Hindawi
Adsorption Science & Technology
Volume 2022, Article ID 9104835, 13 pages
https://doi.org/10.1155/2022/9104835

Review Article

Bioactive Potential of Brown Algae

R. R. Remya,[1] **Antony V. Samrot**,[2] **S. Suresh Kumar**,[1] **V. Mohanavel**,[1] **Alagar Karthick**,[3,4] **V. Kumar Chinnaiyan**,[3] **Dhamodharan Umapathy**,[5] **and M. Muhibbullah**[6]

[1]*Centre for Materials Engineering and Regenerative Medicine, Bharath Institute of Higher Education and Research, Selaiyur, Tamil Nadu 600 073, India*
[2]*School of Bioscience, Faculty of Medicine, Bioscience and Nursing, MAHSA University, Jalan SP2, Bandar Saujana Putra, 42610, Jenjarom, Selangor, Malaysia*
[3]*Renewable Energy Lab, Department of Electrical and Electronics Engineering, KPR Institute of Engineering and Technology, Coimbatore, 641407 Tamil Nadu, India*
[4]*Departamento de Quimica Organica, Universidad de Cordoba, EdificioMarie Curie (C-3), Ctra Nnal IV-A, Km 396, E14014 Cordoba, Spain*
[5]*Department of Medical Biotechnology, Karpaga Vinayaga Institute of Medical Sciences Research Centre, Tamil Nadu 603 308, India*
[6]*Department of Electrical and Electronic Engineering, Bangladesh University, Dhaka 1207, Bangladesh*

Correspondence should be addressed to Antony V. Samrot; antonysamrot@gmail.com

Received 12 October 2021; Revised 4 December 2021; Accepted 24 March 2022; Published 6 May 2022

Academic Editor: Amr Nassar

Marine-derived natural products are rich source of secondary metabolites with huge potentials including novel therapeutic agents. Marine algae are considered to be a good source of secondary metabolites with versatile bioactivities. During the last few decades, researches related to natural products obtained from brown algae have remarkably escalated as they contain active compounds with varied biologically activities like antimicrobial, anticancer, antioxidant, anti-inflammatory, antidiabetic, and antiparasitic properties. The main bioactive components such as phlorotannin, fucoxanthin, alginic acid, fucoidan, and laminarin have been briefly discussed here, together with their composition and biological activities. In this review, the biological function of extracts and the metabolites of brown algae as well as their pharmacological impacts with the description of the possible mechanism of their action are described and discussed. Also, this study is expected to examine the multifunctional properties of brown algae that facilitate natural algal products, including the ability to integrate these functional properties in a variety of applications.

1. Introduction

The oceans are a valuable source of biologically active compounds, where macroalgae and microalgae are the most prolific producers that could be exploited potentially for their high medicinal perspective [1, 2]. There are mainly two types of algae: microalgae found in benthic, coastal, and throughout the sea and macroalgae or seaweeds seen in the coastal region. Macroalgae are eukaryotic organisms that live in saltwater or freshwater and have been discovered as a possible resource of fundamental bioactive molecules. Unlike most terrestrial plants, these macroalgae do not have roots, leaves, and vascular systems and are nurtured through the osmosis process. Based on pigmentation and shape, the algae are grouped as Chlorophyta (green algae), Phaeophyta (brown algae), and Rhodophyta (red algae) [3]. For the past few decades, using electron microscopy pictures and molecular biology analyses, there has been a thoughtful influence on the classification [4]. The presence of chlorophyll pigment renders green color to Chlorophyta, where the same

pigment is present in almost all the higher plants. In Phaeophyta, the brown color is due to the presence of fucoxanthin pigment, and the presence of phycocyanin and phycoerythrin pigments in Rhodophyta makes them look red in color [5].

More than 150,000 macroalgae or seaweed species are originated from the world's seas and tropical waters. On the world's coastlines, about 8000 marine seaweeds have been reported, and some are found up to 270 m deep in the sea. Around 2000 types of brown, 1200 types of green, and 6000 red macroalgae arose globally with an annual production estimating to be 6,756,521 million tons of biomass [6]. The west-central, southwest, and northwest Atlantic and the southwest and central-east Pacific are the primary reservoirs of algae. Due to the long coastline, India has extensive marine reserves along many estuaries and accessible coastlines [7]. Along the southern Tamil Nadu coast between Kanyakumari and Rameswaram, which include21 islands in the Gulf of Mannar, numerous types of red, green, and brown algae with lush growth can be seen [8]. There are almost 814 species of seaweeds on the Indian coast that belong to 217 genera. Many species were recorded on Indian coastlines, including 216 Chlorophyta species, 191 groups of Phaeophyta species, 217 Rhodophyta species, and 3 groups of Xanthophyta species. Among these, approximately 202 species were obtained in Gujarat [9]. More than 1700 species of brown algae have been noticed worldwide, and this group includes some widespread genera. Brown algae are found in 691, 713 locations worldwide. In India, 265 genera and 2040 species of Phaeophyta are reported, where 95% of these groups live in temperate to cold waters [10].

Brown algae are a diverse class of algae renowned for their color, ranging from olive green to light golden brown. They range from small filamentous to large groups of complex seaweeds [11]. This is because their chromatophores contain the golden brown xanthophyll pigment fucoxanthin; because of the large amounts of fucoxanthin and carotenoid covering the residual pigments chlorophyll c and a and other xanthophylls, it looks brownish. The size of brown algae varies in small strings to the most significant marine algae, and the majority of brown algae is found in the intertidal zone [12]. Recently, numerous biologically active secondary metabolites were separated from different oceanic reserves, like marine microbes, phytoplankton, zooplankton, tunicates, sponges, seaweeds, and macroalgae red, green, and brown algae [13]. The study of secondary metabolites has concentrated much on macroalgae rather than phytoplanktons as marine algae produces extensive diversity of excellent natural compounds. Although these molecules contribute minimally to the organism's total biomass, the involvement of these compounds in existence might occasionally be similar to metabolites generated from the primary metabolism. These metabolites exhibit good antimicrobial, antioxidant, anti-inflammatory, antidiabetic, and anticancer properties [14]. Having known about the brown algae, this review concentrates on the characteristics of brown algae and essential secondary metabolites detected in the brown algae, with particular attention on active metabolites with potential pharmaceutical and medicinal applications.

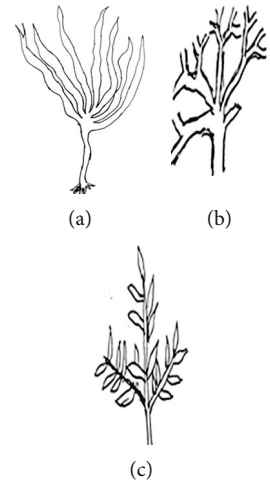

Figure 1: Characteristics of some brown algae (a) *Laminaria*, (b) *Dictyota*, and (c) *Sargassum*.

2. Characteristics of Brown Algae

Most of this group is either unicellular or multicellular. The size may vary from microscopic filaments with branches to macroscopic thalli [15]. A thallus contains stipes, blades, or frond and also a holdfast. As seen in roots of higher plants, the holdfast attaches thallus to the substratum. The stipe is comparable to the stems of higher plants, and fronds are analogous to leaves. The stipe and fronds organization are one of the major morphological characters for identifying several species of brown algae. Morphological changes of the algae are possible based on specific environmental conditions [16, 17]. Some of the familiar brown algae are (1) *Laminaria*, which has a large-sized sporophyte body, grows up to 1-3 m and is attached to bedrock with the help of holdfast; (2) *Dictyota* is a dichotomously branched sporophytic thallus, and the sporangia produce four haploid spores (Figure 1); (3) *Sargassum* is a free-floating or attached form, where the attached form has three parts, holdfast, main axis, and laterals (Figure 1); (4) *Ectocarpus* is a filamentous alga fix to solid substratum using its prostate portion and rhizoid; and (5) *Fucus* is a leathery flat branched brown alga where the branches have conceptacles. Some of these species' cling to the rocks or other supporting substances, whereas others drift on the surface of the water, forming single-celled or pluricellular colonies, while others cling to the seabed through root-like structures (holdfasts). The significant pigments in brown algae consist of chlorophyll a, c_1, c_2, β-carotene, lutein, fucoxanthin, dioanthin, and violaxanthin. Also, some storage food includes laminarin, mannitol, and some oils, and the brown algae cell walls are made up of cellulose and alginic acid [18].

2.1. Composition of Brown Algae. Brown macroalgae are abundant in minerals ranging from 14 to 35% of dry matter. They have relatively lower total protein levels (8–13%) for *Laminaria* and *Saccharina*, respectively, whereas it is about 6–11% for *Sargassum*, 7–13% for *Macrocystis pyrifera* (*M. pyrifera*), and 5–12% for *Ascophyllum nodosum* (*A.*

nodosum). Black (1950a and b) discovered significant variations in chemical composition depending on the year's season, with crude protein ranging from 4–8% in autumn to 12–14% dry matter in spring. Cell walls are made up of alginic acid and cellulose, a heteropolysaccharide with long, abundant chains (20–27%, 20–45%, and 15–30% for *M. pyrifera*, *Laminaria digitata* (*L. digital*), and *A. nodosum*, respectively) [19, 20]. Fucoidans are made up of polysaccharide units with varying amounts of sulfation, and they make up the cell walls of many brown macroalgae, especially Laminariales and Fucales [21]. Distinct from the other seaweeds in which the storage carbohydrate is starch, brown seaweeds store carbohydrates in the form of laminarin, a glucose polysaccharide [22]. Sodium (2.2% in *L. digitata* and 4% in *A. nodosum*), potassium (3.8% and 3% in *L. digitata* and *A. nodosum*, respectively), and iodine (1.1% and 0.1% in *L. digitata* and *A. nodosum*, respectively) are high in brown seaweeds. Certainly, *Laminaria* can absorb iodine at a rate more than thirty thousand times the rate of iodine concentration in the ocean [23]. The composition varies depending on various features; for example, *M. pyrifera* cultivated in the summer along the Mexican shore contains more amino acids and minerals than *M. pyrifera* harvested in the winter [24]. The phenolic compounds (phlorotannins) contained in *A. nodosum* are not soluble in the animals' digestive tract. Many types of seaweed have high amount of free glutamic acid, which is responsible for the "*umami*" flavor found in Japanese dishes and is used as a flavor improver in food. *Sargassum* is low in protein but high in carbohydrates and is an easily accessible mineral. They are also abundant in vitamins and β-carotene and are free of antinutrients [25].

3. Major Bioactive Molecules of Brown Algae

3.1. Phlorotannins. Polyphenols are also known as phytochemicals because they are present in plants. Polyphenols are a wide and heterogeneous group of naturally emerging molecules with phenolic characteristics in aquatic and terrestrial environments as secondary metabolites. Due to their broad range of biological applications, these naturally occurring polyphenols have been identified as possible substitutes for a range of industrial formulations comprising nutraceuticals, foods supplements, cosmeceuticals, and pharmaceuticals [26]. Tannins are polyphenolic compounds that are naturally occurring in plants. They are found in both marine and terrestrial plants. Unlike tannins found in the terrestrial environment, only marine brown algae have been found to contain phlorotannins. They have a simpler structure than terrestrial tannins and are made completely from phloroglucinol polymerization. Many studies over the years have been conducted on the functions and roles of phlorotannins. Moreover, various phlorotannin derivatives were extracted from a range of brown algae: *Ecklonia kurome*, *Ecklonia cava*, *Ecklonia bicyclis*, and *Ecklonia radiate* [27]. Phlorotannins are reported to have sleep-promoting [28], antibacterial [29], antioxidant [30, 31], and algicidal effects [32]. It has been found to have inhibitory action against HIV-1 reverse transcriptase [33].

3.2. Fucoxanthin. Fucoxanthin is one of the most prevalent xanthophylls variants in brown algae, a natural pigment that belongs to the carotenoid family. Along with carotene, it is present in edible brown seaweeds like *Hyalogonium fusiforme*, *Undaria pinnatifida*, *Laminaria japonica*, and *Sargassum fulvellum*. It is one of the most common carotenoids. Externally, in all algal species, the presence of fucoxanthin can be easily accessed by observing their color [34]. As the name implies, it is used as an additive stain in the chloroplasts of brown seaweeds and many other heterokonts, providing them an olive green or brown color. Much research is currently being reported about extracting fucoxanthin from certain brown algal species, which would enable the substance to be used in a variety of functional applications. According to some nutritional and metabolic studies conducted at Hokkaido University on mice and rats, fucoxanthin stimulates fat burning within the white adipose tissue by increasing the thermogenin expression. Furthermore, fucoxanthin has been discovered to offer a broad spectrum of bioapplications, like antioxidant and anti-inflammatory activities [35].

3.3. Alginic Acid and Fucoidan. Polysaccharides based on bioactive natural products have attracted a great deal of interest in pharmacology over the past few years. Seaweeds are rich in soluble polysaccharides and can be used as roughage. Brown algae, in particular, are found to develop efficient polysaccharides, including fucoidans and alginates. Antitumoral, anticoagulant, antiviral, and anti-inflammatory activities are among the different biological properties of alginic acid and fucans derivatives [36, 37]. Alginic acid (algin or alginate) is a gelling polysaccharide of -L-Gulu-ironic, and 1, 4-linked β-D-mannuronic acid arranged in an irregular order through the chain. This hydrophilic colloidal polysaccharide is commonly found in brown algae's intracellular substances and cell walls [38, 39]. It is also one of the most significant structural polysaccharides of brown algae. Fucoidan and alginic acid make up most of the acid polysaccharides in the cell walls of brown algae. Brown algae alginate is commonly used in a variety of pharmaceutical formulations. It is also a beneficial thickening agent for jellies, beverages, and ice cream in the food industry. It is also used for cosmetic production as a water-binding and thickening agent since alginate absorbs water easily, making it a useful additive in cosmetic formulations [40].

Fucoidan is a polysaccharide that comprises significant amounts of sulfate ester and L-fucose groups and is present in many brown algae species. Brown algae have this sulfated polysaccharide in their cell wall [41]. Sulfated polysaccharides, also known as fucoidans in marine brown algae, have potential antioxidant and anti-inflammatory activity. Fucoidans' high degree of sulfation appears to determine their biological functions, but these functions are based on their molecular weight and fine structure [42]. Fucoidan also has the potential to improve the cosmetic properties of the skin. Hence, it is a versatile ingredient with applications in essential cosmetic formulations. Polygalactosides bind with an external layer that protects the skin, forming a protective moisturizing complex by the ion-ion interaction, whereas

Table 1: List of different species of brown algae and their compounds.

S. no	Brown algae	Compounds	References
1.	*Ascophyllum nodosum*	Phlorotannin, flavonoids	[48]
2.	*Fucus vesiculosus*	Phlorotannins	[48]
3.	*Bifurcaria bifurcata*	Phlorotannin, alginate	[48, 49]
4.	*Caulocystis cephalornithos*	6-Undecylsalicylic acid and 6-tridecylsalicylic acid	[50]
5.	*Sargassum ilicifolium*	10,2-Trinorsqualenol, glycolipid 1-O-palmitoyl-2-O-stearidonoyl-3-O-b-D-galactopyranosylglycerol	[51]
6.	*Turbinaria ornata*	Apo-90-fucoxanthinone, 24-ketocholesterol, (22E)-3b-hydroxycholesta-5,22-dien-24-one, saringosterol	[51]
7.	*Ishige okamurae*	Diphlorethohydroxycarmalol	[52]
8.	*Dictyota ciliolata*	Rutein, quercetin, palmitic acid, diterpines	[53, 54]
9.	*Ecklonia cava*	8,8′-bieckol	[55]
10.	*Sargassum polycystum*	Fucoidan	[56]
11.	*Ecklonia maxima*	Eckol and phloroglucinol	[57]
12.	*Dictyota pfaffii*	Diterpenes	[58]
13.	*Sargassum thunbergii*	Indole derivatives	[59]
14.	*Cystoseira tamariscifolia*	Isololiolide	[60]
15.	*Stochospermum marginatum*	Spatane diterpenoids	[61]

fucose polymers are absorbent and act like moisturizing substances. *Fucus* has a high content of essential and nonessential amino acids such as lysine, proline, and glycine, which are present in the skin's elastic fibers. From this perspective, the sulfated polysaccharide fucoidan of brown algae could help maintain skin elasticity by enhancing hydration and thus strengthening the flexible nature of the skin [43, 44].

3.4. Laminarin/Laminarans. Brown seaweed contains essential storage polysaccharide called laminaran or laminarin (e.g., *Laminariaor saccharine*), accounting for up to 32–35% (d.w.) of the total storage polysaccharides. Laminarin are glucans that have polysaccharides that are linear, made up of β-glucose in a 3 : 1 ratio with random β-(1Ñ6) intrachain branching. The amount of polymerization differs from 20 to 50 units. The polymer chains have been classified into two types: G chains with a glucose residue and M chains with a D-mannitol residue. Depending on the degree of polymerization (usually 25), the molecular weight of laminarians is about 5 kDa. It has been reported that laminarin possesses a lot of biological activities, including antitumor, antiapoptotic, anti-inflammatory, anticoagulant, and antioxidant potentials. Remya et al. reported the extraction of laminarin utilizing brown seaweed *Turbinaria ornata* which acts as a potential bioactive component [45].

3.5. Other Bioactive Molecules of Brown Algae. Brown seaweeds are primarily utilized to cure stomach ailments, asthma, headache, hypothyroidism, cellulite, cough, and fatigue. Besides helping with skincare, brown seaweeds also facilitate weight loss. The prospective antioxidant metabolites in brown seaweeds were recognized as almost polyphenols and pigments [46]. They are present in many plants and seaweeds and are well known for their antioxidant activity through reactive oxygen species (ROS) scavenging and the lipid peroxidation inhibition activity. Brown seaweeds are recognized to have enormous of polysaccharides in their cell wall, the most prominent of which are the sulfated polysaccharide fucoidan, which is absent in terrestrial plants. Fucoidan contains a significant amount of sulfated ester and L-fucose groups and has an extensive assortment of pharmacological and biomedicinal properties; there have been more than a few investigations on the diverse bioactivities, structural parameters, molecular weights, and physiological features of seaweed polysaccharides [47]. The list of various species of brown seaweeds and their isolated compounds is mentioned in Table 1.

4. Mechanism of Bioactivity of Brown Algae

4.1. Antimicrobial Activity. The method of extraction and conditioning may affect the yield of bioactive compounds. The drying stage is crucial because high temperatures can cause the deficit of unsteady antimicrobials associated with fresh algae (terpenoid, hydrogen peroxide, bromo-ether compounds, and volatile fatty acids) [62, 63]. Improved cell membrane permeability was observed and discovered in high-temperature treated dried seaweed extracts which showed broader inhibition zones against *Listeria innocua*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, and *Staphylococcus aureus.* It was found that dried *Chondrus crispus* crude ethanolic extracts had a lower MIC than extracts from fresh seaweed against the growth of phytoplankton and bacterial species [64]. Similarly, during drying and hydrothermal processing, a decline was discovered in the antioxidants and the total phenolic content against *H. elongate.* The phytochemical content was increased, and enhanced inhibitory potential was observed by drying

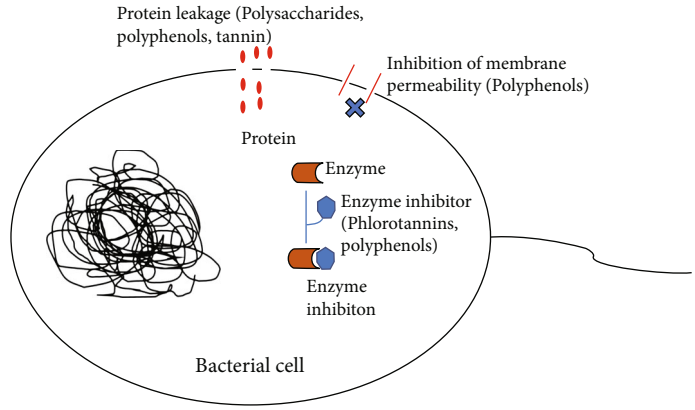

Figure 2: Antibacterial activity of compounds of brown algae.

followed by boiling. Storage and cell wall polysaccharides attained in red, brown, and green algae, such as laminarin, alginates, carrageenans, fucans, and ulvans, can activate plant resistance pathogen control mechanisms [65]. Oligosaccharides produced by depolymerization of algal polysaccharides protect plants from bacterial, fungal, and viral infections, resulting in the accumulation of antimicrobial compounds and proteins. Cytotoxicity study against the murine cell line of macrophages RAW264.7 as well as acute toxicity test on mice indicated that the moderate doses of radioactive *E. cava* derivatives can be used safely by humans [66, 67]. Evidence of significant antimicrobial activity was observed in various algal species. In one study, the effect of *Spatoglossum asperum* brown algal solvent extracts on dermatophytes and nondermatophytes was assessed. The maximum potential of chloroform extract against the nondermatophytic fungus *Aspergillus flavus* was determined. The methanolic extract showed significant antifungal activity against the dermatophyte fungi *Candida albicans* and *Candida tropicalis* in relation to other solvent extracts [68]. In another study, the brown algal extracts from *Laminaria digitata* and *Undaria pinnatifida* showed the strongest antifungal activity against *Botrytis cinerea* on strawberries and *Monilinia laxa* on peaches, followed by *Penicillium digitatum* on lemons [69]. The different solvent extracts from algae were tested against some of the pathogenic human fungi *Candida albicans*, *Candida parapsilosis*, *Fusarium* sp., *Aspergillus flavus*, and *Aspergillus fumigatus*. Hexane, chloroform, and ethanolic extracts were found to be highly inhibitory against *Candida albicans* and *Candida parapsilosis* [70]. Some compounds isolated from brown seaweeds also possess certain antimicrobial activities. The phlorotannin isolated from brown seaweeds has been reported to have antifungal activity against dermal and plant fungi [71]. In the *Chnoospora bicanaliculata*, *Sargassum wightii*, *Padina tetrastromatica*, and *Stocheospermum marginatum* extracts derived from India's southwestern shore provide credible information that brown seaweeds sustain successful antimicrobial activity [68–70]. The mechanism behind these molecules may be because they directly interact with enzyme and inhibit the action of enzymes or induce membrane permeability loss and protein leakage, where these have been exhibited by polysaccharides, polyphenols, and phlorotannins (Figure 2) [71, 72].

4.2. Anticancer Activity. The efficient approach for killing cancer cells is to provoke apoptosis over tumor cells. Tumor necrosis factor- (TNF-) related apoptosis-inducing ligand (TRAIL) is an integral membrane protein which can bind to membrane-bound death receptors [73]. TRAIL and its receptor binds together and transmit an apoptotic signal across their intracellular mortality zones. As a result of this, cancer cells undergoes apoptosis. On gastric cell line (AGS) of humans, the anticancer activity of ethanolic extract of *Hyalogonium fusiforme* (*H. fusiforme*) was investigated, and the findings showed that the extract (0 to 25 μg/mL) could induce apoptosis in tumor cells by upregulating the expression of TNF-α. In a recent research, it was discovered that the extracts were taken using ethyl alcohol of *H. fusiforme* towards the protein expression in human hepatoma cancer cells Hep3B and inhibits matrix metalloproteinase (MMP) activity and was also found to control metastasis-related and tumor invasive genes (TSP-1, claudins, IGF-1R, and E-cadherin) as well as activity-related genes of MMP (TIMP-1, TIMP-2, MMP-1, and MMP-2), which induce apoptosis in cancer cells [74]. 5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone is found in the extracts of ethanol (80%) of *H. fusiforme* which also possesses potential anticancer activity in human's AGS and DR4 cancer cell lines [73, 75] where the compound isolated increased the apoptosis mediators connected to the death receptor like TRADD, Fas, FADD, and Fas L that were in a dose-dependent manner (Figure 3). Son et al. [76] claimed that extracts using ethanol from *H. fusiforme* may minimize the development of aberrant crypt foci regulated by azoxymethane in male rats. Preneoplastic damage to the colon, which result in colorectal cancers, has alluded as aberrant crypt foci [76]. Ethanol extract of *H. fusiforme*can also provoke apoptosis of human leukemia U937 cell lines. The outcomes of the findings stated that the apoptotic cell death in U937 cells was caused by Bcl-2 protein inhibition and downregulation in the form of IAP family members like XIAP, IAP1, and IAP2 [77, 78]. Remya et al. [79] studied the phytochemical composition and profiling of *Turbinaria ornata* and its antiproliferous effect against human retinoblastoma Y79 cells [79]. When compared to the existing chemotherapeutic agents, chemopreventive agents extracted from natural resources have gotten a lot of attention because of their potential to suppress cancer cell development with less or no side effects.

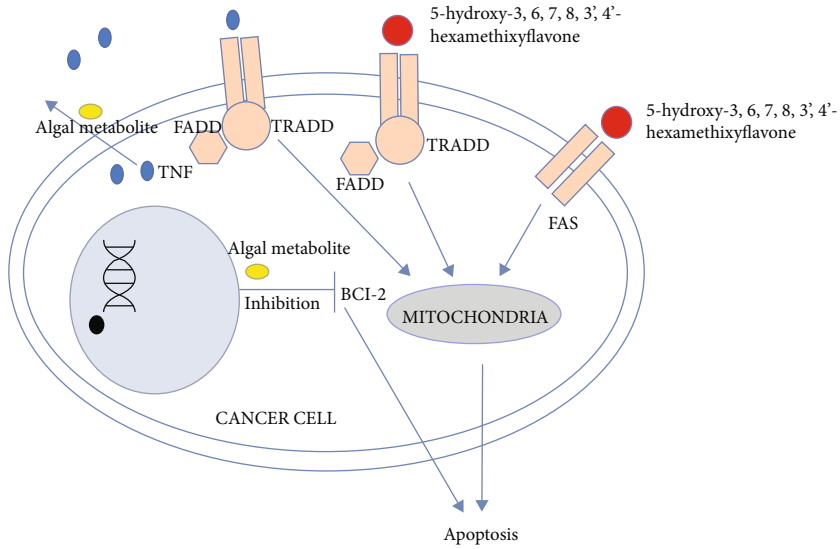

Figure 3: Anticancer activity mechanism algal metabolites.

Cytotoxic effect have been discovered in certain solvent extracts such as ethyl acetate, chloroform, and methanol from different brown algae species such as *Colpomenia sinuosa*, *Cystoseira myrica*, and *Sargassum swartzii*, against NIH 3T3, HT-29, T47D, Caco-2, and MDA-MB468 cells [79–81]. On seven cancer cell lines, *Dictyota dichotoma* (*D. dichotoma*) extracts had strong dose-dependent cytotoxicity but were more selective on PC-3 and MCF-7. The fraction from chloroform extract of *D. dichotoma* had the greatest effect of cytotoxicity against CACO ($IC_{50}2.71 \pm 0.53\,\mu g$/mL), PC3 ($IC_{50}2.2 \pm 0.18$), and MCF-7 ($IC_{50}1.93 \pm 0.25$), respectively. Apart from the extracts, certain bioactive components isolated from numerous brown algae showed good cytotoxic potential against cancer cell lines [82]. By increasing the ROS production, the fucoidan isolated from *Sargassum cinereum* brown seaweed exhibits potential apoptotic and anticancer effect on Caco-2 cells. The anticancer potential of the extracted *Sargassum wightii* polysaccharides have been assessed on breast cancer cell lines MDA-MB-231 and MCF7, and the polysaccharides were detected to substantially decrease the development of cancer cells [83]. At IC_{50} values of 11.6 and 32.0 μg/mL, a few fractional compounds and three additional linear diterpenes isolated from *Bifurcaria bifurcate* mildly prevented the development of the MDA-MB-231 cells [84].

4.3. Antioxidant Activity. Crude extracts and compounds isolated from seaweeds have been used as defenders of health, in cosmetics, and food; and antioxidant activity have been studied. Brown algae have relatively higher levels and powerful antioxidants when compared with green and red algae [85]. Antioxidant property is based on its radical or oxygen scavenging ability; chelation of metal [86] and the free radical scavenging are vital in determining the antioxidant property [87]. Phenolic derivatives (phenolic -OH) have the ability to transfer a hydrogen atom to the free radicals and form a stable product; the longevity of maintaining the stability of the product determines the antioxidant properties of the constituent isolated [88, 89] (Figure 4).

Phenolic acids have a phenolic ring with carboxyl group [90]. Occurrence of phenolic acids, including gallic acid, catechin, caffeic acid, coumaric acid, quercetin, rutin, and kaempferol, are indicated to be present in brown algae, and the antioxidant property of these molecules have been reported [91]. The aromatic benzene ring structure of the aforementioned phenolics with -OH (hydroxyl) moieties play a crucial function in H-donation and free scavenging properties [90, 91]. Benzene ring with -CH = CH-COOH moiety has been reported to increase hydrogen donation and increase antioxidant property [92]. Phlorotannins, a hydrophilic marine algal metabolite of size from 125 to 600 kDa, which are abundant in brown algae, are classified as fuhalols (extra hydroxyl group at third ring), phlorethols (ether linkage), fucols (phenyl linkage), fucophloroethols (ether and phenyl group), and eckols (dibenzodioxin linkage) [92, 93]. These extra functional groups enhances its antioxidant property. The antioxidant potency of brown algae, namely, *Anthophycus longifolius*, *Sargassum plagiophyllum*, and *Sargassum myriocystum*, was assessed using various *in vitro* antioxidant studies. The ethyl acetate extract from *Anthophycus longifolius* showed extensively higher radical scavenging ability of hydroxyl radicals and have been shown to be effective in stabilizing 2,2-azino-bis-3-ethylbenzothiozoline-6-sulphonic acid (ABTS) and also 1,1-diphenyl-2-picryl-hydrazil (DPPH) radicals. There were no substantial differences observed in the scavenging properties of hydrogen peroxide and ferrous ion chelation properties of seaweed ethyl acetate extracts [94]. *Ascophyllum nodosum*, *Laminaria japonica*, *Lessonia trabeculate*, and *Lessonia nigrecens* have been examined for their antioxidant activities. Among all four species, *Ascophyllum nodosum* extracts have the strongest antioxidant activity [95]. In another study, ethanol and water binary solvent system were used to produce raw extracts of edible algae *Ascophyllum nodosum* (*A.*

Figure 4: Antioxidant activity mechanism of algal metabolites.

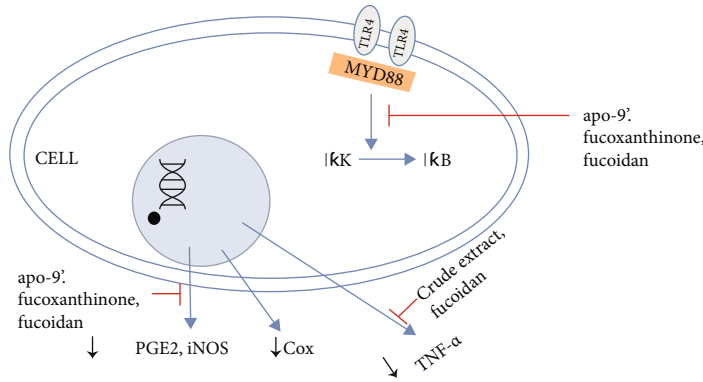

Figure 5: Anti-inflammatory activity mechanism of algal metabolites.

nodosum). The extract of *A. nodosum*was optimized using the Box–Behnken design and also the response surface methodology to achieve extracts with high antioxidant activity or high effectiveness. In the two optimal conditions, the antioxidant property was found to be at 74.05 ± 0.51 mL/g with respect to the yield at 53.80 ± 1.65 mg. This explains the ability of both models to predict with precision and improve antioxidant extraction using *A. nodosum* [96]. *Padina tetrastromatica* comprises a significant quantity of polyphenols that have antioxidant properties [97]. Sodium alginates that were obtained at various seasons from brown seaweed, *Cystoseira schiffneri*, had been checked for antioxidant activity using DPPH and Fe^{2+} chelating potential assays where antioxidant property varied considerably depending on the season [98].

4.4. Anti-Inflammatory Activity. Reactive oxygen species (ROS), at normal condition, involve in signaling pathways as a part of metabolism; mostly, ROS are produced by mitochondria during respiration [99]. When these are produced in higher level than normal, it degrades the biological macromolecules, including lipids, DNA, and proteins, which lead to abnormal cellular function including inflammation [100]. Inflammation-inducing cells mostly mast cells and eosinophils generate chemical signals leading to the release ROS, where it kindles signal transduction and induces nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β). This induction leads to higher inflammation and harms healthy cells which sometimes triggers cancer cells also [99, 100]. Decreasing the expression of these aforementioned genes or any signal transduction pathways or free radical scavenging reduces the inflammatory reaction. Apo-9′-fucoxanthinone, a norisoprenoid isolated from *Sargassum muticum*, is effective against nitric oxide (NO) and prostaglandin E2 (PGE2) synthesis in LPS-mediated inflammation against cell line RAW264.7 where it regulates the activation of NF-κB activation by suppressing IκB-α within macrophages (Figure 5). Ethanolic and DMSO extract of *Cystoseira amentacea* collected from the Ligurian Sea showed a strong anti-inflammatory effect against inflammatory cytokines [101]. The brown algae *Padina commersonii* fucoidan- (PCF-) based sulfated polysaccharide was examined for anti-inflammatory activities and was also tested against LPS-activated RAW 264.7 macrophages. The impact found that PCF is a promising component that inhibits LPS-induced inflammatory reactions by preventing transduction of LRT/MyD88/NF-κB signals [102]. Furthermore, the fucoidan extract of *Turbinaria decurrens* was tested for its anti-inflammatory properties. Fucoidan had an anti-inflammatory potential with upregulation of antioxidant levels through NF-κB, thus suppressing proinflammatory genes. [103].

The anti-inflammatory activity of brown seaweeds such as *Cystoseira crinita* (AQ-C cri), *Cystoseira sedoides* (AQ-C sed), and *Cystoseira compressa* (AQ-C com) was assessed *in vivo*, with carrageenan generated rat paw edema test. The extracts AQ-C cri, AQ-C sed, and AQ-C com displayed an important anti-inflammatory effect depending on the dose correlated to the reference drugs [104]. *Turbinaria conoides*, collected in the Gulf of Mannar, extracted with three substituted 2H pyranoids, which were showing activity against 5-lipoxygenase and cyclooxygenase-2, are found to be more effective than nonsteroidal drugs on the market [105]. In particular, phlorotannin fractions of *Cystoseira sedoides* (PHT-SED) collected on the Tunisian coast have been tested for pharmacological potential with other algae. A substantial anti-inflammatory potency of the fractions was performed using *in vivo* models at the 100 mg/kg dose against the reference drug [101].

4.5. Antidiabetic Activity. The antidiabetic potential of brown algae has has been studied extensively over the last few years due to the presence of several bioactive compounds. Enzymes such as α-amylase and α-glucosidase are

essential in carbohydrate hydrolysis and it releases glucose; inhibiting these enzymes reduces postprandial hyperglycaemia; and inhibitors of these enzymes could be an antidiabetic drug [106]. Other enzymes including aldose reductase, protein tyrosine phosphatase, and protein tyrosine phosphatase 1B do play a major in the formation of glucose, thus its action to be blocked to prevent postprandial hyperglycaemia [105–107]. Phlorotannin has been reported to suppress the activity of α-amylase and α-glucosidase [108, 109]. The methanolic extract and fucoxanthin fraction obtained from *Sargassum siliquosum* and *Sargassum polycystum* showed inhibitory action against angiotensin converting enzymes such asα-amylase, and as well as α-glucosidase [110]. Phlorotannin eckol of *Ecklonia maxima* was found to be an effective α-glucosidase inhibitor [111] where pholotannins compounds like phloroeckol and dieckol from *Eisenia bicyclis* were inhibiting 87% acidity of α-amylase. *Ascophyllum nodosum* was found to be effective against both the above-mentioned enzymes [112]. *Laminaria digitata's* methanol extract and *Undaria pinnatifida*'s acetone extract have shown to inhibit α-amylase with IC_{50} values at 0.74 ± 0.02 mg/mL and 0.81 ± 0.03 mg/mL, respectively. The 2,5-dihydroxybenzoic acid phenolic compound in both algae was an effective α-amylase inhibitor with IC_{50} value of 0.046 ± 0.004 mg/mL. The alginates and polysaccharides present in brown algae exhibit strong inhibitions against α-amylase with an IC_{50} range ranging from 0.075 ± 0.010 to 0.103 ± 0.017 mg/mL. In general, the above results demonstrated that crude extracts, phenolic compounds, and brown edible algae alginates are strong inhibitors of α-amylase [113]. In addition, the extraction of phenolics isolated from four brown algae such as *Ascophyllum nodosum*, *Laminaria japonica*, *Lessonia trabeculate*, and *Lessonia nigrecens* have been studied for activities inhibiting pancreatic lipase and tyrosinase. Among the four algae, *Lessonia trabeculate* extract demonstrated strong activity towards α-amylase, α-glucosidase, pancreatic lipase, and tyrosinase inhibition activities [95]. A brown alga *Padina tetrastromatica* was used to isolate polyphenols and to study their antidiabetic properties. Polyphenols showed a strong α-amylase effect at IC_{50} value $47.2 \pm 2.9\,\mu$g and α-glucosidase at 28.8 ± 2.3 μg of inhibitory activities [97].

There are some metabolites which are active diabetes-induced models. Fucoxanthin obtained using seaweed *Ishige okamurae* has been evaluated for oxidative stress due to high blood sugar against umbilical vein endothelial cells *in vitro* as well as in the zebrafish model *in vivo*. The two studies mentioned above has demonstrated that the isolated fucoxanthin is capable of providing protection against damage to organs and cells [114]. Antidiabetic effectiveness of oligosaccharides from brown algae named *Sargassum confusum* (SCO) has been evaluated *in vivo* with hamsters that are high in sucrose. Following the administration of SCO, the decreased levels of blood glucose levels were observed. The primary function of SCO in the antidiabetic effect was revealed by the 1/phosphatidylinositol 3-kinase and c-Jun N-terminal kinase routes of the insulin regulator receptor substrate. Thus, SCO has been used in people with obesity and diabetes for the regulation of intestinal microbiota [115]. Phlorotannins gained using *Cystoseira compressa*was checked for the antidiabetic effect. The results suggest that phlorotannins significantly reduced the activity of serum glucose, liver malondialdehyde, α-amylase, and glucosidase, and histopathological studies have shown that phlorotannins distinctly reduce and protect lesions in pancreatic β cells [116].

4.6. Antiparasitic Activity. Many terrestrial plants have been shown to have antiparasitic activity and clinically potent medicinl value, but the potential of the algae have been less explored. The *in vitro* activities of *Sargassum oligocystum* gathered across Bushehr coast in south-west Iran against *Leishmania* species were estimated to be highly significant [117]. The prophylactic effect of few algal extracts from the southern coast of England were studied against parasites in the blood stage and liver stage of *Plasmodium*. Based on numerous extracts, *Cystoseira tamariscifolia* (CT) and *Cystoseira baccata* (CB) possessed the utmost antimalarial action of IC_{50} ranging in between 3.3 and 3.8 μg/mL [108]. A further study found that diterpene called eleganolone was obtained using the French algaenamed *Bifurcaria bifurcate* inhibiting *Trypanosoma brucei* and *Plasmodium falciparum* [109]. Similarly, the bioactivity of dichloromethane/methanol extract (DME) of *Dictyota mertensii* on *Leishmania amazonensis*was also assessed. This indicated inhibition effect of IC_{50} at 71.60 μg/mL over growth of promastigote forms. DME showed toxic against the promastigote and amastigote forms that were revealed to be effective, indicating a potential agent in treatment of cutaneous leishmaniasis [118]. Brown macroalagae namely*Cladostephus spongiosum*, *Cystoseira sedoides*, *Dictyota spiralis*, *Padina pavonica*, and *Halopteris scoparia* were gathered in the coastal zone of Tabarka to investigate antiprotozoan activity against *A. castellanii*. All extracts showed parasitic inhibition with an IC_{50} of 3 ± 1.8 μg/mL for ethyl acetate and$134{,}6 \pm 0.7$ μg/mL for hexane extracts. This could lead to the conclusion that it could be used as the best antiamoebic source [119]. Fucosterol isolated with *Sargassum linearifolium* from south-eastern India was investigated for antiplasmodic effect against *Plasmodium falciparum* (*P. falciparum*). IC_{50} values were observed at 7.48 μg/mL and 12.81 μg/mL based on the antiplasmodic effect of fucosterol against *P. falciparum* and chloroquine, respectively [120]. Fucoidan which is an existing polysaccharide present in *Fucus vesiculosus* was identified to have increased immunomodulatory activities against *Schistosoma japonicum*. The above results suggest the emergence of a new therapeutic mechanism initiated by a chronic parasitic infection for hepatic diseases with a higher response [121].

5. Conclusion

Due to the rise in interest in natural products, especially those extracted from marine species, marine seaweeds have become the subject of intense research because of the proven capacity of brown algae to synthesize a vast array of secondary metabolites. The marine ecosystem, which includes a diversified spectrum of algal species, may be a better means

of exploring new therapeutics. Establishing modern and innovative brown algae cultivation methods to increase the variety of cultivable isolates and shorten the cultivation time might be fruitful in obtaining significant amounts of cells for greater efficiencies and improved target molecular production. The key breakthroughs in isolating, extracting, and characterizing new metabolites and their structure may assist in effectively evaluating their therapeutic potential and biological activities. Furthermore, macroalgae are expected as an essential raw material in the manufacturing of vitamins, amino acids, or other pharmaceuticals. Therefore, macroalgae cultivation can offer comprehensive insights into their biotechnological implications and practical uses, which may aid in the production of the compounds with therapeutic potential. The insight into the brown algae phytoconstituents shows that this vast community of marine algae is not only used for the production of food and fodder, but also as a huge source of secondary metabolites. The present review completely focused on the biologically active metabolites of brown seaweeds, which have far more functional characteristics than green and red seaweeds since Phaeophyta community is the key representative of fucoidans and polysaccharides that are accountable for their influential biological processes. It was observed that the varieties and concentrations of secondary metabolites altered by species are influenced by environmental conditions. Multiple mechanisms of action stimulate the production of biologically active secondary metabolites utilizing brown algae that precisely enhance the bioactivity and thus promote the development of drug production by pharmaceutical industries. As a result, efficient research on this population of brown seaweeds will aid in the development of novel drug molecules that can be used to treat numerous lethal human diseases.

Data Availability

The data used to support the findings of this study are included in the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' Contributions

R.R. Remya and Antony V. Samrot have contributed to the conceptualization; S. Suresh Kumar and V Mohanavel have contributed to the data curation; Alagar Karthick and V Kumar Chinnaiyan have contributed to the formal analysis; Dhamodharan Umapathy and M Muhibbullah have contributed to the funding acquisition; R.R. Remya and Antony V. Samrot, S. have contributed to the investigation; R.R. Remya and Antony V. Samrot, S. have contributed to the methodology; S. Suresh Kumar and V Mohanavel have contributed to the resources; R.R. Remya has contributed to the supervision; N R.R. Remya has conttributed to the validation; Alagar Karthick and V Kumar Chinnaiyan have contributed to the visualization; R.R. Remya has contributed to the writing-original draft; Dhamodharan Umapathy and M Muhibbullah have contributed to the writing-review and editing.

Acknowledgments

Alagar Karthick gratefully acknowledges the group FQM-383 from Universidad de Cordoba, Spain, for the provision of a honorary visiting research position in the group.

References

[1] A. V. Samrot and T. Thirunalasundari, "Effect of Oscillatoria willei–a marine cyanobacterium on hydrazine induced toxicity," *Malaysian Journal of Microbiology*, vol. 8, no. 4, pp. 236–241, 2012.

[2] R. E. Renitta, R. Narayanan, J. P. J. Cypriyana, and A. V. Samrot, "Antidiabetic potential of methanolic extracts of Sargassum wightii in streptozotocin induced diabetic mice," *Biocatalysis and Agricultural Biotechnology*, vol. 28, p. 101763, 2020.

[3] S. Gupta and N. Abu-Ghannam, "Bioactive potential and possible health effects of edible brown seaweeds," *Trends in Food Science and Technology*, vol. 22, no. 6, pp. 315–326, 2011.

[4] F. Rindi, A. Soler-Vila, and M. D. Guiry, "Taxonomy of marine macroalgae used as sources of bioactive compounds," in *Marine bioactive compounds*, pp. 1–53, Springer, 2012.

[5] R. S. Rasmussen and M. T. Morrissey, "Marine biotechnology for production of food ingredients," *Advances in Food and Nutrition Research*, vol. 52, pp. 237–292, 2007.

[6] A. Leandro, L. Pereira, and A. M. M. Gonçalves, "Diverse applications of marine macroalgae," *Marine Drugs*, vol. 18, no. 1, p. 17, 2020.

[7] M. M. Hakim and I. C. Patel, "A review on phytoconstituents of marine brown algae," *Future Journal of Pharmaceutical Sciences*, vol. 6, no. 1, pp. 1–11, 2020.

[8] M. Ganesan, N. Trivedi, V. Gupta, S. V. Madhav, C. R. Reddy, and I. A. Levine, "Seaweed resources in India–current status of diversity and cultivation: prospects and challenges," *Botanica Marina*, vol. 62, no. 5, pp. 463–482, 2019.

[9] K. Venkataraman and C. Raghunathan, "Coastal and marine biodiversity of India," in *Marine faunal diversity in India*, pp. 303–348, Elsevier, 2015.

[10] K. Sudhakar, R. Mamat, M. Samykano, W. H. Azmi, W. F. W. Ishak, and T. Yusaf, "An overview of marine macroalgae as bioresource," *Renewable and Sustainable Energy Reviews*, vol. 91, pp. 165–179, 2018.

[11] J. D. Wehr, "Brown algae," in *Freshwater Algae of North America*, pp. 851–871, Elsevier, 2015.

[12] R. Zhang, X. Zhang, Y. Tang, and J. Mao, "Composition, isolation, purification and biological activities of Sargassum fusiforme polysaccharides: a review," *Carbohydrate Polymers*, vol. 228, p. 115381, 2020.

[13] M. Falkenberg, E. Nakano, L. Zambotti-Villela et al., "Bioactive compounds against neglected diseases isolated from macroalgae: a review," *Journal of Applied Phycology*, vol. 31, no. 2, pp. 797–823, 2019.

[14] P. Máximo, L. M. Ferreira, P. Branco, P. Lima, and A. Lourenço, "Secondary metabolites and biological activity

of invasive macroalgae of southern Europe," *Marine Drugs*, vol. 16, no. 8, p. 265, 2018.

[15] C. Hoek, D. Mann, H. M. Jahns, and M. Jahns, *Algae: An Introduction to Phycology*, Cambridge University Press, 1995.

[16] T. Wernberg, K. Krumhansl, K. Filbee-Dexter, and M. F. Pedersen, "Status and trends for the world's kelp forests," in *World seas: an environmental evaluation*, pp. 57–78, Elsevier, 2019.

[17] M. J. Fowler-Walker, T. Wernberg, and S. D. Connell, "Differences in kelp morphology between wave sheltered and exposed localities: morphologically plastic or fixed traits?," *Marine Biology*, vol. 148, no. 4, pp. 755–767, 2006.

[18] J. Fleurence and I. Levine, *Seaweed in Health and Disease Prevention*, Academic Press, 2016.

[19] W. A. P. Black, "The seasonal variation in the cellulose content of the common Scottish Laminariaceae and Fucaceae," *Journal of the Marine Biological Association of the United Kingdom*, vol. 29, no. 2, pp. 379–387, 1950.

[20] W. A. P. Black, "The seasonal variation in weight and chemical composition of the common British Laminariaceae," *Journal of the Marine Biological Association of the United Kingdom*, vol. 29, no. 1, pp. 45–72, 1950.

[21] Y. Qin, "Seaweed bioresources," in *Bioactive Seaweeds for Food Applications*, pp. 3–24, Elsevier, 2018.

[22] K. K. A. Sanjeewa and Y.-J. Jeon, "Edible brown seaweeds: a review," *Journal of Food Bioactives*, vol. 2, pp. 37–50, 2018.

[23] C. S. Dhanalakshmi, P. Madhu, A. Karthick, M. Mathew, and R. V. Kumar, "A comprehensive MCDM-based approach using TOPSIS and EDAS as an auxiliary tool for pyrolysis material selection and its application," *Biomass Conversion and Biorefinery*, 2020.

[24] A. R. Circuncisão, M. D. Catarino, S. M. Cardoso, and A. Silva, "Minerals from macroalgae origin: health benefits and risks for consumers," *Marine Drugs*, vol. 16, no. 11, p. 400, 2018.

[25] D. Purcell-Meyerink, M. A. Packer, T. T. Wheeler, and M. Hayes, "Aquaculture production of the brown seaweeds Laminaria digitata and Macrocystis pyrifera: applications in food and pharmaceuticals," *Molecules*, vol. 26, no. 5, p. 1306, 2021.

[26] A. R. Prasad, R. Shankar, C. K. Patil, A. Karthick, A. Kumar, and R. Rahim, "Performance enhancement of solar photovoltaic system for roof top garden," *Environmental Science and Pollution Research*, vol. 28, no. 36, pp. 50017–50027, 2021.

[27] A. Javed, M. B. Hussain, A. Tahir et al., "Pharmacological applications of phlorotannins: a comprehensive review," *Current Drug Discovery Technologies*, vol. 18, no. 2, pp. 282–292, 2021.

[28] S. Cho and M. Shimizu, "Natural sleep aids and polyphenols as treatments for insomnia," in *Bioactive nutraceuticals and dietary supplements in neurological and brain disease*, pp. 141–151, Elsevier, 2015.

[29] K. Nagayama, Y. Iwamura, T. Shibata, I. Hirayama, and T. Nakamura, "Bactericidal activity of phlorotannins from the brown alga Ecklonia kurome," *The Journal of Antimicrobial Chemotherapy*, vol. 50, no. 6, pp. 889–893, 2002.

[30] R. Rangaraj, S. Sathish, T. L. D. Mansadevi et al., "Investigation of weight fraction and alkaline treatment on Catechu linnaeus/Hibiscus cannabinus/Sansevieria ehrenbergii plant fibers-reinforced epoxy hybrid composites," *Advances in Materials Science and Engineering*, vol. 2022, Article ID 4940531, 9 pages, 2022.

[31] M. Nakai, N. Kageyama, K. Nakahara, and W. Miki, "Phlorotannins as radical scavengers from the extract of Sargassum ringgoldianum," *Marine Biotechnology*, vol. 8, no. 4, pp. 409–414, 2006.

[32] K. Nagayama, T. Shibata, K. Fujimoto, T. Honjo, and T. Nakamura, "Algicidal effect of phlorotannins from the brown alga Ecklonia kurome on red tide microalgae," *Aquaculture*, vol. 218, no. 1–4, pp. 601–611, 2003.

[33] M.-J. Ahn, K.-D. Yoon, S.-Y. Min et al., "Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga Ecklonia cava," *Biological & Pharmaceutical Bulletin*, vol. 27, no. 4, pp. 544–547, 2004.

[34] A. Zarekarizi, L. Hoffmann, and D. Burritt, "Approaches for the sustainable production of fucoxanthin, a xanthophyll with potential health benefits," *Journal of Applied Phycology*, vol. 31, no. 1, pp. 281–299, 2019.

[35] A. Priya, G. Anusha, S. Thanigaivel et al., "Removing microplastics from wastewater using leading-edge treatment technologies: a solution to microplastic pollution—a review," *Bioprocess and Biosystems Engineering*, pp. 1–13, 2022.

[36] J. Li, C. Cai, C. Yang, J. Li, T. Sun, and G. Yu, "Recent advances in pharmaceutical potential of brown algal polysaccharides and their derivatives," *Current Pharmaceutical Design*, vol. 25, no. 11, pp. 1290–1311, 2019.

[37] Q. Shi, A. Wang, Z. Lu, C. Qin, J. Hu, and J. Yin, "Overview on the antiviral activities and mechanisms of marine polysaccharides from seaweeds," *Carbohydrate Research*, vol. 453-454, pp. 1–9, 2017.

[38] X. Guo, Y. Wang, Y. Qin, P. Shen, and Q. Peng, "Structures, properties and application of alginic acid: a review," *International Journal of Biological Macromolecules*, vol. 162, pp. 618–628, 2020.

[39] K. Sreekumar and B. Bindhu, "Alginic acid: a potential biopolymer from brown algae," *Materials International*, vol. 2, pp. 433–438, 2020.

[40] I. Michalak, A. Dmytryk, and K. Chojnacka, "Algae cosmetics," *Encyclopedia of Marine Biotechnology*, vol. 1, pp. 65–85, 2020.

[41] N. A. M. Fauziee, L. S. Chang, W. A. W. Mustapha, A. R. M. Nor, and S. J. Lim, "Functional polysaccharides of fucoidan, laminaran and alginate from Malaysian brown seaweeds (Sargassum polycystum, Turbinaria ornata and Padina boryana)," *International Journal of Biological Macromolecules*, vol. 167, pp. 1135–1145, 2021.

[42] S. M. Etman, Y. S. R. Elnaggar, and O. Y. Abdallah, "Fucoidan, a natural biopolymer in cancer combating: from edible algae to nanocarrier tailoring," *International Journal of Biological Macromolecules*, vol. 147, pp. 799–808, 2020.

[43] K. Thiyagarasaiyar, B.-H. Goh, Y.-J. Jeon, and Y.-Y. Yow, "Algae metabolites in cosmeceutical: an overview of current applications and challenges," *Marine Drugs*, vol. 18, no. 6, p. 323, 2020.

[44] L. Wang, J.-Y. Oh, Y.-S. Kim, H.-G. Lee, J.-S. Lee, and Y.-J. Jeon, "Anti-photoaging and anti-melanogenesis effects of fucoidan isolated from Hizikia fusiforme and its underlying mechanisms," *Marine Drugs*, vol. 18, no. 8, p. 427, 2020.

[45] R. R. Remya, S. R. R. Rajasree, T. Y. Suman et al., "Laminarin based AgNPs using brown seaweed Turbinaria ornata and its induction of apoptosis in human retinoblastoma Y79 cancer cell lines," *Materials Research Express*, vol. 5, no. 3, p. 35403, 2018.

[46] K. R. R. Rengasamy, M. F. Mahomoodally, M. Z. Aumeeruddy, G. Zengin, J. Xiao, and D. H. Kim, "Bioactive compounds in seaweeds: an overview of their biological properties and safety," *Food and Chemical Toxicology*, vol. 135, p. 111013, 2020.

[47] S. Khalid, M. Abbas, F. Saeed, H. Bader-Ul-Ain, and H. A. R. Suleria, *Therapeutic potential of seaweed bioactive compounds*, IntechOpen, 2018.

[48] R. Agregan, P. E. S. Munekata, D. Franco, R. Dominguez, J. Carballo, and J. M. Lorenzo, "Phenolic compounds from three brown seaweed species using LC-DAD–ESI-MS/MS," *Food Research International*, vol. 99, pp. 979–985, 2017.

[49] M. Aitouguinane, S. Bouissil, A. Mouhoub et al., "Induction of natural defenses in tomato seedlings by using alginate and oligoalginates derivatives extracted from Moroccan brown algae," *Marine Drugs*, vol. 18, no. 10, p. 521, 2020.

[50] A. C. Taki, R. Brkljača, T. Wang et al., "Natural compounds from the marine brown alga Caulocystis cephalornithos with potent in vitro-activity against the parasitic nematode Haemonchus contortus," *Pathogens.*, vol. 9, no. 7, p. 550, 2020.

[51] M. P. Rahelivao, M. Gruner, H. Andriamanantoanina, I. Bauer, and H.-J. Knölker, "Brown algae (Phaeophyceae) from the coast of Madagascar: preliminary bioactivity studies and isolation of natural products," *Natural Products and Bioprospecting*, vol. 5, no. 5, pp. 223–235, 2015.

[52] S.-Y. Kim, G. Ahn, H.-S. Kim, J.-G. Je, K.-N. Kim, and Y.-J. Jeon, "Diphlorethohydroxycarmalol (DPHC) isolated from the brown alga ishige okamurae acts on inflammatory myopathy as an inhibitory agent of TNF-α," *Marine Drugs*, vol. 18, no. 11, p. 529, 2020.

[53] S. S. A. Al-Saif, N. Abdel-Raouf, H. A. El-Wazanani, and I. A. Aref, "Antibacterial substances from marine algae isolated from Jeddah coast of Red sea, Saudi Arabia," *Saudi Journal of Biological Sciences*, vol. 21, no. 1, pp. 57–64, 2014.

[54] J. C. De-Paula, E. A. P. Lopes-Filho, F. Salgueiro et al., "Diterpenes content of the brown alga Dictyota ciliolata (Dictyotales, Phaeophyceae) and recognition of a Brazilian haplotype based on psb A sequences," *New Zealand Journal of Botany*, vol. 56, no. 4, pp. 415–429, 2018.

[55] Y.-I. Yang, S.-H. Jung, K.-T. Lee, and J.-H. Choi, "8, 8′-Bieckol, isolated from edible brown algae, exerts its anti-inflammatory effects through inhibition of NF-κB signaling and ROS production in LPS-stimulated macrophages," *International Immunopharmacology*, vol. 23, no. 2, pp. 460–468, 2014.

[56] S. Palanisamy, M. Vinosha, T. Marudhupandi, P. Rajasekar, and N. M. Prabhu, "Isolation of fucoidan from Sargassum polycystum brown algae: structural characterization, in vitro antioxidant and anticancer activity," *International Journal of Biological Macromolecules*, vol. 102, pp. 405–412, 2017.

[57] A. O. Aremu, N. A. Masondo, K. R. R. Rengasamy et al., "Physiological role of phenolic biostimulants isolated from brown seaweed Ecklonia maxima on plant growth and development," *Planta*, vol. 241, no. 6, pp. 1313–1324, 2015.

[58] A. Pardo-Vargas, I. de Barcelos Oliveira, P. R. S. Stephens et al., "Dolabelladienols A–C, new diterpenes isolated from Brazilian brown alga Dictyota pfaffii," *Marine Drugs*, vol. 12, no. 7, pp. 4247–4259, 2014.

[59] M.-C. Kang, Y. Ding, E.-A. Kim et al., "Indole derivatives isolated from brown alga Sargassum thunbergii inhibit adipogenesis through AMPK activation in 3T3-L1 preadipocytes," *Marine Drugs*, vol. 15, no. 4, p. 119, 2017.

[60] C. Vizetto-Duarte, L. Custodio, K. N. Gangadhar et al., "Isololiolide, a carotenoid metabolite isolated from the brown alga Cystoseira tamariscifolia, is cytotoxic and able to induce apoptosis in hepatocarcinoma cells through caspase-3 activation, decreased Bcl-2 levels, increased p53 expression and PARP cleavage," *Phytomedicine*, vol. 23, no. 5, pp. 550–557, 2016.

[61] B. Chinnababu, S. P. Reddy, P. S. Rao et al., "Isolation, semisynthesis and bio-evaluation of spatane derivatives from the brown algae Stoechospermum marginatum," *Bioorganic & Medicinal Chemistry Letters*, vol. 25, no. 12, pp. 2479–2483, 2015.

[62] S. E. A. Zerrifi, F. El Khalloufi, B. Oudra, and V. Vasconcelos, "Seaweed bioactive compounds against pathogens and microalgae: potential uses on pharmacology and harmful algae bloom control," *Marine Drugs*, vol. 16, no. 2, p. 55, 2018.

[63] G. N. A. Charway, P. Yenumula, and Y.-M. Kim, "Marine algae and their potential application as antimicrobial agents," *Journal of Food Hygiene and Safety*, vol. 33, no. 3, pp. 151–156, 2018.

[64] L. D. Chambers, C. Hellio, K. R. Stokes et al., "Investigation of Chondrus crispus as a potential source of new antifouling agents," *International Biodeterioration & Biodegradation*, vol. 65, no. 7, pp. 939–946, 2011.

[65] S. Cox, S. Gupta, and N. Abu-Ghannam, "Effect of different rehydration temperatures on the moisture, content of phenolic compounds, antioxidant capacity and textural properties of edible Irish brown seaweed," *LWT - Food Science and Technology*, vol. 47, no. 2, pp. 300–307, 2012.

[66] F. Álvarez-Gómez, N. Korbee, V. Casas-Arrojo, R. T. Abdala-Díaz, and F. L. Figueroa, "UV photoprotection, cytotoxicity and immunology capacity of red algae extracts," *Molecules*, vol. 24, no. 2, p. 341, 2019.

[67] T. Kuda, M. Nishizawa, D. Toshima et al., "Antioxidant and anti-norovirus properties of aqueous acetic acid macromolecular extracts of edible brown macroalgae," *LWT - Food Science and Technology*, vol. 141, p. 110942, 2021.

[68] M. Pandithurai, M. Subbiah, S. Vajiravelu, and T. Selvan, "Antifungal activity of various solvent extracts of marine brown alga Spatoglossum asperum," *International Journal of Pharmacy and Chemistry*, vol. 5, pp. 277–280, 2015.

[69] U. De Corato, R. Salimbeni, A. De Pretis, N. Avella, and G. Patruno, "Antifungal activity of crude extracts from brown and red seaweeds by a supercritical carbon dioxide technique against fruit postharvest fungal diseases," *Postharvest Biology and Technology*, vol. 131, pp. 16–30, 2017.

[70] A. Shibu, "Antifungal activity of marine brown algae Sargassum wightii collected from Gulf of Mannar biosphere reserve," *International Journal of Recent Scientific Research*, vol. 10, no. 12(E), pp. 1–23, 2019.

[71] B. F. S. P. Negara, J. H. Sohn, J.-S. Kim, and J.-S. Choi, "Antifungal and larvicidal activities of phlorotannins from brown seaweeds," *Marine Drugs*, vol. 19, no. 4, p. 223, 2021.

[72] F. R. C. Mo'o, G. Wilar, H. P. Devkota, and N. Wathoni, "Ulvan, a polysaccharide from macroalga Ulva sp.: a review of chemistry, biological activities and potential for food and biomedical applications," *Applied Sciences*, vol. 10, no. 16, p. 5488, 2020.

[73] A. Annibaldi and H. Walczak, "Death receptors and their ligands in inflammatory disease and cancer," *Cold Spring Harbor Perspectives in Biology*, vol. 12, no. 9, article a036384, 2020.

[74] E.-A. Kim, J.-H. Lee, S.-J. Heo, and Y.-J. Jeon, "Saringosterol acetate isolated from Hizikia fusiforme, an edible brown alga, suppressed hepatocellular carcinoma growth and metastasis in a zebrafish xenograft model," *Chemico-Biological Interactions*, vol. 335, p. 109362, 2021.

[75] Y. Wei, Q. Liu, C. Xu, J. Yu, L. Zhao, and Q. Guo, "Damage to the membrane permeability and cell death of Vibrio parahaemolyticus caused by phlorotannins with low molecular weight from Sargassum thunbergii," *Journal of Aquatic Food Product Technology*, vol. 25, no. 3, pp. 323–333, 2016.

[76] Y.-S. Son, H. M. A. Ullah, A. K. Elfadl et al., "Inhibition of formation of azoxymethane-induced colonic aberrant crypt foci in rats by edible green algae Capsosiphon fulvescens and brown algae Hizikia fusiforme," *In Vivo*, vol. 32, no. 1, pp. 101–108, 2018.

[77] R. Sakthivel and K. P. Devi, "Antioxidant, anti-inflammatory and anticancer potential of natural bioactive compounds from seaweeds," *Studies in Natural Products Chemistry*, vol. 63, pp. 113–160, 2019.

[78] T.-Y. Kim, C.-Y. Jin, G.-Y. Kim et al., "Ethyl alcohol extracts of Hizikia fusiforme sensitize AGS human gastric adenocarcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis," *Journal of Medicinal Food*, vol. 12, no. 4, pp. 782–787, 2009.

[79] R. R. Remya, S. R. R. Rajasree, T. Y. Suman et al., "Studies on proximate composition and phytochemical profiling of Turbinaria ornata and its antiproliferative effect on Y79 cell lines," *Thalass. An Int. J. Mar. Sci.*, vol. 35, no. 2, pp. 495–502, 2019.

[80] T. P. Almeida, A. A. Ramos, J. Ferreira, A. Azqueta, and E. Rocha, "Bioactive compounds from seaweed with anti-leukemic activity: a mini-review on carotenoids and phlorotannins," *Mini Reviews in Medicinal Chemistry*, vol. 20, no. 1, pp. 39–53, 2020.

[81] C.-H. Kang, S.-H. Kang, S.-H. Boo, S.-Y. Park, D.-O. Moon, and G.-Y. Kim, "Ethyl alcohol extract of Hizikia fusiforme induces caspase-dependent apoptosis in human leukemia U937 cells by generation of reactive oxygen species," *Tropical Journal of Pharmaceutical Research*, vol. 10, no. 6, pp. 739–746, 2011.

[82] A. El-Shaibany, M. Al-Habori, T. Al-Maqtari, and H. Al-Mahbashi, "The Yemeni brown algae Dictyota dichotoma exhibit high in vitro anticancer activity independent of its antioxidant capability," *BioMed Research International*, vol. 2020, Article ID 2425693, 9 pages, 2020.

[83] R. Vaikundamoorthy, V. Krishnamoorthy, R. Vilwanathan, and R. Rajendran, "Structural characterization and anticancer activity (MCF7 and MDA-MB-231) of polysaccharides fractionated from brown seaweed Sargassum wightii," *International Journal of Biological Macromolecules*, vol. 111, pp. 1229–1237, 2018.

[84] R. Peñalver, J. M. Lorenzo, G. Ros, R. Amarowicz, M. Pateiro, and G. Nieto, "Seaweeds as a functional ingredient for a healthy diet," *Marine Drugs*, vol. 18, no. 6, p. 301, 2020.

[85] E. M. Balboa, E. Conde, A. Moure, E. Falqué, and H. Domínguez, "In vitro antioxidant properties of crude extracts and compounds from brown algae," *Food Chemistry*, vol. 138, no. 2-3, pp. 1764–1785, 2013.

[86] C. Sánchez-Moreno, J. A. Larrauri, and F. Saura-Calixto, "A procedure to measure the antiradical efficiency of polyphenols," *Journal of the Science of Food and Agriculture*, vol. 76, no. 2, pp. 270–276, 1998.

[87] T. Yamaguchi, H. Takamura, T. Matoba, and J. Terao, "HPLC method for evaluation of the free radical-scavenging activity of foods by using 1, 1-diphenyl-2-picrylhydrazyl," *Bioscience, Biotechnology, and Biochemistry*, vol. 62, no. 6, pp. 1201–1204, 1998.

[88] H. M. Mwangi, J. Van Der Westhuizen, J. Marnewick, W. T. Mabusela, M. M. Kabanda, and E. E. Ebenso, "Isolation, identification and radical scavenging activity of phlorotannin derivatives from brown algae, Ecklonia maxima: an experimental and theoretical study," *Free Radicals and Antioxidants*, vol. 3, pp. S1–S10, 2013.

[89] I. P. S. Fernando, M. Kim, K.-T. Son, Y. Jeong, and Y.-J. Jeon, "Antioxidant activity of marine algal polyphenolic compounds: a mechanistic approach," *Journal of Medicinal Food*, vol. 19, no. 7, pp. 615–628, 2016.

[90] K.-H. Kim, R. Tsao, R. Yang, and S. W. Cui, "Phenolic acid profiles and antioxidant activities of wheat bran extracts and the effect of hydrolysis conditions," *Food Chemistry*, vol. 95, no. 3, pp. 466–473, 2006.

[91] N. M. Aminina, E. P. Karaulova, T. I. Vishnevskaya et al., "Characteristics of polyphenolic content in brown algae of the Pacific Coast of Russia," *Molecules*, vol. 25, no. 17, p. 3909, 2020.

[92] N. Balasundram, K. Sundram, and S. Samman, "Phenolic compounds in plants and agri-industrial by-products: antioxidant activity, occurrence, and potential uses," *Food Chemistry*, vol. 99, no. 1, pp. 191–203, 2006.

[93] J. L. Peron and J. Nkiliza, *Stablised polyphenol derivatives, process for their manufacture, and uses thereof*, 2013, European Patent Office EP2558436A1.

[94] K. Chakraborty, A. Maneesh, and F. Makkar, "Antioxidant activity of brown seaweeds," *Journal of Aquatic Food Product Technology*, vol. 26, no. 4, pp. 406–419, 2017.

[95] Y. Yuan, J. Zhang, J. Fan et al., "Microwave assisted extraction of phenolic compounds from four economic brown macroalgae species and evaluation of their antioxidant activities and inhibitory effects on α-amylase, α-glucosidase, pancreatic lipase and tyrosinase," *Food Research International*, vol. 113, pp. 288–297, 2018.

[96] X. Liu, G. Luo, L. Wang, and W. Yuan, "Optimization of antioxidant extraction from edible brown algae Ascophyllum nodosum using response surface methodology," *Food and Bioproducts Processing*, vol. 114, pp. 205–215, 2019.

[97] J. Naveen, R. Baskaran, and V. Baskaran, "Profiling of bioactives and in vitro evaluation of antioxidant and antidiabetic property of polyphenols of marine algae Padina tetrastromatica," *Algal Research*, vol. 55, p. 102250, 2021.

[98] A. Benslima, S. Sellimi, M. Hamdi et al., "The brown seaweed Cystoseira schiffneri as a source of sodium alginate: chemical and structural characterization, and antioxidant activities," *Food Bioscience*, vol. 40, p. 100873, 2021.

[99] S. Reuter, S. C. Gupta, M. M. Chaturvedi, and B. B. Aggarwal, "Oxidative stress, inflammation, and cancer: how are they linked?," *Free Radical Biology & Medicine*, vol. 49, no. 11, pp. 1603–1616, 2010.

[100] L. M. Coussens and Z. Werb, "Inflammation and cancer," *Nature*, vol. 420, no. 6917, pp. 860–867, 2002.

[101] G. De La Fuente, M. Fontana, V. Asnaghi et al., "The remarkable antioxidant and anti-inflammatory potential of the extracts of the brown alga cystoseira amentacea var. stricta," *Marine Drugs*, vol. 19, no. 1, p. 2, 2021.

[102] K. K. A. Sanjeewa, T. U. Jayawardena, H.-S. Kim et al., "Fucoidan isolated from Padina commersonii inhibit LPS-induced inflammation in macrophages blocking TLR/NF-κB signal pathway," *Carbohydrate Polymers*, vol. 224, p. 115195, 2019.

[103] R. Manikandan, D. Parimalanandhini, K. Mahalakshmi et al., "Studies on isolation, characterization of fucoidan from brown algae Turbinaria decurrens and evaluation of it's in vivo and in vitro anti-inflammatory activities," *International Journal of Biological Macromolecules*, vol. 160, pp. 1263–1276, 2020.

[104] L. Mhadhebi, A. Mhadhebi, J. Robert, and A. Bouraoui, "Antioxidant, anti-inflammatory and antiproliferative effects of aqueous extracts of three mediterranean brown seaweeds of the genus cystoseira," *Iranian Journal of Pharmaceutical Research*, vol. 13, no. 1, pp. 207–220, 2014.

[105] K. Chakraborty and S. Dhara, "First report of substituted 2 H-pyranoids from brown seaweed Turbinaria conoides with antioxidant and anti-inflammatory activities," *Natural Product Research*, vol. 34, no. 24, pp. 3451–3461, 2020.

[106] S. S. Nair, V. Kavrekar, and A. Mishra, "In vitro studies on alpha amylase and alpha glucosidase inhibitory activities of selected plant extracts," *European Journal of Experimental Biology*, vol. 3, no. 1, pp. 128–132, 2013.

[107] C. F. Deacon, "Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes," *Frontiers in Endocrinology*, vol. 10, p. 80, 2019.

[108] J. Spavieri, A. Allmendinger, M. Kaiser et al., "Assessment of dual life stage antiplasmodial activity of British seaweeds," *Marine Drugs*, vol. 11, no. 10, pp. 4019–4034, 2013.

[109] J.-B. Gallé, B. Attioua, M. Kaiser, A.-M. Rusig, A. Lobstein, and C. Vonthron-Sénécheau, "Eleganolone, a diterpene from the French marine alga Bifurcaria bifurcata inhibits growth of the human pathogens Trypanosoma brucei and Plasmodium falciparum," *Marine Drugs*, vol. 11, no. 12, pp. 599–610, 2013.

[110] H. Nagappan, P. P. Pee, S. H. Y. Kee et al., "Malaysian brown seaweeds Sargassum siliquosum and Sargassum polycystum: low density lipoprotein (LDL) oxidation, angiotensin converting enzyme (ACE), α-amylase, and α-glucosidase inhibition activities," *Food Research International*, vol. 99, Part 2, pp. 950–958, 2017.

[111] S. S. Abdelsalam, H. M. Korashy, A. Zeidan, and A. Agouni, "The role of protein tyrosine phosphatase (PTP)-1B in cardiovascular disease and its interplay with insulin resistance," *Biomolecules*, vol. 9, no. 7, p. 286, 2019.

[112] F. Nwosu, J. Morris, V. A. Lund, D. Stewart, H. A. Ross, and G. J. McDougall, "Anti-proliferative and potential anti-diabetic effects of phenolic-rich extracts from edible marine algae," *Food Chemistry*, vol. 126, no. 3, pp. 1006–1012, 2011.

[113] N. Zaharudin, A. A. Salmeán, and L. O. Dragsted, "Inhibitory effects of edible seaweeds, polyphenolics and alginates on the activities of porcine pancreatic α-amylase," *Food Chemistry*, vol. 245, pp. 1196–1203, 2018.

[114] M.-C. Kang, S.-H. Lee, W.-W. Lee et al., "Protective effect of fucoxanthin isolated from Ishige okamurae against high-glucose induced oxidative stress in human umbilical vein endothelial cells and zebrafish model," *Journal of Functional Foods*, vol. 11, pp. 304–312, 2014.

[115] C. Yang, S. Lai, Y. Chen et al., "Anti-diabetic effect of oligosaccharides from seaweed Sargassum confusum via JNK-IRS1/PI3K signalling pathways and regulation of gut microbiota," *Food and Chemical Toxicology*, vol. 131, p. 110562, 2019.

[116] S. Gheda, M. A. Naby, T. Mohamed, L. Pereira, and A. Khamis, "Antidiabetic and antioxidant activity of phlorotannins extracted from the brown seaweed Cystoseira compressa in streptozotocin-induced diabetic rats," *Environmental Science and Pollution Research*, vol. 28, no. 18, pp. 22886–22901, 2021.

[117] M. Fouladvand, A. Barazesh, F. Farokhzad, H. Malekizadeh, and K. Sartavi, "Evaluation of in vitro anti-leishmanial activity of some brown, green and red algae from the Persian Gulf," *European Review for Medical and Pharmacological Sciences*, vol. 15, no. 6, pp. 597–600, 2011.

[118] A. S. Aliança, K. F. Anjos, T. N. de Vasconcelos Reis et al., "The in vitro biological activity of the Brazilian brown seaweed Dictyota mertensii against Leishmania amazonensis," *Molecules*, vol. 19, no. 9, pp. 14052–14065, 2014.

[119] O. Chiboub, L. Ktari, I. Sifaoui et al., "In vitro amoebicidal and antioxidant activities of some Tunisian seaweeds," *Experimental Parasitology*, vol. 183, pp. 76–80, 2017.

[120] P. Perumal, R. Sowmiya, S. Prasanna kumar, S. Ravikumar, P. Deepak, and G. Balasubramani, "Isolation, structural elucidation and antiplasmodial activity of fucosterol compound from brown seaweed, Sargassum linearifolium against malarial parasite Plasmodium falciparum," *Natural Product Research*, vol. 32, no. 11, pp. 1316–1319, 2018.

[121] X. Bai, M. Li, X. Wang et al., "Therapeutic potential of fucoidan in the reduction of hepatic pathology in murine schistosomiasis japonica," *Parasites & Vectors*, vol. 13, no. 1, pp. 1–14, 2020.