



Edible Seaweeds: A Potential Novel Source of Bioactive Metabolites and Nutraceuticals With Human Health Benefits

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There has been an increase in human health concerns, and seaweeds are considered as a potential functional food which can decrease the risk of many diseases, as they contain various bioactive compounds. Seaweeds are of nutritional interest and a rich source of natural bioactive compounds including antioxidants, flavonoids, phenolic compounds, and alkaloids that can be used as an alternative source of food material. Seaweeds contain a high amount of vitamins such as A, D, E, C, and B, and minerals including calcium, potassium, magnesium and iron. Seaweeds containing carrageenan, agar and other polysaccharides not only act as a source of fiber but also can act as prebiotics which may benefit the bacteria present in the large intestine. The lack of technologies to process seaweeds for human consumption at an industrial scale is a serious limitation on growth of the seaweed-based functional foods sector. Seaweeds are one of the most extensively used functional foods, with a long history in Asian countries. Now they are also being explored by many Western and European countries. Evidence from epidemiological research suggests that regular consumption of a marine algae-based diet may boost immunity against a number of diseases including COVID-19 novel virus by angiotensin-I-converting enzyme (ACE) inhibition.

Keywords: antioxidants, bioactive compounds, functional food, nutraceuticals, seaweeds

INTRODUCTION

In the early twentieth century, it was a common belief that food is needed for body growth only. Recent advancements in food and nutritional research have revolutionized this common belief, and food requirements are shifting toward the role of the diet in promoting human health and avoiding disease (Admassu et al., 2015). There have been significant changes in our food habits, such as the diet in urbanized countries being extremely caloric and rich in sugars and saturated fats, even as complex carbohydrates and dietetic fiber are utilized at low concentrations. These factors are responsible for a decrease in physical activity and increase the probability of many diseases in the population. Over the last few years, foodstuffs have been extensively used to achieve better health;

our research data on the connection between food components and fitness are at present being used to obtain better quality food (Holdt and Kraan, 2011). In recent years, research attentions have been developed to search for bioactive molecules due to their various health-beneficial effects (Amorim et al., 2012). Bioactive compounds are components that have been obtained from natural or synthetic sources and are assayed for activity in a number of key therapeutic areas. Bioactive compounds possess activity that is good for health, and it has been shown that bioactive food molecules can change the gene expression of a host at cellular level, thereby influencing health (MacArtain et al., 2007). At present, seaweeds have attracted much interest as a natural source of bioactive compounds with a significant role in the development of nutraceuticals. Seaweeds are extremely varied in terms of species, habitat, maturity, environmental conditions, and period of harvesting but they are excellent sources of different nutrients (Tanna and Mishra, 2018a).

A variety of marine algae are used as healthy food and they have been used in pharmaceuticals due to their supposed health benefits. Seaweeds are chlorophyll-containing organisms, a group of multicellular plants known as macroalgae that grow in marine systems (Kharkwal et al., 2012). Traditionally, seaweeds or macroalgae can be classified into three different groups: green algae (Chlorophyta), brown algae (Ochrophyta, Phaeophyceae), and red algae (Rhodophyta). This classification is based on various factors like the chemical nature of photosynthetic storage products, pigmentation, other morphological appearance, and the organization and components of photosynthetic membranes. The chlorophyll content of seaweeds is responsible for their color; green algae contain chlorophyll a and b in equal amounts, the same as higher plants, that is responsible for their green color. The color of brown algae is due to xanthophyll and fucoxanthin pigments; these are accessory pigments and mask chlorophylls and other xanthophylls, whereas phycoerythrin and phycocyanin are dominant in red algae, masking the effect of other pigments and providing their red color (Kılınç et al., 2013).

Marine algae are a rich source of several bioactive compounds such as dietary fibers, proteins, minerals, and vitamins; they also contain bioactive substances like polysaccharides, polyphenols, phytochemicals, and polyunsaturated fatty acids with potential therapeutic uses against inflammation, cancer, oxidative stress, allergies, diabetes, thrombosis, obesity, hypertension, lipidemia, and many degenerative diseases (Tanna and Mishra, 2019). These compounds gave seaweeds a higher value in the individual diet as a food component and as pharmaceutical supplements (Namvar et al., 2013). The physiologically active substances of seaweeds are separated into two groups according to differences in their mechanisms: (a) high molecular weight materials which are not absorbed, like dietary fibers, and (b) low molecular weight materials which are absorbed and directly affect human homeostasis (Murata and Nakazoe, 2001). In seaweeds, various environmental factors play a significant role in the production of biological molecules, including temperature, UV radiation exposure, and grazers. These factors are responsible for the variation in biomolecules in the same species (Zenthoefer et al., 2017).

WHY SEAWEED FOR HEALTH AND NUTRACEUTICALS?

It is predicted that the global population will be virtually 10 billion people by 2050, up from 7.3 billion today (Ehrlich and Harte, 2015). Even the current population does not have enough food for a healthy and active life. To solve this greater food demand, many countries have started to explore alternative food sources including marine bio-resources. Approximately 70% of the earth's surface is covered by seas and oceans. A broad range of various habitats is provided by the marine environment from which natural sources of diversified products can be derived (Jiménez-Escrig et al., 2012). It has been proved that the marine environment is a rich source of biological and chemical diversity; these marine organisms have high potential as sources of compounds that can be applied in the food industry, cosmetics industry, nutraceutical and pharmaceutical industry, and other industrially important compounds (Tanna and Mishra, 2018b). Seaweeds have considerable environmental appeal because they require neither freshwater nor fertilizer, nor much use of land; they use renewable living resources and are infected by few pests and diseases (Vallinayagam et al., 2009). Seaweeds do not require extra fertilizer to grow and they absorb carbon dioxide from sea runoffs, giving them a carbon-negative footprint. The growth rate of seaweeds is much higher than that of plants and other food sources. Seaweeds can be collected naturally but at this time are increasingly cultivated.

ROLE OF SEAWEEDS IN HUMAN HEALTH

In living organisms, some molecules are formed during aerobic processes, such as reactive oxygen species (ROS) which are a group of highly reactive molecules including free radicals like 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide anion ($O_2^{\bullet-}$) and hydroxyl radicals (HO), and non-radicals such as singlet oxygen (1O_2) or hydrogen peroxide ($H_2O_2^{\bullet}$) (Ahn et al., 2007). ROS are identified as a class of reactive species that can easily act in response to a number of molecules in living organisms and are known as a major source of oxidative stress that may cause gene mutation, direct DNA strand breakage, and DNA-DNA or DNA-protein cross links. ROS are one of the main reasons for many kinds of diseases such as cancer, neurodegenerative disease, cataracts, cardiovascular disease, and atherosclerosis (Salar and Dhall, 2010).

Free radicals can be converted into non-radicals to prevent oxidation by donating electron and hydrogen, dissolving generated peroxidation compounds and chelating transition metals (Enrique and Lester, 2002). Antioxidants are used in the human diet to decrease or avoid oxidation in food products, to improve nutritional quality, to delay the formation of toxic oxidation products and thus to increase the life of food. Food industries generally use synthetic antimicrobial compounds such as sodium nitrite, sodium benzoate and sorbic acid, and artificial antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and tert-butylhydroquinone

(TBHQ) for improving the quality of food (Shahidi et al., 2005). On the other hand, it has been reported that these synthetic biomolecules are harmful and have carcinogenic effects (Chen et al., 1992). Therefore, progressively more research is being done on natural antioxidants, antimicrobials or antioxidants with significant and various claims for health-promoting properties (Andarwulan et al., 2010).

Plants contain some natural pigments like carotenoids that respond rapidly to these free radicals and reduce the amount of oxidative deterioration, and these compounds increase food value (Fernández-López et al., 2020). Different classes of antioxidants have been reported in different kinds of higher plants (Cai et al., 2004). A number of research reports have revealed seaweed to be a rich source of antioxidant compounds (Tanna et al., 2019). Antioxidant activity has developed into an interesting area under discussion of demanding investigations because of the growing interest in the food and pharmaceutical industries to expand natural bioactive compounds that exhibit considerable health benefits (de Souza et al., 2007).

BIOACTIVE METABOLITES OF SEAWEED ORIGIN

Research in recent years suggest that seaweeds have been well considered as organisms that have the potential to provide novel biologically active substances and compounds that are necessary for human nutrition and growth; due to these features, marine algae have high economic importance in pharmaceuticals, nutraceuticals and human health (Smit, 2004; Cardozo et al., 2007; MacArtain et al., 2007). A marine system is an extremely competitive environment in which to survive, seaweeds have to make some remarkably diverse compounds by altering their metabolic pathway to develop defense strategies (Cardozo et al., 2007). These diverse compounds are well known as bioactive compounds and their activity has been linked to improving human health by altering the genetic expression of cellular events for decades (MacArtain et al., 2007). Nowadays, seaweeds have become a multi-billion-dollar industry due to their global utilization in pharmaceuticals, nutraceuticals, and cosmetics (Sultana et al., 2012). The biological compounds in seaweeds are also progressively more used in biochemical and medical research (Smit, 2004). In some countries, marine algae, or macroalgae (seaweeds) are used to improve soil fertility to enhance crop productivity because they contain many compounds that have the capacity of stimulate plant growth (Khan et al., 2009).

Of the total volume of marine macroalgae, it is noticeable that more is used in foods as compared to industrial applications, especially in terms of their economic value and weight. In the Far East, more than two million tons of fresh seaweed per year is processed to obtain food products, while almost 1.5 million tons per year is used in industrial production to obtain alginates, phycocolloids and carrageenan (Jiménez-Escrig and Sánchez-Muniz, 2000). Primary and secondary metabolites obtained from seaweeds are considered as future foods and attract attention for economic exploitation (Cardozo et al., 2007). People living in coastal areas consume seaweeds in both fresh and dried form.

In Japan, 25% of all food contains seaweed-based ingredients or seaweeds served in various forms, thus seaweeds are a basic source of livelihood for fishermen or seaweed farmers (Norziah and Ching, 2000). Consumption of about 100 g of seaweed is sufficient to provide the daily requirement of vitamin A, B₂, and B₁₂; it also provides two-thirds of the daily vitamin C requirement (Škrovánková, 2011).

Nutrients synthesized by the human body or precursor molecules taken in the daily diet are essential for normal growth and development, and also play a very important role in the regulation of body function (Groppe and Smith, 2012). The chemical composition of seaweed is not well known so far compared to that of terrestrial plants but it is known to be rich in metabolites which act as precursor molecules that are important for human body function (Admassu et al., 2015).

Proteins

Proteins are polymers of amino acids which are bound together by peptide bonds. The protein composition and content of marine algae vary among species and depend on season and habitat (Pangestuti and Kim, 2015). Accordingly, the nutritional value of seaweed proteins varies depending on the geographical location and environmental conditions (Kadam et al., 2017). It is well established that brown seaweeds contain the least protein while moderate concentrations of protein are reported from green seaweeds and the highest content is estimated in red seaweeds (Ganesan et al., 2019). Protein content varies a lot over time (season), with the highest concentrations present during the beginning of spring and winter, while the minimum concentration is present during the early autumn period and summer (Denis et al., 2010). Phycobiliproteins and lectins are bioactive proteins obtained from seaweeds that have been exploited for several industrial applications (Bleakley and Hayes, 2017). Lectins are low molecular weight thermostable proteins attached to definite carbohydrates and take part in many biological activities such as intercellular communication (Chojnacka et al., 2012). The nutritional value of protein depends on two factors: amino acid composition and protein digestibility (Tabarsa et al., 2012). A protein which has an exceptional amino acid composition would not have great nutritional value if its digestibility remains low (Tseng, 2001). Most seaweeds are a rich source of glycine, arginine, glutamic acid, and alanine which are essential for human health, and their concentrations make them an excellent part of the diet (Aguilera-Morales et al., 2005). Brown seaweeds are commonly exploited by industries and have a lower protein content, about 15% of their dry weight, but *Saccharina latissima* (formerly *Laminaria saccharina*) (Ochrophyta, Phaeophyceae) is reported to have a protein content of 25.7% its dry weight (Fleurence, 1999). The higher protein content of *S. latissima* is a result of the favorable environmental conditions of its habitat (Fleurence, 1999). *Chlorella vulgaris* (Chlorophyta) is one of the seaweeds commonly exploited by industries for its high protein content, 51–58% of dry weight (Bleakley and Hayes, 2017), whereas the red algal species *Neopyropia tenera* (formerly *Porphyra tenera*) (Rhodophyta) is reported to have a protein content of up to 47% of dry weight (Sánchez-Machado et al., 2004). Some species

of *Ulva* (formerly *Enteromorpha*) (Chlorophyta) contain key amino acids, in which 9 of 10 amino acids play a vital role for human beings and are considered equivalent to soybean proteins (Aguilera-Morales et al., 2005). Seaweed proteins have been reported to have different biological activity such as antihypertensive [angiotensin-I-converting enzyme (ACE) inhibition], antioxidant and antidiabetic effects (Admassu et al., 2018). The physiological activities of the human body are affected by bioactive peptides which are part of the food diet. In parent proteins, a short sequence of amino acids is present in an inactive form, but they break into short bioactive peptides during food processing, gastrointestinal digestion or fermentation, and research suggests that these activated bioactive peptides have nutraceutical potential to promote human health (Wijesekara and Kim, 2010).

Polysaccharides

Seaweeds are considered a source of novel and unique types of polysaccharides having diverse applications (Tanna and Mishra, 2019). Monosaccharides linked together by glycosidic bonds result in the formation of polysaccharides; they may be homopolymers or heteropolymers depending on their monosaccharide composition. Homopolysaccharides comprise repeats of a single type of monosaccharide and/or its derivative such as cellulose, an important structural component of the cell wall of plants and most seaweeds (Stiger-Pouvreau et al., 2016). Unlike homopolymers, heteropolysaccharides consist of repeats of different types of sugar molecules and/or their derivatives such as carrageenan (Rhodophyta) and ulvan (Chlorophyta) (Stiger-Pouvreau et al., 2016). Polysaccharides have several important commercial applications including as thickeners, stabilizers, beverages, feed, emulsifiers, food, etc (Tseng, 2001). Their low calorific value makes seaweeds nutritionally important (Pereira, 2011). The cell wall of seaweeds contains a huge amount of polysaccharides (Pádua et al., 2015). Storage and cell wall polysaccharides are species-specific (Kraan, 2012). The seaweed cell wall typically consists of sulfated polysaccharides that distinguish it from that of land plants (as they do not have such polysaccharides) and these polysaccharides have a useful function in ionic regulation (Rupérez et al., 2002). The characteristics of seaweed polysaccharides differ not only from those of terrestrial plants but also vary according to the taxonomy of seaweeds. Like proteins, polysaccharides have different building blocks (sugar repeats) and their functional properties depend on their structural composition (Wijesinghe et al., 2011a). The compounds present in carbohydrates vary according to age, species, season, and the geographical location of the species (Gupta and Abu-Ghannam, 2011). These fibers may be water-insoluble or water-soluble and is related to different physiological properties (Gómez-Ordóñez et al., 2010). Various soluble polysaccharides like guar gum, pectins, etc., have been correlated with hypoglycemic and hypocholesterolemic effects while water-insoluble polysaccharides like cellulose are linked to reduced digestive tract transit time (Burtin, 2003). Polysaccharides are classified into three groups: (a) storage polysaccharides, (b) intercellular mucilage, and (c) structural polysaccharides (Ito and Hori, 1989). Polysaccharides stimulate

the growth of many bacteria present in the digestive tract and thus they are beneficial for digestion (Vidanarachchi et al., 2009), whereas many bacterial and virus species are inhibited by sulfated polysaccharides (Leonard et al., 2010).

The most important bioactive polysaccharides exclusively found in seaweeds are fucoidan, laminarin and alginates. Fucoidan is a sulfated polysaccharide isolated from the Phaeophyceae group comprised of sulfated L-fucose as the main sugar unit, in which sulfate ester groups are linked to fucose by α -1,3 linkages (Li et al., 2008). Fucoidan is estimated to be about 10% of seaweed dry weight (Chojnacka et al., 2012). The bioavailability and absorption of sugars commonly depend on their molecular weight, and low molecular weight fucoidans are highly bioavailable compared to high molecular weight fucoidans (Zuo et al., 2015). Furthermore, fucoidan shows antioxidant, antiviral, antitumor, antioxidative and anti-inflammatory activity (Song et al., 2012).

Another widely explored polysaccharide, laminarin, commonly obtained from brown seaweeds, is made up of β (1-3)-linked glucose in the main chain with random β (1-6)-linked side-chains (O'Doherty et al., 2010). It has antibacterial and antiviral activity, and also acts as a prebiotic. The antioxidant activity of laminarin depends on its chemical structure and molecular weight (Li and Kim, 2011). Alginates are a unique type of polysaccharide exclusively present in seaweeds, especially brown seaweeds, and absent in terrestrial plants (Kumar et al., 2008). Alginates were reported to account for up to 47% of the dry weight of total biomass (Holdt and Kraan, 2011). Interestingly, alginates may be present in salt or acidic forms. The acidic form of the polymer is called alginic acid and comprises two types of hexuronic acid monomer: β -D-mannuronic acid and α -L-guluronic acid, linked with 1–4 bonds (Andriamanantoanina and Rinaudo, 2010). They have antibacterial and anti-inflammatory activity and also have thickening, stabilizing and general colloidal properties (Aliste et al., 2000). The importance of seaweed polysaccharides in industrial and biomedical applications has been proved. They have been isolated from different classes of seaweeds: carrageenans and agarans from red seaweed; alginates and fucoidans from brown seaweed; and ulvans from green seaweed (Cosenza et al., 2017).

Mineral Content

Seaweeds contain high concentrations of a wide range of diversified minerals due to their habitat. Most of the minerals required for human health such as potassium, sodium, phosphorus, calcium, iodine, magnesium, iron, and zinc are present in sufficient quantities in seaweeds, thus they have the potential to be widely used as health-beneficial supplements (Rao et al., 2007). Trace elements have also been reported in seaweeds (Burtin, 2003). Iodine plays an important role in the performance of thyroid function (Jaspars and Folmer, 2013), and *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) is reported to contain a high iodine concentration of up to 600 mg/g (Bove et al., 2010). Certain minerals have a linkage with anionic polysaccharides including agar, alginates or carrageen, and these linked minerals provide a linkage between anionic polysaccharides which affect their digestibility (Jiménez-Escrig et al., 2011). In contrast,

carboxylic polysaccharides (e.g., alginic acid) have a strong affinity for divalent cations, mostly calcium that regulates the availability of associated minerals (Mabeau and Fleurence, 1993). Some seaweed species are also known for the presence of a high amount of mineral elements with particular catalytic functions, such as *Ulva* (formerly *Enteromorpha*) spp. (Chlorophyta) which have high concentrations of magnesium (2–5% of dry matter).

A high mineral content has been reported in seaweeds, sometimes up to 40% of biomass (Kumar et al., 2011); this happens because seaweeds absorb metal ions from salt water and accumulate them in their fronds as carbonate salts (Chojnacka et al., 2012). Seaweeds contain calcium in the form of calcium phosphate which is considered more bioavailable than the calcium carbonate form commonly present in milk (Rajapakse and Kim, 2011). Iodine is considered one of the prominent requirements for health, and in some seaweeds the iodine concentration is higher than the minimum human dietary requirement (150 mg/day) (Rajapakse and Kim, 2011). The highest iodine content is found in brown seaweeds; while red and green seaweeds have a lower iodine content (Rajapakse and Kim, 2011), it is still higher than that in terrestrial plants. Therefore, seaweeds can also be considered as an alternative food to fulfill the requirement for iodine compared to animal- and plant-derived foods (Rajapakse and Kim, 2011). It has also been observed that the linkage between polysaccharides and iodine is weak, which allows rapid release of the iodine. Iron and copper content is also high in seaweeds compared to plant and animal food sources, even higher than in spinach and meat (Holland et al., 1993). Overall, seaweeds may be considered the best food to be explored for fulfilling the mineral requirements of human body (Pereira, 2011). Research on *Sargassum ringgoldianum* (Ochrophyta, Phaeophyceae) seaweed harvested from Japanese beaches showed a balanced combination of potassium (69 $\mu\text{mol/ml}$), magnesium (7.8 $\mu\text{mol/ml}$), and calcium (4.1 $\mu\text{mol/ml}$) ions (Kuda and Ikemori, 2009). Similarly, *Kappaphycus alvarezii* (Rhodophyta) is rich source of calcium and magnesium, with about 460.11 and 581.20 mg/L, respectively, present in their extracts (Rathore et al., 2009).

Vitamins

Vitamins are important nutrients for achieving specific and essential functions of the body and are also essential for maintaining health (Bellows et al., 2012). Seaweeds are rich in all essential and non-essential vitamins (Ganesan et al., 2019). Some seaweeds possess vitamins that have many health-beneficial effects and antioxidant activity, and thus reduce various health-related problems including high blood pressure, cardiovascular disorders and the risk of cancer (Gupta et al., 2020). Water-soluble vitamins B₁, B₂, B₁₂, and C, and fat-soluble vitamins E and β -carotene with vitamin A activity have been reported from various seaweeds (Škrovánková, 2011). Deficiency of water-soluble vitamins such as B₁₂ causes many diseases like chronic fatigue syndrome (CFS), anemia and many skin problems. Vitamin B₁₂ is not synthesized by most terrestrial plants, but many prokaryotes capable of synthesizing vitamin B₁₂ interact with seaweeds, and this interconnection promotes vitamin levels in macroalgae (Cotas et al., 2020). Vitamin B₁₂

is abundant in *Arthrospira* (formerly *Spirulina*) (Cyanobacteria) which has four times more B₁₂ than raw liver (Falquet and Hurni, 1997); consumption of 1 g of *Arthrospira* (formerly *Spirulina*) is sufficient to provide the daily requirement of B₁₂ (Watanabe et al., 1999). Brown and green seaweeds are a rich source of vitamin A, containing on average between 500 and 3000 mg/kg of dry weight, whereas red algae contain 100–800 mg/kg dry weight (Kumar et al., 2008). Various seaweeds, including *Crassiphycus changii* (formerly *Gracilaria changii*), *Porphyra umbilicalis* (Rhodophyta) and *Himanthalia elongata* (Ochrophyta, Phaeophyceae), are rich in vitamins compared to terrestrial vegetables (Ganesan et al., 2019). Seaweeds rich in vitamins (A, B, C, D, and E) are extensively used for skincare (Jesumani et al., 2019). Vitamin C reduces the harshness of allergic reactions to fight off infection, enhances the immune defense system, regulates the formation of conjunctive tissue and helps in removing free radicals, and also plays a significant role in many diseases and disorders such as diabetes, atherosclerosis, cancer and neurodegenerative problems (Chambial et al., 2013). The vitamin C concentration in the seaweed *Eisenia arborea* (Ochrophyta, Phaeophyceae) (34.4 mg/100 g DW) is similar to that in mandarin oranges (37.7 mg/100 g) (Hernández-Carmona et al., 2009). The brown seaweeds *Ascophyllum* and *Fucus* sp. contain 200–600 mg/Kg DW of vitamin E (α -tocopherols), more than other red and green seaweeds (Mathew and Ravishankar, 2018). The seaweed *Macrocystis pyrifera* (Ochrophyta, Phaeophyceae) is highly rich in vitamin E, similar to the plant oils which are known for being rich in vitamin E such as soybean oil (*Glycine max*), sunflower seed oil (*Helianthus annuus*) and palm oil (*Elaeis guineensis*) (Mathew and Ravishankar, 2018). Vitamin E inhibits oxidation of low-density lipoprotein and also plays a vital role in the prevention of cardiovascular diseases (Solibami and Kamat, 1985). Seaweed consumption (about 100 g/per day) gives more than the daily requirement of vitamins A, B₂, and B₁₂ and fulfils two-thirds of the vitamin C requirement (Ortiz et al., 2006).

Pigments

Pigments are lipid-soluble polyenes, and natural pigments not only function as factors providing color but also participate in many biological activities (Li and Kim, 2011). Pigments are widely found in seaweeds, plants, invertebrates, and mammals. Marine algae are potential sources of unique natural pigments (Pangestuti and Kim, 2015). Seaweeds contain three classes of pigments: chlorophylls, phycobiliproteins and carotenoids (Pereira et al., 2014). Chlorophylls are not absorbed by the human body and are therefore transformed into pheophorbide, pyropheophytin and pheophytin in processed vegetable foods which can be easily absorbed. Chlorophylls have an antimutagenic effect and may play a significant role in cancer prevention (Ferruzzi and Blakeslee, 2007). Phycobiliproteins are water-soluble pigments produced by red seaweeds in high concentrations (Mihova et al., 1996). Phycobilins show antioxidant, antiviral, anti-inflammatory and neuroprotective properties (Holdt and Kraan, 2011). Seaweed carotenoids include xanthophylls (zeaxanthin, violaxanthin, lutein, fucoxanthin, neoxanthin, antheraxanthin, and astaxanthin) and carotenes

(β -carotene) (Manivasagan et al., 2018). Seaweeds that are rich in pigments have potential to be used as dietary supplements. Fucoxanthin is considered a non-provitamin A carotenoid and is found in numerous classes of algae but in Phaeophyceae, fucoxanthins are the most abundant xanthophyll, accounting for 70% of total carotenoid content (Holdt and Kraan, 2011). Fucoxanthin has various health-beneficial activities such as anti-obesity and cancer chemoprevention (Woo et al., 2009). Different types of carotenoid reported from various classes of marine algae show strong antioxidant activity (Galasso et al., 2017). Carotenoids have the ability to quench singlet oxygen and scavenge free radicals (Islamian and Mehrali, 2015). Seaweeds are rich in carotenoids reported to reduce cardiovascular diseases, age-related diseases, dementia, inflammation, diabetes, and cancers as well as ophthalmological diseases (Tan and Norhaizan, 2019). A number of studies have confirmed the antioxidant properties of seaweed carotenoids and their role in preventing diseases that are linked to oxidative stress (Okuzumi et al., 1993). The carotenoid composition of 16 red seaweeds shows that red seaweeds have high concentrations of lutein and zeaxanthin, and in 12 species of the Rhodophyta phylum the carotenoid content shows high concentrations of antheraxanthin, violaxanthin and β -carotene (Schubert et al., 2006). Seaweed β -carotene content ranges from 0.248 to 0.357 mg/g (Abirami and Kowsalya, 2011). Chlorophyll, β -carotene and fucoxanthin have various biologically beneficial activities that include antimutagens, antioxidant and antiproliferative activity for cancer (de Quirós et al., 2010). Chlorophyll a, β -carotene and lutein extracted from the seaweed *Neopyropia tenera* (formerly *Porphyra tenera*) (Rhodophyta) exhibit anti-mutagenic activity by suppressing the expression of the mutagen-induced *umuC* gene (Okai et al., 1996). Seaweed carotenoids are also used for their antimicrobial activity (Rajauria and Abu-Ghannam, 2013).

Polyphenols

Polyphenols are a group of chemical compounds consisting of a hydroxyl group ($-OH$) that is directly linked to an aromatic hydrocarbon group. Polyphenols are derived differently in plants and seaweeds: they are derived from gallic and ellagic acid in plants, whereas in seaweeds they derive from polymerized phloroglucinol units (1,3,5-trihydroxybenzene) (Generalić Mekinić et al., 2019). Seaweed polyphenols include flavonols, catechins and phlorotannins (Gómez-Guzmán et al., 2018). Marine algal phlorotannins are an extremely heterogenous group of molecules (in terms of structure and degree of polymerization) and thus have a wide range of potential biological activity (Li et al., 2017). Phlorotannins range from 5 to 15% of the dried weight, highest in brown seaweeds followed by red and green (Ragan and Jensen, 1978). In green and red algae, the major percentage of phenolic compounds are flavonoids, phenolic acids and bromophenols (Wells et al., 2017). Bromophenol is one of the key phenolic compounds detected in marine algae and is found at a high level in various types of seaweeds such as *Leathesia marina* (formerly *Leathesia nana*) (Ochrophyta, Phaeophyceae), and *Rhodomela confervoides* (Rhodophyta) (Shi et al., 2009). The antioxidant properties of seaweeds are highly affected by their polyphenol composition (Martins et al., 2013; Tanna et al.,

2019). Polyphenols convert free radicals to non-reactive radicals by donating a hydrogen molecule (Gupta and Abu-Ghannam, 2011). Polyphenol content also shows a significant temporal correlation with the reproductive state of seaweeds (Ragan and Jensen, 1978). Phlorotannins isolated from *Eisenia bicyclis* (Ochrophyta, Phaeophyceae) have shown antioxidant activity 10 times higher than that of ascorbic acid and α -tocopherol (Shibata et al., 2007). Seaweeds generate polyphenols to protect themselves from herbivores and external biotic and abiotic stresses (Li and Kim, 2011). In the brown seaweed *Himanthalia elongata*, a total of seven polyphenols (phloroglucinol, gallic acid, chlorogenic acid, caffeic acid, ferulic acid, myricetin, and quercetin) were observed to have a higher antioxidant activity than ascorbic acid (Rajauria, 2018). Polyphenols extracted from the brown seaweed *Fucus vesiculosus* collected from Kiel Fjord, Western Baltic Sea, showed anticancer activity (Zenthofer et al., 2017). *Eucheuma* and *Kappaphycus* spp. (Rhodophyta) have higher antioxidant activity than α -tocopherol (Ganesan et al., 2008). Seaweed phenols have scavenging ability due to the presence of a hydroxyl group, which is why it is an important constituent of seaweed (Wang et al., 2009). Phlorotannin-rich extract of the seaweed *Ascopyllum nodosum* (Ochrophyta, Phaeophyceae) has various biological activities such as inhibition of oxidative stress, and anti-inflammatory and anti-senescence activity (Dutot et al., 2012). Dieckol, a phlorotannin extracted from the brown seaweed *Ecklonia cava* (Ochrophyta, Phaeophyceae), inhibits adipogenesis by activating the AMP signal pathway (Ko et al., 2013). The flavonoids in the green seaweed *Ulva prolifera* (formerly *Enteromorpha prolifera*) (Chlorophyta) have therapeutical potential as type 2 diabetes suppressors (Yan et al., 2019). Seaweed bromophenol is known as a very strong cytotoxic agent against various cancer cells: *Vertebrata lanosa* (formerly *Polysiphonia lanosa*) and *Neorhodomela larix* (formerly *Rhodomela larix*) (Rhodophyta) show cytotoxic activity against DLD-1 cells and HCT-116 cells (Weinstein et al., 1975; Shoeib et al., 2004). Moreover, phenolic compounds are involved in stabilizing lipid peroxidation (Vijayabaskar and Shiyamala, 2012).

Fatty Acids

Seaweeds contain low concentrations of lipids, about 2–10% of their dry weight. It has also been noticed that tropical seaweed species have lower lipid concentrations than cold water algae (Holdt and Kraan, 2011). The most common lipids found in seaweed are phospholipids and glycolipids. Most seaweed lipids are comprised of polyunsaturated fatty acids (PUFAs); further, their concentration is high in those seaweeds which grow in cold regions compared to temperate climate zones (Balić et al., 2020). Commonly, PUFAs are classified in two forms, omega-3 and omega-6 fatty acids. Both lipids consist of at least 20 carbon atoms with at least two double bonds; when the third carbon atom has the first double bond, it is referred to as omega-3, whereas if the first double bond is present at the sixth carbon position, it is known as omega-6. Long chain PUFAs (LC-PUFAs) play a crucial role in cellular and tissue metabolism, including the regulation of membrane fluidity, electron and thermal adaptation, and oxygen transport (van Dooremalen et al., 2009). Both omega-3 and

omega-6 fatty acids are essential for balanced human metabolic procedures, and thus are important ingredients in the human diet. The quantity of omega-3 and omega-6 fatty acids consumed should be balanced because both use the same metabolic enzymes to produce prostaglandins (Simopoulos, 2016). A hugely imbalanced ω -6/ ω -3 ratio is the reason behind various health issues such as cancer and inflammatory, cardiovascular and autoimmune diseases (Simopoulos, 2008). According to the WHO, the ω -6/ ω -3 ratio must be lower than 10 (Francavilla et al., 2013). Seaweeds have many crucial fatty acids, which may add to their efficacy as a dietary supplement or as part of a balanced diet (Admassu et al., 2015). The brown seaweed *Cystoseira humilis* (Ochrophyta, Phaeophyceae) has a high fatty acid content, about 48% compared to other brown seaweeds studied from the Atlantic coast of Morocco, in which PUFAs, linoleic acid (C18:2) and arachidonic acid (C20:4) are abundant (Belattmania et al., 2018). Fatty acids of *Cystoseira humilis* (Ochrophyta, Phaeophyceae) show antioxidant and antibacterial activity (Belattmania et al., 2016). The fatty acid composition of seaweeds varies with the season; for example, in the marine alga *Spatoglossum macrodontum* (Ochrophyta, Phaeophyceae), the highest total fatty acid content (about 83 mg/g DW) is found in the month of July (start of growth), which declined 30% in August (initial growth phase) and the lowest (55–66 mg/g DW) in November (biomass peak stage or end of growth). Their PUFA composition also changes with the season, being initially high (39%) at the start of growth; reducing concomitantly with later stages of growth and reaching up to 31% at the end of the growth period (Gosch et al., 2015). In the seaweed *Gracilaria gracilis* (Rhodophyta), the amount of fatty acids also changes with the season; for example the ω -6/ ω -3 ratio is lowest in April while it increases more than 10 times in January (Francavilla et al., 2013).

BIOLOGICAL ACTIVITY

Antihypertensive Activity

It is well established that hypertension or high blood pressure and oxidative stress are major reasons for the development of various chronic diseases. In hypertension, blood pressure increases concomitantly and results in stroke or many other cardiovascular diseases like coronary infarction. Macroalgal peptides are well-known natural compounds for the inhibition of ACE activity; even peptides from sources other than macroalgae have antihypertensive activity (Li et al., 2016; Lee and Hur, 2017). The blood pressure-lowering peptide bradykinin is degraded by the multifunctional ACE attributing high blood pressure, which plays a key role in cardiovascular diseases (Martin and Deussen, 2019). Inhibition of ACE is considered a useful therapeutic approach and dipeptides isolated from the seaweed *Undaria pinnatifida* (Ochrophyta, Phaeophyceae) showed effective inhibition of ACE (Kim and Wijesekara, 2010). Seven different peptides, Val-Tyr, Ile-Tyr, Ala-Trp, Phe-Tyr, Val-Trp, Ile-Trp, and Leu-Trp, showed antihypertensive activity, with IC₅₀ of 35.2, 6.1, 18.8, 42.3, 3.3, 1.5, and 23.6 μ M, respectively (Sato et al., 2002). Each peptide showed an antihypertensive effect in spontaneously hypertensive rats (SHR); briefly, at a

dose of 1 mg/kg of body weight, the blood pressure was considerably reduced by Ile-Trp, Ile-Tyr, Val-Tyr, and Phe-Tyr (Sato et al., 2002). The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure; is also of interest to researchers in combating hypertension. The enzyme papain isolated from the red seaweed *Palmaria palmata* (Rhodophyta) generates a renin-inhibitory tridecapeptide with a motif of IRLIIVLMPILMA (Fitzgerald et al., 2014). This tridecapeptide and some other seaweed-protein hydrolyzates (yet to be characterized) have shown an antihypertensive effect by decreasing systolic blood pressure (SBP) in the SHR model (Fitzgerald et al., 2014). It was found that protein hydrolyzate (tridecapeptide IRLIIVLMPILMA) from the seaweed *Palmaria palmata* reduces SBP by about 34 mm Hg, from about 188 to 154 mm Hg (Fitzgerald et al., 2014). Five different enzymatic digests extracted from the brown seaweed *Ecklonia cava* have potential ACE I inhibitory activity, with IC₅₀ values ranging from 2.33 to 3.56 μ g/ml (Cha et al., 2006). Phlorotannins (phlorofuocuroeckol A, dieckol, and eckol) isolated from *Ecklonia stolonifera* show the inhibitory activity (IC₅₀ values 12.74 \pm 0.15, 34.25 \pm 3.56, and 70.82 \pm 0.25 μ M, respectively) against ACE (Jung et al., 2006). Among five phlorotannins from the seaweed *E. cava*, triphlorethol A, eckstolonol, dieckol, eckol and phloroglucinol, dieckol exhibited the strongest inhibitory activity against ACE. Dieckol significantly increased the production of NO in EAhy926 cells and does not have any cytotoxic effect (Wijesinghe et al., 2011b; Ko et al., 2017). Fucoxanthin obtained from *Saccharina japonica* and *Sargassum horneri* (Ochrophyta, Phaeophyceae) shows antihypertensive activity (Sivaganam et al., 2015).

Antiproliferative Activity

Cancer is the reason for the increase in mortality rate worldwide, and peptides have effective therapeutic applications. Cancer is the result of irregular growth or development of cells, which leads to the alteration of cell physiology including self-determination of growth signals, insensitivity of growth inhibitory signals, avoidance of programmed cell death (apoptosis), uncontrolled replicative repetition, constant angiogenesis, tissue invasion and metastasis. An anticancer undecapeptide with the amino acid sequence VECYGPNRPQF, isolated from the green microalga *Chlorella vulgaris* waste by pepsin hydrolysis, showed antiproliferation in a dose-dependent manner in AGS cells, with an IC₅₀ value of 70 μ g/ml, and also induced post-G1 cell cycle arrest (Sheih et al., 2010). This peptide also showed high antioxidant activity compared to trolox in the case of peroxy radicals and low-density lipoproteins (Sheih et al., 2009). A number of polysaccharides extracted from different seaweeds were evaluated for their antiproliferative activity on different cell lines. An effective treatment for cancer is still a major research focus, and the quest to find alternative therapies and natural drugs is ongoing. In cancer, uncontrolled cell division occurs, which spreads into nearby tissues and forms tumors. Many factors are responsible for causing cancer, including an unhealthy diet, the use of drugs, environmental toxins, infectious organisms, hormones and inherited genetic mutations. Sulfated polysaccharides obtained

from the green seaweed *Caulerpa prolifera* inhibited cell proliferation by about 57% with a 0.1 mg/ml dose (Costa et al., 2010). Sulfated polysaccharides extracted from *Sargassum filipendula* (Ochrophyta, Phaeophyceae) showed about 60% cell proliferation inhibition at a dose of 0.1 mg/ml (Costa et al., 2011). *S. oligocystum* (Ochrophyta, Phaeophyceae) showed antiproliferative activity at an IC_{50} of $2.52 \pm 0.54 \mu\text{g/ml}$ against an adriamycin-resistant human small cell lung carcinoma (GLC4/Adr) cell line (Praiboon et al., 2018). Polysaccharide fraction SF-0.7v exhibited the most effective antiproliferation activity on HepG2 and PC3 cells, whereas fractions SF-1.0v and SF-1.5v showed strong inhibition of HeLa cells, with IC_{50} values of 15.69 and 13.83 μM , respectively (Costa et al., 2011). Polysaccharides obtained from *Ecklonia cava* had an IC_{50} of 44 $\mu\text{g/ml}$ in the U-937 cell line (Athukorala et al., 2009). Results determined by nuclear staining with Hoechst-33342 showed that the polysaccharides induce apoptosis (Athukorala et al., 2009). A polyphenol-rich extract of *Kappaphycus alvarezii* (formerly *Eucheuma cottonii*) (Rhodophyta), an edible red seaweed, showed antiproliferative activity in the oestrogen-independent human breast cancer cell line MB-MDA-231 with an IC_{50} value of 42 $\mu\text{g/ml}$ and in the oestrogen-dependent MCF-7 with an IC_{50} value of 20 $\mu\text{g/ml}$ (Namvar et al., 2012). Polyphenols have no harmful effect on normal cell lines and a seaweed extract shows dose-dependent anti-oestrogenic effects on the rat oestrous cycle and serum hormone concentration (Namvar et al., 2012). It induces apoptosis without cell cycle arrest to maintain cellular homeostasis; biosynthesis of endogenous oestrogen is downregulated in the rats to suppress the tumor. It also improves antioxidant activity by improving oxidative status (Namvar et al., 2012). The brown seaweed *Sargassum muticum* has antiproliferative activity against MDA-MB-231 and MCF-7 breast cancer cell lines (Namvar et al., 2013). *Fucus vesiculosus*, a brown seaweed harvested from the Baltic Sea, had cytotoxic activity against two human pancreatic cancer cell lines, Panc89 and PancTU1 (Zenthofer et al., 2017). Species of the tropical green seaweed *Caulerpa* from Arabian Sea show potential anticancer activity by regulating differential expression of key cancer-linked genes (Tanna et al., 2020).

Anticoagulant Activity

Bleeding is a very common and serious problem in the case of low anticoagulant activity (Landefeld and Beyth, 1993). Seaweed polysaccharides show anticoagulant activity by affecting antithrombin III (AT III) and promoting heparin cofactor II (HC II), as significant endogenous inhibitor, while some others directly suppress fibrin polymerization and thrombin activity without interacting with AT III and HC II (Shoeib et al., 2004). The sulfated polysaccharide ulvan obtained from the green seaweed *Ulva rigida* has strong biological activity as an anticoagulant compared to Lovenox in the case of both intrinsic and extrinsic coagulation pathways (Adrien et al., 2019). The anticoagulant activity of seaweeds depends on the molecular weight of fucoidans and also on their galactose content. Seven fucoidans extracted from the seaweed *Saccharina japonica* (Ochrophyta, Phaeophyceae) vary in average molecular

weight and four of them vary in both average molecular weight and fucose to galactose molar ratio. The activated partial thromboplastin time (APTT) assay results for these fucoidans explain that higher molecular weight fucoidans have high anticoagulant activity which further increases the galactose content (Jin et al., 2013). An extract of the sulfated polysaccharide-rich green seaweed *Udotea flabellum* (3 μg) showed double the plasma coagulation time in the APTT assay, similar to the results obtained with 1 μg heparin (Mendes Marques et al., 2019). Different fucans obtained from the brown algae *Padina gymnospora* exhibit potential anticoagulant activity (Silva et al., 2005); similarly, sulfated polysaccharides from the brown seaweed *Sargassum fulvellum* also showed strong anticoagulant activity in the APTT assay (De Zoysa et al., 2008). Six families of sulfated polysaccharides extracted from the marine algae *Dictyopteris delicatula* (Ochrophyta, Phaeophyceae) showed anticoagulant activity by the APPT test, proving that these polysaccharides suppress both the intrinsic and common pathways of coagulation and that some polysaccharide fractions have anticoagulant activity similar to that of Clexane (a commercial anticoagulant drug) (Magalhaes et al., 2011). Ion exchange-purified polysaccharides from three seaweeds, *Laurencia filiformis* (formerly *Gracilaria filiformis*) (Rhodophyta), *Ulva compressa* (formerly *Enteromorpha compressa*) (Chlorophyta) and *Turbinaria conoides* (Ochrophyta, Phaeophyceae), prolonged the coagulation of human plasma tested by the APTT assay (39.0 ± 1.0 , 38.6 ± 1.0 and 38.5 ± 1.9 , respectively) (Venkatesan et al., 2019).

Immunomodulatory Activity

Macrophages are considered the most important component in the host defense mechanism against bacterial infection, and various types of invading cells including cancer cells (Hirayama et al., 2018). Activated macrophages secrete key cell factors such as cytokines, chemokines and enzymes for removal of pathogens or inhibition of cancerous cell growth (Gautam et al., 2013). The polysaccharide ulvan extracted from the seaweed *Codium fragile* (Chlorophyta) is suggested as a strong immunomodulator as it enhances the secretion of various cytokines and nitric acid (NO) through activated macrophages in RAW 264.7 murine macrophage cells (Lee et al., 2010). Furthermore, ulvan from *Codium fragile* (Chlorophyta) possesses effective immunostimulatory activity and prevents harmful inflammatory effects by enhancing the production of pro-inflammatory (interleukins; IL-1, IL-6, IL-12, and tumor necrosis factors; TNF) and anti-inflammatory cytokines (Lee et al., 2010). The polysaccharide CrvpPS, isolated from the green alga *Caulerpa chemnitzia* (formerly *Caulerpa racemosa* var. *peltata*), fused with nano-selenium (CrvpPSnano-Se) shows immunomodulatory activity in mice (Shen et al., 2008). The levels of peripheral T lymphocyte subgroups and natural killer cells were significantly increased in mouse spleen during treatment with CrvpPSnano-Se (Shen et al., 2008). The enzymatic extract of the brown seaweed *Ecklonia cava* enhances the production of splenocytes and amplifies the quantity of their monocytes, lymphocytes and granulocytes in ICR mice. It also enhances the number of $CD4^+$ T cells, $CD8^+$ T cells, and $CD45R/B220^+$ B cells in

treated mice as compared to untreated controls (Ahn et al., 2008). Water-soluble sulfated polysaccharides isolated from the red seaweed *Nemalion elminthoides* exhibit *in vitro* and *in vivo* immunomodulatory activity by proliferating macrophages and enhance the synthesis of NO and cytokines (IL-6 and TNF) in the murine cell line RAW 264.7 (Pérez-Recalde et al., 2014). Similarly, fucoidans from *Fucus vesiculosus* (Ochrophyta, Phaeophyceae) have been demonstrated to have *in vitro* immunomodulatory activity by upregulating TNF- α -induced secretion of matrix metalloproteinase-9 (MMP-9), an enzyme required for the migration of immune cells, in the monocytic cell line U937 (Jintang et al., 2010). Sulfated polysaccharides from the seaweed *Fucus evanescens* (Ochrophyta, Phaeophyceae) interact with TLR 2 and TLR 4 to trigger NF- κ B in the eukaryotic cell line HEK293, confirming their immunomodulatory activity (Makarenkova et al., 2012). The edible seaweed *Gelidium spinosum* (formerly *Gelidium latifolium*) (Rhodophyta) that is commonly found in Indonesian coastal regions enhances the phagocytic activity of macrophages and the leukocyte content of neutrophils in BALB/C mice at an efficient dose of 100 mg/kg bw (Prasedya et al., 2019).

Antiviral Activity

Current medical and research data signify that humans are prone to various viral diseases which cause serious injury to the health. Various naturally isolated products exhibit antiviral activity similar to or even better than that of synthetics (Parvez et al., 2019). There is always a quest to develop high efficient natural antiviral drugs that can be used alone or with already discovered antivirals (Wang et al., 2012). However, several questions are unresolved such as the toxicity of drugs, their high cost due to limited availability especially in developing countries, drug efficacy and the high rate of drug resistance (Ventola, 2015). Seaweed polysaccharides are reported to have antiviral properties against a wide range of viruses including the herpes simplex virus (HSV), human immunodeficiency virus (HIV), human cytomegalovirus (HCMV), papilloma virus, vesicular stomatitis virus, and influenza A virus (Jiao et al., 2012). Polysaccharides extracted from six different seaweeds, three red seaweeds [*Furcellaria lumbricalis*, *Vertebrata lanosa* (formerly *Polysiphonia lanosa*) and *Palmaria palmata*], two brown (*Ascophyllum nodosum* and *Fucus vesiculosus*), and one green (*Ulva lactuca*), have been demonstrated to have anti-influenza viral activity. Results showed that polysaccharides from brown seaweeds have higher anti-H1N1 activity compared to green and red algae. Overall, polysaccharides extracted from *F. vesiculosus* showed the highest inhibitory effect on influenza A/PR/8/34 virus (Jiao et al., 2012). Similarly, polysaccharides extracted from *Polycladia indica* (formerly *Cystoseira indica*) (Ochrophyta, Phaeophyceae) showed antiviral activity against HSV, HSV-1 strain F, and HSV-2 strain MS in Vero cells (Mandal et al., 2007). The cytotoxic effect on human diploid foreskin fibroblasts of polysaccharides obtained from *P. indica* was checked and the results confirmed that they do not have any adverse effect on cell viability at concentrations of up to 1000 μ g/ml (Mandal et al., 2007). Various seaweed species contain significant amounts of complex structural sulfated

polysaccharides that exhibit capacity to suppress the duplication of enveloped viruses. Recently, the probability of low-level COVID-19 infection in Japan, China and South Korea has been linked with the traditional utilization of seaweeds (Pereira and Critchley, 2020; Tamama, 2020; Ding et al., 2021). Seaweed-based compounds such as lectin griffithsin, phycocolloid carrageenan, and ulvans are considered potential antiviral therapeutic agents against SARS-CoV-2 (Pereira and Critchley, 2020). Sulfated polysaccharides effectively inhibit SARS-CoV-2 (Kwon et al., 2020). Brown seaweed fucoidan has been tested for antiviral activity against SARS-CoV-2 infection and results show an inhibitory effect at a dose of 15.6 μ g/ml (Song et al., 2020). Cocktail-like targeting polysaccharides extracted from the brown seaweed *Ecklonia cava* subsp. *kurome* (formerly *Ecklonia kurome*) show anti-SARS-CoV-2 activity by blocking essential enzymes required for the replication of coronavirus (Ding et al., 2021). Polysaccharides extracted from the green seaweed *Monostroma nitidum* exhibit the potential inhibition of Enterovirus 71 (EV71) infection by binding viral particles and regulating the host phosphoinositide 3-kinase/protein kinase B signaling pathway, restricting the early steps of the virus life cycle (Wang S. et al., 2020). Two fractions of a cyclic diterpene-rich extract from the brown seaweed *Dictyota menstrualis* have capacity to inhibit replication of Zika virus (ZIKV) by approximately 74%, with an EC₅₀ dose of 1–3 μ g/ml (Cirne-Santos et al., 2019).

Antidiabetic Activity

Diabetes mellitus is the result of insufficient or defective synthesis of insulin by the pancreas. It is a chronic disease; lack of insulin increases the glucose concentration in the blood which harms many systems of the body, mostly the nerves and blood vessels. Diabetes is a global public health problem, and data predictions for 2030 indicate the greatest increase in the number of people affected will be in India, the United States and China (Fröde and Medeiros, 2008). The most important source of glucose in the blood is the hydrolysis of dietary starch; two key enzymes, α -amylase and α -glucosidase, are involved in the breakdown of starch and intestinal absorption, respectively. A mixed carbohydrate diet increases the blood glucose concentration that can be controlled by inhibition of these two enzymes (Lordan et al., 2013). The seaweed *Ascophyllum nodosum* from Atlantic Canada shows antidiabetic activity; its polyphenols have been demonstrated to inhibit α -glucosidase and glucose uptake into 3T3-L1 adipocytes by stimulatory activity in mice (Zhang et al., 2007). Mice treated with *A. nodosum* polyphenolic extract have reduced total concentrations of cholesterol and glycated serum protein in blood compared with untreated diabetic mice (Zhang et al., 2007). The brown seaweed *Ecklonia cava* subsp. *stolonifera* (formerly *Ecklonia stolonifera*) has been demonstrated to be a strong α -glucosidase inhibitor and to have anti-hyperglycemic effects in non-insulin-dependent diabetic male KK-Ay mice (Iwai, 2008). Injection of polyphenols extracted from *E. cava* subsp. *stolonifera* into unfasted KK-Ay mice reduces plasma glucose and lipid peroxidation levels which suppresses hyperglycemia that occurs with aging (Iwai, 2008). Polyphenols extracted from *A. nodosum* by two different methods, cold water and ethanol extraction, have a strong α -amylase inhibitory

TABLE 1 | Potential seaweeds and their metabolites exhibiting potential bioactivities.

Biological activities	Seaweeds	Bioactive metabolites/compounds	References
Antioxidant	<i>Ecklonia cava</i> subsp. <i>stolonifera</i>	Eckol	Manandhar et al., 2019
	<i>Osmundaria obtusiloba</i>	Methanol extract	Vasconcelos et al., 2019
	<i>Mazzaella canaliculata</i>	Polysaccharide	Jaballi et al., 2019
	<i>Sargassum fusiforme</i>	Fucoidan	Wang L. et al., 2020
	<i>Acanthophora nayadiformis</i>	Histidyl dipeptide	Lafarga et al., 2020
	<i>Hypnea musciformis</i>	Water extract	Pangestuti et al., 2019
	<i>Gracilariopsis lemaneiformis</i>	Protien hydrolyzates	Zhang et al., 2019
Anti-proliferative	<i>Ulva reticulata</i>	Polyphenol	Palanisamy et al., 2019
	<i>Egregia menziesii</i>	Ethanol extract	Olivares-Bañuelos et al., 2019
	<i>Nizamuddinina zanardinii</i>	Fucoidan	Alboofetileh et al., 2019a
	<i>Bifurcaria bifurcata</i>	Phlorotannin	Gonçalves-Fernández et al., 2019
	<i>Phaeodactylum tricornutum</i>	Fucosanthin	Neumann et al., 2019
Anticoagulant	<i>Sargassum cinereum</i>	Sulfated polysaccharide	Narayani et al., 2019
	<i>Sargassum cristaeifolium</i>	Flavonoid	Manggau et al., 2019
	<i>Gelidiella acerosa</i>	Sulfated polysaccharide	da Silva Chagas et al., 2020
	<i>Sargassum fusiforme</i>	Polysaccharide	Sun et al., 2018
	<i>Ulva lactuca</i>	Ulvans	de Carvalho et al., 2018
Antiviral (e.g., HIV, HSV-2 influenza A, Zika, or Chikungunya)	<i>Ecklonia cava</i>	Sulfated polysaccharide	Wijesinghe et al., 2011a
	<i>Dictyota bartayesiana</i>	Sulfated polysaccharide	Sanniyasi et al., 2019
	<i>Turbinaria decurrens</i>		
	<i>Nizamuddinina zanardinii</i>	Fucoidans	Alboofetileh et al., 2019b
	<i>Fucus distichus</i> subsp. <i>evanescens</i>	Fucoidans	Krylova et al., 2020
	<i>Ecklonia cava</i>	Phlorotannins	Cho et al., 2019
	<i>Canistrocarpus cervicornis</i>	Crude extract	Cirne-Santos et al., 2020
	<i>Osmundaria obtusiloba</i>	Crude extract	Cirne-Santos et al., 2018
	<i>Ascophyllum nodosum</i>	Phlorotannins	Dutot et al., 2012
	<i>Sargassum wightii</i>	Chloroform methanol extract	Maneesh et al., 2017
Antihypertensive	<i>Ulva linza</i>	Water extract	Ramirez-Higuera et al., 2014
	<i>Lessonia trabeculata</i>		
	<i>Macrocystis pyrifera</i>	Protein content	Vásquez et al., 2019
	<i>Chondracanthus chamissoi</i>		
	<i>Sargassum wightii</i>	Fucopyranan	Maneesh and Chakraborty, 2018
	<i>Ulva prolifera</i>	Sulfated polysaccharides	Kim et al., 2011
	<i>Lobophora variegata</i>	Fucoidans	de Sousa Pinheiro et al., 2017
	<i>Durvillaea antarctica</i>	β-1,3/1,6-glucan	Bobadilla et al., 2013
Immunomodulator	<i>Agarum clathratum</i>	Fucoidans	Cho et al., 2014
	<i>Ecklonia cava</i>	Enzymatic extract	Ahn et al., 2008
	<i>Sargassum wightii</i>	Alginate acid	Kudus et al., 2017
	<i>Halimeda macroloba</i>	Water extracts	Chin et al., 2015
	<i>Sargassum confusum</i>	Oligosaccharide	Yang et al., 2019
	<i>Ulva lactuca</i>	Ethyl acetate extract	Mohapatra et al., 2016
	<i>Sargassum</i>	Polysaccharides	Jia et al., 2020
	<i>Sargassum fusiforme</i>		
	<i>Macrocystis pyrifera</i>		
	<i>Halymenia durvillei</i>	Water extracts	Sanger et al., 2019
Antidiabetic	<i>Sargassum confusum</i>	Polysaccharide hydrolyzates	Yang et al., 2017
	<i>Lessonia nigrescens</i>	Ethanol extract	Zhao et al., 2018
	<i>Sargassum horneri</i>	Chlorophyll c2	Yoshioka et al., 2014
	<i>Fucus</i> spp.	Phlorotannin	Barbosa et al., 2018
	<i>Sargassum hemiphyllum</i>	Methanol extract	Na et al., 2005a
	<i>Polyopes affinis</i>	Methanol extract	Na et al., 2005b
	<i>Ecklonia cava</i>	Water extracts	Kimiya et al., 2008
	<i>Botryocladia wrightii</i>		
	<i>Eisenia arborea</i>	Seaweed powder	Sugiura et al., 2008

effect at concentrations of 53.6 and 44.7 $\mu\text{g/ml}$, respectively (Iwai, 2008). Similarly, polyphenolic extracts from the seaweeds *Fucus vesiculosus* and its polyphenols inhibit the action of α -glucosidase at IC_{50} of 0.32 and 0.49 $\mu\text{g/ml}$, respectively (Lordan et al., 2013).

Anti-allergic Activity

On the basis of immunological responses, allergic or hypersensitive reactions can be characterized into different classes: Type I or Anaphylactic Response, Type II or Cytotoxic-Mediated Response, and Type III or Immunocomplex Reactions (Vaillant et al., 2020). Hypersensitivity results in various clinical syndromes that include asthma, erythema, shock, anaphylaxis and a number of other ailments. Five algae, *Porphyra* sp. (Rhodophyta), *Saccharina japonica* (formerly *Laminaria japonica*; Ochrophyta, Phaeophyceae), the microalga *Chlorella pyrenoidosa* (Chlorophyta), *Scytosiphon* sp. (Ochrophyta, Phaeophyceae), and *Arthrospira platensis* (formerly *Spirulina platensis*) (Cyanobacteria), were studied for their anti-allergic activity using a hyaluronidase inhibition assay (Chen et al., 2015). *Scytosiphon* sp. had the highest total polyphenol content and the lowest IC_{50} (0.67 mg/ml) compared to the other four seaweeds. The anti-allergic activity of polyphenolic extract of *Scytosiphon* sp. was compared with that of the common anti-allergic drug disodium cromoglycate (DSCG), and the results showed that *Scytosiphon* sp. has higher activity than the drug, with an IC_{50} of 1.13 mg/ml. The study also showed that the anti-allergic activity is directly proportional to the concentration of polyphenol in seaweeds (Chen et al., 2015). Similarly, five brown seaweeds, *Sargassum cervicorne* and *S. tenerimum* from Pakistan, *S. graminifolium*, *S. thunbergii* and *Saccharina japonica* from China were compared with DSCG and catechin, a natural tea polyphenol. The results suggested that *S. tenerimum* is the most powerful inhibitor of hyaluronidase, with an IC_{50} of 21 $\mu\text{g/ml}$, lower than that of DSCG and similar to that of catechin (Samee et al., 2009). Further, two brown seaweeds, *Eisenia bicyclis* and *Ecklonia cava* subsp. *kurome*, had a very effective inhibitory effect on hyaluronidase, higher than that of catechins and DSCG (Shibata et al., 2002).

Insomnia

Sound sleep is very important for human health. Sleep deficiency leads to many problems in the immune system, cognitive function and quality of life. Currently, insomnia is a major sleep disorder worldwide and around 10–15% of the population suffers from chronic insomnia, whereas another 25–35% has temporary or infrequent insomnia. The most significant molecular targets for the discovery of sleep-enhancing drugs are GABA_A receptors (Johnston, 2015). Phlorotannins (dieckol, eckol, triphlorethol-A, and eckstolonol) from the seaweed *Ecklonia cava* induce sleep in mice by positive modulation of the GABA type A-benzodiazepine (GABA_A -BZD) receptor (Cho et al., 2012). The GABA_A -BZD receptor is a well-known molecule for sedatives and hypnotics, and phlorotannins obtained from *E. cava* activate the GABA_A -BZD receptor to induce sleep (Cho et al., 2012). Triphlorethol A, one of the most important components of phlorotannins, shows a dose-dependent decrease of sleep latency

in C57BL/6N mice. Results show that triphlorethol A obtained from seaweed is comparable to zolpidem, a well-known hypnotic drug (Yoon and Cho, 2018).

CONCLUSION AND PROSPECTS

Seaweeds grow in large quantities in the sea and are available throughout the year. This review focuses on the bioactivity of seaweeds which are commonly consumed by humans as condiments and vegetables. Seaweed ingredients have many biological properties such as anticancer, antitumor and antiviral activity (Table 1); they also possess interesting and novel properties, particularly flavor and nutritional characteristics. From a nutritional viewpoint, their high magnesium and iron content is of human interest due to their functional or metabolic properties. Seaweeds are also rich in vitamins and specific components including fucosterol, fucoxanthin, and/or phlorotannins. Seaweed polysaccharides, which are not degraded by human enzymes, are a potential source of new types of dietary fibers. Seaweeds contain a high percentage of soluble fibers in comparison with other sources of fibers. Existing data suggest that seaweeds have a distinctive amino acid composition, in contrast to that of most terrestrial vegetables. Further research is required to analyze their nutritional value, especially biochemical analysis using modern technologies and evaluation of their bioavailability. Recent research on new seaweed-derived compounds, a different source of natural products, shows a potential area of nutraceutical study. Future research on chemical compounds derived from seaweeds should aim to study the effects of purified compounds under various conditions to recognize their true potential. Study of the physiological properties and chemical composition of seaweeds proves their aptness to be a good food fiber source for humans. Yet, further research is required to enhance our understanding of the nutritional value of these seaweeds. More research is required to evaluate their nutritional value as seaweeds are still an untapped source of health-beneficial molecules for the food processing and nutraceutical industries. Furthermore, seaweeds are an underutilized resource which can be explored by the food industries as condiments, additives or supplement ingredients for developing different types of flavor in processed foods.

AUTHOR CONTRIBUTIONS

BC collected the literature and wrote the manuscript. OC did literature survey. AM conceived the idea and designed the manuscript. All authors approved the manuscript for publication.

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