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To cite this article: Emer Shannon & Nissreen Abu-Ghannam (2019) Seaweeds as nutraceuticals for health and nutrition , *Phycologia*, 58:5, 563-577, DOI: [10.1080/00318884.2019.1640533](https://doi.org/10.1080/00318884.2019.1640533)

To link to this article: <https://doi.org/10.1080/00318884.2019.1640533>



Published online: 11 Sep 2019.



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Seaweeds as nutraceuticals for health and nutrition

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ABSTRACT

Throughout human history, seaweeds have been used as food, folk remedies, dyes, and mineral-rich fertilisers. Seaweeds as nutraceuticals or functional foods with dietary benefits beyond their fundamental macronutrient content, are now a major research and industrial development concept. The occurrence of dietary and lifestyle-related diseases, notably type 2 diabetes, obesity, cancer, and metabolic syndrome has become a health epidemic in developed countries. Global epidemiological studies have shown that countries where seaweed is consumed on a regular basis have significantly fewer instances of obesity and dietary-related disease. This review outlines recent developments in seaweed applications for human health from an epidemiological perspective and as a functional food ingredient.

Abbreviations: BNF, British Nutrition Foundation; CDC, Centers for Disease Control and Prevention USA; CMMM, Chinese Marine Materia Medica; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GAE, gallic acid equivalents; LDL, low-density lipoprotein; ORAC, oxygen radical absorbance capacity; PUFA, polyunsaturated fatty acid; RNI, adult reference nutrient intake; WHO, World Health Organization.

ARTICLE HISTORY

Received 22 March 2019
Accepted 03 July 2019
Published online 11
September 2019

KEYWORDS

Functional foods; Human health; Lifestyle-related disease; Nutraceuticals; Seaweed

INTRODUCTION

Seaweeds are marine, photosynthetic algae which are abundant in every ocean. There are three main classes, or phyla, of seaweed: Phaeophyceae (brown algae), Rhodophyta (red algae), and Chlorophyta (green algae). Thousands of species comprise each phylum (Guiry & Guiry 2019; Rindi *et al.* 2012). Seaweeds have been used traditionally as food, folk remedies, dyes, and fertilisers. With the development of mass food manufacturing in the early 1900s, seaweed components were harnessed industrially. Hydrocolloids, such as alginate, carrageenan and agar, are still the most commonly used components because of their gelling properties in foods, pharmaceutical and biotechnological applications (Rhein-Knudsen *et al.* 2015; Zollman 2019). The suitability of seaweed for bio-diesel production has been explored for developing green fuel alternatives (Abomohra *et al.* 2018; Chye *et al.* 2018).

In the last three decades, interest has grown in seaweeds as nutraceuticals, or functional foods, which gave dietary benefits beyond their macronutrient content. In addition, seaweed has been mined for metabolites with biological activity, to produce therapeutic products (Davis & Vasanthi 2011; Zerrifi *et al.* 2018). The paradox of obesity concurrent with mineral and vitamin deficiency has become a health epidemic in developed regions such as Europe, the USA, and Australia (WHO 2019). At the same time, the occurrence of dietary and lifestyle-related diseases, notably type 2 diabetes, cancer, and metabolic syndrome has increased. Global dietary studies have found that countries where seaweed is consumed on a regular basis have significantly less obesity and diet-related diseases (Iso 2011; Nanri *et al.* 2017). Although a number of

dietary factors may be involved in this inverse relationship, the study of seaweed alone for its beneficial dietary and medicinal effects has warranted investigation. This review outlines recent developments in seaweed applications for human health from an epidemiological perspective and as a functional food ingredient.

Functional food applications of seaweed

MICRO- AND MACRONUTRIENT PROFILE

Seaweed has been foraged and consumed by coastal communities worldwide since the beginning of human civilisation (Dillehay *et al.* 2008). Incorporating seaweeds or their extracts into foods to improve nutritional properties is a recent practice, prompted by improved understanding of dietary sciences and the nutrient-dense nature of algae.

MINERALS AND VITAMINS

Some seaweeds contain 10 to 100 times more minerals and vitamins per unit dry mass than terrestrial plants or animal-derived foods (Rupérez 2002). These include fat- and water-soluble vitamins A, D, E, K, C, B₁, B₂, B₉, B₁₂ and essential minerals calcium, iron, iodine, magnesium, phosphorus, potassium, zinc, copper, manganese, selenium, and fluoride (Misurcova 2011; Qin 2018). Content varies among species. For example, a study of five brown, eight red, and eight green seaweeds from northern European waters found that total tocopherol (vitamin E) content ranged from 1.6 to 122 mg kg⁻¹ in brown, 10–26 mg kg⁻¹ in red, and 8.8–12.0 mg kg⁻¹ in green species (dry mass, DW) (Biancarosa *et al.* 2018). From

Table 1. List of algal species mentioned in the text, by taxonomic group with common names. Note: The initial name is that used in the cited literature; the name after the equal sign is the one currently accepted. Synonymy and common names (where available) follow AlgaeBase (Guiry & Guiry 2019).

Phylum or Class	Species	Selected common names
Cyanobacteria	<i>Spirulina platensis</i> (Gomont) Geitler = <i>Arthrospira platensis</i> Gomont	Spirulina
Chlorophyta (green algae)	<i>Chaetomorpha linum</i> (O.F.Müller) Kützing	Warakuzumo, flax brick weed (U.K.)
	<i>Chlorella vulgaris</i> Beyerinck	
	<i>Ulva lactuca</i> Linnaeus	Sea lettuce
Rhodophyta (red algae)	<i>Enteromorpha prolifera</i> O.F.Müller = <i>Ulva prolifera</i> (O.F.Müller) J.Agardh	
	<i>Euclima cottonii</i> Weber van Bosse = <i>Kappaphycus alvarezii</i> (Doty) Doty ex Silva	Elkhorn sea moss
	<i>Gracilariopsis lemaneiformis</i> (Bory de Saint-Vincent) E.Y.Dawson, Cleto & Foldvik	
	<i>Palmaria palmata</i> (Linnaeus) F.Weber & D.Mohr	Dulse
	<i>Porphyra/Pyropia</i>	Nori, gim, laver
	<i>Porphyra umbilicalis</i> Kützing	Nori, laver
Phaeophyceae (brown algae)	<i>Pyropia columbina</i> (Montagne) W.A.Nelson	Nori, southern laver
	<i>Ascophyllum nodosum</i> (Linnaeus) Le Jolis	Knobbed wrack
	<i>Cystoseira barbata</i> (Stackhouse) C.Agardh	
	<i>Durvillaea antarctica</i> (Chamisso) Hariot	Cochayugo
	<i>Ecklonia cava</i> Kjellman	Kajime
	<i>Fucus spiralis</i> Linnaeus	Spiral wrack
	<i>Fucus vesiculosus</i> Linnaeus	Bladder wrack
	<i>Himantalia elongata</i> (Linnaeus) S.F.Gray	Sea spaghetti
	<i>Laminaria hyperborea</i> (Gunnerus) Foslie	Kelpie
	<i>Laminaria japonica</i> Areschoug = <i>Saccharina japonica</i> (Areschoug) C.E.Lane, C.Mayes, Druehl & G.W.Saunders	Sea Tangle, dasima
	<i>Macrocystis pyrifera</i> (Linnaeus) C.Agardh	Giant kelp
	<i>Saccharina latissima</i> (Linnaeus) C.E.Lane, C.Mayes, Druehl & G.W.Saunders	Sugar kelp, kombu
	<i>Saccorhiza polyschides</i> (Lightfoot) Batters	Furbelows
	<i>Sargassum thunbergii</i> (Mertens ex Roth) Kuntze	Sargassum
	<i>Sargassum fusiforme</i> (Harvey) Setchell	Hijiki
	<i>Sargassum vulgare</i> C.Agardh nom. illeg.	Beerentang
	<i>Sargassum crassifolium</i> J.Agardh = <i>Sargassum aquifolium</i> (Turner) C.Agardh	Binder's Sargassum weed
	<i>Undaria pinnatifida</i> (Harvey) Suringar	Wakame

a portion perspective, taking 8 g (DW) as a typical serving size, many seaweeds perform better than plant and animal foods in terms of adult reference nutrient intake (RNI; Astorga-España *et al.* 2015). For example, the British Nutrition Foundation recommends 8.7 mg iron/day⁻¹ for adult males (BNF 2016). The red seaweed *Palmaria palmata* (see Table 1 for authorities, common names and higher taxonomic position) contains on average 6.4 mg of iron per 8 g serving, compared to only 1.2–3.1 mg in a 100 g portion of lean beef (Branscheid & Judas 2011). Similarly, 8 g of the green seaweed *Ulva lactuca* contains on average 260 mg of calcium or 37% of the RNI, while 8 g of cheddar cheese provides on average 5% of the RNI (Finglas *et al.* 2015; MacArtain *et al.* 2007).

Protein

Protein constitutes 5%–47% of seaweed dry mass. Red seaweeds have the greatest protein content, while green has less, and brown the least (Černá 2011). Of the total amino acids (aa) in seaweeds, approximately 42% to 48% are essential aa (Wong & Cheung 2000). In terms of a score (on a scale of 0.0–1.0), where egg protein has a score of 1.0, most seaweeds have a higher score than all plant-based proteins, with the exception of soy, which has a score

of 1.0. For example, *Undaria pinnatifida* has an amino acid score of 1.0, equal to that of egg and soy, *Pyropia/Porphyra* 0.91, and *Laminaria saccharina* 0.82 (Murata & Nakazoe 2001). However, the high polyphenolic content of seaweeds can reduce the digestibility of algal proteins, giving a slightly lower score on the protein digestibility-corrected aa scale (Wong & Cheung 2001). Despite this, seaweeds still represent a viable alternative to animal-derived protein; if other high-aa scoring vegan foods, such as soy or mycoprotein, are included in the diet.

POLYSACCHARIDES

Total polysaccharide or sugar content of seaweed ranges from 4% to 76% (dry mass) (Paniagua-Michel *et al.* 2014). Cellulose is an indigestible, non-nutritive polysaccharide that gives structure to cell walls of many seaweeds and constitutes from 2% to 10% of total polysaccharides. Digestible polysaccharides differ between phyla. Alginates, fucoidans, and laminarin are the main polysaccharides in brown algae (Rodrigues *et al.* 2015); carrageenans and agarans occur in red algae; and ulvans in green algae (Jiao *et al.* 2011). Most algal polysaccharides are non-starchy fibre, which helps balance normal blood glucose levels, and can contribute to the RNI of 30 g fibre day⁻¹ (BNF 2016). The structural chemistry of algal fibre differs from that found in terrestrial

plants. This gives them functional and bioactive properties not found in land-based fibre sources (Jimenez-Escrig & Goñi 1999).

Lipids

Total lipid content of seaweeds ranges from 0.60% to 4.14% (El Maghraby & Fakhry 2015; Rodrigues *et al.* 2015). Most algal lipids are polyunsaturated, composed of (*n*-3, or omega-3) fatty acids such as docosahexaenoic and eicosapentaenoic acid. Linoleic and arachidonic acids are the most common algal mono-unsaturated (*n*-6, or omega-6) fatty acids (Belattmania *et al.* 2018). Principle saturated fatty acids include palmitic and myristic acids. From a dietary perspective, both *n*-6 and *n*-3 fatty acids are essential; however, consuming them in an imbalanced ratio can result in chronic inflammatory diseases such as obesity, rheumatoid arthritis, non-alcoholic fatty liver, and cardiovascular disease (Patterson *et al.* 2012). The ratio of *n*-6:*n*-3 consumption in developed, Western countries has risen to approximately 20:1 in the last two decades (Husted & Bouzinova 2016; Logan 2003). A ratio between 2.5:1 and 4:1 (*n*-6:*n*-3) is generally recommended to prevent chronic diseases associated with excess *n*-6 monounsaturated fat consumption (Simopoulos 2016). The *n*-6:*n*-3 ratio of fatty acids in seaweeds is within this low ratio (Biancarosa *et al.* 2018), making them excellent dietary lipid sources (Dawczynski *et al.* 2007).

Other nutrient compounds unique to seaweeds, such as fucoxanthin, phycobiliproteins, phlorotannins, and sulphated polysaccharides have therapeutic effects beyond basic nutrition (Mysliwa-Kurdziel & Solymosi 2017; Pérez *et al.* 2016). These will be discussed below.

INCORPORATION IN TO FOOD PRODUCTS

The nutrient-dense nature of seaweeds makes them excellent candidates for functional food use. In addition, their physical ability to emulsify and retain water enhances their techno-functional properties as food ingredients. Examples of nutritional, structural, antimicrobial, organoleptic, and shelf-life enhancement of meat- and plant-based food products by the addition of seaweed are outlined below.

MEAT-BASED PRODUCTS: Meat is part of the staple diet of billions of people worldwide and is a good source of protein, bioavailable iron, zinc, selenium, magnesium, and vitamins B, D, and A. However, meats, particularly pork and beef, contain substantial levels of saturated fat which can raise LDL cholesterol levels. Meat-derived products such as burgers, frankfurters, salami, and deli-sliced meats also contain salt as a necessary ingredient for preservation, flavour and texture enhancement. Some manufacturers also add artificial flavour enhancers and preservatives such as monosodium glutamate and sodium nitrate, which have been linked to cancer and other disorders (Ramesh & Muthuraman 2018). Regular consumption of saturated fat, salt, and artificial additives has contributed to disorders such as heart disease and obesity worldwide. The search for compounds to reduce salt and

saturated fat, and eliminate artificial additives in meat products has led to use of seaweed components as healthy functional ingredients. The incorporation of a variety of seaweeds has produced several meat products of high consumer acceptance with significantly lower levels of saturated fat and salt, no artificial additives, plus increased fibre and polyunsaturated fat content (Cofrades *et al.* 2017). In addition, polyphenolic compounds, selenium, and vitamins A, C, and E in seaweed act as natural antioxidants and preservatives within the meat matrix.

Using *Undaria pinnatifida*, *Porphyra umbilicalis*, and *Himanthalia elongata*, López-López *et al.* (2009) incorporated 5.6% dried, milled seaweed into pork frankfurters, beef burgers, and restructured poultry steaks with consumer sensory acceptance. The seaweeds significantly decreased the thrombogenic index of the products' fatty acid profile, by increasing the ratio of *n*-3 to *n*-6 polyunsaturated fats. Sodium was significantly decreased, while calcium, magnesium and manganese, vitamin K, and soluble polyphenolic compounds levels were increased. Total polyphenolic content was highest in meats enriched with *H. elongata* (25.7 mg gallic acid equivalents (GAE)g⁻¹), followed by *P. umbilicalis* (21.7 mg GAE g⁻¹) and *U. pinnatifida* (0.82 mg GAE g⁻¹). The same trend was seen in antioxidant capacity – measured by the ferric reducing antioxidant power assay – where meat enriched with *H. elongata* had an antioxidant capacity of 3.69 µmol Trolox equivalents (TE) g⁻¹, followed by *P. umbilicalis* (1.18 µmol TE g⁻¹) and *U. pinnatifida* (1.09 µmol TE g⁻¹). The seaweed-enriched meats were later tested in animal models and significantly improved lipoprotein metabolism was found, suggesting that these products could be developed as a hypercholesterolaemic in human dietary interventions (Olivero-David *et al.* 2011).

Himanthalia elongata was also used to enrich beef patties (Cox & Abu-Ghannam 2013); however, the seaweed was not used as a dried powder as per López-López *et al.* (2009). Instead, whole, dried *H. elongata* was blanched in water for 20 min at 80 °C before being blended to a paste, and combined with fresh-minced beef (10%–40% w/w). Unlike most studies, which report the highest sensory acceptability in products with the lowest concentrations of seaweed, patties containing 40% seaweed were rated by the sensory panel as having the best overall acceptability in terms of aroma, texture, taste and appearance. Throughout chilled storage, all chemical, physical, sensory and microbial parameters were significantly improved by the addition of *H. elongata*. Fibre increased from zero in the control to 1.64 g total dietary fibre per 100 g (fresh weight). Water-retention is a useful property of algal fibre where fat content is reduced, as it retains moisture in foods. Beef used in this study had a fat content of 14%. Replacing 40% of the meat with seaweed reduced the fat content to just 8.4%, while maintaining full sensory acceptance by the panel of judges. In addition, moisture loss (by mass) during cooking was reduced by 6.4%. After 30 days at 4 °C, total viable microbiological plate counts in the cooked, control burger were 5.41 log CFU g⁻¹ compared to zero CFU g⁻¹ in the 20%, 30% and 40% seaweed-enriched burgers. Growth occurred (1.09 log CFU g⁻¹) only in the 10% seaweed burgers after 30 days. Final lipid oxidation levels were 45% lower in the 40% seaweed-enriched burgers

(0.61 mg malondialdehyde kg⁻¹) compared to 1.12 mg MDA kg⁻¹ in the control. Total phenolic content and DPPH radical scavenging activity were zero in the control sample, and as high as 28.11 mg GAE 100 g⁻¹ and 52.32%, respectively (fresh weight) in the 40% seaweed-enriched burgers. Tenderness also improved significantly as shown by Instron measurement of firmness/hardness after storage for 30 days. Hardness was 40.23 N mm⁻¹ in the control sample, compared to only 21.33 N mm⁻¹ in the 40% seaweed-enriched burgers, indicating that they were almost 47% more tender.

Sellimi *et al.* (2017) improved the functional and nutritional attributes of cured turkey meat sausages with the addition of fucoxanthin, extracted from *Cystoseira barbata*. Over 15 days, there was a significant increase in antioxidant capacity, colour stability, inhibition of lipid peroxidation, and angiotensin-I converting enzyme, which raises blood pressure. There was also a 47% reduction in the amount of sodium nitrite required as an anti-bacterial, from 150 ppm to 80 ppm. Only 0.04% (total ingredient composition) of fucoxanthin was required to achieve these improvements, while still maintaining consumer sensory acceptance.

These nutritional and technological quality enhancements, combined with sensory acceptance, were achieved with a cost-effective, sustainable ingredient and minimal preparation, making the addition of seaweed a viable option for meat product enrichment. Seaweed as a functional food ingredient can allow consumers to continue eating meat products while reducing their risk of adverse health effects.

PLANT-BASED PRODUCTS: Aside from unprocessed vegetables, fruit, pulses, and rice, the majority of plant-based (processed) products consumed globally are derived from grains, and constitute part of the daily diet of almost all human populations (Stephen *et al.* 2017). These grain- or cereal-based products are consumed as thousands of different varieties of bread, pasta, noodles, and pastries. Since the majority of these foods are produced using refined white flours, the fibre, protein, mineral and vitamin content is poor, while starch content is high. Therefore, enrichment of cereal-based products with high fibre, nutrient-dense functional ingredients such as seaweed has the potential to increase the dietary intake of essential nutrients. Several studies have successfully incorporated seaweed and their extracts into cereal-based products.

Kumoro *et al.* (2016) improved the fibre, protein, lipid, and mineral profile of wheat flour noodles with the addition of dried, milled *Euचेuma cottonii*. In addition to seaweed, two dried microalgal powders of *Spirulina platensis* and *Chlorella vulgaris* were added. The control noodles were made using 100 g of white Indonesian wheat flour, eggs, water, and salt. Dried *E. cottonii* was added alone, or combined with *S. platensis* and *C. vulgaris*, in 10 to 30 g amounts, with wheat flour at 90–70 g as required to produce a total dry mass of 100 g for each batch of noodles. In terms of nutritional improvement and sensory acceptance, the optimum composition was 90 g wheat flour, with 5 g *E. cottonii* and 5 g *S. platensis*. This produced noodles with the most protein, lowest fat content, and greatest consumer acceptability. Total carbohydrate content (mostly starch), was reduced from 78%

to 68% in control noodles; and crude fibre increased by 125%, from 1.72 g per 100 g in the control to 3.87 g per 100 g in algal-enriched samples. This was due to the high fibre content (25%) of dried *E. cottonii* compared to only 0.5% fibre in wheat flour. Protein increased by 87% (from 9.34 g per 100 g to 17.53 g per 100 g), while total mineral (ash) content almost tripled, from 1.01% to 3.01%. Organoleptic parameters of texture, flavour, aroma, and colour scored positively, similar to the wheat-flour-only control. Some parameters were, in fact, higher in the 10% *E. cottonii*- and *S. platensis*-enriched samples, with panellists showing a preference for the light green colour and savoury aroma of the noodles.

Arufe *et al.* (2018) harnessed the techno-functional properties of *Fucus vesiculosus* to improve the antioxidant profile of white bread while maintaining acceptable density and crumb texture. *Fucus vesiculosus* was dried and milled in to a powder. A control recipe of white wheat flour (300 g), fresh yeast (6 g), tap water (192 g), salt (5.4 g) and ascorbic acid (0.006 g) was used. The algal powder was added as 2% to 8% (6–24 g) of total flour mass. After all other ingredients were added and kneaded together the dough was proofed (27 °C, 35 min). The dough was divided and proofed again (27 °C, 70 min), then baked (245 °C, 21 min). The proofing behaviour and rheological properties of the doughs were measured to determine the maximum percentage of *F. vesiculosus* that could be added without impairing the techno-functional properties of the breads. During the first 90 min of proofing, *F. vesiculosus* improved the capacity of the dough to maintain shape by increasing elongational viscosity. However, increased viscosity reduced bubble growth, limiting dough expansion; this impaired the desired final dough porosity. After baking, this increased bread density and apparent crumb modulus. Up to 2% seaweed could be added without altering density, and up to 4% could be added without negatively affecting the acceptability of density and crumb texture. Additions greater than 4% significantly modified texture parameters of the bread crumb and created a noticeable green colour.

Cox & Abu-Ghannam (2013) significantly enhanced the phytochemical content of wholemeal and white wheat flour breadsticks by adding *Himanthalia elongata*. Seaweed was air-dried, milled, and added to the dough mix in proportions of 5%–15%, along with white flour from 10% to 30% of the overall flour concentration. The remainder was brought to 100% with wholemeal flour. The same amounts of yeast (2.13%), water (34.65%), butter (1.21%) and salt (1.21%) were added to the control and enriched doughs. Doughs were kneaded, proofed (33 °C, 45 min), rolled into sticks, proofed again (33 °C, 40 min), and baked (210 °C, 20 min). Maximum nutritional enhancement and acceptability of texture and colour were achieved with 17.07% *H. elongata* and 21.89% white flour. Total phenolic content rose by 427%, from 27.67 mg GAE/100 g in the control to 145.88 mg GAE per 100 g in the *H. elongata*-enriched sample. Antioxidant capacity, measured by DPPH activity, increased by 87%. Total dietary fibre increased by 71%. The sensory analysis found that taste, texture, colour, aroma, and overall acceptability of the seaweed-enriched breadsticks was slightly below the control, but not statistically different. The study showed that there is definite potential for nutritional enrichment of

baked goods with seaweed resulting in healthy alternatives to commonly available, nutrient-poor products.

PLANT- AND MEAT-BASED FOODS: Three seaweeds from Chile, were incorporated into a range of plant and meat-based foods by Astorga-España *et al.* (2017). After drying, the seaweeds were used as ingredients in dishes commonly consumed in the region. *Durvillaea antarctica* was incorporated at 3% in fettuccine; 5% in bread; and 5% in hamburger. *Macrocystis pyrifera* was added at 8% in breadsticks and 7% in fritters; while 28% *Pyropia columbina* was used in parsley pesto. In the seaweed-enriched dishes, kilocalories per 100 g and protein percentage had a wide range, i.e. fritters (143 kcal, 6.9%), hamburger (145 kcal, 12.73%), fettuccine (209 kcal, 11.4%), parsley pesto (225 kcal, 4.16%), bread (252 kcal, 9.9%), and breadsticks (316 kcal, 9.5%). Of the three seaweeds, *D. antarctica* exhibited the highest protein increase. Compared to regular versions of each dish, fibre content (dry mass) was significantly greater in the seaweed versions, with the exceptions of the breadsticks with 3.6% fibre versus 4.0% in regular breadsticks, and 1.8% fibre in the parsley pesto versus 1.9% in a non-seaweed version. Polyunsaturated fatty acid (PUFA) profiles were improved with seaweed addition. Total lipid content of the seaweed-enriched dishes ranged from 4.1% in breadsticks containing *M. pyrifera* to 23.1% in pesto containing *P. columbina*. Of this total lipid percentage, PUFAs were the most abundant fatty acid with the exception of the fettuccine with *D. antarctica* in which monounsaturated fatty acids (oleic and nervonic) were more prevalent. Two PUFAs were quantified: linoleic (*n*-6) and α -linolenic (*n*-3) acids. Linoleic acid as a percentage of total lipids in the seaweed-enriched dishes ranged from 22.3% (fettuccine), 32.0% (hamburger), 33.6% (pesto), 37.2% (fritters), 44.5% (bread) to 46.2% (breadsticks). As a percentage of total lipids, α -linolenic acid was 1.2% (fettuccine), 2.8% (hamburger), 4.3% (fritters), 5.4% (bread), 5.6% (breadsticks), while no α -linolenic acid was detected in the pesto. Total PUFA content (linoleic and α -linolenic combined) of the seaweed-enriched dishes ranged from 23.4% in fettuccine to 51.8% in breadsticks. This is from 10 to 50 times more than the total PUFA content of the dishes before seaweed addition: 0% (pesto), 0.4% (fettuccine), 1.5% (fritters), 1.6% (breadsticks), 2.1% (bread) and 2.3% (hamburger). The addition of seaweed, therefore, significantly increased the essential polyunsaturated fatty acid content.

Other functional nutrients derived from seaweed include polyols, or sugar alcohols, such as mannitol from brown seaweeds (a sweetener), with some reported medicinal properties in the case of reducing oedema and aiding kidney function (Liu *et al.* 2012). Mannitol has a far lower glycaemic index and 40% fewer calories than sucrose, and is non-cariogenic (Grembecka 2015). Ulvans are sulphated acidic polysaccharides that occur in green seaweeds and have gelling and rheological properties similar to gum arabic due to solubility in water. Ulvans are being developed as vegan alternatives to beef-derived gelatin due to consumer concerns about bovine BSE contamination (Kraan 2012).

Aside from meat and grain-based foods, seaweed has been used to enhance many other products such as dairy, fish, desserts, mayonnaise, sauces and fermented products (Abu-Ghannam & Shannon 2017; Dolea *et al.* 2018; Honold *et al.*

2016; Pongpichaiudom & Songsermpong 2018; Roohinejad *et al.* 2017; Uchida *et al.* 2018). Seaweed as an ingredient has become more acceptable and mainstream outside of Asia. For example, the global furniture company, IKEA, has developed sustainable alternatives to beef meatballs and pork hotdogs using seaweed, vegetables, and insect protein; these were launched in their store restaurants in 2018 (Algaeworld 2018).

World population is predicted to increase to nine billion by 2050 (Zhou *et al.* 2018). Traditional crop-growing and animal-grazing practices exacerbate competition for land use. Livestock farming is also a major contributor to greenhouse gas emissions of carbon dioxide and methane. Seaweed reduce carbon emissions generated by animal protein production. Seaweeds are suitable for vegan, kosher, and halal diets. As functional foods, seaweeds offer a low-cost, alternative, sustainable source of protein without the saturated fat associated with meat, and are an excellent source of fibre, vitamins, minerals, and polyunsaturated fats.

EPIDEMIOLOGICAL EVIDENCE AND DIETARY INTERVENTION STUDIES

The incidence of chronic dietary-associated disorders such as type 2 diabetes, obesity and cardiovascular disease has become a health epidemic in the Western world. First-line therapy by the medical profession often involves pharmaceutical drugs to treat disorders and their symptoms. While these can be helpful, many orthodox drugs have serious side-effects and can lose their efficacy over time. Nutritional intervention has long been proposed as a solution, both to prevent and to alleviate chronic dietary-associated health disorders. However, this is often viewed as anecdotal evidence compared to data from pharmaceutical studies, where effective doses are specified at the micro-molar level. The fields of natural products chemistry and pharmacognosy have developed in recent years, elucidating numerous plant, fungal and algal compounds with therapeutic effects. Seaweed have unique chemical properties compared to terrestrial plants due to their mineral-rich marine habitat, and the requirements to survive this environment. Seaweeds generate antioxidising, antimicrobial and other bioactive agents to combat abiotic stress such as UV photo-damage, high salinity, constant oxygen exposure, and biotic stress from bacterial colonisation and marine herbivores. Various seaweeds, as part of the diet or in the form of isolated extracts, have been documented for disease-preventative effects. Epidemiological evidence from broad population studies, and from controlled experimental intervention showing the positive effect of seaweed in the diet with respect to numerous human health disorders, is discussed.

Cancer

The US Food and Drug Administration, European Pharmacopoeia, and European Food Safety Authority consider seaweeds as food, not medicine (Turck *et al.* 2016; USFDA 2017). However, in many Asian countries seaweeds are considered as medicinal and are packaged with details of their effects and

directions for use. Examples are included in the Japanese and Korean pharmacopoeias and the *Chinese Marine Materia Medica* (CMMM). In traditional Chinese medicine, seaweeds and other marine organisms are documented separately from terrestrial *Materia Medica*. In the CMMM, 171 species of medicinal algae are listed (Fu *et al.* 2016; Qin 2018). Since seaweed has been used as a regular part of the diet and accepted as medicine for millennia in Asia, this may account for the majority of epidemiological evidence originating there (Kim 2017).

A direct relationship has been identified between high levels of seaweed consumption and lower instances of dietary-related disease such as cancer (Iso 2011). At the National Cancer Centre of South Korea, Park *et al.* (2016) assessed the dietary patterns of 923 men and women with an average age of 56 who had previously undergone surgery for colorectal cancer (plus 1846 control participants). Three dietary types were identified: prudent, traditional Korean, and Westernised. A highly significant reduction of risk factors for colorectal cancer was identified in subjects in the prudent group who consumed the most seaweed and vegetables, followed by the traditional diet (slightly less seaweed), with the highest risk found in the Westernised diet group who consumed little or no seaweed but high levels of red meat and processed foods.

Nelson *et al.* (2017) found the same association in a study of 627 people (age 35–74) across 42 hospitals in China. Risk factors for the development of biliary tract cancer were measured using 39 food groups. Only four food groups had either a significantly positive or negative association with risk factors for biliary tract cancer. These groups were seaweed, allium (onions and garlic), salted meats, and preserved vegetables (pickled with salt-brine). The seaweed and allium groups both had an inverse association (i.e. reduced risk) with cancer. The salted meat and preserved vegetable groups had a positive association with cancer (increased risk). The authors surmised that the high fibre and anti-inflammatory properties of seaweed reduced this group's risk of developing cancer.

In a case-control study of breast cancer in South Korea, Yang *et al.* (2010) reported the daily intake of several species of *Pyropia* (as *Porphyra*), to be inversely associated with the risk of developing cancer. *Pyropia* ('gim' in Korea) is commonly eaten dried and roasted (Herath *et al.* 2018; Jung & Choe 2017). A cohort of 362 women with histologically confirmed breast cancer (aged 30–65), and 362 control participants of equal age and menopausal status, completed a food frequency questionnaire for 12 months containing 121 food items, including seaweed. An inverse dose-response association with the risk of breast cancer was seen in women who consumed the most gim over the twelve months (at least 1.17 g day⁻¹, dry mass).

Within the Japanese population of 127 million, where the daily intake of seaweed averages 14.3 g per adult per day (fresh mass), cancer rates are among the lowest in the world (Délérís *et al.* 2016). Fukuda *et al.* (2006) conducted a dietary survey evaluating the dietary fibre intake of 577 Japanese men and women. Amongst eleven fibre-rich foods – including pulses, vegetables, mushrooms, and grains – seaweed contributed the most dietary fibre. In a Japanese Public Health Centre-based

Prospective Study for colorectal cancer risk in middle-aged adults, the dietary patterns of 93,062 men and women were assessed over four years. The lowest risk of developing colorectal cancer was associated with the highest seaweed consumption.

Cancer risk increases due to the effect of dietary changes in people who emigrate from Asian to Western countries (Deapen *et al.* 2002; Shimizu *et al.* 1991; Vogel 2018). For example, a population-based, case-control study of breast cancer conducted over 4 years among Japanese, Chinese, and Filipino women who had emigrated to the United States (597 subjects, age 20–55, plus 966 controls) showed a six-fold increase in breast cancer risk by migration patterns. Asian-American women born in the United States also had a cancer risk 60% greater those born in Asia, while those living in the West for ten years or more had a risk 80% higher than more recent migrants (Ziegler *et al.* 1993). Numerous epidemiological studies of breast cancer have shown that weight is a key risk element. Thus diet, which significantly determines weight, must be considered a fundamental risk factor.

The multiple mechanisms by which seaweeds induce apoptosis in cancer cells have been linked to several compounds such as fucoxanthin, polyphenols and other antioxidants; phlorotannins; iodine; and sulphated polysaccharides such as fucoidan (Gutiérrez-Rodríguez *et al.* 2018; Jiang & Shi 2018; Namvar *et al.* 2012).

Obesity and metabolic disorder

The Organisation for Economic Co-operation and Development reported that in 2015 38.2% of the adult population in the United States were obese, opposed to only 3.7% in Japan, and 5.3% in Korea (OECD 2017). Obesity – combined with mineral and vitamin deficiency at the same time – has become a health epidemic in many developed regions. Obesity increases the risk of developing other diseases, including type 2 diabetes, hypertension, dyslipidaemia, and coronary heart disease (Medina-Remón *et al.* 2018). Consumption of fibre-rich foods like seaweed, and seaweed isolates including carotenoids and alginate, has been linked to positive effects on appetite, satiety, blood glucose and cholesterol (Brown *et al.* 2014; Kim *et al.* 2008).

Fucoxanthin occurs in brown seaweeds and many microalgae, and has anti-obesity properties (Shannon & Abu-Ghannam 2017). Hitoe & Shimoda (2017) examined the effect of fucoxanthin on 50 women and men (aged 20–59) with a body mass index (BMI) above 26–30 kg m², and a waist circumference of ≥ 90 cm (women) and ≥ 85 cm (men). Aside from having a BMI above the recommended 18–25 kg m², subjects were healthy. Either fucoxanthin capsules or placebos were given at a dosage of 1 mg or 3 mg d⁻¹ for four weeks. In the 3 mg day group, significant decreases occurred in BMI, visceral fat, basal metabolic rate, abdominal fat and circumferences of the neck, arm and thigh compared to the placebo group. In the 1 mg d⁻¹ group total fat mass, subcutaneous fat area, waist circumference and right thigh circumference had significantly decreased. No adverse effects on blood pressure, pulse rate, blood parameters, or urinalysis parameters were reported during the study.

Abidov *et al.* (2010) administered fucoxanthin capsules over a 16-week period to 115 obese, non-diabetic, premenopausal women with a liver fat content above 11%. Each daily dose consisted of a capsule containing 300 mg of dried, brown seaweed extract with a fucoxanthin content of 2.4 mg, combined with 300 mg pomegranate seed oil. The placebo group received olive oil capsules. A significant average weight loss of 4.9 kg, and an increase in resting energy expenditure were observed across the treatment group.

In combination with lifestyle changes such as exercise and dietary changes, seaweed and its extracts could be used as an aid in obesity treatment.

Type 2 diabetes

Worldwide, 108 million adults had diabetes in 1980 (4.7% of global population). This increased to 422 million (8.5% of global population) by 2014. Of these diabetic cases, 90–95% were type 2 diabetes (NCD-RisC 2016). Currently, in the United Kingdom, 7.7% of adults have been diagnosed with type 2 diabetes. In the United States it is 9.1%, while a further 86 million (26.4% of the population) have pre-diabetes (CDC 2017; WHO 2016a, b). Type 2 diabetes mellitus, also known as adult-onset diabetes, is a diet-related metabolic disorder that responds well to dietary intervention, unlike the often genetically inherited type 1 diabetes (an autoimmune disorder), that destroys the beta cells of the pancreas, and must be treated with insulin injections. Drugs commonly used to treat type 2 diabetes, such as the α -amylase and α -glucosidase inhibitor Acarbose, may cause gastric discomfort and diarrhoea (Moore 2018).

The *in vivo* anti-diabetic efficacy of seaweed has been shown in many animal studies (Gabbia *et al.* 2017; Roy *et al.* 2011; Song *et al.* 2018; Zhao *et al.* 2018). In human clinical trials, daily supplementation with *Undaria pinnatifida* and *Sacchariza polyschides* (as *Gigantea bulbosa*) balances blood glucose levels, decreases serum triglyceride concentrations, and increases high-density lipoprotein cholesterol in subjects with type 2 diabetes (Kim *et al.* 2008). Paradis *et al.* (2011) studied the effect of a commercial seaweed extract (*InSea*²) on postprandial plasma glucose and insulin concentrations of twelve women and eleven men (aged 19–59, mean BMI 24.9 kg m²). The *InSea*² extract used *Fucus vesiculosus* and *Ascophyllum nodosum* and contained natural α -amylase and α -glucosidase inhibitors. The extract had previously demonstrated anti-diabetic properties *in vitro* by inhibiting these digestive enzymes that convert polysaccharides into simple sugars in the intestine and raise blood glucose levels (Roy *et al.* 2011). Thirty minutes before a meal of 50 g white bread, capsules containing 500 mg *InSea*² powder were administered to twelve subjects, while placebo capsules were given to a control group. For 3 h after meal consumption, plasma glucose levels were reduced by 9% in the seaweed group (1188 mmol L⁻¹ min⁻¹ in the placebo group compared to only 1081 mmol L⁻¹ min⁻¹ in the seaweed group), although the difference was not statistically significant ($P > .05$). However, a significant insulin reduction of 12.1% was seen in plasma levels of the seaweed group. In addition, the peripheral insulin sensitivity and muscular glucose uptake (Cederholm index)

increased by 7.9%. The improvements in glucose and insulin profiles produced by the seaweed extracts suggest that they could be used to maintain insulin homeostasis in subjects with type 2 diabetes.

The same *InSea*² extract significantly enhanced postprandial cognitive performance in 33 women and 27 men (age 18–65) who commonly experienced acute postprandial drowsiness (Haskell-Ramsay *et al.* 2018). Attention, performance, and error rates during cognitive tests such as immediate word recall, simple reaction time, digit vigilance, and choice reaction time, were recorded before and after a high-carbohydrate meal. A dose of 500 mg *InSea*² extract was administered 30 min before the carbohydrate (50 g) meal of waffles and pure maple syrup, after which the subjects had to repeat the cognitive tests. The group who consumed the seaweed extract displayed greater accuracy and a 15% reduction in error rates compared to the placebo group. The effects were attributed to modulation of glucose metabolism by the high fibre and polyphenolic content (20% chlorogenic acid equivalent) of the *InSea*² extract, since similar polyphenols from plants, e.g. cocoa and grapes, increase cerebral blood flow.

Tanemura *et al.* (2014) examined the postprandial blood glucose profiles of 12 healthy adults (eight men, four women, average age 25) after a meal with and without the inclusion of fresh, cooked, whole *U. pinnatifida* (wakame), or sporophylls of *U. pinnatifida* (mekabu). An average Japanese cooked breakfast of white rice (200 g), boiled soya beans, broccoli, and potatoes was supplemented with either 70 g fresh wakame or 70 g fresh mekabu. The control breakfast contained 455 kcal and 87.5 g carbohydrates; while the wakame breakfast contained 466 kcal and 91.5 g carbohydrates; and the mekabu had 463 kcal and 90 g carbohydrates. Since white rice is a high glycaemic-index food, the study aim was to measure the reduction in blood sugar induced by the seaweeds. Half an hour after the meals, glucose levels were significantly lower ($P < .05$) in the group who consumed the meal with mekabu, compared to the control group. The authors surmised that it was the fucoxanthin fraction and the polysaccharide-rich content of the mekabu sporophylls that exerted the anti-glycaemic effect. The small mekabu shoots that grow from the parent wakame seaweed thallus are more viscous when cooked. This is due to their higher content of soluble viscous fibre, which affects carbohydrate metabolism and delays gastric emptying (Tanemura *et al.* 2014). It was concluded that the addition of fresh, brown seaweed to meals could be useful in controlling blood glucose levels for people with type 2 diabetes.

The mechanisms of anti-diabetic action by seaweed have been attributed to compounds including phlorotannins, fucoxanthin, polyphenolics, and polysaccharides (Kellogg *et al.* 2014; Murray *et al.* 2018) which inhibit hepatic gluconeogenesis, and reduce the activity of digestive enzymes such as α -amylase, α -glucosidase, lipase, and aldose reductase (Sharifuddin *et al.* 2015). Seaweeds and their extracts may alleviate the health epidemic of type 2 diabetes which can lead to nephropathy, blindness, peripheral neuropathy with loss of limb extremities, and premature death (Yamazaki *et al.* 2018).

Hypertension and cardiac disease

Hypertension increases the risk of cardiovascular disease to a greater extent than other causes such as cigarette smoking and type 2 diabetes (Roth *et al.* 2015). The aetiology of hypertension and cardiovascular disease involves non-modifiable risk factors such as age, gender, ethnicity and genetics; however, modifiable risk factors such as diet and lifestyle can be improved to greatly reduce the risk of developing high blood pressure and heart disease. Worldwide, heart disease is the leading cause of mortality. In the United States, the annual cost of health care, medication and lost productivity because of heart disease is estimated to be at least \$200 billion (CDC 2016). Worldwide, 40% of adults aged 25 and over have been diagnosed with high blood pressure. This figure is estimated to increase by 2025 (WHO 2017). Numerous pharmaceuticals for the treatment of high blood pressure and heart disease have been developed, such as the angiotensin-I converting enzyme (ACE) inhibitor Captopril; and the aldosterone inhibitor Eplerenone. They are effective but can have adverse effects: persistent dry cough, impaired kidney function, and extremely low blood pressure. Statins, such as Lipitor, lower LDL cholesterol to combat hyperlipidaemia and prevent the progress of atherosclerosis. However, statins can have side-effects such as muscle myopathy, elevated blood sugar, impaired liver function, and memory loss (Thompson *et al.* 2016).

An inverse relationship between regular seaweed consumption and reduced risk of hypertension and cardiovascular disease was observed in epidemiological studies (Nanri *et al.* 2017; Maruyama *et al.* 2013; Chu *et al.* 2015; review by Cornish *et al.* 2015). Japan and South Korea have two of the longest average life spans and take less medication for hypertension and cardiovascular disease than populations with lower seaweed intakes (Lee *et al.* 2016; Yamori *et al.* 2017). For example, a 15-year study of dietary patterns in 79,594 Japanese men and women (aged 45–75) found that a closer adherence to Japanese dietary guidelines was associated with a lower risk of death from all causes and cardiovascular disease, particularly cerebrovascular disease within the experimental population (Kurotani *et al.* 2016).

Hata *et al.* (2001) conducted a dietary intervention trial on 36 elderly outpatients with hypertension in Japan, using 3.3 g day⁻¹ of *U. pinnatifida* powder. A control group of 18 gender-matched subjects (\pm 2 years) were given a placebo. Systolic blood pressure fell significantly in the seaweed group by 13 mmHg after 4 weeks, and by 8 mmHg after 8 weeks. Diastolic pressure fell by 9 mmHg after 4 weeks, and by 8 mmHg after 8 weeks. In addition, hypercholesterolemia in the treatment group decreased by 8% after 4 weeks. Teas *et al.* (2009) conducted a similar study with *U. pinnatifida*. Powder (6 g day⁻¹) was administered for one month to 30 men and women with diagnosed metabolic syndrome. In the seaweed group there was a significant decrease in systolic blood pressure ($-$ 10.5 mmHg) in all participants, and a reduction in waist circumference ($-$ 3.6 cm, in women only), compared to the placebo group.

Peptide extracts of seaweeds in human cell culture, and animal *in vivo* trials, can significantly reduce blood pressure

in single doses and long-term administration (Ko *et al.* 2017; Sato *et al.* 2002; Suetsuna & Nakano 2000). Peptides can bind to the active site of the angiotensin-I converting enzyme, thereby reducing blood pressure. For example, peptides extracted from *Gracilariopsis lemaneiformis* had potent ACE-inhibitory activity *in vitro* (Cao *et al.* 2017). Compounds such as sulphated polysaccharides, from *Ulva prolifera* (as *Enteromorpha*) reduce hyperlipidaemia in animal models – one of the principle causes of heart disease (Ren *et al.* 2017, 2018). Eicosapentaenoic and docosahexaenoic acids in seaweed may also play a part in the mechanism of heart disease risk reduction. Within cardiac cell membrane phospholipids, these *n*-3 fatty acids can have an antiarrhythmic effect by influencing ionic channels and maintaining intracellular calcium homeostasis (Judé *et al.* 2006; Kanoh *et al.* 2017).

Antioxidants

Damage to living cells by free radicals, such as reactive oxygen species, is linked to many chronic disorders. Although the endogenous defence mechanisms of humans can combat oxidation by free radicals to a certain extent, an imbalance still exists in many individuals, especially where the diet is low in antioxidants and there are high levels of stress. Epidemiological studies have found that dietary compounds, such as phlorotannins and fucoxanthin, can reduce the risk of developing disorders associated with free radical cellular damage, including metabolic syndrome, cancer, cardiovascular disease, osteoporosis, renal disease, Parkinson's, Alzheimer's, and neurodegenerative disorders (Barbosa *et al.* 2014; Cornish & Garbary 2010; Shannon *et al.* 2018; Valko *et al.* 2016). The environmental stresses of UV light and oxygen exposure imposed on seaweed in their marine habitat have induced the production of antioxidant metabolites. Numerous studies have reported that the clinical bioactivity of algal extracts is directly related to their antioxidant capacity as measured by assays such as DPPH and ORAC (Narasimhan *et al.* 2013; Pinteus *et al.* 2017a)

Kang *et al.* (2012) studied *Saccharina japonica* (as *Laminaria*), for its antioxidant health potential. This species has been used as a folk remedy in Korea for centuries. A human clinical trial examined whether *S. japonica* could enhance the antioxidant defence system of 48 Korean men (age 25–60). The alga was fermented with a lactic-acid-producing bacterium, *Lactobacillus brevis*, for five days to potentially augment seaweed bioactivity and digestibility. The fermented seaweed was dried and 250 mg of the powder was encapsulated. For one month, six capsules per day (1.5 g of alga) were administered to healthy subjects, but who had high levels ($<$ 132 U/L) of the enzyme, γ -glutamyltransferase (γ -GT). Volunteers with high levels of γ -GT were selected for the study because this enzyme is a predictive biomarker of cellular antioxidant inadequacy and disease risk, and is linked to underlying alcohol-related liver dysfunction (Koenig & Seneff 2015). Serum γ -GT levels decreased significantly from 102.21 to 78.70 U/L in the seaweed group after one month, and actually increased from 104.25 to 116.75 U/L in the placebo group. Levels of four other biological compounds in

blood serum were measured: malondialdehyde, catalase, superoxide dismutase, and glutathione peroxidase, chosen because they are involved in cell defences against free radical damage by eliminating free radicals and reactive oxygen species. The aim was to increase levels of these enzymes in blood serum. Malondialdehyde is a product of lipid peroxidation in the body; therefore its reduction is an indication of a healthy antioxidant defence system. Administering fermented *S. japonica* for one month significantly increased levels of catalase and superoxide dismutase, while levels of γ -GT and malondialdehyde were significantly decreased compared to the placebo group. No difference was observed in glutathione peroxidase levels between treatment and control groups. These findings are very encouraging since healthy biomarkers of the antioxidant defence system were increased, while unhealthy biomarkers were simultaneously decreased. The authors concluded that fermented *S. japonica* could be developed as an antioxidant functional food ingredient.

Phlorotannins are compounds unique to brown seaweeds. They are similar to polyphenols, but are composed of repeating phloroglucinol units (three hydroxyls bound to a benzene ring) rather than phenolic units (one hydroxyl bound to benzene; Sathya *et al.* 2017). Phlorotannins are powerful antioxidants due to their ability to act as chelating agents with reactive oxygen species, thereby preventing oxidative stress and cell damage. Pinteus *et al.* (2017b) evaluated the protective effect of phlorotannin extracts on human (MCF-7) cells against oxidative stress using a methanolic extraction of *Fucus spiralis*. Oxidative stress was induced in cells by addition of hydrogen peroxide. Cell death resulting from oxidative stress decreased 51% with the addition of phlorotannin extracts (1 mg m⁻¹ for 24 h), compared to the control. It was concluded that the phlorotannin extracts maintained normal membrane potential in the cells by decreasing caspase-9 activity which is involved in cell death mechanisms, thereby protecting the cells from oxidative damage.

A human clinical trial by Shin *et al.* (2012) found that phlorotannins extracted from *Ecklonia cava* had an antioxidant effect, by alleviating hyperglycaemia-induced oxidative stress. Ninety-seven overweight men and women (average age 40, BMI 26.5 kg m²) were given either 144 mg d⁻¹ or 72 mg d⁻¹ of the phlorotannin extract for 3 months, while a parallel control group received a placebo. Both dosage groups experienced a significant reduction of total cholesterol, LDL cholesterol, BMI, atherogenic index, and waist circumference compared to a placebo group. The higher dosage group also experienced a significant decrease in blood glucose and systolic blood pressure, and increased HDL cholesterol. Lee & Jeon (2015) also isolated antioxidant-rich phlorotannins from *E. cava* and administered 1500 mg d⁻¹ of the extract to 80 pre-diabetic adults (aged 20–65). After three months, a significant decrease in postprandial glucose levels was measured in the phlorotannin extract group. The authors concluded that the phlorotannin-rich (46%) extract, and the high content of the phlorotannin dieckol (10%) in particular, were responsible for the anti-diabetic effect.

Fucoxanthin is a tetraterpenoid carotenoid reported to be a powerful dietary antioxidant. Due to its unusual chemical structure, fucoxanthin donates an electron to quench reactive

oxygen species, instead of a proton, as in most antioxidants such as β -carotene or ascorbic acid. Fucoxanthin can also function as an antioxidant under anoxic conditions, whereas most antioxidants cannot. This is advantageous for humans since there are low levels of oxygen within physiological tissues (Abu-Ghannam & Shannon 2017; D’Orazio *et al.* 2012; Yan *et al.* 1999). Jang *et al.* (2018) demonstrated the antioxidative protective effect of fucoxanthin extracted from *L. japonica* on human liver (HepG2) cells *in vitro*. Oxidative stress was induced in the HepG2 cells by the addition of arachidonic acid and iron. Cells pretreated with fucoxanthin (30 μ g ml⁻¹ for 1 h) had significantly greater viability than untreated cells. The mechanism by which fucoxanthin protected liver cells against oxidative stress was thought to be associated with the LKB1-AMPK α signalling pathway. LKB1 is a liver kinase. AMPK α is adenosine monophosphate-activated protein kinase – an enzyme involved in energy homeostasis. Jang *et al.* (2018) concluded that the LKB1-AMPK α signalling pathway was enhanced, which triggered autophagy, evidenced by the significant increase of two autophagic protein markers (beclin-1 and LC3II). The enhanced autophagy helped maintain homeostasis and survival in the HepG2 cells treated with fucoxanthin. *Ex vivo* studies in animal models have reported that dietary supplementation of fucoxanthin (0.2% of total food for one month) improved the antioxidant capacity of blood serum levels in obese rats via activation of the nuclear erythroid factor like-2 pathway, which regulates antioxidative defence responses and genes such as NQO1. NAD(P)H quinone oxidoreductase (NQO1) is one of the genes involved in the maintenance of intracellular reducing potential, and the scavenging of reactive oxygen or nitrogen species (Ha *et al.* 2013). Zaragozá *et al.* (2008) used ethanol extraction to isolate fucoxanthin from *F. vesiculosus*. For four weeks, rats were fed fucoxanthin as part of their food (0.2 g kg⁻¹ body weight). Significantly increased antioxidant activity was observed in *ex vivo* assays of erythrocytes and plasma. The activity of copper-zinc superoxide dismutase (Cu-Zn SOD) was measured. Cu-Zn SOD is involved in the protective mechanism against oxidative stress in cells. Cu-Zn SOD activity increased 32% in rats fed with fucoxanthin after four weeks.

Antibacterial properties

The global burden of infectious disease caused by bacteria, viruses, fungi, and protozoans continues to grow despite the development of antibiotics in the 1940s. In the Western world, the issue is not the availability of antimicrobial treatments, but the developed immunity of micro-organisms to pharmaceutical drugs and disinfectants. Bacteria, in particular, pose a threat due to their ability to evolve and survive within human hosts and on surfaces. Currently, at least 700,000 people die worldwide each year from drug-resistant bacterial infections such as *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and methicillin-resistant *Staphylococcus aureus* (MRSA). It is estimated that by 2050, drug-resistant bacteria will cause 10 million deaths annually worldwide – more than cancer (Richter &

Hergenrother 2018; Willyard 2017). In the fight against resistant infectious bacteria, seaweed products offer alternatives to orthodox antibiotics.

Several compounds that occur naturally in seaweed have demonstrated antibacterial efficacy equal to that of pharmaceutical drugs. These include phlorotannins, polysaccharides, fatty acids, terpenes, peptides, lactones, pigments, and chrysohaentins (Shannon & Abu-Ghannam 2016). The assessment of antimicrobial activity in human clinical trials is very restricted; therefore, *in vitro*, *ex vivo*, and animal studies are key to assessing novel algal antimicrobial extracts. Biofilm formation by infectious bacteria is one of the most problematic issues affecting antibiotic treatment, medical devices, implants, and surface contamination. Many species of bacteria secrete a combination of polysaccharides, proteins, and extracellular DNA that forms a protective layer under which they can thrive. It is estimated that biofilms are present in 65% to 85% of all bacterial infections (Aynapudi *et al.* 2017). These films can form in wounds and inside the lungs. For those suffering from cystic fibrosis, biofilm formation in lungs by *Pseudomonas aeruginosa* can be fatal. Polysaccharides from algae, such as alginates, have been studied for their activity against biofilms. Currently, a biopolymer with the commercial name OligoG, which is derived from *Laminaria hyperborea*, is undergoing human clinical trials in cystic fibrosis patients (AlgiPharma 2018). OligoG is an edible alginate oligosaccharide derivative which has already been shown *in vitro* to disrupt *P. aeruginosa* biofilms.

Pritchard *et al.* (2017) used artificial sputum medium with clinical cystic fibrosis isolates to measure the effect of OligoG on a model, multidrug-resistant pseudomonal biofilm, and also evaluated whether OligoG (CF-5/20) could reduce the dose of drugs normally required to treat infections. The antibiotic Colistin was used as a pharmaceutical standard in combination with the seaweed derivative. Treatment with 2% OligoG significantly disrupted colony formation of *P. aeruginosa* by reducing quorum-sensing signalling in the bacterial cells. In a control medium without OligoG, the minimum inhibitory concentration (MIC) of the antibiotic Colistin increased from 0.1 to 0.4 $\mu\text{g ml}^{-1}$ in the presence of the multidrug-resistant *P. aeruginosa*. Therefore, without the seaweed extract, four times more antibiotic would have to be administered to patients. However, the addition of 2% seaweed extract led to Colistin retaining its antimicrobial activity at the lower dose.

The same extract of *L. hyperborea* successfully treated *P. aeruginosa* infection in mice (Hengzhuang *et al.* 2016). Lung biofilms were established in mice by tracheal instillation of *P. aeruginosa* (1×10^8 CFU ml^{-1}) on alginate beads; treatment groups received the same alginate beads combined with saline and a dose of 0.2%, 1%, or 5% OligoG (CF-5/20). Within 24 h, a highly significant 2.5 log reduction in bacterial colony forming units was observed in the lungs of the 5% OligoG group. Blood tests revealed that levels of the interleukin IL-1 α also decreased in the treated mice – proof of a general reduction in the inflammatory response. In addition to the murine study, Hengzhuang *et al.* (2016) conducted *in vitro* biofilm plate tests on two strains of *P. aeruginosa* (PAO1 and NH57388A) using OligoG combined with Colistin and another antibiotic, Ciprofloxacin. Minimum biofilm eradication concentration (MBEC) assays

were carried out on the plated bacteria and antibiotic/OligoG combinations. A synergistic effect was observed for both antibiotics. However, the most significant was a 128-fold reduction in the amount of Colistin required to treat the NH57388A strain of *P. aeruginosa*. After 8 h, the 5% OligoG sample had reduced the Colistin MBEC from 512 $\mu\text{g ml}^{-1}$ to just 4 $\mu\text{g ml}^{-1}$. There was synergism between Ciprofloxacin and OligoG for the PAO1 *P. aeruginosa* strain, but not for NH58388A. Even at concentrations of 1% OligoG, synergistic effects were observed, with reductions in the MBECs for both drugs. The EC₅₀ for OligoG was calculated to be 0.8%. Sigmoidal modelling predicted that one dose of 3% OligoG would eradicate of 99% of the biofilm infection within 24 h.

These studies highlight the potential of some seaweed derivatives to treat multidrug-resistant biofilm infections, while simultaneously dramatically reducing the dosage of antibiotic required. The ongoing human clinical trial with OligoG is investigating whether a fine-powdered form of alginate can be inhaled by people suffering from cystic fibrosis to combat lung biofilm formation (AlgiPharma 2018).

Other seaweed extracts have shown *in vitro* antibacterial efficacy. For example, phlorotannins inhibit oxidative phosphorylation in bacteria, and bind with proteins such as enzymes and cell membrane structures, resulting in lysis of the cell. Wei *et al.* (2016) inactivated *Vibrio parahaemolyticus* with phlorotannins from *Sargassum thunbergii* with a potential to develop the extracts as food antimicrobials, and aquacultured drugs. The fatty acids cyclopentaneacetic acid, and 10,13-octadecadienoic acid were isolated from *Sargassum vulgare* and *S. fusiforme* by El Shafay *et al.* (2016). The cell walls of *Staphylococcus aureus* and *Klebsiella pneumoniae* were visibly perforated, killing the bacteria after treatment with of *S. fusiforme* (100 μl diethyl ether extract) and *S. vulgare* (50 μl ethanolic extract). Polysaccharides, such as fucoidans, have been used as antibacterial agents. Huang *et al.* (2018) extracted fucoidan from *Sargassum crassifolium* using hot water and degradation by hydrogen peroxide and ascorbic acid. The extract had *in vitro* antibacterial activity against gram-positive *S. aureus* and gram-negative *E. coli*. The authors surmised that this was due to the ability of the negatively charged sulphated fucoidan to trap cationic molecules. This meant that positively charged molecules, such as calcium and other minerals in the culture medium, were made unavailable to the bacteria, thereby starving them. The fucoidan also reversed H₂O₂-induced cell death in 3T3-L1 adipocytes. It was concluded that the edible seaweed extract had potential as a natural antibacterial and anti-adipogenic agent for functional food and cosmetic applications (review by Jahan *et al.* 2017).

The emerging field of medical textiles provides opportunities for seaweed for its wound healing properties in combination with other natural fibres to make absorbent, biodegradable, dressings that minimise bacterial contamination. Janarthanan & Senthil Kumar (2018) developed a bioactive wound dressing material using filamentous strands of *Chaetomorpha linum* woven with cotton in the ratio of 70:30 seaweed:cotton. Sections of the dressing were soaked in three pathogenic bacterial solutions and tested for bacterial inhibitory power after 12 h. *E. coli* was inhibited by 95%; *S. aureus* by 90%; and *P. aeruginosa* by 88%. The seaweed gauze dressing was also more absorbent than the 100% cotton version, making it more effective for absorbing wound exudate.

The bioactive gauze fabric was recommended for use as a non-implantable material in bandages, surgical masks and gowns, or as a multi-use hygienic textile.

Lokhande *et al.* (2018) used κ -carrageenan (κ CA), to produce a haemostatic product, i.e. an agent that stops bleeding. However, rather than a surface wound dressing, the nano-engineered agent controls internal bleeding and is injected as a liquid. The formulation consisted of 1% κ CA and 2% nanosilicate [Na^+ , Mg^{2+} , $\text{Si}(\text{OH})_4$, Li^+]. A two fold improvement in clotting time and wound healing was demonstrated *in vitro*. The authors concluded that combining nanosilicates with κ CA increased protein adsorption on nanocomposite hydrogels, enhanced cell adhesion and spreading, and increased platelet-binding, thereby reducing blood clotting time. Since haemorrhage from internal bleeding is the main cause of death in battlefield wounds, the hydrogel could be used as an injectable haemostat in emergency situations or during surgery.

CONCLUSIONS

Seaweeds are a sustainable source of bioactive compounds for human health and functional food applications. The global burden of non-communicable, lifestyle-related diseases such as type 2 diabetes, hypertension, obesity, cancer, antibiotic resistance, and heart disease places a huge strain on the finances and resources of health services in affected countries. This may be alleviated by the inclusion of seaweed and seaweed isolates in the diet, as part of overall lifestyle improvement. Prescription drugs have many unpleasant and often serious side effects, whereas none have been reported from seaweed dietary therapy or extracts. Apart from side-effects, orthodox drugs are a financial burden on patients. The global seaweed market was valued at \$10.4 billion in 2015 and is projected to reach \$14.7 billion by 2021. It is driven mainly by the growing use of seaweed for medicinal applications. 'Food as pharma' could be promoted in terms of the natural health and nutritional benefits of dietary macroalgae based on epidemiological studies of long-term impact, and intervention studies – the 'dose concept' of part of your 'five a day'. Having reviewed the literature on the benefits of seaweed consumption, data from scientific medical studies may inform public health systems in the design of dietary intervention plans, and may be beneficial for policymakers, educators, practitioners, researchers and academics who contribute to the promotion of public health. Collaboration in research and public programs is needed to prevent disease through integration in society at all levels. The techno-functional properties of seaweed can be incorporated into food, from fat replacers to antioxidant, fibre, and antimicrobial enhancers. Seaweeds are a low-calorie food that add protein without saturated fat, and are an excellent dietary lipid alternative to EPA and DHA derived from fish. Seaweed is a sustainable, low-cost crop that takes up no land and produces no green house gases. Farmed seaweed produces more food biomass per acre of the ocean than crops do on land. Cultivation processes are important, and can be developed to justify the production of seaweed industrially, instead of as a cottage industry. We need to learn from countries where marine agronomy, mariculture, and bioengineering of seaweed are common practices. The concept of seaweed 'from farm to fork' can be developed in terms of the whole

cultivation of seaweed, using technologies already available in the meat and dairy industries. Before seaweed can become mainstream in Western countries, culinary issues must be dealt with. Seaweed is unfamiliar to many populations outside Asia, but can be promoted through clever product design, development, advertising, and incorporation into everyday products already being consumed. Unpalatable odour compounds and textures in seaweed foods can be reduced by clever ingredient formulations, processing, or by fermentation with lactic acid bacteria or *Aspergillus oryzae*. Chemical synthesis of algal bioactive compounds could be developed to increase supply and protect the marine environment from overharvesting.

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