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Review

Prevention of cardiovascular disease through modulation of endothelial cell function by dietary seaweed intake

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ABSTRACT

Seaweed is consumed as part of the traditional diet in Southeast Asia and has been shown to have the potential to prevent several chronic diseases. Recent studies have focused on the relationships between the components contained in seaweed and their usefulness for the treatment of cardiovascular disease (CVD). This review describes the protective effects of seaweed components on vascular endothelial cell damage and its prophylactic role against CVD. Information on clinical trials (e.g., randomized controlled trials and meta-analyses) was obtained from PubMed, Science Direct, and Web of Science, by searching for studies on the usefulness of seaweed consumption by humans and seaweed constituents. In addition, the CVD-related effects of the components contained in seaweed were analyzed based on information from cellular and animal models. Seaweed has been shown to have preventive effects on CVDs, such as arteriosclerosis and hypertension. Furthermore, researchers have clarified the mechanisms through which the components contained in seaweed prevent damage to vascular endothelial cells and alleviate arteriosclerosis, dyslipidemia, and hypertension. In particular, fucoidan, fucoxanthin, astaxanthin, and phlorotannin have been shown to exert potential antioxidant and anti-inflammatory effects, thereby contributing to CVD prevention by protecting vascular endothelial cells. Components contained in seaweed may prevent damage to vascular endothelial cells and block the development of CVD. The protective effects of the components contained in these seaweeds against vascular endothelial dysfunction suggest that consumption of seaweed may have applications in the prevention of CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are diseases of the heart and vascular system, including ischemic heart diseases, such as myocardial infarction; these conditions are associated with high mortality rates, necessitating early and aggressive preventive measures (Roth et al., 2015). Among these diseases, lifestyle-related conditions, such as hypertension, hyperlipidemia, diabetes, and obesity, are risk factors for CVD and promote arteriosclerosis, which can lead to CVD (Murray et al., 1997). Atherosclerosis induced by lifestyle-related diseases begins with dysfunction of vascular endothelial cells, followed by the formation of arteriosclerotic lesions in blood vessels via the actions of monocytes/macrophages, leading to the development of CVDs. For example, healthy vascular endothelial cells exert sufficient normal functions, such as anticoagulant, vasodilatory, and fibrinolysis-promoting effects, to prevent the formation of arteriosclerosis (Vane et al., 1990). However, when abnormalities persist in vascular endothelial cells, dysfunctions such as high vascular tone and redox imbalance appear, resulting in promotion of arteriosclerosis (Gimbrone et al., 2016).

Nitric oxide (NO) has important roles in maintaining the normal mechanisms of vascular endothelial cells via multiple actions other than vascular relaxation function (Grassi et al., 2011). However, vascular endothelial cell dysfunction and damage are fully repaired during the early stages of arteriosclerosis formation (Matsuzawa et al., 2015). Indeed, vascular endothelial cells throughout the body are constantly affected by various factors, and some cells are damaged by stimulation. However, the rapid proliferative potential and strong repair capacity of the cells during injury maintain normal systemic vascular function (Evans et al., 2020).

Abbreviations: CVD, cardiovascular disease; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NRF2, nuclear erythroid-2 like factor-2; ARE, antioxidant response element; RCT, cholesterol reverse transport; apoE, apolipoprotein E; IL, interleukin; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; iNOS, inducible NOS; MMP-2, matrix metalloproteinase-2; ROS, reactive oxygen species; HO, heme oxygenase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; AMPK, AMP-activated protein kinase; ACE, angiotensin-converting enzyme; ICAM-1, intercellular adhesion molecule 1; JNK, C-Jun N-terminal kinase; VEGF, vascular endothelial growth factor; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; SOD, superoxide dismutase; TXA2, thromboxane A2; COX, cyclooxygenase.

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Seaweed is traditionally consumed as food in Southeast Asian regions, such as China, Japan, and South Korea (Seca et al., 2018), and has recently become one of the most popular foods in some Western diets because of its beneficial effects on prolongation of life expectancy and prevention of CVDs (Brown et al., 2014). Seaweeds are taxonomically classified into green, brown, and red algae (Penalver et al., 2020). Among them, brown algae (Ochrophyta, a class of seaweed) include *Ascophyllum nodosum, Bifurcaria bifurcata*, and *Laminaria* spp., and comprise a very large group of seaweeds. Brown algae include *Chondrus crispus, Grateloupia turuturu*, and *Jania rubens*, and change from yellow to dark brown due to a change in the deposited pigment. Green algae are less abundant than red algae and include *Caulerpa lentillifera* and sea lettuce *Ulva clathrata*. Green algae vary in color from greenish yellow to dark green. Seaweeds are distributed worldwide and are found in all climatic zones, from warm tropical waters to cold waters, with more than 10,000 species of known seaweed (Collins et al., 2016). Commercial aquaculture of seaweed is carried out in France and Spain (Murphy et al., 2013). Seaweeds are used in a variety of ways, for example, as unique polysaccharides (agar, carrageenan, and alginate) in the pharmaceutical and food industries as an important source of gelling and thickening agents (Khalil et al., 2017). In particular, wakame seaweed, kelp, seaweed, and hijiki seaweed are used in traditional dishes in Korea, China, and Japan (Seca et al., 2018). Furthermore, seaweeds are considered high-value health food ingredients, owing to their low fat content and high polysaccharide, fiber, and polyunsaturated fatty acid content Gabbia and Martin (2020). In addition to the important nutrients, minerals, functional ingredients, and carotenoids contained in vegetables, seaweed also contains unique ingredients, which can further reduce the onset of diseases and promote health (Lordan et al., 2011; Fitzgerald et al., 2011).

Recent epidemiological studies have shown that a diet high in seaweed, vegetables, and fruits prevents arteriosclerosis (Moyama et al., 2017). Another epidemiological study reported that a diet rich in seaweeds, vegetables, soy products, and mushrooms is associated with prevention of CVD and type 2 diabetes (Osonoi et al., 2016). In particular, in Japan, where kelp and wakame seaweed intake is high, its relationship with increased longevity due to decreased CVD has been reported (Shimadzu et al., 2007; Moyama et al., 2017). Seaweeds contain components such as carotenoids, phycobilins, fatty acids, polysaccharides, vitamins, sterols, tocopherols, and phycocyanins, suggesting that they may be associated with CVD prevention (Lordan et al., 2011). In addition, peptides contained in seaweed have been reported to control blood pressure (Fitzgerald et al., 2011). Thus, the risk of CVD may be decreased by intake of the components contained in seaweed.

Edible seaweeds in Japan include kelp, hijiki, and wakame seaweeds, which are classified as brown algae, green algae (sea lettuce), and red algae (seaweed), respectively. Kelp and wakame seaweed are expected to have beneficial effects on health, and dietary fibers; for example, viscous alginic acid and fucoidan contained in these seaweeds are known to have various physiological effects. Further, fucoidan intake has been shown to block increases in serum total cholesterol, triglycerides (TGs), and low-density lipoprotein (LDL) cholesterol levels and increase high-density lipoprotein (HDL) cholesterol levels (Park et al., 2019). In addition, fucoxanthin reduces oxidative stress by activating the strong antioxidant nuclear erythroid-2 like factor-2 (NRF2)/antioxidant response element (ARE) system (Liu et al., 2011). Additionally, infrequently used edible seaweeds, such as Arame, *Ecklonia cava*, and *Ecklonia stolon*, contain abundant polyphenols unique to seaweeds, such as fluorotannin, in addition to dietary fiber. Many of the polyphenols present in these seaweeds are localized in the cell wall and play roles in reducing oxidative damage caused by ultraviolet light (Gomez-Guzman et al., 2018). In addition, several other polyphenols, such as fluorotannin, prevent lifestyle-related diseases, including diabetes, and exert other beneficial effects on health (Lopes et al., 2016).

In recent years, seaweed has been recognized as a new food product in Europe, and its consumption is expected to have health-related effects (Bouga and Combet, 2015). The growing interest in seaweed is associated with the bioactive substances it contains, which reduce the risk of noncommunicable diseases (Collins et al., 2016). However, the mechanisms of action of the components contained in seaweed and their effects on vascular endothelial cells are not well understood. In this review, the effects of dietary seaweed components on the prevention of vascular endothelial cell dysfunction are discussed. In addition, the potential for prevention of atherosclerosis and CVD caused by endothelial dysfunction is described.

2. Epidemiological studies of the prevention of CVD by ingestion of seaweed

Several epidemiological studies have shown that dietary seaweeds prevent the development of deadly CVDs Zaporozhets and Besednova (2016). For example, the comparative WHO-CARDIAC study compared dietary factors in Hawaii, Brazil, and Okinawa and showed that longevity in Okinawa was associated with seaweed, soybean, fish, and green vegetable intake (Yamori et al., 2001). In this intervention study, participants of Brazilian Nikkei (10 men and 10 women aged 47–57 years at a high risk of cardiovascular diseases) were included. The daily intake of 3 g docosahexaenoic acid (DHA) significantly reduced blood pressure (BP). In addition, the daily intake of 5 g of seaweed powder significantly reduced the serum cholesterol level. In other study, the results from two large cohorts (age range: 40–69 years, 40,707 men and 45,406 women) showed that seaweed intake was inversely associated with the risk of ischemic heart disease (Murai et al., 2019). Furthermore, another Japanese cohort study (40,547 individuals, 40–79 years old, men and women) showed a relationship between dietary intake patterns, such as seaweed, soy products, fish, vegetables, fruits, and green tea, and reduced CVD risk (Shimadzu et al., 2007). The following three dietary patterns were compared in this study: (1) Japanese diet patterns rich in soy, such as, fish, seaweed, vegetables, fruits, and green tea (2) animal-derived dietary patterns; and (3) high dairy product, fruit, and vegetable, and low alcohol dietary patterns. In particular, researchers showed that dietary patterns derived from animal materials are associated with an increased risk of CVD, whereas Japanese foods containing seaweed are associated with CVD prevention.

Atherosclerosis is a strong risk factor for myocardial infarction and stroke; thus, research on food intake for the prevention of atherosclerosis is important (Murray et al., 1997). For example, Moyama et al. (2017) investigated the relationships of food intake patterns and atherosclerosis in 70 Japanese individuals (39 men and 31 women) who had no history of stroke, coronary heart disease, or cancer. The results showed that abundant intake of seaweed, vegetables, seafood, and fruits reduced the pulse wave velocity of the upper arm ankle. Pulse wave velocity is used to assess cardiovascular risk, and an increase in pulse wave velocity is thought to be associated with the formation of atherosclerosis of the aorta. Thus, these results indicate that eating a diet containing seaweed may prevent the formation of arteriosclerosis by slowing the pulse wave velocity and reducing the risk of death (Sequi-Domingue et al., 2020).

Hypertension, diabetes, and dyslipidemia promote atherosclerosis, obesity, metabolic syndrome, and death from CVD (Ueshima et al., 2008). Recent reports have shown that seaweed intake reduces metabolic syndrome and its complications Gabbia and Martin (2020). Specifically, 58 obese individuals with hypercholesterolemia were given a seaweed extract (containing 600 mg polyphenols and 1200 mg fucoidan) daily for 12 weeks. They then examined changes in serum cholesterol (total, low-density lipoprotein, and high-density lipoprotein), TG levels, plasma glucose levels, insulin levels, and inflammation markers (Murray et al., 2018). The results showed that ingestion of seaweed extract improved blood cholesterol, TGs, glucose, insulin, and inflammatory markers. In addition, another study examined the effects of seaweed intake on blood pressure in children and adults (Wada et al., 2011). Intake of seaweed in preschool children ($n = 459$) was calculated from a dietary questionnaire, and the relationship between body weight

Table 1
Ingredients contained and carbohydrate compositions in seaweed.

Seaweeds	Class	Compositions (%) Carbohydrates	Protein	Lipid	Ash	Total fiber#	Carbohydrate compositions
Sargassum fulvellum	Brown	39.6	13	1.4	46	-	Laminarin, Mannitol, Alginate, Fucoidan, Cellulose
Laminaria japonica		51.9–59.5	8.1–14.8	1.5–1.8	30.9–31.5	-	Laminarin, Mannitol, Alginate, Fucoidan, Cellulose
Gelidium amansii	Red	75.2–83.6	12.2–18.5	0.6–1.1	3.3–5.7	-	Agar, Carrageenan, Cellulose
Ulva lactuca lactuca	Green	54.3	20.6	6.2	18.9	3.8#	Starch, Cellulose
Ulva pertusa pertusa		65.2	7.0	2.6	25.2	3.8 #	

(g/100g wet weight) (MacArtain et al., 2007) (Murphy et al., 2013)

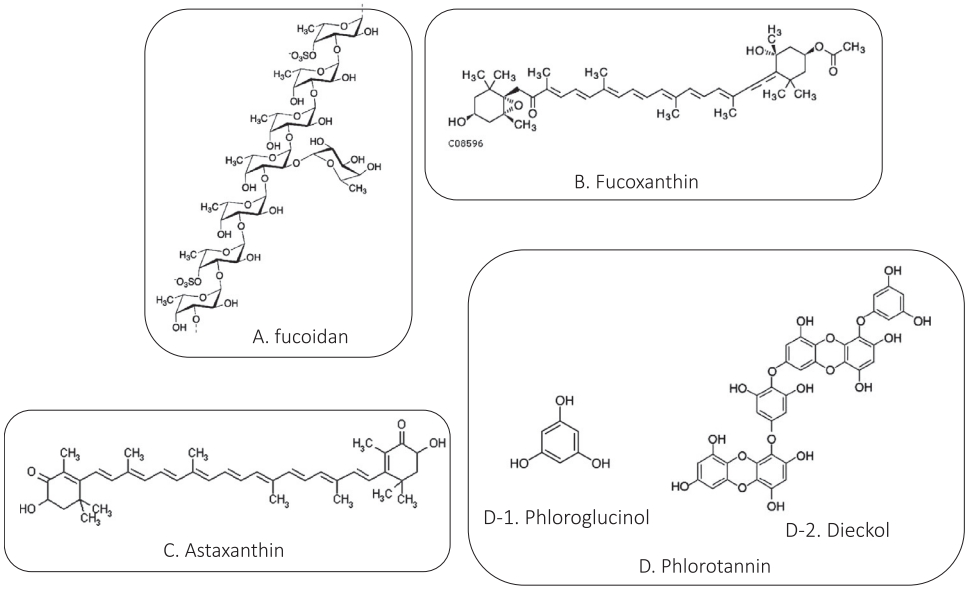

Fig. 1. Chemical structures of seaweed-derived components related to prevention of vascular endothelial cell damage.
A. Fucoidan contains sugar monomers in addition to a large number of fucose molecules. It also forms a branched structure (Deniaud-Bouet et al., 2017). B. The structure of fucoxanthin has special structures, such as allen bonds, conjugated double bonds, and epoxides (Zhang et al., 2015). C. Although the structure of astaxanthin is similar to that of β-carotene, a hydroxy group and a carbonyl group are bonded to both ends. D. The structure of fluorotannin is formed by polymerizing the monomeric phloroglucinol (D-1) (Catarino et al., 2017). The phloroglucinol dieckol (D-1) has multiple polymers of phloroglucinol.

and blood pressure was examined. The results of the analysis revealed a strong inverse correlation between seaweed intake and systolic blood pressure in preschool girls. In addition, ingestion of seaweed improved blood lipid levels. In another study in humans, the seaweed carotenoid astaxanthin (0, 6, 12, or 18 mg/day) was administered to humans aged 25–60 years without diabetes and hypertension for 12 weeks. The results showed that astaxanthin intake decreased blood TG levels and significantly increased blood HDL levels (Yoshida et al., 2010). Additionally, astaxanthin intake also increased serum adiponectin levels. Accordingly, the beneficial effects of seaweed ingestion may be related to the action of components such as astaxanthin contained in seaweed.

3. Ingredients contained in seaweed

Many types of seaweed have been identified. Brown algae (Phaeophyceae) seaweeds mainly include *Laminaria japonica* and *Sargassum fulvellum*, whereas *Gelidium amansii* belongs to the red algae (Rhodophyceae) family, and *Ulva lactuca* and *U. pertusa* belong to the green algae (Chlorophyceae) seaweed family. *L. japonica, S. fulvellum*, and *G. amansii* contain the highest amounts of carbohydrates (51.9–59.5%, 75.2–83.86%, and 39.6%, respectively; Table 1). In addition, the protein contents of these species are 8.1–14.8%, 12.2–18.5, and 13%, respectively, and the lipid contents are only 1.5–1.8%, 0.6–1.1%, and 1.4%, respectively (Murphy et al., 2013). The large amount of carbohydrates contained in seaweed makes up the cell walls. *L. japonica* (a brown algae seaweed) also contains multiple other components, including laminarin, mannitol, alginate, fucoidan, and cellulose. Moreover, *G. amansii* (a red algae seaweed) contains agar, carrageenan, and cellulose, whereas *U. lactuca* and *U. pertusa* contain starch and cellulose.

Seaweeds also contain polyphenols, such as catechins, flavonols, and fluorotannins (Gomez-Guzman et al., 2018). In particular, the brown alga *Fucus vesiculosus* and bladder wrack are rich in polyphenols, such as fluorotannin, and sulfated polysaccharides, such as fucoidan. Fig. 1 shows the names and structures of physiologically active components contained in typical seaweeds.

3.1. Fucoidan

Fucoidan is a polysaccharide that is abundant in the extracellular matrix of brown algae. As shown in Fig. 1A, the structure of fucoidan contains many fucose molecules and a large number of sugar monomers, which are sulfated to form a further branched skeletal structure (Deniaud-Bouet et al., 2017). Fucoidan constituents also include small amounts of monosaccharides, such as glucose, galactose, xylose, and mannose. Fucoidan is thought to contribute to maintaining cell stability and cell water retention by crosslinking between cellulose and hemicellulose Zayed and Ulbe (2020).

3.2. Fucoxanthin

Fucoxanthin, which is present in brown algae, is classified as a carotenoid xanthophyll, but has a unique structure different from those of other carotenoids (Fig. 1B). The structure of fucoxanthin includes allen bonds, nine conjugated double bonds, and epoxides (Zhang et al., 2015).

3.3. Astaxanthin

Astaxanthin, similar to fucoxanthin, is a red pigment classified as a carotenoid xanthophyll. Astaxanthin has almost the same structure as β-carotene; however, its structure is characterized by replacement of the hydrogen atoms bound to the cyclohexene rings at both ends with a

hydroxy group and a carbonyl group (Fig. 1C). The green alga *Haematococcus pluvialis* contains up to 4% astaxanthin (Deng et al., 2017). Because humans are unable to synthesize carotenoids, they must be ingested in the diet from sources such as seaweed-containing algae, plants, and fungi Sandmann (1994).

3.4. Fluorotannins

Fluorotannins are classified as polyphenols contained in brown algae (Catarino et al., 2017).

In recent years, researchers have evaluated the potential health benefits of fluorotannins. The structure of fluorotannin is formed by oxidatively polymerizing phloroglucinol, which is unique to brown algae, and various structures are formed depending on the polymerization method. Phloroglucinol is produced in seaweed as a monomeric phloroglucinol, which is then polymerized to form simple to very large molecules (Catarino et al., 2017). Fig. 1D shows the chemical structure of phloroglucinol and its polymer dieckol. Fluorotannin and phloroglucinol have many effects, including antioxidant, antibacterial, antiviral, antitumor, antidiabetic, and anti-inflammatory effects, and the anti-inflammatory effects of these components are particularly interesting (Yang et al., 2014).

4. Effect of seaweed components on endothelial cell damage

4.1. Fucoidan

Hyperlipidemia is a major cause of atherosclerosis. Cholesterol reverse transport (RCT) moves cholesterol from peripheral tissues to the liver and thus suppresses the formation of arteriosclerosis. HDL is responsible for transporting excess cholesterol from atherosclerotic lesions to the liver via RCT. Fucoidan administration has been shown to block increased plasma TG and cholesterol induced by high-fat diet intake in apolipoprotein E-deficient (apoE$^{-/-}$) mice and to significantly increase HDL cholesterol (Yin et al., 2019). In another study of hyperlipidemic mice, fucoidan intake markedly blocked increases in serum total cholesterol, TG, and LDL cholesterol levels with Poloxamer-407 administration. In addition, fucoidan intake has been shown to increase HDL cholesterol levels (Park et al., 2016) by blocking the gene expression of fatty acid synthase and acetyl-CoA carboxylase, which are responsible for fat synthesis, in HepG2 hepatocytes and liver tissues (Table-2). Moreover, fucoidan reduces the expression of 3-hydroxy-3-methyl-glutaryl-CoA reductase, the rate-limiting enzyme in the cholesterol synthesis pathway, and the transcription factor sterol regulatory element-binding protein (SREBP)-2 in the liver. Fucoidan also increases the gene expression of the LDL receptor and blocks the formation of vascular lesions in chronically Poloxamer-407-treated aortic atherosclerosis. These results indicate that fucoidan regulates the expression of RCT-related proteins and genes to reduce hyperlipidemia-induced atherosclerosis (Yang et al., 2019).

Induction of an inflammatory response by dyslipidemia is deeply involved in the formation and progression of arteriosclerosis. The mechanisms of action through which fucoidan blocks arteriosclerosis due to these stimuli have been reported. For example, ingestion of small molecule fucoidan in apoE-knockout mice reduces TG and oxidized LDL levels and promotes stabilization of atherosclerotic lesions (Xu et al., 2018). Fucoidan intake also reduces the inflammatory response by decreasing blood interleukin (IL)-6 levels in apoE-knockout mice. Furthermore, fucoidan increases the expression of IL-10 and lowers phospho-c-Jun N-terminal kinase (JNK) and cyclin D1 levels to the normal range. In addition, ingestion of fucoidan has also been shown to suppress the increased expression of the *CD11b* gene in the aorta and decrease *CD11b* expression in the intima layer. CD11b is an inflammatory surface marker expressed on macrophages with increased phagocytosis and has been used as an indicator of foaming Mehta and Dhawan (2020). Thus, fucoidan may block monocyte/macrophage foaming in apoE-knockout mice and inhibit the migration of smooth muscle cells to the intima layer in the aorta. Furthermore, fucoidan has also been shown to block tumor metastasis through anti-inflammatory, anticoagulant, anti-angiogenic, and anti-adhesive activities (Cumashi et al., 2007). In addition, experiments with a mouse thrombus model have shown that fucoidan induces the release of tissue plasminogen activator (t-PA) (Min et al., 2016). In particular, the thrombus-dissolving action of fucoidan t-PA is important because induction of plasminogen activator inhibitor (PAI)-1 causes the development of vascular diseases, such as stroke and heart disease, through thrombus formation (Chen et al., 2017). The antithrombotic effects of fucoidan are likely to prevent arteriosclerosis through thrombus formation and reduce the development of vascular disease.

High blood pressure causes increased mortality rates due to heart disease and stroke. Most cases of hypertension are related to dysfunctions of vasodilation due to endothelial NO synthase (eNOS) in vascular endothelial cells. Experiments with cultured human endothelial cells have shown that fucoidan treatment activates eNOS and Akt phosphorylation to increase NO production (Li et al., 2016). Moreover, fucoidan treatment reduces vascular inflammation and oxidative stress due to inducible NOS (iNOS) expression. These results indicate that fucoidan may function prophylactically through NOS production in the prevention and treatment of hypertension. In addition, impaired eNOS activity and NO bioavailability due to endothelial dysfunction are strongly associated with diabetes-related cardiovascular disorders (Kim et al., 2006). For example, in an experiment with Goto-Kakizaki type 2 diabetic rats, administration of fucoidan (50, 100, or 200 mg/kg/day, 12 weeks) resulted in endothelium-dependent relaxation of the mesenteric artery, ankle artery, and aorta. Fucoisan has also been reported to strongly alleviate hypertension. Additionally, administration of fucoidan prevents eNOS phosphorylation, eNOS expression, and decreased NO production due to diabetes. Ingestion of low-molecular-weight fucoidan also reduce intimal hyperplasia of the thoracic aortic wall after balloon injury. Matrix metalloproteinase-2 (MMP-2) has been shown to be involved in the inhibitory effects of fucoisan on intimal hyperplasia. Indeed, increased MMP-2 expression is associated with carotid artery thickness and plaque stability in atherosclerosis, thereby increasing the risk of acute stroke (Chen et al., 2018). Therefore, the inhibitory effects of fucoidan on MMP-2 may be important for the health of the arterial wall. Furthermore, the action of fucoidan has been shown to be associated with hyperplastic protective effects on both vascular endothelial cells and vascular smooth muscle cells (Hlawaty et al., 2011). The arterial wall is composed of three layers: intima, media, and adventitia; damage to the intima and hyperextension of the media lead to the proliferation of vascular smooth muscle cells, deposition of platelets, and recruitment of leukocytes (Feldman et al., 2000). These effects of fucoidan may be important for blocking the development of arteriosclerosis, maintaining the health of endothelial cells, and facilitating the integrity of blood vessel walls.

4.2. Fucoxanthin

Fucoxanthin is known to have antidiabetic, anti-obesity, and antioxidant effects (Peng et al., 2011) (Table 2). Fucoxanthin induces antioxidant (Sachindra et al., 2007) and anti-inflammatory effects (Shiratori et al., 2005), resulting in removal of reactive oxygen species (ROS) and prevention of disease. Moreover, previous studies have shown that fucoxanthin effectively removes radical scavengers (Nomura et al., 1997) and blocks DNA damage and apoptosis via modulation of intracellular ROS by increasing the expression of the antioxidant enzyme catalase (Peng et al., 2011). Fucoxanthin has also been shown to activate the NRF2/ARE antioxidant system and enhance the expression of heme oxygenase (HO)-1 and NAD(P)H quinone dehydrogenase 1, which act on antioxidants in mouse hepatocyte lines (Liu et al., 2011).

The prophylactic effects and mechanisms of action of fucoxanthin in atherosclerosis have been demonstrated using cultured human endothelial cells. For example, in vascular endothelial cells, fucoxanthin inhibits

Table 2
CVD-related effects of seaweed-derived components in cells and animals.

Component	In vitro or in vivo	Experimental model	Effects	References
	In vivo	Poloxamer-407 (250 mg/ kg, i.p) stimulation model in hyperlipidemic mice.	• Reduces increases in serum total cholesterol, TG, and LDL cholesterol levels ↓ • Increases HDL cholesterol ↑	Park et al., (2019)
	In vitro	HepG2 hepatocytes and liver tissue. Fucoidan (10, 30. 50, 100 μg/ml, 24 h).	• Decreases *FAS* and *ACC* gene expression ↓ • Decreases HMG CoA reductase and SREBP-2 expression ↓ • Increases LDL receptor gene expression ↑	
	In vitro	Vascular endothelial cells and vascular smooth muscle cells Fucoidan, *in vivo* (5 mg / kg / day), *in vitro* (10μg/ml).	•MMP-2 expression ↓	Hlawaty et al., (2011)
	In vivo	Mouse diabetes/obesity model. Fucoidan (0.2%).	•Decrease in serum cholesterol level ↓ • Increase in serum HDL ↑ • Decrease in liver cholesterol content ↓ • SREBP induction is associated with increase in HDL	Beppu et al., (2012)
	In vivo	Mouse high-fat diet model. High-fat control (HFC; 20% fat), Low-fucoxanthin groups (HFC + 0.05% Fucoxanthin), High-fucoxanthin groups (HFC + 0.2% Fucoxanthin).	•Reduces liver TG synthesis, adipocyte fatty acid synthesis, and cholesterol-regulating enzyme activity ↓ • Increases plasma HDL cholesterol ↑ • Increases fecal TG level ↑	Woo et al., (2010)
Astaxanthin	*In vivo*	Isoproterenol-induced myocardial infarction and cardiac hypertrophy model in rats (Long Evans male rats). Group I (Control group, normal water), Group II (isoproterenol (ISO) 50 mg/kg), Group III (ISO + Astaxanthin 25 mg/kg).	•Decreases ROS generation in heart tissue ↓ • Decreases oxidative damage ↓ • Increases antioxidant enzyme activity ↑ • Decreases lipid peroxidation ↓ • Decreases free radical and MDA levels ↓ •Increases NO levels ↑	Alam et al., (2018)
	In vitro	Homocysteine stimulation in cultured vascular endothelial cells. Astaxanthin (1, 2, 5 and 10 µM, 6h).	• Increases homocysteine-induced ROS production and decreases VEGF production ↓	Wang et al., (2019)
	In vivo	Rat diabetes endothelial cell damage model (streptozotocin). Astaxanthin (10 mg/kg/d).	• Inhibits aorta-induced oxidative stress and LOX-1 expression ↓ • eNOS expression ↑	Zhao et al., (2011)
	In vivo	Spontaneously hypertensive rats. Astaxanthin (58.2 µg/g yolk powder).	• Decreases blood pressure ↓	Hatabu et al., (2020)
	In vivo	Spontaneously hypertensive and stroke prone rats. Astaxanthin (3 and 6 mg/kg/d) .	• Antithrombotic and antihypertensive effects	Sasaki et al., (2011)
	In vivo	Rat coronary artery occlusion model. Astaxanthin (40 mg/kg/day for 2 weeks).	• Inhibits cardiac dysfunction and myocardial infarction ↓ • Decreases cardiomyocyte apoptosis inhibition ↑ • NRF2/HO-1 signal transduction activity ↑	Xue et al., (2019)
	In vivo	High-fat diet intake model in hyperlipidemic rats. Astaxanthin (5, 10 and 30 mg/kg/day, p.o.).	•Decreases platelet aggregation ↓ • Promotes fibrinolytic activity ↑ • Serum SOD activity and serum GPx activity ↑ • Increases serum NO and serum 6-ketoprostaglandin Fα ↑	Deng et al., (2017)
Phloroglucinol	*In vitro*	Arachidonic acid and PMA stimulation in polymorphic leukocytes. Phloroglucinol (10–50 μM).	•Inhibits platelet aggregation and TXB2 production ↓ • Inhibits ROS production ↓ • Inhibits COX, ROS, and TXA2 production ↓	Chang et al., (2012)
Dieckol	*In vitro*	High glucose stimulation in cultured vascular endothelial cells. Dieckol (10 or 50 μg/ml).	• Blocks ROS production ↓ • Reduces iNOS, COX-2, and NF-κB expression ↓	Lee et al., (2010)
Eckol	*In vitro*	Cultured vascular endothelial cells. 50~200 (μg/ml).	• Antithrombotic and fibrinolysis-promoting effects	Kim et al., (2012b)
	In vitro	Cultured vascular endothelial cells. (50~200 μg/ml).	• Protects the vascular barrier	Kim et al., (2012b)

Abbreviations. ACC, acetyl-CoA carboxylase; AKT, protein kinase B; COX, cyclooxygenase; eNOS, endothelial nitric oxide synthase; FAS, fatty acid synthase; GPx, glutathione peroxidase; HDL, high-density lipoprotein; HMG CoA, hydroxymethylglutaryl-CoA; HO-1, heme oxygenase; LDL, low-density lipoprotein; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; MDA, malondialdehyde; MMP-2, matrix metalloproteinase-2; NRF2, nuclear erythroid-2 like factor-2; NO, nitric oxide; NF-κB, Nuclear Factor kappa B; oxLDL, oxLDL; ROS, reactive oxygen species; SREBP, sterol regulatory element binding protein; SOD, superoxide dismutase; TG, triglyceride; t-PA, tissue plasminogen activator; TXA2, thromboxane A2; TXB2, thromboxane B2.

mitochondrial function attenuation and apoptosis induction caused by oxidative damage via decreasing superoxide dismutatse (SOD) activity induced by oxLDL (Ou et al., 2019) (Table 2). That is, fucoxanthin restores the protective effects of oxLDL on endothelial cell damage through dephosphorylation of phosphoinositide-3-kinase/AKT. Moreover, fucoxanthin also restores cAMP response element-binding protein and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) expression to near normal levels. Furthermore, fucoxanthin upregulates AMP-activated protein kinase (AMPK). These mechanisms of action demonstrate that fucoxanthin protects against oxLDL-induced endothelial cell damage. In addition, fucoxanthin reduces serum cholesterol levels in rodents (Beppu et al., 2012). In this experiment, dietary fucoxanthin (0.2%) was found to increase serum HDL and decrease hepatic cholesterol content in diabetes/obese model mice. Thus, the induction of SREBP was shown to be related to the HDL-promoting effects of fucoxanthin. In another experiment, fucoxanthin was found to significantly reduce plasma and hepatic TG synthesis, adipocyte fatty acid synthesis, and cholesterol-regulating enzyme activity induced in a mouse high-fat

diet model. Fucoxanthin also increased plasma HDL cholesterol and fecal TG levels. These results indicate that fucoxanthin may alter serum patterns of TGs and promote the excretion of TGs (Woo et al., 2010).

Importantly, fucoxanthin derived from actual seaweed has also been shown to exert several biological effects. For example, fucoxanthin isolated from the brown alga *Sargassum* has been shown to have antioxidant and angiotensin-converting enzyme (ACE) inhibitory effects in an in vitro study (Raji et al., 2020). Additionally, fucoxanthin exerts inhibitory effects by interacting with the zinc ion at the active site of amino acids in human ACE. These actions are important for the prevention of hypertension. Another study has shown that wakame-derived fucoxanthin reduces nerve damage induced by reoxygenation after hypoxia in spontaneously hypertensive rats in a model of stroke (Ikeda et al., 2003).

4.3. Astaxanthin

Astaxanthin has strong antioxidant effects and removes singlet oxygen and free radicals to prevent lipid peroxidation (Yuan et al., 2011). In particular, astaxanthin has a unique molecular structure and exerts its effects by penetrating into the surface and inside of the cell membrane (Ambati et al., 2014). By entering into the cell membrane, astaxanthin can effectively block the ROS generated in the membrane and exert stronger antioxidant effects than other antioxidants. Because the increase in oxidative stress caused by chronic inflammation is a general feature of cardiovascular diseases, the antioxidant effects of astaxanthin are expected to prevent these diseases. For example, the effects of astaxanthin on isoproterenol-induced myocardial infarction and cardiac hypertrophy have been demonstrated (Alam et al., 2018) (Table 2). Moreover, astaxanthin blocks ROS generation, oxidative damage, inflammation-related signal transduction, and lipid peroxidation but increases antioxidant enzyme activity in rat heart tissue. In another study, researchers evaluated the effects of astaxanthin on the expression of antioxidant enzymes in rabbits fed a high-cholesterol diet for 60 days (Augusti et al., 2012). Astaxanthin inhibited hypercholesterolemia-induced protein oxidation and reduced protein oxidation per se. Furthermore, the activities of superoxide dismutase and thioredoxin reductase were potentiated. In addition, astaxanthin has been shown to exert antioxidant effects on the production of excess ROS induced by ischemia and reperfusion injury (Zuluaga et al., 2018).

Hyperglycemia induces damage to vascular endothelial cells and increases the risk of diabetes-related CVD. In one study, human endothelial cells were cultured in a high glucose state for 3 days, and the effects of astaxanthin were investigated (Abdelzaher et al., 2016) (Table 2). Researchers showed that astaxanthin blocked the high glucose-induced increase in ROS production and p22phox expression and suppressed the inhibition of PGC-1α expression. In addition, astaxanthin blocked the decrease in eNOS phosphorylation at serine 1177 induced by high glucose. Furthermore, astaxanthin also blocked the expression of high glucose-related pro-inflammatory mediators, including IL-6 and intercellular adhesion molecule 1 (ICAM-1). Similarly, astaxanthin reduced the phosphate esterification levels of JNK and p38, which are induced by high glucose stimulation. These results indicate that astaxanthin may block ROS production and protect against hyperglucose-stimulated vascular endothelial cell damage. Other experiments using cultured human vascular endothelial cells have shown that astaxanthin promotes homocysteine-induced reductions in cell migration and tube formation in a dose-dependent manner (Wang et al., 2019) (Table 2). In addition, in this experiment, astaxanthin reversed homocysteine-induced increases in ROS production and decreases in vascular endothelial growth factor (VEGF) production. This action of astaxanthin reduced cell damage caused by oxidative stress and increased VEGF production in endothelial cells to accelerate the regeneration of vascular tissue. Stimulation of vascular endothelial cells with the methionine metabolite homocysteine causes strong damage to vascular endothelial cells, induces arteriosclerosis, and causes vascular conditions such as cerebrovascular disease (Skovierova et. al., 2016). Therefore, astaxanthin may repair damaged endothelial cells and participate in the regeneration of vascular tissue. This action of astaxanthin involves promotion of the angiogenic process of vascular tissue regeneration, suggesting that astaxanthin may inhibit endothelial dysfunction and contribute to alleviation of CVDs through the regeneration of vascular tissue. Another study demonstrated the inhibitory effects of astaxanthin on endothelial cell damage using a rat diabetes model (Zhao et al., 2011). Astaxanthin was found to inhibit aortic-induced oxidative stress and oxLDL receptor 1, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression in diabetic rats induced by streptozotocin injection, resulting in increased eNOS expression. LOX-1 is a 50 kDa transmembrane protein that recognizes oxLDL in endothelial cells and enhances atherosclerosis through endothelial dysfunction, oxLDL uptake, and apoptosis (Barreto et al., 2020). Therefore, astaxanthin may reduce diabetes-induced endothelial dysfunction through suppression of LOX-1 expression. In addition, another study showed that feeding spontaneously hypertensive rats daily with an astaxanthin-rich diet for 15 weeks reduced blood pressure in a dose-dependent manner (Hatabu et al., 2020).

In a rat model, oral administration of astaxanthin (50 mg/kg/day) for 22 weeks significantly reduced the arterial blood pressure of SHRcp rats (Hussein et al., 2007). In this experiment, fasting blood glucose levels and insulin resistance indexes were significantly reduced, and improved insulin sensitivity was observed. Moreover, astaxanthin intake was found to result in marked increases in adiponectin levels and HDL cholesterol and a marked decrease in plasma TG levels. In addition, astaxanthin intake reduced the sizes of adipocytes. Thus, these results indicated that astaxanthin was effective for preventing diabetes by improving insulin resistance through multiple mechanisms.

Astaxanthin is also effective for preventing several other CVD-related pathologies (Yoshida et al., 2010; Iizuka et al., 2012). For example, experiments with spontaneously hypersensitive stroke prone rats have shown that astaxanthin has antithrombotic and antihypertensive effects (Sasaki et al., 2011). Additionally, astaxanthin treatment combined with coronary artery occlusion treatment reduced the occurrence of cardiac dysfunction, myocardial infarction, and cardiomyocyte apoptosis (Xue et al., 2019). As a mechanism of this cardioprotective effect of astaxanthin, oxidative stress, which is increased by coronary artery occlusion, enhances the activity of NRF2/HO-1 signaling. In another experiment, hyperlipidemic rats fed a high-fat diet were administered astaxanthin (5, 10, or 30 mg/kg/day, orally) for 4 weeks with increased blood coagulation; following this treatment, platelet aggregation was reduced, and fibrinolytic activity was promoted (Deng et al., 2017). Additionally, serum SOD activity (2.1 times), serum glutathione peroxidase activity (1.8 times), plasma prothrombin time (1.3 times), plasma activated partial thromboplastin time (1.7 times), serum NO (1.4 times), and serum 6-keto prostaglandin F 1α (1.3 times) were increased with astaxanthin treatment. These results indicate that astaxanthin reduces the induction of the blood coagulation system by hyperlipidemia, likely by maintaining the balance of NO/ROS and thromboxane A2 (TXA2)/prostacyclin with t-PA/PAI-1.

High levels of blood HDL cholesterol are associated with a reduced risk of atherosclerosis. One of the protective effects of HDL atheroma is the mechanism of RCT. In a mouse study, the effects of astaxanthin on RCT and atherosclerosis were investigated (Zou et al., 2017). Ingestion of astaxanthin promotes the reduction of plaque present in the aortic sinus and the removal of cholesterol from the aorta. This result indicates that astaxanthin may reverse the transport of cholesterol accumulated in blood vessels, leading to removal of cholesterol and prevention of arteriosclerosis. In another study, the effects of protocatechuic acid, a major metabolite of anthocyanins, on atherosclerosis were demonstrated in in vivo studies of apoE-deficient mice (Wang et al., 2010). That is, administration of protocatechuic acid reduced the levels of vascular cell adhesion molecule-1 and ICAM-1 expression and nuclear factor-κB activity in mouse aortic endothelial cells. This effect of protocatechuic acid may prevent the formation of atherosclerosis through its anti-inflammatory effects.

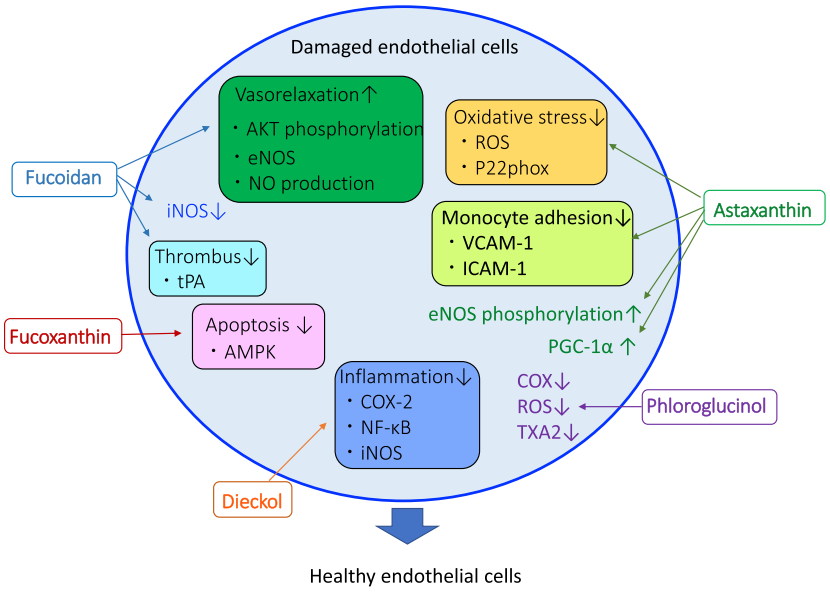

Fig. 2. Preventive effects of seaweed components on vascular endothelial cells. Stimulatory effects of fucoidan on vascular endothelial cells, resulting in phosphorylation of AKT and increased nitric oxide production through activation of eNOS (Li et al., 2016). In addition, astaxanthin inhibits the production of ROS (Wang et al., 2019). Furthermore, the polyphenols phloroglucinol and dieckol reduce nuclear factor-κB-mediated COX and prevent inflammation (Lee et al., 2010; Chang et al., 2012)). Similarly, fucoxanthin blocks oxidative stress-induced apoptosis of endothelial cells through activation of AMP-activated protein kinase (AMPK) (Ou et al., 2019).

4.4. Phlorotannin

Phloroglucinol derivatives, including phloroglucinol, diecol, 2,7-phloroglucinol-6,6-biecol, pyrogallol-phloroglucinol-6,6-biecol, and phloroglucinol A, are involved in monocyte inflammation and are expected to have protective effects on endothelial cells (Son et al., 2019). Thus, phloroglucinol pyrogallol-phloroglucinol-6,6-biecol was examined by oral administration in a diet-induced obesity model and a dietary hypertension model in mice (Son et al., 2019). The results showed that 4-week administration of pyrogallol-phloroglucinol-6,6-viecol reduced cell adhesion molecule expression, endothelial cell death, and vascular smooth muscle cell proliferation and migration compared with the untreated group. In addition, pyrogallol-phloroglucinol-6,6-viecol treatment had beneficial effects on blood pressure, lipoprotein levels, and cholesterol levels. Another in vitro analysis showed that pyrogallol-phloroglucinol-6,6-viecol blocked monocyte migration and macrophage inflammation (Oh et al., 2018). Furthermore, pyrogallol-phloroglucinol-6,6-biecol has been shown to prevent monocyte-induced endothelial cell death, caspase activation, and monocyte-induced hyperproliferation and migration of vascular smooth muscle cells.

Platelet dysfunction is involved in the development of CVDs, such as atherosclerosis, stroke, and myocardial infarction. Phloroglucinol is a bioactive substance isolated from seaweed that has been shown to block arachidonic acid-induced platelet aggregation and thromboxane B2 (TXA2) production (Chang et al., 2012) (Table 2). In this experiment, phloroglucinol was shown to inhibit phorbol myristate acetate-stimulated ROS production from polymorphic leukocytes. In addition, inhibition of cyclooxygenase (COX), ROS, and TXA2 production was associated with the antithrombotic and anti-inflammatory effects of phloroglucinol. In particular, phloroglucinol has been shown to regulate extracellular signal-regulated kinase/p38 phosphorylation in platelets and act as an antithrombotic agent.

Dieckol is a major polyphenol of fluorotannin and has been shown to inhibit hyperglucose-induced damage to human vascular endothelial cells (Lee et al., 2010). Dieckol inhibits hyperglucose-induced endothelial cell damage and blocked ROS production. In addition, dieckol reduces high glucose-induced protein expression of iNOS, COX-2, and nuclear factor-κB. These results indicate that dieckol may reduce endothelial cell damage caused by diabetic hyperglycemia-induced oxidative stress. Similar to dieckol, eckol, which belongs to the same fluorotannin, has been shown to have antithrombotic and profibrinolytic effects (Kim et al., 2012a) (Table 2). In addition, eckol has been shown to act on endothelial cells to protect the vascular barrier (Kim et al., 2012b).

5. Conclusion

Seaweeds contain a variety of bioactive substances and may have many beneficial effects on human health. In this review, the prevention of CVDs by seaweed intake was discussed, and the actions of components contained in seaweed, such as fucoidan, fucoxanthin, and astaxanthin, on vascular endothelial cells were evaluated. Importantly, the specific components contained in seaweed may prevent damage to vascular endothelial cells through multiple mechanisms, including repair of healthy endothelial cells, to prevent the development of CVD. As shown in Fig. 2, for vascular endothelial cells, fucoidan induces NO production, astaxanthin blocks ROS production, and polyphenols (such as phloroglucinol and dieckol) block inflammation by decreasing COX expression. Furthermore, fucoxanthin blocks the induction of apoptosis. During the development of arteriosclerosis, damage to vascular endothelial cells can be repaired, even through the weak actions of seaweed components, because the repair ability of endothelial cells is high during early stages of the disease. Therefore, seaweed components may act on endothelial cells to contribute to CVD prevention (Evans et al., 2020). However, longer-term human studies are needed to assess the efficacy of these seaweed components against CVD. Overall, these studies support that seaweed may have preventive effects on CVD and could be used as a functional food.

Author contributions

Kazuo Yamagata: Conceptualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision.

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