure 11. Cont.
Figure 11. Cont.
was evaluated. Jang [73] reported the isolation of 

was obtained from sargaquinoic acid 68.

The concentration of 100 µg/mL of the compounds exhibited significant radical-scavenging activity in the range of 87–91% at the concentration of 100 µg/mL. Compound 68 significantly decreased generation of intracellular ROS and inhibited lipid peroxidation while they increased levels of intracellular GSH at a concentration of 5 × 10^{-6} µg/mL. Compound 68 was also isolated from S. thunbergii [58], together with 120–126.

Table 3. Chromenes from Sargassum sp.

| Species               | Compounds | Biological Activity                                      |
|-----------------------|-----------|----------------------------------------------------------|
| S. paradoxum [58]     | 98        | -                                                        |
| S. serratifolium [60] | 99        | -                                                        |
| S. siliquastrum Yoon  | 100–120,127 | Anti-inflammatory, antioxidant, radical-scavenging activity, inhibition of butylcholine esterase |
| S. sagamianum [64,65] | 125       | Proapoptotic activity, anticholinesterase activity       |
| S. thunbergii [62]    | 121,122,125 | Radical scavenging                                       |
| S. tortile [74–76]    | 123,124,126 | Larval attractants                                       |

From S. paradoxum [58], 98 was isolated and from S. serratifolium [60], 99 was isolated. This compound was obtained from sargaquinoic acid 68 upon standing in methanol; it is therefore suggested to be an artifact.

From S. sagamianum, the isolation of 125 and its proapoptotic activity is described [65]. Its anticholinesterase activity and potential use in Alzheimer’s disease is also described [64].

From S. siliquastrum, Yoon [70] reported the isolation of 100, and its potential as a novel anti-inflammatory agent was investigated. Lee [71] reported the isolation of 101–106. The antioxidant activity of these compounds was evaluated by various antioxidant tests, such as scavenging effects on generation of intracellular ROS (reactive oxygen species), increments of GSH (glutathione) level, and inhibitory effects on lipid peroxidation in human fibrosarcoma HT 1080 cells. Compounds 101–106 significantly decreased generation of intracellular ROS and inhibited lipid peroxidation while they increased levels of intracellular GSH at a concentration of 5 µg/mL. Compound 101 was also isolated by Heo [72] and its anti-inflammatory activity against lipopolysaccharide-exposed RAW 264.7 cells was evaluated. Jang [73] reported the isolation of 101 and 102, together with 107–120. Although the configurations of 101, 102, and 120 are relative, for 109–115 the absolute configurations of the hydroxyl groups were determined by a Mosher’s method. Using DPPA (1,1-diphenyl-2-picrylhydrazyl), all of the compounds exhibited significant radical-scavenging activity in the range of 87–91% at the concentration of 100 µg/mL. In addition, compounds 111 and 117 displayed 82.7 and 80.0% inhibition,
respectively, toward butyrylcholine esterase at the same concentration, while the other sargachromanols showed weaker or negligible activity. Cho reported the isolation of 127 and its antioxidant activity [77].

From *S. thunbergii* [62], 125, 121, and 122 were isolated. They were evaluated as to their capacity to scavenge DPPH radicals, and they exhibited EC$_{50}$ values of 30 and 31 µg/mL, respectively, compared with BHT (butylated hydroxytoluene) (EC$_{50}$, 32 µg/mL) and α-tocopherol (EC$_{50}$, 18 µg/mL). On their scavenging activity on authentic ONOO$^-$/induced ONOO$^-$ from morpholinosydnonimine (SIN-1), their scavenging ratios on authentic ONOO$^-$ were 60.0 and 57.1% at 5 µg/mL, respectively, while their inhibition ratios against the generation of ONOO$^-$ from SIN-1 were 98.6 and 90.6% at the same concentration, respectively. Scavenging activities of L-ascorbic acid and penicillamine, positive controls, on authentic/induced ONOO$^-$ were 98.1 and 90.4%, and 93.5 and 88.2%, respectively.

From *S. tortile*, Kato [74] reported the isolation of 123 and 124, together with their activity as attractants of the swimming larvae of *Coryne uchidai*. Kikuchi [75,76] reported the isolation and identification of 126. Absolute configurations were determined by ECD (electronic circular dichroism).

2.5. Other Compounds

Within the constitution of *Sargassum* sp. we can also find various compounds [48,54,56,61,78–82]. Their structures are in Figure 12 and occurrences are in Table 4.

![Figure 12. Cont.](image-url)
Figure 12. Cont.
Figure 12. Other structures from Sargassum sp.

Table 4. Other structures from Sargassum sp.

| Species                | Compounds | Biological Activity                                |
|------------------------|-----------|----------------------------------------------------|
| S. asperifolium [48]   | 128,129   | -                                                  |
| S. autumnale [78]      | 130–139   | Endothelin antagonists                             |
| S. elegans [54]        | 140       | Antioxidant                                        |
| S. fusiformis [79]     | 140       | -                                                  |
| S. heterophyllum [56]  | 140       | Antiplasmodial, cytotoxicity                       |
| S. Kjellmanium [80,81]| 141,142   | -                                                  |
| S. siliquastrum [61]   | 143–159   | Radical scavenging, active against isocitrate lyase|
| S. thunbergii [82]     | 160,161   | -                                                  |
From *S. asperifolium* [48], two hydroazulenoids, 128 and 129, were isolated. From *S. autumnale* [78], compounds 130–139 were isolated and were tested as endothelin antagonists; they were not always potent and selective.

From *S. fusiformis* [79], fucoxanthine 140 was isolated by microwave-assisted extraction coupled with high-speed countercurrent chromatography. This compound was also isolated from *S. elegans* [54] and *S. heterophyllum* [56]. The antioxidant potential of 140 was evaluated [54] and it also showed a moderate antiplasmodial activity (IC$_{50}$ = 1.5 µm) [56]. In order to assess the selectivity of fucoxanthin 140 for *P. falciparum*, the toxicity against a Chinese hamster ovarian cell line was evaluated. The relatively low cytotoxicity of fucoxanthin (IC$_{50}$ = 83.7 µm) translated into a promising selectivity index (SI = antiplasmodial IC$_{50}$/cytotoxicity IC$_{50}$) of 54 [56]. Compounds 141 and 142 [80] were isolated. For both compounds, the structure was confirmed by single-crystal X-ray analysis.

From *S. Kjellmanium*, compounds 143–159 were isolated. For both compounds, the structure was confirmed by single-crystal X-ray analysis.

From *S. siliquastrum* [61], compounds 143–159 were isolated. They showed moderate to significant radical-scavenging activity in DPPH assays. The 100-fold increase in radical-scavenging activity of the diphenolic isonahocols relative to the monophenolic nahocols indicated the role of the phenolic group in this activity. None of these compounds exhibited antimicrobial activity against Gram-positive or -negative bacteria or against pathogenic fungi. Conversely, the isonahocols 154–159 showed slight activity against sortase A derived from *Staphylococcus aureus*. The nahocols 143–153 showed no inhibitory activity against sortase A. These compounds were, however, weakly active against isocitrate lyase derived from *Candida albicans*.

Finally, we can also find reports on the antifouling activity of fats and phthalic acid derivatives from *S. confusum* [83] and the isolation of farnesylacetones from *S. micracanthum* [84,85], from *S. sagamianum* with moderate anticholinesterase activity [86], and from *S. siliquastrum* with a moderate vasodilatation effect on the basilar arteries of rabbits [87]. Three linear bisnorditerpenes were also isolated from unidentified *Sargassum* sp. [88].

### 3. Biological Activity of Extracts

Macroalgae continue to attract the attention of researchers, as several reports on the activity of extracts in the literature testify. From the chosen genera here mentioned the following reports can be found.

#### 3.1. *Asparagopsis* sp.

On the bioactivity of extracts from *Asparagopsis* sp. we can find reports on marine and biomedical antibacterial and antifungal activities of in both species of this genus [89–97]; nematicidal activity of *A. taxiformis* against the larvae of *Meloidogyne javanica* [98]; antifouling, anticyanobacterial, piscicidal, and crustacean toxicity of *A. taxiformis* [99]; and antioxidant and cytotoxic activities of *A. armata* [100].

#### 3.2. *Caulerpa* sp.

For *Caulerpa* sp., studies on the bioactivity of extracts include antimicrobial activity of *C. occidentalis* [101], *C. cupressoides* [102], and *Caulerpa* sp. [103]; nematicidal activity of *C. racemosa* against the larvae of *Meloidogyne javanica* [98]; antioxidant activity of *C. lentifera* and *C. racemosa* [104]; antinoceptive activity of *C. racemosa* [105], *C. mexicana*, and *C. sertularioides* [106]; anti-inflammatory activity of *C. mexicana* and *C. sertularioides* [106] and *C. peltata* [107]; antileishmania of *C. cupressoides* [102]; and antiviral activity against Dengue of *C. racemosa* [108] and HSV-1 (herpes simplex virus 1) of *C. cupressoides* [102]. Aqueous and methanolic extracts of *C. mexicana* were also found to suppress cell migration and ear edema induced by inflammatory agents [109].

#### 3.3. *Sargassum* sp.

Reports on the bioactivity of extracts of *Sargassum* sp. include antifouling activity of *S. muticum* [110]; anticoagulant [111], antioxidant [112], and anti-inflammatory [113] activity of *S. horneri*; antioxidant
activity of *S. siliquastrum* [114,115], *S. polycystum* [116], and *Sargassum* sp. [117]; antioxidant and anti-cholinesterase activity of *S. wightii* [118]; inhibitory effect on lipid peroxidation of *S. micracanthum* [119]; antimicrobial activity of *S. siliquastrum* [120]; antipyretic, analgesic, and anti-inflammatory *S. fulvellum* and *S. thunbergii* [121]; anti-inflammatory activity of *S. Serratifolium* [122]; antiallergenic activity of *S. tennerimum* [123]; anti-diabetic and hypolipidemic activity of *S. yezoense* [124]; larvicidal activity against malaria vector *Anopheles stephensi* of *S. swartzii* [125]; antigenotoxic activity of *S. dentifolium* [126]; antitumour activity of *S. wightii* against Dalton’s ascites lymphoma [127] and of *S. tenerimimum* against Ehrlich ascites carcinoma [128]; and antimelanogenesis activity of *S. polycystum* [129]. The action of *S. fulvellum* on skin dermatitis [130] and on neuronal maturation and synaptogenesis [131] is also documented, as well as the chemical genetic effects of *S. wightii* during embryonic development in zebrafish [132].

4. Conclusions

It is interesting to find the differences between the chemical compositions of all three genera. *Asparagopsis* is mainly rich in halogenated compounds, *Caulerpa* shows metabolites from varied biosynthetic routes, and *Sargassum* is rich in meroterpenoids. While biological activity of *Asparagopsis* metabolites is scarce, *Caulerpa* metabolites were shown to have inhibitory activity of PTPs, and to be neuroprotective, deterrents, and antibacterial. *Sargassum* metabolites are cytotoxic to cancer cells, and are antiplasmodial and antioxidants. Of course, only the more recent literature mentions biological activity results for the isolated metabolites. Extracts from all three genera show varied biological activities that make this a promising area of research. There is, however, a need to reinvestigate these genera as particular invasive species in their new host habitat since almost no reports are found on their chemistry. Their success in new environments can surely be correlated to their secondary metabolism and could provide new uses for otherwise noxious species.

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**Abbreviations**

1A9 human ovarian cancer
A549 human lung carcinoma
Aβ25-35 amyloid-peptide fragment 25–35
CDC25B cell division cycle 25 homolog B
DPPA 1,1-diphenyl-2-picrylhydrazyl
DPPH 1,1-diphenyl-2-picrylhydrazyl
ECD electronic circular dichroism
EC Effective concentration
ED effective dose
EGCG epigallocatechin gallate
GSH glutathione
HCT8 human ilececal cancer
HIV human immunodeficiency virus
HL60 promyelocytic leukemia cells
HOS human bone tumor
HSV-1 herpes simplex virus 1
IC inhibitory concentration
LAR leukocyte antigen-related phosphatase
LXR liver X receptor
MCF-7 breast adenocarcinoma
MIC minimum inhibitory concentration
MRSA Methicillin-resistant Staphylococcus aureus
P388 mouse lymphocytic leukemia
PC3 human prostate cancer
PPARs Peroxisome proliferator-activated receptors
PTP1B protein tyrosine phosphatase 1B
PTPs protein phosphatases
ROS reactive oxygen species
SHP-1 src homology phosphatase-1
SHP-2 src homology phosphatase-2
SH-SY5Y neuroblastoma cell line
SK13 Gram-positive spore-forming bacteria requiring Mn for growth
TCPTP T-cell PTP

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