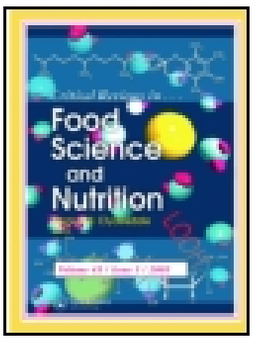

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REVIEW

Toxicological effects of marine seaweeds: a cautious insight for human consumption

Maushmi S. Kumar and Simran A. Sharma

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

ABSTRACT

Marine environment is a rich and diverse source for many biologically active substances including functional foods and nutraceuticals. It is well exploited for useful compounds, natural products and aquaculture industry; and seaweeds is one of the major contributors in terms of both food security and healthy nutrition. They are well-known due to their enormous benefits and is consumed globally in many countries. However, there is lack of attention toward their toxicity reports which might be due toxic chemical compounds from seaweed, epiphytic bacteria or harmful algal bloom and absorbed heavy metals from seawater. The excess of these components might lead to harmful interactions with drugs and hormone levels in the human body. Due to their global consumption and to meet increasing demands, it is necessary to address their hazardous and toxic aspects. In this review, we have done extensive literature for healthy seaweeds, their nutritional composition while summarizing the toxic effects of selected seaweeds from red, brown and green group which includes- *Gracilaria*, *Acanthophora*, *Caulerpa*, *Cladosiphon*, and *Laminaria* sp. *Spirulina*, a microalgae (cyanobacteria) biomass is also included in toxicity discussion as it an important food supplement and many times shows adverse reactions and drug interactions. The identified compounds from seaweeds were concluded to be toxic to humans, though they exhibited certain beneficial effects too. They have an easy access in food chain and thus invade the higher trophic level organisms. This review will create an awareness among scientific and nonscientific community, as well as government organization to regulate edible seaweed consumption and keep them under surveillance for their beneficial and safe consumption.

KEYWORDS

Acanthophora; *Caulerpa* sp.; *Cladosiphon*; *Gracilaria* sp.; *Laminaria japonica*

Introduction

Most life forms on earth have evolved approximately 450 million years ago as marine habitats (Dring 1982). Considering volumetric scale, sea provides almost 90 percent of the living space on the planet. Among all the living forms of life in water, fish is the earliest and exclusive vertebrate habitat in water. Out of them, many evolved into land mammals such as seals, dolphins or whales later. There are total ~226,000 eukaryotic marine species, which includes 20,000 fish species, though there are about two million marine species which still haven't been documented (Appeltans et al. 2012). These species measure from microscopic (plankton and phytoplankton- 0.02 micrometres) to huge mammals (whales and dolphins-33 metres). Phytoplankton are primary producers and play an integral role in the ocean food chain. Water plants such as algae are the basis of some underwater ecosystems and are a part of well-established aquaculture industry, and accounts for approximately 10% growth rate (Ginneken and de Vries 2016). The Food and Agriculture Organization (FAO) states aquaculture as farming of aquatic organisms such as fish, mollusks, crustaceans and aquatic plants. It can be classified into fish, shrimp, oyster and ornamental fish farming; mariculture and alga culture (seaweed farming).

Source of bioactive compounds and nutrients

Bioactive compounds can be either natural or synthetic in origin, and are biologically assayed for activities in a number of key therapeutic areas (MacArtain et al. 2007). Seaweeds are rich source of biologically active compounds including minerals, lipids, proteins and polyphenols (Kumar et al. 2008). They synthesize a variety of these compounds such as amino acids, terpenoids, acetogenins, alkaloids, chlorophyll, carotenoids, xanthophylls, saturated fatty acids as well as unsaturated fatty acids, halogenated compounds, vitamins K, B, A; along with alginate, proteoglycans, laminarin, fucoidan, carrageenan and galactosyl glycerol (Renn 1997; Masuda et al. 1997; Ito and Hori 1989; Skrovankova 2011; Kadam et al. 2015; Manzelat et al. 2018). These compounds exhibit antimicrobial, anti-viral, anti-coagulant, herbivore deterrent, allelopathic, and antifouling activities (Richards et al. 1978; Del Val et al. 2001; Marechal et al. 2004; Athukorala et al. 2006). They can contain up to 47% protein of the dry

CONTACT Maushmi S. Kumar maushmiskumar@gmail.com Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, V.L. Mehta Road, Vile Parle (west), Mumbai 400056, India.

weight depending on the species and their cultivation and harvesting conditions.

Porphyra is one of the most valuable alga culture crop, belonging to group Rhodophyta. It is popularly known as nori and provides excellent nutrition. It has high vitamin C, protein, minerals and trace elements (Huisman 2006). It also contains bioactive polysaccharides (porphyrin), polyphenols, proteins, chlorophyll and carotenoids. It is helpful in reducing breast cancer risks in postmenopausal (35%) and premenopausal (65%) women (Brown et al. 2014). *Porphyra umbilicalis* contain 34.2 mg/100 g wet weight of calcium, 301.2 mg/100 g wet weight of potassium, 108.3 mg/100 g wet weight of magnesium, 119.7 mg/100 g wet weight of sodium, 0.1 mg/100 g wet weight of copper, 5.2 mg/100 g wet weight of iron, 1.3 mg/100 g wet weight of iodine, and 0.7 mg/100 g wet weight of zinc. 8 g of this seaweed can provide a carbohydrate content of almost 3.8 units of carbohydrates and 2.7 units of total fiber, whereas Institute of Grocery Distribution has a guideline of daily amount (GDA) of 11.25% (MacArtain et al. 2007).

Ulva is a blade-like species belonging to Chlorophyta group, commonly known as sea lettuce. They are thin and membranous leaves, with merely two cells thickness width. It is consumed directly in the raw form (Huisman 2006). They contain approximately 24.4% of proteins on dry weight basis (Kumar et al. 2008). 8 g of Ulva provides 3 units of total fiber which is more than what a banana contains, while the GDA limit for carbohydrate content is 12.5 units. It is also a novel source for minerals, consisting of 325 mg/100 g wet weight of calcium, 245 mg/100 g wet weight of potassium, 465 mg/100 g wet weight of magnesium, 340 mg/100 g wet weight of sodium, 0.3 mg/100 g wet weight of copper, 15.3 mg/100 g wet weight of iron, 1.6 iodin*e* and 0.9 mg/100 g wet weight of zinc.

Ascophyllum nodosum regulates insulin level positively (Catarino, Silva, and Cardoso 2018). It is commonly known as Egg wrack contains a total fiber content of about 8.8 units per 8 g of seaweed. It has 575 mg of calcium, 765 mg of potassium, 225 mg of magnesium, 1173.8 mg of sodium, 0.8 mg of copper, 14.9 mg of iron, 18.2 mg of iodine, where all the minerals are in the unit mg/100 g wet weight (MacArtain et al. 2007). *Undaria pinnatifida* belong to the class of phaeophyte and contains approximately 9.14% of carbohydrates and dietary fibers, about 3.03% of proteins and approximately 0.64% of lipids (Wang et al. 2018). It reduces postprandial and fasting glucose levels, and also alters lipid profile by reducing the triglyceride levels and increasing HDL levels (Grasa-Lopez et al. 2016).

Hematococcus pluvialis contain astaxanthin, a natural antioxidant which is three times more potent than β carotene. It exhibits anti-inflammatory, immunomodulatory and anti-ageing activity (Chu 2011; Davinelli, Nielsen, and Scapagnini 2018).

Seaweeds also contain hypotensive peptides, which play an important role in combating cardiovascular disease risk factors. Thus, incorporation of hypotensive peptides containing seaweeds as functional food in form of beverages and soups is beneficial (Fitzgerald et al. 2011). Red, brown and green algae have been detected with cytostatic, anthelmintic, antibacterial, antiviral and antifungal properties. Pharmaceutically, they are employed in drug development to treat AIDS, arthritis, cancer, inflammation and pain (Lee et al. 2013). They are claimed to produce purer form of fatty acids found in human milk, considered as the building blocks for visual and mental development (De Almeida et al. 2011). They also contain unique polysaccharides and phlorotannins with many health promoting benefits (Brown et al. 2014). Brown algae contain antioxidant and anticancer compounds like carotenoid- fucoxanthin and polyphenolic compound- phloroglucinol (Padua et al. 2015). In an attempt to determine the anticancer activities of fucoxanthin and phloroglucinol alone or in combination, studies were performed in two colorectal cancer cell lines (HCT116 and HT29), and was compared to a normal colon cell line (CCD-18Co). Fucoxanthin and phloroglucinol alone reduced cancer cell line viability without an effect on normal cells, and when used in combination it enhanced the cytotoxic effect of 5-fluorouracil in colon cancer cells (Costa et al. 2017). Brown algae is rich in biologically active compounds belonging to the class of carotenoids, $\omega - 3$ fatty acids, polysaccharides, lipids, proteins and also secondary metabolites, such as terpenes and polyphenols (Reboleira et al. 2019). Pectin, guar gum etc. are soluble polysaccharides from algae and possess hypocholesterolemic and hypoglycemic activity, whereas cellulose a water insoluble polysaccharaide is associated to cause a decrease indigestive tract transit time (Kolanjinath, Ganesh, and Sanraj 2014). Algae are also known as super foods due to their enormous benefits as a source of dietary protein, B-vitamins and iron. They help in weight loss, attention deficit-hyperactivity disorder (ADHD), maintain sugar level, relieve stress, fatigue, anxiety, help in premenstrual syndrome (PMS) and in other health issues in women. The enormous beneficial effects of seaweeds also offer its use in coronary heart disease, cancer and hyperlipidemia in Japan and Western countries (Kim et al. 2009; Iso 2011; Brown et al. 2014). Seaweeds belonging to the class Phaeophyta such as Laminaria and *Undaria* contain 83–97% of fucosterol in total sterol content (662–2320 μg/g dry weight) whereas *Palmaria* and *Porphyra* which belong to Rhodophyta contain 87–93% desmosterol of total sterol content (87–337 μg/g dry weight). Few red seaweeds for example *C. crispus* has cholesterol as major sterol. It is reported that plant sterol like β-sitosterol and fucosterol leads to the decrease in the concentration of cholesterol in the serum experimentation in animals and human. Fucoidan (**5**) obtained from brown seaweeds is said to have reported *in vivo* and *in vitro* heparin like activity that demonstrate anti- thrombic and anticoagulant activity. A strong anticancer activity is demonstrated by Brown seaweeds extract obtained from *Laminaria japonica* (Kombu). Since it decreases the expansion of cancer. Regular use of *Laminaria japonica* inhibit the risk of the breast cancer considerably (Pal, Kamthania, Kumar 2014)

Toxic effects of seaweed

Seaweeds contain heavy metals and is a matter of concern due to the associated potential health risks. Inspite offering such extensive array of healthy effects, there are some

worrying incidents where avoiding excessive amounts of intake may prevent adverse effects on health of human individuals.

In Japanese population, iodine-induced goiter and transient hypothyroidism are common and gets altered by limiting the seaweed intake and thus balance the high iodine intake due to the seaweeds as a regular diet (Zava and Zava 2011). Seaweeds contain heavy metal arsenic in the form of arsenosugars, which can be further metabolized to various arsenic compounds in humans. Taylor et al. (2017) tested urinary arsenosugars and their metabolites in samples prior and post seaweed consumption in 24-hour urine samples while consuming seaweeds; tested compounds were dimethyl arsenate (DMA), thio-dimethylarsinoylethanol (thio-DMAE), thio-dimethylarsinoylacetate (thio-DMAA), and thio-dimethyl arsenate (thio-DMA) in the urine samples. Unbroken arsenosugars along with DMA, thio-DMAA, and thio-DMAE increased in urine, after ingesting nori, wakame, and kombu seaweeds. Trace amount of thio-DMA, a known toxic metabolite was present across the individuals. As commercial products from whole seaweed contain considerable concentrations of arsenic (12–84 µg/g), an assessment of these toxic compounds can help to monitor dietary intake of arsenic.

In earlier study carried out for the risk assessment of the inorganic arsenic in five edible seaweeds, they did not show any human health hazards. *Laminaria japonica*, *Porphyra yezoensis*, *Undaria pinnatifida*, *Hizikia fusiformis* and *Enteromorpha prolifera* were analyzed for arsenite, arsenate, methylarsonate, and dimethylarsinate (Zhao et al. 2014). Desideri et al. (2016) analyzed all the essential, nonessential and toxic elements present in seaweeds commonly consumed in Italy. Iodine level was highest in *Laminaria digitata* at 7316 mg/kg dry. *Ulva lactuca* contained the highest levels of Cu, Ni, Mn, and Pb. *Lithothamnium calcareum* had highest levels of Ca, Al, Si, Fe, and Ti; *Palmaria palmata* had the highest concentrations of K, Rb, and Cl; *Chondrus crispus* had the highest level of S. *Laminaria digitata* also exhibited highest concentrations of total As, Cd, Sn, Br, and I; *Chlorella pyrenoidosa* showed highest concentration of Zn. With a growing concern and awareness of heavy metals in seaweeds, Chen et al. (2018) recently investigated the distribution of 10 metals and metalloids in 295 dried brown and red seaweeds and calculated the hazard index for them. Mean value of elements in seaweeds were sequenced in descending order as: Al > Mn > As > Cu > Cr > Ni > Cd > Se > Pb > Hg. The levels of Cd, Cu, Mn and Ni were significantly higher in red seaweeds than brown seaweeds ($P < 0.01$). The results suggest a continuous surveillance for Cd, Pb and Hg in edible seaweeds. The high nutritional composition of essential elements found in algae might serve as an important source to fulfill the health requirements. However, the non-essential elements, which are toxic in nature is estimated with associated risks and its estimators.

There are no reports of poisonings by the most popular and commercially viable seaweeds such as *Porphyra* (nori), *Laminaria* (kombu), and *Undaria* (wakame), however there are few seaweeds reported to cause illness and death for e.g. *Gracilaria*, *Acanthophora*, and *Caulerpa*. Till date, there are 14 deaths reported due to consuming seaweed, but the reports claim it to be due to the bacteria grown on the seaweed responsible for these deaths (Cheney 2016). *U. fasciate, C. taxifolia, E. linza* and *S. johnstonii* acute toxicity was tested by direct feeding of powdered samples to wistar-CFT strain (Rams norvegicus, albicus) rats of each sex (body weight 200–250 g) at 0.5, 2.0 and 5.0 g/kg body weight. The doses were equivalent to consumption of 10, 50 and 100 g of seaweed per 60 kg of human body weight. Hemagglutinating mechanism was understood to be reason for toxicity, which is generally given by lectins. This may also lead to growth retardation in animals, probably due to their ability to bind to specific receptor sites on the surface of the intestinal epithelial cells resulting in impairment of nutrient absorption (Naidu et al. 1992).

In this review, we have discussed seaweeds reported for illnesses and toxicity with their chemical compounds which might affect humans. We have selected seaweeds which have been reported for number of poisonings from Rhodophyta (red) – *Gracilaria*, *Acanthophora*; Chlorophyta (green) – *Caulerpa* and Ochrophyta (brown) – *Cladosiphon, Laminaria* species and have done extensive literature search for their chemical constituents. Figure 1 shows the selected seaweeds which we discussed in our study. Since Spirulina, a cyanobacteria is widely consumed globally and have been mostly reported for their significant beneficial properties, we have also added its toxic reaction, as it is imperative to review human population of their toxicity due to its high consumption mostly in coastal region and for their cautious use.

Toxic seaweeds

Gracilaria genus

Gracilaria Greville, 1830 is a Rhodophyta and belong to the Gracilariaceae family. There are total 160 species accepted taxonomically, among more than 300 species. They are mostly found in the tropical and subtropical region and widely cultivated in Asia, South America and Africa. It shows presence of important chemical compounds such as phycocolloid, acrylic acid and other bioactive metabolites (De Almeida et al. 2011). They generally grow as large beds either in the eulittoral or sublittoral zone, on muddy or sandy sediments which are protected from waves and are employed for nutraceutical, pharmaceutical and biotechnological applications (Francavilla et al. 2013).

Gracilaria is an important source of agar, which is a non-toxic sulfated carbohydrate gelatinous in nature and widely used in the preparation of various food products, ice-creams, cosmetics and bacteriological samples. It is employed pharmaceutically as a bulking agent, anticoagulant agent, and laxatives in capsules and tablets. Agarose, highly purified agar is used in molecular biology for separation techniques like electrophoresis, immunodiffusion and gel chromatography (Pal, Kamthania, and Kumar 2014). It is also employed as a producer of carrageenan and alginate in western countries like Venezuela, USA and Canada. Alginate is used to prolong the activity of drugs (Konecny 1969). Carrageenan can also be used as a potential pharmaceutical

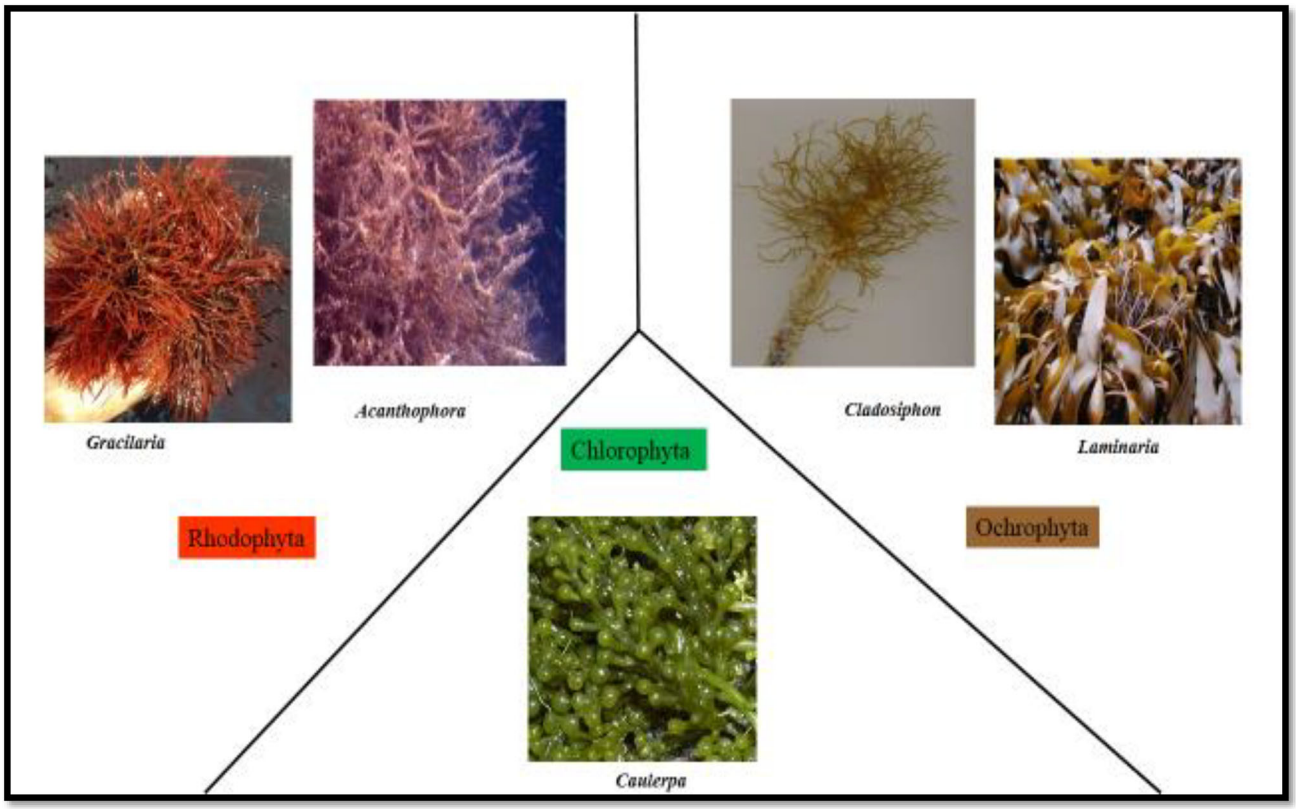

Figure 1. Seaweeds reported for their toxicity from different groups.

drug in fields such as anti-coagulant therapy, anti-tumour therapy, anti-viral therapy and immunomodulation activities (Pal, Kamthania, and Kumar 2014).

It is consumed widely in Japan, Hawaii, Guam, Malaysia and the Philippines. The human intoxications from *Gracilaria* ingestion have occurred in Japan, Sakata, Yamagata Prefecture, Toyo and Ehime (Konecny 1969). Till date, it has been found responsible for the maximum number of illnesses and deaths in the Pacific Rim countries. Majority of the incidents of death and illness were caused by the species *G. verrucosa* and *G. edulis* which is also known as *Polycarvernosa tsudai* (Cheney 2016). One of the major cases of human intoxication due to ingestion of red algae *G. edulis* reported 3 deaths and 13 people falling ill. The worst outbreaks with maximum number of deaths occurred in Japan in the year 1980, 1982 and 1993 along with one in Guam in the year 1991 and two in Philippines in the year 2002 and 2003. The other poisoning was reported in California in 1992, and in Hawaii in the year 1994 (Cheney 2016). In another incident, one of two patients died due to mere ingestion of *G. verrucosa* (Japanese name, ogonori) in Kanagawa, Japan in the year 1993 (Noguchi et al. 1994; Yotsu-Yamashita et al. 2004). The poisoning caused by *G. verrucosa* and *G. chorda* (tsurushiramo) occurred in 1980, 1982 and 1993 in Japan and were characterized by symptoms such as nausea, vomiting, stomach pain and diarrhea. *G. chorda* diseased four individuals and resulted into one death among them. *G. verrucosa* infected six and caused one death in 1982; later infected two and caused one death in 1993 (Fusetani and Hashimoto 1984). A similar incident had occurred due to consumption of *Gracillaria vermiculphylla*, where symptoms appeared within one hour of consumption followed by the other gastric disturbances such as nausea, vomiting and diarrhea (Hammann et al. 2016). In the investigations carried out by Fusetani and Hashimoto (1984), water soluble fractions of *G. verrucosa* and *G. chorda* led to death of mice within 9 mins to 20 hours at a dose equivalent to 1–2 g of wet material, whereas diarrhea was reported in mice within 5–10 mins at a dose equivalent to 0.5 g of the extract or less. This study resulted into isolation of two prostaglandins i.e. prostaglandin A_2 (PGA_2) (**1**) and prostaglandin E_2 (PGE_2) (**2**), which were suspected for the ogonori poisoning. These prostaglandins were isolated from *G. vermiculophylla* and *G. verrucosa*, wherein PGE_2 (**2**) was found to be more toxic than PGA_2 (**1**) indicating it as a probable agent for causing poisoning. PGE_2 (**2**) is also reported to be present in *G. verrucosa* and *G. lichenoides*. This prostaglandin is known to cause a wide range of physiological activities in humans, such as diarrhea, nausea, bleeding and hypertension. It is administered for inducing child birth through artificial means. About 0.5 mg of PGE_2 (**2**) is administered orally to pregnant women (Osathanondh et al. 1980; Hammann et al. 2016). Symptoms such as temporary hypertension backed by hypotension with bleeding, headache, vomiting, diarrhea and nausea is observed in these cases. With an increase in the dose by almost twelve folds, the casualty can suffer from nausea, abdominal pain and vomiting instantaneously. Hypotension can also result in a very short span of time which would eventually lead to death due to hypotensive shock. The hypotension caused can be attributed to PGE_2 (**2**) due to its activity of shrinking the womb. It also leads to an excessive

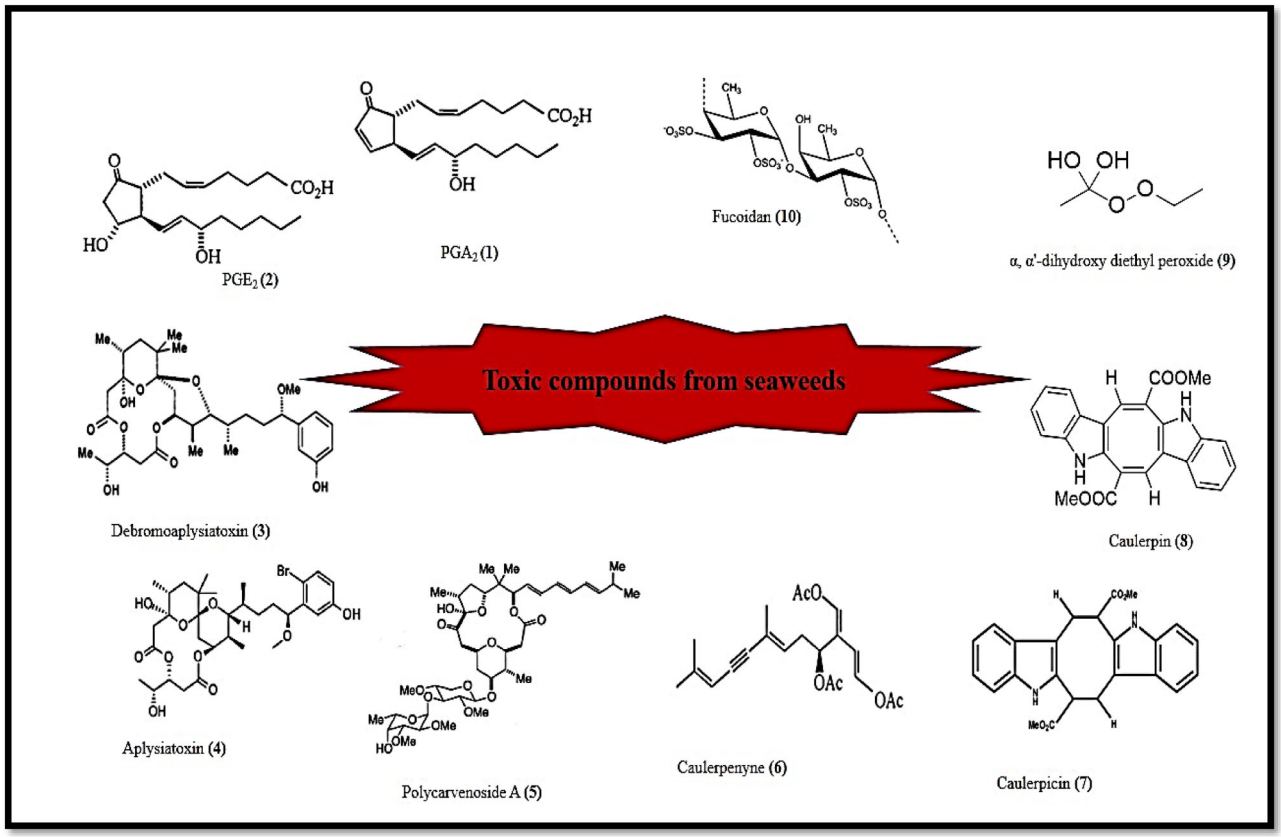

Figure 2. Compounds obtained from different seaweeds found responsible for their toxicity.

excretion of urine (Konecny 1969). PGE_2 (**2**) can also increase cardiovascular risk by contributing to atherogenesis and influence inflammatory, immune, and oxidative stress responses, which are reported to alter growth, fibrosis, and apoptosis in renal cells (Nasrallah, Hassouneh, and Hebert 2016). The possible reason for the toxicity due to PGE_2 (**2**) can be attributed to the fact that, the cyclooxygenase (COX) in raw seaweeds use the highly unsaturated fatty acids to produce large amounts of $PGE_{2\ (2)}$ in the stomach of victims in a short lapse of time. As per the paper recently a COX gene producing $PGF_{2\alpha}$ was cloned from this alga and heterologous expressed (Hsu et al. 2007; Di Costanzo et al. 2019).

In an unpleasant incident, a couple had fallen ill within 3 hours of consumption of 20–30 g of raw and freshly collected *G. verrucosa*. The wife developed low blood pressure and eventually leading to unconsciousness and death after 14 hours because of hypotensive shock, whereas the husband gradually recovered and survived. The sample consumed was investigated to have PGE_2. Though the concentration of PGE_2 (**2**) was not high, yet the toxic levels were produced due to the presence of an unsaturated fatty acid -arachidonic acid in combination with PGE_2 (Cheney 2016). However, it is also reported to show immunopotentiating activity when administered orally and intraperitoneally to mice at a dose of 4.0 mg, along with promoting phagocytosis (De Almeida et al. 2011).

When Hawaii was affected by *G. coronopifolia* poisoning, it affected seven people in 1994. The symptoms included vomiting and diarrhea, along with an additional symptom of burning sensation in mouth and throat. Debromoaplysiatoxin (**3**) and Aplysiatoxin (**4**) were found to be the causative constituents for the additional symptoms (Figure 2). Debromoaplysiatoxin (**3**) was found to be less toxic than aplysiatoxin (**4**) from the toxicity studies performed in mice; the symptoms included immediate diarrhea within 30 minutes of consumption. Apart from this symptom, lethargy, muscular contractions and paralysis of hind legs were also observed. They also caused irritation on physical contact (Nagai, Yasumoto, and Hokama 1996). Aplysiatoxin (**4**) causes bleeding, followed by hemorrhagic shock in mice. When a morphological evaluation of diarrhea caused by aplysiatoxin (**4**) in mice was carried out, it showed that the diarrheic components apparently originated from capillaries in large intestine and were secreted directly into the lumen. The number of goblet cells increased exceptionally while showing fine cracks in the epithelium, the effect was observable within 4.5 hrs and then for 4 hrs intermittently even when the mice was administered a sub lethal dose of aplysiatoxin intraperitoneally (Ito and Nagai 1998). It was also found that different routes of administration had different site of actions but bleeding took place in both the cases. When the toxin was administered through an i.p. injection at about 250 mg/kg, initially the lymphatic vessels were dilated and later there was congestion in the lamina propria after 10 mins of the administration, where as an IV administration of about 100–200 μg/kg resulted in the death of the mice within 15 mins and bleeding was observed only in the lungs around the distended pulmonary artery (Ito and Nagai 2000).

The poisoning due to *G. edulis* (Polycavernosa *tsudai*) in Guam in the year 1991 and in the Philippines in the year 2002 is considered to be one of the deadliest poisonings (Yotsu-Yamashita, Haddock, and Yasumoto 1993). Both outbreaks collectively caused five deaths and sickness to twenty-two people. This outbreak symptom included vomiting, diarrhea and numbness of the extremities including muscle spasms. The chemical compounds responsible for the toxicity were found to be polycarvenoside A (**5**) and polycarvenoside B and were suspected to be the causative agent of the poisoning. The structure of polycarvenoside A (**5**) is very similar to that of the aplysiatoxin (**4**) which is found in *G. cornopifolia* and *G. confervoides* (Nagai, Yasumoto, and Hokama 1996). Polycarvenoside A (**5**) is a glycosidic toxin and constitutes of a lactone macrocyclic core. A trienyl side chain and a methylated disaccharide component is coupled in polycarvenoside A (**5**). Several toxicity studies were carried out for polycarvenoside A (**5**), which showed that it is responsible for neurological alterations like muscle spasms, scratching and paralysis. It also induces gastrointestinal disturbances like vomiting, diarrhea, depolarization of the neuroblastoma cells and increase the calcium level in the cytosol (Cagide et al. 2007). Estimated LD_{99} for polycarvenoside A (**5**) and polycarvenoside B was determined to be 200–400 µg/kg in mice (Yotsu-Yamashita et al. 2004). *G. edulis* showed 100% sperm motility inhibition, due to the disruption of the plasma caused by the presence of spermicidal compounds (De Almeida et al. 2011). Apart from the above-mentioned compounds, *Gracilaria* poisoning could also be attributed to manauealides A, manauealide B, manauealide C, malyngamide M and malyngamides N. Nagai, Yasumoto, and Hokama (1997) reported that aplysiatoxin-like compounds, the manauealides, were present in *Gracilaria coronopifolia*. Weak cytotoxicity was shown by malyngamide compound in mice neuroblastoma cell line. It caused diarrhea in mice in the similar manner to aplysiatoxin (**4**) and debromoaplysiatoxin (**3**) (Higa and Kuniyoshi 2000).

On the basis of above reported studies, *Gracilaria* genus can be concluded to be taken with caution, and a detailed investigation of its or associated epiphytic compounds can be helpful to keep the species from this genus under surveillance.

Acanthophora genus

Acanthophora is a Rhodophyta, belonging to the family Rhodomelaceae (Preskitt 2001). It is widely distributed in Guam, Houtman Abrolhos and Hawaii. In Hawaii, it is considered a non-indigenous species, since it got involuntarily introduced from Guam to Oahu Pearl Harbor, Hawaii in the year 1952. Eventually, it turned out to be the most common non-indigenous algal species in the main Hawaiian Islands, supplanting many native prevalent species (Smith, Hunter, and Smith 2002). It successfully invaded the benthic habitats, due to its highly adaptable nature in diverse range of hydrological conditions, efficacious epiphytism and reproduction by both sexual and vegetative means as *A. specifera* undergoes fragmentation too. It is a highly favored and palatable food for herbivorous fishes and is consumed by green sea turtles as well. It is a good source of β-carotene, antheraxanthin and carrageenan. It also contains large amount of other nutrients, polysaccharides, sterols, lipids, dipeptides and diketosterol. Recently two bioactive flavonoids having preventive procoagulant activity in adherent human monocytes, antiplatelet and antioxidant properties have been isolated (Zeng et al. 2010). Polycarvenoside already characterized in *Gracilaria* was also found in *Acanthophora* species, wherein it contained side chains of conjugated diene and triene along with an o-methylated L-fucosyl-D-xylose. The toxicity studies performed for the polycarvenoside analog in mice revealed that the aglycone part along with the conjugated polyene side is responsible for the fatal toxicity by *A. specifera* and *G. edulis*. The amount of polycarvenoside was found to be 72 nmol/kg by LC/ESI-MS; whereas other polycavernoside congeners, debromoaplysiatoxin (**3**) and aplysiatoxin (**4**) were beyond the detection limit (Yotsu-Yamashita et al. 2004).

A. specifera caused two major outbreaks in the year 2002 and 2003 in the Philippines. These outbreaks caused thirty-three deaths cumulatively. The symptoms were very similar to *G. edulis* poisoning, *viz.* neurological disorders accompanied by gastrointestinal disorders such as nausea, vomiting etc. A brine shrimp lethality test performed with the methanolic extract of the seaweed showed a dose dependent relationship, where the mortality was found to increase with the concentration in the range of 2–10 μg/ml. The same extract obtained from the seaweed has also reported in antioxidant effects which was found to be correlated to the total phenolic content (Ailli Zakaria et al. 2011). A. specifera showed presence of polycarvenoside A. G. edulis poisoning in the year 1991 in Guam and in the year 2002 in Philippines showed presence of polycarvenoside A (Cheney 2016). The synthesis of this lethal toxin from both edible *G. edulis* and *A. specifera* alga gained momentum since 2012, where many researchers started its synthesis in lab for its potential use in antibiotic activity model (Pereira, Latino, and Gaudencio 2014). Firstly, Kasai, Ito, and Sasaki (2012) achieved total synthesis of (−)-polycavernoside A (**5**), via a convergent approach; later total synthesis by Brewitz et al. (2013) and stereo selective synthesis of γ-butyrolactones subunit of polycavernoside A (**5**) is reported by Kadari et al. (2018). It has also been reported for the accumulation of copper and cadmium from the Gulf of Mannar with 7.83 mg/g of copper that was accumulated in the seaweeds and the maximum concentration of cadmium that was found was 1.30 mg/g. Babu et al. (2014) revealed that copper was comparatively more toxic than cadmium and led to glutathione reduction, fluctuations of superoxide dismutase, catalase and glutathione peroxidase activity corresponding to the time of exposure. It also led to a decrease in the antioxidant properties due to the metal accumulation, which can be attributed to increased oxidative stress and induced antioxidant Defense system against ROS and DNA damage was also reported.

Further investigations revealed that it contains a flavone compound later to be identified as apigenin and on further studies it was found out that apigenin had promising

analgesic and anti-inflammatory activities. To confirm the bioactivity hot plate and writhing test in mice, as well as tail-immersion, carrageenan-induced paw edema and cotton pellet-induced granuloma formation in rats were performed. The possible mechanism for the above responses was the ability of apigenin to inhibit $PGE_{2\ (2)}$ as well as proinflammatory cytokines such as interleukin-1β, interleukin-6, and TNF-α (El Shoubaky et al. 2016).

Caulerpa genus

Caulerpa genus belongs to the chlorophyta group in the family Caulerpaceae. The green algae *Caulerpa* genus consists of a thallus containing one cell with many nuclei and is coenocytic in nature. Three species, particularly *C. racemosa*, *C. racemosa* var. *laetevirens* and *C. lentillifera* are widely consumed (Nagappan and Vairappan 2014). It is a non-native, invasive species in the Mediterranean, and an important stressor for several native organisms (Gorbi et al. 2014). *Caulerpa racemosa* var. *cylindracea* was introduced from south-western Australia (Klein and Verlaque 2008). Since 1990, it has been invading the Mediterranean Sea and the Canary Islands, raising ecological problems. It is widely distributed in the tropical seas. In the Southeast Asian waters, there are at least ten known species. It has become serious biological pollutant due to its invasive property and grows on substrates like sand, rocks and mud. It grows in the Mediterranean Sea, where it was accidently introduced in the year 1984. Due to its fast spreading property, it proliferated rapidly from Italy to Spain. They produce repulsive secondary metabolites which is used against grazers and epiphytes. Caulerpenyne (**6**) has been identified from total 11 species belonging to *Caulerpa*. Out of these 11 species, two species *C. prolifera* and *C. taxifolia* are found in the Mediterranean Sea, among which *C. taxifolia* garnered the nickname of "killer alga". Chemically, caulerpenyne (**7**) is a sesquiterpene having a diacetoxy-butadiene function (Figure 2) and exhibit antitumoral effect which has been hardly explored (Sfecci et al. 2017). There are many other minor metabolites which are also studied for their toxic activity, as they are transferred to the marine food chain. There are many poisoning cases reported due to consumption of fish *Sarpa salpa*, also known as the Mediterranean Sea bream.

Ciguatera poisoning a foodborne disease, is caused by consumption of *S. salpa* fish contaminated by ciguatera toxin. Chemically, it is a lipid soluble compound generally produced by dinoflagellates. It generally causes nausea and pain, and can lead to neurological disorders such as hallucinations, vertigo and amnesia along with cardiac symptoms in humans (Massin 1996; Kurt et al. 2009). However, later it was found that the causative fish had been feeding on *C. prolifera*. *S. salpa* from the Tunisian coast was also found to be toxic. As reported by Kurt et al. 2009 caulerpenyne (**7**) alters ATP-dependent calcium storage in the intracellular organelles, protein phosphorylation and in DNA synthesis. The antiproliferative activity of this toxin was similar to the anticancer drug -fotemustine and cisplatin. Cisplatin shows its action by binding with DNA and tubulin constituent of the cytoskeleton. Additionally, a few mollusks feeding on *Caulerpa* also exhibited a significant increase in their toxic metabolites, resulting into toxicity to its predators.

Its toxicity to humans in very high doses was also reported. It proved its toxicity to human melanocytes, keratinocytes and fibroblasts. It revealed cytotoxic activity at the concentration of 60-90 μM leading to the destruction of human hematopoietic progenitors. It didn't prove to be toxic to normal melanocytes in concentrations < 10.5 μM and normal keratinocyte $<$ 12.6 μM (Massin 1996). Caulerpenyne (**7**) is found to be neurotoxic since it inhibits the onset of neurite which acted as a trigger for apoptosis leading to cell degeneration and death. Apoptosis was identified by chromatin condensation within the nucleus and intact nuclear boundaries whereas the late apoptotic cells were identified by nuclear fragmentation (Kurt et al. 2009). There are also reports of a toxic constituent named caulerpicin (**7**) (Figure 2), obtained from *C. racemosa* which has anesthetizing sensation and causes numbness of the tongue, lips and cold sensation in the fingers and the feet. Felline et al. (2012) showed an indirect mechanism which contributed to change in fish stocks by accumulation of caulerpin (**8**) in fish tissues. Some enzymatic pathways were activated while few got inactivated. Catalase, glutathione peroxidases, glutathione S-transferases, total glutathione were enzymes which were activated; acetylcholinesterase and acylCoA oxidase were inactivated which indicates their neurotoxic potential. Sudden difficulty in breathing is also reported. Caulerpin (**8**) isolated from *C. racemosa, C. serrulata* and *C. sertularioides* is an orangish red pigment. It was chemically characterized as a dimer of indole-3-acrylic acid (Nagappan and Vairappan 2014). It also demonstrated plant growth activities (Higa and Kuniyoshi 2000). Apart from the *Caulerpa* toxins, caulerpin and caulerpinic acid possess insecticidal activity against *Culex pipiens*, which is a common house mosquito (Cheney 2016). Caulerpin (**8**) produces mild anesthetic action, difficulty in breathing, sedation and loss of balance (Figure 2). These toxins can be explored for their use for diseases caused by mosquitoes for effective and efficient treatment.

Cladosiphon genus

These brown seaweeds belong to the family Chordariaceae. Marine brown algae belonging to families Nemacystaceae and Chordariaceae are extensively consumed in Japan. These have caused poisoning in people occasionally. One such poisoning was named as mozuku poisoning. There have been two mozuku poisonings. In the first incidence, *Nemacystus decipiens* commonly known as mozuku in Japanese, occurred in Ogashi, Akita in the year 1967. The second incident was caused by *C. okamuranus* commonly known as Okinawa-mozuku. This had taken place on the Yoron Island in the year 1974. Toxicity studies were performed in mice with water and fat-soluble extracts and were administered intraperitoneally and orally. The fat-soluble extracts killed the mice overnight. The symptoms of lacrimation, paralysis of hind legs, fatigue, piloerection, and difficulty in respiration, convulsions and death were recorded. Structural

elucidation of the chemical compound characterized it as a diethyl peroxide (**9**) namely α, α'-dihydroxy diethyl peroxide. The poisoning was also confirmed by a synthetic peroxide, which demonstrated the same toxicity when administered orally and intraperitoneally. Similar peroxide compounds are also found in brown alga *Analipus japonicus* and in the red alga *Gracilariopsis chorda* (Fusetani and Hashimoto 1981; Fusetani and Hashimoto 1984).

Fucoidan (**10**) (Figure 2) is an important polysaccharide found in *C. okamuranus*, being consumed since early times in countries like China, Korea and Japan (Kusaykin et al. 2008). They belong to the class of L-fucose enriched sulfated polysaccharides, mainly to be seen in the extracellular matrix of brown algae (phaeophyceae) (Cumashi et al. 2007; Li et al. 2008; Lim et al. 2019; Tako, Yoza, and Tohma 2000). It generally contains high amount of L-fucose and sulfate, along with few other sugars such as xylulose, glucuronic acid, galactose and mannose. Fucoidan (**10**) from *Cladosiphon okamuranus* contained fucose, glucuronic acid and sulfate in a molar ratio of about 6.1:1.0:2.9 (Nagaoka et al. 1999). Fucoidan (**5**) extracted from *C. okamuranus* contained 30.9% w/w of fucose, 0.7% w/w xylulose, 2.2% w/w glucose, 23.4% w/w of uronic acid and 15.1% w/w of sulfonic acid with no mannose (Cumashi et al. 2007). It's anti-ulcer activity was investigated in gastric mucosa, which exhibited anti-peptic activity of fucoidan (**10**), dextran sulfate, carrageenan without any inflammatory activity Fucoidan (**10**) also prevents *H. pylori* infection thus reducing the risk of gastric cancer associated with it (Shibata et al. 2000). It also improved murine chronic colitis by down-regulating interleukin-6 production from colonic epithelial cells suggesting its usefulness in inflammatory bowel disease and thus suggested to be taken as dietary substance in humans. Fucoidan was accumulated in the sinusoidal non-parenchymal and mononuclear cells present in the jejunal lamina propria in female Balb/c mice and also blocked the adhesion of *Helicobacter pylori* to human gastric cell line (Matsumoto et al. 2004). They possess antithrombic, antiproliferative, antitumoral and anticoagulant activities. It is also found that fucoidan (**5**) from *Cladosiphon* seaweed could alter the ratio of CD_4^+/CD_8^+ cells, thus increasing the number of cytotoxic T cells. It is also reported to be an effective cardio protective agent by Thomes et al. (2010); it could protect the cardiac cells from isoproterenol induced myocardial infarction which could be attributed to detoxification of isoproterenol by antioxidant Defense system and alteration in the HDL and LDL values. Fucoidan (**10**) cannot be degraded by human digestive enzymes and is utilized in very low to negligible quantities by intestinal bacteria. Toxicity study of fucoidan (**10**) in wistar rats did not show any toxicity at low dose, but it significantly prolonged the clotting time at higher dose (Gideon and Rengasamy 2008) due to its binding to various adhesion proteins, growth factors, cytokines and enzymes such as coagulation proteases (Thomes et al. 2010); incidences of diarrhea occurred with a dose of about 6 g/day up to 13 months (Gideon and Rengasamy 2008; Fitton 2011). They are also known for their potent anti-inflammatory activities (Cumashi et al. 2007). It was successful in reducing total and low-lipoprotein cholesterol (Abe et al. 2013). Also fucoidan (**10**) obtained from *C. okamuranus* showed anti *H. pylori*, anti-ulcer and anti-functional dyspepsia effects (Bellmann et al. 2014). These benefits can have a promising future which needs to be explored.

Fucoidan is also proven to have an antagonistic effect to most of the pathogens, and to have antitumor activity (Kusaykin et al. 2008). Fucoidan (**10**) obtained from *C. okamuranus* causes enlargement of natural killer cells (Azuma et al. 2012). Fucoidan (**10**) from *C. okamuranus* exhibited a low-toxic antiviral compound to be used in the poultry industry (Elizondo-Gonzalez et al. 2012). Another study also evaluated its anti-viral activity against Newcastle disease virus (NDV) which is dreadful to the poultry (Trejo-Avila et al. 2016). Results showed that fucoidan (10) is also active against this virus when applied in ovo, while it was nontoxic at therapeutic doses (Aguilar-Briseño et al. 2015). Thus, it can be a prospective lead to serve as an anti-viral and anti-tumor drug, for which further studies are required.

C. okamuranus contains another compound structurally similar to toxin A, obtained from *Sphaerotrichia divertica*. Toxin A was found to be lethal to mice at a dose of around 250 µg/g (Anthoni et al. 1987). The fat soluble fractions from *S. divaricata* and *C. okamuranus* have been found toxic in the study carried out by Fusetani and Hashimoto (1981). The toxins were generated only when the algal body was heated with surrounding water.

Laminaria genus

Laminaria is a kelp that belongs to family Phaeophyceae. They are widely distributed in the North Atlantic Ocean, Pacific Ocean and in the warm waters of Mediterranean Sea. It is an economically important seaweed cultured in China and distributed widely in Korea and Japan (Li, Zhang and Song 2005). *Laminaria* consists of 50.7% dietary fibers, reported as the maximum content among all other seaweeds as well as plants. It contains 32.8% water-soluble and about 17.9% water insoluble dietary fibers. The water-soluble dietary fibers are bioactive to a larger extent in humans. It contains a high molecular weight polysaccharide namely algin, and good amount of iodine, potassium, magnesium, calcium and iron (Kim and Bhatnagar 2011). Apart from these, they are also reported to have cadmium and copper. These metal ions are considered to be highly toxic as they may cause damage to the liver, nerves and bones since they can interfere with membrane ion transport. Functional groups of various vital enzymes can be blocked by this seaweed (Ye, Wang, and Tseng 2005). However, it can be used for the treatment for goiter since it contains highest amount of iodine (Mason 1959). *L. digitata* arsenic is found in the form of arsenosugars is natural ingredient of *L. japonica* (Kuehnelt, Irgolic, and Goessler 2001; Hwang et al. 2016). *L. japonica* is reported to have high amounts of total arsenic, inorganic arsenic, total and chemical forms of cadmium (Zhao et al. 2012). Dibutyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) also occurs naturally in *L. japonica* (Namikoshi

et al. 2006). *L. japonica*, *L. saccharina*, and *L. cloustoni* are approved as a food additive as a source of iodine for direct human consumption. *L. hyperborean* is commonly used for thyroid regulation in herbal medicine (PDR for herbal medicines 2000). *L. japonica* contains 54% bio-accessible iodine (Alves et al. 2018). It has been a part of traditional Chinese medicine since a long time now. Studies show that the polysaccharides that are isolated from this seaweed has endogenous enzymes with antioxidant properties (Peng et al. 2012). It is also reported to have anticoagulant and antioxidant properties (Peng et al. 2013). Aqueous extract of *L. japonica* exhibited the hypotensive activity in rats with normal blood pressure. In the studies performed for their effects on the cardiac functions, the extracts from *L. japonica* decreased atrial beats in a dose dependent manner (Chiu and Fung 1997).

Laminaria used for cervical dilation is also predicted to cause toxic shock syndrome. Women experience dyspnea, tachycardia, and hypotension after application, and the sample showed presence of heavy growth of *Staphylococcus aureus* and expression of *Staphylococcal* enterotoxin C when amniotic membrane culture was tested (Sutkin et al. 2001). *L. japonica* also contains fucoidan (**10**) which demonstrated protective effect against chronic renal failure. Fucoidan increased the clotting time significantly in wistar rats during the toxicologic studies. The increase in clotting time was dose dependent (Li, Zhang and Song 2005). It was shown that at a dose of more than 300 mg/kg of body wt./day of fucoidan from *L. japonica* significantly increased clotting time and reduced aspartate transaminase (AST); significant reduction in glucose levels was also observed at the dose of 2,500 mg/kg of body wt./day (Gideon and Rengasamy 2008). Fucoidan (**10**) obtained from *L. japonica* has the potential to stop free radical chain reactions and act as a potent antioxidant (Zhao et al. 2004). *L. japonica* extract (up to 400 mg/kg) caused decrease in body weight, fat-pad weights, and serum and hepatic lipid levels in rats, when administered by gavage for 6 weeks (Jang and Choung 2013). In patch test on human skin, cream containing a 50/50 aqueous/propylene glycol extract of *L. japonica* (10%; 20 mg) it exhibited nonirritating effect (Choi et al. 2013). A low-molecular-weight fucoidan of approximately 7.6 kDa obtained from *L. japonica* had better absorption profile and antithrombotic activity in male wistar rats when compared to medium-molecular-weight fucoidan of approximately 35 kDa. Oral administration of the low-molecular-weight fucoidan at 400–800 mg/kg prolonged the activated partial thromboplastin time (APTT) and thrombin time (TT) in male wistar rats (Sanjeewa and Jeon 2018). Cao et al. (2016) stated that polysaccharides obtained from *L. japonica* can be used as a new therapy against respiratory syncytial virus (RSV) which belongs to the family *Paramyxoviridae* and responsible for respiratory viral infection.

Table 1 is an extensive compiled list of edible seaweeds belonging to different class and their nutritional composition with reference to the daily average requirements recommended by USFDA guidelines for adults and children above 4 years of age (CFR-USFDA 2018).

Impact of toxic seaweeds, microalgae and algal blooms in the food chain

Seaweeds are highly nutritious and have multiple benefits like it helps thyroid function, diabetes, gut health, weight loss and cardio protective action. Along with high nutrition value and therapeutic properties, they may suffer high risks due to the presence of excess iodine and heavy metals. *Hizikia fusiforme* has arsenic concentrations $>$ 50 mg/kg (Ichikawa et al. 2006). Edible seaweeds if boiled, their arsenic content reduces by 43–50% (Laparra et al. 2003; 2004) and by soaking up to 60% reduction in arsenic content occurs (Hanaoka et al. 2001). In a study in Korea, 426 seaweed samples were tested for arsenic, lead, mercury, and cadmium levels. Arsenic was highest at 17.4 mg/kg dry weight, and assuming 8.5 g per day seaweed consumption, the intake was falling in the WHO recommended weekly limit (0.2–6.7%). The study confirmed minimum chances of health risks from the metals consumed via seaweed (Hwang et al. 2010).

In marine ecosystem, food webs constitute of food chain, which connect at different trophic levels. They support long, intricate, complicated, as well as short food chains. All the food webs have the same basic trophic levels throughout the world, with only variation in numbers and types of species that constitutes each level with the ecosystem. The consumers of seaweeds can be herbivores, omnivores or carnivores. People are mostly exposed to algal toxins through contaminated seafood products consumption. They are amnesic shellfish, ciguatera fish, diarrhetic shellfish, neurotoxic shellfish and paralytic shellfish poisoning. The most significant problem to human health have been caused by harmful algae, diatoms, dinoflagellates poisoning. Amnesic Shellfish Poisoning (ASP) is caused by diatom *Pseudo-nitzschia* sp. due to produced toxin named domoic acid. Fish and crab viscera can also contain domoic acid, causing high risk to human consumers and animals in food chain (Subba Rao, Quilliam, and Pocklington 1988; Lawrence et al. 1989; Novelli et al. 1992). Ciguatera fish poisoning (CFP) is caused by ciguatoxin/maitotoxin produced by *Gambierdiscus toxicus*, *Prorocentrum* spp., *Ostreopsis* sp., *Coolia monotis*, *Thecadinium* sp. and *Amphidinium carterae*. Diarrhetic shellfish poisoning (DSP) is caused by okadaic acid produced by *Dinophysis* sp. *Karenia brevis*, a marine dinoflagellate causes neurotoxic shellfish poisoning (NSP) by produced brevetoxins. Saxitoxins produced by *Alexandrium* sp., *Gymnodinium catenatum*, *Pyrodinium bahamense* causes paralytic shellfish poisoning (PSP). It is prevented by active monitoring programs to check toxin level in mussels, oysters, scallops, clams etc. (Baden, Fleming, and Bean 1995). Many fatal outbreaks have taken place due to shellfish poisoning leading to the death of birds, mammals from the marine environment. In 1998, sea lions suffered from an unknown disease with seizures symptoms at the California coast. While earlier it was thought of mercury poisoning, later it was co-related to a similar incidence with a few people in Canada; wherein they were diagnosed by amnesic shellfish poisoning caused by the consumption of blue mussels infected by domoic acid, which is generally produced by

Table 1. Edible seaweeds and their nutritional content with specific reference to the daily intake of minerals per day as per FAO guidelines.

USFDA avg. daily limits in adults and children above 4 years	Carbohydrate 1275 g	Dietary fiber 128 g	Lipid 178 g	Protein 150 g	Na 2300 mg	K 4700 mg	P 1250 mg	Ca 1300 mg	Mg 420 mg	Fe 18 mg	I 150 μg	Ref. (CFR-USFDA 2018)
Chlorophyta												
Caulerpa lentillifera	38–59	33	0.86–1.11	10–13	8917	700-1142	1030	780–1874	630–1650	9.3–21.4	–	(Matanjun et al. 2009; Pattam and Chirapart 2006; Yuan 2008)
Caulerpa racemosa	33–41	64.9	9.8	17.8–18.4	2574	318	29.71	1852	384–1610	30–81	–	(El-Sarraf and El-Shaarawy 1994; Akhtar and Sultana 2002; Santoso, Yoshie-Stark, and Suzuki 2006; Kumar, Gupta, et al. 2010)
Codium fragile	39–67	5.1	0.5–1.5	08–11								(Ortiz et al. 2009; Guerra-Rivas et al. 2010)
Ulva compressa	48.2	29–45	0.3–4.2	21–32							–	(Burtin 2003; Mamatha et al. 2007; Patarra et al. 2010; Yuan 2008)
Ulva lactuca	36–43	29–55	0.6–1.6	01–25		–	140	840	–	66	–	(Fleurence et al. 1995; Manivannan et al. 2008; Morrissey, Kraan, and Guiry 2001; Yuan 2008)
Ulva pertusa	47	–	–	20–26								(Fujiwara-Arasaki, Mino and Kuroda 1984; Fleurence et al. 1995)
Ulva rigida	43–56	38–41	0.9–2.0	18–19	1595	1561	210	524	2094	283		(García, Castroviejo, and Neira 1993; Kumar, Gupta, et al. 2010; Santoso, Youshie-Stark and Suzuki 2006; Taboada, Millán and Míguez 2010)
Ulva reticulata	50–58	65.7	1.7–2.3	17–20							–	(Kumar, Gupta, et al. 2010; Shanmugam and Palpandi 2008)
Phaeophyceae												
Alaria esculenta	46–51	42.86	1 to 2	9–20								(Abbott 1988; Morrissey, Kraan, and Guiry 2001)
Durvillaea antarctica	70.9 ± 2.7	71.4 ± 0.5	08 ± 0.2	10.4 ± 0.3	52.9 ± 1.0 (g/kg)	15.6 ± 2.7 (g/kg)	–	–	–	13.7 ± 1.8 (mg/kg)	29.1 ± 2.7 (mg/kg)	(Ortiz et al. 2006; Smith, Summers, and Wong 2010)
Eisenia bicyclis	60.6	10–75	0.1	7.5								(Misurcová et al. 2010; Yuan 2008)
Fucus spiralis	–	63.88	–	10.77								(Patarra et al. 2010)
Fucus vesiculosus	46.8	45-59	1.9	3–14	2450–5469	2500–4322	315	725–938	670–994	4–11	14.5	(Applegate and Gray 1995; Díaz-Rubio, Pérez-Jiménez, and Saura-Calixto, 2009; Fleurence et al. 1995; Rupérez 2002; Saá 2002; Truus, Vaher, and Taure 2001)
Himanthalia elongata	44–61	33–37	0.5–1.1	5–15	4100	8250	240	720	435	59	14.7	(Brutin 2003; Gómez-Ordóñez, Jiménez-Escrig, and Rupérez 2010; López-López et al. 2009; Plaza, Cifuentes, and Ibáñez 2008; Saá 2002; Yuan 2008)
Laminaria digitata	48	36–37	1	8–15	3818	11,5 79	–	1005	659	3.29	–	(Brutin 2003; Fleurence et al. 1995; Morrissey, Kraan, and Guiry 2001; Rupérez 2002; Yuan 2008)
Laminaria ochroleuca	–	–	0.92	7.49								(Yuan 2008)
Nereocystis luetkeana	38.82	1.30	1.94	15.28	5.08 ± 0.025 (% dry wt.)	1.30 ± 0.099 (% dry wt.)	–	51 (% dry wt.)	–	43.3 (% dry wt.)	–	(Barta, Branen, and Leung 1981)
Saccharina japonica	51.9	10–41	1.0–1.9	7–8	2532–3260	4350–5951	150–300	225–910	550–757	1.19–43	130–690	(Funaki et al. 2001; Mabeau and Fleurence 1993; Mišurcová et al. 2010; Yuan 2008)

(*continued*)

Table 1. Continued.

USFDA avg. daily limits in adults and children above 4 years	Carbohydrate 1275 g	Dietary fiber 128 g	Lipid 178 g	Protein 150 g	Na 2300 mg	K 4700 mg	P 1250 mg	Ca 1300 mg	Mg 420 mg	Fe 18 mg	I 150 μg	Ref. (CFR-USFDA 2018)
Saccharina latissima	52–61	30	0.5–1.1	6- 26	2620	4330	165	810	715	–	15.9	(Gómez-Ordóñez, Jiménez-Escrig and Rupérez 2010; Morrissey, Kraan, and Guiry 2001; Saá 2002)
Sargassum fusiforme	30.6	17–69	1.4	11.6	–	–	–	1860	687	88.6	–	(Funaki et al. 2001; Mabeau and Fleurence 1993; Mišurcová et al. 2010; Yuan 2008; Sugawa-Katayama and Katayama 2009)
Sargassum vulgare	67.80	7.73	0.45	15.76								(Marinho-Soriano et al. 2005)
Undaria pinnatifida	45–51	16–51	1.05–4.5	12–23	1600–7000	5500–6810	235–450	680–1380	405–680	1.54–30	10–100	(Brutin 2003; Holdt and Kraan 2011; Kolb et al. 2004; López-López et al. 2009; Mišurcová et al. 2010; Rupérez 2002; Saá 2002; Yuan 2008)
Rhodophyta												
Chondrus crispus	55–68	10–34	1.0–3.0	11–21	1200–4270	1350–3184	135	420–1120	600–732	4–17	17.3	(Holdt and Kraan 2011; Morrissey, Kraan, and Guiry 2001; Saá 2002; Rupérez 2002; Yuan 2008)
Gracilaria changii		24.7	3.3	6.9	5465	3417	–	402	565	3.6–5	–	(Krishnaiah et al. 2008; Yuan 2008)
Gracilaria chilensis	66.1	–	1.3	13.7	5465	3417	–	402	565	3.6–5	–	(Krishnaiah et al. 2008; Ortiz et al. 2009)
Palmaria palmata	46–56	29–46	0.7–3	8–35	1600–2500	7000–9000	235	560–1200	170–610	50	10-100	(Holdt and Kraan 2011; Morrissey, Kraan, and Guiry 2001; Saá 2002; Rupérez 2002; Yuan 2008)
Porphyra tenera	44.3	12–35	0.7–1.3	28–47	3627	3500	–	390	565	10–11	1.7	(Brutin 2003; Fleurence et al. 1995; Mišurcová et al. 2010; Rupérez 2002; Yuan 2008)
Porphyra umbilicalis	43	29–35	0.3	29–39	940	2030	235	330	370	23	17.3	(López-López et al. 2009; Saá 2002)
Porphyra yezoensis	44.4	30–59	2.1	31–44	570	2400	–	440	650	13		(Indergaard and Minsaas 1991; Noda 1993; Yuan 2008)

The composition of carbohydrate, dietary fibers, lipids and proteins are in % dry weight; minerals sodium (Na), potassium (K), phosphorus (P), calcium (Ca), magnesium (Mg), iron (Fe) are in mg and Iodine (I) is in μg.

a certain type of algae belonging to *Pseudo-nitzschia* genus, and is essentially a neurotoxin. Further investigations also reported domoic acid being found in the gastrointestinal contents and body fluids of thirteen different mammal species from the Alaskan waters (Husson et al. 2016).

Over the last two decades, due to the increase in pollution and eutrophication there has been a growing concern about the impact of microalgal and cyanobacterial blooms. Harmful effects, including the development of high biomass and scums is decreasing the water quality and adversely affecting the aquatic ecosystems, simultaneously affecting the aquaculture industry and human health (Zerrifi et al. 2018). Hundreds of fish and shellfish are often found dead and following many people getting ill after consuming certain shellfish, only to later discover deadly toxins in the sick or dead species. Tiny phytoplankton cells produce potent toxins, which is eaten by zooplankton. Zooplanktons are microscopic animals, which remain unaffected by these toxins. Zooplankton and phytoplankton are eaten by many animals from tiny shrimp, krill, mussels and fish to the largest of mammals. The minuscule toxin produced by phytoplankton cell gets bio-accumulated through the food web as each organism consumes more and more of the toxin, ending in a bigger dose of toxin in higher mammals causing their death. It may be also transported to humans through the food web, mostly through contaminated shellfish. These toxins affect the nerve and muscle cells, causes respiratory irritation, distress, gastrointestinal disturbances, paralysis and death (Pokapū Akoranga Pūtaiao 2012)

Spirulina is used as a vegan source of vitamin B12 and protein, and is also known to improve lipid and glucose metabolism and reduce liver fat and exhibit cardio protective property. It has few active compounds such as phycocyanobilin, which mimics the body's bilirubin and inhibit the NADPH oxidase enzyme (McCarty 2007). It also provides potent anti-oxidative and anti-inflammatory activity. A daily dose of about 1-8 g daily is effective for cholesterol, 2–7.5 g daily is found to be impactful in muscle performance. Mild effects are observed with a daily consumption of 2 g per day for blood glucose control. Fatty liver results are effective at dose of about 4.5 g daily and blood pressure at a daily dose of 3.5–4.5 g daily. Polyphenols rich seaweed has an important additional role in cardiovascular-associated disorders (Gómez-Guzmán et al. 2018). Seaweeds act as preventive agents for cardiovascular diseases (Cardoso et al. 2015). Though consumption of these seaweeds seem to be very nutritious and advantageous but unchecked consumption of these may cause severe issues and autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis, pemphigus vulgaris etc. *Spirulina* is a widely consumed cyanobacteria biomass which is often contaminated with blue-green algae, such as

M. aeruginosa, that produces toxic microcystins. *Spirulina plantensis* contains good amount of phycocyanin and carotenoid, which are good antioxidant compounds (Liu et al. 2016). Its antiatherogenic properties were observed due to reduction of total cholesterol in rat, hamster and rabbit. It depicts antiatherosclerotic properties among people suffering from atherogenic dyslipidemia and ischemic heart disease. It is also found to have an apoptosis preventing property in cardiomyocytes and plays a role in preventing oxidative stress. The chronic intake of Se-rich Spirulina phycocyanin averts the development of atherosclerosis, mainly due to reduction of pro-oxidant factors and by improving the serum lipid profile (Riss et al. 2007). One study reported an allergic reaction toward c-phycocyanin component present in spirulina (Petrus et al. 2009). It is also reported in case of allergic reaction within six hours of consuming 2.5 g of seaweed in a 14 years old volunteer. The Dietary Supplements Information Expert Committee (DSI-EC) of United States Pharmacopeial Convention (USP) reviewed 31 reported adverse events of spirulina to evaluate related health concerns. *Spirulina maxima* and *S. platensis* were admitted in USP-NF and class A safety grade dietary supplements (Marles et al. 2011).

Microcystins are cyclic heptapeptides produced by cyanobacteria during algal blooms; they are hepatotoxic and carcinogenic due to their property of inhibiting protein phosphatases and possible contamination with heavy metals such as cadmium, lead, mercury and arsenic (Marles et al. 2011; Marsan et al. 2018). The safe consumption of microcystin is set at 0.04 µg/kg/day (Dietrich and Hoeger 2005). An early analysis of fifteen commercial *Spirulina* supplements reported an average microcystin concentration of 0.15 µg/g (range: 0.06–0.32 µg/g) and 0.52 µg/g (range: 0.0–2.12 µg/g) in the year 1998 and 1999 respectively. This suggests that an 80 kg adult can safely consume up to 6–21 g of *Spirulina* (3.2 µg of microcystin) based on the reported average contamination levels (Gilroy et al. 2000). Though, it is suggested that *Spirulina* does not show a health risk, however it may due to contaminants from other species such as toxic microcystins produced by other bacteria growing in close vicinity of *Spirulina* (Marles et al. 2011).

Recently, researchers explored the functional characterization of marine macroalgae, in order to understand its genome protecting potential. The antigenotoxic potential of *Ulva rigida*, *Fucus vesiculosus*, and *Gracilaria* sp. was assessed in *Drosophila melanogaster* following macroalgae diet exposure and somatic mutation and recombination test approach (SMART). All macroalgae species exhibited genoprotection activity, when challenged against streptonigrin as an exogenous material. *Gracilaria* species provided indecisive indications, as 10% of *G. vermiculophylla* inhibited the egg and larvae development and 10% *G. gracilis* increased genotoxicity. *U. rigida* demonstrated higher genoprotection in an aquaculture-controlled system. *F. vesiculosus* did not produce significant changes in the growing condition. These findings can help the role of seaweed as functional food and their advantages (Marques et al. 2018). Another study by Desideri et al. (2018) investigated the bio accessibility of toxic elements, including Al, As, Ni, Cd, and Pb in five commercially available and commonly consumed algae in Italy. The bio accessibility of the toxic elements showed some interesting results with Cd having

high bio accessibility; while As and Ni exhibited up to 40–55% bio accessibility, Al and Pb exhibited poor bio accessibility (5–15%).

Even though these seaweeds act as a source of essential antioxidants, minerals and vitamins; they may lead to toxic accumulation to a higher extent due to their high absorption capacity. An overview of toxicity of edible seaweeds is presented in Table 2. These organisms are even capable of absorbing and accumulating metals without suffering any damage (Paz et al. 2019). This aspect requires continuous monitoring of edible seaweeds as a functional food and its heavy metals limit.

Side effects and adverse interactions

Seaweeds are widely consumed and is one of the most nutritious food in nature, due to their rich nutrient content of iodine, calcium, iron, vitamins B6, and B12. The most widely consumed seaweed is Kelp *viz*. kombu, arame, and wakame belonging to the family Phaeophyceae. Kombu is a highly nutritious seaweed containing calcium, carotene, phytohormones, mannitol, and vitamins. Arame is an excellent source of iron and iodine. Wakame is the richest source of calcium. Nori has highest consumption and is a good source of protein. Dulse another seaweed, commonly known as sea lettuce is known for its nutritional value. It has high content of vitamins B12, B6, A, C, E, calcium, protein, iodine and magnesium. Hijiki is another widely consumed seaweed, and is rich source of algin, calcium and dietary fibers (Murray, Pizzorno, and Pizzorno 2005).

Nori is rich in various nutrients and minerals but also impose hazardous risk like congestive heart failure, cirrhosis and chronic kidney disease. These effects are seen due to the presence of large amount of sodium. It may also reduce blood pressure thus is also contraindicated for patients undergoing treatment for hypertension this effect is attributed to the presence of docosahexaenoic acid (DHA). They also impose risks such as contact dermatitis, goiter, cholera and inflammation in large consumption of these seaweeds (Seaweed 2011).

Kelp which is previously mentioned has been reported to have various interactions and side effects. Side effects such as allergic reactions, itching, rashes, trouble in breathing, tightness in the chest, arrhythmia, nervousness, trouble in sleeping, unusual bleeding and cramps are observed. They have a tendency to interact with drugs like digoxin, potassium supplements, spironolactone, amiloride, thyroid supplements, thus patients on these medications should be careful and avoid Kelp (Kobriger 2011).

Laminaria a widely consumed seaweed for its high iodine and iron content, and benefits in weight loss, blood pressure maintenance, heartburn and cancer prevention, may also cause issue in the thyroid functioning, since an ideal intake of 150 µg of iodine is required for the normal functioning of thyroid, but *Laminaria* can provide iodine content as high as 1000 µg which eventually can lead to deranged thyroid levels (Zava and Zava 2011). They also contain significant levels of arsenic, which is poisonous and rendered unsafe; if administered directly to the cervix during childbirth or pregnancy, it may lead to rupture of cervix and infant death. High potassium levels in *Laminaria* may also lead to kidney damage and thus is contraindicated with anti-hypertensive agents. *Laminaria* contains large amount of potassium, which can increase the effects and side effects of digoxin (Atlas et al. 1998).

A study was performed in the UK, to identify all the seaweed containing products sold in the grocery market. Out of 224 products, only 22 products stated iodine content information on their labels; 40 products provided information which was sufficient to estimate the iodine content. There was a lack of information about the seaweed, its type, source and iodine content in the seaweed product, which makes the safety of these products questionable especially in people sensitive for high iodine exposure i.e. pregnant women (Bouga and Combet 2015). Thus it's very important to have the information of seaweed which is being consumed by people to predict its safety in individuals on respective diet and conditions.

Seaweeds may also decrease the pharmacological effect of anticoagulants (aspirin, warfarin) (Holbrook et al. 2005). A patient on high-iodine diet will require higher doses of antithyroid drugs. Antithyroid drugs (propylthiouracil or thyroxine) prevent iodine absorption in the stomach and with increase in the dose of antithyroid drugs, the chances of side effects such as rashes, hives, and liver disease increases (Bareuther 2008). *Fucus vesiculosus* is a slimming supplement which may compromise on the therapeutic efficacy of the amiodarone drug (Rodrigues et al. 2013). Major adverse reactions and drug interactions of seaweeds are compiled in Table 3. The herb-drug interaction between the consumable seaweeds and prescription or over the counter drugs should be studied further to accept its complete safety in patients. The amiodarone bioavailability decreased in rats, therefore the therapeutic efficacy of drugs might be being compromised by the concurrent administration of seaweed in diet or supplements. These aspects should be mostly looked into where the content and pharmaceutical composition are opposite in nature.

A toxicological study conducted by Banu and Umamageswari (2011) suggested that seaweeds are safe for human consumption and a daily consumption in the range of 5–10 g is considered safe.

Future prospects and conclusion

Seaweeds are a boon to the mankind if consumed appropriately, otherwise they may impose a major risk to humans. They are reported of many bioactive compounds which aren't found in other natural food source, and are beneficial for the human well-being by providing better health and preventing various diseases. There is need of an awareness for consuming seaweeds among people from countries where it still remains away from daily food list. As of now seaweeds are utilized mostly to extract the phycocolloid. It has great potential as a dietary source with almost all the nutrients and as reported earlier they can be looked upon as

Table 2. Overview of toxicity of seaweeds.

Name	Chemical compounds/extracts	Toxicity reported	Dose	Study data	Reference
***Gracilaria* sp.**					
a) *G. verrucosa*	Prostaglandin E_2 (PGE_2) Prostaglandin A_2 (PGA_2)	Hypotension eventually leading to death	0.5 mg was found to be beneficial to control gastrointestinal disorders.	Toxic levels produced from arachidonic acid, in the combination of the seaweed and the raw fish consumption. Hemorrhaged blood reported from the stomach.	(Noguchi et al. 1994; Cheney 2016; Se-Kwon, 2017)
		Excessive phagocytosis	2 g/kg as supplement found to have a positive immune response 4.0 mg/animal (mice) showed immunopotentiating activity stimulating phagocytosis when administered orally and by ip route.	positive effect with higher immune response in shrimps	(Jasmanindar et al. 2018; De Almeida et al. 2011)
b) *G. cornopifolia*	Aplysiatoxin Debromoaplysia-toxin	Gastrointestinal disturbances		Toxic effect studied in human adult by oral route	(Nagai, Yasumoto, and Hokama 1996)
c) *G. edulis*	Polycarvenoside A Polycarvenoside B	Gastrointestinal toxicity	Toxicity studied in mouse and LD-50 was reported as 0.825 mg/kg-ip	Semi purified toxic fraction studied on mouse bioassay contained polycarvenoside A	(Yotsu-Yamashita et al. 2004; De Almeida et al., 2011)
d) *G. chorda*	Prostaglandin E_2 (PGE_2) Prostaglandin A_2(PGA_2)	Gastrointestinal toxicity	Toxic at concentrations of about 1.2 mg/rat administered ip; 0.5 mg was found beneficial to control gastrointestinal disorders		(Fusetani and Hashimoto 1984; Cheney 2016; Se-Kwon, 2017)
e) *G. corticata*	50% EtOH-H_2O extract	Autonomic effects in dogs, CNS effects, analgesic activity in mouse	500 or 1000 mg/kg/day to female rats produced significant post-coital contraceptive activity; toxicity was assessed in mouse and LD50 reported at 1000 mg/kg-ip		(Kamat et al. 1992; De Almeida et al. 2011)
f) *G.verrucosa*		Mouse- 0.5 mg/ gastric intubation	Toxicity assessment-mouse-1.2 mg/ animal-i.p. was positive		(Fusetani and Hashimoto 1984)
g) *G. chorda*	H_2O extract	1.2 mg/animal i.p.			(Fusetani and Hashimoto 1984)
2.*Cladosiphon okamuranus*	Diethyl peroxide (α,α'-Dihydroxy diethyl peroxide)	Psychotic disturbances, Paralysis		Toxicity was tested in mice, fat soluble fraction was given after emulsified with 1% Tween 60 saline solution	(Fusetani and Hashimoto 1981)
	Fucoidan	Significant increase in clotting time	Increased clotting time >1,200 mg/ kg of body weight in wistar rats		(Gideon and Rengasamy 2008)
3. *Acanthophora specifera*	Polycarvenoside A	Neurological disorders	*A. spicifera* 100 and 200 mg /kg body weight suggested the anti-tumour properties; at doses above 2000 mg/kg body weight reported mortality and clinical signs	No sufficient amount in initial studies by authors later claimed to be polycarvenoside A	(Yotsu-Yamashita et al. 2004; Lavakumar, Ahamed and Ravichandiran 2012)

			Gastrointestinal disorders	Semi purified toxic fraction studied on mouse bioassay contained polycarvenoside A	(Preskitt 2001)
4. *Caulerpa* sp.					
a) *C. taxifolia*	Caulerpenyne	Risks of cutaneous and food intoxication was estimated minimal to humans		Skin cells, melanocytes, keratinocytes, immortalized keratinocytes, and bone marrow cells	(Massin 1996; Agardh 1822)
b) *C. prolifera*	Caulerpenyne	Neurotoxic activity		Nuclear fragmentation of apoptotic cells	(Kurt et al. 2009)
c) *C. racemosa*	Caulerpin	Cellular and Physiological Responses in fish		Inhibition of acetylcholinesterase and acylCoA oxidase	(Felline et al. 2012)
5. *Laminaria japonica*	Fucoidan	Chronotropic effect	Significant increase in clotting time at 900 and 2500 mg/kg body weight per day.	Protective effect against Diabetic cardiomyopathy	(Yu et al. 2014; Citkowska, Szekalska, and Winnicka 2019)
	Heavy metals	Hypotension		Damage to the liver, nerves and bones	(Kim and Bhatnagar 2011)

Dose of *G. verrucosa* is in mg and in g/kg for excessive phagocytosis, whereas for *G. eduli, G. Chorda, A. specifera* and *L. japonica* are in my/kg body weight.

treatments for various acute and chronic ailments and diseases. They contain maximum amount of nutrients and vitamins compared to any other food product. Antioxidant compounds like sulfated polysaccharides from them can help in treating diseases such as AIDs and cancer.

There is a need of guidelines over the limit and quality of consumption of the seaweeds by the regulatory bodies including specific drug seaweed interactions. This is mostly understood in the respect of high level of iodine in seaweeds, for e.g. *Laminaria* spp. (kombu) are brown seaweeds especially high in iodine, thus daily intake of 3–6 g of dried seaweeds is sufficient for adequate dietary iodine. Individuals who are extremely sensitive to iodine, should be cautious about the amount of seaweed in their diet to avoid symptoms of hyperthyroidism such as nervousness, insomnia, increased heart rate etc. Too much of iodine consumption can develop goiter, by increasing thyroid-stimulating hormone and skin problems. High sodium content can lead to high blood pressure and heart disease. Seaweed supplementation causes gastrointestinal disturbances with abdominal pain which decreases over a period of time due to getting used to the supplementation. Any step toward regulation of heavy metal and arsenic contamination in seaweeds from water, and public awareness over the food security from consumption of seaweeds will be a good move to enjoy highly beneficial sea plants as vegetables.

There are other equally important aspects in applications such as soil fertilizers, animal feed, fish feed, cosmetics, in integrated aquaculture, and in wastewater treatment. Integrated aquaculture is developing fast as one of the solutions to environmental sustainability problems and for the management of disposal of effluents in coastal areas from large-scale aquaculture activities. They can also be used as efficient biofuels. Their abundance in marine environment make it an easy alternative source for biofuels and thus reducing the pollution as well. Their anti-clotting properties should be widely explored and used for the treatment of cardiac diseases. Their ability to increase the T-cell count can also be employed for the treatment of cancer. Studies should be performed in the area obesity, diabetes and thyroid related disorders that have affected a large population to make use of these seaweeds effectively. These properties and its constituents can prove to have a promising future but might be affected by ocean acidification and increased temperatures due to climate change. As seaweeds remain available, edible and sustainable source to mankind, a careful regime of consumption can prevent the toxic effects and can allow people to enjoy its beneficial properties, thus its efficacious use should be promoted. While buying seaweed based packed products, people should look for the relevant information such as the source of seaweed, water quality and processing etc. which can be helpful to assess the safety of the product, and will also help to understand the potential toxic compounds. These steps will strengthen the seaweed market and its commercialization and will also attain consumer's satisfaction.

Table 3. Side effects and drug interactions of seaweeds.

Seaweeds	Side effects	Contraindications	Drug interactions	Reference
Porphyra sp.	Congestive heart failure, cirrhosis, chronic kidney disease, contact dermatitis, goiter, cholera and inflammation	Patients undergoing treatment for hypertension	No interactions are reported. Peptides from *Porphyra* show antihypertensive effects	(Lee 2019)
Kelp	Allergic reactions arrhythmia, nervousness, unusual bleeding and cramps	Patients on thyroid medication	It could potentially interact with: digoxin, potassium supplements, spironolactone, amiloride, thyroid medications blood pressure medication	(Kelp. Accessed November 24, 2018 from http:www.naturalstandard.com)
Laminaria	Hyper-thyroidism	Childbirth or pregnancy and to patients undergoing for hypertension	Digoxin	(Accessed September 28, 2019 from https://www.rxlist.com/laminaria/supplements.htm)
Spirulina Blue green algae	might decrease the effectiveness of immunosuppressants	Patients taking immunosuppressants	Azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), corticosteroids (glucocorticoids), and others.	(Accessed September 27, 2019 from https://www.webmd.com/vitamins/ai/ingredientmono-923/blue-green-algae)
Fucoidon		Additive effects with anticoagulants. Because fucoidan can slow down the blood-clotting process, and may increase bleeding	Warfarin and heparin- due to its anti-thrombotic effects, there are chances of increased bleeding.	(Accessed September 28, 2019 from https://www.mskcc.org/cancer-care/integrative-medicine/herbs/fucoidan)

Disclosure statement

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