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Pharmacological and natural products diversity of the brown algae genus *Sargassum*

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Sargassum (F. Sargassaceae) is an important seaweed excessively distributed in tropical and subtropical regions. Different species of *Sargassum* have folk applications in human nutrition and are considered a rich source of vitamins, carotenoids, proteins, and minerals. Many bioactive compounds chemically classified as terpenoids, sterols, sulfated polysaccharides, polyphenols, sargaquinoic acids, sargachromenol, and pheophytin were isolated from different *Sargassum* species. These isolated compounds and/or extracts exhibit diverse biological activities, including analgesic, anti-inflammatory, antioxidant, neuroprotective, anti-microbial, anti-tumor, fibrinolytic, immune-modulatory, anti-coagulant, hepatoprotective, and anti-viral activities. This review covers the literature from 1974 to 2020 on the genus *Sargassum*, and reveal the active components together with their biological activities according to their structure to create a base for additional studies on the clinical applications of *Sargassum*.

1. Introduction

Marine natural products have been characterized by their chemical structural diversity, along with different biological activities. The Red Sea is considered one of the most important marine hotspots comprising high biodiversity. Many marine algae are native to the Red Sea, which could be classified into brown algae (Phaeophyta), green algae (Chlorophyta), and red algae (Rhodophyta). Brown seaweeds are predominantly brown in color because of their contents of carotenoid fucoxanthin and polysaccharides, namely alginates, laminarins, fucans, and cellulose. Green seaweeds are characterized by their chlorophyll a and b content with ulvan being the major polysaccharide. While, in red seaweeds, the principal pigments are phycoerythrin, phycocyanin, and the primary polysaccharides are agars and carrageenans.[1] Also, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities, although only a few species have been chemically examined in the last decades.[1]

Sargassum (F. Sargassaceae), of the order Fucales, subclass Cyclosporeae, and class Phaeophyceae, is a genus of brown algae, communally known as gulfweed or sea holly, and is considered one of the most complex Phaeophyceae genera.[2] *Sargassum* was discovered by Agardh in 1820 and is reported to contain 537 species names in the algae database, of which 358 species have been accepted taxonomically.[2] It comprises many different species that are distributed worldwide, although primarily found in tropical and subtropical marine waters, and also generally growing on rocky reefs.

Sargassum thallus (10–200 cm) may be linear or bushy, with stipes 1–20 cm long arising from a discoid–conical holdfast, and do not penetrate the substratum. Its main axes are perennial, short, and cylindrical or flattened in sections, and bear the scars of deciduous branches. The shape of the leaves can be simple, bifid, or divided several times, round, spatulate, turbinate, lanceolate, ovoid, linear or of any intermediate form with air bladders (vesicles) normally present, subspherical to the ovoid, petiolate, mutic or apiculate, replacing the ramuli or axillary to the laterals. The basis of the leaves is rounded or attenuate, symmetrical or not. The pedicel may be variable in length, cylindrical, or flattened in sections and smooth. The leaves margin may be simple or doubled at the apex, and may be smooth, undulated, finely serrated, deeply dentated, or any intermediate aspect. The midrib may be short and thick or

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Fig. 1 *Sargassum sanyaense* from Hurghada City coast line, Red Sea (Egypt).

thinner and reaching the apex or any intermediate length. The apex may be acute, rounded, or truncated, simple, or showing a cup-like shaped depression (Fig. 1).[2]

A survey of folk uses of *Sargassum* spp. in the last 20 years period (1977–1996), showed that different regions in the tropical country use the brown seaweed differently. Commonly, *Sargassum* spp., is used as a cover or wrapper of fish to maintain their freshness. In the Ilocos Region in the Northern Philippines, *Sargassum* spp. is used as a vegetable; whereas in the Visayas and Northern Mindanao, natives utilize *Sargassum* spp. as a fertilizer, flower inducer, and insect repellant. The Boholano people also use the brown seaweed as animal feed. In certain parts of the island of Bohol, a *Sargassum* drink is made and is reported to have health benefits.[1]

For nearly 2000 years, *Sargassum* spp. has been also used in Traditional Chinese Medicine (TCM) to treat a variety of diseases, including thyroid.[1] Although *Sargassum* has not attracted the attention of most researchers, the therapeutic potentials of pure compounds isolated from *Sargassum* are promising for their antiviral, antimicrobial, cytotoxic, antipyretic, anti-inflammatory, cardioprotective, hepatoprotective, and hypolipidemic properties.[3] Some metabolites, such as embelin, tanacetol A, and oxygenated fucosterols, have attracted great attention because of their uncommon structural complexity and interesting pharmacological properties.[1,3] Some species are economically important, especially in the food, textile, cosmetics, and pharmaceutical industries. This review covers the literature on the genus *Sargassum* along with its chemical and medicinal potential.

2. *Sargassum angustifolium*

S. angustifolium, commonly known as narrow leaf *Sargassum* weed, is widely distributed around the Western Indian Ocean.[4] The *n*-hexane, dichloromethane, and *n*-butanol fractions isolated from *S. angustifolium*, collected from the Persian Gulf, were reported to have a cytotoxic effect against HeLa (cervical cancer) and MCF-7 (breast cancer) cells, where the cell survival was inversely proportional to the increase in the concentration of the different extracts, respectively, from 150 μg mL^{-1} to 900 μg mL^{-1}. The, *n*-hexane fraction was shown to have a median growth inhibitory concentration value (MIC) of 71 and 77 μg mL^{-1}, against HeLa and MCF-7, while the MIC of the dichloromethane fraction was 36 and 88 μg mL^{-1}, respectively. The *n*-butanol fraction showed an MIC of 25 μg mL^{-1} against MCF-7.[4] Sulfated polysaccharides isolated from *S. angustifolium* were reported to have potent immuno-stimulant activity, through inducing RAW264.7 macrophage cells to release nitric oxide, IL-1β, TNF-α, IL-6, IL-10, and IL-12 through activation of the NF-κB and MAPKs signaling pathways.[5] Also, the phosphate buffer extract of *S. angustifolium* had a low α-amylase inhibition activity with an IC_{50} of 1.85 mg mL^{-1}.[6]

3. *Sargassum aquifolium*

GC-MS of a crude petroleum ether extract of *S. aquifolium* (Turner), collected from the Red Sea of Jazan (KSA), was reported containing phenol, 2,4-bis(1,1-dimethylethyl) **1**, phenol, 2,2′-methylenebis[6-(1,1-dimethylethyl)-4-methyl **2**, stigmasta-5,24(28)-dien-3-ol, (3*á*,24*Z*) **3**, and stigmasterol **4** (Fig. 2).[7] The crystals of a petroleum ether extract of *S. aquifolium* dissolved in Millipore water were tested for antibacterial activity against *S. aureus*, *S. pyogenes*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and *K. pneumonia*. The maximum antibacterial activity was exerted against *E. coli*, with an MIC of 100–150 mg mL^{-1}.[7] L-Fucose, D-galactose, D-mannose, D-glucuronic acid, D-xylose, and sulfate were found to be the main constituents of fucoidan detected in *S. aquifolium*, collected from Vietnam, with anticoagulant,

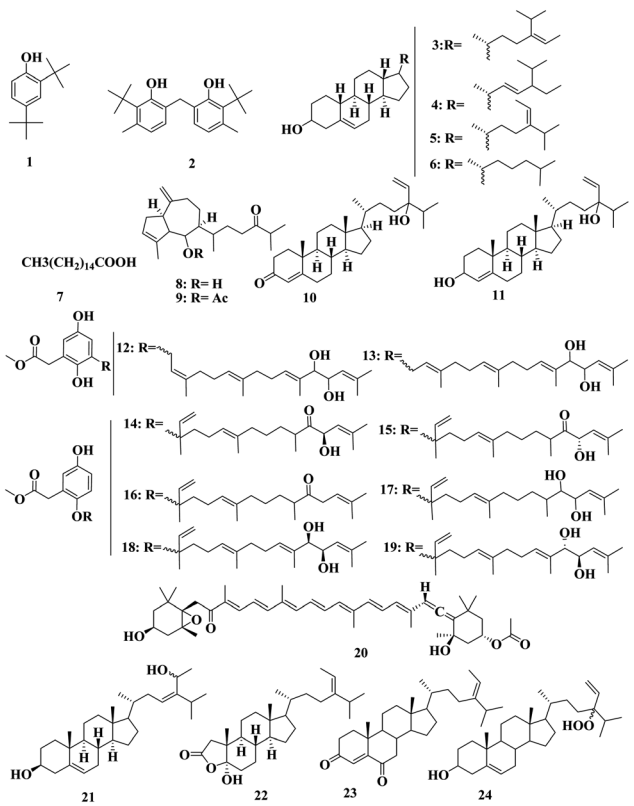

Fig. 2 Chemical structures of compounds **1–24**.

cytotoxic, and antitumor activities, which increase with sulfation.[8]

4. *Sargassum asperifolium*

The polysaccharide extracts of *S. asperifolium*, collected from the Red Sea (Egypt), possessed anti-inflammatory activity, through the significant inhibition of nitric oxide generation, and LPS-induced TNF-α.[9] Analysis of the volatile fraction of *S. asperifolium* led to the identification of fucosterol **5**, cholesterol **6**, and palmitic acid **7**.[10] Dictyone **8**, dictyone acetate **9**, saringosterone **10**, and saringosterol **11** were also detected in *S. asperifolium* collected from Hurghada (Egypt) (Fig. 2).[11]

5. *Sargassum autumnale*

Isonahocol D1 **12**, D2 **13**, nahocol-A **14**, nahocol-A1 **15**, nahocol-B, C, D1, and D2 **16–19**, were detected in a methanol extract of *S. autumnale*, collected from Omosu Bay (Japan). Nahocols were shown to have an aryl prenyl ether structure, which is considered a precursor of the prenyl hydroquinones or prenyl benzoquinones in the plant and animal kingdoms.[12]

6. *Sargassum binderi*

Fucoxanthin **20** was detected in Malaysian *S. binderi* and *S. duplicatum*. The amount of fucoxanthin **20** and the total lipid contents of *S. duplicatum* (1.01 ± 0.10 and 21.3 ± 0.10 mg g^{-1} dry weight, respectively) were significantly higher than those of *S. binderi* (0.73 ± 0.39 and 16.6 ± 4.10, respectively). Docosahexanoic acid, eicosapentanoic acid, arachidonic acid, linoleic acid and α-linolenic unsaturated fatty contents in *S. duplicatum* were found to be higher (0.76%, 2.55%, 13.64%, 5.81%, and 5.35%, respectively) than in *S. binderi* (0.70%, 1.82%, 9.13%, 6.37% and 4.39%, respectively), while palmitic acid (7) the major fatty acid in both samples.[13]

7. *Sargassum boveanum*

The different fractions of *n*-hexane, trichloroethane, chloroform, and *n*-butanol of the methanol-ethyl acetate extract of *S. boveanum*, collected from the Persian Gulf, showed a decrease in the cell survival of HeLa cells with increasing the concentration of the extracts, with IC_{50} values of 150.3 ± 23.10, 437.0 ± 147.3, 110.4 ± 33.67, and 1025.0 ± 15.20 μg mL^{-1}, respectively.[14]

8. *Sargassum carpophyllum*

28ξ-Dihydroxy-24-ethylcholesta-5,23-*Z*-dien **21** and 2*a*-oxa-2-oxo-5*f*-hydroxy-3,4-dinor-24-ethylcholesta-24(28)-ene **22** together with five steroids, namely fucosterol **5**, 24-ethylcholesta-4,24(28)-dien-3,6-dione **23**, 24ξ-hydroperoxy-24-vinylcholesterol **24**, 24-ketocholesterol **25**, and 24*R*,28*R*- and 24*S*,28*S*-epoxy-24-ethylcholesterol **26** (Fig. 2 and 3) were detected in an ethanol extract of *S. carpophyllum*, collected from the Beihai (China) Sea. Compounds **21** and **24** reportedly had

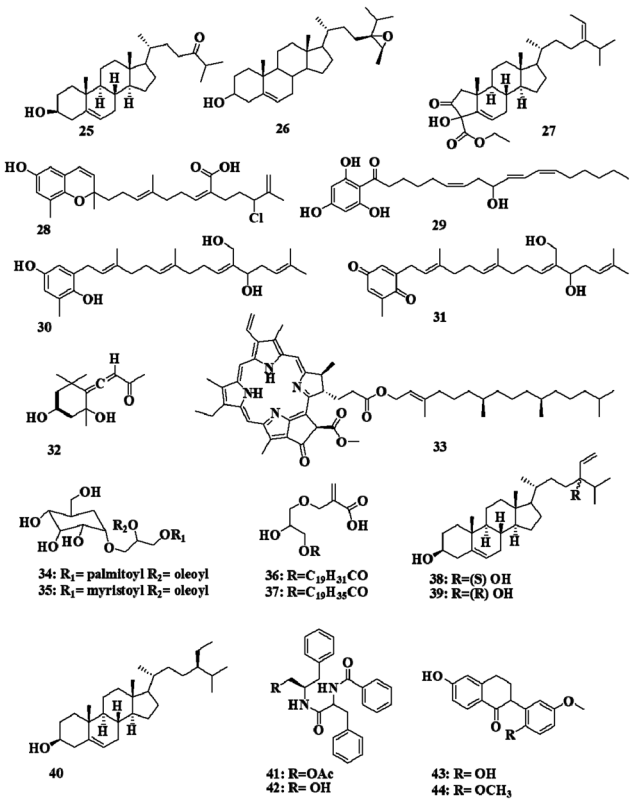

Fig. 3 Chemical structures of compounds **21–44**.

cytotoxic activities against HL-60, with IC_{50} values of 7.8 and 8.5 μg mL^{-1}, respectively, while compounds **5** and **23** showed potent cytotoxic activities against P-388, with IC_{50} values of 0.7 and 0.8 μg mL^{-1}, respectively. Compound **26** showed cytotoxic activity against MCF-7, HCT-8, 1A9, HOS, and PC-3, with IC_{50} values of 4.0, 8.8, 10.0, 10.0, and 7.2 μg mL^{-1}, respectively.[15] Another compound, 24-ethyl-3-carbethoxy-3-hydroxy-A-norcholesta-5,24(28)-dien-2-one **27**, was also detected in *S. carpophyllum*, collected from the South China Sea, which was the first reported non-steroidal ester from natural sources.[16]

9. *Sargassum cinereum*

Fucoidan was detected in *S. cinereum*, collected from Tuticorin Lat. (India). Fucoidan was reported to contain 65.753% of L-fucose and $3.7\% \pm 1.54\%$ of sulfate, respectively, with a monosaccharide composition, such as L-fucose, D-galactose, D-mannose, and D-xylose. The maximum 2,2′-diphenyl-1-picrylhydrazyl (DPPH) scavenger activity for the fucoidan extract was found at the concentration of 100 μg, whereas the crude extract of *S. cinereum* showed $63.58\% \pm 0.56\%$ scavenging activity. Fucoidan extract showed 50% cell death after 24 h of incubation (75 ± 0.9037 μg mL^{-1}) against the colon cancer cell line HCT-15.[17] The mechanism of fucoidan was a dose-dependent inhibited growth of the colon cancer cell line Caco-2, ($IC_{50} = 250$ μg mL^{-1}), the increased production of reactive oxygen species (ROS), and augmented mitochondrial membrane permeability.[18]

10. *Sargassum crassifolium*

An *S. crassifolium* ethanol extract, collected from Diora-Zinungan, showed antimicrobial activity against *A. hydrophila*, with an MIC value of 24.33 ± 0.58 mm.[19]

11. *Sargassum cristaefolium*

Sodium alginate was detected in *S. cristaefolium*, collected from Poteran Island (Indonesia). This alginate had a molecular weight of 217.94 ± 7.14 kDa with a mannuronic acid to guluronic acid ratio (M/G) of 0.28, and the L-guluronic acid block was 0.78, which was higher than the D-mannuronic acid block.[20]

12. *Sargassum dentifolium*

Polysaccharide extracts of *S. dentifolium* collected from the Red Sea (Egypt) had a protective effect against cyclophosphamide (CP)-induced genotoxicity in mice bone marrow cells (BMCs).[21] Also, the ethanol extract of *S. dentifolium*, reported as hepatoprotective in carbon tetrachloride (CCl_4)-induced hepatitis in rats, had antioxidant activity.[22]

13. *Sargassum fallax*

Fallachromenoic acid **28**, an unusual halogenated meroditerpenoid, retroflexanone **29**, fallahydroquinone **30**, and fallaquinone **31** (Fig. 3), were isolated from the Southern Australian *S. fallax*, and were shown to have antitumor activities against a P388 Murine Leukaemia cell line, with an IC_{50} > 27–29 μM.[23]

14. *Sargassum filipendula*

Heterofucan extracted from *S. filipendula* was shown to have antiproliferative and apoptosis activities against human cervical cancer (HeLa) cells, at a concentration of 0.1 to 2.0 mg mL^{-1}.[24]

15. *Sargassum fluitans*

The *in vivo* anti-fibrotic effect of a fucoidan extract of *S. fluitans* (chemically composed of carbohydrates, sulfates, uronic acids, protein, and phenols), collected from Puerto Morelos (Mexico), was detected in a CCl_4-induced liver damage model in rats. The daily oral administration of fucoidan extract (50 mg kg^{-1}) showed a significant reduction in liver enzymatic activity, liver infiltration of inflammatory cells, collagen fiber deposition, and gene expression cytokines.[25]

16. *Sargassum fulvellum*

Grasshopper ketone **32** was detected in an ethanol extract of *S. fulvellum* (SFEE) collected from Jindo (Korea). Grasshopper ketone **32** and SFEE were investigated on 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD)-like skin lesions in BALB/c mice. SFEE and grasshopper ketone **32** were found to have an inhibitory effect on AD by regulating immune mediators and cells and thus may be a potentially effective alternative therapy for AD.[26] Boiling water, ethanol, and dichloromethane extracts of *S. fulvellum*, collected from Wando aquaculture farm (Korea), were tested for anti-inflammatory, antipyretic, and analgesic activities in mice. The dichloromethane extract (0.4 mg per ear) significantly inhibited the inflammatory symptoms of mouse ear edema by 79.1%.[27] Pheophytin A **33** was detected in *S. fulvellum* collected from the Japanese coastline. When PC12 cells were treated with a low concentration of pheophytin A **33** (3.9 μg mL^{-1}) in the presence of a low level of nerve growth factor (10 ng mL^{-1}), the compound produced neuritis outgrowth similar to that produced by a high level of nerve growth factor (50 ng mL^{-1}). Pheophytin A **33** also enhanced signal transduction in the mitogen-activated protein kinase signaling pathway, which is also induced by nerve growth factor.[28] 1-*O*-Palmitoyl-2-*O*-oleoyl-3-*O*-(α-D-glucopyranosyl)glycerol (POGG) **34** and 1-*O*-myristoyl-2-*O*-oleoyl-3-*O*-(α-D-glucopyranosyl)-glycerol (MOGG) **35** were obtained from *S. fulvellum* collected from the East Sea in China. POGG **34** and MOGG **35** showed fibrinolytic activity in the reaction system of pro-u-PA and plasminogen.[29] Fulvellic acid esters **36** and **37** are glycerides bearing a methacrylic acid moiety and were detected in a methanol extract of *S. fulvellum* collected from Awakominato (Chiba) (Fig. 3).[30]

17. *Sargassum fusiforme*

The polysaccharide fraction detected in *S. fusiforme* collected from Qingdao (China) consisted of L-fucose, D-mannose, L-rhamnose, D-glucose, D-galactose, and D-glucuronic acid with different molar ratios. Regarding the hypoglycemic and hypolipidemic effects, the oral administration of these polysaccharide fractions prominently restrained the loss of body weight and increase of water intake, and also significantly controlled the increase in the levels of fasting blood glucose of diabetic rats, as well as showed better effects in controlling fasting blood glucose, alanine aminotransferase (ALT), uric acid (UA) and urea nitrogen (BUN) levels.[31] The polysaccharide also showed a significant protective effect against ultraviolet B (UVB) radiation in hairless Kun Ming (KM) mice.[32]

18. *Sargassum glaucescens*

Stigmasterol **4**, fucosterol **5**, cholesterol **6**, 24(*S*)-hydroxy-24-vinylcholesterol **38**, 24(*R*)-hydroxy-24-vinylcholesterol **39**, and β-sitosterol **40** (Fig. 3) were detected in *S. glaucescens* collected from Southern Iran. *In vitro* α-amylase inhibitory activities were detected with a methanol extract, whereby a potent inhibition (IC_{50} = 8.9 ± 2.4 mg mL^{-1}) of the enzyme compared to acarbose as a positive control was detected.[33] Fucoidan was detected in *S. glaucescens* collected from Kenting (Taiwan), where the monosaccharide composition was L-fucose, sulfate, and uronic acid, and it was also shown to exhibit antioxidant activities, in a dose-dependent manner, against DPPH.[34]

19. *Sargassum hemiphyllum*

A hot-water extract of *S. hemiphyllum* collected from the coast of Penghu County (Taiwan) was found to have antioxidant activity and immune-stimulating activities when using HB4C5, and J774.1 cells. The antioxidant activity increased with a concentration <3.5 mg mL^{-1}. The HB4C5 cells showed the maximum relative activities of cell proliferation (174%) and IgM secretion (132%) with 120 μg mL^{-1} of the hot-water extract at 80 μg mL^{-1}, while J774.1 cells showed the maximum relative activities of cell proliferation (141%) and phagocytosis (147%).[35] The major polyphenols (17.35 ± 0.93–36.66 ± 2.01 mg g^{-1}) were extracted using water, ethanol, and acetone (WES, EES, and AES, respectively) for *S. hemiphyllum*. The inhibition of α-amylase, α-glucosidase, sucrose, and maltase activities and stimulation of insulin secretion were greater with AES than with WES or EES. Moreover, 250 μg mL^{-1} EES and AES significantly increased insulin secretion in the presence of 25 mg mL^{-1} glibenclamide compared to with 50 mg mL^{-1} glibenclamide.[36] Sulfated polysaccharide extracted from *S. hemiphyllum* (SHSP) was detected on the mouse macrophage cell line (RAW 264.7) activated by lipopolysaccharide (LPS), which can used as a model system. The secretion profiles of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and NO, were found to be significantly reduced in 1–5 mg mL^{-1} dose ranges of SHSP treatments, in which the anti-inflammatory properties of SHSP may be attributed to the downregulation of NF-κB in the nucleus.[37]

20. *Sargassum henslowianum*

Saringosterol **11**, aurantiamide acetate **41**, aurantiamide **42**, vestitone **43**, 7-hydroxy-2′,4′-dimethoxyisoflavanone **44**, liquiritigenin **45**, 5,6-dihydroxy-7-methoxyflavone **46**, and 5,7-dihydroxy-8-methoxyflavone **47** (Fig. 3 and 4) were detected in an ethanol extract of *S. henslowianum* collected from Guangdong and Fujian Provinces (China).[38] Fucoidan was also detected in *S. henslowianum* collected from Hai Van–Son Cha peninsula (Vietnam). The oral dose (100 mg kg^{-1}) of fucoidan was shown to decrease cholesterol, triglyceride, and LDL-cholesterol levels in obese mice.[39] Fucose-containing sulfated polysaccharides (FCSPs) extracted from *S. henslowianum*

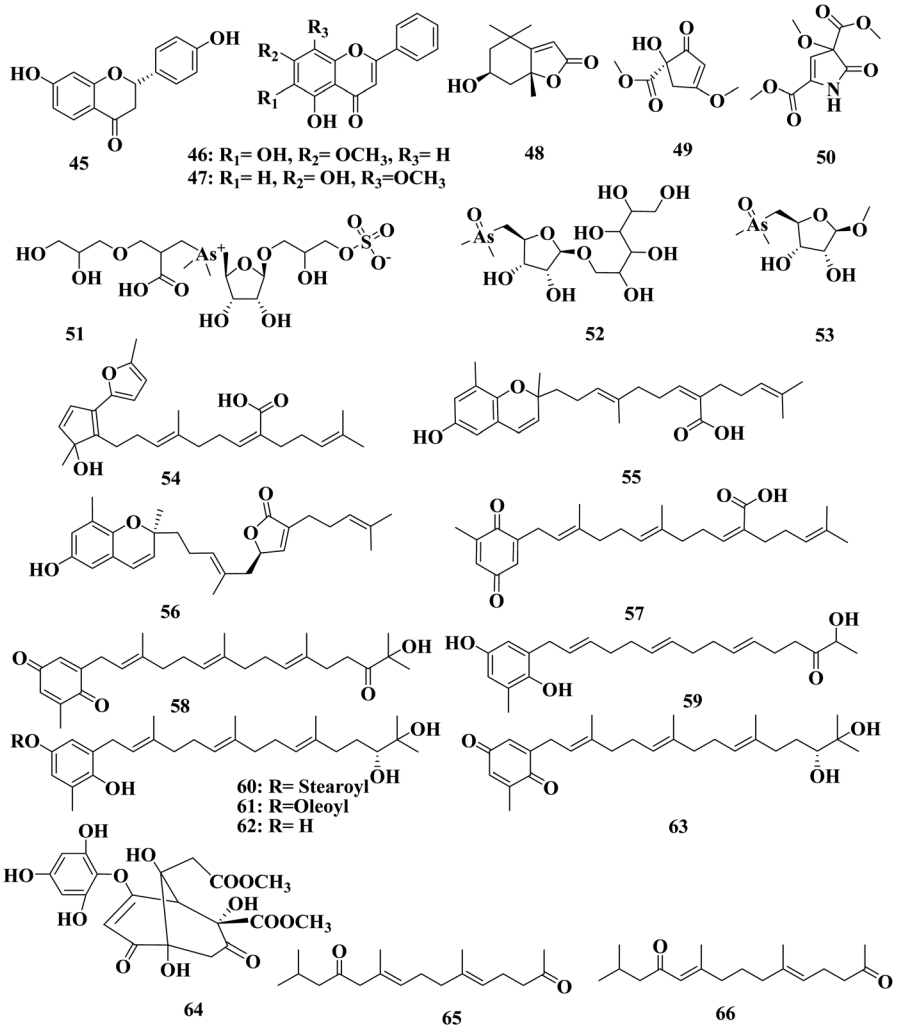

Fig. 4 Chemical structures of compounds 45–66.

notably had dose-dependent growth-inhibitory effects on the proliferation of melanoma B16 cells.[40]

21. *Sargassum horneri*

The anti-inflammatory effects of an ethanol extract of *S. horneri* (ESH) on the RAW 264.7 murine macrophage cell line were tested. ESH was not cytotoxic to RAW 264.7, while a dose of ESH 200 μg mL^{-1} was shown to reduce the mRNA level of cytokines, including IL-1β, and pro-inflammatory genes as iNOS and COX-2 in LPS-stimulated macrophage activation. ESH was also found to elicit anti-inflammatory effects by inhibiting ERK, p-p38, and NF-κB phosphorylation.[41] Also, 6-hydroxy-4,4,7*a*-trimethyl-5,6,7,7*a*-tetrahydrobenzofuran-2(4*H*)-one **48** (Fig. 4) has been detected in ESH.[42]

22. *Sargassum kjellmanianum*

(+)-Kjellmanianone **49** (Fig. 4), is a highly oxygenated cyclopentenone isolated from *S. kjellmanianum* collected from the Bay of Hiroshima (Japan), and was shown to have moderate antibacterial activity against *E. coli* and *B. subtilis* var. niger, Gram-positive microorganisms.[43] Sargassumlactam **50** (Fig. 4) was also detected in *S. kjellmanianum* and was shown to have a moderate antibacterial effect against *S. aureus* and *E. coli*.[44] An aqueous extract of *S. kjellmanianum* collected from Hahakimoku (Japan) was effective in the *in vivo* growth inhibition of implanted Sarcoma-180 cells, but showed no effect against L-1210-bearing mice. Polysaccharide fractions containing L-fucose and ester sulfate in the amounts of 12.6%, and 15.4%, 23.5%, and 17.2%, respectively, were extracted from *S. kjellmanianum*. The sulfated polysaccharide was effective against L-1210 leukemia with an ILS value of 26%.[45] The *in vitro* immune-regulatory and anti-tumor activities of sulfated polysaccharides from a hot-water crude extract of *S. kjellmanianum* (SKP) were detected; the polysaccharides were composed of L-fucose, D-galactose, D-xylose, and D-mannose. All three types of polysaccharides were sulfated, with the sulfate group accounting for 3.4%, 25.6%, and 29.9% of SKP1, SKP2, and SKP3, respectively. SKP2 and SKP3 significantly enhanced the immune function of immunocytes, and SKP2 increased the proliferation rate of spleen lymphocytes and peritoneal macrophages by up to 53.56% and 51.41%. Cell culture showed that SKP1, SKP2, and SKP3 all inhibited the proliferation of HT-29 and HeLa cells.[46]

23. *Sargassum ilicifolium*

The anticonvulsant activity of *S. ilicifolium* collected from Bhatkarwada (India) in maximal electroshock (MES)- and pentylenetetrazole (PTZ)-induced convulsion in mice was detected. Chloroform (600 mg kg^{-1}) and ethanol extracts (400 mg kg^{-1} and 600 mg kg^{-1}) of *S. ilicifolium* significantly downregulated the duration of tonic hind limb extension in a maximal electroshock (MES) model and upregulated the latency to the onset of convulsions in a pentylenetetrazol (PTZ) model. These results were comparatively similar to the effects of phenytoin (25 mg kg^{-1}) and phenobarbitone (20 mg kg^{-1}).[47]

24. *Sargassum integerrimum*

Heteropolysaccharides were detected in *S. integerrimum*, and were shown to have neuroprotective and antioxidant activities.[48]

25. *Sargassum lacerifolium*

Dimethylarsonioboside **51**, [deoxy(dimethylarsinoyl)ribosyl] mannitol **52**, and methyl 5-deoxy(dimethylarsinoyl) riboside **53** (Fig. 4) are arsenic-containing ribosides, isolated from the methanol extract of *S. lacerifolium* collected from Mullaloo Beach (Australia).[49]

26. *Sargassum latifolium*

Polysaccharides (E1–E4) were detected in *S. latifolium* collected from in the Red Sea (Egypt). E1 and E4 were potent anti-initiators, where they lead not only to an inhibition in the carcinogen activator cytochrome P450 1A (IC_{50} 2.54 and 10.30 μg mL^{-1}, respectively) but also to an induction in the carcinogen detoxification enzymes glutathione-*S*-transferases (144% and 225% of the control, respectively). E1 and E4 inhibited 59% and 63% of the induced-DNA damage. The anti-inflammatory activity of E1 and E4 enhanced the macrophage proliferation, inhibited the stimulated NO (30.7% and 59.3%), TNF-α (38.2% and 54.9), and COX-2 (20% and 18%), respectively. E3 showed also a selective cytotoxicity against lymphoblastic leukemia (1301 cells).[50]

27. *Sargassum linifolium*

The carbohydrate moiety of sargassan involves a backbone chain of D-glucuronic acid and D-mannose residues, and side chains involving residues of D-galactose, D-xylose, and L-fucose with sulfate attached to some galactose and fucose residues were detected in *S. linifolium* collected from Alexandria (Egypt).[51]

28. *Sargassum macrocarpum*

Sargafuran **54** (Fig. 4) was detected in a methanol extract of *S. macrocarpum*, collected from north to south along the Japanese coastline, and showed activity against *Propionibacterium acnes*, with an MIC of 15 μg mL^{-1}.[52] Sargachromenol **55**, isolated from *S. macrocarpum*, had a marked nerve growth factor (NGF)-dependent neurite outgrowth promoting activity to PC12D cells with a median effective dose (ED_{50}) of 9 μM, against PC12D cells in the presence of 10 ng mL^{-1} NGF. Sargachromenol **55** significantly promoted the survival of neuronal PC12D cells at 0–50 ng mL^{-1} NGF in a serum-free medium.[53] Tuberatolide B **56** (Fig. 4) is a diastereomeric meroterpenoid detected in *S. macrocarpum*, and inhibits tumor growth in breast, lung, colon, prostate, and cervical cancer cells, and suppresses cancer progression by promoting the ROS-mediated inhibition of STAT3 signaling.[54] The anti-inflammatory effects of an extract of *S. macrocarpum* (SME), collected from Jeju Island (Korea), in bone marrow-derived macrophages (BMDMs) and dendritic

cells (BMDCs) were detected. Primary BMDMs and BMDCs were used for cytokine production and western blot analysis. SME (0–50 μg mL^{-1}) pre-treatment led to a strong inhibitory effect against IL-12 p40, IL-6, and TNF-α, production in CpG-stimulated BMDMs and BMDCs. SME pre-treatment caused a strong inhibitory effect against NF-κB activation.[55]

29. *Sargassum mangarevense*

S. mangarevense collected from Tahiti contained alginate (9.3% ± 1.7% dw, M/G = 1.42 ± 0.24), mannitol (12.2% ± 2.1% dw), and phenolic contents (2.85% ± 1.12% dw). The aqueous and ethanol extracts of *S. mangarevense* showed antimicrobial activity against *S. aureus* with MICs of 9.5 and 12.5 mm, respectively.[56]

30. *Sargassum marginatum*

The growth inhibition of human pro-myelocytic leukemia (HL-60) cells by lipid extracts of *S. marginatum* collected from Goa (west coast of India) was detected with special reference to the fatty acid composition. PL exhibited cytotoxic activity at concentrations <20 μg mL^{-1}.[57]

31. *Sargassum micracanthum*

Fucosterol **5**, sargachromenol **55**, and sargaquinoic acid **57** were detected in *S. micracanthum* collected on Jeju Island (Korea). Sargachromenol **55** and sargaquinoic acid **57** were found to scavenge DPPH (IC_{50} = 49.3 and 100.2 μM).[58] 2-[(2*E*,6*E*,10*E*)-15-Hydroxy-3,7,11,15-tetramethyl-14-oxohexadeca-2,6,10-trien-1-yl]-6-methylcyclohexa-2,5-diene-1,4-dione **58**, (6*E*,10*E*,14*E*)-16-(2,5-dihydroxy-3-methylphenyl)-2-hydroxy-2,6,10,14-tetramethylhexadeca-6,10,14-trien-3-one **59**, 3-[(2*E*,6*E*,10*E*,14*R*)-14,15-dihydroxy-3,7,11,15-tetramethylhexadeca-2,6,10-trien-1-yl]-4-hydroxy-5-methylphenyl octadecanoate **60**, 3-[(2*E*,6*E*,10*E*,14*R*)-14,15-dihydroxy-3,7,11,15-tetramethylhexadeca-2,6,10-trien-1-yl]-4-hydroxy-5-methylphenyl(9*Z*)-octadec-9-enoate **61**, and 2-geranylgeranyl-6-methylhydroquinone **62** are plastoquinones detected in a methanol extract of *S. micracanthum* collected from the Toyama Bay coast (Japan). Compounds **59–61** have a reductive effect on DPPH (3.00%, 52.6%, and 32.3%, respectively), and cytotoxicity against colon 26-L5 (IC_{50} 1.51, 17.5, and 1.69 μg mL^{-1}, respectively) at a dose of 100 mg mL^{-1} of the sample.[59] 2-Geranylgeranyl-6-methylhydroquinone **62** and 2-geranylgeranyl-6-methylbenzoquinone **63** were detected also in a methanol extract of *S. micracanthum* collected from the Toyama Bay (Japan). Compounds **62** and **63** showed an inhibitory effect on lipid peroxidation with IC_{50} = 0.11 and 1.0 μg mL^{-1}, respectively. While their antiviral effects were detected against HSV-1, HSV-2, HCMV, mumps virus, measles virus, adeno virus, influenza virus, polio virus, and coxsackie virus, with IC_{50} ranging from 7.7 to 35 μM.[60] Sargassumol **64** was detected in a methanol extract of *S. micracanthum* collected from Wando County (Korea). Sargassumol **64** showed minimal scavenging activity against DPPH radical, but exhibited the potent ABTS radical-scavenging activity with an IC_{50} of 47 μM, comparable to that of trolox (IC_{50} 45 μM).[61] Dihydromonooxofranesylacetone **65** and Δ10-(11)-dihydromonooxofranesylacetone **66** were detected in an acetone extract of *S. micracanthum* collected from the coast of Gosa (Japan) (Fig. 4).[62] Dihydromonooxofarnesylacetone **67**, (5*Z*,10*E*)-14-hydroxy-2,6,10-trimethylpentadeca-5,10-dien-4-one **68**, (5*E*)-6,10,14-trimethylpentadec-5-ene-2,12-dione **69**, (5*E*,10*E*)-6,10,14-trimethylpentadeca-5,10,13-triene-2,12-dione **70**, (5*E*,9*E*)-6,10,14-trimethylpentadeca-5,9,13-triene-2,12-dione **71**, (10*E*)-14-hydroxy-2,6,10-trimethylpentadec-10-en-4-one **72**, and (6*E*,10*E*)-14-hydroxy-2,6,10-trimethylpentadeca-6,10-dien-4-one **73** are farnesylacetone derivatives isolated from a methanol extract of Japanese *S. micracanthum*.[63] (2*R*,8′*S*)-7′,8′-Dihydro-9′-oxo-δ-tocotrienol **74**, and (2*R*)-9′-oxo-δ-tocotrienol **75** were detected in a methanol extract of *S. micracanthum*, collected from Toyama Bay (Japan) (Fig. 5).[64]

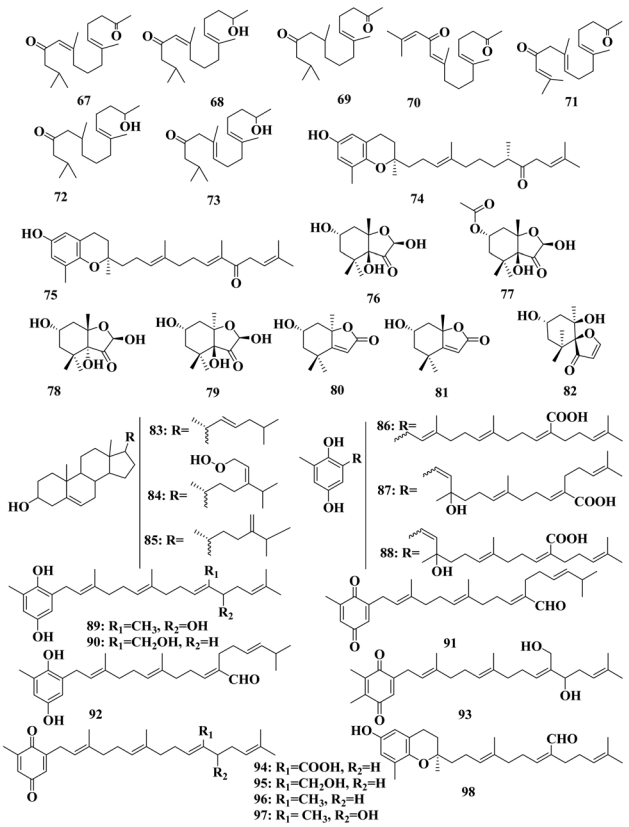

Fig. 5 Chemical structures of compounds **67–97**.

32. *Sargassum muticum*

1-Dodecene, 1-tetradecene, 1-pentadecene, *n*-pentadecene, 1-hexadecene, *n*-heptadecane, 1-octadecene, (*E*)-3-eicosene, *n*-tricosane, *n*-tetracosane, *n*-pentacosane, *n*-hexacosane, and *n*-heptacosane hydrocarbons, myristic acid, pentadecanoic acid, palmitic acid **7**, stearic, palmitoleic, oleic, vaccenic acid, hexadecadienoic acid, linolenic, stearidonic, arachidonic, and eicosapentaenoic fatty acids were detected in GC-MS of a chloroform extract of *S. muticum* collected from Plouzané (France).[65] Saringosterol **11** was detected in *S. muticum*, which is widely distributed in Korea, and exhibited an anti-obesity effect. The inhibitory effect of saringosterol **11** on adipogenesis was

detected *via* Oil Red O staining in 3T3-L1 preadipocytes in a dose-dependent manner, which inhibited adipocyte differentiation and expression of adipogenic marker genes.[66]

33. *Sargassum myriocystum*

Sulfated polysaccharides extracted from *S. myriocystum* (SMP) were investigated for gentamicin-induced nephrotoxicity in adult zebrafish. The SMP showed maximum carbohydrate, sulfate and L-fucose contents, which suppressed mRNA expression levels of KIM-1, NF-κB, TNF-α, and IL-6 in a dose-dependent manner.[67]

34. *Sargassum naozhouense*

Glutamic acid (13.21 g/100 g protein), aspartic acid (8.39 g/100 g protein), alanine(5.27 g/100 g protein), glycine (4.38 g/100 g protein), tyrosine, threonine, phenylalanine, serine, histidine, lysine, proline, arginine, tryptophan, valine, methionine, cysteine, isoleucine, and leucine comprised the amino acid composition of cultivated *S. naozhouense*, collected from Techeng Island (China), while the main fatty acids in the cultivated *S. naozhouense* were myristic acid, palmitic acid, oleic acid, and arachidonic acid. Water-soluble polysaccharides were detected in an extract of *S. naozhouense*, which contained sulfate groups, and exhibited strong antiviral activity against HSV-1 strain, with an IC_{50} of 8.92 μg mL^{-1}.[68] Sargassumone **76**, (2*R*,6*S*,8*S*,9*S*)-hexahydro-2,9-dihydroxy-4,4,8-trimethyl-6-acetyloxy-3(2*H*)-benzofuranone **77**, (6*S*,8*S*,9*R*)-hexahydro-6,9-dihydroxy-4,4,8-trimethyl-2(2*H*)-benzofuranone **78**, (6*S*,8*S*,9*R*)-hexahydro-6,9-dihydroxy-4,4,8-trimethyl-2(2*H*)-benzofuranone **79**, loliolide **80**, (+)-epiloliolide **81**, and spheciospongones A **82** as norisoprenoid derivatives and a highly oxygenated cyclopentene were detected in *S. naozhouense* (Fig. 5).[69]

35. *Sargassum natans*

Sodium alginate was detected in *S. natans* collected from both Manzanilla and Mayaro Bays (Trinidad).[70]

36. *Sargassum oligocystum*

Fucosterol **5**, cholesterol **6**, 24-hydroperoxy-24-vinylcholesterol **24**, a mixture of 24(*S*)-hydroxy-24-vinylcholesterol **38**, and 24(*R*)-hydroxy-24-vinylcholesterol **39**, 22-dehydrocholesterol **83**, 29-hydroperoxystigmasta-5,24(28)-dien-3β-ol **84**, and ostreasterol **85** were detected in *S. oligocystum* collected from the Persian Gulf (Fig. 5). A chloroform extract of *S. oligocystum* was moderately effective against *A. salina* nauplii (LC_{50} = 159 μg mL^{-1}).[71] A water extract of *S. oligocystum* collected from the Persian Gulf was detected to have antitumor activity against K562 and Daudi cell lines at concentrations of 500 μg mL^{-1}, and 400 μg mL^{-1}, respectively.[72]

37. *Sargassum pallidum*

An ethanol crude extract of *S. pallidum* collected from Weihai (China) showed antioxidant activity against DPPH.[73]

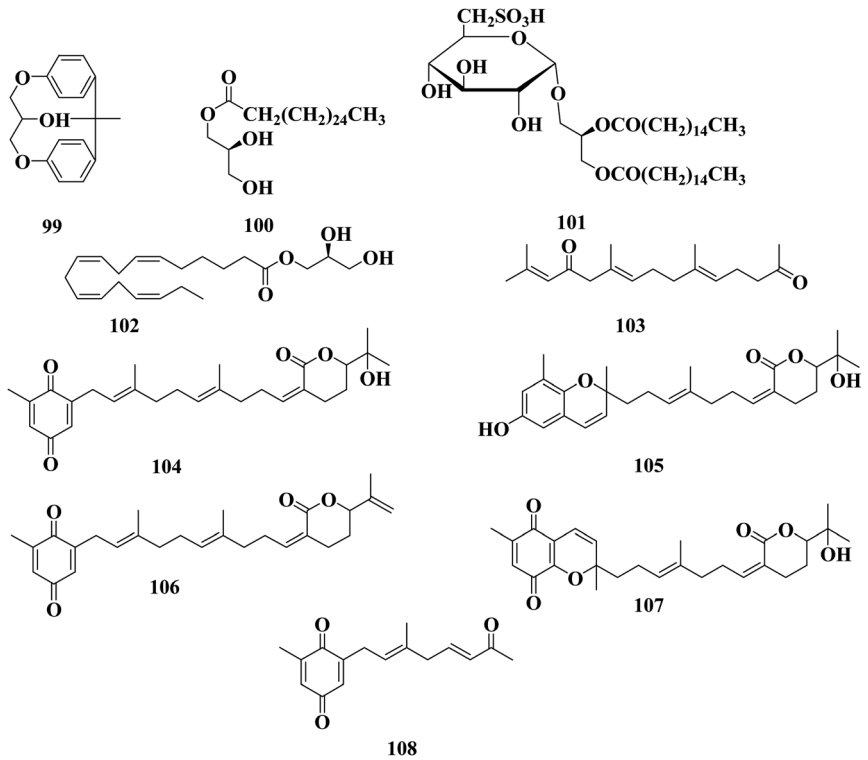

Fig. 6 Chemical structures of compounds 99–108.

38. *Sargassum patens*

The anti-inflammatory effect of an ethanol extract of *S. patens* (SPEE) collected from Busan (Korea) was detected. The production of NO was suppressed by SPEE to 28%, at 100 μg mL^{-1}, and the levels of IL-6, TNF-α, and IL-1β were dose-dependently suppressed. *In vivo*, a croton oil-induced mouse ear edema was attenuated by SPEE and the infiltration of mast cells into the tissue was suppressed.[74] A sulfated polysaccharide was detected in *S. patens*, and was reported to inhibit the replication of herpes simplex virus type 2 (HSV-2) in a dose-dependent manner by 38.5–96.1%, of the control level, after incubation with 0.78–12.5 μg mL^{-1} of the polysaccharide. The sulfated polysaccharide exhibited extracellular virucidal activity only in high concentrations (≥12.5 μg mL^{-1}), but suppressed the virus attachment to its host cells by 45.1%, at a concentration < 1 μg mL^{-1}.[75]

39. *Sargassum paradoxum*

Fallahydroquinone **30**, fallaquinone **31**, sargahydroquinoic acid **86**, chabrolohydroxybenzaquinone A **87**, chabrolohydroxybenzaquinone C **88**, paradoxhydroquinone **89**, 2-[11-(hydroxymethyl)-3,7,15-trimethyl-2,6,10,14-hexadecatetraen-1-yl]-6-methyl-1,4-benzenediol **90**, sargaquinal **91**, sargahydroquinal **92**, paradoxquinol **93**, sargahydroquinoic acid **94**, 2-[11-(hydroxymethyl)-3,7,15-trimethyl-2,6,10,14-hexadecatetraen-1-yl]-6-methyl-1,4-benzoquinone, **95**, sargaquinone **96**, paradoxquinone **97**, and (3′*E*,7′*Z*)-9-(6-hydroxy-2,8-dimethyl-2*H*-1-benzopyran-2-yl)-6-methyl-2-(4-methyl-3penten-1-yl)-2,6-nonadienal **98** were detected in a crude extract of *S. paradoxum* collected from Port Phillip (Australia) (Fig. 5).[76]

40. *Sargassum parvivesiculosum*

1,3-Di-*O*-[2′,2′-di-(*p*-phenylene) isopropylidene]glycerol **99**, (2*S*)-1-*O*-heptatriacontanoyl glycerol **100**, and (2*S*)-1,2-di-*O*-palmitoyl-3-*O*-(6-sulfo-α-D-quinovopyranosyl)glycerol **101** are glycerol derivatives isolated from an ethanol extract of *S. parvivesiculosum* collected from Sanya (China) (Fig. 6).[77]

41. *Sargassum polycystum*

The total yield of fucoidan isolated from *S. polycystum* was 4.51 ± 0.24%, and contained 46.8% of L-fucose and 22.35% ± 0.23% of sulfate respectively. The cytotoxicity effect of fucoidan, showed a higher percentage (90.4% ± 0.25%) of inhibition against the MCF-7 cell line, at 150 μg mL^{-1}, with an IC_{50} of 50 μg mL^{-1}.[78]

42. *Sargassum ringgoldianum*

An extract *of S. ringgoldianum* collected from Jeju Island (Korea), showed the inhibition of α-glucosidase and α-amylase, and alleviated postprandial hyperglycemia in streptozotocin-induced diabetic mice. The IC_{50} values of *S. ringgoldianum* extract against α-glucosidase and α-amylase were 0.12, and 0.18 mg mL^{-1}, respectively. The blood glucose levels of the *S. ringgoldianum* extract in the administered group were significantly lower in the streptozotocin-induced diabetic mice compared to in the control group.[79]

43. *Sargassum sagamianum*

An ethanol extract of *S. sagamianum* collected from Yeonhwari (Korea) was detected to include an anti-inflammatory agent, whereby the rate of formation of edema in a mouse ear model was reduced by 46%, using a dose of 250 mg kg^{-1}. The ethanol extract showed potent inhibitory effects on the LPS-induced expression of inflammatory mediators, such as NO, iNOS, COX-2, and cytokines, in macrophages through suppression of the NF-κB p65 pathway.[80] An ethanol extract of *S. sagamianum* collected from Jeju Island (Korea) was investigated on INS-1 pancreatic β cells against high glucose-induced oxidative stress and apoptosis at high concentrations (30 mM) causing β cell apoptosis, whereby treatment with SSE protected the β cells from high glucose-induced damage by recovering the cell viability. Treatment with the ethanol extract at concentrations of 10–100 μg mL^{-1} decreased lipid peroxidation, intracellular ROS, and nitric oxide levels, as well as increased cell viability and insulin secretion in high glucose pre-treated INS-1 cells, in a dose-dependent manner.[81] 1-Octadecatetraenoyl glycerol **102** is a polyunsaturated fatty acid-derived monoglyceride detected in *S. sagamianum* collected from Jeju Island (Korea). A series of monoglycerides were synthesized using glycerol and various fatty acids. Several synthesized compounds showed a moderate to significant inhibition of phospholipase A2 and cyclooxygenase-2.[82] Sargachromenol **55**, sargaquinoic acid **57**, dihydromonofarnesylacetone **65**, and monooxofarnesylacetone **103** were isolated from a methanol extract of *S. sagamianum*. These compounds showed moderate acetylcholinesterase (AChE) inhibitory activity in a micromole range.[83] *In vitro*, treatment with sargachromenol **55** and sargaquinoic acid **57** promoted cell death and the activation of caspase-3, caspase-8, caspase-9, and poly (ADP-ribose) polymerase (PARP) in a concentration-dependent manner. Sargaquinoic acid- or sargachromenol-induced apoptosis was enhanced by co-treatment with UVB irradiation. The topical application of sargaquinoic acid (1 mg mL^{-1}) before UVB irradiation (2.5 kJ m^{-2}) to hairless mice also enhanced apoptosis, including the activation of caspase-3.[84] 15′-Hydroxysargaquinolide **104**, 11′-hydroxysargachromelide **105**, 15′-methylenesargaquinolide **106**, chromequinolide **107**, and (2′*E*,5′*E*)-2-methyl-6-(7′-oxo-3′-methylocta-2′,5′-dienyl)-1,4-benzoquinone **108** were detected in *S. sagamianum* collected from Manazuru in the Kanagawa prefecture. Compounds **104**, **105**, and **108**, had antibacterial activity against *S. aureus*, (MIC 16, 128, and 2 μg mL^{-1}, respectively) (Fig. 6).[85]

44. *Sargassum serratifolium*

An ethanol extract of *S. serratifolium* collected from Busan (Korea) ameliorated paw swelling, reduced the arthritis score, decreased the secretion of pro-inflammatory cytokines in the serum and joint tissue, and suppressed the collagen-induced rheumatoid arthritis of mice. The ethanol extract showed a downregulated

NF-κB signaling pathway by suppressing the phosphorylation of protein kinase B, c-Jun N-terminal kinase, and p38 mitogen-activated protein kinases.[86] An ethanol extract of *S. serratifolium* exhibited potential antimicrobial activity against pathogenic commensal bacteria related to *acne vulgaris* (*P. acnes*, *S. epidermidis*, *S. aureus*, and *P. aeruginosa*), and *C. albicans*, which causes cutaneous candidiasis. Among the solvent-soluble fractions from the ethanol extract, the *n*-hexane fraction showed the strongest antimicrobial activity against all the tested human skin pathogens (MIC from 32 to 512 μg mL^{-1}).[87] An ethanol extract of *S. serratifolium*, collected from Tongyoung (Korea), which mainly contained sargachromenol **55** and sargaquinoic acid **57**, efficiently suppressed adipocyte differentiation and lipid accumulation in 3T3-L1 cells by downregulating the proteins involved in cell cycle progression and adipogenesis, and also downregulated the key transcription factors, such as C/EBPβ, C/EBPα, PPARγ, RXRα, SREBP1c, and STAT3, which were responsible for the observed suppression of lipid accumulation upon treatment with an ethanol extract of *S. serratifolium*.[88]

45. *Sargassum siliquastrum*

Sargachromanol A–P **109–124** are meroterpenoids detected in *S. siliquastrum*. These compounds exhibited significant antioxidant activity in the DPPH assay. Compounds **115** and **123** also showed inhibitory activity toward butylcholine esterase.[89] Sargachromanol Q **125** and sargachromanol R **126** were detected in *S. siliquastrum* collected from Cheju Island (Korea). Sargachromanol R **126** had potent cytotoxic activity against AGS, HT-29, and HT-1080 cell lines, with IC_{50} values of 6.5, 3.4, and 13.9 μg mL^{-1}, respectively, compared with paclitaxel and doxorubicin.[90] Mojabanchromanol **127** was detected in an ethanol extract of *S. siliquastrum* collected from the seashore of Pusan (Fig. 7).[91] Isonahocol E3 **128**, detected in *S. siliquastrum*, has functional antagonistic activities against ET-1 induced inflammatory and pro-angiogenic effects, through inhibition of ET-1-induced cell proliferation, as well as inflammatory mediators, like IL-6, IL-8, and TNF-α, and pro-angiogenic factors, including metalloproteinases in immortalized human keratinocytes. Isonahocol E3 **128** also reduced the expression level of endothelin ETA receptor and endothelin ETB receptor, as well as suppressed ET-1-induced extracellular signal-regulated kinase (ERK) phosphorylation.[92] Sargachromanol D **112**, sargachromanol E **113**, sargachromanol K **119**, sargachromanol P **124**, (9*S*,10*S*)-13-(3,4-dihydro-6-hydroxy-2,8-dimethy-2*H*-1-benzopyran-2-yl)-2,6,10-trimethyl-trideca-(2*E*,6*E*)-diene-4,5,10-triol **129**, (9*S*,10*R*)-13-(3,4-dihydro-6-hydroxy-2,8-dimethy-2*H*-1-benzo-pyran-2-yl)-2,6,10-trimethyl-trideca-(2*E*,6*E*)-diene-4,5,10-triol **130**, and 9-(3,4-dihydro-6-hydroxy-2,8-dimethy-2*H*-1-benzopyran-2-yl)-2,6-dimethyl-(6*E*)-nonenoic acid **131** were detected

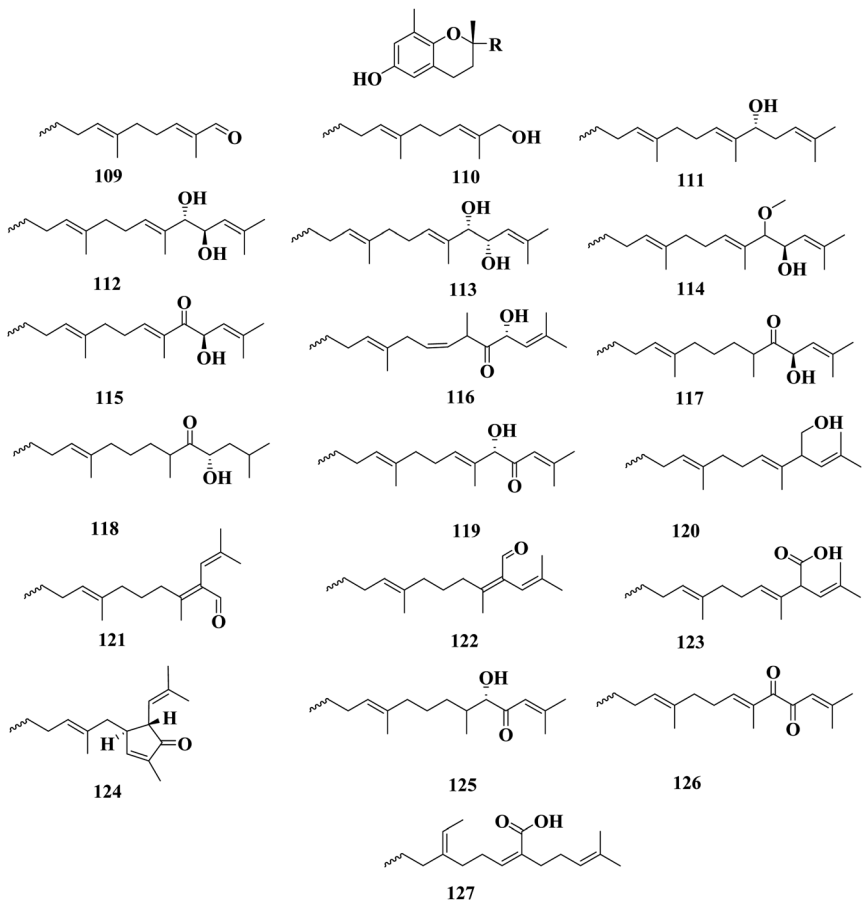

Fig. 7 Chemical structures of compounds **109–127**.

in *S. siliquastrum* collected from JeJu Island (Korea). Sargachromanols A **109**, B **110**, and K **119**, had strong cytotoxicity against AGS, HT-29, HT-1080, and MCF-7 cell lines, with IC_{50} values of 0.7, 6.1, 0.7, and 28.1 μg mL; 0.5, 1.0, 3.3, and 23.6 μg mL^{-1} and 5.7, 0.8, 1.8, and 10.3 μg mL^{-1}, respectively, comparable with paclitaxel and doxorubicin.[93] (6*E*,10*E*)-16-(2,5-Dihydroxy-3-methylphenyl)-4,14-dihydroxy-2,6,10,14-tetramethylhexadeca-2,6,10-trien-5-one **132**, methyl(5-hydroxy-2-{[(6*E*,10*E*,13*S*)-13-hydroxy-3,7,11,15-tetramethyl-12-oxohexadeca-1,6,10,14-tetraen-3-yl]oxy}phenyl)acetate **133**, methyl(5-hydroxy-2-{[(6*E*,10*E*,12*S*)-12-hydroxy-3,7,11,15-tetramethyl-13-oxohexadeca-1,6,10,14-tetraen-3-yl]oxy}phenyl) acetate **134**, methyl(5-hydroxy-2-{[(6*E*,10*Z*,12*R*)-12-hydroxy-3,7,11,15-tetramethyl-13-oxohexadeca-1,6,10,14-tetraen-3-yl] oxy}phenyl)acetate **135**, methyl(5-hydroxy-2-{[(6*E*,13*E*)-12-hydroxy-3,7,11,15-tetramethylhexadeca-1,6,13,15-tetraen-3-yl] oxy}phenyl)acetate **136**, methyl[2-({(6*E*)-3,7-dimethyl-8-[(1*R*,5*R*)-3-methyl-5-(2-methylprop-1-en-1-yl)-4-oxocyclopent-2-en-1-yl] octa-1,6-dien-3-yl}oxy)-5-hydroxyphenyl]acetate **137**, methyl{2,5-dihydroxy-3-[(2*E*,6*E*,10*E*,13*S*)-13-hydroxy-3,7,11,15-tetramethyl-12-oxohexadeca-2,6,10,14-tetraen-1-yl]phenyl}acetate **138**, methyl{2,5-dihydroxy-3-[(2*E*,6*E*,13*S*)-13-hydroxy-3,7,11,15-tetramethyl-12-oxohexadeca-2,6,14-trien-1-yl]phenyl}acetate **139**, methyl{2,5-dihydroxy-3-[(2*Z*,10*E*,13*S*)-13-hydroxy-3,7,11,15-tetramethyl-6-oxohexadeca-2,10,14-trien-1-yl]phenyl}acetate **140** and methyl{1-[(2*E*,6*E*,10*E*,12*R*,13*S*)-12,13-dihydroxy-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl]-2,5-dioxocyclohex-3-en-1-yl}acetate **141** were detected in *S. siliquastrum*. Compounds **132–141** were revealed to have a common tetraprenyl hydroquinone structure, which belonged to the nahocol, isonahocol, and sargahydroquinoic acid classes. The dihydroquinone moiety of **141** was unique and unprecedented in a brown alga. These compounds exhibited moderate to significant radical-scavenging activity as well as weak inhibitory activities against sortase A, and isocitrate lyase (Fig. 8).[94]

46. *Sargassum siliquosum*

Methanol extracts of *S. siliquosum* (ME) and a fucoxanthin-rich fraction (FRF) showed antioxidant activity, with IC_{50} values of 0.2, and 0.04 mg mL^{-1}, respectively. Also, the IC_{50} values for the angiotensin-converting enzyme (ACE) inhibitory activity of ME (IC_{50} = 0.03–0.42 mg mL^{-1}) was lower than that of FRF (0.94–1.53 mg mL^{-1}). CE and FRF also showed α-glucosidase inhibitory activity, with IC_{50} values of 0.57, and 0.50 mg mL^{-1}, respectively.[95]

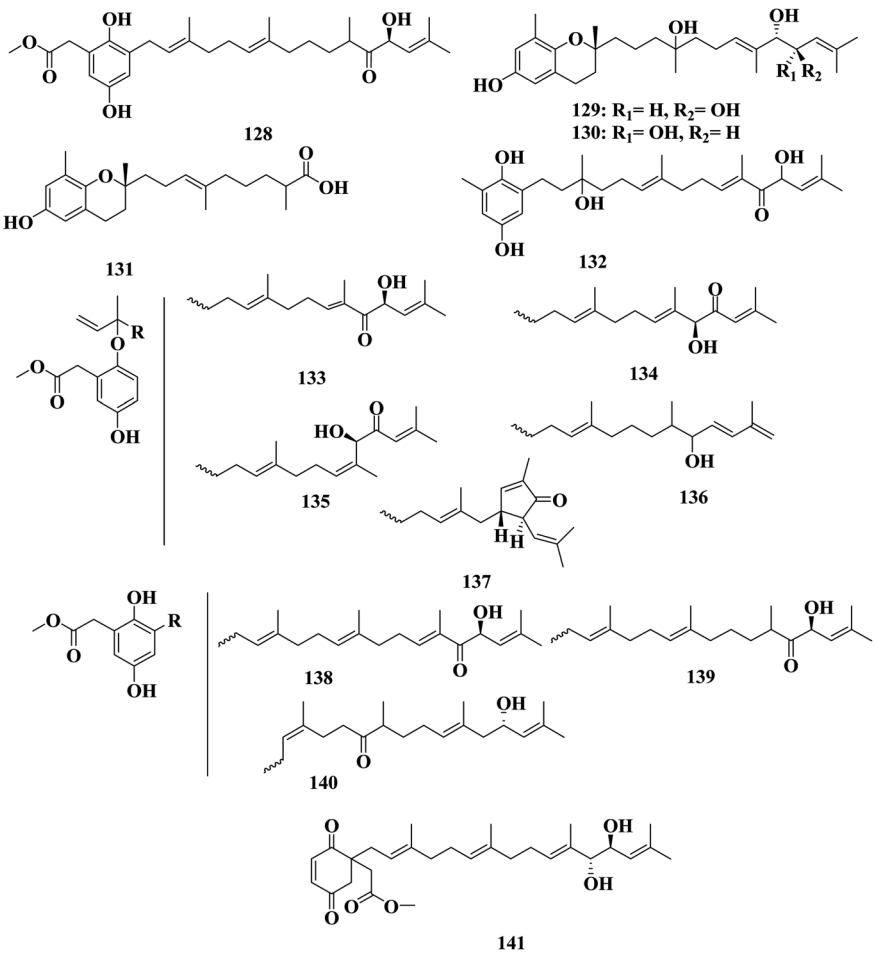

Fig. 8 Chemical structures of compounds 128–141.

47. *Sargassum spinuligerum*

Deshydroxytetrafuhalol-A, tetrafuhalol-A, pentafuhalol-A, hexafuhalol-A, heptafuhalol-A, octafuhalol-A, nonafuhalol-A and undecafuhalol-A, the acetylated derivatives of deshydro xytetrafuhalol-C, deshydroxyhexafuhalol-A, deshydroxyhexafuhalol-C and deshydroxyhexafuhalol-D, deshydroxyoctafuhalol-C, octafuhalol-B, decafuhalol-A, dodecafuhalol-A, tetradecafuhalol-A, hexadecafuhalol-A, octadecafuhalol-A and eicosafuhalol-A were the largest phlorotannins found in an ethanol extract of *S. spinuligerum*, collected from Whangaparoa Island, (Auckland).[96] Phlorotannins, fucophlorethol-B octa-acetate, fucodiphlorethol-B, fucodiphlorethol-D and fucodiphlorethol-F deca-acetate, hydroxyfucodiphlorethol-A undeca-acetate, bisfucotriphlorethol-A pentadeca-acetate, hydroxybisfucophlorethol-A hexadeca-acetate, bisfucotetra phlorethol-A heptadeca-acetate, dihydroxyfucotriphlorethol-A and dihydroxyfucotriphlorethol-B tetradeca-acetate, bisfucopenta phlorethol-B nonadeca-acetate, chlorobisfucopentaphlorethol-A nonadeca-acetate, difucodiphlorethol-A trideca-acetate, fucodi fucotetraphlorethol-A icosa-acetate, bisfucotriphlorethol-A penta deca-acetate, chlorobisfucopentaphlorethol-A nonadeca-acetate , and fucodifucotetraphlorethol-A icosa-acetate were detected in *S. spinuligerum*.[97] Pseudotrifuhalol-A, pseudotetrafuhalol-A, pseudopentafuhalols-A–D, pseudohexafuhols-A–C, pseudoheptafuhalols-A–D and psuedooctafuhalols-B–D were detected in an ethanolic extract of *S. spinuligerum*.[98]

48. *Sargassum swartzii*

Sulfated polysaccharide extracted (SPE) from *S. swartzii* was collected from a coastal region of Mandapam (India), with a molecular weight of 50 kDa, and with a high percentage of carbohydrate (7.40% ± 0.63%), followed by sulfate (5.3% ± 1.54%). The antioxidant activity of SPE detected for ABTS, H_2O_2 and DPPH, was 55% ± 3.61%, 47.23% ± 2.81%, and 25.33% ± 2.52%, respectively.[99] Bioactive fucoidan fractions (CFF, FF1, and FF2) were detected in *S. swartzii* collected from the Gulf of Mannar (India), which contained mainly sugars, sulfate, and uronic acid. Fraction FF2 was found to exhibit significant anti-HIV-1 activity at concentrations of 1.56 μg mL^{-1} as observed by a >50% reduction in HIV-1 p24 antigen levels and reverse transcriptase activity.[100]

49. *Sargassum tenerrimum*

Sulfated polysaccharides, detected in *S. tenerrimum* collected from Mandapam (India), showed a higher percentage of carbohydrate (8.20% ± 1.23%) followed by sulfate (6.6% ± 1.42%) and protein (0.86% ± 0.42%). The free radical scavenging potential was found to be higher in ABTS (70.33% ± 2.33%) followed by DPPH (64.66% ± 2.08%) and H_2O_2 (61.56% ± 2.05%). The total antioxidant capacity (TAC) was found to be 62.55% ± 1.40%.[101]

50. *Sargassum thunbergii*

3-{[5-Deoxy-5-(trimethylarsonio) pentofuranosyl]oxy}-2-hydroxy propyl sulfate **142**, arseno-sugar was detected in *S. thunbergii* collected from Nakaminato (Japan).[102] Sargachrominol **55**, sargaquinoic acid **57**, sargahydroquinoic acid **94**, and sargathunbergol A **143** were detected in *S. thunbergii* collected from Youngdo Island (Korea), which exhibited antioxidant activities (EC_{50} values of 32, 27,20, and 38 μg mL^{-1} respectively), compared to BHT (EC_{50} = 42 μg mL^{-1}) and α-tocopherol (EC_{50} 23 μg mL^{-1}).[103] Sargahydroquinoic acid **95**, sargaquinoic acid **2**, and sargachromenol **55**, thunbergol A **144**, and thunbergol B **145**, were detected in *S. thunbergii* collected from Busan (Korea). The evaluating capacity of compounds **144**, and **145** to scavenge DPPH radical, showed they exhibited EC_{50} values of 30 and 31 μg mL^{-1}, respectively.[104]

(2*S*)-1-*O*-(5*Z*,8*Z*,11*Z*,14*Z*,17*Z*-Eicosapentaenoyl)-2-*O*-(9*Z*,12*Z*,15*Z*-octadecatrienoyl)-3-*O*-β-D-galactopyranosyl-*sn*-glycerol **146** and (2*S*)-1-*O*-(9*Z*,12*Z*,15*Z*-octadecatrienoyl)-2-*O*-(6*Z*,9*Z*,12*Z*,15*Z*-octadecatetraenoyl)-3-*O*-β-D-galactopyranosyl-*sn*-glycerol **147** were glycolipids detected in the methanol extract of *S. thunbergii*, collected from the West Sea in Korea.[105] Thunberol **148**, along with 24-ethylcholesta-4,24(28)-dien-3-one **149**, stigmasta-5,28-dien-3β-ol **150**, cholesta-5,23-dien-3β,25-diol **151**, and cholesta-5,14-dien-3β-ol **152**, were detected in *S. thunbergii*, collected from Nanji Island (China). Thunberol **148** exhibited significant inhibitory activity against protein tyrosine phosphatase 1B, a potential compound target for the treatment of Type-II diabetes and obesity, with an IC_{50} value of 2.24 μg ml^{-1}.[106] (STCs)—indole-2-carboxaldehyde (STC-1) **153**, indole-3-carboxaldehyde (STC-2) **154**, indole-4-carboxaldehyde (STC-3) **155**, indole-5-carboxaldehyde (STC-4) **156**, indole-6-carboxaldehyde (STC-5) **157**, and indole-7-carboxaldehyde (STC-6) **158** were detected in *S. thunbergii* and their inhibitory effects were evaluated on adipocyte differentiation in 3T3-L1 cells. STC-1 and STC-5 showed non-toxic inhibition of the differentiation of 3T3-L1 adipocytes. STC-1 and STC-5 significantly inhibited lipid accumulation and downregulated the expression of peroxisome proliferator-activated receptor-γ (PPARγ), CCAAT/enhancer-binding protein α (C/EBPα), and sterol regulatory element-binding protein 1c (SREBP-1c) in a dose-dependent manner. The specific mechanism mediating the effects of STC-1 and STC-5 was shown to be AMP-activated protein kinase (AMPK) activation. The inhibitory effect of STC-1, and STC-5 on adipogenesis was through activation of the AMPK signal pathway. STC-1 and STC-5 may be effective candidates for the prevention of obesity or obesity-related diseases.[107] (+)-Epiloliolide **81**, (−)-loliolide **80**, and apo-9′-fucoxanthinone **159** norisoprenoids were detected in *S. thunbergii*, collected from Korea.[108] 1-(5-Acetyl-2,4-dihydroxyphenyl)-3-methylbutan-1-one **160** and 1-(5-acetyl-2-hydroxy-4-methoxyphenyl)-3-methylbutan-1-one **161** were detected in a methanol extract of *S. thunbergii*, collected from Weihai City (China).[109] Saringosterol **11**, chlorophyll a **162**, and isofucosterol **163**, were also isolated from the chloroform fraction of *S. thunbergii* extract (Fig. 9).[110]

51. *Sargassum trichophyllum*

Laminaran, alginate, and fucoidan were detected in *S. trichophyllum*. Laminaran was found to be a β-glucan consisting of

terminal- (14.5 mol%), 1,3- (69.4%), 1,6- (33.4%), and 1,3,6-linked (12.8%) residues. Alginate was found to be a mannuronic acid-rich alginate (M/G = 1.88). Fucoidan consisted of L-fucose (79.1 mol%) and D-galactose (19.9 mol%), and its sulfate content was estimated to be 25.5%, with antiviral activity against the herpes simplex virus type 2.[111]

52. *Sargassum turbinarioides*

Alginate was detected in *S. turbinarioides* collected from Nosy Bey (Madagascar), with a molecular weight of 5.528×10^5 g mol^{-1}.[112]

53. *Sargassum vachellianum*

Fucoidan-rich polysaccharide extract (SPS) and polyphenol-rich extract (SPP) from *S. vachellianum*, collected from Nan'ao Island (China), showed a protective effect on the skin from UV damage. SPP showed good free radical scavenging ability, antimicrobial activity against *E. coli* and *S. aureus*, and effectively absorbed UVB and UVA rays. Whereas SPS hardly absorbs UVA and UVB rays and showed weak free radical scavenging ability and no antimicrobial activity. SPS showed considerable inhibition of tyrosinase (51.21%) and had better moisture absorption (52.1%) and retention (63.24%) abilities than SPP.[113] (4*Z*,9*Z*)-4-Methyl-

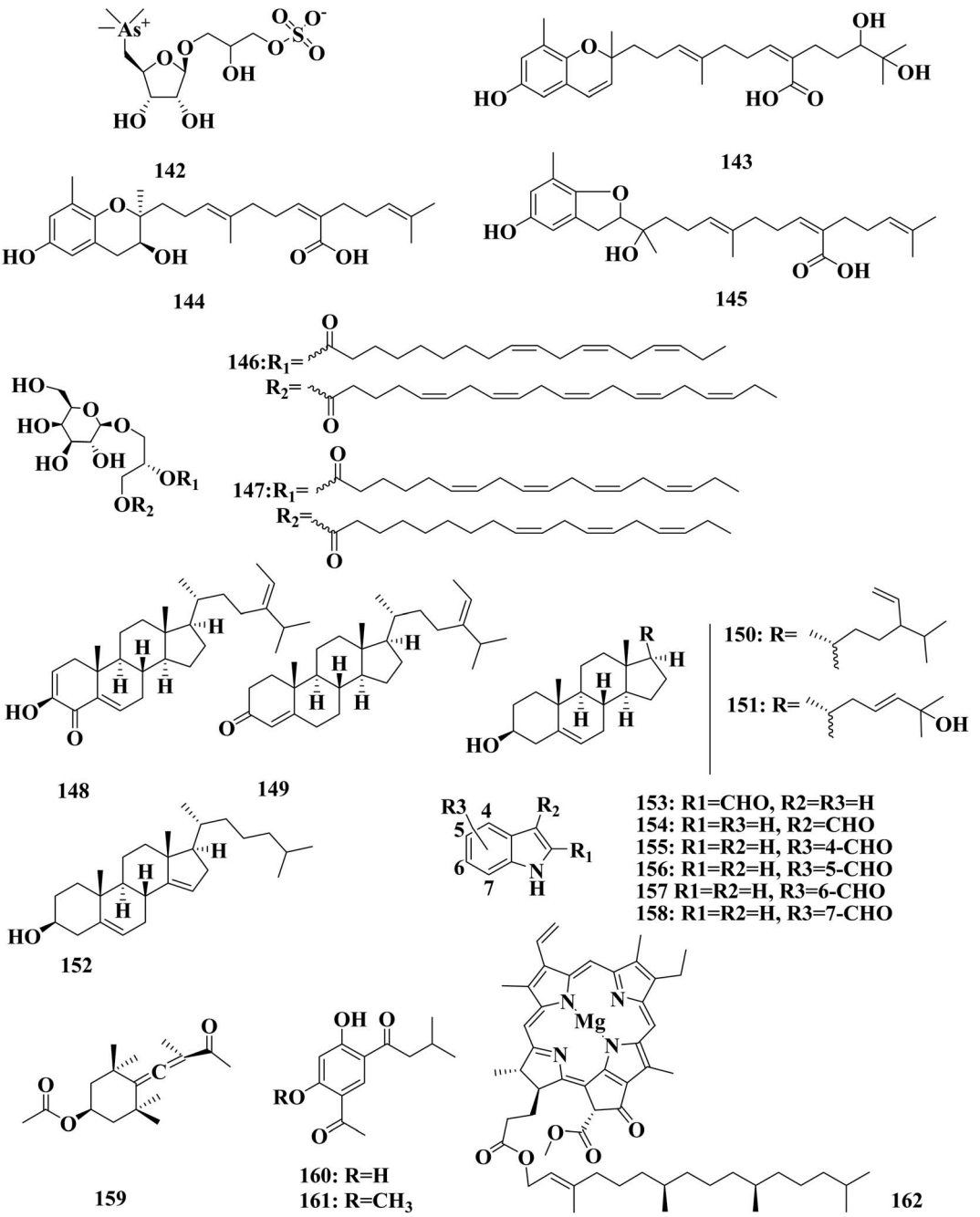

Fig. 9 Chemical structures of compounds 142–162.

1,2,6,8-tetraazacycloundeca-4,9-diene-3,7,11-trione **164** is an eleven-membered macrocyclic hydrazide detected in *S. vachellianum* collected in the South China Sea (Fig. 10).[114]

54. *Sargassum wightii*

1-0 Palmitoyl-3-0(6′-sulfo-alpha-quinovopyranosyl)-glycerol **165**, sulfoglycerolipid, was detected in a methanol extract of *S. wightii*, and showed antibacterial activity against *Xanthomonas oryzae* pv. *oryzae*, which causes bacterial blight of rice.[115] 4-(8-Ethyl-tetrahydro-7-oxo-2*H*-pyran-5-yl)-propyl-4′-methylbenzoate **166** and methyl-2-(12-oxo-7-phenyl-8-vinyl-1-oxa-4,9-cyclododecadien-3-yl)-acetate **167**, detected in the methanol extract of *S. wightii*, showed antioxidant activities against DPPH radical scavenging, with (IC_{50} values of 0.24–0.32 mg mL^{-1}), compared to α-tocopherol (IC_{50} 0.63 mg mL^{-1}). Also, **166** and **167** showed 5-lipoxygenase inhibitory activity with IC_{50} values of 0.56 and 0.29 mg mL^{-1}, respectively.[116] 2α-Hydroxy-(28,29)-frido-olean-12 **13**, 21(22)-dien-20-propyl-21-hex-40(*E*)-enoate **168**, and 2α-hydroxy-(28,29)-frido-olean-12 **13**, 21(22)-dien-20-prop-2-(*E*)-en-21-butanoate **169**, frido-oleanene triterpenoids derivatives, 2α-hydroxy-8(17),12*E*,14-labdatriene **170**, and 3β,6β,13α-trihydroxy-8(17),12*E*,14-labdatriene **171**, labdane diterpenoids, were detected in an extract of *S. wightii*, were shown to be potential anti-hyperglycaemic pharmacophore leads to reduce the risk of elevated postprandial glucose levels. The oxygenated labdane diterpenoids displayed significantly lesser antioxidant and tyrosine phosphatase-1B inhibitory properties than those exhibited by the frido-oleanenes.[117] 3″-Isopropyl-3*c*-{3*b*-[(2-oxo-3,4-dihydro-2*H*-chromen-3-yl)methyl]butyl}-2″-butenyl-3′-hydroxy-2′-(2′*b*-methoxy-2′-oxoethyl)-3′,4′-dihydro-2*H*-pyran-4′-carboxylate **172**, 2*c*-methylbutyl-6-[6*c*-(benzoyloxy)propyl]-6-methyl-tetrahydro-2*H*-pyran-2-carboxylate **173**, 6-{6*b*-[3′-(5′*a*-methyl

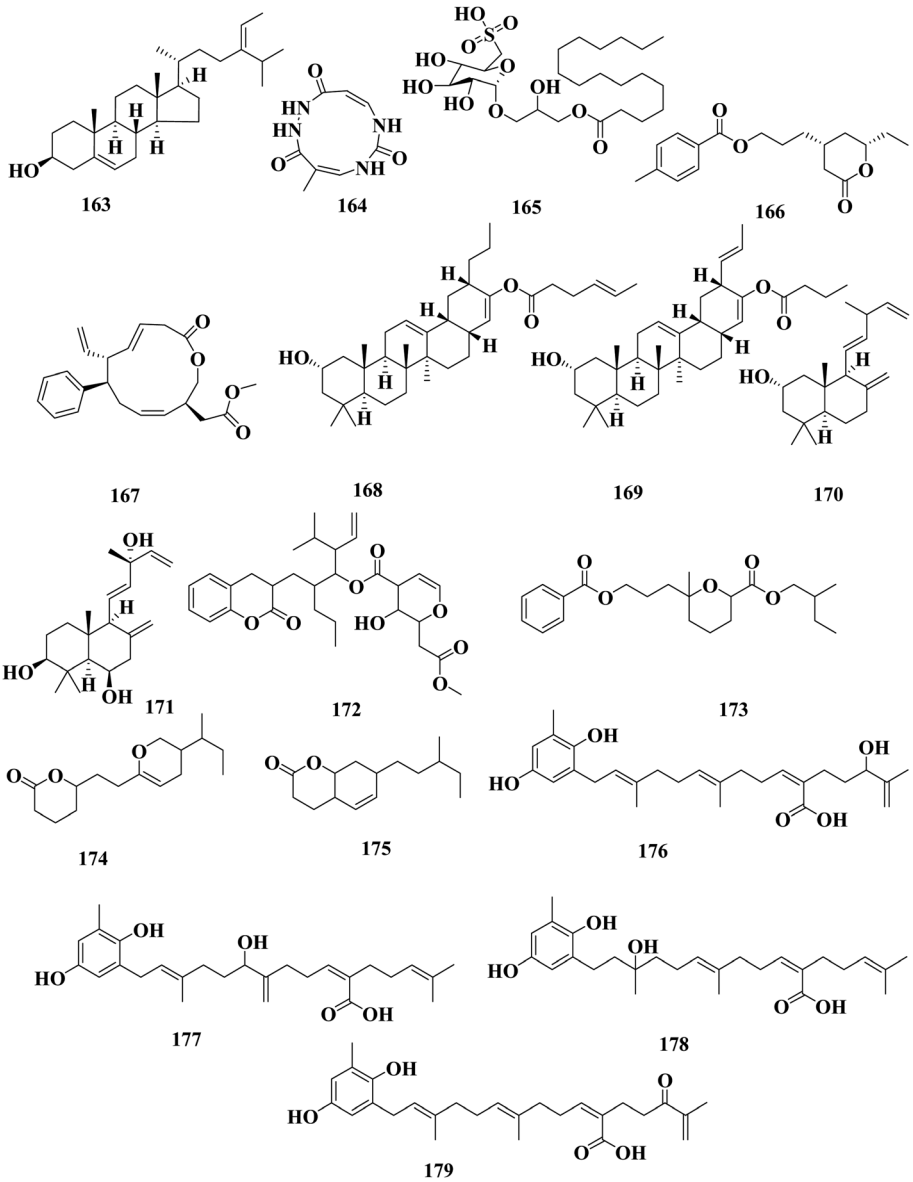

Fig. 10 Chemical structures of compounds **163–179**.

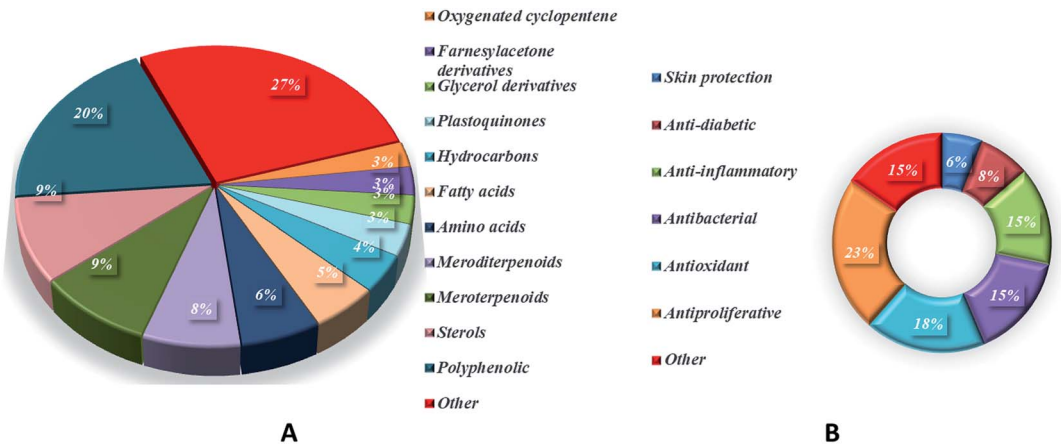

Fig. 11 Secondary metabolites (A) and their reported bioactivity (B) produced by *Sargassum* species.

propyl)-3′,4′-dihydro-2*H*-pyran-6′-yl]ethyl}-tetrahydro-2*H*-pyran-2-one **174** and 7-(7*c*-methylpentyl)-3,4,6,7,8,8*a*-hexahydro-2*H*-chromen-2-one **175** are hitherto undescribed O-heterocyclic derivatives with use natural antioxidant and antihypertensive functional food supplements and are also utilized as therapeutic leads in antihypertensive management as angiotensin-converting enzyme inhibitors (Fig. 10).[118]

55. *Sargassum yezoense*

Meroterphenol A **176**, meroterphenol B **177**, meroterphenol C **178**, and meroterphenol D **179**, plastoquinones, were detected in *S. yezoense*, with the structures of these compounds characterized by a 6-methyl-1,4-benzohydroquinone moiety with an oxygenated diterpenoic acid chain. Compounds **176–179** showed potent activation effects on the peroxisome proliferator-activated receptor gamma (PPARγ) (Fig. 10).[119]

56. Conclusion

Sargassum is an important seaweed that is widely and excessively distributed in tropical and subtropical regions and has been reported to contain 537 species, with 358 of them accepted taxonomically. *Sargassum* species are used in many folk applications in human nutrition and are considered a rich source of vitamins, carotenoids, proteins, and minerals. Significant progress has been detected in the publication rates of studies mentioning the genus *Sargassum* over the past five years (Fig. 11), with many bioactive compounds reported with diverse chemical structures, from oxygenated cyclopentene, farnesylacetone, glycerol derivatives, plastoquinones, hydrocarbons, fatty acids, amino acids, to meroditerpenoids, meroterpenoids, sterols, polyphenolic, and sulfated polysaccharides (Fig. 2–10). According to the reported data concerning the phytochemical metabolites identified in the different *Sargassum* spp., the sulfated polysaccharides and polyphenolic compounds represent 27% and 20% of the major isolates, followed by meroterpenoids, sterols 9%, meroditerpenoids 8%, and amino acids 6%, reflecting their history as a nutrient in folk use (Fig. 11). These isolated compounds and/or extracts exhibit diverse biological activities; such as skin protection for the polysaccharide rich extract of *S. vachellianum*, and *S. fusiforme*, whereas the polysaccharide hardly absorbs UVA, UVB rays, and has shown considerable inhibition on tyrosinase (51.21%), as well as better moisture absorption (52.1%) and retention (63.24%) abilities. Also, *Sargassum* spp. contains mainly sulfated polysaccharides, and polyphenolic compounds (Fig. 11), reflecting major reports of their analgesic, anti-inflammatory 15%, antioxidant 18%, neuroprotective, anti-microbial 15%, anti-tumor 23% activities. The polysaccharide extracted from *S. asperifolium*, *S. hemiphyllum*, and *S. latifolium*, with *S. fulvellum*, *S. macrocarpum*, *S. horneri*, *S. patens*, *S. sagamianum*, and *S. serratifolium* possess anti-inflammatory activity, through a significant inhibition of nitric oxide generation, and LPS-induced TNF-α, IL-12 p40, IL-6, causing a strong inhibitory effect against NF-κB activation. While isonahocol E3 **128**, detected in *S. siliquastrum*, has functional antagonistic activities against ET-1 induced inflammation. Moreover, *S. angustifolium*, *S. boveanum*, and fucoidan *S. polycystum* extracts have been reported to have a cytotoxic effect against HeLa (cervical cancer) and MCF-7 (breast cancer) cells, where the cell survival is inversely proportional to the increase in the concentration of the extracts. Polysaccharides extracted from *S. latifolium* showed a selective cytotoxicity against lymphoblastic leukemia. 28*S*-Epoxy-24-ethylcholesterol **26** showed cytotoxic activity against MCF-7, HCT-8, 1A9, HOS, and PC-3 with IC_{50} values of 4.0, 8.8, 10.0, 10.0, and 7.2 μg mL^{-1}, respectively. Sargachromanols A **109**, B **110**, and K **119** had strong cytotoxicity against AGS, HT-29, HT-1080, and MCF-7 cell lines, with IC_{50} values of 0.7, 6.1, 0.7, and 28.1 μg mL; 0.5, 1.0, 3.3, and 23.6 μg mL^{-1}, and 5.7, 0.8, 1.8, and 10.3 μg mL^{-1}, respectively. 28ξ-Dihydroxy-24-ethylcholesta-5,23*Z*-dien **21**, and 24ξ-hydroperoxy-24-vinylcholesterol **24** were reported to have cytotoxic activities against HL-60, with IC_{50} values of 7.8 and 8.5 μg mL^{-1}, respectively. While, fucosterol **5** and 24-ethylcholesta-4,24(28)-dien-3,6-dione **23** showed potent cytotoxic activities against P-388, with IC_{50} values of 0.7 and 0.8 μg mL^{-1}, respectively. Sargachromanol R **126** had potent cytotoxic activity against AGS, HT-29, and HT-1080 cell lines, with IC_{50} values of 6.5, 3.4, and 13.9 μg mL^{-1}, respectively, compared with paclitaxel and

doxorubicin. Also, fucoidan extracted from *S. glaucescens*, *S. siliquosum*, *S. swartzii*, *S. tenerrimum*, and *S. pallidum* exhibited antioxidant activities in a dose-dependent manner against DPPH. A hot-water extract of *S. hemiphyllum* collected from the coast of Penghu County (Taiwan) had antioxidant activity and an immune-stimulating one. The antioxidant activity was showed to be increased related to a concentration <3.5 mg mL^{-1}. Heteropolysaccharides extracted from *S. integerrimum* were shown to have neuroprotective and antioxidant activities. Sargachromanol A–P **109–124**, isolated from *S. siliquastrum*, exhibited significant antioxidant activity in the DPPH assay. Sargachrominol **55**, sargaquinoic acid **57**, sargahydroquinoic acid **94**, and sargathunbergol A **143** were detected in *S. thunbergii*, and showed antioxidant activities (EC_{50} values of 32, 27, 20, and 38 μg mL^{-1} respectively), compared to BHT (EC_{50} = 42 μg mL^{-1}) and α-tocopherol (EC_{50} = 23 μg mL^{-1}). Also, thunbergol A **144**, and thunbergol B **145**, isolated from *S. thunbergii*, were showed to scavenge DPPH radicals, with EC_{50} values of 30 and 31 μg mL^{-1}, respectively. Additionally, an extract of *S. fulvellum* (SFEE) and grasshopper ketone **32** was shown to have an inhibitory effect on atopic dermatitis (AD)-like skin lesions in BALB/c mice by regulating immune mediators and cells and may be a potentially effective alternative therapy for AD. The sulfated polysaccharides from a hot-water crude extract of *S. kjellmanianum* showed an immune-regulatory effect, through the enhanced immune function of immunocytes and increased the proliferation rate of spleen lymphocytes and peritoneal macrophages up to 53.56% and 51.41%. *Sargassum* spp., isolated compounds and/or extracts, also exhibited anti-diabetic, fibrinolytic, anti-coagulant, hepatoprotective, and anti-viral activities. Despite the wide diversity in the reported biological activates for *Sargassum* spp., only 54/537 species, representing about 10.05% from the species accepted taxonomically, were detected as having chemically and pharmacologically relevant activities. Consequently, further studies on the remaining species, their constituents, and biological activities are needed to exploit their maximum therapeutic potential in the field of medicinal and pharmaceutical sciences for novel and fruitful applications.

In 2007, the genus *Sargassum* extracts were the focus of a patent as a cosmetic product (KR1020090064079A) for their activities in lowering photo-induced cytotoxicity, whitening effect, inhibiting MMP-1 biosynthesis in human fibroblasts, and promoting the synthesis of biosynthesis type 1 procollagen, thereby improving skin elasticity and fine wrinkles, and effectively inhibiting the photo-aging phenomenon promoted by ultraviolet rays, *etc.*[120] Specially *Sargassum horneri* (KR1020120065631A), which has a deep relation to the photo-aging inhibitory effect on skin cells using the chromenes compound derived from it, increased the expression of collagen synthesis markers, such as procollagen and type I collagen in UV-A treated fibroblasts, and also enhanced elastin by modulating elastase activity, and thus could be used as a material and cosmetic for improving skin wrinkles and preventing wrinkles by UV.[121] Also, *Sargassum natans* was part of a patent for removing gold ions from aqueous solution or suspension using a biomass-derived from it, and this process can be utilized to remove gold from industrial or natural waters.[122]

Conflicts of interest

The authors declare there were no conflicts of interest.

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