REVIEW

A role for dietary macroalgae in the amelioration of certain risk factors associated with cardiovascular disease

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ABSTRACT: Many of the pathologies leading to premature death from cardiovascular diseases (CVDs) in humans are influenced by an individual's nutritional habitus. Diet-related risk factors for these pervasive, noncommunicable diseases include obesity, hypertension, endothelial dysfunction, diabetes, and disproportionate cellular free-radical production. CVDs are the number one cause of premature death globally, and effective methods for ameliorating CVD risk factors associated with diet should be a primary target. Although various intervention strategies are being developed and implemented, such as healthy lunch programs, improved menus in school cafeterias, and government mandates for food manufacturers regarding the reduction of salt and trans fats in processed products, a broader, more universal approach is in order. The proliferation and ready availability of high-calorie, nutrient-poor foods and the powerful marketing tools used by multinational food companies seriously compromise the health and wellness potential of a significant proportion of the global population. In this review, some of the underlying mechanisms contributing to cardiovascular health are discussed in terms of human nutritional status. Unhealthy plasma cholesterol levels, obesity, nutritional energy imbalances, and inflammatory responses are identified as some of the likely precursors in the manifestation of cardiovascular issues. The favourable therapeutic impact dietary macroalgae could have by the provision of robust antioxidant suites, macro- and micronutritional elements, fibre content, and fatty acid profiles makes seaweeds viable and important contenders for involuntary intervention strategies related to food manufacturing. These components are discussed in relation to their functionality with respect to human health, and numerous edible macroalgae, such as *Hypnea charoides*, *Mastocarpus stellatus*, *Palmaria palmata*, *Laminaria japonica*, and *Ulva pertusa* are mentioned in light of their amelioration value. Opportunities for the practical utilization of marine macroalgae into ordinary foodstuffs are highlighted.

KEY WORDS: Antioxidants, Cardiovascular disease, Dietary fibre, Dietary seaweed, Macroalgae, Obesity, Seaweed consumption

INTRODUCTION

Risk factors for cardiovascular disease

The cardiovascular system is a complex network of capillaries and blood vessels through which the heart pumps blood. It has a functional capillary area as large as 700 m^2 and it plays a fundamental role in every cell in the body (Fawcett & Bloom 1994). The World Health Organization (WHO) stated in Fact Sheet No. 317 (September 2012) that cardiovascular diseases (CVDs) are the number one cause of premature death globally. Statistics show that more people die annually from CVDs than from any other cause. Ironically, many of the pathologies leading to premature death from CVD are not only widespread, but they are modifiable, if not preventable. There are several risk factors for CVD, and they include unbalanced nutrition, of which obesity plays a significant role from the perspective of overconsumption of high-energy foods (Pabayo *et al.* 2012; Van Kleef *et al.* 2012). Although the most basic causal agents directly contributing to obesity are diets high in calories, saturated fats, sugars, and salt, which are often coupled with physical inactivity, it is prudent to also acknowledge the impacts of socioeconomic and environmental influences. For example, children of obese parents run a greater risk of becoming obese, and this consequence is not necessarily of genetic origin, but related more to family environment and conditioning (Birch & Fisher 1998). Other studies have found that gender inequality, parental education, physical and social environment, and socioeconomic indices can all affect eating habits of children and adults (Vereecken & Maes 2010; Pabayo *et al.* 2012; Wells *et al.* 2012).

Additional risk factors for CVD include diabetes mellitus (Schoenaker *et al.* 2012), sedentary lifestyle (Healy *et al.* 2011), and hypertension (Parati *et al.* 2012), all of which are major components of a cluster of metabolic abnormalities known as the 'metabolic syndrome' (MetS), and which contribute to CVD pathologies (Monteiro & Azevedo 2010; Babio *et al.* 2012; Barona *et al.* 2012). Primary hypertension occurs when there is a sustained increase in blood pressure (Tierney *et al.* 2010), a condition subject to a worldwide epidemic growth and influenced by increased dietary intakes of sodium chloride (Bibbins-Domingo *et al.* 2010; He & MacGregor 2010). Parati

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DOI: 10.2216/15-77.1

et al. (2012) reported that highly fluctuating but increased blood pressure level is associated with even greater CVD risk, and this is also affected by obesity. Obesity in children has been repeatedly correlated to endothelial dysfunction in that the associated overproduction of reactive oxygen species (ROS) contributes markedly to that condition by reducing the bioactivity of nitric oxide (NO) within the vascular system. Such inactivation of NO, a key regulator of endothelial function, has been closely correlated to the development of CVD (Förstermann 2010; Montero *et al.* 2011; Iantorno *et al.* 2014). Overall, disproportionate free-radical production is linked to MetS and the restoration of metabolic balance is an important intervention strategy for improving and maintaining cardiovascular health. Obesity, as one of the most widespread, and therefore prevalent, risk factors leading to CVD, requires an effective, global intervention strategy. It is the contention of this review that the particular composition of marine algae, including bioactive compounds, polyunsaturated fatty acids (PUFAs), considerable antioxidant capacities, dietary fibre, potassium salts, as well as versatility of applications makes them impressive candidates for amelioration of controllable elements leading to CVD.

In this literature review, some of the underlying mechanisms that contribute to cardiovascular health will be discussed, including data from studies implicating chronic pathologies such as obesity, the impacts of consuming high-fat diets, and suboptimal nutritional status. Edible macroalgae such as *Fucus vesiculosus* Linnaeus, *Undaria pinnatifida* (Harvey) Suringar, *Ecklonia cava* Kjellman, *Porphyra* spp., and *Gracilaria changii* (B.M. Xia & I.A. Abbott) I.A. Abbott, J. Zhang & B.M. Xia are included in this discussion. Their high fibre contribution, PUFA content, the therapeutic role of macroalgal antioxidants, and ample provision of micronutrients leading to a well-rounded nutritional regime will be highlighted from the perspective of judicious utilization of macroalgae in the human diet. Opportunities for incorporating seaweeds into ordinary foodstuffs are offered.

Nutrition

Abnormally high concentrations of cholesterol can occur in the body as a result of various factors. These include genetic disorders, ingestion of certain drugs, or dietary imbalances caused by the consumption of excessive calories, saturated fatty acids, and excess cholesterol (Cox & García-Palmieri 1990). Unhealthy plasma cholesterol levels results from an increase in low-density lipoprotein (LDL) or a decrease in high-density lipoprotein (HDL) (Salter 2013). Excess triglycerides in the diet, the main constituents of fats and oils, have been implicated when in combination with low levels of HDL as increasing the risk for heart attack and stroke (Bulliyya 2000; Centers for Disease Control and Prevention 2015). Although the evidence remains controversial (Siri-Tarino *et al.* 2010; de Souza *et al.* 2015), excess dietary saturated fats from the overconsumption of red meats and certain dairy products, for example, play a principal role in the prevalence and incidence of MetS and central obesity (Babio *et al.* 2012). Trans fats found in a wide variety of baked goods and fast food products have been identified as critical elements in the development and manifestation of CVD in humans (Mann 1994; Cercaci *et al.* 2006; Ganguly & Pierce 2012) and in an extensive cohort study of young Finnish people, Raiko *et al.* (2012) observed independent, direct associations of waist circumference and serum triglycerides with increased CVD risk.

Nutritional energy imbalances affect the susceptibility to CVD, and are not only related to inadequate food consumption whereby nutritional deficiencies occur, but are also influenced by obesity-induced oxidative stress caused by chronic metabolic overactivity (Codoñer-Franch *et al.* 2011). Consistent excess energy intake is as serious a risk factor for CVD as is under- or suboptimal nutrition (Mandavia *et al.* 2012), and in many cases CVD may relate to economic status, with poor and middle-income families tending to eat more high-fat, high-carbohydrate foods (Wells *et al.* 2012). In general, a well-balanced diet not only includes the recommendations for macronutrient intake, but also for elemental nutrients such as zinc, iodine, selenium, and magnesium, as examples (Health Canada 2013). In terms of CVD, low dietary zinc intake has been linked to raised plasma chloresterol levels and raised markers associated with increased risk in a mouse model. The mode of action is associated with antioxidant capacity and anti-inflammatory properties (Beattie *et al.* 2012). Dietary magnesium is also an important nutrient, and deficiencies can lead to cardiovascular conditions, including hypertension (Nakamura *et al.* 2011).

Vitamin B_{12} is an essential nutrient unavailable from higher plants (Croft *et al.* 2005). It is important in human growth and development, playing pivotal roles in normal nervous system functioning, metabolism, and blood cell formation (Vogiatzoglou *et al.* 2009; Bor *et al.* 2010). Quinlivan *et al.* (2002) suggested that addition of vitamin B_{12} to a folic acid fortification formula used to prevent neural tube defects in babies would effectively reduce vascular disease risks, although a clinical trial by Lonn *et al.* (2006) did not fully support this hypothesis. However, it is reasonable to expect that a chronic B_{12} deficiency would negatively affect the normal inflammatory response in the endothelial cells within the vascular system, as it is a component in this response cascade (Halliwell & Gutteridge 2007). Amino acids are fundamental nutritional components, and in an analysis of the data from a cohort study of CVD patients and dietary amino acid intake, Tuttle *et al.* (2012) determined that specific amino acids differentially influenced blood pressure. This group found that intakes of methionine and alanine were associated with higher blood pressure, and threonine and histidine had inverse associations with blood pressure. However, it is important to recognize the difficulties inherent in assessing the metabolic impacts of single elements in the diet without extensive and detailed scientific research, and under a variety of conditions. The genetic make-up of individuals, the influence of other food-based metabolites in the gastrointestinal tract (GIT), and the composition of the gut microbiome are some of the factors that must also be considered in relation to the nutritional integrity of dietary elements.

Other important nutritional compounds that showed positive roles in the mitigation of obesity and CVD are long-chain fatty acids with two or more methylene-interrupted double bonds (Cardozo *et al.* 2007). These PUFAs have 20 or more carbons with two or more double bonds from the methyl (omega) terminus. They and their derivatives contribute to human health as essential components of cell and organelle membranes, playing a critical role in regulating inflammatory responses, blood flow, and blood clotting, and they are significant as precursors for mediating biochemical and physiological responses (Mouritsen 2005; Holdt & Kraan 2011; Calder 2012). The human fatty-acid portfolio is complicated, and overall biological outcomes are the result of activities and interactions among several fatty acids. In an extensive review of the evidence related to ω-3 PUFA, Duda *et al.* (2009) discussed the potential effects of increased ω-3 PUFA intake in the prevention and treatment of heart failure. WHO (2008) stated that there is no compelling scientific rationale for the recommendation of a specific ratio of ω-6 to ω-3 fatty acids, provided intakes of each of these fats fall within the established dietary recommendations. Still, WHO also acknowledged in the same report that there is compelling evidence that the ω-3 long-chain PUFAs in the human diet may contribute to the prevention of coronary heart disease. To validate this important information, Delgado-Lista *et al.* (2012) evaluated the evidence from numerous clinical and randomized controlled trials. This group concluded that marine ω-3, when administered as food or in supplements for at least 6 months, reduced cardiovascular events by 10%, cardiac death by 9%, and coronary events by 18%, while showing a trend for a lower total mortality (5%, $P = 0.13$). A recent meta-analysis, however, concluded that ω-3 supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (Rizos *et al.* 2012). In light of this information, such a potentially useful dietary intervention strategy demands further scientific study.

Oxidative imbalance

Lipid sensing in the gut and the brain functions in the maintenance of nutrient balance by triggering energy regulation and glucose homeostasis. This is a normal metabolic strategy designed to balance energy intake with energy expenditure, and it is influenced by several factors, including nutrient mix and bioavailability (Breen *et al.* 2011). The deterioration of metabolic homeostasis, such as occurs when digestive activities are consistently overwhelmed by prolonged exposure to excess calories, results in several stress responses. These include oxidative and inflammatory stresses, usually leading to cellular dysfunction and affecting vascular health (Monteiro & Azevedo 2010). Obesity is associated with a persistent systemic low-grade state of inflammation and a corresponding production of excess ROS (Wu & Schauss 2012).

Chronic hypertension is also an established risk factor for CVD and it is exacerbated by obesity. As a vascular issue, erectile dysfunction (ED) is closely associated with hypertension and is a known predictor of future cardiovascular events, particularly in younger and middle-aged men (Jackson 2012; Miner *et al.* 2012). There is a distinct correlation between men with clinical abdominal obesity and ED (Fillo *et al.* 2012). Kang *et al.* (2003) pointed out that oxidative modification of LDLs by ROS is influential in the pathogenesis of endothelial dysfunction. Furthermore, oxidative stress is implicated in many diseases, including myocardial infarction, heart failure, atherosclerosis, and chronic fatigue syndrome (Sahni *et al.* 2012), and its balance is critical to the preservation of good health. Normal endothelial function appears to have a significant dependence on the homeostatic balance between NO and ROS, and exposure to increased antioxidant capacity should support this status (Halliwell & Gutteridge 2007). However, investigations into treatments for CVD with carotenoid supplementation in interventional trials have provided ambiguous results (Riccioni 2009). Carotenoids are a class of fat-soluble pigments with antioxidative potential found only in plants, algae, and certain microorganisms, and they are inevitably influenced by numerous endogenous factors, including the matrix within which they are administered (Parada & Aguilera 2007; Palafox-Carlos *et al.* 2011).

THERAPEUTIC ROLES FOR DIETARY MACROALGAE IN CARDIOVASCULAR DISEASE

Dietary fibre

Dietary fibre (DF) is known to be effective in the promotion and maintenance of healthy body weight. Its regular consumption not only reduces the risk of CVD, but it also minimizes the risks of hypertension, diabetes, and obesity (Anderson *et al.* 2009; Schoenaker *et al.* 2012; Ye *et al.* 2012). Fibre-rich foods promote satiety, delay glucose absorption, and contribute to improved plasma lipid profiles (Burton-Freeman 2000; Aleixandre & Miguel 2008; Papathanasopoulos & Camilleri 2010; Riccioni *et al.* 2012). However, these effects are influenced by a variety of factors, such as food composition and solubility, energy density, and individual metabolic or psychological responses (Kong & Singh 2008; Riccioni *et al.* 2012; Van Kleef *et al.* 2012). An investigation into the mechanisms underlying the beneficial effects of DF on metabolic syndrome led to an hypothesis that activated protein kinase (AMPK) is up-regulated in the liver by a high-fibre diet. This occurs because AMPK functions in large part as a regulator of metabolic homeostasis, and it is readily activated by short-chain fatty acids that are produced by the whole or partial anaerobic breakdown of DF in the colon (Hu *et al.* 2010). Other mechanisms by which DF is thought to exert beneficial effects on MetS include its effect on the secretion of gut hormones or peptides acting as satiety factors, and by lowering the hepatic cholesterol pool as a result of the physicochemical properties of soluble fibre acting on metabolites within the intestinal lumen (Fernandez 2001; Galisteo *et al.* 2008). Although DF is generally described as nondigestible food ingredients including nonstarch polysaccharides, oligosaccharides, and lignins, the physicochemical properties vary, and are related to its viscosity and fermentability (Kaczmarczyk *et al.* 2012). Fibre type has been demonstrated to affect subjective appetite, acute energy intake, long-term energy intake and body weight in different ways, in large part as a function of the various physicochemical properties of the DFs consumed and utilized (Slavin 2005; Palafox-Carlos *et al.* 2011; Wanders *et al.* 2011).

Currently DF is classified either as soluble or insoluble, but the proposed new names are more descriptive of their function than their chemical structure. Viscosity and fermentability better describe the physiological benefits attributed to the two types of DF (Institute of Medicine Food and Nutrition Board 2002; Riccioni *et al.* 2012).

Marine algae contain both fermentable fibres and highly viscous fibre compounds, but the amounts and compositions vary widely amongst species (Holdt & Kraan 2011). High-molecular-weight algal polysaccharides composed of polymers of sugars are known as phycocolloids, and are abundantly associated with seaweed cell walls (Potin *et al.* 1999; Cardozo *et al.* 2007). Fibre takes the form of a wide range of carbohydrates in algae, including alginates, galactomannans, agars, and carrageenans (Redgwell & Fischer 2005). These compounds are not readily digestible in the human GIT (Dawczynski *et al.* 2007; Gómez-Ordóñez *et al.* 2010), and as such they are robust sources of DF.

In an analysis of DF content in the brown alga *Fucus vesiculosus*, Díaz-Rubio *et al.* (2009) reported total DF at 59.12% dry weight (d.w.) with a soluble-to-insoluble ratio of approximately 1:5. Wheat bran analyzed in the same study had 42.7% d.w. total fibre, most of which consisted of insoluble DF. Depending upon species, strain, and various environmental factors, the total DF complement of seaweed can be as high as 75% d.w. (Ramnani *et al.* 2012). Wong & Cheung (2000) found just over 50% DF in the red algae *Hypnea charoides* J.V. Lamouroux, *H. japonica* Tanaka and the green alga *Ulva lactuca* Linnaeus. Gómez-Ordóñez *et al.* (2010) found a range from 29 to 37% d.w. total DF in five edible seaweeds, including the red macroalga *Mastocarpus stellatus* (Stackhouse) Guiry. Contrary to the soluble vs insoluble fibre ratios found in terrestrial plants, macroalgae are generally higher in the soluble, or more viscous, fibre component, which is known to delay gastric emptying, thereby facilitating more gradual nutrient absorption, and leading to increased satiety (Burton-Freeman 2000; Anderson *et al.* 2009; Papathanasopoulos & Camilleri 2010). In a study of 2108 European patients with type 1 diabetes, Schoenaker *et al.* (2012) found a significant inverse relationship between reported DF intake and CVD risk and all-cause mortality, with a stronger protective association for soluble fibre compared with insoluble fibre. Intervention studies involving alginate supplementation has furthermore been shown to reduce energy consumption and lead to weight loss in obese subjects (Jensen *et al.* 2012; Lange *et al.* 2015).

Beyond the physical manifestations of the benefits of DF intake, the chemical aspects are interesting in that they contribute to our understanding of the homeostatic maintenance of metabolic activities. An increase in the short-chain fatty-acid profile in the colon underlies the beneficial prebiotic effects realized by consuming a high-fibre diet (Wong *et al.* 2006; Hu *et al.* 2010). Ramnani *et al.* (2012) reported that increased levels of specific short-chain fatty acids were produced from low-molecular-weight seaweed extracts fermented in fecal samples from healthy human volunteers. The extracts were hydrolyzed from commercially sourced alginate or agar powders, as well as directly from the agar- or alginate-bearing seaweeds themselves, e.g. *Gracilaria* spp., *Gelidium sesquipidale* (Clemente) Thuret, and *Ascophyllum nodosum* (Linnaeus) Le Jolis. These preliminary results indicated that gut microbiota are able to effectively ferment the low-molecular-weight seaweed polysaccharides investigated in this study, with the red alga *G. sesquipidale* exhibiting the most significant increase in short-chain fatty acids. Although these results suggested that *G. sesquipdale* may make an effective prebiotic, the mechanisms involved were not clear, and more comprehensive studies must be completed to improve our understanding of how this could affect diet-related pathologies such as obesity and cardiovascular health.

The high total DF content of some seaweeds is well established (MacArtain *et al.* 2007), and so are the extensive health benefits of these fibres in relation to obesity, diabetes, and CVD associated with the consumption of a high-fibre diet. However, as with all human food intake studies, reliable *in vivo* results are difficult to obtain because of the complexities and dynamics of multiple cellular interactions. Progress continues to be made in this extremely worthwhile area of study, and with the advent of metabolomics, it is feasible that there will soon be evidence of specific cause-and-effect responses of various macroalgae included in the diet along with their defined health benefits (Rochfort 2005; Favé *et al.* 2009; Manach *et al.* 2009).

Nutritional aspects

Given an even playing field for societal or poverty-related causes, human nutritional integrity is a modifiable factor. The complex and dynamic cellular interactions involved in maintaining metabolic homeostasis relies, in part, upon a feedback mechanism triggered by nutrients such as lipids that demonstrated a sensory connection with the brain (Breen *et al.* 2011; Rasmussen *et al.* 2012). Chronic nutritional imbalances can trigger inflammatory responses that in turn can lead to the manifestation of noncommunicable diseases such as atherosclerosis, ischemic heart disease, obesity and diabetes (Weiss 2008; Wu & Schauss 2012).

When considering seaweeds as an integral part of the human diet it should be pointed out that although they contain most of the nutrients humans need (Fig. 1), seaweeds will only constitute a small part of the overall diet, in particular because they contain too few calories for complete nutrition. It is difficult to set a recommendable daily intake, but by comparison with populations, e.g. Japanese, who traditionally have seaweeds as a staple in their cuisines, a reasonable estimate for the average person would be 5–10 g d.w. daily, on the basis of a selection of different seaweeds (Mouritsen 2013). Small amounts consumed in a variety of ways would be an optimal approach, especially for those not already accustomed to eating macroalgae. In addition to being packed with protein, carbohydrates, and soluble and insoluble fibre, most macroalgae contain a wide range of vitamins and minerals required for human nutrition (Dawczyynski *et al.* 2007; Holdt & Kraan 2011; Pomin 2012). The mineral and trace-element content of samples of *Fucus vesiculosus*, *Laminaria digitata* (Hudson) J.V. Lamouroux, *Undaria pinnatifida*, *Chondrus crispus* Stackhouse, and *Porphyra tenera* Kjellman was shown to be more than adequate to meet nutritional demands, even as relative proportions varied among species (Rupérez 2002). Rupérez used atomic absorption spectrophotometry to report that these seaweeds ranged from 8000 to 17,900 mg/100 g of the macrominerals Na, K, Ca, and Mg, and they had a trace-element content of iron, zinc, manganese, and copper that ranged from 5 to 15 mg/100 g. By comparison, the macromineral content of carrots is reported in their publication to be 3300 mg/100 g; sweet corn, 1350 mg/100 g; green peas, 1450 mg/100 g; potato, 6000 mg/100 g; tomato,

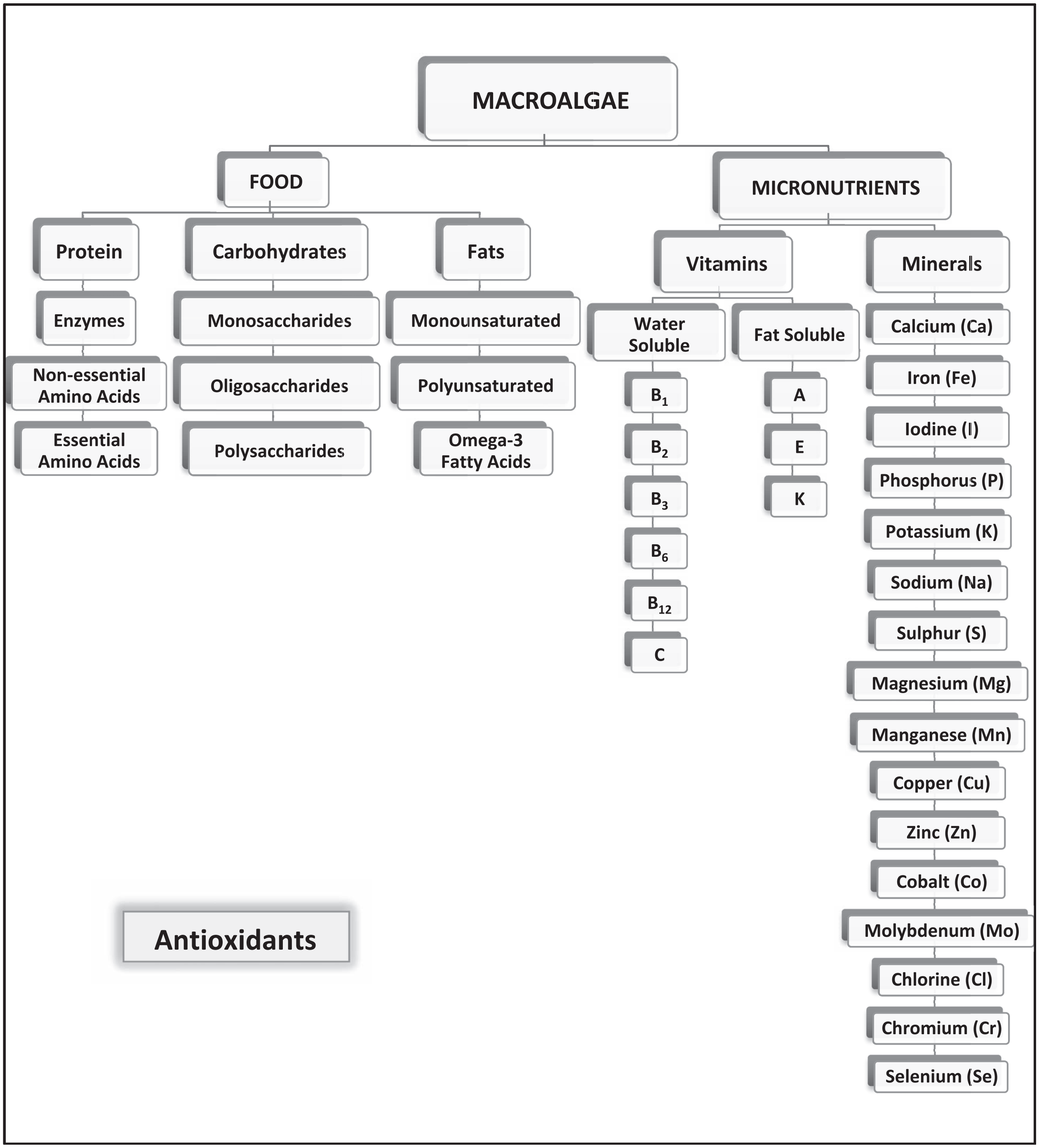

Fig. 1. Basic nutritional components found in most seaweeds. Information compiled from Mouritsen (2013) and numerous other authors cited throughout this review.

3400 mg/100 g; and spinach, 9700 mg/100 g following the USDA (2001) nutrient database. Other analytical work on the red carrageenophyte, *Kappaphycus alvarezii* (Doty), by Fayaz *et al*. (2005) showed the alga to not only be high in protein (16.2% d.w.) and carbohydrates (27.4% d.w.), but also a source of available iron.

Norziah & Ching (2000) analyzed samples of *Gracilaria changii* collected from culture ponds in Malaysia for determination of nutritional composition. They found that in addition to containing 74% unsaturated fatty acids, mostly of the omega form, *G. changii* contained 6.9% protein, compared with white soybeans at 33.8% and broccoli with 4.1%. Total lipid content was 3.3% compared with 19.9% in the soybeans and 0.2% in tomato. All values were based on wet weight.

Although total lipid content is relatively low in macroalgae, in some species, the PUFA component is reported to be particularly rich in the nutritionally beneficial ω-6 and ω-3

PUFAs, such as linoleic, alpha-linolenic, arachidonic (ARA), and eicosapentaenoic (EPA). Of particular importance is that macroalgae, as well as microalgae, have a very favorable ω-3/ω-6 ratio, being around 1, and in some cases considerably larger than 1 (Dawczynski *et al.* 2007; Mouritsen 2013). This is in stark contrast to most modern Western diets where the ratio is in the range 0.05–0.1, i.e. a large surplus of ω-6 PUFA. Although there is no consensus yet about the optimal ratio for human health, it is likely that an ω-3/ω-6 ratio around 1 is near the optimal (Simopoulos 2002; Mouritsen 2012b). This makes sense, considering the human species is thought to have developed improved brain function upon reaching the seaside and an abundant source of these important PUFAs (Mouritsen & Crawford 2007). Although seaweeds contain relatively low amounts of fatty acids it may well be that the quality of the PUFA in foodstuff made of the whole macroalgae is very high because of the protective role played by the naturally occurring antioxidants in the seaweed tissues.

In a study to evaluate total lipid and fatty acid content, Kumari *et al.* (2010) analyzed 27 different macroalgal species, and determined that the lipid content varied widely among them (0.57 to 3.5% d.w. basis). However, both the red and the brown seaweeds had substantial amounts of the fatty acids EPA and ARA, whereas the green macroalgae contained docosahexaenoic acid. The nutritional quality of the lipids most often found in seaweeds suggested that the incorporation of a variety of macroalgae into the human diet on a frequent basis would be advantageous for health and nutrition. In an analysis of 34 edible seaweeds, Dawczynski *et al.* (2007) found rather low lipid contents (∼3 g/100 g) and the predominant lipid was EPA. The red algal varieties in particular contained abundant protein levels and scored highest in terms of amino acids and the essential amino acid index. The algal samples analyzed were obtained in dry format from China, Japan, and Korea (full list of spp. given in the publication). *Palmaria palmata* (Linneaus) Weber & Mohr contained high levels of EPA, registering 59% of the total fatty acid content of the sample. The important ω-3 and ω-6 long-chain fatty acids typically derived from fish oil made up 1–5% of the dry matter in nine seaweeds analyzed by Van Ginneken *et al.* (2011). The red seaweeds (*Chondrus crispus, Palmaria palmata*) and the brown seaweeds [*Laminaria hyperborea* (Gunnerus) Foslie*, Fucus serratus* Linnaeus*, Undaria pinnatifida, Ascophyllum nodosum*] contained the highest proportions of these important PUFAs.

Protein content, although not recognized as having a direct impact on CVD risk factors, is known to help induce satiety (Paddon-Jones *et al.* 2008; Van Kleef *et al.* 2012), and the hydrolysis, or breakdown of some proteins, produces health-promoting bioactive peptides (BAPs) (Udenigwe & Aluko 2011). Macroalgae are found to be a relatively new and bountiful source of beneficial, and in some cases unique, BAPs such as phycobiliproteins, which are specific to the red algae, for example, and lectins, which are widespread. These protein fractions are known to have potent cellular bioactivities and many express significant therapeutic capacities depending upon the species of seaweed from which they are derived (Cardozo *et al.* 2007; Fitzgerald *et al.* 2011). In general, as rich sources of protein, as much as 25.7% in *Laminaria* sp. to 47% of the dry weight in *Pyropia* sp. (Fleurence 1999; Gómez-Ordóñez *et al.* 2010), macroalgae constitute a valuable reservoir of novel biologically active peptides and essential amino acids (Harnedy & FitzGerald 2011). In addition to the essential amino acids, most seaweeds also contain a high proportion of free aspartic and glutamic acids, and these can represent between 22 and 44% of the total amino acid content in brown seaweeds, up to 32% in the green algae, and approximately 15–20% in the reds (Fleurence 1999; Mouritsen *et al.* 2012). Glutamic acid is particularly interesting in that its sodium salt, monosodium glutamate, in a synergistic fashion with certain ribonucleotides, enhances the sensory awareness of a meal by stimulating the perception of umami, and reducing our craving for salt, fat, and sugar (Mouritsen 2012a). Proteinaceous compounds found in seaweeds, however, tend to fluctuate widely in concentration and specific composition, on the basis of seasonal, environmental, and nutritive variations (Harnedy & FitzGerald 2011).

Gracilaria salicornia (C. Agardh, E.Y. Dawson), a red alga, and *Ulva lactuca*, a green, were hand harvested from the intertidal zone in the Persian Gulf for nutritional analysis (Tabarsa *et al.* 2012). Each of the seaweeds contained nine essential amino acids and seven nonessential amino acids in varied proportions, with generally higher amounts in *G. salicornia*. These amino acids are listed in Tabarsa et al. (2012). Furthermore, K, Ca, Na, and Fe in the seaweeds were reported to be 11,400–2400 mg/100 g d.w.; 2800–900 mg/100 g d.w.; 1800–1000 mg/100 g d.w., and 200–70 mg/100 g d.w. respectively. In addition, Rohani-Ghadikolaei *et al.* (2011) included in their analysis the green algae, *Enteromorpha intestinalis* (Linnaeus) Nees and *U. lactuca*, two red algae, *Hypnea valentiae* (Turner) Montagne and *Gracilaria corticata* (J. Agardh) J. Agardh, and two brown algae, *Sargassum ilicifolium* (Turner) C. Agardh and *Colpomenia sinuosa* (Mertens ex Roth) Derbès & Solier collected from the northern coast of the Persian Gulf. Results demonstrated wide variability among species, as well as differences between macromineral contents of the *U. lactuca* analyzed in this study (K, 515 mg/100 g and Fe, 46 mg/100 g d.w.) compared with that determined by Tarbarsa *et al.* (2012). This discrepancy attests to the current difficulties associated with standardization of seaweed samples and analytical procedures.

As with all investigations involving multiple biological systems with numerous overlaps and interactions, GIT studies are challenging to carry out and decipher, but steady progress is being made. Assessing the bioavailability of specific nutrients is not a simple thing, and even nutritionists evaluating land plant-based diets have tended to avoid this aspect for lack of appropriate analytical tools, but important scientific studies continue to generate information (Crozier *et al.* 2010; Thilakarathna & Rupasinghe 2013). For example, Mg deficiency in humans plays a role in the pathogenesis of ischemic heart disease, congestive heart failure, and other adverse cardiac events (Arsenian 1993; Altura & Altura 1995). To investigate the bioavailability of dietary Mg from the green *Ulva pertusa* Kjellman, the brown *Laminaria japonica* Areschoug, and the red *Gloiopeltis furcata* (Postels & Ruprecht) J. Agardh, Nakamura *et al.* (2011) used an *in vitro* digestion trial and Sprague–Dawley rats. Their results showed that the three seaweeds ranged from 6.55 to 10.47 mg Mg g^{-1}, with the greatest bioavailability in *U. pertusa* and *L. japonica*. Obviously, species will vary in the manner in which they perform in the digestive tract, on the basis primarily of their individual structural and metabolic components. The experimental development of an *in vitro* method of dialysis to assess nutrient bioavailability led Moreda-Piñeiro *et al.* (2012) to achieve high digestibility percentages of trace metals (30.0–74.7%) in edible seaweeds as compared with low to moderate levels in fish and mollusks. Seven edible macroalgae were analyzed in this study, all harvested off the coast of Spain, and purchased from a local manufacturer as described in the publication. Univariate and multivariate analysis showed that the metal bioavailability ratios exhibited positive correlations with the carbohydrate and DF components.

Enteromorpha sp. and *Porphyra* sp. contain high levels of vitamin B_{12}, 32–78 μg/100 g d.w. (FAO 2010), making them unique nonmeat sources of this essential vitamin (Watanabe 2007). B_{12} is a complex metabolite, requiring at least 19 separate enzymatic steps for its synthesis (Croft *et al.* 2005), and issues with its complete absorption from foods have been investigated. Studies have shown that as a dietary nutrient, the bioavailability of B_{12} per meal significantly decreases with increasing intake because the intrinsic factor, a gastric vitamin B_{12} binding protein, is estimated to be saturated at 1.5–2.0 μg/meal, under physiological conditions (Scott 1997; Allen 2010). This suggests that B_{12} supplements taken as a single daily dose may be ineffective in regard to meeting their physiological target concentration if their total B_{12} content exceeds 2.0 μg. The recommended daily allowance of vitamin B_{12} for adults is set at 2.4 μg/d (Institute of Medicine 1998). In a feeding trial with B_{12}-deficient rats, Takenaka *et al.* (2001) showed that B_{12} from freshly collected, lyophilized purple laver (*Porphyra* sp.) was bioavailable under the conditions of that study. The rats were given free access to the experimental diet and fresh water for 20 d, and in this manner of feeding, the B_{12}-deficient rats were able to overcome their deficiency status. It is important when evaluating nutritional studies to always be cognizant of the postharvest treatment of the samples, in particular, drying times, methods, temperatures, and storage time, all of which can affect the quality or concentration of the compound of interest (Wong & Cheung 2001; Gregory *et al.* 2005). This point serves as a reminder that nutritional values and availabilities from foods for specialized diets need to be carefully assessed.

Antioxidant capacity

The chronic oxidative stress associated with obesity occurs because ROS production is increased. ROS production is accelerated because excess adipocytes are constantly being formed, increasing both in size and number (Monteiro & Azevedo 2010; Lee *et al.* 2011). In a well-documented review, Hercberg *et al.* (1997) reported high intake of dietary antioxidants in vitamin form to be associated with a reduced risk of CVD. It is currently well accepted that the cellular reduction of excess reactive oxidation compounds contributes to the maintenance of cellular homeostasis, which, when chronically unbalanced, leads to a wide range of deleterious pathologies (Wiseman & Halliwell 1996; Valko *et al.* 2007). Accurate measurement of antioxidant capacity of foodstuffs still requires some standardization among the various available assays (Prior *et al.* 2005; Wang *et al.* 2009; Cornish & Garbary 2010; Tierney *et al.* 2010) and the validation of the bioactivity and bioavailability in humans of a food sample is exceedingly complicated. By necessity, current assays can only be based upon chemical reactions taking place *in vitro*, which at least validates the presence of the antioxidant activity in a particular sample. Consideration must also be given to when and where compounds are released from the food matrix in the GIT, the physical and chemical interactions stimulated by the consumption of other foods, and their impact on the food microstructure (Huang *et al.* 2005; Palafox-Carlos *et al.* 2010).

Scientific investigations have shown that specific macroalgae are robust and diversified sources of antioxidants, antioxidant compounds, and enzymes, important in human health and nutrition (for a review see Cornish & Garbary 2010; Tierney *et al.* 2010). Seaweeds contain an array of compounds, some of which are never found in terrestrial plants, such as sulphated polysaccharides, phycobilins, and vitamin B_{12} (Lahaye & Kaffer 1997; Veena *et al.* 2007; Jiao *et al.* 2011). In the majority of cases, seaweed and the associated antioxidant investigations have been performed on extracts rather than on the whole food, although there are some exceptions to this. For example, Gómez-Ordóñez *et al.* (2012a) fed dried, milled samples of *Mastocarpus stellatus* to healthy Wistar rats to assess the effect on lipid metabolism and antioxidant status. Seaweed intake significantly reduced the serum triglycerides and cholesterol in healthy rats, but not the artherogenic index, which is a method of evaluating changes in plasma lipoprotein profile. It is again important to understand that many external factors can affect the antioxidant capacity of a food before its ingestion and subsequent multifaceted *in vivo* activities. The species, even strain, time, and location of harvest, culture conditions, and postharvest treatment are all environmental factors that may have influenced the antioxidant content and activity of foods. Although this is a well-known reality, it is often not publicized, but it applies to all foodstuffs, even natural supplements, and is not restricted to just macroalgae.

The diversity and ancient lineage of macroalgae has endowed them with enormous abilities to cope with stress, which is directly linked to their antioxidant capacities. Collectively, edible seaweeds possess a multifunctional and extensive antioxidant profile (Jiménez-Escrig *et al.* 2012) and could, in theory, mitigate the presence of excessive ROS to restore homeostatic balance. The major groups of antioxidant compounds found in the macroalgae are included under the general categories of carotenoids, phenolic compounds, phycobilin pigments, polyphenols, sulphated polysaccharides, and vitamins (Cornish & Garbary 2010; Kadam & Prabhasankar 2010). Much research is underway with regard to assessing the antioxidant capacity and beneficial effects of isolated compounds on chronic disease risk factors and pathologies in both prevention and treatment. Kim & Lee (2012) demonstrated the effect of fucoidan on the expression of inflammation-related genes during increased adipocyte production. Fucoidan is a sulphated polysaccharide found in several brown seaweeds, and in this study it was extracted from the sporophyll of *Undaria pinnatifida* and added at various concentrations to fully differentiated adipocyte cell cultures. Results clearly showed that in cell culture, fucoidan inhibited major adipocyte markers, inflammatory cytokines, and ROS production. The next challenge will be to investigate this inhibitory effect *in vivo* to determine if the cytokine signaling induced by fucoidan is effective in a natural gastrointestinal environment. A partitioned fraction of an ethanol extract prepared by Kim *et al.* (2012) from *Gracilaria vermiculophylla* (Ohmi) Papenfuss was found to be a potent inhibitor of adipogenesis of preadipocytes in cell culture. Addition of the extract fraction to the cell cultures decreased triglycerol accumulation and up-regulated messenger RNA levels of genes involved in lipid catabolism, important factors in obesity management.

Fucus vesiculosus is another good source of fucoidan and Veena *et al.* (2007) demonstrated its efficacy in terms of antioxidant status of homogenates of rat liver and kidney tissues 28 d after subcutaneous administration. Extensive oxidative stress was moderated by an up-regulation of antioxidant enzyme activities, such as increased superoxide dismutase, catalase, and glutathione peroxidase, and by limiting lipid peroxidation. Although there is extensive published research to show that seaweeds are rich in antioxidants and antioxidant compounds, more recent studies now focus on the impact of specific antioxidants and their effect on targeted metabolic systems (Favé *et al.* 2009; Manach *et al.* 2009). Other studies have verified the copious antioxidant capacity of seaweed extracts such as from the brown alga *Ecklonia cava* (Athukorala *et al.* 2006) and the red algae *Kappaphycus alvarezii* (Fayaz *et al.* 2005), *Palmaria palmata* (Yuan *et al.* 2005a, b), *Porphyra haitanesis* (T.J. Chang & B.F. Zheng) N. Kikuchi & M. Miyata and *Porphyra* sp. (Zhang *et al.* 2003, Yabuta *et al.* 2010), and *Turbinaria conoides* J. Agardh (Chattopadhyay *et al.* 2009). All 11 species of seaweed collected by Costa *et al.* (2010) demonstrated antioxidant activities from their extracted sulphated polysaccharides. In an interesting study by Park *et al.* (2012), obese-induced mice were fed extracts of the brown alga *E. cava* harvested from one of two locations, either Gijang, Korea or from Jeju, Korea. Results of the study showed that extract from Gijang-sourced seaweed improved obesity by decreasing body weight gain and total body fat, and glucose tolerance was enhanced by anti-inflammatory actions and an improvement in lipid metabolism.

An important risk factor for CVD and a fairly reliable predictor of future CVD events is ED (Jackson 2012; Miner *et al.* 2012). ED affects men and is described as a persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance (NIH Consensus Conference 1993). Studies on extracts from brown macroalgae have shown improved function, and overall sexual satisfaction in men with mild to moderate ED, the results of which are attributed to the therapeutic antioxidant activity of polyphenolic compounds (Kang *et al.* 2003; Zhang *et al.* 2010; Sansalone *et al.* 2014). NO has been identified as a critical molecule in male erection physiology. Studies showed that increased ROS led to vascular impairment by reducing NO production or bioavailability, ultimately resulting in ED (Jin & Burnett 2008; Barassi *et al.* 2009; Kolluru *et al.* 2012). In a review of the published literature Decaluwé *et al.* (2011) reported that reliable evidence existed for the therapeutic effects of increased antioxidant activity for the amelioration of ED. A study by Zhang *et al.* (2010) on ED-induced rabbits, treated with polyphenols extracted from pomegranate, showed prompt and efficient effects on the molecular and ultrastructural alterations of ED as a result of increased antioxidant activity. However, the authors found no evidence that antioxidant therapy induced improvements to distinct pathological changes such as fibrosis and functional deficit in the 8-wk trial, and further studies are definitely in order. After an 8-wk human clinical trial of a standardized edible form of brown algal polyphenolics, Kang *et al.* (2003) reported that daily administration of 2400 mg of a commercially available brown algae polyphenolic food ingredient (VNP™) significantly ($P < 0.01$) improved the function of the penile artery, which physically controls erections. Furthermore, patients reported a 20% improvement in sexual desire, an 87% improvement in orgasmic function, and 74% improved intercourse satisfaction. Commercial follow-up of these interesting results led to the development of a composite natural drug containing polyphenols from the alga *Ecklonia bicyclis* Kjellman for the orally administered treatment of ED (Iacono *et al.* 2011). These are but a very small sampling of the research that has been done to date on the antioxidant capacities of macroalgae. It is not difficult to conclude that collectively, a significant number of seaweeds represent a valuable and versatile resource of a very broad range of effective antioxidants. Although it is highly unlikely that such benefits are species specific, more work is required to determine how widespread amongst the red, green, and brown seaweeds these beneficial properties are distributed. In the meantime, perhaps the best approach is to include a variety of macroalgae in our daily diets, in much the same way we include several servings of vegetables to promote health and well being.

Food for thought

As an additive to food, seaweeds can provide DF and functional influence as well as an associated boost in the antioxidant capacity of the bloodstream. Research suggests that in obese or health-compromised individuals, ROS production is chronically increased, and that a corresponding increase in antioxidant capacity is required to cope (Huang *et al.* 2005). The versatility of seaweeds in terms of food formulations enables them to be utilized as an ingredient in a variety of commonly consumed products, including fast foods, bakery products, and snacks. Much of their salt content takes the form of potassium salt, a much more nutritious form than sodium salt that is found in many processed foods and is a risk factor for hypertension. The cardiovascular health benefits associated with diets high in fruits, vegetables, and fish have been well documented (Sobko *et al.* 2010; Barona *et al.* 2012; Vercambre *et al.* 2012) and the inclusion of kombu in the diet of the Okinawan residents in Japan has been implicated in the prolonged optimization of health and longevity effects (Sho 2001).

With thousands of edible macroalgae populating the oceans of the world it would seem that opportunities to produce new fibre-rich, nutrient-dense functional foods from a proportion of them are enormous. The functional aspects of macroalgae alludes to their purported health-promoting functions beyond basic nutrition (Table 1), and this will naturally vary among species (Day *et al.* 2009). The currently accepted definition of a functional food is ‘a food that is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant

Table 1. CVD related pathologies that are influenced by dietary components.

CVD risk factor or marker	Amelioration agent(s)	Research type	Reference
Obesity	minimized oxidative stress and inflammation processes	human double-blind crossover study	Bakker *et al.* 2010
	dietary impact on gene expression of inflammation	human intervention trial	Van Dijk *et al.* 2012
	anti-inflammatory impact of soluble fibre	rat trial	Sánchez *et al.* 2011
	reduction in weight and waist circumference – dietary fibre	prospective cohort study $n = 89{,}432$	Du *et al.* 2010
	reduction in total cholesterol and in body fat	human intervention trial	Maeda *et al.* 2005
	decreased fat deposition; nutritional (taurine)	*Caenorhabditis elegans*	Kim *et al.* 2009
Erectile dysfunction	improved nitric oxide availability and reduced oxidative stress	human intervention trial – males	Roberts *et al.* 2002
	lowered ratio ω-6 to ω-3	randomized controlled trial – males	Esposito *et al.* 2004
	dietary antioxidants	rabbit model	Zhang *et al.* 2010
	antioxidative status	human comparison study – males	Aldemir *et al.* 2011
	improved nitric oxide availability and reduced oxidative stress	activity index in aphrodisiac herbs	Muanya & Odukoya 2008
	antioxidative status	human comparison study – males	Barassi *et al.* 2009
Nutritional status (imbalance)	blood pressure affected differentially (dietary amino acids)	observational cohort study	Tuttle *et al.* 2012
	lowered homocysteine concentrations (B_{12})	human intervention study	Quinlivan *et al.* 2002.
	overall decrease of CVD risk (dietary omega-3 fatty acids)	database study and analysis	Delgado-Lista *et al.* 2012
	inhibition of lipogenesis; fibre and short-chain fatty-acid production; metabolic homeostasis	evidence for AMPK hypothesis presented	Hu *et al.* 2010
	hypotriglyceridemic properties n-3 fatty acids	pooled meta-analysis	Jacobsen 2008
	overall decreased risk of CVD (dietary pattern)	prospective long-term cohort study (factor analysis)	Shimazu *et al.* 2007

to either an improved state of health and well-being and/or reduction in risk of disease' (Ross 2000; American Dietetic Association 2004). However, parts of the definition could be interpreted in different ways, such as determining what exactly constitutes 'basic nutrition'.

As a tool in the dietary intervention strategy for pathologies associated with obesity leading to CVD the fibre components of seaweeds rate highly. The unique hydrocolloid content provides soluble fibre that can be used in novel or innovative ways to improve and optimize the textural and organoleptic properties of products (Redgwell & Fischer 2005). These large polysaccharide macromolecules can be effectively used in food products as fat replacers, as vehicles for the moderation of nutrient release and availability in the gut and intestine, and as a rich source of antioxidants (Warrand 2006; Shahidi 2009). In relation to the generally accepted definition of a functional food, macroalgae, if incorporated appropriately, could be considered to contribute to an improved state of health and well-being beyond basic nutritional efficacy. However, considerable work must yet be done to make this a realization, not only from a biological and analytical perspective, but as a food or a food component, for which specifications must be established and standards maintained.

Aside from the typical Asian consumption of whole seaweeds as snacks, and in soups and salads, management of particle size allows for the utilization of whole seaweeds into bakery products, pastas, pizzas, and snack bars, for example. In a review of marine foods as functional ingredients in bakery and pasta products, Kadam & Prabhasankar (2010) reported that certain brown seaweeds, e.g. *Sargassum marginatum* (C. Agardh) J. Argardh and *Undaria pinnatifida*, have been incorporated into pasta products with minimal intervention in sensory quality while providing improved DF and increased antioxidant capacity. Bread enriched up to 4% with the brown alga *Ascophyllum nosodum* passed acceptability tests by overweight, but otherwise healthy, male participants (Hall *et al.* 2012). Analysis of the DF content of the *A. nodosum*-enriched bread showed that it contained 4.5 g more DF/100 g than the control whole-meal bread. Even more interesting, the study demonstrated that subjects who consumed the seaweed-enriched bread experienced an involuntary reduction (16.4%) in energy intake in the 24-h period after consumption of the test bread.

The nonstarch polysaccharides make up most of the soluble fibre components in seaweeds, alginate in the brown algae, carrageenan and agar in the red, and ulvan in the green seaweeds. The polysaccharide components of the former two have primarily been exploited industrially as thickening and stabilizing agents, and in this utility, carrageenan is commonly added to low-fat sausages, beef burgers, and beef patties (Warrand 2006). The brown seaweeds *Himanthalia elongata* (Linnaeus) S.F. Gray and *Undaria pinnatifida* were collected on the northwest Iberian coast, along with samples of the red alga, *Porphyra umbilicalis* Kützing, dried in the shade, ground, screened, and added to ground pork portions (Confrades *et al.* 2008). Not surprisingly, the brown seaweeds performed much differently from the red seaweed, especially in terms of DF, but the *P. umbilicalis* contributed higher protein to the seaweed-enriched meat model. Overall, addition of any of the macroalgae to the low-salt gel/emulsion meat system improved the water- and fat-binding properties, but the stability of the emulsions was affected by the type and amount of seaweed added. Adding more seaweed improved the stability. In a follow-up study, López-López *et al.* (2009) assessed the antioxidant capacity of a low-salt meat emulsion system with added *H. elongata, U. pinnatifida*, and *P. umbilicalis* and found significant increases of antioxidant activity in all cases. This suggested that some seaweeds can improve the health-promoting status of meats and meat products by enhancing antioxidant capacity, by providing nutritional components, and by contributing wholesome DF. In an investigation into the effects of added *U. pinnatifida* or *P. umbilicalis* to restructured pork meat to create increased functional antioxidant activities, Moreira *et al.* (2010) verified that different seaweeds produced different physiological effects when fed to Wistar rats. Groups of 10 rats were fed cholesterol-enriched diets containing restructured meat with either 5% *U. pinnatifida* or 5% *P. umbilicalis* added to the mix. Results clearly demonstrated that meat containing the brown alga, *U. pinnatifida*, offered significantly increased antioxidant activities within the rats, whereas the red alga, *P. umbilicalis*, provided hypocholesterolemic effects (lowered blood cholesterol levels). Generally it should be expected that in particular, brown seaweeds that contain fucosterol and desmosterol rather than cholesterol, in a manner similar to plant-based food with an abundance of phytosterols, will serve to lower cholesterol levels in the blood. Studies involving the addition of specific seaweeds to meats show promise for further development of foods designed to help ameliorate important risk factors leading to CVDs.

Other food products, utilizing different macroalgae for their health and nutritional benefits, have been developed and the potential for providing improved antioxidant capacities, appropriate ratios of soluble and insoluble fibre, and overall nutritional value over a broad range of commonly consumed foods showed promise. Such items included functional beverages prepared with *Undaria pinnatifida, Ecklonia cava, Hizikia fusiformis* Okamura, or *Undaria pertusa* (Nagai & Yukimoto 2003), spice adjuncts with *Kappaphycus alvarezii* (Senthil *et al.* 2011), and snack food from *Enteromorpha compressa* (Linnaeus) Nees, (Mamatha *et al.* 2007). Furthermore, various cottage industries have sprung up to provide seaweed-enhanced products to the marketplace, circumventing the often long and convoluted route necessary to establish specific claims. This is possible, because the macroalgae used in these applications have a historical record of being commonly eaten as foods in many coastal communities. Along with whole seaweed products currently available in many places in the world, such as salads and salad blends and various dehydrated snacks, frozen pizza and gourmet entrées containing different types of seaweed can also be found.

Although researchers continue to study the therapeutic effects of dietary seaweeds and the various mechanisms involved (Table 2), there remain some cautions, especially with respect to the high absorbancy capabilities of many seaweeds. Growing in the open ocean can leave them vulnerable to metal bioaccumulation, or to increased concentrations of potentially deleterious compounds (Stengel & Dring 2000; Baumann *et al.* 2009; Yokoi & Konomi 2012), conditions that may not be obvious to consumers. Moreover, some brown seaweeds, e.g. *Sargassum fusiforme* (Harvey) Setchell, which is a staple seaweed in Japanese cuisine, can contain very large amounts of arsenic, e.g. 140 μg/g arsenic, of which 85 μg/g is inorganic (Almela *et al.* 2002). Therefore, rigid controls need to be in place to ensure the health, safety, consistency, and traceability of commercial products containing seaweeds.

A special concern may exist in relation to CVD that pertains to individuals who are subjected to blood-thinning medication, e.g. warfarin. Some seaweeds, similar to green plants like fresh parsley, spinach, watercress, and broccoli, contain vitamin K, which acts as a blood coagulation factor (Mouritsen *et al.* 2013). The concern is that excessive consumption of vitamin K-containing foods could affect the effectiveness of blood-thinning medications, although clinical studies have shown that intermittent small changes in vitamin K intake do not, however, require permanent changes in the dosing of warfarin (Bartie *et al.* 2001).

Progress is being made in developing new and innovative functional food systems, including the use of protein–polysaccharide complexes and coacervates as targeted delivery vehicles for bioactives or sensitive food molecules (Schmitt & Turgeon 2011). Perhaps the hydrocolloid components, so plentiful in many macroalgae, will play significant roles in this respect. Only the compounds released from the food matrix or absorbed by the small intestine are potentially bioavailable (Tagliazucchi *et al.* 2009), and if efforts are to be focused on reaching molecular targets within the human GIT, science may still be some distance from obtaining tangible results. However, new techniques continually evolve to accommodate the ever-increasing need to understand and measure the complex interactions within the various biological systems in humans. Methodologies for precise and accurate analysis of molecular weight distribution of polysaccharides in edible seaweeds (Gómez-Ordóñez *et al.* 2012b) will help assess raw materials, and metabolomic techniques will provide answers regarding efficacy of specific foods.

Advances toward reducing the adverse impacts of obesity are being substantiated globally, but the challenges of reaching all levels of society with adequate intervention strategies are enormous. The complexities associated with socioeconomic status, parental education levels, sociodemographics, social and physical environment, and even gender inequality all contribute to nutritional inadequacies leading to obesity (Vereecken & Maes 2010; Finucane *et al.* 2011; Hillier *et al.* 2012; Pabayo *et al.* 2012; Wells *et al.* 2012). With such diversity of factors contributing to global obesity, effective interventions need to be both explicit and universal, and eventually, the incorporation of specific macroalgal components into a wide variety of commonly consumed foods could aid in facilitating antiobesity strategies. There are approved antiobesity drugs available for therapeutic use, but they have the potential to increase blood pressure and heart rate, thereby contributing to increased CVD risk and offsetting benefits derived from weight loss (Hiatt *et al.* 2012; Park *et al.* 2012). It is far better to recommend eating a healthier, low-fat, nutrient-dense diet that maintains all the desirable sensory characteristics society has become accustomed to. In a press release from the European Society of Cardiology on 19 January 2011, Sir Michael Marmot, head of the University College London Department of Epidemiology and Public Health, wrote that the required consumption of eight portions (640 g) of fruit and vegetables per day, necessary to lower the risk of dying from

Table 2. Examples of macroalgal species associated with CVD amelioration factors.

Species	CVD amelioration factor(s)	Test organism	Delivery format	References
Ascophyllum nodosum (Linnaeus)	fermentable fibre–short-chain fatty-acid production	human gut microbes	extract	Ramnani *et al*. 2012
Callophyllis japonica Okamura C. Agardh	reduction in total cholesterol and serum triglycerides	mice	extract	Kang *et al*. 2012
Chondrus crispus Stackhouse	oxidative stress tolerance	*Caenorhabditis elegans*	extract	Sangha *et al*. 2013
	n-3 PUFA; inflammation inhibition	human macrophages	extract	Robertson *et al*. 2015
	nitric oxide inhibition	macrophage RAW264.7 cells	extract	Banskota *et al*. 2013
Chondrus ocellatus Holmes	inhibition of adipocyte differentiation	adipocyte cell lines	extract	Lee *et al*. 2011
Derbesia tenuissima (Moris & De Notaris) P.L. Crouan & H.M. Crouan	decreased plasma triglycerides and total cholesterol (insol. fibre)	rat model of human MetS	supplement	Kumar *et al*. 2015
Dictyopteris undulata Holmes	inhibition of adipocyte differentiation	adipocyte cell lines	extract	Lee *et al*. 2011
Ecklonia bicyclis (Kjellman) Setchell	vascular oxidative stress tolerance	human (males)	extract	Kang *et al*. 2003
		human (males)	tablet	Iacona *et al*. 2011 Sansalone *et al*. 2014
Ecklonia cava Kjellman	reduction in body fat	mice	extract	Park *et al*. 2012
	ROS inhibition	adipocyte cell lines	extract	Lee *et al*. 2011
Gelidium sesquipedale (Clemente) Thuret	fermentable fibre–short-chain fatty-acid production	human gut microbes	extract	Ramnani *et al*. 2012
Gloiopeltis furcata (Postels & Ruprecht)	nitric oxide inhibition	mouse macrophage cell line	extract	Yang *et al*. 2010
Gracilaria sp.	fermentable fibre–short-chain fatty-acid production	human gut microbes	extract	Ramnani *et al*. 2012
Grateloupia elliptica Holmes	nitric oxide inhibition	mouse macrophage cell line	extract	Yang *et al*. 2010
Himanthalia elongata (Linnaeus) Gray	decreased plasma cholesterol antioxidant activities	rats	whole food	Moreira *et al*. 2011
Hizikia fusiformis (Harvey) Okamura	nitric oxide inhibition	mouse macrophage cell line	extract	Yang *et al*. 2010
Ishige okamurae Yendo	ROS inhibition	adipocyte cell lines	extract	Lee *et al*. 2011
Laminaria japonica Areschoug	reduction in total cholesterol and serum triglycerides	mice	extract mixture	Shin & Yoon 2012
Laurencia okamurae Yamada	nitric oxide inhibition	mouse macrophage cell line	extract	Yang *et al*. 2010
Laurencia intermedia Yamada	ROS inhibition	adipocyte cell lines	extract	Lee *et al*. 2011
Lessonia trabeculata Villouta & Santelices	reduction in cholesterol and serum triglycerides		whole food	Ramirez-Higuera *et al*. 2014
Mastocarpus stellatus (Stackhouse) Guiry	reduction in triglycerides and total cholesterol	rats	whole food	Gómez-Ordóñez *et al*. 2012a
Palmaria palmata (Linnaeus) Weber & Mohr	n-3 PUFA; inflammation inhibition	human macrophages	extract	Robertson *et al*. 2015
Porphyra dioica J. Brodie & L.M. Irvine	n-3 PUFA; inflammation inhibition	rats	extract	Robertson *et al*. 2015
Porphyra umbilicalis (Linnaeus) J. Agardh	reduction in plasma cholesterol levels	human macrophages	whole food	Moreira *et al*. 2010
Sargassum fulvellum (Turner) C. Agardh	supression of triglyceride absorption	human macrophages	extract	Matsumoto *et al*. 2010
Sargassum polycystum C. Agardh	decreased plasma total cholesterol and triglycerides	rats	whole food	Awang *et al*. 2014
Sargassum thunbergii (Mertens ex Roth) Kuntz	nitric oxide inhibition	rats	extract	Yang *et al*. 2010
Ulva linza Linnaeus	reduction in cholesterol and serum triglycerides	rats	whole foods	Ramirez-Higuera *et al*. 2014
Ulva ohnoi M. Hiraoka & S. Shimada	decreased plasma triglycerides and total cholesterol (insol. fibre)	rat model of human MetS	supplement	Kumar *et al*. 2015
Undaria pinnatifida (Harvey) Suringar	supression of triglyceride absorption	rats	extract	Matsumoto *et al*. 2010
	reduction in plasma cholesterol levels	rats	whole foods	Moreira *et al*. 2010
	inflammation inhibition	adipocyte cell lines	extract	Kim & Lee 2012
Unspecified variety	nutritional balance–vitamin B_{12}; longevity (indirect factor)	elderly human population; $n = 127$; avg. age 98 yr	whole food (diet)	Kwak *et al*. 2010
	lowered blood pressure	preschool Japanese children	whole food (diet)	Wada *et al*. 2011

CVD by 22%, is only found in 18% of men and women in the (EPIC) heart study. He further commented that 'this intervention strategy would require a huge shift in the dietary patterns of the general public'. Given all the factors associated with lifestyle, socioeconomic status, education, and environment as they contribute to the global obesity epidemic, it would seem that an obese society needs involuntary intervention. It is interesting to note that populations, e.g. the Japanese, who used to live on a traditional diet with a large component of food from the sea, do not typically suffer from obesity. A traditional cuisine like the Japanese, influenced by vegetarian Buddhists who learned how to use seaweed extracts (dashi) with large amounts of umami-tasting free glutamate to flavour vegetable dishes (Mouritsen 2012a; Mouritsen *et al.* 2012), managed to establish a diet consisting predominantly of low-calorie, high-fibre vegetables, seaweeds, and fruits.

Much circumstantial evidence (extreme and widespread obesity rates) suggests that many members of society are unwilling or unable to make wise and healthy food choices (Hillier *et al.* 2012). It is obvious that a comprehensive, multifaceted approach is necessary to combat this debilitating obesity epidemic, which contributes significantly to the manifestation of CVD. Mandating the ready availability of nonobesogenic foodstuffs to the general populace is a key intervention strategy capable of reaching across all demographic levels (Monteiro & Azevedo 2010; El & Simsek 2012). As important as education is, its implementation has experienced limited success in reducing the global overweight and obesity problems (Van Kleef *et al.* 2012), and more direct approaches must be taken.

Perspectives

In this relatively short review, there have been no less than 35 species of edible macroalgae cited, all with reported capabilities for ameliorating risk factors leading to CVD health benefits. Aside from their broad range of therapeutic effects, seaweeds lend themselves to a diversity of applications, and are valid contenders for whole-food utilization. Hydrocolloids have been used in the food industry for many years, with roots extending back to the 1930s (Bixler & Porse 2011), and much is known about their various physiochemical properties. Capitalizing on the diversity of algae around the world could potentially lead to custom blending to achieve desired sensory effects and nutritional benefits. As a rich source of umami, described as the essence of deliciousness (Mouritsen 2012a), some seaweeds enhance sensory perception of a meal and limit our craving for salt, fat, and sugar. The textural and flavour opportunities for utilizing macroalgae in the daily diet appear to be abundant, and the nutritional benefits are clear. Future research initiatives will see the development of novel and healthful seaweed-enhanced foods.

There is research to suggest that, unfortunately, not all consumers are able to distinguish between nutritionally rich and nutritionally poor functional foods, which is a consequence often related to shrewd marketing strategies rather than to education (Cornish 2012). Regulatory bodies, however, are beginning to recognize the therapeutic value of certain foods and food ingredients, and Health Canada (January 2014) issued a statement allowing for a cholesterol-reducing claim associated with dietary ground flaxseed. As another example, the US Department of Agriculture has approved health claims supporting the role of DF in the prevention of coronary heart disease (2010). These allowances will also help stimulate the development of naturally healthy foods with the judicious inclusion of macroalgae and covering a broad spectrum of processed foods. According to WHO (Fact Sheet No. 311, January 2015), the fundamental cause of obesity is an energy imbalance between calories consumed and calories expended. The overconsumption of fast food products, high in fats, sugars, and salt, underlies much of the global caloric imbalance issue, and it is facilitated by food manufacturing corporations (Moss 2013). If all these foods could be made even moderately healthier, perhaps even functional, by the addition of specific seaweeds, then an effective and long-term intervention strategy for pathologies related to CVD could be initiated.

ACKNOWLEDGEMENTS

The work by O.G.M. is supported by Lundbeckfonden (re: R95-A10447).

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Received 16 July 2015; accepted 15 September 2015