Chapter 25
Safety, Toxicological and Allergenic Aspects of Using Algae for Food

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Abstract Consumption of algae has been historically practiced, especially in East Asia and the Pacific region cultures. However, sporadic events and empirical studies have suggested that some compounds could be triggering intoxications, allergic reactions and mortalities in humans who consumed algae. This chapter is an effort to explore with in-depth attention the safety, toxicological and allergic reactions following human consumption of algae. Based on retrieved literature, it is clear that toxicities and allergies from ingestion of algae are not a rarity, and to date, at least seventy (70) illnesses, six (6) allergic reactions and fourteen (14) mortalities have

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been reported globally. Toxicities and mortalities from intake of edible algae has been reported in species of *Gracilaria*, *Caulerpa* and *Acanthophora* genus, and are associated with their bioaccumulation of contaminants such as excess iodine, heavy metals, cyanotoxins or toxic inherent compounds such as caulerpenyne, manauealides A and C, prostaglandin E_2, polycavernosides, aplysiatoxins and their derivatives. Allergenicity has been reported in *Arthrospira*, *Chlorella*, *Chondrus*, *Eucheuma*, *Gigartina* and *Palmaria* species, with the sulfated polysaccharide (carrageenan) and the photosynthetic pigment (C-phycocyanin) being the implicated allergens. These allergic reactions are mediated through activation of innate immune pathways of inflammation that trigger NF-kB activation, modification of gut microbiota and thickness of mucus barrier. We contend that appropriate labelling of algae-derived food products, public education, proper cleaning of fresh algae before consumption and profiling of toxic and allergenic algal species and compounds could aid in reducing intoxications and allergic reactions from algae used in food and food products. Future studies should consider examining edible algae for contaminants of emerging concern such as microplastics, cyanotoxins, emerging per- and polyfluoroalkyl substances, pharmaceutical residues and personal care products.

Keywords Arsenic · *Caulerpa* toxins · Carrageenan · *Hizikia fusiforme* · Iodine · Polycavernosides

25.1 Global Overview of Algae and Allied Products Consumption

Edible micro- and macroalgae (especially seaweeds; SWDs) are a class of pigmented autotrophic organisms with undifferentiated roots, stems, leaves and total absence of vascular bundles. They are consumed, used as medicinal and nutraceutical products or incorporated into foods (as additives, extracts and sources of functional ingredients) (Debbarma et al. 2022; Ibrahim et al. 2022; Lomartire et al. 2021; Mendes et al. 2022; Michalak and Chojnacka 2018).

Consumption of algae is historic, and has been part of habitual diets in many East Asian cultures (Preeprame et al. 2001). Algae consumption can be traced to as early as 500 BCE (14,000 years ago) according to records on American, Asian and European culinary recipes (dietary staples) and complimentary therapies (Boukid and Castellari 2022; Dillehay et al. 2008; Hallsson 1961; Haroun et al. 2019; Mouritsen et al. 2013; Nisizawa et al. 1987; Pereira 2016). For instance, *Sargassum horneri* is a savoury algae (seaweed) that is popularly consumed in Japan (Preeprame et al. 2001). Similarly, *Grateloupia turuturu* (a red seaweed) on the Atlantic Coast of Europe forms part of the Japanese and Korean oriental diet (da Costa et al. 2021; Pacheco et al. 2020). In Great Britain and Ireland, the seaweed (*Porphyra umbilicalis*) is a popular ingredient of laverbread (Harford 2023). The red algae "*ogonori*" (*Gracilaria*

verrucosa) is widely eaten in form of a Japanese salad, *Sashimi* (Higa and Kuniyoshi 2000).

Commercialization of algae farming has surged in an effort to address global food security and this is evidenced by various algae-based functional foods and dietary supplements in form of snacks, condiments, pasta and salads on the market (European Food Safety Authority et al. 2023; Zhang et al. 2022a, b). According to the Algae Products Global Market Report 2023, algal products market soared from to US $12.1 billion in 2022 to US $13.2 billion in 2023, representing a compound annual growth rate (CAGR) of 8.9%. This is anticipated to approach $17.89 billion by 2027, growing at a CAGR of 7.9% (Cision 2023). These values account for foods, bioplastics, industrial lubricants, green chemicals, and cosmetics. Dietary intake (37%) is the major use of algae (mostly red and brown SWDs), followed by pharmaceutical and nutraceutical applications at 8.1% (FAO 2018; FAO and WHO 2022; Transparency Market Research 2022).

The renewed interest in algae is due to the expanding view of macroalgae as healthy foods i.e., 'super-foods' and their antimicrobial, neuroprotective, anti-allergic, anti-oxidant, antitumor, anti-fungal, chemoprotective, anti-obesity, antidiabetic and hepatoprotective properties (Aakre et al. 2021; Cotas et al. 2021; Ganesan et al. 2019; Shannon and Abu-Ghannam 2019). Despite the exponential growth in algae consumption and their use as perfect functional ingredients, there is brooding body of knowledge that their ingestion and inclusion in food products present food safety risks (Filippini et al. 2021; Wu et al. 2022). The food safety hazards in algae and algal products are of physical, microbiological and chemical nature, with the latter being more associated with illnesses, allergies and mortalities. The following subsections will discuss the toxicities and allergic reactions associated with consumption of algae and algae-derived products, the constitutive compounds and their supposed mechanisms of action.

25.2 Poisoning and Mortality Incidences Due to Consumption of Edible Algae and Their Products

To date, illnesses, toxicities and mortalities from ingestion of algae is traced to mainly three genera namely; *Acanthophora*, *Caulerpa* and *Gracilaria.* Majority of the cases were recorded in countries of the Pacific Rim (Guam, California and Japan), arguably due to the voluminous consumption of SWDs in this region (Marshall and Vogt 1998) (Table 25.1). The largest number of incidences pertaining to algal poisoning comes from the genus *Gracilaria* (represented by four species, one of which now fall under genus *Polycavernosa*). Again, this is explained by the wide consumption of raw species from this genus in traditional cuisines of Asia and the Pacific Rim (Cheney 2016; Marshall and Vogt 1998). Two poisoning cases have been associated with the Japanese favorite brown algae *Nemacystus decipiens* (*ito-mozuku*) (Fusetani and

Hashimoto 1981) which is common in Okinawa prefecture (Nishitsuji et al. 2019)—and *Cladosiphon okamuranus*—which is endemic to the Ryukyu Islands (Sato et al. 2023). Taken together, seventy (70) illnesses and fourteen (14) fatality cases due to intake of algae have been reported globally (Table 25.1).

25.3 Chemicals Implicated in the Toxicity of Edible Algae and Their Mechanisms of Action

The toxicity of algae has been ascribed to both biosynthesized compounds and xenobiotics such as heavy metals (arsenic), excess iodine absorbed, carrageenans and cyanotoxins (Desideri et al. 2016; Vellinga et al. 2022). These are discussed in the following with other potential contaminants that can induce toxicity and illnesses.

25.3.1 Toxins in Caulerpa *Algae*

The first incidence of poisoning from ingestion of algae was described by Doty and Aguilar-Santos (1966) and their chemical analysis pointed to the presence of a sphingosine derivative (caulerpicin, **1**) from *Caulerpa racemosa* (Fig. 25.1). Further efforts of Doty and Aguilar-Santos (1970) led to the identification of another potentially toxic orange-red pigment (caulerpin, **2**) in *C. racemosa* and *C. lamourouxii*. Their study led to the discovery that there was potential trophic transfer and biomagnification of the toxins (**1** and **2**) by sea slug (*Oxynoe panamensis*) which feeds on *Caulerpa* species (Doty and Aguilar-Santos 1970).

Another unusual *Caulerpa* toxin (caulerpenyne, **3**) was isolated from the Mediterranean *C. prolifera* (Amico et al. 1978) and *C. taxifolia* (Marić et al. 2017). It has since been isolated from nearly all (other nine) *Caulerpa* species native to the tropical Pacific and the Caribbean Sea. This acetylenic sesquiterpenoid was appreciated to possess strong ichthyo-toxicity and antigrazer activities (Paul et al. 1987), cytoxicity (Lemée et al. 1993) as well as inhibitory effects on uptake transporters of organic anions (Oatp1d1) and cations (Oct1) (Marić et al. 2017). Caulerpinic acid (**4**), also common in the *Caulerpa* genus, is known to be as mosquitocidal as the bisindole alkaloid caulerpin (Alarif et al. 2010). Therefore, these secondary metabolites isolated from *Caulerpa* genus (**1**–**4**) are evolutionarily-developed chemical defense mechanisms against various herbivores, epiphytes and other competitors (Marić et al. 2017). This may explain the fact that poisoning from this genus occurs during the rainy season when toxin concentrations increase and in part reflects the influence of seasons on the biosynthesis of these metabolites (Lemée et al. 1993). For example, a potential allelopathic effect of caulerpenyne (**3**) from *C. racemosa* var. *cylindracea* was cited, and this could be fundamental in the species' out competition of other

Table 25.1 Synopsis of poisoning, illnesses and mortality events arising from consumption of edible algae based on published literature

Algae	Report on incidence	Year	Country	Implicated compounds	Reference(s)
Acanthophora specifera	15 illnesses and 3 mortalities recorded	2003	Philippines	Polycavernoside A, C and C2	Yotsu-Yamashita et al. (2004, 2007)
	12 illnesses and 3 mortalities recorded	2002			
Gracilaria edulis	9 illnesses and 2 mortalities recorded	2002	Philippines	Polycavernoside A, Polycavernoside D	Haddock and Cruz (1991), Yotsu-Yamashita et al. (1993, 2004) and Navarro et al. (2015)
Gracilaria coronopifolia	Vomiting, diarrhea, burning sensation of the mouth and throat and generalized myalgia. Seven (7) illnesses	1994	Hawaii	Aplysiatoxins and debromoaplysiatoxin, manauealides A–C	Marshall and Vogt (1998) and Nagai et al. (1996, 1997)
Gracilaria verrucosa	Nausea, hypotension and death of a woman due to hypotensive shock 14 h following ingestion of 20–30 g of steeped algae. Husband recovered	1993	Japan	Prostaglandin E	Fusetani and Hashimoto (1984) and Noguchi et al. (1994)
Polycavernosa tsudai (previously *Gracilaria edulis*)	13 suffered illnesses and 3 died	1991	Guam (USA)	Polycavernoside A and B (LD_{99} = 200–400 μg/kg for both)	Haddock and Cruz (1991)

(continued)

Table 25.1 (continued)

Algae	Report on incidence	Year	Country	Implicated compounds	Reference(s)
Gracilaria chorda	Six victims suffered from nausea, vomiting, stomach pain, diarrhea and 1 died	1982	Japan	Prostaglandin E	Fusetani and Hashimoto (1984) and Noguchi et al. (1994)
	Four victims suffered from nausea, vomiting, stomach pain and diarrhea; 1 died	1980			
Cladosiphon okamuranus and *Nemacystus decipiens*	2 illnesses	1967	Japan	Diethyl peroxides	Fusetani and Hashimoto (1981)
Caulerpa racemosa	Not reported	1966	Philippines	Caulerpin, caulerpicin	Doty and Aguilar-Santos (1966, 1970)

plants with macrophytes such as the seagrass: *Cymodocea nodosa* (Raniello et al. 2007).

Other potentially toxic compounds have been elucidated in *Caulerpa* species. For example, 10,11-epoxy-caulerpenyne along with oxytoxin 1, taxifolial A, B, C and D has been reported in *C. taxifolia* (Guerriero et al. 1992; Lemée et al. 1993). Though taxifolial A and D are not toxic to both mice and mammalian cells, 10,11-epoxy-caulerpenyne was lethal to mice at 75 mg/kg and had $IC_{50} = 11$ μg/mL against mammalian cells (Lemée et al. 1993).

The mechanism of toxicity of most *Caulerpa* toxins are not clearly understood. Caulerpicin (**1**) has been implicated in the manifestation of toxic symptoms such as mild anaesthetizing sensation, numbness of the tongue and cold sensation in the feet and fingers (Doty and Aguilar-Santos 1966). Although discussed controversially, caulerpin (**2**) is known to induce mild anesthetic action, trigger difficulties in breathing, sedation, and loss of balance which is similar to the toxic syndromes observed in victims intoxicated by ciguatoxins i.e., ciguatera fish poisoning (Kase et al. 2020). Both **1** and **2** were initially indicated to be toxic to mice and rats (Doty and Aguilar-Santos 1970), but this toxicity is not supported by acute toxicity studies of Vidal et al. (1984) in mice.

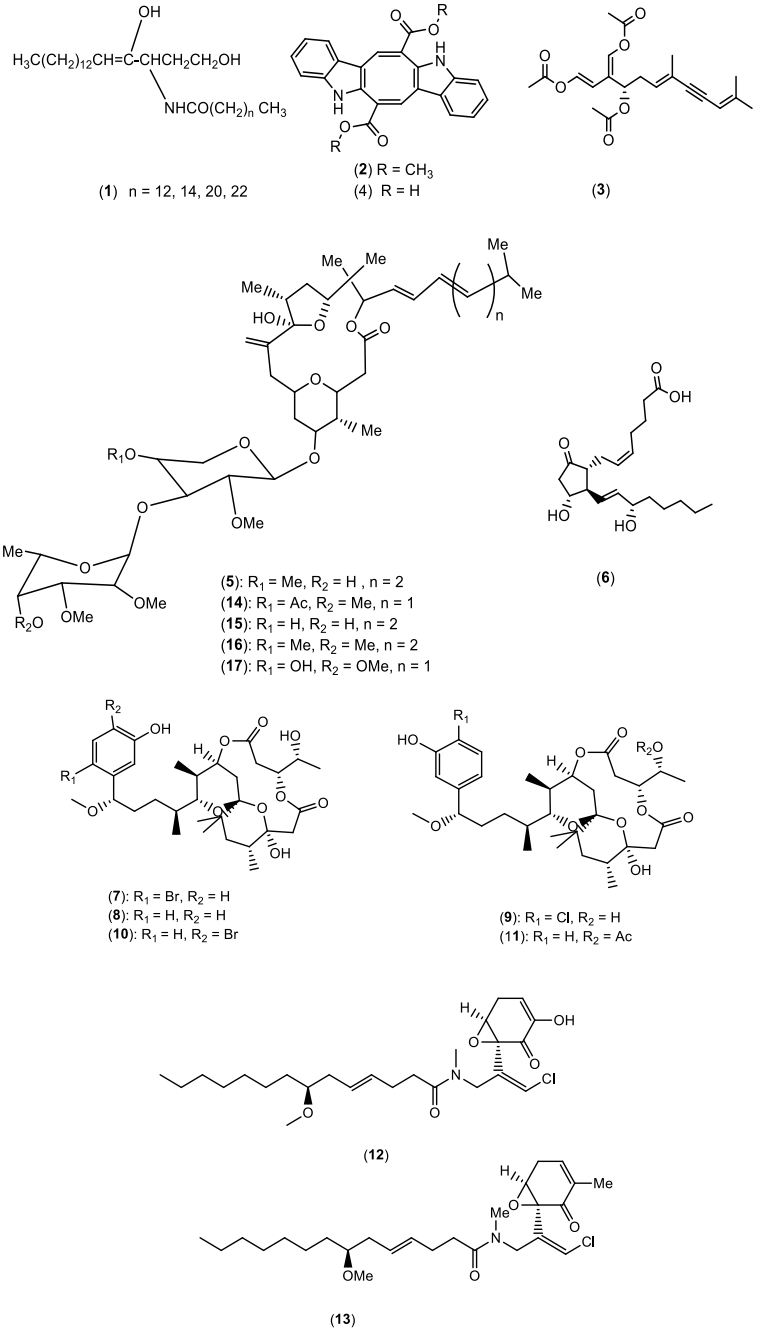

Fig. 25.1 Chemical structure of compounds implicated in illnesses, toxicities and mortalities from consumption of edible algae

Recently, the bioaccumulation and biochemical perturbations due to caulerpin (upto 50 μg/g) from *C. racemosa* in stomach contents of the white seabream (*Diplodus sargus*) was reported (Felline et al. 2012). At a molecular level, caulerpin induced alterations in fish antioxidant defenses (e.g., glutathione reductase and glutathione levels), augmented activities of cytochrome P450 (through triggering the activity of 7-etoxyresorufin O-deethylase) (Felline et al. 2012), glutathione S-transferases and acyl CoA oxidase, gene transcription for peroxisome proliferator-activated receptor alpha, cytochrome P4501A and vitellogenin 1 (Gorbi et al. 2014). Because caulerpin, a bisindolic alkaloid, possess a molecular structure comparable to indole alkaloids (i.e., possesses two ^{1}H indole moieties joined by an eight-membered cyclooctatetraene ring) (Zhan et al. 2010), lower levels of acetylcholinesterase reported in fish with caulerpin suggest that it may be largely neurotoxic (Felline et al. 2012). Alteration of lipid metabolism (De Pascali et al. 2015; Del Coco et al. 2018) has also been cited in fish following caulerpin ingestion.

The most potent of the *Caulerpa* toxins (**3**) is known to negatively affect P-glycoprotein-ATPase and inhibits overall protein phosphorylation (Pesando et al. 1996). It also directly modified the electrical properties of touch mechanosensory cells of leech (*Hirudo medicinalis*), leading to partially irreversible afterhyperpolarization mediated by the activity of Na^+/K^+-ATPase and to some extent a calcium-dependent potassium current (Brunelli et al. 2000; Mozzachiodi et al. 2001). Caulerpenyne is also an inhibitor of human 5-lipoxygenase (Richter et al. 2014). To date, only caulerpenyne (**3**) is considered to be the major toxin in *Caulerpa* SWDs (Guerriero et al. 1992; Higa and Kuniyoshi 2000), and its concentration necessary to induce toxicity in human hematopoietic progenitors, melanocytes and keratinocytes (IC_{50} = 6–24 μM) is high (Parent-Massin et al. 1996).

25.3.2 Toxins in Acanthophora *Algae*

By percentage, the *Acanthophora specifera* intoxication which occurred in Philippines in 2002 and then again in 2003 represents the highest number of illnesses and fatalities in algal poisoning history (Table 25.1). However, no satisfactory empirical data exists on the causative compounds partly due to absence of adequate samples that could be analyzed at that time (Yotsu-Yamashita et al. 2004). Nevertheless, the symptoms associated with these events were in complete agreement with those due to ingestion of *G. edulis* in 2002. Based on a later argument by the same research group (Yotsu-Yamashita et al. 2007), polycavernoside A (**5**) (initially identified in *G. edulis*) was characterized in *A. specifera.* This discovery made it plausible to cite that the *Acanthorphora* outbreaks recorded in Philippines mirrored *G. edulis* outbreaks in the same country, and could have been triggered by one or more blue-green algae (Cheney 2016). Blue-green algae (also called cyanobacteria) are known to produce hepatotoxic, neurotoxic and immunotoxic secondary metabolites which are potentially lethal to humans (Omara et al. 2023).

25.3.3 *Toxins in* Gracilaria *Algae*

In *Gracilaria* species, the major toxins incriminated in algae toxicity are prostaglandins (Fusetani and Hashimoto 1984; Noguchi et al. 1994). Specifically, prostaglandin E_2 (**6**) has been isolated from *G. verrucosa* and *G. lichenoides* (Gregson et al. 1979). Also known as dinoprostone, prostaglandin E_2 (PGE_2) is a naturally-occurring prostaglandin established to induce physiological reactions in humans such as nausea, diarrhea, hypertension and bleeding (Noguchi et al. 1994). Moreover, the concentration of bioavailable and toxic PGE_2 levels seem to come from unsaturated fatty acids (suspectedly arachidonic acid) (Änggård and Oliw 1981; Gregson et al. 1979; Noguchi et al. 1994), a fact that has been proven over the years by other research groups (Ricciotti and FitzGerald 2011). PGE_2 along with PGF2a was found in *G. lichenoides* from Australia, and it occurs that the concentrations always found in the intact algae are safe (Gregson et al. 1979). However, toxicity events involving PGE_2 where those in which the victims consumed freshly harvested algae (and at least one of the victims steeped it in fresh water overnight). It is argued that such a treatment might have washed out the inherent inhibitor of prostaglandin synthesis, which could have induced PGE_2 generation to toxic concentrations (Fusetani and Hashimoto 1984).

The 1994 successive poisoning incidences by *G. coronopifolia* in islands of Maui, Hawaii and Oahu presented a new symptom (burning sensation of the throat and mouth), suggesting that it involved some other unknown toxins. In an attempt to arrive at the causative agents, Nagai et al. (1996) identified aplysiatoxin (**7**) and debromoaplysiatoxin (**8**) from the original algal collection. In addition to these, manauealides A–C (**9**–**11**) (Nagai et al. 1997), malyngamides M (**12**) and N (**13**) were subsequently isolated and characterised (Kan et al. 1998). Manauealides—just as aplysiatoxin and debromoaplysiatoxin—are known to induce diarrhea in mice (Nagai et al. 1997). On the other hand, malyngamides elicited low cytotoxic effects on mouse neuroblastoma cells (Kan et al. 1998).

Another toxicity incidence in USA detailed by Haddock and Cruz (1991) pointed to the presence of glycosidic macrolides: polycavernoside A (**5**) and B (**14**) in *Polycavernosa tsudai* (previously *Gracilaria edulis*) as the cause of illnesses and deaths. Indeed, polycavernoside A has a glycosidic macrolide with an unusual tricyclic aglycon stemming from a partially dehydrated and unsaturated 3,5,7,13,15-pentahydroxy-9,10-dioxotricosanoic acid (Blakemore and White 2005). In addition to **14**, three novel potentially toxic glycosidie macrolides (polycavernoside A2, A3 and B2; **15**–**17**) has been implicated in the poisoning incident which ensued ingestion of the red algae *Polycavernosa tsudai* (Yotsu-Yamashita et al. 1995). Polycavernosides are toxic but the mechanism of their toxicities are not well elucidated (Louzao et al. 2014).

25.3.4 *Toxins in* Cladosiphon*,* Sphaerotrichia *and* Nemacystus *Algae*

Two cases of algae poisoning, the so called—"*mozuku*" poisoning—was reported to be from brown algae: *Cladosiphon okamuranus* and *Nemacystus decipiens* (Fusetani and Hashimoto 1981). Owing to the absence of adequate samples, the team examined another edible brown algae (*Sphaerotrichia divaricata*) and characterized diethyl peroxides in fat-soluble fractions that were lethal to mice when hot, suggesting that illnesses associated with these species arise following steeping (Fusetani and Hashimoto 1981). In this context, there exists knowledge gaps that need to be unveiled to understand the mechanisms and responsible compounds for poisonings recorded in some of these algae species.

25.3.5 *Bioaccumulated Potentially Toxic Metals, Metalloids and Organic Contaminants*

Unlike in fresh algae, concerns on the safety of algal products stretch beyond inherent toxic algal metabolites but relates to bioaccumulation and translocation of potentially toxic elements (PTEs) as well as other organic contaminants in algae tissues (Vellinga et al. 2022). Table 25.2 shows a summary of reports on PTEs, and conclusions made on the levels obtained in some edible algae.

At a glance, the concentration of PTEs reported in edible algae appears to be safe. However, very high levels of inorganic and total arsenic (up to 117 and 149 mg/kg dw, respectively) has been reported in *Hizikia fusiforme* (*H. fusiforme*; synonym: *Sargassum fusiforme*) (Almela et al. 2006). Such arsenic levels are far beyond the compliance limit(s) for this metalloid in food products (3 mg/kg or less) in USA and France. In the same study (Almela et al. 2006), unacceptably high levels of Cd in some species of edible *Porphyra* (0.089–3.19 mg/kg) and *H. fusiforme* SWDs (0.511–1.53 mg/kg) were recorded. Very high levels of inorganic arsenic (32–70 and 67–96 mg/kg) and total As (18–124 and 103–147 mg/kg) has also been reported in *H. fusiforme* from UK (Rose et al. 2007) and Spain (Besada et al. 2009).

In regards to organic contaminants, SWDs (*Fucus distichus*, *F. spiralis* and *Nereocystis luetkeana*) sampled from the Salish Sea of Western United States and Canada were found to contain Cd (1.15–7.91 mg/kg), Cr (below detection limit (BDL)—5.49 mg/kg), Hg (BDL—0.25 mg/kg), Pb (BDL—13.4 mg/kg), persistent organic pollutants and polychlorinated biphenyls (0.139–3.12 μg/kg) at levels that surpassed either US EPA noncancer-based screening levels or international compliance limits (Hahn et al. 2022). It should be noted that the effects of PTEs maybe cumulative, and therefore even at very low levels, the overall health effects maybe not negligible. It should be reiterated that both inorganic and organic arsenic are carcinogenic, but the former is more readily absorbed into the body. For example, *H. fusiforme* was

Table 25.2 Concentration of potentially toxic elements (PTEs) reported in some edible algae and implications for public health protection

Area (country)	Algae	PTEs (mg/kg)[a]	Daily intake level or hazard index	Implications for public health	References
Salish Sea (United States and Canada)	*Fucus distichus*, *F. spiralis* and *Nereocystis luetkeana*	Cd (1.15–7.91), Cr (BDL—5.49), Hg (BDL—0.25), Pb (BDL—13.4)	Not calculated	High health risk	Hahn et al. (2022)
Italy	*Ascophyllum*, *Himanthalia*, *Laminaria*, *Palmaria*, *Porphyra*, *Saccharina*, *Ulva* and *Undaria* species	Cd (0.02–0.93), Cr (0.09–0.30), Ni (0.24–0.51), Hg (BDL—0.01), Zn (1.58–18.12), total As (0.62–6.74), inorganic As (0.12–0.18)	Hazard index was less than 1	Low health risk	Filippini et al. (2021)
Zhejiang (China)	Red and brown seaweeds	As (0.185–71), Cd (0.002–6.4), Cr (0.089–35.7), Cu (BDL—39.2), Hg (BDL—0.391), Mn (0.404–407), Ni (BDL—8.82), Pb (BDL—6.96)	Hazard index was less than 1	Low health risk	Chen et al. (2018)

(continued)

Table 25.2 (continued)

Area (country)	Algae	PTEs (mg/kg)[a]	Daily intake level or hazard index	Implications for public health	References
Bodø, Trondheim, Trondheimsfjord (Norway), Pleubian (France)	*Alaria esculenta*, *Palmaria palmata*, *Saccharina latissima*	Total As (7.192–99.112), Cd (0.024–2.622), Hg (0.0009–0.3139), Pb (0.0301–0.7126)	Hazard index was less than 1	Low health risk	Roleda et al. (2019)
Seoul (South Korea)	Laver, brown seaweeds, Kelp and Sea lettuce (n = 426)	Total As (BDL—88.8), Hg (0.001–0.050), Pb (BDL—2.7), Cd (BDL—2.9)	0.11, 0.65, and 0.45 μg/kg body weight/ week for total Hg, Pb and Cd, respectively	Low health risk	Hwang et al. (2010)
Auckland and Nelson (New Zealand)	*Macrocystis pyrifera*, *Undaria pinnatifida*, *Porphyra* and *Ecklonia radiata*, *Ulva stenophylla*, *Durvillaea antarctica*, *Hormosira banksii*	Total As (3.8–97), inorganic As (0.1–1.5), Fe (13.7–1227), Zn (10.74–45.03), Hg (0.01–0.17), Pb (0.20–0.41)	Tolerable intake levels were not exceeded	Low health risk	Smith et al. (2010)

(continued)

Table 25.2 (continued)

Area (country)	Algae	PTEs (mg/kg)[a]	Daily intake level or hazard index	Implications for public health	References
Spain	*Chondrus crispus*, *Eisenia bicyclis*, *Gelidium* species, *Himanthalia elongata*, *Hizikia fusiforme*, *Laminaria* species, *Porphyra umbilicales*, *Undaria pinnatifida*, and *Ulva rigida*	Cd (0.025–4.82), Pb (< 0.008–1.35), Hg (0.001–0.057), Cu (0.410–7.70), inorganic As (67–96), total As (103–147)	High arsenic levels in *Hizikia fusiforme*	High risk	Besada et al. (2009)
London and its environs (UK)	Hijiki, Nori, Kombu, Wakame, Arame	Total As (18–124), inorganic As (67–96)	0.57 mg/kg/body weight	High risk. UK Food Standards Agency advised not consuming products with *Hizikia fusiforme*	Rose et al. (2007)

(continued)

Table 25.2 (continued)

Area (country)	Algae	PTEs (mg/kg)[a]	Daily intake level or hazard index	Implications for public health	References
Spain	Various seaweeds of Japanese, Korean, Spanish and Chilean origins[b]	Cd (< 0.003–3.55), total As (0.031–149), inorganic As (< 0.014–117), Pb (< 0.050–12.1)	Limit of total As per national regulatory limit	High health risk, especially due to high As levels in *Hizikia fusiforme*	Almela et al. (2006)

Note BDL below method detection limit

[a] PTEs: *Pb* lead, *As* arsenic, *Ni* nickel, *Mn* manganese, *Zn* zinc, *Cd* cadmium, *Cr* chromium, *Hg* mercury, *Fe* iron

[b] Species included: *Enteromorpha* species, *Ulva pertusa*, *Porphyra tenera*, *P. umbilicalis*, *Palmaria palmata*, *Palmaria* species, *Rhodymenia palmata*, *Chondrus crispus*, *Laminaria* species, *L. japonica*, *L. digitata*, *Eisenia bicyclis*, *Undaria pinnatifida*, *Hizikia fusiforme*, *Fucus vesiculosus*, *Himanthalia elongata*, *Durvillaea antartica* (Almela et al. 2006)

indicated to have led to arsenic urinary excretion levels similar to those in individuals affected by arsenic poisoning when a volunteer consumed the equivalent of eight servings of commercial *H. fusiforme* food (Nakajima et al. 2006). An incidence of a 54-year-old woman from California who presented with symptoms of arsenic poisoning after taking two to four tablets of a kelp (*Laminaria*) supplement per day for several months has been published (Amster et al. 2007). Later, McGuffin and Dentali (2007) argued that the case in question should have emanated from intake of excess iodine, which is known to share toxicity symptoms with arsenic. Nevertheless, similar elevation of inorganic arsenic levels have recently been appreciated among Japanese children and expectant mothers who consumed *H. fusiforme* (Mise et al. 2019).

In addition to other organic contaminants, the accumulation of microplastics on edible SWDs such as nori (0.9–3.0 items/g dw) (Li et al. 2020), *Gracilaria fisheri* and *Caulerpa lentillifera* (16.46–181.73 particles per 100 g wet weight) (Klomjit et al. 2021) has joined algae literature. Microplastics are known to act as binders, concentrators and vectors of toxic contaminants and pathogenic microorganisms (Liu et al. 2021a, b; Tumwesigye et al. 2023). There is therefore need for future studies to examine the relationship between microplastic levels in algae and heavy metal contents as well as other organic contaminants. Further research efforts should consider examining edible algae for contaminants of emerging concern such as microplastics (Gutow et al. 2016), cyanotoxins, emerging per- and polyfluoroalkyl substances (e.g., ADONA and GenX), current use pesticides, active pharmaceutical ingredients and personal care products (Hahn et al. 2022).

25.3.6 Absorbed Iodine

The iodine content of algae (SWDs) is often high (Desideri et al. 2016), and this makes them a veritable source of iodine for tackling dietary iodine insufficiency among individuals (Aakre et al. 2021; Bouga and Combet 2015; Ficheux et al. 2023). Across the three taxonomic categories of green (Chlorophyta), red (Rhodophyta), and brown (Phaeophyceae) SWDs, the latter (specifically species of *Laminaria* genus and *Laminariale* genus i.e., kelp) may absorb iodine up to 100,000 times higher than that in seawater in which they are growing (Milinovic et al. 2021; Yeh et al. 2014). A survey of 224 products with SWDs in the United Kingdom by Bouga and Combet (2015) showed that 26 (11.6%) of the products could translate into iodine intakes higher than the European tolerable adult upper level of 600 μg/day. This study suggested that there is scope to improve product labelling of algae-containing products to promote their safe consumption. Similar alarming levels of iodine exceeding tolerable limits (30–62,400 μg and upto 6770 mg/kg) were recently found in commercial macroalgae-based foods and supplements in Norway (Aakre et al. 2021) and edible SWDs marketed in Italy (Filippini et al. 2021).

Although dietary intake of iodine is instrumental for good human health, low and very high intake are known to increase risks of diseases such as goiter, thyroiditis,

hypothyroidism, hyperthyroidism and papillary thyroid cancer (European Food Safety Authority et al. 2023; Winder et al. 2022). Michikawa et al. (2012), for instance, investigated the relationship between SWDs consumption and the supposed risk of thyroid cancer in Japanese women, and concluded that consumption of SWDs by postmenopausal women exposed them to higher risks of papillary carcinoma. Maternal consumption of SWDs is a common practice in some Asian cultures as a natural way to promote breast milk supply (Emder and Jack 2011). A report from Korea found high daily intakes as well as breast milk iodine levels in women who took large volumes of *Undaria pinnatifida* (kelp) soup during their early postpartum (Rhee et al. 2011).

Most preceding epidemiological and experimental studies of algae ingestion did not find such an association, or gave controversial and diametrically opposite conclusions regarding effect of excess iodine intake from edible algae on papillary thyroid cancer incidences. That notwithstanding, it has been confirmed that iodine nutrition influences the overall prevalence, distribution of histological types, and clinicopathological aggressiveness of papillary thyroid cancer (Zhang et al. 2022a, b).

As a matter of fact, huge economic losses have been associated with iodine poisoning in SWDs. A Bonsoy soy milk manufacturer in Australia which incorporated powder of the seaweed (*Laminaria* species) was ordered to compensate nearly 500 victims with US $25 million. The victims had suffered various health consequences of consuming soy with excessive levels of iodine (The Sydney Morning Herald 2014).

25.3.7 Carrageenan

Carrageenans (CGNs) is a group of indigestible sulphated polygalactans (kappa, iota, and lambda; chemically differentiable by the repetition of their sulphation units) obtained from edible red SWDs: *Chondrus* (the original commercial source), *Eucheuma*, and *Kappaphycus* (Guan et al. 2017; McKim 2014). They are made up of D-galactose residues linked by β-1,4 and α-1,3 galactose-galactose bond (Borsani et al. 2021). The CGNs content of SWDs vary (22–88% dw), contingent on the species and ecophysiological variables (Asni and Najamuddin 2021; Rupert et al. 2022).

Native (undegraded) CGNs have the "generally recognised as safe" food additives status as per the Food and Drug Administration of the United States, European Economic Community and the WHO Joint Expert Committee on Food Additives list (Liu et al. 2021a, b). CGNs typically possess no known nutritive values, but is used as a food additive (E-407) i.e., thickener, gelling agent, emulsifier or stabilizer (Borsani et al. 2021). However, studies dating as far back as 1980 have illustrated that CGNs may induce inflammatory reactions and toxic effects on colon microbiota, thereby contributing to gastrointestinal disorders such as ulcers and colon cancer (David et al. 2018; Venkatesan et al. 2015). While this specific group of compounds are implicated

in some toxic effects of algal products, a recent communication by the European Food Safety Authority (EFSA Panel on Food Additives and Nutrient Sources Added to Food et al. 2018) has refuted the correlation of CGNs and cancer, which may be due to inappropriate additive application (e.g., using very high concentrations), generalization of in vitro outcomes to possible in vivo health effects as well as utilization of lower molecular weight (degraded) CGNs other than the approved undegraded form (poligeenan). This is supported by a recent observation (Alli et al. 2022) where CGNs did not significantly decrease cell and tissue viability of human salivary gland cells and reconstructed human oral epithelium when compared to sodium dodecyl sulphate. Potential allergenicity of CGNs is discussed in the later part of this chapter but its definite toxicity in humans is an inconclusive debate and appears to be rather concentration-dependent.

25.4 Incidences of Allergies from Consumption of Edible Algae and Their Products

Allergenicity in food science refers to the tendency of a food or food product to induce adverse immunologic (immunoglobulin E)-mediated response(s) or side effect(s), usually in genetically predisposed (atopic) individuals (Waserman et al. 2018). Allergenicity is among the overriding concerns impeding effective utilization of algae as food in sensitive individuals (FAO and WHO 2022; James et al. 2023). Although algal biomass and extracts are useful food ingredients which could suffice as nutrient-rich, sustainable and healthy foods, allergenicity of algae has retarded their acceptability in some parts of the world. The first concern pertains to the palatability of algae in terms of sensory attributes and allergen content (James et al. 2023).

Algae allergenicity has been encountered following consumption of products containing *Spirulina* (*Arthrospira*), *Chlorella*, *Chondrus*, *Palmaria*, *Eucheuma* and *Gigartina* species. The complete range of reactions varied from mild simple allergic reactions to incidences of anaphylaxis (Table 25.3). One of the rare cases involving *Chlorella vulgaris* allergenicity was recorded following consumption of a powdered supplement based on this alga (Abasszade et al. 2020). The causative compounds inducing allergic reactions have not been identified in all the reported incidences. The sulfated polysaccharide (carrageenan) and the photosynthetic pigment (C-phycocyanin) are the major allergens that has so far identified in algae and algal products (Kular et al. 2018; Petrus et al. 2010). Other cases involving algae allergenicity has been reported in a randomized clinical trial (Vojdani and Vojdani 2015) and cross-sectional studies (Tiberg et al. 1990, 1995; Tiberg and Einarsson 1989).

Table 25.3 Incidences of allergic reactions from consumption of algae

Country	Algae species	Symptoms	Responsible allergen	References
Australia	*Chlorella vulgaris*	A 75-year-old male presented with wheeze, severe hypotension, urticarial rash, diarrhoea and elevated blood tryptase levels, suggesting anaphylaxis	Not reported	Abasszade et al. (2020)
UK	Nori, along with *Chondrus crispus*, and *Palmaria palmata*	A twenty-seven-year-old male with abdominal discomfort and high body temperature	Not reported	Thomas et al. (2018)
Canada	*Eucheuma*, *Chondrus*, *Gigartina* SWDs	A ten-month-old infant developed lip angioedema after eating fruit cake icing	Carrageenan	Kular et al. (2018)
The Netherlands	*Spirulina platensis* (tablet)	Seventeen-year-old male developed anaphylaxis after ingesting a *Spirulina*	Not reported	Le et al. (2014)
France	*Arthrospira platensis*	Fourteen-year-old adolescent presented with urticaria, labial oedema and asthma six hours of taking 5 *Spirulina* tablets	C-phycocyanin	Petrus et al. (2010)
South Korea	*Chlorella* species	Eleven-year-old male who took *Chlorella* tablets for 3 months had anemia, increased levels of creatinine, hypokalemia, hypo-uricemia, hypophosphatemia, proteinuria, hypergammaglobulinemia, leukocyturia and glucosuria	Not reported	Yim et al. (2007)

25.5 Mechanisms of Allergenicity of Compounds in Edible Algae

As shown in Table 25.3, carrageenan and C-phycocyanin are the major allergens identified in algae and algal products. Carrageenan has been labelled as a pseudo-latex allergy implicated in triggering anaphylaxis during barium enema (Tarlo et al. 1995). The underlying cause of carrageenan allergenicity is believed to be due to triggering of an immune response i.e., it mediates its allergenic effect through activation of innate immune pathways of inflammation encompassing pathways of NF-kB activation with a central role in transcriptional activation of the interleukin-8 gene, modification of gut microbiota constitution and thickness of mucus barrier (Bhattacharyya et al. 2008; Borthakur et al. 2007; Fahoum et al. 2017).

The mechanism of allergy induction by C-phycocyanin is not reported in open literature but it should be emphasized that appropriate labelling of algae products should be encouraged to reduce incidences of allergies from ingestion of algal products in sensitive individuals.

25.6 Future Perspectives

Consumption of algae and algal products have markedly increased globally but research to date indicates that there are potential health risks that could arise from their unregulated consumption. Several illnesses, allergic reactions and deaths so far reported have specifically been in the algae genera of *Acanthophora*, *Caulerpa* and *Gracilaria* genus. However, it should be expected that such toxicities may occur in other edible algae as well. Future research efforts should consider examining edible algae for contaminants of emerging concern such as microplastics, cyanotoxins, emerging per- and polyfluoroalkyl substances (e.g., ADONA and GenX), current use pesticides, active pharmaceutical ingredients and personal care products. Moreover, appropriate labelling of algae-derived food products (for example with their allergen or iodine contents), wider public education, cleaning of fresh algae before consumption and profiling of toxic and allergenic algal species and compounds could reduce intoxications and allergic reactions from algae consumption.

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