Open Access

Recent Progress in Nutrition

LIDSEN Publishing Inc.

Review

Macroalgae as a Source of Functional Foods in the Prevention of Cardiovascular Diseases

Ana Valado [1, 2, 3, †], Polina Ponedilok [1, †], Armando Caseiro [1, 2, 4], Leonel Pereira [3, 5, *]

1. Polytechnic Institute of Coimbra, ESTeSC-Coimbra Health School, Biomedical Laboratory Sciences, Rua 5 de Outubro – SM Bispo, 3045-043 Coimbra, Portugal; E-Mails: valado@estesc.ipc.pt; polinap2021@gmail.com; armandocaseiroe@estesc.ipc.pt
2. Laboratory for Applied Health Research (LabinSaúde), ESTeSC-IPC, Coimbra, Portugal
3. MARE-Marine and Environmental Sciences Centre/ARNET-Aquatic Research Network, University of Coimbra, Coimbra, Portugal; E-Mail: leonel.pereira@uc.pt
4. Unidade I&D Química-Física Molecular, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, 3030-790 Coimbra, Portugal
5. Department of Life Sciences, Faculty of Sciences and Technology, University of Coimbra, 3000-456 Coimbra, Portugal

† These authors contributed equally to this work.

* **Correspondence:** Leonel Pereira; E-Mail: leonel.pereira@uc.pt

Academic Editor: Arrigo F. G. Cicero

Special Issue: Algal Bioactives for the Management of Metabolic Syndrome and Gut Health

Recent Progress in Nutrition
2023, volume 3, issue 4
doi:10.21926/rpn.2304024

Received: July 22, 2023
Accepted: November 22, 2023
Published: November 29, 2023

Abstract

Noncommunicable diseases (NCD), such as cardiovascular diseases (CVD), are responsible for the majority of annual deaths worldwide. Dyslipidemia, hypertension, diabetes, and obesity, among others, can enhance the onset of metabolic syndrome (MetS). The integration of natural products in the diet, such as marine macroalgae or hydrocolloids extracted from them, has been extensively studied. The application of these substances in the prevention of pathologies is expanding due to the high content of bioactive compounds and as dietary fiber,

constituting an excellent source of organic components to produce functional foods. The objective of this review will be to compile the effectiveness of algal polysaccharides, specifically agar, alginates and carrageenan, in the prevention of CVD, focusing on its action on the pathophysiology underlying this group of diseases, as well as exploring the various human and animal studies available. Additionally, we emphasize the benefits of dietary fiber consumption and the mechanisms of its action throughout the gastrointestinal tract. The present work will also present information about the benefits of consuming macroalgae in regulating intestinal health and its general relationship with CVD.

Keywords
Seaweed; polysaccharides; cardiovascular diseases; metabolic syndrome; functional foods; gut microbiota

1. Introduction

Noncommunicable diseases (NCD), which include cancer, autoimmune conditions, cardiovascular diseases (CVD), and diabetes, among others, are a group of chronic diseases responsible for 74% of yearly deaths worldwide [1]. Among these, CVD is the most prevalent globally, surpassing deaths by malignant neoplasms and respiratory disease. Stroke and heart attack account for 85% of cases [1, 2]. Dyslipidemia and related conditions are the leading causes of CVD.

Natural products such as marine macroalgae, with numerous bioactive compounds, such as hydrocolloids (e.g., carrageenan, agar, alginates), are becoming increasingly appealing for the treatment and prevention of disease due to the attenuated adverse reactions, lower cost, and higher accessibility in comparison to currently available therapeutics [3, 4]. Consequences of a demanding modern lifestyle have led to the development of habits such as smoking, alcohol consumption, sedentarism and poor nutrition, which in turn have increased the prevalence of alterations in the lipid profile, blood pressure, and glucose homeostasis, often leading to obesity, metabolic syndrome (MetS), and diabetes mellitus [5, 6]. These risk factors are, more often than not, correlated.

Diet is a highly adaptable factor that has been proven to affect people independently of their age, sex, and their countries' sociodemographic development. Thus, reducing the consumption of foods that are processed and rich in saturated fat and having the habit of consuming foods considered functional is recommended [7-9]. Correlating direct consumption of macroalgae or compounds, supplements, or extracts such as hydrocolloids to attenuating modern lifestyle health consequences has been a target of interest.

Phycocolloids are high molecular weight hydrophilic sulfated (Galatans) and non-sulfated polysaccharides widely used in the food and pharmaceutical industries due to their gelling and thickening properties for the production of desserts, dressings, dairy and hygiene/cosmetics products, drug delivery aid and several biomedical applications [10, 11]. These hydrocolloids are structural constitutes of red (Rhodophyta), brown (Ochrophyta, Phaeophyceae) and green (Chlorophyta) algae cell walls and are some of the most widely explored seaweed components among vitamins, omega-3 fatty acids, minerals, iodine, peptides and, with particular interest,

dietary fibers [12]. Consequently, many therapeutic properties, such as anti-tumoral, hypolipidemic, anti-thrombotic, hypoglycemic, and immunomodulatory, have placed marine algae within the functional food concept, offering a possibility for quality-of-life improvement [13].

The possibility that the intestinal microbiota may have a role in the occurrence and progression of CVD has come to light more recently. The gut microbiota can metabolize polysaccharides from macroalgae into short-chain fatty acids (SCFA), which are highly related to lipid and glucose metabolism [14, 15].

Dietary fibers encompass a diverse group of plant-derived carbohydrates that resist digestion in the human small intestine. Instead, they undergo partial or complete fermentation in the colon by gut microbiota. This process yields short-chain fatty acids and other metabolites, converting various health benefits. Agar, alginates, and carrageenans (hydrocolloids), derived from seaweed, exhibit characteristics that align with the definition of dietary fibers. These polysaccharides possess complex structures that resist enzymatic breakdown, allowing them to pass through the digestive system intact. Once in the colon, they serve as substrates for fermentation, promoting a healthy gut microbiome and producing beneficial metabolites.

Additionally, they have been associated with various health advantages, including cholesterol reduction, satiety promotion, and blood sugar regulation. Their capacity to support gastrointestinal health by enhancing regularity and preventing constipation further solidifies their classification as valuable dietary fibers. Overall, the unique properties of agar, alginates, and carrageenans make them important components of a fiber-rich diet [16].

This review's goal is to give some insight into the role of dietary fiber in CVD prevention, mainly focusing on the potential of seaweed polysaccharides, such as agar, alginates, and carrageenan, through the compilation of existing research on the subject.

2. Diet for Disease Prevention

The prevention of NCD depends heavily on maintaining a balanced diet. Proper nutrition supports healthy digestion, aids in weight management, regulates blood pressure and cholesterol levels, and improves digestive health and immune function. In addition, it lowers the risk of obesity and other NCD such as heart disease, stroke, diabetes mellitus, and several malignancies. According to WHO, these comprise 82% of all deaths [1].

For example, the Mediterranean Diet has shown to be effective in decreasing metabolic alteration manifestations and was found to be inversely associated with CVD risk factors in randomized extensive cohort studies in Spain, such as the PREDIMED [7]. Similarly, Japan Collaborative Cohort for Evaluation of Cancer Risk (JACC) and Japan Public Health Center-based Prospective (JPHC) studies have connected lower risk and mortality from CVD to the consumption of foods such as seaweed, typical in the Japanese diet [8, 9].

According to The Food and Agriculture Organization of the United Nations (FAO) [17], although several definitions of functional foods have been put out, none are universally agreed upon. Even so, it is generally accepted that for an aliment to be considered an available food, it should abound in bioactive or functional substances that may be able to perform physiological functions beyond meeting dietary needs for essential nutrients, such as promoting overall health or even lowering the chance of developing chronic diseases [17]. Recently, a new definition of functional foods has been proposed to clarify which foods have the potential to be included in this concept, stating that they

must contain a safe concentration of these active substances but are high enough to deliver the desired result [17].

Dietary fiber is one of the examples of said bioactive ingredients since, according to EU regulation 1169/2011 [18], it is organically present in the food consumed and demonstrates a positive physiological benefit broadly recognized by scientific data. Various prospective cohort studies have presented A wealth of evidence, including the European Prospective Investigation into Cancer and Nutrition-Heart study (EPIC-Heart). This study demonstrated a 15% lower risk of ischemic heart disease associated with the daily intake of fiber from fruits, cereals, and vegetables [19]. The study lasted 11.5 years, and participants from 10 European countries were involved. The dietary assessment was based on food consumption and lifestyle questionnaires, and a 24 h diet recall method was used to compare the obtained data [19] better.

In a broader view, soluble and insoluble dietary fiber is connected to intestinal wellbeing, whether by regulation of intestinal tract movements or by attenuation of gut dysbiosis [20, 21]. In contrast, soluble fiber has been shown to regulate lipidic and glycemic levels in the blood, a valuable property in aiding health conditions like MetS [22-24]. These differences can be explained by analyzing their behavior when in contact with water since soluble fibers usually form gels, while insoluble fibers tend to incorporate said water [10, 25].

Through the compilation of studies and surveys conducted in several countries around the globe, Stephen et al. (2017) concluded that the total fiber intake didn't reach the recommended values, with average information of 16-24 g/day in Europe and even less in North America (17 g on average) [26]. According to national nutrition surveys, the countries with the highest total fiber intakes in Europe were Germany, Hungary, and Poland (ranging from 23 to 24 g/day). This is especially concerning since the Scientific Advisory Committee of Nutrition (SACN) stated that the daily reference value for adults should be 30 g [27].

3. Dietary Fiber from Seaweed and Its Benefits

In South Asian countries, seaweed consumption dates to before the 10th Century, and to this day, Japan remains one of the countries with the highest amount of seaweed incorporated into the diet, with up to 9.9 g per day [16, 28]. The Japan Collaborative Cohort Study (JACC study) stated that, on average, the Japanese population consumes seaweed three to four times a week [8, 29]. As opposed to that, seaweed intake is not as relevant in European countries as these mostly follow a Western dietary pattern. Coincidentally or not, the incidence of NCD, such as cardiovascular diseases and cancer in Westernized countries where diets mainly consist of quick-preparation meals high in sugars and salt, saturated fats, and processed meats, has been proven to be much higher in many epidemiological studies [30-32].

Besides nutrients, macroalgae contain various components that exhibit valuable biological properties that could benefit human health if used as ingredients to produce functional foods. These include polysaccharides, constituting a significant percentage of dietary fiber composition and the largest group of carbohydrates [33]. According to the European Food Safety Authority (EFSA), the definition of dietary fiber comprises non-digestible carbohydrates as non-starch polysaccharides, which include hydrocolloids [34].

Seaweed dietary fiber content is much higher than in vegetables, and even though seaweed nutritional composition varies according to environmental factors such as light availability, water

temperature, and geographic localization when compared to vegetables, they are easier to cultivate since their growth in the wild is relatively abundant and environmentally friendly [35, 36]. The overall carbohydrate composition of seaweeds can be estimated to be between 20 and 76%, much higher than the percentages of most other constituents [37, 38]. Matanjun et al. (2009) determined that selected algae belonging to the three main species (Rhodophyta, Chlorophyta, and Phaeophyceae) presented an approximate content of fiber between 25 and 39%, considerably higher than the content of other components. *Kappaphycopsis cottonii* (formerly *Eucheuma cottonii*) (Rhodophyta), the main source of carrageenan for industrial purposes [39], had a percentage of 18.25% of soluble fiber [40]. On top of that, it is also a great source of insoluble fiber, as its content after extraction can be up to 90% [39]. Likewise, *Ascophyllum* (Ochrophyta, Phaeophyceae), a significant source of alginate in Europe [41], has a substantial percentage of polysaccharides [37].

Due to their ability to thicken and gel when in contact with water, these polysaccharides or hydrocolloids (high molecular weight hydrophilic polysaccharides that can be sulfated or non-sulfated) are utilized extensively in the food, cosmetics and pharmaceutical industries in Western European countries [10, 11]. Particularly in the food industry, they mainly provide textural functionality, stability, or emulsification qualities [42] for producing syrups, dressings, desserts, and confect meat and deep-fried products [43].

From this perspective, incorporating dietary fiber in the diet by adding seaweed extracts into commonly consumed foods in westernized countries, such as dairy products, syrups, bread, and meats, emerges as a promising area of research. This approach can potentially mitigate risk factors associated with cardiovascular diseases and enhance overall quality of life.

3.1 Phycocolloids Most Used in Food

The expanding awareness of the modifiable risk factors for NCD and the consciousness of their connection with the food we consume has increased the interest in including seaweed in the diet worldwide. Attributing the label of “superfoods” to foods and beverages containing seaweed deriving ingredients in their matrixes to improve their overall composition by also attempting to diminish the concentration of less desired compounds such as fat and salt to produce low-calorie foods [44] has become increasingly popular [45]. It is well known that due to the richness in specific proteins, pigments, polyunsaturated fatty acids, polyphenols, and polysaccharides that differ from those usually exploited for food production, marine algae exhibit a plethora of beneficial effects such as hypocholesterolemic, hypoglycemic, anticoagulant, antitumoral, among others [12, 46-48].

A recent study that sought to shed light on the scope of commercial algae use found that 5720 new products were released in Europe out of thirteen thousand released globally. Foods made up most items with algal extracts or biomass, while beverages comprised 21% [45]. Most of these foods were dairy products and desserts. Since the hydrocolloid properties of seaweed make them ideal for producing jellies, their consumption as a desserts has already been studied and showed promising results in attenuating dyslipidemia [47].

As mentioned, colloids from algae, or phycocolloids, can benefit their dietary fiber properties. Among them, carrageenan (E 407) and agar (E 406), extracted from red seaweeds (phylum Rhodophyta), alginic acid and alginates (E 400-E 405), extracted from brow seaweeds (class Phaeophyceae) [35], have a high popularity in the industry. The Food and Drug Administration (FDA) officially recognizes these food additives as safe for human consumption based on their extraction

method and molecular structure [49-52]. It is essential to point out that depending on the methods used for extraction, the purity and yield may vary, as do their molecular structures and gelling properties, based on the growth environment, molecular make-up, and composition of the reagents. For this reason, regulations regarding their extraction must be followed strictly, especially for their use in the food industry [53].

Alginate is a non-sulfated linear polysaccharide made up of two saccharide units that are organized in sequences of -D-mannuronic acid (M) and -L-guluronic acid (G) [54]. It has ion-exchanging properties and is most commonly used to produce juices, syrups, dessert fillings and sauces [11, 53]. The three commercially extracted types of carrageenan are kappa carrageenan (κ-carrageenan), iota carrageenan (ι-carrageenan) and lambda carrageenan (λ-carrageenan), classified based mainly on chemical structure and properties, which determine their solubility [42]. These linear sulfated galactans are made of repeated units of disaccharides [53]. Carrageenan is distinctively used to enhance the texture of dairy products by stabilizing and binding to milk proteins. Both alginate and carrageenan are used to replace fat and improve food quality [55].

The main distinction between the composition of agar and carrageenan is the absence of sulfate ester in the first. In its composition, agaropectin is responsible for the viscous properties, while agarose provides gelling ability. The first contains more anionic groups and is essentially removed during industrial processing. Agar mainly forms a rigid gel in contact with water, which helps produce candy and canned meats [11, 53].

4. Cardiovascular Diseases and Underlying Conditions

According to Heart Disease and Stroke statistics, 19 million people died of CVD worldwide in 2020, 18.7% more than in 2010 [2]. In the United States, 874,613 deaths by CVD occurred in 2019, with an increase to 928,741 in the following year. This heterogeneous group of diseases of the heart and circulatory system, which include coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other conditions [1], has an assortment of risk factors that can range from non-modifiable, such as age, sex, and genetics to modifiable such as those provoked by a primarily modern sedentary lifestyle. These comprise alcohol and tobacco consumption, an inadequate diet rich in saturated fats, and physical inactivity, which in turn can lead to changes in the lipid profile and conditions deeply related to CVD progression, like high blood pressure, obesity, and diabetes. Since most risk factors are intertwined, they are commonly called Metabolic Syndrome (MetS). Dyslipidemia, caused by alterations in lipid metabolism, is a significant risk factor for the emergence of underlying CVD risk factors [56]. One characteristic is elevated serum levels of low-density lipoproteins cholesterol (LDL-C) [24, 56]. It is estimated that high levels of LDL-C gave rise to 4.51 million deaths in 2020 [2]. These molecules are directly correlated with the pathogenesis of atherosclerosis, which is the leading cause of cardiovascular-related death worldwide [6, 57].

4.1 Metabolic Syndrome

MetS gathers complicated symptoms, including obesity, insulin resistance, diabetes mellitus, and cardiovascular complications. The pathogenesis of metabolic syndrome involves a multitude of factors. It has not been fully understood, but it is well known that these factors are deeply linked both with each other and with the onset and progression of CVD.

One of the early triggers of MetS is the increase in visceral adiposity. This increase can ultimately lead to the onset of obesity and contribute to dysfunctionality within adipose tissue, releasing free fatty acids (FFA) and reactive oxygen species (ROS) [58, 59]. Once cellular function is affected, insulin sensitivity and glucose uptake decrease, leading to insulin resistance and hyperglycemia. Triglycerides (TG) are mobilized from adipocytes through lipolysis enabled by insulin resistance. This increases the concentration of FFA in the blood. FFA produces very low-density lipoprotein cholesterol (VLDL-C), which allows the production of small, dense low-density lipoprotein [41, 59]. Due to their size and composition, these are quickly deposited within the arterial walls, presenting a higher risk for atherosclerosis. Low-density lipoprotein cholesterol (LDL-C) can be modified by ROS, causing oxidation, enabling inflammation, and exacerbating the pro-oxidative state within the vascular lining. Low high-density lipoprotein cholesterol (HDL-C) levels due to triglyceride enrichment and subsequent removal from circulation are also potent risk factors for heart disease due to the decrease of their antioxidant and anti-inflammatory protective properties [56].

From this viewpoint, obesity can lead to MetS causative factors such as dyslipidemia, and in turn, dyslipidemia can be preceded by insulin resistance. The overall combination of these effects may result in atherosclerotic events. As early as 1961, several risk factors for coronary heart disease were described, among them hypercholesterolemia [60]. Today, it is well known that a plasma cholesterol level above 150 mg/dL is undoubtedly associated with the development of this disease [57]. Since visceral adiposity plays a crucial role in the pathophysiology of MetS, waist circumference and body mass index measurements are fundamental for risk evaluation [58].

4.2 Hypertension

In 10 years, the deaths resulting from high blood pressure increased by 65.3% [2], indicating that hypertension plays a significant role in the CVD pathophysiology. It is diagnosed when systolic blood pressure is above 140 mm Hg and diastolic blood pressure is above 90 mm Hg [2]. Even though hypertension can be an independent risk factor for CVD, endothelial dysfunction at the basis of this condition can arise as a consequence of dyslipidemia [57]. Primarily, hypertensive activity from seaweeds is based on inhibiting the angiotensin-converting enzyme, preventing the conversion of angiotensin I to angiotensin II, an active vasoconstrictor. These abilities are mostly related to the biological activities of seaweed compounds such as phlorotannins and extracted peptides [61, 62]. According to evidence, Peptides, which have also been proven to reduce plasma and hepatic cholesterol and glucose levels, are the most extensively researched natural substances for this matter [37]. Seaweed polysaccharides are not highlighted when it comes to hypotensive effects. Nevertheless, alginate has been implicated in lowering blood pressure by binding to sodium in the gastrointestinal tract [63].

5. Dietary Fiber from Macroalgae – Mechanisms of Action

The search for alternative therapeutics for controlling blood cholesterol and glycemia is gaining popularity and relevance since synthetic cholesterol-lowering drugs, for example, statins or fibrates, like all pharmacological approaches, commonly present relevant side effects. There is immense evidence of the dietary supplementation of algae in the form of compounds, supplements, or extracts from seaweeds and their potential to overcome the challenges of traditional treatment [23, 47].

Based on the EU regulation 1169/2011, dietary fiber is defined as "carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine" [18]. For this reason, although the human body cannot directly benefit from it in terms of nourishment, it contributes to human nutrition by playing a role in some crucial processes that help to sustain digestive health [64]. It is well known that dietary cholesterol intake influences cholesterol concentration, but dietary fiber's cholesterol-lowering effects have been known for many years [65]. The exact mechanisms of action of dietary fiber in the gastrointestinal tract are yet to be precisely understood. Due to its hydrocolloid properties, it can reduce the rate at which food is digested, and nutrients are absorbed on top of contributing with little to no calories to the diet. By elevating gastric viscosity, it also provides a feeling of satiety. It may aid in postprandial glucose modulation [64, 66], which may lower LDL-C and TC by hampering insulin production [67]. Thus, since the prevention of CVD by consumption of dietary fiber lies mainly in its abilities to regulate metabolic dysfunction, it has excellent value given that it can intervene in what is thought to be one of the very first triggers for the development of MetS, the high caloric intake [58]. Besides that, its downstream action, namely in mediating blood cholesterol and glucose levels, has been the target of several studies [25, 68].

One of the most widely accepted mechanisms involves binding soluble dietary fiber to bile salts. These play a crucial role in lipid metabolism. They are synthesized from cholesterol in the liver and kept in the gallbladder until digestion releases them into the small intestine, where they are then reabsorbed. By binding to fiber, their reabsorption is prevented, resulting in the *de novo* synthesis of bile salts through the utilization of TG from adipose tissue reserves [56]. On this basis, Gunness and Gidley (2010) proposed three hypotheses regarding the relationship between exogenous cholesterol absorption and bile salts. They discussed that soluble dietary fiber either creates a barrier between bile salt-cholesterol micelles and intestinal cells, is complexed to the micelles by molecular interactions, or forms a matrix that entraps them [68].

As mentioned above, dietary fiber might also have a role in blood glucose level stabilization, although not through direct contact. A similar approach was made by Goff et al. (2018), who outlined the current theories behind the mechanism of reduction of postprandial glycemia. Through the analysis of several *in vivo* and *in vitro* studies, they have established that since gastric emptying is correlated with feedback from the small intestine, the slower nutrient delivery rate for digestion might subsequently influence the glycemic levels in the blood by delaying sugar absorption. On the other hand, this decreased absorption might be achieved by downregulating glucose transporters in the cell. This feedback, mediated mainly through hormone release, namely insulin and glucagon, is vital for maintaining energy homeostasis [25].

Although most of the effects of dietary fiber in the studies discussed above are due to fiber not derived from seaweed, several studies using algae have produced comparable results, which makes us assume they are equally effective. A selected compilation of these studies is reviewed in the next chapter.

5.1 Polysaccharides from Macroalgae for the Prevention of Cardiovascular Disease

A selection of representative studies was conducted to evaluate the effectiveness of adding carrageenan, alginate, and agar to the diet of humans and rodents on metabolic risk factors associated with CVD, such as appetite, glycemia, body weight, blood pressure, and lipid profile.

Based on this, studies where no more than one seaweed polysaccharide or other dietary fiber was used, and any of the three mentioned above were excluded to eliminate interferences. Studies where whole algae was used were also excluded for the same reason. In general, few studies have been conducted on this topic, neither in humans nor rodents. We have compiled the results from these studies in Table 1.

Table 1 Selection of studies carried out in animal and human models.

Polysaccharide	Model	Period	Quantity	Mode	Effects	References
Carrageenan	Wistar rats	30 days	1% CC	diet	↔FG; ↓PG; ↓BW; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C	Qiu, 2018 [46]
			1% LC		↔FG; ↓PG; ↓BW; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C	
			3% LC		↔FG; ↓PG; ↓BW; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C	
	Male C57BL/6J mice	16 weeks	5% *K. alvarezii*	diet	↓BG; ↓BW; ↓BF; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C;	Chin, 2019 [69]
			5% k-CGN		↓BG; ↓BW; ↓BF; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C;	
			5% SCCGN		↓BG; ↓BW; ↓BF; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C;	
	healthy volunteers	30 days	100 mL/day	commercial vegetable jelly	↓TC; ↑TG; ↓LDL-C; ↓HDL-C	Valado, 2020 [47]
		60 days			↓TC; ↑TG; ↓LDL-C; ↓HDL-C	
	hospitalized patients	20 weeks	250 g	capsules	↔BW; ↓TC; ↑ TG; ↓LDL-C; ↑HDL-C	Sokolova, 2014 [70]
	healthy volunteers	8 weeks	40 g/day	powder	↔BW; ↓TC; ↓ TG ↑LDL-C; ↑HDL-C	Panlasigui, 2003 [71]
	healthy females	4 weeks (2.10 h)	2.5 g	milk	↓A; ↓PG	Arshad, 2016 [22]
Alginate	female Wistar rats	28 days	1%	diet	↓SBP; ↓TC; ↓TG; ↓LDL-C; ↑HDL-C	Ren, 1994 [48]
	male Wistar rats	1 h	1 mL natural SA	alginate solution	↑CE; ↓I; ↓BG	Kimura, 1996 [72]
			1 mL 10 kDa SA		↔CE; ↔I; ↔BG	
			1 mL 50 kDa SA		↑CE; ↔I; ↓BG	
			1 mL 100 kDa SA		↑CE; ↓I; ↓BG	
	C57BL/6J male mice	28 days	50 mg	diet	↓BG; ↓BW; ↓TC; ↓TG	Wang, 2018 [73]
	healthy females	4 weeks (2.10 h)	2.5 g	milk	↓A; ↓PG	Arshad, 2016 [22]
	healthy males	4 weeks (4.20 h)	1.25% 2.5%	chocolate milk	↓A; ↓I; ↓PG	Khoury, 2014 [66]

	overweight males	4 h	1.5 g	beverage	↓PG; ↓TC; ↔TG	Paxman, 2008 [23]
	healthy males	5.30 h	1.5 g	beverage	↓PG	Harden, 2012 [74]
	obese volunteers	2 weeks	3%	powder	↔WC; ↓Hb A_{1c}; ↓FI; ↓SBP; ↓BF; ↓BW; ↔TC; ↔TG; ↔LDLC; ↔HDL-C	Jensen, 2012 [75]
Agar	female Wistar rats	28 days	1%	diet	↔SBP; ↓TC; ↓LDL-C; ↓HDL-C	Ren, 1994 [48]
	Sprague-Dawley rats	14 days	5%	diet	↔BW; ↔TC	Kelley, 1978 [76]
	C57BL/6J mice	8 weeks	5% AO 10% AO	diet	↑BG; ↓BMI; ↓BW; ↓BF; ↓TC; ↓LDL-C; ↓HDL-C ↑BG; ↓BMI; ↓BW; ↓BF; ↓TC; ↓LDL-C; ↓HDL-C	Lee, 2022 [77]
	obese patients	12 weeks	180 g	diet	↓BMI; ↓BW; ↓BF; ↓Hb A_{1c}; ↓FI; ↓PI; ↓PG ↓TC; ↓TG; ↑HDL-C	Maeda, 2005 [78]
	healthy male volunteers	6 h 2 h	2.0 g	test meal with commercial agar	↓GE ↔PG	Sanaka, 2007 [79]
	healthy volunteers	3 h	4 g	fruit-flavored jelly	↓GE; ↑A; ↔PG	Clegg, 2014 [80]

Abbreviations: ↓: decrease; ↑: increase; ↔: no change; A: appetite; AO: agaro-oligosaccharides; BG: blood glucose; BF: body fat; BW: body weight; CC: carrageenan; CE: cholesterol excretion; FG: fasting glucose; FI: fasting insulin; GE: gastric emptying; Hb A_{1c}: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; I: insulin; k-CGN: native k-carrageenan; LC: low molecular weight carrageenan; PG: postprandial glycemia; PI: postprandial insulin; SA: sodium alginate; SPB: systolic blood pressure; SCCGN: sans-carrageenan fraction; TC: total cholesterol; TG: triglycerides; WC: waist circumference

5.1.1 Carrageenans

In terms of evaluating glycemic response studies using carrageenan specifically, only two studies in rats have been identified [46, 69]. Qiu et al. (2018) used low-molecular-weight carrageenans (1% LC and 3% LC) from the red seaweed *Eucheuma denticulatum* (Rhodophyta) (Figure 1a) on Wistar rats that were fed for 30 days with a high-fat diet (HFD) (3.5% cholesterol, 10% lard, 0.2% propylthiouracil, 0.5% sodium cholate and 5% refined sugar). The standard control group was fed with a powder containing 19% fats, 55%, carbohydrates, 22% proteins, 7% ash, and 5% cellulose,

while the treated control group was administered 1 g of carrageenan (CC) per 100 g of HFD. Even though no statistically significant changes in the fasting glycemia levels were observed, the postprandial levels in all three groups had lowered significantly compared to the HFD group [46]. In the study by Chin et al. (2019) [69] blood glucose determination by an oral glucose tolerance test showed that supplementation with native κ-carrageenan and sans-carrageenan fractions from *Kappaphycus alvarezii* (Figure 1b) had favorable outcomes. Interestingly, less improvement was observed upon the use of the whole K. alvarezii. In this study, native κ-carrageenan extracted from *K. alvarezii* and a remaining sans-carrageenan fraction were used to compare anti-obesity effectiveness with whole *K. alvarezii* supplementation. For this purpose, C57BL/6J mice were fed a low-fat diet (10% kcal energy from fat) and a HFD (45% kcal energy from fat) for 10 weeks, which was supplemented with 5% native κ-carrageenan, 5% sans-carrageenan fraction and 5% *K. alvarezii*, after 6 weeks [69].

Figure 1 Carrageenophytes: a – *Eucheuma denticulatum*; b – *Kappaphycus alvarezii.* Scale = 1 cm.

Both studies evaluated carrageenan supplementation's effects on body weight. In the first study [46], the 3% LC group experienced body weight reduction sooner than the other groups, but by the end of the study, all three (3% LC, 1% LC, and CC) showed a statistically significant difference in weight loss. Similarly, in the second study [69], body weight showed a more substantial reduction in the group supplemented with the sans-carrageenan fraction, even though a decrease in the fat mass was observed in the three groups.

Carrageenan's hypolipidemic effects were also investigated in these studies. Regarding the research by Qiu et al., serum TC, TG, and LDL-C were significantly decreased in the 1% LC and 3% LC groups when compared to data from the HFD group, suggesting dose-dependency, and on the other hand, HDL-C levels significantly increased, while CC effects weren't as notable [46]. The same tendency was seen in the study of Chin et al., where there was also a decrease in TC, TG, and LDL-

C, although it was not significant. Statistical significance was only reached by the sans-carrageenan fraction effect on the elevation of HDL-C levels, even though some increase was also observed in the other groups [69].

To date, three studies were conducted on humans regarding the hypolipidemic effects of carrageenan. All three detected a positive effect of carrageenan on TC levels [47, 70, 71]. The most recent study is by Valado et al. (2020), where the daily intake of commercial vegetable jelly (100 mL/day), for both 30 and 60 days resulted in the decrease of TC and LDL-C, the latter specifically significantly decreased in females. However, TG levels experienced an increase while levels of HDL-C decreased [47]. This decrease in HDL-C wasn't compatible with the results in the other studies. Sokolova et al. (2014) studied the effects of administering a supplement containing κ and λ carrageenans from *Chondrus armatus* (Rhodophyta) on the lipid profile of hospitalized patients with ischemic heart disease. There supplementation period lasted for 20 days, and afterwards, a significant decrease in TC and LDL-C concentrations was reported. Additionally, the atherogenic index was determined and also showed a significant decrease. Even though the levels of TG increased, the increase was less in the supplemented group [70]. Lastly, Panlasigui et al. (2003) used carrageenan in powder form added to food products as part of the diet of a group of volunteers for 8 weeks. As a result of daily consumption of 40 g of carrageenan powder, the volunteers experienced an overall significant decrease in TC and TG and an increase in HDL-C [71].

Both Sokolova et al. and Panlasigui et al. evaluated body weight by assessing participants' body mass indexes but found no significant differences in the measurements before and after the experiments [70, 71].

Only one study by Arshad et al. (2016) investigated the effect of dietary polysaccharides carrageenan on human blood glucose. Carrageenan-supplemented milk consumption after a meal resulted in significantly lower postprandial glycemia. However, the overall performance of alginate-supplemented milk was more significant [22].

5.1.2 Alginates

All the research regarding the effects of alginates in humans has evaluated its outcomes in blood glucose regulation. One of the studies was done on female volunteers [22] and four on males [23, 66, 74, 75], of which one was conducted on overweight males [75]. In four studies, calcium was added to the alginate supplement to enhance gelation [23, 66, 74, 75]. Only two of the studies assessed the effect of alginate on lipid metabolism [23, 75].

The previously mentioned study by Arshad et al. evaluated the effects of milk (250 mL) supplemented with alginate (2.5 g) on blood glucose levels and satiety in 30 healthy females. The ingestion of the preload happened weekly, during four sessions, before the consumption of a pizza meal, and the blood glucose measurements were repeated at different times after ingestion of the polysaccharide-supplemented milk. The preload containing alginate showed statistically significant effectiveness in the suppression of appetite and feeling of fullness. Moreover, alginate and carrageenan reduced postprandial blood glucose levels immediately after the meal. At the end of the experiment, carrageenan showed the biggest decrease although alginate was able to have a more significant impact on cumulative concentration measurements [22]. Similar conclusions were made in the study conducted by Khoury et al. (2014) where chocolate milk was used as the base for alginate supplementation along with a pizza meal. The milk contained increasing concentrations of

alginate (1.25% and 2.5%) extracted from *Laminaria hyperborea* (Ochrophyta, Phaeophyceae), and its significant effects on pre and postprandial appetite, glycemia, and insulinemia were revealed to be dose-dependent [66].

Two other studies where postprandial glycemia was evaluated used the same sodium alginate-based beverage (1.5 g alginate) [23, 74]. Paxman et al. (2008) assessed the effects of pre-prandial consumption of 100 mL of the beverage, followed by a meal rich in fat and carbohydrates, on blood glucose and cholesterol uptake in overweight males, based on their body fat measurements. A strategy similar to the previous studies was used, where samples were taken at different times pre- and post-prandial. Results revealed that volunteers with more significant body fat percentages and body mass indexes significantly decreased the uptake of cholesterol and peak of blood cholesterol, respectively, as did glucose uptake [23]. In the second study, by Harden et al. (2012) followed the same design on healthy males and obtained the same result regarding glycemic response [74].

Lastly, Jensen et al. (2012) conducted a 12-week study to evaluate the consequences of an alginate preload (3% alginate extracted from *Laminaria hyperborea* and *Laminaria digitata*) (Figure 2). The alginate supplement was administered as a powder mix three times a day before each main meal by 96 obese volunteers (intention-to-treat group). Only 80 subjects (completer population) completed the study. In these individuals, body weight, body fat percentage, fasting insulin, systolic blood pressure, and Hb A1c levels showed a significant decrease compared to the control group. Changes in the lipid profile, waist circumference, and fasting glucose levels weren't identified [75].

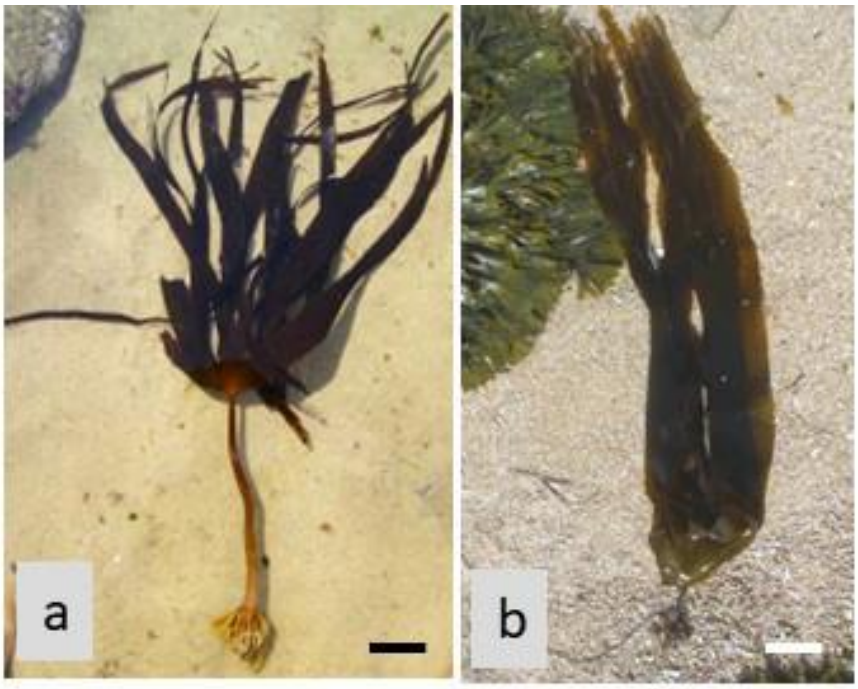

Figure 2 Alginophytes: a - *Laminaria hyperborea;* b - *Laminaria digitata* (Phaeophyceae). Scale = 1 cm.

With regards to animal studies, all three [48, 72, 73] evaluated the hypolipidemic effects of sodium alginate. Two were conducted on Wistar rats [48, 72] and one on C57BL/6J mice [73].

Ren et al. (1994) tested the antihypertensive and antihyperlipidemic effects of several polysaccharides among which alginates (1% sodium alginate from *Analipus japonicus*) (Ochrophyta,

Phaeophyceae). Female Wistar rats were fed a synthetic diet with the polysaccharide for 28 days. By the end of the experiment, systolic blood pressure, TC, TG, and LDL-C levels decreased compared to the control group that only consumed 1.5% saline solution along with the synthetic diet. Additionally, there was a moderate elevation of HDL-C levels. Consumption of alginate allowed a significant reduction of the Atherogenic Index in hypercholesterolemic rats [48]. Kimura et al. (1996) studied the effects of natural sodium alginate from *Saccharina angustata* (formerly *Laminaria angustata*) (Ochrophyta, Phaeophyceae) and low molecular weight alginates (10, 50 and 100 kDa) on glucose tolerance and cholesterol excretion. The male Wistar rats were fed cholesterol and glucose, immediately after which they were administered the alginate solutions. Results showed significant cholesterol excretion upon natural, 50, and 100 kDa sodium alginate administration. All three also inhibited the rise of blood glucose and insulin except for 50 kDa alginate, which didn't impact insulin levels. Ten kDa alginate didn't alter blood glucose or insulin levels [72]. In a most recent study, Wang and collaborators (2018) proved the effectiveness of sodium alginate on amelioration of body weight and lipid profile. C57BL/6J male mice were fed a low-fat diet in the control group (10% kcal fat from lard) and a HFD (45% kcal fat from lard). The latter were fed for 8 weeks, after which supplementation with sodium alginate (50 mg/kg) was done. After 28 days, the ratio between food intake and body weight was significantly decreased. Sodium alginate successfully eased glucose intolerance provoked by HFD and accelerated its elimination. TC and TG levels were also reduced, although not considerably [73].

5.1.3 Agar

Studies using agar are even more scarce than the ones using the previous extracts. On top of that, most of them revealed that agar was less successful in managing metabolic parameters when compared to carrageenan and alginate. In fact, in the previously mentioned study [48], where antihypertensive and antihyperlipidemic properties of polysaccharides were assessed, agar showed a considerably lower success rate when compared to alginate. Agar supplementation showed no differences in systolic blood pressure and had the lowest capacity to reduce serum LDL-C levels. The reduction of TC levels was comparable to that in the control group (95%). However, HDL-C levels were raised moderately, as in the case of alginate. In the work of Kelley and Tsai (1978), male Sprague-Dawley rats were fed a cholesterol-rich diet (0.2% in hot oil) and supplemented with 5% agar for 14 days. The results revealed that agar had no effect on body weight and had an inconsistent effect on serum and liver cholesterol levels despite reducing cholesterol absorption by 16% [76]. Lee et al. (2022) have recently studied the effects of oligosaccharides from agar on the regulation of obesity in C57BL/6 mice during 8 weeks of ingestion of 5 and 10% agaro-oligosaccharides (AO) added to a HFD (60% kcal fat). As opposed to the previous studies, both concentrations of AO had positive effects on body weight and abdominal fat and could significantly reduce serum TC and LDL-C levels. Even though blood glucose and HDL-C levels experienced a slight increase and decrease, respectively, the outcome of AO consumption on obesity attenuation was significant [77].

In human studies, Maeda et al. (2005) incorporated commercially available agar (180 g) into a conventional Japanese diet to evaluate its effects when consumed by 76 obese patients with diabetes and impaired glucose tolerance, for 12 weeks. They consumed a diet mainly consistent of carbohydrates and not exceeding 300 mg of cholesterol. Body weight, body fat and BMI reduction

was greater in the agar group. Hb A_{1c} and TC experienced significant decrease in the agar group specifically, while HDL-C, TG, and fasting insulin, and postprandial glucose differences weren't important. On the other hand, postprandial insulin levels decreased more significantly in the agar group than in the control group [78]. On the contrary, Sanaka and colleagues (2007) didn't find any improvement in the postprandial glucose levels upon intake of three meals containing 2 g of commercial agar by 10 healthy male volunteers. Still, agar did delay gastric emptying in these subjects [79]. The same effect regarding both gastric emptying and glycemic response was seen in a more recent study by Clegg and Shafat (2014), where 11 subjects were given fruit-flavored jelly with 4 g of agar and 50 g of carbohydrates [80]. Interestingly, there was an increase in appetite induced by agar consumption in this study, which is not usually the case in other studies where the effects of dietary fiber are evaluated.

6. Dietary Fiber from Seaweed and Gut Health

Evidence has shown that gut microbiota dysbiosis is related to obesity, diabetes, cardiovascular diseases, and cancer [81] since there is a tight relationship between gut and heart health. Gut health also depends highly on the composition of the gut microbiota, which can be regulated by intake of dietary fiber [15, 82].

In the course of this review, we have already established that enzymes of the stomach and duodenum don't hydrolyze fiber from seaweed. It can, however, be degraded, absorbed, and utilized by significant intestine microorganisms into SCFA, such as acetate, butyrate, and propionate, making it valuable as a prebiotic [83]. The primary source of energy in the gut is butyrate [58], and its main action is to regulate gene expression by stimulating free fatty acid receptors. It is implicated in the genetic activation of mechanisms leading to adipocyte differentiation, essential for reducing circulating lipids. As a result, butyrate has been shown to efficiently prevent MetS by regulating body weight, insulin sensitivity, glycemia, lipid profile, and other factors, as it is also implicated in dietary cholesterol uptake [84]. Similar properties are observed for acetate and propionate.

The degradation of polysaccharides from seaweed is possible due to the specific enzymes, such as glycoside hydrolase and polysaccharide lyase, encoded by genes present in these microbes. The resulting metabolites can then be utilized either through absorption by metabolically active tissues by binding to G-protein coupled receptors or through the ingestion by other microorganisms, contributing to maintaining a healthy microflora as well as appetite regulation and glucose and lipid homeostasis [81, 83].

Lactobacillus and *Bifidobacteria* are some of the gut microbes responsible for its health. Their increase has been shown after supplementation with carrageenan extracts and other sulfated polysaccharides from macroalgae [14]. Moreover, κ-carrageenan has been shown to restore the ratio of Firmicutes to Bacteroidetes, which disruption is associated with gut inflammation and is commonly observed in obesity. κ-carrageenan also improved SCFA levels, particularly butyrate, in mice fed an HFD [69], which is known to induce the disruption of intestinal integrity [15]. The same effect was observed with the ingestion of sodium alginate, and, on top of that, acetate concentration was also increased [73].

Gut dysbiosis can also be a risk factor for the development of hypertension, mainly through its pathophysiological association with atherosclerosis since it can induce inflammation by promoting the expression of pro-inflammatory cytokines. The decrease in beneficial bacteria resulting in the

generation of toxins like bacterial lipopolysaccharides is a significant contributing factor to this inflammation. The resulting vascular oxidative stress, with increased oxidation of LDL, may affect vasoconstriction and vasodilation, overthrowing the balance that prevents hypertension [15, 85].

Although the research of metabolic regulation through the modulation of the gut microbiota is becoming a popular and quite promising approach, the lack of uniformization of methodologies, specifically regarding human trials, poses an obstacle to obtaining a broader understanding of this topic.

7. Beneficial Activities of Other Algal Compounds

Various seaweed polyphenolic compounds, such as flavonoids and phlorotannins, play a crucial role in mitigating oxidative stress and inflammation, both of which are significant contributing factors to the development of cardiovascular diseases [86]. Flavonoids are a diverse group of naturally occurring plant compounds known for their potent antioxidant properties. These compounds are particularly abundant in seaweeds, offering a formidable defense against harmful free radicals that can damage cells and tissues within the body. By scavenging these free radicals, flavonoids help prevent cellular oxidative stress, a pivotal mechanism underlying the progression of cardiovascular diseases [87].

Phlorotannins, on the other hand, are unique polyphenolic compounds exclusive to seaweeds. They possess an impressive array of bioactive properties, including antioxidant, anti-inflammatory, and anti-coagulant effects. These compounds are renowned for neutralizing reactive oxygen species (ROS) and inhibiting inflammatory pathways, thereby reducing the risk of chronic inflammation, a key driver of atherosclerosis and other cardiovascular conditions [88]. Moreover, phlorotannins have been shown to enhance endothelial function, promoting healthy blood vessel dilation and maintaining proper blood flow, further safeguarding against the onset of cardiovascular diseases [89].

The synergistic action of flavonoids and phlorotannins found in seaweed provides a multifaceted defense against cardiovascular diseases [90]. These compounds work in tandem to bolster the body's natural defense mechanisms, fortifying cells and tissues against the harmful effects of oxidative stress and inflammation [91]. Additionally, consuming seaweed as part of a balanced diet has been associated with improved lipid profiles, reduced blood pressure, and enhanced vascular health. Incorporating seaweed into one's dietary regimen can thus be a prudent strategy for promoting cardiovascular well-being and mitigating the risk of heart-related ailments. As research in this area continues to unfold, harnessing the potential of seaweed polyphenolic compounds may hold great promise in preventing and managing cardiovascular diseases [92].

Certain seaweeds are natural reservoirs of crucial minerals, notably magnesium and potassium, paramount for optimal heart health. Potassium, a mineral abundantly found in seaweeds like Kelp (*Laminaria* and *Saccharina*), and Dulse (*Palmaria palmata*), is pivotal in regulating blood pressure levels. Its presence aids in counterbalancing the effects of sodium, helping to prevent hypertension—a major risk factor for cardiovascular diseases. Meanwhile, magnesium, another vital mineral prevalent in seaweeds, is crucial in sustaining a regular heart rhythm [93]. This mineral supports the electrical impulses that coordinate the heart's contractions, ensuring a steady and harmonious beat. Thus, the inclusion of seaweed in one's diet can serve as a natural means of

fortifying the body with these essential minerals, ultimately contributing to a healthy and resilient cardiovascular system [94].

Certain algal species include *Ulva lactuca* (Chlorophyta) and *Porphyra* spp. (Rhodophyta), boast a noteworthy attribute—they are rich sources of Omega-3 fatty acids, including eicosapentaenoic acid (EPA), renowned for their potent cardioprotective effects. EPA, a long-chain polyunsaturated fatty acid, has garnered recognition for supporting heart health by reducing inflammation, lowering triglyceride levels, and improving overall lipid profiles [95]. Found abundantly in algae such as Kelp and the green microalga *Chlorella vulgaris*, EPA offers a valuable alternative to traditional marine sources like fish for individuals seeking to enhance their cardiovascular well-being. Embracing these algal-derived omega-3 fatty acids as part of a balanced diet can play a pivotal role in safeguarding against cardiovascular diseases, underscoring the remarkable potential of algae as a nutritional powerhouse [96].

Specific compounds found in seaweed, such as fucoidan and carrageenan, exhibit remarkable potential in promoting cardiovascular health. These sulfated polysaccharides not only play a role in lowering total cholesterol levels, but they also possess anti-coagulant properties, potentially reducing the risk of blood clot formation and related cardiovascular events [97]. This dual action underscores the valuable contribution of seaweed-derived compounds like fucoidan and carrageenan in maintaining optimal cardiovascular function. However, it is crucial to emphasize that ongoing research highlights the importance of considering various factors. The specific health effects can vary depending on the type of seaweed, its preparation, and the individual's overall diet and health status. As our understanding of these complex interactions grows, harnessing the benefits of seaweed compounds may emerge as a promising avenue in pursuing cardiovascular well-being [98].

8. Conclusions and Future Perspectives

As NCD prevalence continues to rise across the globe, new strategies for their prevention are becoming popular. Diet is a very well-known but often overlooked risk factor for CVD, the deadliest group of non-communicable conditions. Seaweeds are an underexplored source of compounds with diverse applications that have been proven to act as valuable ingredients for functional food production.

While seaweed polysaccharides may have some positive health impacts, such as the ones mentioned in this review, further research is necessary before fully comprehending how cardiovascular disease pathophysiology can be affected by their addition to the diet.

Through the analysis of the presented studies, agar, alginate, and carrageenan were shown to have an overall positive impact on the regulation of metabolic parameters, leading us to believe in their efficacy in, to some extent, CVD prevention. Nevertheless, a significant limitation to understanding their true impact lies in the scarcity of specific studies on this matter. On the other hand, the studies discussed here have limitations such as lack of homogeneity, study design, and volunteer compliance. For example, most of the studies done with carrageenan only evaluate its hypolipidemic potential, while many other factors are equally relevant, such as high blood pressure and hyperglycemia. On the contrary, studies using alginate mainly focus on its hypoglycemic potential. Lastly, specific studies on agar are generally scant, as most studies on the databases concentrate on assessing the potential of whole red algae for these purposes.

In the future, regulatory considerations, standardization of extraction and supplementation techniques, and extensive trials are required to establish their effectiveness, safety, and usefulness in the prevention and treatment of CVD.

Author Contributions

AV: Conceptualization, Writing-review, Validation. PP: Conceptualization, Writing-original draft. AC: Writing-review, Validation. LP: Writing-review & editing, Supervision. All authors read and approved the submitted version.

Funding

This work was financed by national funds through the FCT—Foundation for Science and Technology, I.P., within the scope of the project LA/P/0069/2020 granted to the Associate Laboratory ARNET, UIDB/04292/2020 granted to MARE—Marine and Environmental Sciences Centre.

Competing Interests

The authors have declared that no competing interests exist.

References

1. WHO. Communicable and noncommunicable diseases, and mental health [Internet]. Geneva: WHO; 2022 [cited date 2022 November 18]. Available from: https://www.who.int/our-work/communicable-and-noncommunicable-diseases-and-mental-health.
2. Tsao CW, Aday AW, Almarzooq ZI, Anderson CA, Arora P, Avery CL, et al. Heart disease and stroke statistics—2023 update: A report from the American Heart Association. Circulation. 2023; 147: e93-e621.
3. Liang B, Cai XY, Gu N. Marine natural products and coronary artery disease. Front Cardiovasc Med. 2021; 8: 739932.
4. Wan-Loy C, Siew-Moi P. Marine algae as a potential source for anti-obesity agents. Mar Drugs. 2016; 14: 222.
5. Sharifi-Rad J, Rodrigues CF, Sharopov F, Docea AO, Can Karaca A, Sharifi-Rad M, et al. Diet, lifestyle and cardiovascular diseases: Linking pathophysiology to cardioprotective effects of natural bioactive compounds. Int J Environ Res Public Health. 2020; 17: 2326.
6. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.
7. Martínez-González MÁ, Corella D, Salas-salvadó J, Ros E, Covas MI, Fiol M, et al. Cohort profile: Design and methods of the PREDIMED study. Int J Epidemiol. 2012; 41: 377-385.
8. Kishida R, Yamagishi K, Muraki I, Sata M, Tamakoshi A, Iso H, et al. Frequency of seaweed intake and its association with cardiovascular disease mortality: The JACC Study. J Atheroscler Thromb. 2020; 27: 1340-1347.

9. Murai U, Yamagishi K, Sata M, Kokubo Y, Saito I, Yatsuya H, et al. Seaweed intake and risk of cardiovascular disease: The Japan Public Health Center-based Prospective (JPHC) Study. Am J Clin Nutr. 2019; 110: 1449-1455.
10. Lin J, Jiao G, Kermanshahi-Pour A. Algal polysaccharides-based hydrogels: Extraction, synthesis, characterization, and applications. Mar Drugs. 2022; 20: 306.
11. Pangestuti R, Kim SK. Chapter 19—An overview of phycocolloids: The principal commercial seaweed extracts. In: Marine algae extracts: Processes, products, and applications. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2015. pp. 319-330.
12. Pereira L. Characterization of bioactive components in edible algae. Mar Drugs. 2020; 18: 65.
13. Collins KG, Fitzgerald GF, Stanton C, Ross RP. Looking beyond the terrestrial: The potential of seaweed derived bioactives to treat non-communicable diseases. Mar Drugs. 2016; 14: 60.
14. Li Y, Qin J, Cheng Y, Lv D, Li M, Qi Y, et al. Marine sulfated polysaccharides: Preventive and therapeutic effects on metabolic syndrome: A review. Mar Drugs. 2021; 19: 608.
15. Lau K, Srivatsav V, Rizwan A, Nashed A, Liu R, Shen R, et al. Bridging the gap between gut microbial dysbiosis and cardiovascular diseases. Nutrients. 2017; 9: 859.
16. Peñalver R, Lorenzo JM, Ros G, Amarowicz R, Pateiro M, Nieto G. Seaweeds as a functional ingredient for a healthy diet. Mar Drugs. 2020; 18: 301.
17. Temple NJ. A rational definition for functional foods: A perspective. Front Nutr. 2022; 9: 957516.
18. European Union. Regulation (EU) No 1169/2011 of the European Parliament and of the Council. Luxembourg: European Union; 2011; No 1169/2011.
19. Crowe FL, Key TJ, Appleby PN, Overvad K, Schmidt EB, Egeberg R, et al. Dietary fibre intake and ischaemic heart disease mortality: The European prospective investigation into cancer and nutrition-heart study. Eur J Clin Nutr. 2012; 66: 950-956.
20. Adamberg K, Kolk K, Jaagura M, Vilu R, Adamberg S. The composition and metabolism of faecal microbiota is specifically modulated by different dietary polysaccharides and mucin: An isothermal microcalorimetry study. Benef Microbes. 2018; 9: 21-34.
21. Erdogan A, Rao SS, Thiruvaiyaru D, Lee YY, Coss Adame E, Valestin J, et al. Randomised clinical trial: Mixed soluble/insoluble fibre vs. psyllium for chronic constipation. Aliment Pharmacol Ther. 2016; 44: 35-44.
22. Arshad MU, Ishtiaq S, Anjum FM, Saeed F, Chatha SA, Imran A. Acute effects of different dietary polysaccharides added in milk on food intake, postprandial appetite and glycemic responses in healthy young females. Int J Food Sci Nutr. 2016; 67: 715-722.
23. Paxman JR, Richardson JC, Dettmar PW, Corfe BM. Alginate reduces the increased uptake of cholesterol and glucose in overweight male subjects: A pilot study. Nutr Res. 2008; 28: 501-505.
24. Valado A, Pereira M, Amaral M, Cotas J, Pereira L. Bioactivity of carrageenans in metabolic syndrome and cardiovascular diseases. Nutraceuticals. 2022; 2: 441-454.
25. Goff HD, Repin N, Fabek H, El Khoury D, Gidley MJ. Dietary fibre for glycaemia control: Towards a mechanistic understanding. Bioact Carbohydr Diet Fibre. 2018; 14: 39-53.
26. Stephen AM, Champ MM, Cloran SJ, Fleith M, Van Lieshout L, Mejborn H, et al. Dietary fibre in Europe: Current state of knowledge on definitions, sources, recommendations, intakes and relationships to health. Nutr Res Rev. 2017; 30: 149-190.
27. Scientific Advisory Committee on Nutrition. Carbohydrates and health report. London: Scientific Advisory Committee on Nutrition; 2015.
28. Matsumura Y. Nutrition trends in Japan. Asia Pac J Clin Nutr. 2001; 10: S40-S47.

29. Iso H, Date C, Noda H, Yoshimura T, Tamakoshi A, Mori M, et al. Frequency of food intake and estimated nutrient intake among men and women: The JACC Study. J Epidemiol. 2005; 15: S24-S42.
30. Chazelas E, Debras C, Srour B, Fezeu LK, Julia C, Hercberg S, et al. Sugary drinks, artificially-sweetened beverages, and cardiovascular disease in the NutriNet-Santé cohort. J Am Coll Cardiol. 2020; 76: 2175-2177.
31. Chlebowski RT, Aragaki AK, Anderson GL, Pan K, Neuhouser ML, Manson JE, et al. Dietary modification and breast cancer mortality: Long-term follow-up of the Women's Health Initiative randomized trial. J Clin Oncol. 2020; 38: 1419-1428.
32. Odermatt A. The western-style diet: A major risk factor for impaired kidney function and chronic kidney disease. Am J Physiol Renal Physiol. 2011; 301: 919-931.
33. Gómez-Ordóñez E, Jiménez-Escrig A, Rupérez P. Dietary fibre and physicochemical properties of several edible seaweeds from the northwestern Spanish coast. Food Res Int. 2010; 43: 2289-2294.
34. Agostoni CV, Bresson JL, Fairweather Tait S, Flynn A, Golly I, Korhonen H, et al. Scientific opinion on dietary reference values for carbohydrates and dietary fibre. EFSA J. 2010; 8: 1462.
35. Kılınç B, Cirik S, Turan G, Tekogul H, Koru E. Seaweeds for food and industrial applications. In: Food industry. London: IntechOpen; 2013. pp. 475-482.
36. Bizzaro G, Vatland AK, Pampanin DM. The one-health approach in seaweed food production. Environ Int. 2022; 158: 106948.
37. Holdt SL, Kraan S. Bioactive compounds in seaweed: Functional food applications and legislation. J Appl Phycol. 2011; 23: 543-597.
38. Lu LW, Chen JH. Seaweeds as ingredients to lower glycemic potency of cereal foods synergistically—A perspective. Foods. 2022; 11: 714.
39. Guo J, Shi F, Sun M, Ma F, Li Y. Antioxidant and aflatoxin B1 adsorption properties of Eucheuma cottonii insoluble dietary fiber. Food Biosci. 2022; 50: 102043.
40. Matanjun P, Mohamed S, Mustapha NM, Muhammad K. Nutrient content of tropical edible seaweeds, Eucheuma cottonii, Caulerpa lentillifera and Sargassum polycystum. J Appl Phycol. 2009; 21: 75-80.
41. Bocanegra A, Macho-González A, Garcimartín A, Benedí J, Sánchez-Muniz FJ. Whole alga, algal extracts, and compounds as ingredients of functional foods: Composition and action mechanism relationships in the prevention and treatment of type-2 diabetes mellitus. Int J Mol Sci. 2021; 22: 3816.
42. Williams P, Phillips G. Introduction to food hydrocolloids. In: Handbook of hydrocolloids. 2nd ed. Sawston: Woodhead Publishing Limited; 2009. pp. 1-22.
43. Hotchkiss S. Food texture and nutrition: The changing roles of hydrocolloids and food fibers [Internet]. Urbana, IL: AOCS Headquarters; 2015 [cited date 2023 June 11]. Available from: https://www.aocs.org/stay-informed/inform-magazine/featured-articles/food-texture-and-nutrition-the-changing-roles-of-hydrocolloids-and-food-fibers-march-2015?SSO=True.
44. Cofrades S, Serdaroğlu M, Jiménez-Colmenero F. Design of healthier foods and beverages containing whole algae. In: Functional ingredients from algae for foods and nutraceuticals. Sawston: Woodhead Publishing; 2013. pp. 609-633.

45. Boukid F, Castellari M. Food and beverages containing algae and derived ingredients launched in the market from 2015 to 2019: A front-of-pack labeling perspective with a special focus on Spain. Foods. 2021; 10: 173.
46. Qiu X, Zhong W. Antihyperglycemic and antihyperlipidemic effects of low-molecular-weight carrageenan in rats. Open Life Sci. 2018; 13: 379-384.
47. Valado A, Pereira M, Caseiro A, Figueiredo JP, Loureiro H, Almeida C, et al. Effect of carrageenans on vegetable jelly in humans with hypercholesterolemia. Mar Drugs. 2020; 18: 19.
48. Ren D, Noda H, Amano H, Nishino T, Nishizawa K. Study on antihypertensive and antihyperlipidemic effects of marine algae. Fish Sci. 1994; 60: 83-88.
49. U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21 [Internet]. Silver Spring, MD: U.S. Food and Drug Administration; 2023 [cited date 2023 June 12]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=172.620.
50. Younes M, Aggett P, Aguilar F, Crebelli R, Filipič M, Frutos MJ, et al. Re-evaluation of carrageenan (E 407) and processed Eucheuma seaweed (E 407a) as food additives. EFSA J. 2018; 16: e05238.
51. Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Frutos MJ, Galtier P, et al. Re-evaluation of agar (E 406) as a food additive. EFSA J. 2016; 14: e04645.
52. Younes M, Aggett P, Aguilar F, Crebelli R, Filipič M, Frutos MJ, et al. Re-evaluation of alginic acid and its sodium, potassium, ammonium and calcium salts (E 400–E 404) as food additives. EFSA J. 2017; 15: e05049.
53. Jayakody MM, Vanniarachchy MP, Wijesekara I. Seaweed derived alginate, agar, and carrageenan based edible coatings and films for the food industry: A review. J Food Meas Charact. 2022; 16: 1195-1227.
54. Ścieszka S, Klewicka E. Algae in food: A general review. Crit Rev Food Sci Nutr. 2019; 59: 3538-3547.
55. Quitério E, Soares C, Ferraz R, Delerue-Matos C, Grosso C. Marine health-promoting compounds: Recent trends for their characterization and human applications. Foods. 2021; 10: 3100.
56. Franssen R, Monajemi H, Stroes ES, Kastelein JJ. Obesity and dyslipidemia. Med Clin North Am. 2011; 95: 893-902.
57. Frąk W, Wojtasińska A, Lisińska W, Młynarska E, Franczyk B, Rysz J. Pathophysiology of cardiovascular diseases: New insights into molecular mechanisms of atherosclerosis, arterial hypertension, and coronary artery disease. Biomedicines. 2022; 10: 1938.
58. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic syndrome: Updates on pathophysiology and management in 2021. Int J Mol Sci. 2022; 23: 786.
59. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol. 2018; 17: 122.
60. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961; 55: 33-50.
61. Jung HA, Hyun SK, Kim HR, Choi JS. Angiotensin-converting enzyme I inhibitory activity of phlorotannins from *Ecklonia stolonifera*. Fish Sci. 2006; 72: 1292-1299.
62. Mendis E, Kim SK. Present and future prospects of seaweeds in developing functional foods. Adv Food Nutr Res. 2011; 64: 1-15.

63. Teas J, Baldeón ME, Chiriboga DE, Davis JR, Sarriés AJ, Braverman LE. Could dietary seaweed reverse the metabolic syndrome? Asia Pac J Clin Nutr. 2009; 18: 145-154.
64. Rajapakse N, Kim SK. Nutritional and digestive health benefits of seaweed. Adv Food Nutr Res. 2011; 64: 17-28.
65. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: A meta-analysis. Am J Clin Nutr. 1999; 69: 30-42.
66. El Khoury D, Goff HD, Berengut S, Kubant R, Anderson GH. Effect of sodium alginate addition to chocolate milk on glycemia, insulin, appetite and food intake in healthy adult men. Eur J Clin Nutr. 2014; 68: 613-618.
67. Erkkilä AT, Lichtenstein AH. Fiber and cardiovascular disease risk: How strong is the evidence? J Cardiovasc Nurs. 2006; 21: 3-8.
68. Gunness P, Gidley MJ. Mechanisms underlying the cholesterol-lowering properties of soluble dietary fibre polysaccharides. Food Funct. 2010; 1: 149-155.
69. Chin YX, Mi Y, Cao WX, Lim PE, Xue CH, Tang QJ. A pilot study on anti-obesity mechanisms of *Kappaphycus alvarezii*: The role of native κ-carrageenan and the leftover sans-carrageenan fraction. Nutrients. 2019; 11: 1133.
70. Sokolova EV, Bogdanovich LN, Ivanova TB, Byankina AO, Kryzhanovskiy SP, Yermak IM. Effect of carrageenan food supplement on patients with cardiovascular disease results in normalization of lipid profile and moderate modulation of immunity system markers. PharmaNutrition. 2014; 2: 33-37.
71. Panlasigui LN, Baello OQ, Dimatangal JM, Dumelod BD. Blood cholesterol and lipid-lowering effects of carrageenan on human volunteers. Asia Pac J Clin Nutr. 2003; 12: 209-214.
72. Kimura Y, Watanabe K, Okuda H. Effects of soluble sodium alginate on cholesterol excretion and glucose tolerance in rats. J Ethnopharmacol. 1996; 54: 47-54.
73. Wang X, Liu F, Gao Y, Xue CH, Li RW, Tang QJ. Transcriptome analysis revealed anti-obesity effects of the Sodium Alginate in high-fat diet-induced obese mice. Int J Biol Macromol. 2018; 115: 861-870.
74. Harden CJ, Craig Richardson J, Dettmar PW, Corfe BM, Paxman JR. An ionic-gelling alginate drink attenuates postprandial glycaemia in males. J Funct Foods. 2012; 4: 122-128.
75. Jensen MG, Kristensen M, Astrup A. Effect of alginate supplementation on weight loss in obese subjects completing a 12-wk energy-restricted diet: A randomized controlled trial. Am J Clin Nutr. 2012; 96: 5-13.
76. Kelley JJ, Tsai AC. Effect of pectin, gum arabic and agar on cholesterol absorption, synthesis, and turnover in rats. J Nutr. 1978; 108: 630-639.
77. Lee MR, Kim JE, Jin YJ, Roh YJ, Seol A, Song HJ, et al. Anti-obesity effects of agar (*Gelidium amansii*)-derived oligosaccharides in high-fat diet-treated C57BL/6N mice due to differential regulations of lipogenesis and lipolysis. Biosci Biotechnol Biochem. 2022; 86: 1648-1657.
78. Maeda H, Yamamoto R, Hirao K, Tochikubo O. Effects of agar (*kanten*) diet on obese patients with impaired glucose tolerance and type 2 diabetes. Diabetes Obes Metab. 2005; 7: 40-46.
79. Sanaka M, Yamamoto T, Anjiki H, Nagasawa K, Kuyama Y. Effects of agar and pectin on gastric emptying and post-prandial glycaemic profiles in healthy human volunteers. Clin Exp Pharmacol Physiol. 2007; 34: 1151-1155.
80. Clegg ME, Shafat A. The effect of agar jelly on energy expenditure, appetite, gastric emptying and glycaemic response. Eur J Nutr. 2014; 53: 533-539.

81. Myhrstad MC, Tunsjø H, Charnock C, Telle-Hansen VH. Dietary fiber, gut microbiota, and metabolic regulation—Current status in human randomized trials. Nutrients. 2020; 12: 859.
82. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. Appl Environ Microbiol. 2007; 73: 1073-1078.
83. Charoensiddhi S, Abraham RE, Su P, Zhang W. Seaweed and seaweed-derived metabolites as prebiotics. Adv Food Nutr Res. 2019; 91: 97-156.
84. Chen Y, Xu C, Huang R, Song J, Li D, Xia M. Butyrate from pectin fermentation inhibits intestinal cholesterol absorption and attenuates atherosclerosis in apolipoprotein E-deficient mice. J Nutr Biochem. 2018; 56: 175-182.
85. Rahman MM, Islam F, Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. Front Cell Infect Microbiol. 2022; 12: 903570.
86. Lomartire S, Gonçalves AM. Marine macroalgae polyphenols as potential neuroprotective antioxidants in neurodegenerative diseases. Mar Drugs. 2023; 21: 261.
87. Pereira L, Cotas J. Therapeutic potential of polyphenols and other micronutrients of marine origin. Mar Drugs. 2023; 21: 323.
88. Zheng H, Zhao Y, Guo L. A bioactive substance derived from brown seaweeds: Phlorotannins. Mar Drugs. 2022; 20: 742.
89. Yamagata K. Prevention of cardiovascular disease through modulation of endothelial cell function by dietary seaweed intake. Phytomed Plus. 2021; 1: 100026.
90. Ilyas Z, Ali Redha A, Wu YS, Ozeer FZ, Aluko RE. Nutritional and health benefits of the brown seaweed *Himanthalia elongata*. Plant Foods Hum Nutr. 2023; 78: 233-242.
91. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. Arch Toxicol. 2023; 97: 2499-2574.
92. Xu J, Liao W, Liu Y, Guo Y, Jiang S, Zhao C. An overview on the nutritional and bioactive components of green seaweeds. Food Prod Process Nutr. 2023; 5: 18.
93. Mišurcová L, Machů L, Orsavová J. Seaweed minerals as nutraceuticals. Adv Food Nutr Res. 2011; 64: 371-390.
94. Circuncisão AR, Catarino MD, Cardoso SM, Silva AM. Minerals from macroalgae origin: Health benefits and risks for consumers. Mar Drugs. 2018; 16: 400.
95. El-Beltagi HS, Mohamed AA, Mohamed HI, Ramadan KM, Barqawi AA, Mansour AT. Phytochemical and potential properties of seaweeds and their recent applications: A review. Mar Drugs. 2022; 20: 342.
96. Wu JY, Tso R, Teo HS, Haldar S. The utility of algae as sources of high value nutritional ingredients, particularly for alternative/complementary proteins to improve human health. Front Nutr. 2023; 10: 1277343.
97. Patel S. Therapeutic importance of sulfated polysaccharides from seaweeds: Updating the recent findings. 3 Biotech. 2012; 2: 171-185.
98. Oliyaei N, Moosavi-Nasab M, Mazloomi SM. Therapeutic activity of fucoidan and carrageenan as marine algal poly