Review

Effects of Marine-Derived Components on Cardiovascular Diseases Risk Factors and Gut Microbiota Diversity

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Review

Effects of Marine-Derived Components on Cardiovascular Diseases Risk Factors and Gut Microbiota Diversity

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Abstract: Cardiovascular diseases (CVDs), which comprise coronary heart disease, hypertension and stroke, collectively represent the number one cause of death globally. Atherosclerosis is the dominant cause of CVDs; and its risk factors are elevated levels of low-density lipoprotein-cholesterol and triglycerides, hypertension, cigarette smoking, obesity and diabetes mellitus. In addition, diverse evidence highlighted the role played by inflammation and clonal haematopoiesis, eventually leading to the immunity involvement. The human microbiota project and subsequent studies using next-generation sequencing technology have highlighted that thousands of different microbial species are present in the human gut. The disturbances in the gut microbiota (GM) composition, i.e., gut dysbiosis, have been associated with diseases ranging from localized gastrointestinal disorders to metabolic and cardiovascular illnesses. Of note, experimental studies suggested that GM, host immune cells and marine-derived ingredients work together to ensure the intestinal wall integrity. This review discusses current evidence concerning the links among GM, marine-derived ingredients and human inflammatory disease. In detail, we summarize the impact of fish-derived proteins and algae components, on CVDs risk factors and gut microbiome. Furthermore, we describe the interplay among these dietary components, probiotics/prebiotics and CVDs.

Keywords: cardiovascular diseases; atherosclerosis risk factors; microbiota; fish protein hydrolysates; seaweeds; probiotics

1. Introduction

1.1. Cardiovascular Diseases Risk Factors

Cardiovascular diseases (CVDs), which comprise coronary heart disease, hypertension and stroke, collectively represent the number one cause of death globally [1]. Atherosclerosis, the dominant CVDs cause, is the process leading to the accumulation of fatty and/or fibrous material in the innermost layer of arteries, aka the intima. Subsequently, atherosclerotic plaque can acquire more fibrous material and gather calcium mineral. Advanced atherosclerotic plaques can produce a flow-limiting obstruction or disrupt and promote the thrombus development, both these phenomena lead to tissue ischaemia and, eventually, to the clinical manifestations of atherosclerosis, i.e., myocardial infarction, strokes and peripheral artery disease [2]. Risk factors for atherosclerotic lesion's development and its thrombotic complications are elevated levels of low-density lipoprotein-

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cholesterol (LDL-C) and triglycerides (TG), hypertension, cigarette smoking, obesity and diabetes mellitus. Diverse evidence also highlighted the role played by inflammation and clonal haematopoiesis, eventually leading to the immunity involvement [3,4].

Of note, a recent study demonstrated that in patients already taking statin therapy, residual inflammatory risk appears to be strongly associated with future CV events than residual cholesterol risk [5,6]. These data strengthen the hypothesis that concomitant targeting of inflammation and atherogenic lipids, will further diminish CVDs' risk. However, conventional therapeutic approaches, often exhibit limitations, i.e., side effects [7] and inadequate disease control [8–10]. Additionally, it is well known that all the above-mentioned CVD's risk factors are susceptible to lifestyle modifications, such as diet and physical exercise [11]. In line with this evidence, in recent years diverse natural products and their derivates have garnered increasing attention as care standard, along with pharmacotherapy, for the CVDs treatment [12].

1.2. Microbiota-Immune Axis and CVDs: State of the Art

10–100 trillion symbiotic microbial cells reside in the human body and are known as the human microbiota. The totality of these cells, belonging to bacteria, fungi and parasites together with genetic material (e.g. from viruses) make up the human microbiome. Our genetic ancestry is made by a combination of human and microbial species; thus, our metabolism is determined by microbial and human signatures [13].

Recent research has shown that the gut microbiota (GM) acts as an endocrine organ, playing a role in modulating immunity and influencing the development of inflammatory, metabolic and infectious diseases [14]. Dietary fibre, which is the indigestible components of fruits, vegetables, and grains, is recognized as a significant energy source for bacteria that produce short chain fatty acids (SCFAs) [15]. When there is a balanced composition of human microbiome, it leads to a healthy intestinal epithelial barrier and the recruitment and activation of the appropriate immune cells through the secretion of metabolites, particularly SCFAs, and the expression of microbial components [16]. The Western diet, rich in simple carbohydrates and saturated fats, along with reduced physical activity, has contributed to gut and skin dysbiosis, altering immune balance. A shift from living in close contact with natural environments, combined with changes in eating habits, such as an increase in ultra-processed foods, red meats and a reduction in fibre-rich foods, has led to a GM depletion [17,18]. Eventually these conditions can lead to metabolic problems and variations in symbiotic microorganisms, rushing the CVDs development [19]. An increasing body of research indicates that intestinal bacteria and their metabolites are crucial in the development of CVDs. Some studies suggest that hypertension patients often show a lower diversified gut microbiota, along with an increased prevalence of certain bacteria like *Clostridiales* and *Bacteroidales* [20,21]. These microbiota changes, observed in both humans and animal models, may play a role in hypertension's development by affecting blood pressure regulation through microbial by-products such as SCFAs [20,21]. Systolic blood pressure instead is correlated with *Robinsoniella* and *Catabacter* abundance in a study on Coronary Artery Risk Development in Young Adults (CARDIA) [22].

In addition, cigarette smoke may affect the GM composition and function by upregulating oxidative stress-related enzymes, modifying the gut mucin layer and the expression of intestinal tight junction proteins, as well as by stimulating the spread of non-commensal bacteria [23]. The smokers GM differs from that of non-smokers, with a higher relative abundance of *Actinobacteria* and *Cyanobacteria* [24].

Different investigations indicate a correlation between GM and CVDs, with trimethylamine-N-oxide (TMAO) identified as a crucial metabolite [25]. Indeed, TMAO is synthesized from dietary choline and carnitine [26], by gut bacterial TMA-lyase, which produces TMA that is subsequently adsorbed by intestinal cells and transported to the liver. There it is oxidized by the enzyme flavin-containing monooxygenase 3 (FMO3). A meta-analysis of prospective studies revealed that individuals with elevated plasma TMAO levels had a 23% higher risk of CV events [27] and a 62% greater risk of all-cause mortality [28]. Altogether, these data suggest that TMAO has been linked to an elevated CVDs risk [29].

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Conversely, the gut microbiota produces metabolites like SCFAs and in detail the butyrate that shows beneficial effects on the host, including promoting growth and reducing inflammation in intestinal epithelial cells. Additionally, butyrate plays a key role in maintaining immune balance in the gut by facilitating communication between the host and microbiota [16].

Nutritional interventions targeting the gut microbiota, such as probiotics, prebiotics, and postbiotics, have shown promise in preventing CVDs, especially when implemented early in life [30].

1.3. Marine-Derived Compounds and CVDs

Marine species, aka mammals, fish, seaweeds, sea anemones, sponges, represent approximately one-half of the global biodiversity. Therefore, the sea offers a wonderful resource for novel compounds, potentially able to improve the health of the worldwide population. Attention has been drawn to the beneficial effects of fish consumption, due to the ability of fish ingredients, mainly omega-3 polyunsaturated fatty acids (n-3 PUFAs) and proteins, to lower CVDs risk factors [31–33] and modulate inflammation [34–37].

Based on these data, the US Food and Drug Administration (FDA) have formally declared that consumption of up to 3 g/d of marine-derived n-3 PUFAs is generally considered as safe. In line with this health claim, fish consumption is still recommended in the 2020-2025 Dietary Guidelines for Americans and by the American Heart Association [38]. Additionally, a recent positional paper strengthened the positive relationship between the replacement of proteins from red meat with proteins from fish and reduced risk of CVDs [39]. In agreement, two meta-analyses reported a significant inverse association between fish consumption and all-cause of mortality, with a nadir at consumption of 60-80 g/d and that this inverse association is marked influenced by regional differences, respectively [40,41]. More in detail, Jayedi et al, found that in Western studies the risk of all-cause and CVD mortality decreased in a dose-dependent manner and then increased with a relatively sharp trend, suggesting a U-shape curve association. While, in Asian studies this dose-response relationship was linear [41]. Recently, Zhou et al in a general Chinese population found a reverse J-shaped association between fish-derived protein and new-onset hypertension [42]. Meaning that, there is a window of consumption (appropriate level) where the risk of new-onset hypertension is lower. These data confirmed previously results that showed a U-shaped curve association between protein intake and health [43]. Additionally, recent data have documented seaweeds as promising reservoirs of bioactive compounds able at targeting multiple aspects of CVDs, including inflammation [44,45]. Specifically, seaweeds contain polysaccharides, proteins, pigments, lipids, sterols, terpenes and phenolic compounds [46].

This review summarizes the impact of marine-derived ingredients, aka fish-derived proteins and algae components, on CVDs risk factors and gut microbiome. Furthermore, we describe the interplay among these dietary components, probiotics/prebiotics and CVDs.

2. Fish-Derived Proteins and CVDs Risk Factors

Fish-derived proteins contain all the essential amino acids, mainly lysine and leucine, some non-essential amino acids (aspartic acid, glutamic acid, and alanine), together with the amino acid-derived organic acid taurine [47–49]. Different studies have proved that the enzymatic digestion of fish by-products is an efficient means of producing peptides with enhanced bioactivity [48]. Furthermore, experimental and clinical data have investigated the impact of fish-derived proteins/bioactive peptides on lipid profile, glucose metabolism, inflammation, and blood pressure.

2.1. Experimental Studies

A recent systematic review and meta-analysis described all the pre-clinical data performed in rodents and published before July 15, 2022 [33]. This paper concluded that intake of protein from fish muscles or fish by-products significantly decrease circulating total cholesterol (TC) concentration when compared to their control group. Of note, the authors highlighted that the stronger effect of fish-derived proteins' intake was observed in the subgroup comprising genetically modified rodent

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models, which spontaneously develop hypertension after birth, and rodents fed diets enriched with cholesterol alone or in combination with cholate (added to exacerbate hypercholesterolemia [50–52]. This data, indicating that the potency for preventing an increase of TC was higher than that for lowering TC plasma levels, may have relevant clinical application, albeit not directly transferable to human. Furthermore, the authors analysed diverse mechanisms of action to justify the hypocholesterolemic effects exerted by the dietary intake of fish or fish proteins (Figure 1).

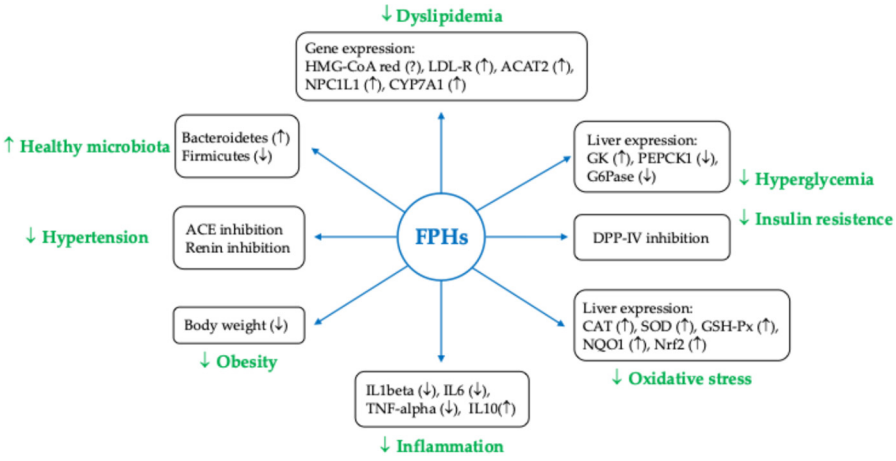

Figure 1. Schematic representation of the fish proteins hydrolysates (FPHs) mechanism of actions. HMGCoA red: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; LDL-R: low-density lipoprotein-receptor, ACAT2: acyl-CoA:cholesterol acyltransferase; NPC1L1: Niemann-Pick C1-like 1; CYP7A1: cholesterol 7-alpha-hydroxylase; GK: glucokinase; PEPCK1; phosphoenolpyruvate carboxikinase1; G6Pase: glucose-6-phosphate; DPP-IV: dipeptidyl peptidase-IV; CAT: catalase; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; NQO1: quinone oxidoreductase 1; Nrf2: nuclear factor-erythroid 2-related factor 2; IL: interleukin; TNF: tumour necrosis factor; ACE: angiotensin-I-converting enzyme.

They found that in almost half of the analysed studies a lower TC concentration was associated with higher faecal excretion of cholesterol and/or bile acids. Furthermore, in two papers [53,54] the above-described effects were also combined with higher mRNA expression levels of cholesterol 7-alpha-hydroxylase (CYP7A1) [55], which is the first and rate-liming enzyme in the cholesterol metabolism, such as the bile acid synthesis. On the contrary, the impact of fish or fish-proteins on the expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), LDL-receptor (LDL-R), and acyl-CoA:cholesterol acyltransferase (ACAT2) was difficult to assess, because it was marked influenced by the rodent model used. However, an elegant and recent work demonstrated that the hypocholesterolemic effect exerted by Alcalase-silver carp hydrolysate (Alcalase-SCH) was associated with an up-regulation of LDL-R expression and a down-regulation of Niemann-Pick C1-like 1 (NPC1L1) and ACAT2 [56]. In addition, these authors identified novel peptides, present in the Alcalase-SCH, as main contributors to the hypocholesterolemic activity of Alcalase-SCH [56]. Of note, in line with data obtained with soya, potatoes and rice proteins, lower methionine/glycine and lysine/arginine ratios were also observed in fish proteins compared with casein, together with a lower TC plasma level. In addition, salmon protamine is a strongly alkaline polycationic low-molecular-weight protein, in which nearly two-thirds of the amino acid composition is arginine [57–59]. It is well known that arginine, being a precursor for nitric oxide (NO) synthesis, may positively affect vascular function [60]. Indeed, arginine supplementation has been shown to decrease neointimal formation in animal models [61,62], and to improve flow-mediated vasodilation in humans [63].

These data were subsequently confirmed by diverse experiments. Oral administration of jellyfish collagen hydrolysate (JCH) was able to prevent the increase of serum glucose, TC and TG

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levels, together with the body gain weight in a mouse model of obesity, aka mice fed a high-fat diet (HFD) [64]. Additionally, JCH administration modulated oxidative stress and inflammatory response, crucial factors implicated in obesity-related pathologies, and helped recover the alteration on microbiota composition induced by high-fat diet, specifically by contrasting the lowering of *Romboutsia*'s abundance [64]. Similar data were published by Shi et al, in healthy mice fed a chow diet and treated with Half-fin Anchovy hydrolysate (HAHp) or with its Maillard reaction products (HAHp-MRPs) by oral gavage [65]. Significantly, the glycation process or Maillard reaction, aka the chemical process involving proteins and sugars during food processing, can enhance protein and peptide functionalities, including antioxidant and antihypertensive activity. The glycated proteins or peptides may resist digestion and undergo fermentation in the colon, potentially benefiting gut health. Studies have shown that glycated proteins, such as those from pea [66] and milk, can exhibit similar probiotic effects as Galactooligosaccharides (GOS) alone [67]. GOS are a type of prebiotic that support beneficial intestinal bacteria and produce SCFAs that have a variety of biological functions, hence promoting gut health [68]. GOS ferments quickly, producing gas and bloating. This has raised interest in prebiotics that affect the distal colon and are linked to a lower risk of colon cancer [69]. Glycated peptides' effect on the gut microbiota is yet unclear, though [70]. Jin et al. [71] investigated the effects of GOS glycated with fish peptides on GM of rats using the Maillard reaction. The composition of the gut microbiota and colonic fermentation were affected by the new glycoconjugates, offering the first *in vivo* proof of these prebiotic effects. Additionally, Han et al. [72] explored the chemical characteristics of glycoconjugates of myofibrillar proteins from grass carp that were conjugated with glucose via the Maillard reaction during dry heating. Glycation increased furosine levels, promoted structural changes in the proteins and reduced protein digestibility. The butyrate production during fermentation was influenced by glycation and showed positive correlation with *Mitsuokella, Lachnospiraceae_UCG-004, Sutterella, Salinimicrobium, Fodinibius* and *Nitriliruptor*, but anti-correlation with *Enterococcus, Dorea, Escherichia-Shigella,* and *Phascolarctobacterium*. These findings demonstrated that the glycation of myofibrillar proteins could have positive outcomes on gut health [72].

Lin et al, found that small-molecule peptides from the bone collagen of *Harpadon nehereus* (HNCP) exerted antidiabetic effects in Streptozotocin induced diabetes mice [73]. Specifically, HNCP administration significantly decreased the plasma levels of glucose, TC, TG, LDL-C and increased HDL-C concentration and insulin secretion. Moreover, HNCP improved glucose metabolism and showed remarkable antioxidant activity in this type 1 diabetic mouse model by regulating the expression levels of glycosynthesis and gluconeogenesis-related [i.e., glucokinase (GK), phosphoenolpyruvate carboxikinase1 (PEPCK1) and glucose-6-phosphate (G6Pase)] and antioxidant enzymes [i.e., catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and quinone oxidoreductase 1 (NQO1)], respectively. Additionally, the same authors demonstrated that this latter effect, aka the antioxidant activity, was mediated by the activation of the nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway [73]. It has been established the crucial role played by Nrf2 in redox balance, inflammation, cytotoxicity and cellular metabolism, and its involvement in many oxidative stress-based diseases [74]. Similar results were obtained in Streptozotocin-induced diabetes rats treated with the small peptide (<1kDa) fraction from *Takifugu bimaculatus* skin hydrolysate (TBP) [75]. Specifically, TBP was chosen because in an *in vitro* assay exhibited the strongest dipeptidyl peptidase-IV (DPP-IV) inhibitory activity. DPP-IV inhibition hinders the degradation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) that are released post-prandially, increasing their half-life and amplifying the insulin effect on glucose homeostasis [76]. In the i*n vivo* experiment, TBS diminished weight loss, lowered fasting blood glucose concentrations, increased insulin secretion, improved irregular hormonal fluctuations and lipid metabolism, and mitigated histopathological damage in the pancreas and liver. Additionally, the relative abundance of Firmicutes decreased, alongside the increase in Bacteroidetes, significant modifications were observed at the genus level, and two metabolites, hippuric acid and ergosta-5,7,22,24(28)-tetraen-3beta-al were identified following TBP administration [75]. In line with these data, a salmon peptide fraction (SPF), containing low-molecular-weight peptides, was able to

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prevent the development of obesity and metabolic disorders, dampening inflammation in both hepatic and intestinal tissues, and to modulate thrombosis risk factors in high-fat-high-sugar-fed vitamin D-deficient dyslipidemic mice [77]. Interestingly, Fang et al. applied a multistage strategy, in detail, a molecular docking-based virtual screening within a small library of marine-derived natural products with follow-up *in vitro* and *in vivo* phenotypic assays, aiming at discovery new lipid lowering molecules [78].

Hypertension, as above already mentioned, is a major risk factor for CVDs. One pharmacological approach aiming at reducing blood pressure is represented by the angiotensin-I-converting enzyme (ACE) inhibitors. ACE is a key enzyme that catalyzes the conversion of angiotensin I (an inactive decapeptide) to angiotensin II (octapeptide), a potent vasoconstrictor, which stimulates the release of aldosterone, and eventually increases the blood pressure. Fish-derived bioactive peptides have been widely investigated for their anti-hypertensive effects, such as ACE inhibition. All the studies published before 2020, have been collected in reviews [32,79,80]. According to the results obtained, the bio-efficacy and bioavailability of the final peptide products are marked affected by the used extraction processes (the enzymatic hydrolysis as well as isolation/purification techniques). Additionally, size and chain length together with the presence of some amino acids (tyrosine, tryptophan, proline, and phenylalanine) at the C-terminal of the fish-derived peptide' structures are crucial for ACE inhibition and antihypertensive effects [32,79,80]. *In vitro* experiments demonstrated that protein hydrolysates from fish by-products exerted competitive, non-competitive and mixed inhibition modes against ACE. In line with these data, *in vivo* experiments, mainly performed in spontaneously hypertensive rats (SHRs), proved the strong antihypertensive activity of protein hydrolysate from diverse marine organisms. Of note, grass carp peptides, rich in phenylalanine, leucine, aspartic acid, and glycine, significantly reduced the systolic blood pressure compared to the control group treated with captopril, the drug of choice for hypertensive patients [81]. Similar data were obtained by Chen et al, by administrating the Leu-Ser-Gly-Tyr-Gly-Pro peptide [82] from tilapia skin gelatine to SHRs [83]. Moreover, these authors via molecular docking comparison identified four connecting residues of the ACE active site, which may justify the mechanism of inhibition [83]. Recently, an experimental study demonstrated that both intact and hydrolysed blue whiting proteins reduced blood pressure in an obese rat model, inhibiting renin activity but not showing ACE inhibitory effect [84]. Whereas, a peptide composed of 13 amino acid residues, DPALATEPDPMPF, obtained from Nile tilapia (*Orechromis niloticus*) exhibited potent ACE inhibitory and radical scavenging activities, suggesting a potential it use in functional foods [85]. Indeed, ZBPHs administration to rats fed a high-cholesterol/cholic acid containing diet attenuated cholesterol-caused cardiac injury, testified by biochemical and histological improvement as well as significantly protecting heart genomic DNA's oxidative damage induced by Fenton's reagent [86]. Finally, Maneesai et al, investigated the impact of tuna protein hydrolysate (TPH) on CV remodelling and dysfunction in a rat model of metabolic syndrome (MS) [87]. The results of this study demonstrated that TPH supplementation improved all the metabolic parameters, including dyslipidemia, hyperglycemia, obesity, hypertension, cardiac hypertension, endothelial dysfunction, oxidative stress and inflammation, in the in a dose-dependent manner. These effects were related to the TPH ability at modulating angiotensin II receptor type 1 (AT_1R)/NADPH oxidase 2 (NOX2), endothelial nitric oxide (eNOS), Nfr2/heme oxygenase 1 (HO-1) and peroxisome proliferator-activated receptor (PPAR)gamma/nuclear factor kappa B (NF-kB) protein expression in heart and aorta [87].

Various experimental studies have investigated the impact of fish protein hydrolysates (FPHs), from salmon or anchovy by products (spine, viscera, collagen), on atherosclerosis development. All the studies were performed on genetically modified mice, aka apoE-deficient mice, fed high-fat [88,89] or high-fat/high cholesterol diet [90,91]. Altogether, the results demonstrated that these FPHs reduced plaque area and lipid accumulation in the aorta as well as in the aortic sinus. Conversely, no differences in extracellular matrix, macrophages and T-lymphocytes were observed in the plaque area of FPHs-fed mice compared to control animals. Of note, these effects were associated with lower levels of pro-inflammatory cytokines in the serum and aorta [88–92]. Interestingly, two studies showed that taurine proved efficacy in reducing the atherosclerosis development in both apoE-

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deficient mice fed chow diet with or without TMAO [93,94]. Furthermore, the authors demonstrated that dietary taurine exerted its anti-atherosclerotic effects via increasing the hepatic gene expression of conjugated bile acid synthesis and eventually, increasing the conjugated BA to unconjugated BA ratio in the liver as well as serum. Meanwhile, taurine improved the TMAO-induced abnormal bile acid profile in the gallbladder. Moreover, taurine increased bile acid deconjugation, by enhancing the genera *Ruminiclostridium* level, and excretion of fecal neutral sterols. In line with the data obtained with the FPHs, taurine positively modified the TMAO-induced inflammation in both serum and aorta [93,94].

2.2. Clinical Studies

Diverse clinical study investigating the impact of fish-derived peptides on CVD' risk factors have been performed thus far. Three reviews summarized the clinical trials published before 2020 [31,48,79]. Additionally, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) investigated the impact of lean fish and fish-derived proteins consumption on lipid profile [95]. Even though some of the studies reported an overall positive metabolic effect of consuming different fish protein hydrolysate, such as effect on body weight [96,97], TG and TC concentration [98–100], glucose metabolism [101–104] and hypertension [105], the majority of RCTs show highly inconsistent results. Indeed, Tou et al. concluded that additional better-designed, longer, and larger RCTs are mandatory to achieve a final statement of the impact of lean fish and fish proteins on serum lipid levels. Moreover, these new clinical studies are needed to appropriately inform the public about nutritional differences among fish species, eventually helping consumers to make more evidence-based dietary choices [95]. In line with the above-citated experimental data, more clinical studies documented the beneficial activity of taurine on CVD' risk factors [31]. Notably, taurine seems to reduce blood pressure by acting as an antagonist of angiotensin II [106].

3. Seaweed Components and CVDs Risk Factors

Different studies have shown beneficial effects of seaweed polyphenols, especially florotannins, on inflammation, oxidative stress, hyperglycemia, and hyperlipidaemia [107]. Additionally, fucoxanthin and brown seaweed-derived florotannins have significant anti-inflammatory and antioxidant activities, which may contribute to CV protection [108]. Moreover, marine microalgae provide vital nutrients and metabolites, including carotenoids and polysaccharides, which may help prevent heart disease [109]. By including these substances into functional foods, the worldwide burden of CVDs may be reduced and CV health may be improved. Overall, despite ongoing clinical application challenges the range of pharmacological activity of marine compounds offer a unique possibility for novel CVD treatments [110].

3.1. Experimental Studies

Algal polysaccharides, particularly fucoidan and laminarin, have attracted attention for their therapeutic potential in atherosclerosis. *In vitro* studies have shown that algal polysaccharides can inhibit LDL oxidation, a critical step in the atherosclerosis development. This antioxidant effect is essential for preventing the formation of foam cells, which contribute to plaque formation in the arteries [111]. In addition, the observed anti-inflammatory properties of these polysaccharides, may help at reducing vascular inflammation, eventually supporting CV health. Moreover, these compounds have been shown to inhibit atherosclerotic plaque formation and improve endothelial function [111].

Studies in genetically modified mice demonstrated the role of fucoidan (a polysaccharide composed of L-fucose extracted from brown seaweed) in the atherosclerosis management [112,113]. Specifically, these studies shown that intragastric gavage or intraperitoneal administration of fucoidan proved efficacy in decreasing arterial plaque formation as well as macrophage plaque accumulation and smooth muscle cell proliferation (Table 1).

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Table 1. The main mechanisms of action of seaweed compounds in promoting cardiovascular health involve their antioxidant, anti-inflammatory, and metabolic modulation effects.

Antioxidant Activity	Seaweed polyphenols, especially florotannins and fucoxanthin, exhibit significant antioxidant properties that help inhibit LDL oxidation—a crucial step in the development of atherosclerosis. This activity reduces the formation of foam cells, which contribute to arterial plaque formation [107,111].
Anti-inflammatory Effects	Algal polysaccharides like fucoidan and laminarin demonstrate anti-inflammatory properties that can help lower vascular inflammation. This reduction in inflammation is essential for maintaining CV health and preventing atherosclerosis [111–113]
Lipid Metabolism Regulation	Fucoidan has been shown to improve lipid profiles by down-regulating genes involved in lipid synthesis (like SREBP1, ACC, and FAS) and up-regulating genes involved in lipid uptake (such as LDL-R). This modulation leads to reduced TC, LDL-C, and TG [112,113]
Improvement of Endothelial Function	Seaweed extracts have been linked to improved endothelial function, which is critical for vascular health [111].
Impact on Glucose Metabolism	Compounds like oligosaccharides from *Enteromorpha prolifera* have demonstrated anti-diabetic effects, by enhancing glucose tolerance and reducing blood glucose levels through mechanisms involving the AKT pathway and the inhibition of gluconeogenesis [117,118].
Gut Microbiota Modulation	Some seaweed compounds can alter gut microbiota composition, promoting beneficial bacteria and pathways associated with metabolic health, which may contribute to their anti-obesity effects [115].
Clinical Evidence	Clinical studies, including those on Chlorella and Gdue (a blend of Ascophyllum nodosum and Fucus vesiculosus), support the efficacy of these compounds in reducing CVDs risk factors such as fasting blood glucose, LDL-C, and overall metabolic syndrome markers [134–136].

In addition, the authors reported the fucoidan ability to improve the lipid profile, such as a reduction of TC, HDL-C and TG and a rise of HDL-C. By looking for the potential mechanisms of action, they found that in fucoidan-treated mice the hepatic gene expression of sterol regulatory element-binding protein 1 (SREBP1), acetyl-CoA carboxylase (ACC), fatty acid synthetase (FAS), SREBP2 and HMG-CoA reductase was down-regulated, whereas LDL-R gene expression was up-regulated compared with control animals [112,113]. In conclusion, these data suggest that fucoidan is able to impair atherosclerotic plaque development by increasing the lipid metabolism/uptake and decreasing the lipid synthesis. Finally, they also reported a reduction of reactive oxidative species (ROS) as well as of pro-inflammatory mediators. In other words, these compounds could be used as dietary supplements for the atherosclerosis prevention and management.

Eisenia bicyclis (Kjellman) Setchell (EEB) 30% ethanol extract's anti-obesity action has been tested on 3T3-L1 preadipocytes and C57BL/6 mice fed (HFD) [114]. The 3T3-L1 cells' differentiation, proliferation, and mitotic clonal expansion (MCE) were all lowered by EEB treatment. In the subcutaneous and liver tissues of HFD-fed mice, oral treatment of EEB inhibited lipogenesis and adipogenesis. While, EEB increased thermogenesis in brown adipose tissue (BAT) [114]. Mice given oral doses of *Monostroma nitidum*'s rhamnan sulphate (RS), showed a considerable rise in body weight and food intake, accompanied by a decrease in plasma TC, glucose and insulin levels. This latter effect testifies that RS improves insulin resistance. RS feeding modified GM by activating pathways linked to glycolysis and the tricarboxylic acid cycle (TCA) and reducing the *Firmicutes*/*Bacteroidetes* (F/B) ratio, thus exerting an-anti-obesity action [115].

In mice fed high-fat/high cholesterol diet, the serum levels of TC, LDL-C, and TG were significantly lowered, and the expression of NPC1L1, a crucial transporter for intestinal cholesterol absorption was downregulated, by laminarin treatment [116].

Oligosaccharide extracted from *Enteromorpha prolifera* oligosaccharide (EPO) manifested antioxidative, anti-inflammatory, and anti-diabetic effects, when administrated to mice [117]. EPO regulates the crotonylation of XPO1 (Exportin for nuclear export of NES-containing proteins and RNAs) and HSPA8 HSPA8 (heat shock protein family A member 8) proteins, modulating the

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expression of key genes involved in cell cycle and aging. EPO is also involved in glucose metabolism by inhibiting the crotonylation of HSPA8-K126 and activating the AKT pathway. Finally, the crotonylation of histones in intestinal cells, increasing the abundance of butyric acid-producing bacteria *Ruminococcaceae*, are promoted by EPO as well [117]. In a diabetic mouse model, *Enteromorpha prolifera*'s sulfated polysaccharide (EP) enhanced glucose tolerance, decreased blood glucose levels, and boosted liver glycogen content. EP's ability to boost AKT phosphorylation was found to be responsible for its antidiabetic benefits. This, in turn, led to the reduction of Glycogen synthase kinase-3β (GSK-3β) and Forkhead box protein O1 (FOXO1) activity, which in turn encouraged glycogen production and reduced gluconeogenesis [117]. In addition, EP inhibited the elevated expression of O-GlcNAc transferase (OGT) induced by diabetes, suggesting that it acted similarly to an OGT inhibitor and contributed to mitigate hyperglycaemia [118].

The three *Undaria pinnatifida* extracts, UPLW, *Undaria pinnatifida* low-temperature water extract; UPHW, *Undaria pinnatifida* high-temperature water extract; UPE, *Undaria pinnatifida* ethanol extract (UPLW, UPHW, and UPE) had different chemical profiles, suggesting that the extraction approach had an impact on the extracts' composition [119]. UPLW exhibited the highest inhibitory impact on sucrose, but UPHW extract was more effective in inhibiting α-glucosidase activity toward maltose. After oral delivery of glucose, maltose, or sucrose to mice, the UPLW extract was the most successful in lowering postprandial blood glucose levels in those animals [119].

A recent review by Fernando et al. [120] describes the methodologies to obtain protein and protein-hydrolysates from microalgae, and the studies demonstrated their biological properties. The nutritional relevance of the microalgae is due to their high protein content, ranging from 50 to 70%, based on species, growth phase and light quality [120]. Similar to what mentioned earlier for FPHs, these microalgae-derived proteins, mainly their bioactive peptides obtained through hydrolysis by proteolytic enzymes or microorganisms, display antioxidant, anti-inflammatory, antihypertensive, and immunomodulatory effects, which are crucial in reducing CVD risk factors. Antioxidant peptides have been produced by the hydrolysis of *Chlorella* sp. [121], *Navicula* sp. [122] and *Spiurulina* sp [123] and extensively investigated in *in vitro* experiments. However, more studies are need to well identify the amino acid sequences with antioxidant capacity and then to verify this data *in vivo* models as well as clinical trials. Antihypertensive peptides derived from *Chlorella vulgaris*, *Chlorella ellipsiodea*, *Spirulina platensis* and *Nannochloropsis oculate* have been tested using both *in vitro* and *in vivo* (mainly using SHRs) experimental settings [124,125]. The most potent antihypertensive peptides seem to contain a high percentage of hydrophobic amino acid residues, such as proline, and the basic mechanisms are related to ACE and renin inhibitions [126]. Finally, two *in vitro* studies demonstrated the capacity of peptides isolated from *Chlorella pyrenoidosa* and *Spirulina maxima* to down-regulated the gene expression levels of E- and P-selectins, intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein (MCP-1) and endothelin-1 (ET-1) [127,128].

Although the potential CVD efficacy of proteins produced from algae appear promising, more *in vivo* experimental studies are required to confirm these results. Finally, clinical trials are needed to validate the pre-clinical data and to investigate the potential applications of these proteins in functional foods and nutraceuticals [120,129].

3.2. Clinical Studies

According to a review, polyphenol-rich marine extracts can successfully can significantly reduce plasma TC, LDL-C, and glucose levels, but didn't find relevant effects of seaweed polyphenols on other biomarkers, such as postprandial blood glucose, fasting insulin, related to CVDs, indicating the need for further research to clarify these relationships [130]. The contrasting results could be explained by variations in the types of polyphenols used, population characteristics, and study design.

A form of green microalgae called *Chlorella* has also been the subject of several clinical studies examining its impact on CV risk factors [131–133]. A systematic review found that supplementation with *Chlorella* can reduce fasting blood glucose, TC and LDL-C concentrations and systolic and

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diastolic blood pressure, but no effects were observed on TG and HDL-C levels [134]. *Chlorella*'s rich nutritional profile, which includes antioxidants and phytochemicals that may act in concert to support CV health, is believed to be the source of its health benefits [133].

Gdue is an algal extract made from the combination of *Ascophyllum nodosum* and *Fucus vesiculosus*, together with chromium picolinate [135]. The two algae that make up Gdue have a 95:5 ratio (*Ascophyllum nodosum* 95, *Fucus vesiculosus* 5), and can help at maintaining body weight and promoting metabolism, especially for fats and carbohydrates [135]. Specifically, overweight or obese patients with elevated fasting LDL-C were treated with Gdue for six-months. Gdue-treated patients showed metabolic syndrome metrics improvements, i.e., reduction of body weight and waist circumference, blood pressure, fasting blood TG, LDL-C and glucose concentrations, associated with a drop in HbA1c, and a rise of HDL-C levels. Overall, the study showed a 27.7% relative CVD risk reduction [135].

Finally, ProAlgaZyme is a novel and proprietary infusion of freshwater algae in purified water. The infusion effects on the CV risk factors associated with metabolic syndrome are assessed in a randomized double-blind placebo-controlled study with 60 overweight and obese individuals aged 25 to 60 [136]. Over the course of ten weeks, ProAlgaZyme consumption significantly improved serum lipid profiles, reduced inflammatory markers, and significantly decreased weight and glucose levels in overweight and obese subjects [136]. According to a recent review [137], marine polyphenols found in algae, fish and crustaceans possess anti-inflammatory properties that may help at reducing inflammatory responses, eventually improving to CVD profile.

4. Beneficial Effects of Probiotic/Prebiotics and Marine Derived Compounds

Due to potential health benefits, especially regarding GM and CVDs, marine-derived ingredients have stimulated a bunch of investigations. Additionally, marine sources are a rich source of prebiotics, which are non-digestible food components that specifically promote the growth and activity of healthy gut microbiota.

Probiotics are able to reduce TMAO concentrations, with *Lactobacillus rhamnosus GG* showing efficacy in both human and animal studies. However, the probiotics' effects on TMAO reduction appear to be strain-specific [138]. Furthermore probiotics, prebiotics, and synbiotics have demonstrated efficacy in lowering cholesterol concentrations, mitigating inflammation, and exhibiting antioxidative and antiplatelet effects [139]. Both probiotics and prebiotics can modify the GM composition, promoting the proliferation of beneficial bacterial strains and rectifying dysbiosis linked to CVD risk factors [140].

Additionally, faecal microbiota transplantation has emerged as a potential therapeutic approach for CVDs [141]. Altogether, these data underscore the relevance of gut microbiota-targeted strategies in CVD prevention and treatment. Nevertheless, despite encouraging findings from *in vitro* studies, animal research, and select human clinical trials, additional rigorously designed clinical investigations are imperative to comprehensively elucidate the long-term effects and underlying mechanisms of these dietary interventions in the context of CVD prevention and treatment [139].

Recent studies have placed a great deal of efforts in studying the function of fish-derived proteins and how they affect the human microbiome. In detail one study documents that dietary protein sources, including fish hydrolysates, can alter GM composition and enhance beneficial bacteria [25]. Importantly, FPHs possess excellent digestibility, absorption, water-holding capacity, texture, gelling, whipping, and emulsification properties when introduced into the food matrix [142].

Gabolysat®, a fish protein hydrolysate extracted from cod and mackerel, known for having anxiolytic [143] and gastric protective effects [42], may exert beneficial actions on the colonic mucosal barrier integrity, especially by increasing the mRNA levels of the anti-inflammatory cytokine, interleukin 10 (IL-10) [145]. Fish protein hydrolysates, such as those from salmon and mackerel, have been shown to increase beneficial bacteria while reducing harmful strains in mice GM, suggesting a protective role against metabolic diseases [146]. In addition, Sivixay et al demonstrated that the combination of fish proteins and the prebiotic raffinose positively affect the GM composition and its metabolic functions. Specifically, the data evidenced that this dietary combination influenced the GM

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diversity by increasing the *Akkermansia muciniphila* abundance. This bacterium is the most abundant species in the human intestinal microbiota and it has been inversely associated with body weight, inflammatory index, insulin resistance, glucose tolerance, and development of atherosclerosis in several experimental studies [147,148].

Marine Algae Polysaccharides (MAPs) have the potential to modify the gut microbiota in a way that improves heart failure treatment and CV health. MAPs can stimulate GM to produce healthier SCFAs. By influencing gut microbiome's regulation of bile acid metabolism MAPs can also improve CV health [149]. According to De Brito Alves et al. [150], supplementation of *Spirulina platensis* increases production of beneficial microbial metabolites like SCFAs, improve gut barrier function, enhancing the GM diversity and composition, which, as previously reported, has been linked to a number of health advantages, including anti-inflammatory, anti-obesity, and anti-diabetic effects. Anyways, to evaluate *Spirulina platensis*'s impact directly on the gut microbiome, more clinical trials are still needed.

5. Conclusions

CVDs represent the number one cause of death globally and atherosclerosis is the dominant cause of CVDs. Risk factors for atherosclerotic lesion's development are dyslipidaemia, hypertension, cigarette smoking, obesity and diabetes mellitus. Diverse evidence also highlighted the role played by inflammation and clonal haematopoiesis, eventually leading to the immunity involvement. Of note, it has been observed that in patients already taking statin therapy, residual inflammatory risk appears to be strongly associated with future CV events than residual cholesterol risk. The GM acts as an endocrine organ, playing a role in modulating immunity and influencing the development of inflammatory, metabolic and infectious diseases. In fact, gut dysbiosis have been associated with inflammatory based-diseases ranging from localized gastrointestinal disorders to metabolic and CV illnesses. There is growing evidence that FPHs and marine-derived compounds, especially those generated by algae, have positive effects on the CV system. In addition, including marine-derived compounds in dietary choices is a viable way to improve the GM health and lower the risk of CVDs. Prebiotics and marine probiotics work synergistically to promote gut health, which is essential for preserving CV health. However, additional and specific *in vivo* experimental and clinical studies are needed to draw an adequate conclusion. Finally, tailored clinical trials including patients in primary and secondary CV preventions, are mandatory to design new therapeutic protocols, where the "standard of care" therapies will be implemented with these marine-derived ingredients, aiming at reducing the side effects of the traditional drugs [109].

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