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Review

Therapeutic Potential of Seaweed-Derived Bioactive Compounds for Cardiovascular Disease Treatment

Chi-Heung Cho [1,†], Yu-An Lu [2,†], Ming-Yeong Kim [1,3], You-Jin Jeon [2,4] and Sang-Hoon Lee [1,3,*]

[1] Korea Food Research Institute, 245 Nongsaengmyeong-ro, Iseo-myeon, Wanju-gun 55365, Korea; Chiheugncho@kfri.re.kr (C.-H.C.); 50034@kfri.re.kr (M.-Y.K.)
[2] Department of Marine Life Science, Jeju National University, Jeju 63243, Korea; annie.lu1213@gmail.com (Y.-A.L.); youjinj@jejunu.ac.kr (Y.-J.J.)
[3] Department of Food Biotechnology, Korea University of Science and Technology, 217 Gajeong-ro, Yuseong-gu, Daejeon 34113, Korea
[4] Marine Science Institute, Jeju National University, Jeju 63333, Korea
* Correspondence: shnlee@kfri.re.kr; Tel.: +82-063-219-9357
† These authors contributed equally to this work.

Abstract: Cardiovascular diseases are closely related to hypertension, type 2 diabetes mellitus, obesity, and hyperlipidemia. Many studies have reported that an unhealthy diet and sedentary lifestyle are critical factors that enhance these diseases. Recently, many bioactive compounds isolated from marine seaweeds have been studied for their benefits in improving human health. In particular, several unique bioactive metabolites such as polyphenols, polysaccharides, peptides, carotene, and sterol are the most effective components responsible for these activities. This review summarizes the current in vitro, in vivo, and clinical studies related to the protective effects of bioactive compounds isolated from seaweeds against cardiovascular disorders, including anti-diabetic, anti-hypertensive, anti-hyperlipidemia, and anti-obesity effects. Therefore, this present review summarizes these concepts and provides a basis for further in-depth research.

Keywords: seaweed; phlorotannin; polysaccharide; metabolic disease; cardiovascular disease

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1. Introduction

Cardiovascular disease (CVD) is known as the primary cause of death globally, and it is estimated that approximately 17.7 million people die from CVD, accounting for 31% of global deaths. In recent decades, the increasing prevalence of CVD has deteriorated children's and adults' physical and mental health, affecting their quality of life [1]. The main risk factors linked to CVD are hypertension (HTN), elevated blood low-density cholesterol, type 2 diabetes mellitus (T2DM), endothelial dysfunction, overweightness or obesity, high triglyceride levels, and dietary patterns [2].

Previous evidence has shown that hyperinsulinemia and obesity increase sympathetic nerve traffic, promoting salt reabsorption in the renal tubules and activating the renin–angiotensin system (RAS) [3,4]. Additionally, endothelial dysfunction and vascular oxidative stress were observed in the development of obesity. These reactions would amplify the reactive oxygen species (ROS), decrease the availability of nitric oxide (NO), and further affect the vascular tone [5,6]. The progression of the pathophysiological mechanisms of HTN and obesity-related T2DM are closely connected. Thus, it is necessary to find effective treatments to reduce risks and help decrease the epidemic levels of cardiovascular-related deaths.

Currently, multiple biological mechanisms underlying CVDs have been confirmed, providing evidence for the direct development of pharmacological tools and treatments. The most common medical treatments include calcium channel blockers, diuretics, and inhibitors of angiotensin-converting enzyme (ACE). ACE, which is a metalloproteinase,

a strong vasoconstrictor implicated in the pathophysiology of hypertension, is important in regulating blood pressure by catalyzing the conversion of angiotensin I to angiotensin II [7,8]. As a result, the inhibition of ACE activity has become a prominent target for HTN management. Conversely, in vitro, the biochemical pathways between vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) are vital and are involved in regulating the vascular tone [9]. Therefore, we reviewed numerous in vitro and in vivo studies to summarize the newest therapeutic strategies.

The growing interest in natural products to promote human health has resulted in seaweeds becoming popular due to their high bioactive compound contents, especially those exhibiting effects related to cardiovascular protection and metabolism regulation. Because of their high nutritional value, seaweeds have been traditionally consumed as a healthy food in many Asian countries since ancient times [10]. Brown seaweeds (Ochrophyta), red seaweeds (Rhodophyta), and green seaweeds (Chlorophyta) are the three primary classifications or species of seaweeds [11,12]. Different types of brown seaweeds, such as *Undaria*, *Laminaria*, *Gim*, and *Hiziki* have been used in traditional Asian meals for a long time. They contain low levels of lipids and high levels of polysaccharides, fibers, and polyunsaturated fatty acids (PUFAs), which are considered high-quality nutritional components for food preparation. The consumption of seaweed in western countries is relatively low compared with Asian countries because of their food habits. However, over the last few decades, interest in seaweeds has gradually increased because of their various properties as food ingredients and the identification of their invaluable health effects [13]. Due to its chemical diversity and unique components, seaweed has been of interest in many studies and is widely used in the medical, nutraceutical, and cosmetic industries. The primary seaweed metabolites include proteins, polysaccharides, and lipids, whereas secondary metabolites contain phenolic compounds, halogenated compounds, sterols, terpenes, and small peptides among other bioactive compounds produced in seaweed tissues [12,14]. Seaweed not only contains various primary and secondary metabolites but can also be used as a latent material for bioactive oligopeptides and oligosaccharides via bioconversion processes such as fermentation and enzyme hydrolysis [15]. These bioactive substances derived from seaweeds have numerous therapeutic roles in metabolic disease prevention, with functional properties such as anti-oxidant, anti-bacterial, anti-cancer, anti-diabetic, anti-tumor, anti-inflammatory, and cardiovascular protection activities. Recent studies have reported evidence of their effects on human health, and mechanisms of biological activity have been reported [13]. Seaweeds are photosynthetic eukaryotes that possess simple reproductive structures with diverse forms and sizes. Seaweeds exhibit rapid adaptabilities to survive due to the complex ocean environment, such as changes in salinity, temperature variations, nutrient-deficient habitats, and UV irradiation, which are attributed to their bioactive secondary metabolites which cannot be found in other terrestrial organisms [16]. In addition to its bioactive properties, other important advantages are their easy cultivation, rapid growth, and availability to produce high value-added bioactive compounds by manipulating environmental conditions, as well as through gene modification and mutagenesis.

Based on these viewpoints, we reviewed the available data from animal studies and clinical trials regarding the pathophysiological mechanisms under bioactive compound treatment and the links between cardiovascular and metabolic disorders (Figure 1). Despite numerous efforts to improve the industrial use of bioactive seaweed compounds to prevent CVD, there have been many limitations. The nutraceutical industry demands more rigorous quality, standardization of components, and a clearer bioactivity mechanism than previously provided for seaweeds. To overcome this problem, it is necessary to secure information on the characteristics and diversity of seaweed's bioactive substances and systematically understand their overall biological activities in the metabolic disorders closely related to CVD. We believe this review can provide useful insights and open up great potential for many research groups considering the huge interest regarding seaweed's bioactive compounds in the prevention of CVD.

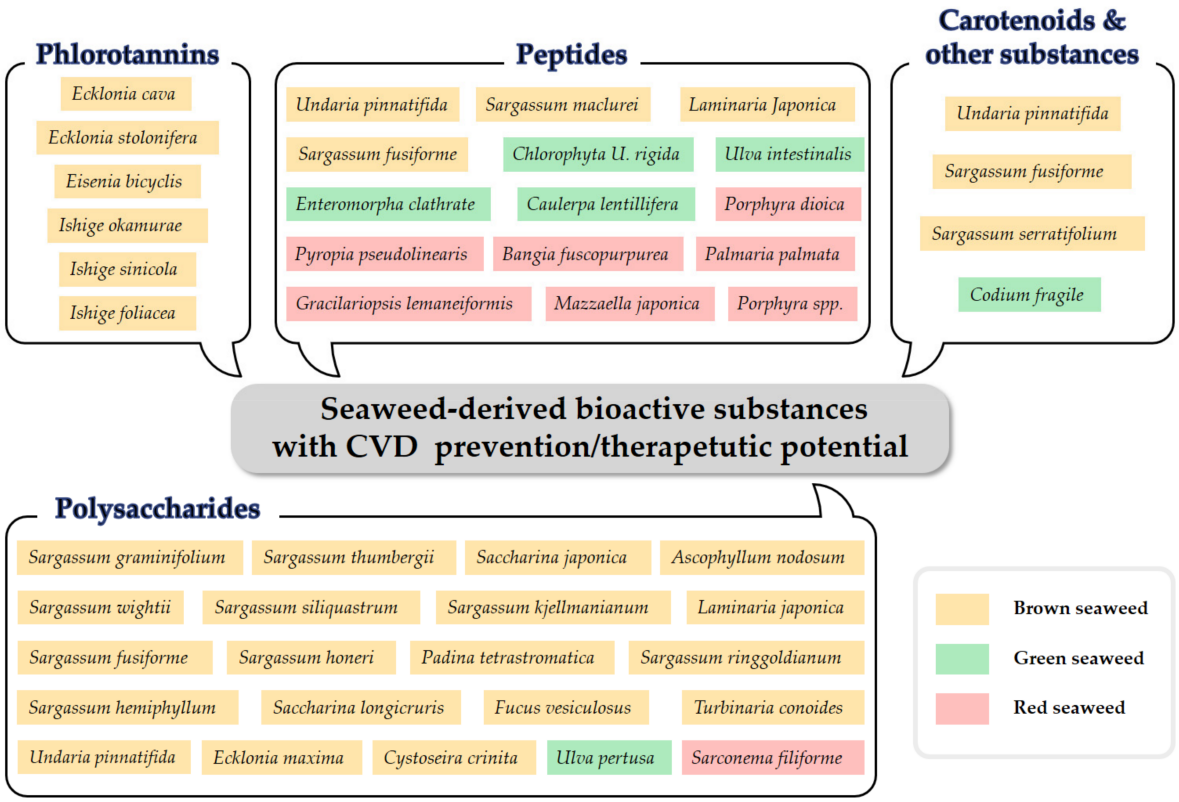

Figure 1. The preventive potential of various seaweed-derived natural components associated with cardiovascular disease (CVD) pathogenesis, such as diabetes mellitus, obesity, hypertension, and hyperlipidemia.

2. Seaweed-Derived Phlorotannins with Therapeutic Potential against CVD

Phlorotannins are polyphenol molecules generated as secondary metabolites by seaweed and consist of polymerization of phloroglucinol (1,3,5-tryhydroxybenzene) monomer units, which are biosynthesized via the acetate-malonate pathway, also known as the polyketide pathway [17]. In particular, some phlorotannins can be found exclusively in brown seaweeds, such as *Ecklonia* species [18]. Phlorotannins can be classified into four subclasses according to the type of linkage between the phloroglucinol units. Fuhalols and phlorethols, as well as phloroglucinol units, are linked by aryl ether bonds. Fucols are composed of phloroglucinol units linked with aryl-aryl bonds. Fucophloroethols are linked to ether and phenyl bonds. Eckols and carmalols are characterized by the presence of dibenzodioxin units and differ from carmalol in that they generally have a lower molecular weight and a phenoxyl moiety at C4 [19,20]. Many researchers have revealed various beneficial biological activities of phlorotannins (mainly brown seaweed such as *Ecklonia* and *Ishige* species), including anti-oxidant, anti-cancer, anti-bacterial, anti-allergic, anti-mutagenic, anti-diabetic, anti-inflammatiory, anti-proliferatiive, anti-hypertensive, and anti-obesity effects [18,21–24]. Therefore, phlorotannins have been recognized for many years as promising bioactive compounds with health benefits for preventing and treating various human diseases.

Hypertension is known as a major risk factor for cardiovascular disease (CVD). Normally, the anti-hypertensive ability is determined as the IC_{50} value, which represents the angiotensin-converting enzyme (ACE) inhibitor concentration causing 50% inhibition of ACE activity. Captopril, a well-known ACE inhibitor, exhibits competitive inhibition [25]. Additionally, several previous studies have confirmed that phlorotannins such as eckol [26,27], dieckol [26,27], 6,6′-bieckol [28], phloroglucinol [26,27], phlorofucofuroeckol A [27], triphlorethol-A [26,27], eckstolonol [26,27], fucosterol [27], and octaphlorethol A [29], isolated from *Ecklonia cava*, *Ecklonia stolonifera*, and *Ishige foliacea*, showed non-competitive

ACE inhibition (Table 1). These phlorotannins demonstrated ACE inhibitory activity similar to or even higher than that of captopril.

In addition to ACE inhibition, vasodilators also contribute greatly to the anti-hypertensive properties. NO is a well-known vessel-relaxing factor produced from L-arginine by endothelial nitric oxide synthase (eNOS) in the presence of oxygen and the cofactors Ca^{2+} and calmodulin (CaM) [30]. A previous study has indicated that genetically deficient eNOS mice are hypertensive with lower circulating NO levels, thus indicating the critical role of eNOS and NO in CVD [5,9]. It has also been reported that multiple mechanisms control NO production via eNOS activation [31].

The phosphatidylinositol 3-kinase (PI3K) pathway members, including their downstream molecule, protein kinase B (Akt), are essential regulators. Activated Akt would directly phosphorylate ser1177 on eNOS, enhancing the $[Ca^{2+}]$/CaM complex [32]. Second, the concentration of intracellular Ca^{2+} ($[Ca^{2+}]_i$) in ECs and VSMCs is closely related to the vascular tone and influences blood pressure [33]. Third, the L-type calcium channel is one of the critical ion channels that regulates vasoconstriction and vasodilation. Nitrodilators promote vasodilation by increasing soluble guanylyl cyclase (cGMP) and decreasing the $[Ca^{2+}]_i$ levels in VSMCs. These actions would reduce the phosphorylation of the Ca^{2+}-sensitive myosin light chains, resulting in vasodilation [34]. One study demonstrated that Lu et al. used the EA.hy926 cells and zebrafish model to systematically establish the potential mechanisms of the vasodilation produced by diekol and diphlorethohydroxycarmalol isolated from *Ecklonia cava* (*E. cava*) and *Ishige okamurae* (I. okamurae) [35,36] (Table 1). In addition, four major phlorotannins—dieckol, 2,7-phloroglucinol-6,6-bieckol, phlorofucofuroeckol A, and pyrogallol-phloroglucinol-6,6-bieckol—isolated from *Ecklonia cava* effectively inhibited monocyte-associated vascular inflammation and dysfunction by suppressing monocyte migration and protecting monocyte-associated endothelial cell death [37]. Moreover, pyrogallol-phloroglucinol-6,6′-bieckol and dieckol isolated from *E. Cava* have been shown to improve blood circulation in mice fed diets to induce obesity and hypertension [36,38]. Therefore, while numerous factors contribute to hypertension, it is well recognized that an increased vascular tone is always the ultimate goal.

The evidence mentioned above has great pharmaceutical potential, with some already being used in the clinical trial phase. Clinical studies have shown cardiovascular protection, supporting the benefits of polyphenols extracted from land plants [39]. Nevertheless, only a few epidemiological studies have discussed the association between the consumption of specific components of seaweed and blood pressure. Despite investigating the benefits of single compounds from seaweed, the general components, including minerals, fiber, and peptides, were more popular in clinical trials. This might be because high doses of these compounds have comparatively low side effects. A case control study demonstrated the anti-hypertensive effect of *Undaria pinnatifida* powder (5 g/capsule/day) by significantly reducing blood pressure in elderly Japanese patients following 8 weeks of administration [40]. However, Murray et al. reported that no reduction in blood pressure occurred in healthy adults who were administered the *Fucus vesiculosus* extract [41]. As mentioned above, several phlorotannins have been confirmed to possess effects against hypertension by ACE inhibition, calcium regulation, antagonism of L-type calcium channels, or activation of the critical pathway (PI3K/Akt/eNOS). Despite these mechanisms being verified, many other physiological signaling pathways in vascular regulation remain unclear. It will be helpful to explore the cardiovascular protection or anti-hypertension properties of phlorotannin via its use as a potassium channel opener and angiotensin receptor blocker.

Diabetes mellitus (DM) is a prime risk factor for dramatically increasing CVD, contributing to more than 3 million cardiovascular deaths worldwide each year [42]. Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder involving insulin resistance, impaired insulin signaling and β-cell dysfunction, and abnormal glucose and lipid metabolism. Hyperglycemia is the most important criterion for all types of diabetes and is the cause of diabetic complications such as CVD. Therefore, it is important to prevent or delay the onset of diabetes by controlling blood glucose levels in diabetic patients, as hyperglycemia

increases the risk of developing CVD long before clinical diabetes begins [43]. In humans, α-glucosidase and α-amylase in the small intestine play an important role in the digesting dietary carbohydrates into glucose. Therefore, reducing postprandial hyperglycemia by delaying the absorption of glucose in the body through the inhibition of α-amylase and α-glucosidase is an important approach for treating T2DM [44,45]. The enzyme inhibitors used for this action suppress the digestion of carbohydrates and consequently slow the postprandial plasma glucose rise, thereby delaying the rate of glucose absorption [46]. The inhibition of starch-digesting enzymes using synthetic drugs exhibiting antidiabetic effects with α-glucosidase inhibitory properties, such as acarbose, voglibose, miglitol, and emiglitate, is an important clinical strategy for controlling postprandial hyperglycemia. However, these synthetic drugs have been reported to effectively lower postprandial blood glucose levels but cause serious side effects, such as liver disorders [45,47]. The use of enzyme inhibitors derived from natural products (terrestrial plants or seaweeds) with a lower risk of the potential side effects caused by synthetic enzyme inhibitors is recommended. Therefore, to avoid or reduce the side effects caused by currently used synthetase inhibitors, the use of enzyme inhibitors (α-amylase and α-glucosidase) from natural products is considered the best alternative. It has been reported that minor phlorotannin derivatives such as eckol, 2-phloroeckol, 8,8′-bieckol, 6,8′-bieckol, and 2-O-(2,4,6-trihydroxyphenyl)-6,6′-bieckol isolated from *E. cava* showed α-glucosidase inhibitory activity, with an IC_{50} value ranging from 2.3 to 59.8 μM (Table 1). Among the minor phlorotannin derivatives, 8,8′-bieckol and 6,8′-bieckol exhibited the strongest α-glucosidase inhibitory activity. In addition, molecular docking studies revealed that both phlorotannins act as α-glucosidase inhibitors by competitive inhibition [48]. In addition, several researchers have found that phlorotannins such as fucodiphloroethol G, dieckol, 6,6′-bieckol, 7-phloroeckol, phlorofucofuroeckol A, and 2,7′-phloroglucinol-6,6′-bieckol isolated from *Ecklonia cava* have inhibitory activity against α-glucosidase and α-amylase [49–51]. Moon et al. revealed that phlorotannins, such as phloroglucinol, dioxinodehydroeckol, eckol, phlorofucofuroeckol-A, dieckol, and 7-phloroeckol isolated from Ecklonia stolinifera (E. stolinifera) have anti-diabetic effects by inhibiting α-glucosidase. In addition, it was confirmed that these phlorotannins effectively inhibit protein tyrosine phosphatase 1 B, an enzyme that plays an important role in the development of insulin resistance, thereby preventing a rapid increase in postprandial blood glucose levels [52]. In addition, diphlorethohydroxycarmalol (DPHC), ishophloroglucin A (IPA), and octaphlorethol A (OPA) were isolated from *I. okamurae* and *Ishige foliacea* (I. foliacea) from the Ishigeaceae family and showed α-glucosidase and α-amylase inhibitory activity [53,54]. In particular, oral administration of 100 mg/kg DPHC significantly suppressed the postprandial blood glucose levels in streptozotocin-induced diabetic mice [55]. According to Lee et al., molecular docking analysis revealed that OPA interacts with amino acid residues in the region close to the active site of α-glucosidase. Hence, OPA has the potential to be used as a non-competitive inhibitor with a high-affinity binding site for α-glucosidase [54].

Insulin resistance and impaired glucose metabolism are the most common factors promoting the development of type 2 diabetes mellitus. Type 2 diabetes mellitus is typically caused by two factors: impaired insulin production by pancreatic β cells and a failure of insulin-sensitive tissues to respond appropriately to insulin [56]. Signaling pathways involved in insulin secretion in β-cells under physiological conditions can be divided into a few stages. First, insulin release is primarily triggered by high glucose concentrations, mainly via glucose transporter 2 (GLUT2). When glucose catabolism is stimulated, intracellular ATP levels increase and close the cell membrane potassium channels, increasing intracellular Ca^{2+} concentrations and amplifying insulin secretion [57,58]. Furthermore, the AMP-activated protein kinase (AMPK) system simulates the effect of insulin on glucose transport in the muscle and glucose production in the liver. Because the AMPK system plays an important role in glucose homeostasis, it is a key target for discovering anti-diabetic agents [59]. Some evidence has demonstrated that 2,7″-phloroglucinol-6,6′-bieckol isolated from *E. cava* protects against high glucose-induced glucotoxicity and apoptotic cell death in

INS-1 cells [60] (Table 1). In addition, in C57BL/KsJ-db/db mice, the oral administration of 20 mg/kg dieckol isolated from *E. cava* significantly reduced blood glucose levels, serum insulin levels, and body weight [61]. Yang et al. demonstrated that oral administration of ishophloroglucin A (IPA) and oxtaphlorethol A (OPA) isolated from *I. okamurae* and *I. foliacea* significantly ameliorated glucose intolerance and the fasting glucose levels in high-fat diet (HFD)-fed mice, thereby reducing fasting and 2 h blood glucose levels, as well as stimulated GLUT4 in HFD mouse muscle [62,63]. Furthermore, phlorotannins such as DPHC and IPA isolated from *I. okamurae* treatment exhibited an anti-angiogenic effect by interfering with the VEGFR-2 signaling pathway [64,65]. These phlorotannin compounds isolated from various seaweeds exhibit anti-diabetic efficacy through various mechanisms in vivo and in vitro, demonstrating the potential as natural agents that can replace synthetic anti-diabetic treatments. Despite the evidence suggesting that type 2 diabetes mellitus might be caused by more complex molecular pathways implicated in cell biology, the main concepts of treatments still mainly focus on the pathway we mentioned above, and clinical trials using single compounds isolated from seaweeds have not been reported.

Despite its relatively simple definition, obesity, defined as excess body fat, is a complex condition resulting from a chronic positive energy balance when the dietary energy intake exceeds energy expenditure. Excess energy is converted to triglycerides and stored in adipose tissue depots, expanding in size, producing weight gain, and increasing body fat. The adipose tissue includes several types of cells, such as mature adipocytes, pre-adipocytes, fibroblasts, endothelial cells, and immune cells [66]. Adipose tissue undergoes dynamic histological changes as obesity progresses, including adipocyte enlargement, enhanced angiogenesis, immune cell infiltration, and extracellular matrix overproduction [67]. In contrast, adipocytes undergo differentiation, and specific proteins, including sterol regulatory element-binding protein 1 (SREBP1c), CCAAT/enhancer-binding protein (C/EBPα), and peroxisome proliferator-activated receptor γ (PPARγ) are involved in all processes [68,69]. Several lines of evidence indicate that the phlorotannins contained in seaweed such as *E. cava* (eckol, dieckol, triphlorethol-A, 6,6′-bieckol, and phlorofucoeckol A), *Ecklonia stolonifera* (phloroglucinol, eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol A), *Eisenia bicyclis* (6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, and dieckol, phlorofucofuroeckol A), and *I. okamurae* (diphlorethohydroxycarmalol) exhibit anti-obesity properties by inhibiting intracellular lipid accumulation, suppressing adipogenesis in 3T3-L1 cells via inhibiting the expression of PPARγ, C/EBPα, SREBP-1, and FABP4, and activating AMP-activated protein kinase (AMPK) and ACC phosphorylation [70–77] (Table 1). In addition to these mechanisms, some phlorotannins isolated from brown seaweed exhibited anti-obesity effects by reducing leptin resistance or inhibiting pancreatic lipase [78,79]. Additionally, oral administration of phlorotannins such as eckol and dieckol isolated from *E. cava* and *Ecklonia stolonifera* showed antihyperlipidemic effects by decreasing the total cholesterol levels, triglyceride levels, and low-density lipoprotein levels and increasing the high-density lipoprotein in the serum of high-fat diet mice [80,81].

Table 1. Phlorotannin compounds isolated from seaweeds with therapeutic potential against cardiovascular disease.

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Ecklonia cava	Diabetes mellitus/α-glucosidase and α-amylase inhibition	Fucodiphloroethol G, dieckol, 6,6′-bieckol, 7-phloroeckol, phlorofucofuroeckol A	in vitro	– α-Glucosidase inhibitory activity (IC_{50}): fucodiphloroethol G (19.52 μM/L^{-1}), dieckol (10.79 μM/L^{-1}), 6,6′-bieckol (22.22 μM/L^{-1}), 7-phloroeckol G (49.49 μM/L^{-1}), phlorofucofuroeckol A (19.71 μM/L^{-1}) – α-Amylase inhibitory activity (IC_{50}): fucodiphloroethol G (>500 μM/L^{-1}), dieckol (124.98 μM/L^{-1}), 6,6′-bieckol (>500 μM/L^{-1}), 7-phloroeckol G (250.02 μM/L^{-1}), phlorofucofuroeckol A (>500 μM/L^{-1})	[49]
	Diabetes mellitus/α-glucosidase inhibition	Eckol, 2-phloroeckol, 8,8′-bieckol, 6,8′-bieckol, 2-*O*-(2,4,6-trihydroxyphenyl)-6,6′-bieckol	in vitro	– α-Glucosidase inhibitory activity (IC_{50}): Eckol (59.8 ± 0.8 μM), 2-phloroeckol (32.5 ± 2.1 μM), 8,8′-bieckol (12.5 ± 3.1 μM, competitive), 6,8′-bieckol (2.3 ± 1.2 μM, competitive), 2-*O*-(2,4,6-trihydroxyphenyl)-6,6′-bieckol (123.1 ± 2.4 μM, competitive)	[48]
	Diabetes mellitus/α-glucosidase and α-amylase inhibition, INS-1 cell protection against glucotoxicity	2,7″-phloroglucinol-6,6′-bieckol	in vitro and in vivo	– α-Glucosidase inhibitory activity (IC_{50}): 2,7″-phloroglucinol-6,6′-bieckol (23.35 μM) – α-Amylase inhibitory activity (IC_{50}): 2,7″-phloroglucinol-6,6′-bieckol (6.94 μM) – Glucose response curve: 2,7″-phloroglucinol-6,6′-bieckol (2349.3 mmol·min/L) – 2,7″-phloroglucinol-6,6′-bieckol protects pancreatic β cells against high glucose-induced apoptosis	[50,60]
	Diabetes mellitus/α-glucosidase and α-amylase inhibition, postprandial hyperglycemia inhibition	Dieckol	in vitro and in vivo	– α-Glucosidase inhibitory activity (IC_{50}): dieckol (0.24 mM) – α-amylase inhibitory activity (IC_{50}): dieckol (0.66 mM) – Area under the curve of postprandial glucose responses in streptozotocin-induced diabetic mice: diabetic mice (483 mmol·min/L), dieckol 100 mg/kg body weight (259 mmol·min/L)	[51]
Ecklonia cava	Diabetes mellitus/activation of both AMPK and Akt signaling pathways	Dieckol	in vivo	– Administration of 20 mg/kg body weight dieckol was reduced blood glucose, serum insulin level, and body weight	[61]
	Obesity/anti-adipogenesis	Triphlorethol-A, eckol, dieckol	in vitro	– Triphlorethol-A, eckol, dieckol (20 μM): decreased intracellular lipid accumulation and increased intracellular calcification with an intervention in differentiation pathways at 3T3-L1 and MC3T3-E1 cell lines, respectively	[70]
	Obesity/inhibition of adipogenesis	Dieckol, 6,6′-bieckol, phlorofucoeckol A	in vitro	– Phlorotannin compounds such as dieckol, 6,6′-bieckol, and phlorofucoeckol A in *Ecklonia cava* inhibit intracellular lipid accumulation. In particular, dieckol suppressed adipogenesis in 3T3-L1 cells by suppressing the expression of PPARγ, C/EBPα, SREBP-1, and FABP4.	[71]
	Obesity/suppresses lipid accumulation and adipogenesis	Dieckol	in vitro and in vivo	– Dieckol inhibits early adipogenic events by suppressing cell cycle progression, and plays important roles in regulating AMPKα, ERK, and AKT signaling to inhibit lipid accumulation on high-fat diet-fed zebrafish, mice and 3T3-L1 models	[72]
	Obesity/reduced leptin resistance	Dieckol, 2,7-phloroglucinol-6,6-bieckol, pyrogallol-phloroglucinol-6,6-bieckol, phlorofucofuroeckol A	in vitro	– Phlorotannin compounds such as dieckol, 2,7-phloroglucinol-6,6-bieckol, pyrogallol-phloroglucinol-6,6-bieckol, and phlorofucofuroeckol A isolated from *Ecklonia cava* had the most potent effect on attenuating leptin resistance	[79]
	Hypertension/ACE inhibition	6,6′-Bieckol	in vitro	– ACE inhibitory activity (IC_{50}): 0.42 mM	[28]
	Hypertension/ACE inhibition	Phloroglucinol, Triphlorethol-A, eckol, dieckol, eckstolonol	in vitro	– ACE inhibitory activity (IC_{50}): phloroglucinol (2.57 mM), triphlorethol-A (2.01 mM), eckol (2.27 mM), dieckol (1.47 mM), eckstolonol (2.95 mM)	[26]

Table 1. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
	Hypertension/vascular smooth muscle cell proliferation and migration	Dieckol, 2,7-phloroglucinol-6,6-bieckol, phlorofucofuroeckol A, pyrogallol-phloroglucinol-6,6-bieckol	in vitro	– Inhibits monocyte migration and differentiation to inflammatory macrophages and monocyte associated vascular cell dysfunction	[37]
Ecklonia cava	Hypertension/improved blood circulation	Pyrogallol-phloroglucinol-6,6′-bieckol (PPB)	in vitro and in vivo	– PPB improved blood circulation, including reduced adhesion molecule expression, endothelial cell death, excessive vascular smooth muscle cell proliferation, and migration– PPB remarkably reduced blood pressure, serum cholesterol, and lipoprotein levels in vivo	[38]
	Hypertension/promotion of vasodilation	Dieckol	in vitro and in vivo	– Dieckol effectively promoted endothelial-dependent NO production by activating the PI3K/Akt/eNOS pathway and $[Ca^{2+}]_{cytosol}$ regulation – Dieckol promotes vasodilation by increasing the DA diameter, further regulating blood-flow velocity in a zebrafish model	[35]
	Hyperlipidemia/reduction of total cholesterol, triglyceride, low-density lipoprotein	Dieckol	in vitro and in vivo	– In vitro: 200 μg/mL dieckol inhibited adipocyte differentiation, intracellular triglyceride accumulation, and lipid accumulation in 3T3-L1 cells – In vivo: administration of dieckol reduced total cholesterols, triglycerides and low-density lipoproteins in the serum of high-fat diet mice	[82]
Ecklonia stolonifera	Diabetes mellitus/protein tyrosine phosphatase 1B, α-glucosidase inhibition	Phloroglucinol, dioxinodehydroeckol, eckol, phlorofucofuroeckol-A, dieckol, 7-phloroeckol	in vitro	– Protein tyrosine phosphatase 1B inhibitory activity (IC_{50}): phloroglucinol (55.48 μM), dioxinodehydroeckol (29.97 μM), eckol (2.64 μM), phlorofucofuroeckol-A (0.56 μM), dieckol (1.18 μM), 7-phloroeckol (2.09 μM) – α-Glucosidase inhibitory activity (IC_{50}): phloroglucinol (141.18 μM), dioxinodehydroeckol (34.60 μM), eckol (22.78 μM), phlorofucofuroeckol-A (1.37 μM), dieckol (1.61 μM), 7-phloroeckol (6.13 μM)	[52]
	Obesity/inhibition of lipid accumulation and adipocyte differentiation, modulation of adipocyte marker gene expression	Phloroglucinol, eckol, dieckol, dioxinodehydroeckol, phlorofucofuroeckol A	in vitro	– Phlorotannins, such as phloroglucinol, eckol, dieckol, dioxinodehydroeckol, and phlorofucofuroeckol A isolated from *Ecklonia stolonifera* was reduced lipid accumulation in 3T3-L1 cell line – These phlorotannin compounds suppressed adipocyte differentiation through inhibiting C/EBPα and PPARγ expression	[73]
	Hypertension/ACE inhibition	Phloroglucinol, eckstolonol, eckol, phlorofucofuroeckol A, dieckol, Triphlorethol-A, fucosterol	in vitro	– ACE inhibitory activity (IC_{50}) of phloroglucinol: (N.A.), eckstolonol (410.12 μM), eckol (70.82 μM), phlorofucofuroeckol A (12.74 μM), dieckol (34.25 μM), Triphlorethol-A (700.9 μM), fucosterol (N.A.)	[27]
	Hyperlipidemia/reduction of Cu^{2+}-induced LDL oxidation	Phloroglucinol, dioxinodehydroeckol, eckol, phlorofucofuroeckol-A, dieckol, 7-phloroeckol	in vitro	– Cu^{2+}-induced LDL oxidation inhibitory activity (IC_{50}): phloroglucinol (87.30 μM), dioxinodehydroeckol (16.57 μM), eckol (7.47 μM), phlorofucofuroeckol-A (4.34 μM), dieckol (3.10 μM), 7-phloroeckol (9.07 μM)	[80]

Table 1. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Ecklonia stolonifera	Hyperlipidemia/reduction of total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and atherogenic index	Eckol, dieckol	in vivo	– Poloxamer 407-induced hyperlipidemic rats model: 20 mg/kg BW eckol—TC level (255.6 mg/dL → 157.0 mg/dL), TG level (240.2 mg/dL → 174.9 mg/dL), LDL-C level (145.1 mg/dL →63.1 mg/dL), AI (3.47 → 1.77) 20 mg/kg BW dieckol—TC level (255.6 mg/dL → 144.7 mg/dL), TG level (240.2 mg/dL → 165.7 mg/dL), LDL-C level (145.1 mg/dL →35.5 mg/dL), AI (3.47 → 0.95) – High-cholesterol diet rats model: 20 mg/kg BW eckol—TC level (239.9 mg/dL → 226.3 mg/dL), TG[3] level (271.1 mg/dL → 256.7 mg/dL), LDL-C[3] level (160.6 mg/dL → 146.8 mg/dL), AI (7.55 → 7.14) 20 mg/kg BW dieckol—TC level (239.9 mg/dL → 200.7 mg/dL), TG level (271.1 mg/dL → 219.8 mg/dL), LDL-C level (160.6 mg/dL → 125.4 mg/dL), AI (7.55 → 5.53)	[81]
Eisenia bicyclis	Diabetes mellitus/α-fucosidase, β-galactosidase, β-mannosidase inhibition	Phloroglucinol, phloroglucinol tetramer, eckol, phlorofucofuroeckol A, dieckol, 8,8′-bieckol	in vitro	– Among the 6 phlorotannin compounds isolated from *Eisenia bicyclis*, phlorofucofuroeckol A, dieckol, and 8,8′-bieckol showed α-fucosidase, β-galactosidase, and β-mannosidase inhibitory activity. On the other hand, phloroglucinol, phloroglucinol tetramer, and eckol showed a weak activity of inhibiting these enzymes. – Dieckol was exhibited as a competitive inhibitor of α-fucosidase with an inhibition constant (K_1) of 0.12 mM	[83]
	Obesity/pancreatic lipase inhibitory activity	Eckol, fucofuroeckol A, 7-phloroeckol, dioxindehydroeckol, phlorofucofuroeckol A, dieckol	in vitro	– Pancreatic lipase inhibitory activity (IC_{50}): eckol (76.6 μM), fucofuroeckol A (37.2 μM), 7-phloroeckol (12.7 μM), dioxindehydroeckol (>200 μM), phlorofucofuroeckol A (>200 μM), dieckol (99.3 μM)	[78]
	Obesity/inhibition of lipid accumulation and adipocyte differentiation	6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, dieckol, phlorofucofuroeckol-A	in vitro	– Phlorotannin compounds such as 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, dieckol, and phlorofucofuroeckol-A isolated from *Eisenia bicyclis* showed suppressed differentiation of 3T3-L1 adipocyte through downregulation of adipogenesis and lipogenesis	[74]
Ishige okamurae	Diabetes mellitus/improve glucose homeostasis	Ishophloroglucin A (IPA)	in vivo	– Administration of 1.35 mg/kg BW IPA improved glucose homeostasis in high-fat diet-fed mice – IPA ameliorated glucose intolerance, reducing fasting glucose levels and 2 h glucose levels in high-fat diet-fed mice – IPA protect pancreatic function in high-fat diet-fed mice through pancreatic β-cells and C-peptide – Administration of IPA improves glucose homeostasis by increasing glucose transporter 4 levels in the muscles of high-fat diet-fed mice	[62]
	Diabetes mellitus/human umbilical vein endothelial cell protection against high glucose-induced oxidative stress	Diphlorethohydroxycarmalol (DPHC)	in vitro	– DPHC prevented human umbilical vein endothelial cells from high glucose-induced damage through restoring cell viability, suppressed lipid peroxidation, reduced intracellular reactive oxygen species, and nitric oxide level	[84]
	Diabetes mellitus/α-glucosidase and α-amylase inhibition	Diphlorethohydroxycarmalol (DPHC)	in vitro and in vivo	– α-Glucosidase inhibitory activity (IC_{50}): 0.16 mM – α-Amylase inhibitory activity (IC_{50}): 0.53 mM – Administration of 100 mg/kg DPHC was reduced blood glucose level in streptozotocin-induced diabetic mice – Postprandial glucose response: normal mice (965 mmol·min/L), diabetic mice (2210 mmol·min/L), DPHC treated mice (1964 mmol·min/L)	[55]

Table 1. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
	Diabetes mellitus/α-glucosidase inhibition	Ishophloroglucin A (IPA), diphlorethohydroxycarmalol (DPHC)	in vitro	– α-Glucosidase inhibitory activity (IC_{50}): IPA (54.97 μM), DPHC (175.78 μM)	[53]
	Diabetes mellitus/inhibition of abnormal angiogenesis, vascular dysfunction	Diphlorethohydroxycarmalol (DPHC)	in vitro and in vitro	– DPHC treatment suppressed the phosphorylation of VEGFR-2 and down-regulation of angiogenesis-related key mechanisms	[64]
	Diabetes mellitus/protect RINm5F pancreatic β cells from high glucose-induced damage	Diphlorethohydroxycarmalol (DPHC)	in vivo	– DPHC treatment inhibited the apoptotic cell death of RINm5F pancreatic β cell via decrease of thiobarbituric acid reactive substances, intracellular reactive oxygen species generation, and nitric oxide level	[85]
Ishige okamurae	Diabetes mellitus/anti-angiogenic effect	Ishophloroglucin A (IPA)	in vitro	– IPA effectively inhibited high glucose-induced endothelial cell proliferation, migration, and capillary formation, and exhibited an anti-angiogenic effect by interfering with the VEGFR-2 signaling pathway	[65]
	Obesity/reduction of total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and atherogenic index	Diphlorethohydroxycarmalol (DPHC)	in vivo	– Triglyceride levels: high-fat diet mice 137.88 mg/dL → 50 mg/kg BW 86.73 mg/dL – High-density lipoprotein cholesterol levels: high-fat diet mice 50.49 mg/dL → 50 mg/kg BW 72.71 mg/dL – Low-density lipoprotein cholesterol levels: high-fat diet mice 22.24 mg/dL → 50 mg/kg BW 16.82 mg/dL – Leptin levels: high-fat diet mice 2.04 ng/dL → 50 mg/kg BW 1.23 ng/dL	[86]
	Obesity/induces apoptosis in 3T3-L1 preadipocytes	Diphlorethohydroxycarmalol (DPHC)	in vitro	– DPHC treatment increased the number of early and late apoptotic cells in 3T3-L1 pre-adipocytes – DPHC mediated apoptotic cell death via the activation of caspase-3, caspase-8, and Bax	[75]
	Obesity/anti-adipogenesis	Diphlorethohydroxycarmalol (DPHC)	in vitro	– DPHC showed an anti-adipogenic effect via regulation of ECM during adipogenesis – DPHC treatment positively affects normal adipose tissue generation and acts as a suppressor of abnormal ECM structures	[76]
	Obesity/inhibition of lipid accumulation and suppressed adipogenesis via AMPK activation	Diphlorethohydroxycarmalol (DPHC)	in vitro	– DPHC treatment inhibited the fat accumulation by activating AMPK and ACC phosphorylation in 3T3-L1 adipocytes	[77]
	Hypertension/vasodilatory effect through increasing calcium intake level	Diphlorethohydroxycarmalol (DPHC)	in vitro and in vivo	– DPHC stimulated NO production by increasing calcium levels and endothelial nitric oxide synthase expression – DPHC modulated Ca^{2+} levels by activating AchR and VEGFR2 – DPHC modulated calcium transit through AchR and VEGFR2, increasing endothelial-dependent NO production in a zebrafish model	[36]
Ishige foliacea	Diabetes mellitus/anti-diabetogenic effect	Octaphlorethol A (OPA)	in vivo	– Administration of 10 mg/kg BW OPA increased anti-apoptotic (Bcl-xL) and pro-apoptotic (Bax) protein expression level and increased antioxidant enzymes (SOD, CAT, GSH).	[87]

Table 1. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Ishige foliacea	Diabetes mellitus/impaired glucose tolerance improvement	Octaphlorethol A (OPA)	in vivo	– OPA treatment significantly decreased postprandial blood glucose levels in db/db mice – OPA supplements significantly improved fasting blood glucose levels and impaired glucose tolerance, decreased serum insulin levels, augmented the activation of AMPK, and increased the expression of GLUT4 in skeletal muscle	[63]
	Diabetes mellitus/pancreatic β cells protection	Octaphlorethol A (OPA)	in vitro	– Pretreatment with 50 μg/mL OPA decreased the streptozotocin-induced pancreatic β cells damage by reducing the thiobarbituric acid reactive substances and intracellular ROS generation – OPA treatment increased the activity of antioxidant enzymes such as CAT, SOD, GSH in STZ-treated pancreatic β cells	[88]
	Diabetes mellitus/α-glucosidase inhibition	Octaphlorethol A (OPA)	in vitro and in vivo	– α-glucosidase inhibitory activity (IC50): OPA (0.11 mM) – α-glucosidase molecular docking: binding energy (−140.98 kcal mol^{-1}) – OPA interacts with Phe575, His600, Arg526, Met444, Asp542, Tyr605, Ser448, Asp203, Lys480, and Phe450 – OPA treatment suppressed increases in postprandial blood glucose levels	[54]
Ishige sinicola	Hypertension/ACE inhibition	Octaphlorethol A (OPA)	in vitro	– ACE inhibitory activity (IC_{50}): OPA (59 μM) – OPA exhibited an anti-hypertensive effect via AMPK and Akt activation in endothelial cells	[29]

ACE, angiotensin I-converting enzyme; DA, dorsal aorta; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; AI, atherogenic index.

3. Seaweed-Derived Polysaccharides with Therapeutic Potential against CVD

In terms of economic value, seaweed polysaccharides are the most important products derived from seaweeds. Several studies have demonstrated the pharmacological activities of polysaccharides obtained from seaweeds. They are the multi-component mixtures made up of one or more monosaccharides linked by one, three, or four glycosidic linkages distributed between and inside seaweed cells [89]. In recent years, the most famous polysaccharides such as ulvan (sulfated glucuronoxylorhamnans), fucoidan (L-fucose and sulfate ester groups), and carrageenan (sulfated galactans) extracted from green, brown, and red seaweeds, respectively, have been extensively investigated for their health-promoting effects [90–93].

Among the risk factors for cardiovascular disease, seaweed-derived polysaccharides have been the focus of anti-diabetic research, and studies using fucoidan are the most widely reported. Fucoidan derived from *Sargassum wightii*, *Sargassum thumbergii*, *Sragassum honeri*, *Sargassum ringgoldianum*, *Sargassum*, *siliquastrum*, *Sargassum graminifolium*, *Sargassum kjellmanianum*, *Fucus vesiculosus*, *Ascophyllum nodosum*, *Saccharina longicruris*, *Cystoseira crinite*, *Ecklonia maxima*, and *Turbinaria conoides* exhibit anti-diabetic activity through the inhibition of α-amylase and α-glucosidase alone or both enzymes [94–102] (Table 2). Interestingly, Kim et al. revealed that the α-amylase and α-glucosidase inhibition of fucoidan differed depending on the species from which the fucoidan was extracted and by the month and year of collection [98]. In addition, the oral administration of *Sargassum fusiforme*-derived fucoidan decreased the fasting blood glucose levels in high-fat diet/streptozotocin-induced diabetic mice model and reduced diabetes-related intestinal bacteria, which may potentially aid diabetes [103–105]. Many studies have demonstrated cardioprotection by polysaccharides. Sulfated polysaccharides from *Padina tetrastromatica* exerted cardioprotective effects by activating the PI3K/Akt/Nrf2 signaling pathway in in vitro and Sprague Dawley rat models [106]. Fucoidan is a well-known L-fucose-enriched sulfate. Low molecular weight fucoidan (MW = 7000 Da) produced from *Laminaria japonica* (*L. japonica*) could induce endothelium-dependent vasodilation via the eNOS expression upregulation in cerebral microvascular endothelial cells and effectively improve blood pressure and local blood flow in rats [107]. *Cystoseira crinite*-derived fucoidan exhibits ACE inhibitory activity in vitro and in vivo [108]. In addition, Li et al. suggested that fucoidan (100 mg/kg/day) from *Undaria pinnatifida* prevents vascular dysfunction through PI3K/Akt/eNOS-dependent mechanisms in a hypertensive rat model [109]. Furthermore, continuous feeding with kappa-carrageenan produced from *Kappaphycus alvarezii* or iota-carrageenan from *Sarconema filiform* to high-fat diet-fed rats attenuated the parameters defining cardiovascular and metabolic health such as body weight, abdominal and liver fat, systolic blood pressure, plasma total cholesterol concentrations, and the plasma activities of alanine transaminase and aspartate transaminase [110]. In green seaweeds, ulvan is one of the major polysaccharide structures isolated from *Ulva pertusa* which had anti-hyperlipidemic effects via the modulation of lipid levels and the mRNA expression of FXR, LXR, and PPARγ in an in vivo rat model [111]. However, the anti-hypertensive effect of ulvan is not clear. Thus, further detailed investigations are required.

These functional compounds from seaweed protect the muscle and platelets and stimulate blood vessel dilatation [112]. In human trials, one previous report demonstrated that daily fucoidan consumption from *L. japonica* could remarkably suppress thrombus formation and further protect cardiovascular health [113]. However, there have been limited studies on the anti-hypertensive effects in human subjects. Most of the related research is closely associated with cardioprotective effects, such as anticoagulant polysaccharides in in vitro and in vivo models [114–116]. Therefore, due to the bioactivity of polysaccharides, more detailed human trials are important for verifying and developing alternative therapies soon.

Table 2. Polysaccharides isolated from seaweeds with therapeutic potential against cardiovascular disease.

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Sargassum wightii	Diabetes mellitus/α-glucosidase and α-amylase inhibition Hypertension/ACE inhibition	Sulfated polygalactofucan	in vitro	– α-Glucosidase activity (IC_{50}): 1.48 mg/mL – α-Amylase activity (IC_{50}): 0.93 mg/mL – ACE inhibitory activity (IC_{50}): 0.22 mg/mL	[94]
	Diabetes mellitus/α-amylase inhibition	Fucoidan	in vitro	– α-Amylase activity (IC_{50}): 103.83 µg	[95]
	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-Glucosidase activity (IC_{50}): 132 µg	[96]
Sargassum fusiforme	Diabetes mellitus/inhibition of hyperglycemia, altered the composition of gut microbiota	Fucoidan	in vivo	– Administration of fucoidan decreased fasting blood glucose levels, dietary and water intake, and alleviated pathological changes in the heart and liver – Fucoidan supplements altered the composition of gut microbiota in STZ-induced diabetic mice	[103]
	Diabetes mellitus/inhibition of hyperglycemia, altered the composition of gut microbiota	Fucoidan	in vivo	– Administration of fucoidan decreased fasting blood glucose, food consumption, water intake, and serum lipid levels in high-fat diet/STZ-induced diabetic mice – Administration of fucoidan altered the composition of gut microbiota and increased the levels of carnitine and choline in the colon	[105]
	Diabetes mellitus/improved insulin sensitivity, altered the composition of gut microbiota	Fucoidan	in vivo	– Administration of fucoidan reduced fasting blood glucose and insulin resistance indexes and improved glucose tolerance – Administration of fucoidan increased the abundance and diversity of gut microbiota in obese mice and improved intestinal integrity	[104]
Sargassum hemiphyllum	Diabetes mellitus/prevention of pancreatic β cell damage and dysfunction	Fucoidan	in vitro and in vivo	– Fucoidan treatment attenuated pancreatic β cell death, pancreatic islet mass loss, and dysfunction – Fucoidan treatment increased insulin synthesis via activation of Sirt-1-dependent upregulation of PDX and GLP-1R	[117]
Undaria pinnatifida	Diabetes mellitus/regulation of blood glucose homeostasis	Fucoidan	in vivo	– Serum insulin (µIU/mL): db/db mice (41.6) → db/db mice + fucoidan (37.7) – Fasting blood glucose (mg/dL): db/db mice (445) → db/db mice + fucoidan (257)	[118]
	Diabetes mellitus/improved insulin-stimulated glucose uptake	Fucoidan	in vitro	– Fucoidan treatment stimulated glucose uptake and inhibited basal lipolysis in hypertrophied insulin resistance	[119]
	Hypertension/vascular dysfunction prevention	Fucoidan	in vivo	– Fucoidan treatment induce NO release and eNOS activation – In $_{L}$-NAME-induced hypertensive rats, administration of fucoidan attenuated elevated blood pressure, increased endothelium-dependent vasodilation, and improved vascular elasticity	[109]
Undaria pinnatifida	Obesity/inhibition of adipocyte differentiation	Fucoidan	in vitro	– Fucoidan treatment suppressed adipogenesis by inhibiting proliferator-activated receptor γ, CCAAR/enhancer-binding protein α, adipocyte protein 2, and lipid accumulation in 3T3-L1 cells	[120]
Saccharina longicruris	Diabetes mellitus/α-amylase inhibition	Fucoidan	in vitro	– α-amylase activity (%):fucoidan (1 mg/mL) inhibited α-amylase activity by 80.3%	[97]
	Diabetes mellitus/α-amylase inhibition	Fucoidan	in vitro	– α-amylase activity (%): harvested in October 2002: NA, commercial fucoidan from *F. vesiculosus*: NA	[97]

Table 2. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Fucus vesiculosus	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase activity (IC_{50}): 0.049 mg/mL	[98]
	Diabetes mellitus/insulin stimulation and pancreatic protection	Fucoidan	in vitro and in vivo	– Fucoidan supplements increase insulin secretion and provide pancreatic protection via the cAMP signaling pathway	[121]
	Diabetes mellitus/α-amylase inhibition	Fucoidan	in vitro	– α-amylase inhibitory activity (IC_{50}): 0.04 mg/mL	[99]
	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 67.9 µg/mL	[100]
Ascophyllum nodosum	Diabetes mellitus/α-amylase inhibition	Fucoidan	in vitro	– α-amylase activity (%):fucoidan (1 mg/mL) inhibited α-amylase activity by 83.2%	[97]
	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase activity according to harvest seasons (IC_{50}): May (0.047 mg/mL), June (0.037 mg/mL), July (0.014–0.036 mg/mL), August (0.017–0.046 mg/mL), September (0.026–0.029 mg/mL), October (0.013 mg/mL), and November (0.014 mg/mL)	[98]
	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 165.4 µg/mL	[100]
Cystoseira crinita	Diabetes mellitus/α-amylase inhibition	Sulfated polysaccharide	in vitro and in vivo	– α-amylase inhibitory activity (IC_{50}): 39.16 µg/mL – α-amylase inhibitory activity (IC_{50}): in serum (23%), in pancreas (44.38%), and intestine (45%)	[108]
	Hypertenstion/ACE inhibition	Sulfated polysaccharide	in vitro and in vivo	– ACE inhibitory activity (IC_{50}): 58.35 µg/mL	[108]
Saccharina japonica	Diabetes mellitus/reduced hyperglycemia	Fucoidan	in vivo	– Administration of 1200 mg/kg BW fucoidan reduced the blood glucose level by 34% – Increased serum insulin levels – Fucoidan supplements alter plasma lipid levels by lowering cholesterol, triglyceride, and low-density lipoprotein concentrations	[101]
Ecklonia maxima	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-amylase inhibitory activity (IC_{50}): 0.29 mg/mL	[99]
Sargassum thumbergii	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 376.7 µg/mL	[100]
Sargassum honeri	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 351.0 µg/mL	[100]
Sargassum ringgoldianum	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 172.9 µg/mL	[100]
Sargassum siliquastrum	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 399.6 µg/mL	[100]
Sargassum graminifolium	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 271.7 µg/mL	[100]
Sargassum kjellmanianum	Diabetes mellitus/α-glucosidase inhibition	Fucoidan	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 415.2 µg/mL	[100]

Table 2. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Turbinaria conoides	Diabetes mellitus/α-amylase and α-d-glucosidase inhibition	Fucoidan	in vitro	– α-amylase inhibitory activity (IC_{50}): 1.07 μM – α-d-glucosidase inhibitory activity (IC_{50}): 0.68 μM	[102]
Laminaria japonica	Diabetes mellitus/protects endothelial function	Low-molecular-weight fucoidan	in vivo	– Administration of 200 mg/kg/day fucoidan protects vasoendothelial function and reduces basal blood pressure in type 2 diabetes rats	[107]
Padina tetrastromatica	Hypertension/cardioprotective effect	Sulfated polysaccharides	in vitro and in vivo	– Treatment of sulfated polysaccharides isolated from *Padina tetrastromatica* reduced isoproterenol-induced cardiac damage via activation of PI3K/Akt/Nrf2 signaling pathway	[106]
	Atherosclerosis/reduced hyperlipidemia, endothelial dysfunction	Sulfated polysaccharides	in vitro and in vivo	– Sulfated polysaccharides treatment maintained lipid homeostasis by regulating the expressions of SREBP-2 and LDL-R – Administration of sulfated polysaccharides normalized ISO-induced oxidative damage, hyperlipidemia, endothelial dysfunction, and inflammation in a rat model.	[122]
Sarconema filiforme	Modulation of cardiovascular and metabolic health parameters	Carrageenan	in vivo	– Administration of 5% carrageenan in high-fat diet-fed rats attenuated cardiovascular diseases and metabolic health parameters	[110]
Ulva Pertusa	Hyperlipidemia/modulating hyperlipidemia related parameters	Ulvan	in vivo	– Ulvan decreased total cholesterol and low-density lipoprotein levels in high cholesterol-fed rats – Ulvan treatment improved lipid profiles via regulating FXR, PPARγ, and LXR expression levels	[111]

ACE, angiotensin I-converting enzyme; STZ, streptozotocin.

4. Seaweed-Derived Peptides with Therapeutic Potential against CVD

As the importance of marine organisms as sources of novel bioactive substances is growing, marine bioactive peptides have received much attention recently. Bioactive peptides are usually 2−20 amino acid residues [123]. Depending on the amino acid sequence, they may be involved in various biological functions such as antioxidant, anti-cancer, opioid agonists or antagonists, immunomodulatory, anti-thrombotic, anti-atherosclerotic, and antimicrobial activities, in addition to nutrient utilization [123]. A pepsin-hydrolyzed peptide (VECYGPNRPQF) from *Chlorella vulgaris* protein waste possessed potent antioxidant activity against various free radicals and exhibited gastrointestinal enzyme resistance. Still, no cytotoxicity was observed in human lung fibroblast cell lines (WI-38) [124]. The antitumor polypeptide Y2 was obtained from the trypsin digest of *Spirulina platensis* proteins [125]. Cian et al. found that enzymatic hydrolysates from a phycobili protein byproduct of *Porphyra columbina* exhibited immunosuppressive effects on rat splenocytes by enhancing IL-10 production and inhibiting the production of TNF-α and IFN-γ [126].

Several bioactive peptides have been identified from *Undaria pinnatifida* (*U. pinnatifida*) and *Palmaria palmate* (*P. palmate*), which exerted an anti-hypertensive effect in vitro by showing potent ACE inhibition activity and a significant reduction in blood pressure observed in an oral feeding rat model [127–131]. In particular, bioactive peptides derived from various seaweeds (brown seaweed 10, red seaweed 10, and green seaweed 10) have antihypertensive effects through ACE inhibition (Table 3). One mg/kg BW of Leu-Trp, Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Tyr from *U. pinnatifida* decreased the systolic blood pressure in spontaneously hypertensive rats (SHRs) [127]. Furthermore, Suetsuna et al. reported that both single administration and repeated oral administration of synthetic dipeptides (Tyr-His, Lys-Tyr, Phe-Tyr, and Ile-Tyr) from *U. pinnatifida* significantly decreased the blood pressure in spontaneously hypertensive rats (SHRs) [129]. The α and β subunits of phycoerythrin (a major light-harvesting protein pigment of red seaweed) from *P. palmate* showed ACE inhibition activity [130]. Ile-Leu-Ala-Pro, Leu-Leu-Ala-Pro, and Met-Ala-Gly-Val-Asp-His-Ile purified from *P. palmate* inhibited DPP-IV, a novel biomarker of ischemic cardiovascular disease, and had insulinotropic potency [131,132]. Ile-Pro and Ala-Phe-Leu isolated from *Chlorophyta U. rigida* exhibited ACE inhibition activity. Ko et al. [25] demonstrated significant systolic blood pressure reduction in hypertensive rats following 10 mg/kg body weight of Val-Glu-Gly-Tyr administered orally. *Gracilariopsis lemaneiformis* inhibited ACE-I with IC_{50} values of 9.64. 23.94, and 474.36 μM for the peptides FQIN [M(O)] CILR, TGAPCR, and Gln-Val-Glu-Tyr, respectively [133,134]. The administration of 10 mg/kg of FQIN [M(O)] CILR and TGAPCR had antihypertensive effects in spontaneously hypertensive rats [133].

Table 3. Peptides isolated from seaweeds with therapeutic potential against cardiovascular disease.

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Undaria pinnatifida	Hypertension/ACE inhibition, lower SBP	Val-Tyr, Ile-Tyr, Ala-Trp, Phe-Tyr, Val-Trp, Ile-Trp, and Leu-Trp, Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Tyr	in vitro	– ACE inhibitory activity (IC_{50}): Val-Tyr (35.2 μM), Ile-Tyr (6.1 μM), Ala-Trp (18.8 μM), Phe-Tyr (42.3 μM), Val-Trp (3.3 μM), Ile-Trp (1.5 μM) and Leu-Trp (23.6 μM) – Lower SBP (Val-Tyr; 206.7 mmHg, Ile-Tyr; 184.3 mmHg, Phe-Tyr; 193.0 mmHg, and Ile-Trp;199.5 mmHg)	[127]
	Hypertension/ACE inhibition	Ala-Ile-Tyr-Lys, Tyr-Lys-Tyr-Tyr, Lys-Phe-Tyr-Gly, and Tyr-Asn-Lys-Leu	in vitro	– ACE inhibitory activity (IC_{50}): Ala-Ile-Tyr-Lys (213 μM), Tyr-Lys-Tyr-Tyr (64.2 μM), Lys-Phe-Tyr-Gly (90.5 μM) and Tyr-Asn-Lys-Leu (21 μM)	[128]
Undaria pinnatifida	Hypertension/ACE inhibition	Tyr-His, Lys-Tyr, Phe-Tyr, and Ile-Tyr	in vitro	– ACE inhibitory activity (IC_{50}): Tyr-His (5.1 μM), Lys-Tyr (7.7 μM), Phe-Tyr (3.7 μM) and Ile-Tyr (2.7 μM)	[129]
Gracilariopsis lemaneiformis	Hypertension/ACE inhibition	FQIN [M(O)] CILR and TGAPCR	in vitro and in vivo	– ACE inhibitory activity (IC_{50}): FQIN [M(O)] CILR (9.64 μM) and TGAPCR (23.94 μM) – Decrements in SBP: FQIN [M(O)] CILR (27 mmHg) and TGAPCR (25 mmHg)	[133]
	Hypertension/ACE inhibition	Gln-Val-Glu-Tyr	in vitro	– ACE inhibitory activity (IC_{50}): Gln-Val-Glu-Tyr (474.36 μM)	[134]
Chlorophyta U. rigida	Hypertension/ACE inhibition	Ile-Pro and Ala-Phe-Leu	in vitro	– ACE inhibitory activity (IC_{50}): Ile-Pro (87.6 μM), Ala-Phe-Leu (65.9 μM)	[135]
Sargassum maclurei	Hypertension/ACE inhibition	RWDISQPY	in vitro	– ACE inhibitory activity (IC_{50}): 72.24 μM – Endothelin-1 suppressing capacity: 26.21% at 1.5 mg/mL	[136]
Mazzaella japonica	Hypertension/ACE inhibition	YRD	in vitro	– ACE inhibitory activity (IC_{50}): YRD (320 μM)	[137]
Sargassum fusiforme	Hypertension/ACE inhibition	ly-Lys-Tyr, Ser-Val-Tyr and Ser-Lys-Thr-Tyr	in vitro	– ACE inhibitory effect (IC_{50}): Gly-Lys-Tyr (3.92 μM) Ser-Val-Tyr (8.12 μM) and Ser-Lys-Tyr-Tyr (11.07 μM)	[138]
Ulva intestinalis	Hypertension/ACE inhibition	Phe-Gly-Met-Pro-Leu-Asp-Arg and Met-Glu-Leu-Val-Leu-Arg	in vitro	– ACE inhibitory activity (IC_{50}): Phe-Gly-Met-Pro-Leu-Asp-Arg (219.35 μM) and Met-Glu-Leu-Val-Leu-Arg (236.85 μM)	[139]
Enteromorpha clathrate	Hypertension/ACE inhibition	Pro-Ala-Phe-Gly	in vitro	– ACE inhibitory activity (IC_{50}): Pro-Ala-Phe-Gly(35.9 μM)	[140]
Pyropia Pseudolinearis	Hypertension/ACE inhibition	LRM	in vitro	– ACE inhibitory activity (IC_{50}): LRM (0.15 μM)	[141]
Palmaria palmata	Hypertension/ACE inhibition	α subunits of PE (rPEα and rPEβ)	in vitro	– ACE inhibitory effect (%): rPEα (94.4%) and rPEβ (87.0%)	[130]

Table 3. *Cont.*

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
	Diabetes mellitus/DPP-IV inhibitory activity	Ile-Leu-Ala-Pro, Leu-Leu-Ala-Pro and Met-Ala-Gly-Val-Asp-His-Ile	in vitro	– DPP-IV inhibitory activity (IC_{50}): Ile-Leu-Ala-Pro (17.90 μg/mL), Leu-Leu-Ala-Pro (22.14 μg/mL), and Met-Ala-Gly-Val-Asp-His-Ile (118.23 μg/mL)	[131]
Laminaria Japonica	Hypertension/ACE inhibition	KY, GKY, SKTY, AKY, AKYSY, KKFY, FY and KFKY	in vitro	– ACE inhibitory activity (IC_{50}): KY (5.24 μM), GKY (7.94 μM), SKTY (20.63 μM), AKY (7.52 μM), AKYSY (2.42 μM), KKFY (15.33 μM), FY (4.83 μM), and KFKY (10.73 μM)	[142]
Bangia fusco-purpurea	Hypertension/ACE inhibition	r-phycoerythrin, ALLAGDPSVLEDR and VVGGTGPVDEWGIAGAR	in vitro	– ACE inhibitory activity (IC_{50}): r-phycoerythrin (191.1 μg/mL), ALLAGDPSVLEDR (57.2 μg/mL), and VVGGTGPVDEWGIAGAR (66.2 μg/mL)	[143]
Porphyra spp. *Caulerpa lentillifera*	Diabetes mellitus/	Gly-Gly-Ser-Lys and Glu-Leu-Ser	in vitro	– α-amylase inhibitory activity (IC_{50}): Gly-Gly-Ser-Lys (2.58 mM) and Glu-Leu-Ser (2.62 mM)	[144]
	Hypertension/ACE inhibition	FDGIP and AIDPVRA	in vitro	– ACE inhibitory activity (IC_{50}): FDGIP (58.89 μM) and AIDPVRA (65.76 μM)	[145]
Porphyra dioica	Hypertension/ACE inhibition	Thr-Tyr-Ile-Ala and Tyr-Leu-Val-Ala	in vitro	– ACE inhibitory activity (IC_{50}): Thr-Tyr-Ile-Ala (197.5 μM), Tyr-Leu-Val-Ala (259.7 μM), and Asp-Tyr-Tyr-Lys-Arg (628.9 μM) – DPP-IV inhibitory activity (IC_{50}): Tyr-Leu-Val-Ala (439.5 μM)	[146]

ACE, angiotensin I-converting enzyme; SBP, streptozotocin; PE, phycoerythrin; DPP-IV, dipeptidyl peptidase-IV.

5. Seaweed-Derived Carotenoids and Other Components with Therapeutic Potential against CVD

All carotenoids, including fucoxanthin, carotene, lycopene, and siphonaxanthin, are bioactive substances from seaweeds. Green seaweed extracts rich in carotenoids exhibit significant antigenotoxic activities [147]. Fucoxanthin is a recognized secondary metabolite found in macroalgae, and its biological properties are well established [23]. Fucoxanthin from brown seaweed exerts prebiotic and anti-inflammatory activities in human intestinal epithelial cells [148]. Fucoxanthin upregulates the expression of UCP1 in white adipose tissue (WAT) in KK-Ay mice [149]. Fucoxanthin and siphonaxanthin inhibit angiogenesis by downregulating the FGF-2-mediated intracellular signals in vascular endothelial cells [150]. Siphonaxanthin has been reported to have anti-angiogenic and anti-inflammatory effects [151]. Siphonaxanthin induces apoptosis by decreasing Bcl-2 expression and activating caspase-3 in human leukemia (HL-60) cells [152].

In Ae's study, fucoxanthin extracted from *Undaria pinnatifida* (*U. pinnatifida*) increased the serum HDL. It decreased the triglyceride levels in high-fat diet-fed rats at a 0.2% diet dose for 4 weeks [153] (Table 4). In addition, the α-amylase and α-glucosidase inhibitory activities of fucoxanthin were observed in Kawee-Ai's study [154]. The administration of a 3-g/kg 9-cis β-carotene diet disrupted the increases in plasma cholesterol and LDL in LDL-receptor knockout mice [155]. Feeding 8% 9-Cis β-carotene feed for 23 days disrupted triglyceride elevation in 5-week-old female db/db mice [156]. Other carotenoids have also been shown to have anti-atherogenic effects. Zhuo et al. showed that siphonaxanthin extracted from *Codium fragile* disrupts the elevation of the serum total cholesterol, triglyceride, and HDL in KK-Ay mice [157]. In addition, (all-E)-lutein and (9-Z)-zeaxanthin displayed anti-diabetes mellitus potency via α-glucosidase inhibition [158].

Seaweeds have a variety of physiologically active ingredients in addition to phlorotannins, polysaccharides, peptides, and carotenoids. It has been reported that seaweeds contain various sterol compounds [159]. Sterols are an important family of lipids present in most eukaryotic cells. They are categorized into the steroid group, which contains the same fused four-ring core structure and has different biological roles than hormones and signaling molecules. The search for natural bioactive sterols as safe alternatives from marine seaweed is important in the food industry. Fucosterol isolated from the marine seaweed *Pelvetia siliquosa* causes a significant elevation of free radical scavenging enzyme activities, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-px) [160]. Moreover, 3 g,28 ξ-dihydroxy-24-ethylcholesta-5,23 Z-dien and 24 ξ-hydroperoxy-24-vinylcholesterol isolated from the brown seaweed *Sargassum carpophyllum* showed cytotoxic activity against human promyelocytic leukemia cells [161].

Zhen and Su studied bioactive compounds isolated from the edible brown seaweed *Sargassum fusiforme* (*S. fusiforme*), and 24(S)-saringosterol showed the strongest LXRβ-mediated transactivity among the seven phytosterols isolated from *S. fusiforme* containing fucosterol, 24-hydroperoxy-24-vinyl-cholesterol, 29-hydroperoxy-stigmasta-5,24(28)-dien-3β-ol, 24-methylenecholesterol, 24-keto-cholesterol, and 5α,8α-epidioxyergosta-6,22-dien-3β-ol [162], while 18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid were extracted from *S. fusiforme*-inhibited α-glucosidase. Other compounds, including unsaturated FAs C20:4 ($\Delta^{7,9,11,13}$), C17:3 ($\Delta^{8,11,14}$), neolignan, and trace amines also potently inhibited α-glucosidase [163]. Two plastoquinones (sargachromenol and sargaquinoic acid) isolated from the active n-hexane fraction of *Sargassum serratifolium* produced concentration-dependent inhibition against α-glucosidase [164].

These physiologically active dietary components derived from seaweeds have been actively studied at the in vitro and in vivo levels to inhibit or alleviate the symptoms of diabetes, obesity, hypertension, and hyperglycemia and hyperlipidemia, which are closely related to the pathogenesis of CVD. However, research on the clinical trial stage using the seaweeds and bioactive dietary substances is insufficient. Bioactive dietary components derived from food are known to affect epigenetic gene expression in humans through various mechanisms, such as alteration of the chromatin structure or non-coding RNA,

activation of transcription factors by signaling cascades, and direct ligand binding to nuclear receptors. Studies on the influence of polyphenols, PUFAs, and vitamins, which are bioactive dietary components contained in terrestrial plant resources, on epigenetic gene expression in humans through epigenetic change in the genome, miRNA level change, IncRNA level change, and transcription factor activity change are continuously being conducted [165]. By clearly analyzing the mechanisms of interaction between these dietary components and human genome structure and gene activity, a better understanding of these relationships will help design dietary guidelines that can help maintain good health by providing more effective dietary recommendations for individuals. Therefore, it is considered necessary to study not only the various bioactive dietary substances contained in seaweeds but also their influence on epigenetic changes in parallel.

Table 4. Carotenoids and other bioactive substances isolated from seaweeds with therapeutic potential against cardiovascular disease.

Source	Target Disease/Mechanism	Bioactive Component	Model Used	Biological Effect	Reference
Undaria Pinnatifida	Atherosclerosis/decreased in serum TG levels	Fucoxanthin	in vivo	– Decreased tryglycerides in plasma: 19.4 mg/100 mL – Enhancement of HDL-cholesterol in plasma: 7.5 mg/100 mL	[153]
Codium fragile	Obesity/altered in serum lipid	Siphonaxanthin	in vivo	– Decreased serum lipid: total-C (21 mg/dL) and tryglyceride (16 mg/dL)	[157]
Phaeodactylum tricornutum	Diabetes mellitus/α-amylase and α-glucosidase inhibition	Fucoxanthin	in vitro	– Enzyme inhibitory activity (Ki): α-amylase (0.13 mM) and α-glucosidase (0.05 mM)	[154]
Sargassum fusiforme	Atherosclerosis/LXRβ agonist activity	24(S)-Saringosterol	in vitro	– LXRβ-mediated transactivation: 3.50-fold vs 1.63-fold compared with control	[162]
	Diabetes mellitus/α-glucosidase inhibition	18α-glycyrrhetinic acid,18β-glycyrrhetinic acid, FAs C20:4 ($\Delta^{7,9,11,13}$), C17:3 ($\Delta^{8,11,14}$), neolignan, and trace	in vitro	– α-glucosidase inhibitory activity (IC_{50}): 18α-glycyrrhetinic acid (113.30 μM), 18β-glycyrrhetinic acid (128.72 μM), FAs C20:4 (Δ7,9,11,13) (34.85 μM), C17:3 (Δ8,11,14) (43.90 μM), neolignan (133.84 μM), and trace amine (273.23 μM)	[163]
Sargassum Serratifolium	Diabetes mellitus/α-glucosidase inhibition	Sargachromenol and sargaquinoic acid	in vitro	– α-glucosidase inhibitory activity (IC_{50}): sargachromenol (42.41 μM) and sargaquinoic acid (96.17 μM)	[164]

TG, triglyceride; LXR, liver X receptor.

6. Conclusions

The active compounds extracted from seaweed have been widely used for a long time, owing to their many benefits for improving human health. Increasing evidence has indicated that increasing the consumption of seaweeds helps decrease the risks of CVD and other related diseases by modulating different biological signaling pathways in vivo and in vitro. Further detailed human research is necessary to verify the clinical relevance of bioactive compounds isolated from seaweeds. In summary, this review lists the bioactive compounds isolated from different seaweeds to ameliorate CVD. This review will help summarize these concepts and promote further in-depth research.

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