Role of Marine Drugs in Cardiovascular Diseases Management

Subjects: Food Science & Technology

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Cardiovascular diseases (CVDs) are among the most impactful illnesses globally. The available therapeutic option has several side effects, including hypotension, bradycardia, arrhythmia, and alteration in different ion concentrations. Recently, bioactive compounds from natural sources, including plants, microorganisms, and marine creatures, have gained a lot of interest. Marine sources serve as reservoirs for new bioactive metabolites with various pharmacological activities. The marine-derived compound such as omega-3 acid ethyl esters, xyloketal B, asperlin, and saringosterol showed promising results in several CVDs.

Keywords: marine drugs ; cardiovascular diseases ; atherosclerosis

1. Hypertension

Hypertension is one of the most severe problems among all cardiovascular diseases (CVDs), and is responsible for stroke, ischemic heart disease, dementia, chronic kidney disease, and other CVDs [1]. According to 2019 age-standardized prevalence data, 32% of women and 34% of men aged 30–79 worldwide had hypertension [2]. Many marine natural compounds, including bioactive molecules, chito-oligosaccharide derivatives (COS), and phlorotannins, were obtained from marine species and are potential leads for ACE inhibitors and evolved as nutraceutical medicinal compounds for the treatment of hypertension [3][4]. Natural marine ACE inhibitors are being studied as alternatives to synthetic drugs to avoid several serious side effects and hold a significant potential to become new therapeutic options for the treatment of hypertension [5]. Biopeptides or ACE-inhibitory peptides derived from fish proteins are often made under controlled circumstances by proteolyzing marine proteins advanced for the treatment of hypertension [6]. Furthermore, marine red algae *Gracilariopsis lemaneiformis* have been identified as producing several marine-based new ACE inhibiting peptides, FQIN [M(O)] CILR and TGAPCR, discovered by LC-MS/MS screening in *G. lemaneiformis* protein hydrolysates. These peptides significantly decreased systolic and diastolic blood pressure (DBP) in the spontaneously hypertensive rat model [7]. In the same direction, Sato M. et al. identified seven peptides: Val-Tyr, Ile-Tyr, Ala-Trp, Phe-Tyr, Val-Trp, Ile-Trp, and Leu-Trp from hydrolysates of wakame (*Undaria pinnatifida*) brown seaweed using three steps, HPLC and liquid chromatography-mass spectroscopy. Four of seven seaweed-derived peptides (Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Trp) significantly reduced systolic blood pressure in spontaneously hypertensive rats at a dose of 1 mg/kg. This offers a possible source of new AEC inhibitors as antihypertensives [8]. In addition, Sun et al. also identified two Phe-Gly-Met-Pro-Leu-Asp-Arg (FGMPLDR; MW 834.41 Da) and Met-Glu-Leu-Val-Leu-Arg (MELVLR; MW 759.43 Da) ACE inhibitory peptides from the protein hydrolysate marine macroalga of *Ulva intestinalis.* In silico and in vitro molecular docking studies revealed these two peptides have ACE binding and inhibitory activity [9].

One of the most well-known marine-derived compounds is alginate oligosaccharides (AOS) that offer protection against perivascular inflammation, reduction in the vascular luminal area, and hemodynamic alterations of pulmonary hypertension in the rat produced by monocrotaline (MCT) model via downregulating P-selectin [10]. Another study demonstrated that omega-3 Q10, a polyunsaturated fatty acid (n3-PUFA) formulation, appears to be more effective than soybean oil supplementation at reducing diastolic blood pressure and associated symptoms with hypertension in older adults [11]. Moreover, mangrove fungus-isolated xyloketal B showed phenylephrine (Phe)-induced contractions induced hypertension protection by decreasing the systolic and diastolic blood pressure via enhancing endothelial NO release through the Akt/eNOS pathway [12]. In addition, a controlled trial study conducted by Sámano MJ et al. evaluated the combination of *Spirulina (Arthrospira) maxima* (filamentous, gram-negative cyanobacterium) with angiotensin-converting enzyme (ACE) inhibitors in patients with systemic arterial hypertension (SAH) and accessed its effects on endothelial damage and oxidative stress. Results showed that *Spirulina* significantly reduced systolic blood pressure, increased anti-oxidant level (glutathione peroxidase activity and oxidized glutathione), and decreased endothelial damage markers (sVCAM-1, sE-selectin, and endothelin-1) [13]. It has other properties such as antiviral, anti-dyslipidemic, and antioxidant [14]. Low molecular mass potassium alginate (L-PA), brown algae, shows an antihypertensive effect on DOCA salt-induced hypertension in rats (**Figure 1**) [15]. Overall, data suggested that marine-derived compounds have the potential to cure hypertension, but a detailed mechanistic study is still needed. Moreover, Therapeutic potential of marine drugs in CVDs management has been tubulated in **Table 1**.

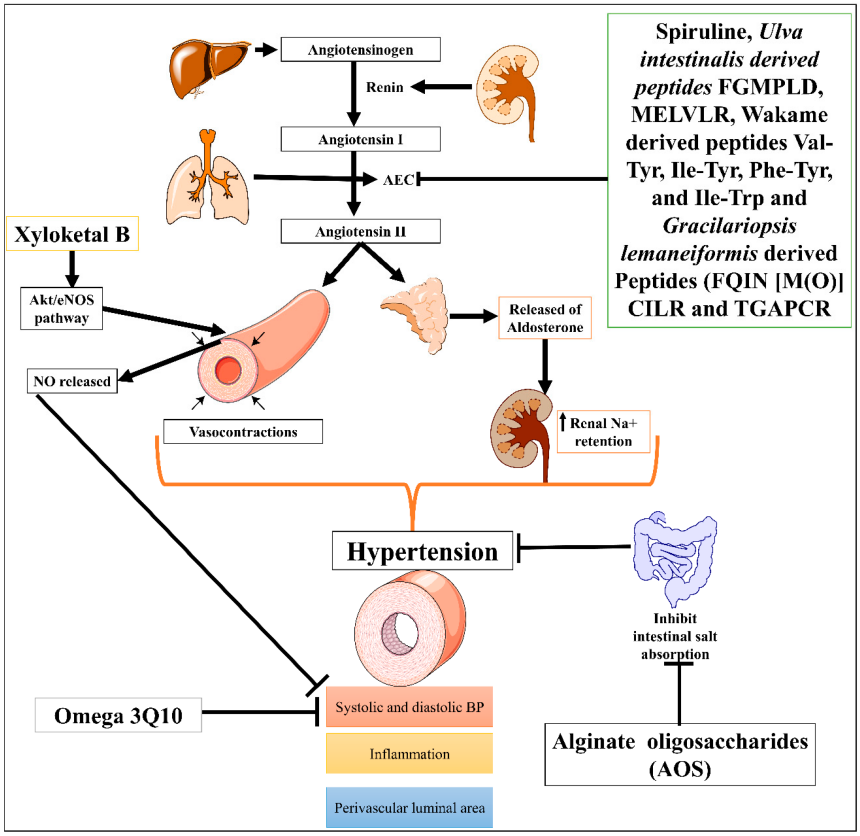

Figure 1. Possible mechanism of different marine-derived compounds in CVDs.

Table 1. Preclinical study of marine drugs in various CVDs.

S. No.	CVDs	Marine Drug Name	Species	Dose, Route and Time	MOA	Model Inducing Agents	Outcomes/Biological Effects
1.	Hypertension	Protein hydrolysate *Ulva intestinalis derived peptides* FGMPLD and MELVLR	In vitro	2.5 mg/mL of each hydrolysate	Inhibit ACE	ACE-induced hypertension	Antihypertensive effect
		Wakame (Undaria pinnatifida) derived peptides (Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Trp)	Rats	1 mg/kg	Inhibit ACE	Spontaneously hypertensive rats	Antihypertensive effect
		Low molecular mass potassium alginate (L-PA)	Rats	250, 500 mg/kg, once orally for 30 days	Increased the excretion of sodium salt	Deoxycorticosterone acetate (DOCA)-salt-induced hypertension	Antihypertensive effect
		Alginate oligosaccharides (AOS)		5, 10 and 20 mg/kg for 5 weeks	Suppressed intestinal absorption of salts leads to vasodilatory effect	Monocrotaline (MCT)-induced pulmonary hypertension	Decrease P-selectin expression in serum, pulmonary tissue, and pulmonary arteries
		Gracilariopsis lemaneiformis derived Peptides (FQIN [M(O)] CILR and TGAPCR)	Rats	10 mg/kg, orally for 24 hrs.	Inhibit angiotensin-converting enzyme (ACE)	ACE-induced hypertension	Antihypertensive effects, reduced both systolic and diastolic blood pressure
		Xyloketal B		20 mg/kg/day, 20 for 12 weeks	Promoted endothelial NO release and protected against atherosclerosis through the Akt/eNOS pathway.	Phenylephrine (Phe)-induced contractions cause hypertension	Antihypertensive effect, Decrease the systolic and diastolic blood pressure, vasorelaxant effect, anti-inflammatory and anti-atherosclerotic effects

S. No.	CVDs	Marine Drug Name	Species	Dose, Route and Time	MOA	Model Inducing Agents	Outcomes/Biological Effects
2.	Atherosclerosis	Asperlin		80 mg/kg/day, orally for 12 weeks	Inhibit the pro-inflammatory markers	In vitro (LPS-induced foam cell formation in macrophages) and in vivo (high-fat diet-induced-atherosclerosis lesion in ApoE$^{-/-}$ mice)	Athero-protection via decreasing the expression levels of iNOS, IL-1β, and TNF-α, and increased the expression of IL-10 and IL-4,
		Xyloketal B	Mice	7, 14 and 28 mg/kg/day, orally for 16 weeks	Inhibit the oxidative endothelial dysfunction and increase nitric oxide (NO) bioavailability	High-fat diet-induced atherosclerotic lesion	Strong antioxidant actions, reduced the levels of vascular oxidative stress, improving the impaired endothelium integrity and NO-dependent aortic vasorelaxation in atherosclerotic
		Saringosterol	Mice	50 mg/kg/day, orally for 2 weeks	Altered the liver X receptor (LXR)-regulated gene expression	High-fat diet-induced atherosclerosis	Decrease cholesterol level and anti-atherogenic effect
		Manzamine	ApoE-/-deficient mice	30 mg/kg/day, orally for 80 days	Inhibited the acyl-CoA: cholesterol acyl-transferase (ACAT) activity		Decrease the level of total, free and LDL-cholesterol, and triglycerides
		Astaxanthin	ApoE-/-deficient mice	0.03% (equivalent to approx. 200 mg/day in humans), orally for 4 weeks	By increasing the expression of LDL receptor (LDLR)	High-fat diet (high fat 15% and high cholesterol 0.2%)-induced atherosclerosis	Decrease the level of total triglyceride, and cholesterol
		Vitamin E	Rabbit	450 mg/1000 g chow fed orally for 6-weeks	Decrease creatine kinase elevation	High cholesterol-enriched diet induced atherosclerosis	Lowered aortic TBARS levels, favorable prostanoid generation, and diminished atherosclerotic lesions
3.	Myocardial Infarction (MI)	Fascaplysin	BALB/c mice	5 mg/kg, intraperitoneally 19 h and 1 h before inducing thrombus	Inhibited kinase enzyme, and decreased GPIIb/IIIa activation	Photochemical-induced thrombus	Anti-platelet, and anti-thrombus effect via inhibiting GPIIb/IIIa integrin complex
		Isaridin E	C57BL/6J mice	12.5, 25, 50 and 100 mg/kg, orally at 1, 24 and 48 h before $FeCl_3$-Induced thrombus	Inhibited adenosine diphosphate	$FeCl_3$-induced thrombus	Antithrombotic, and antiplatelet effect in atherosclerosis
		Cyanobacterial extract (CBE) and CBE+ GNPs	Rats	200 mg/kg/day, intraperitoneally for 14 days	Inhibit the depletion of the anti-oxidant enzymes (GRx and SOD)	Isoproterenol-induced MI	Decrease ST and QT segments, heart rate, and serum activities of creatine phosphokinase (CPK), reduced systolic and diastolic blood pressure
		Docosahexaenoic acid (DHA)	Pig	45 mg or 1 mg/kg, infused in pericardial space for 40 min.	Inhibited Ca^{2+} and Na^{+}/Ca^{2+} exchanger currents and prevented intracellularly Ca^{2+} concentration	Sternotomy method was used to expose the heart and induce MI	Decrease fatal arrhythmias and infarct sizes, decrease heart rates and reduce ventricular arrhythmia scores during ischemia.

S. No.	CVDs	Marine Drug Name	Species	Dose, Route and Time	MOA	Model Inducing Agents	Outcomes/Biological Effects
4.	Cardiac Stroke	Xyloketal B	Mice	50 mg/kg intraperitoneally 0, 1 and 2 h. after ischemia	By suppressing TLR4/NF-κB/ROS signaling pathway	Transient middle cerebral artery occlusion-induced stroke	Decrease ROS production, focal cerebral ischemia, and reduce infarction volume.
5.	Cardiac Arrythmia	Botulinum toxin-chitosan nanoparticles (BTN)	Rat	5 U/kg, subepicardial injection for 14 days	Decreased the activation of Ca^{2+}, K^{+} and Na^{+} channels	Calcium chloride-, barium chloride- and electrically induced arrhythmia	Inhibit ventricular fibrillation, reduce the incidence of ventricular arrhythmias
		Eicosapentaenoic acid (EPA)	Dog	5–15 µmol/L, intravenous infusion for 50–60 min.	Inhibition of Ca^{2+} and Na^{+}/Ca^{2+} exchanger currents increase Ca^{2+} concentrations intracellularly	High Ca^{2+}, ouabain, lysophosphatidylcholine, acylcarnitine, β-adrenergic agonist, and Ca^{2+} ionophore-induced arrhythmia	Inhibit cardiac arrhythmia through inhibition of fatal ischemia, prevents tachyarrhythmias
6.	Heart value disease	Fucoxanthin (Fx)	Dog	60 mg/kg twice daily for 2 years	Reduced oxidative stress-induced DNA damage	H_2O_2-induced oxidative stress-induced heart value damages	Strong antioxidant, anti-inflammatory, and antitumor properties, improved cell survival and, protective effect against calcification
7.	Cardiac dysfunction	Zeaxanthin (ZH)	Rats	250 µg/kg, orally for 4 weeks	Elevated retinoid receptor alpha (RAR-α) expression in cardiac tissue	d-galactose-induced cardiac dysfunction	Improve serum levels of homocysteine, creatinine kinase isoenzyme and lactate dehydrogenase, increase the cardiac contents of glucose transporter-4 and superoxide dismutase, decrease inducible nitric oxide synthetase and interleukin-6

2. Atherosclerosis

Atherosclerosis is a chronic, inflammatory, progressive cardiovascular disease that results from ongoing blood vessel damage brought on by hyperlipidemia and increased cholesterol levels [33]. Marine-based derived compounds have been effective against atherosclerosis since ancient times. These compounds have advantages over synthetic compounds in atherosclerosis due to greater effectiveness and lower side effects [34]. Marine-derived algal polysaccharides are the active ingredients in products made from marine sources that have a hypolipidemic impact and cure atherosclerosis.

Saringosterol, a phytosterol derived from the edible marine seaweed *Sargassum fusiforme*, has high and selective liver X receptor (LXR) activity [35]. Yan et. al. reported that saringosterol treatment reduced the burden of atherosclerotic plaques while having no negative effects on the liver of apoE-deficient rats. Saringosterol reduces cholesterol homeostasis disruption, influencing atherosclerosis's progression [19]. However, asperlin is derived from the marine fungus *Aspergillus versicolor* LZD4403 and possesses antifungal and anti-inflammatory properties. Zhou Y et. al. reported that asperlin has atheroprotective potential in vitro and in vivo. Results indicated that asperlin treatment significantly reduced inflammatory cytokines (iNOS, IL-1β, and TNF-α), increased protective cytokines (IL-10 and IL-4), and reduced aortic dilation and atherosclerosis plaque formation in the aorta [17]. This suggested that the anti-inflammatory properties of asperlin could be beneficial against atherosclerosis. Manzamine A is a naturally occurring alkaloid obtained from the sea sponge *Acanthostrongylophora ingens* [36]. In atherosclerosis, Eguchi et al. conducted a study where Manzamine A suppressed acyl-CoA: cholesterol acyl-transferase activity in hamster ovary cells. In addition, Manzamine A treatment significantly reduced the serum level of total cholesterol, free cholesterol, LDL-cholesterol, triglyceride, and atherosclerotic lesion formation in apolipoprotein E (apoE)-deficient mice [20]. Astaxanthin is a xanthophyll pigment obtained from microalgae, fungi, complex plants, seafood, and flamingos. As an antioxidant with anti-inflammatory characteristics, it has the potential to be used as a treatment for atherosclerotic cardiovascular disease [37]. Yang Y et. al. demonstrated the hypocholesterolemic effect of astaxanthin via reducing total plasma cholesterol, TG and increased LDL receptor (LDLR), 3-hydroxy-3-methylglutaryl CoA reductase, and sterol regulatory element binding-protein 2 (SREBP-2) and greater mature SREBP-2 protein apoE(-/-) mice (**Figure 2**) [21]. In high-fat diet mice, Xyloketal B also protects against atherosclerosis through a strong antioxidant effect [18].

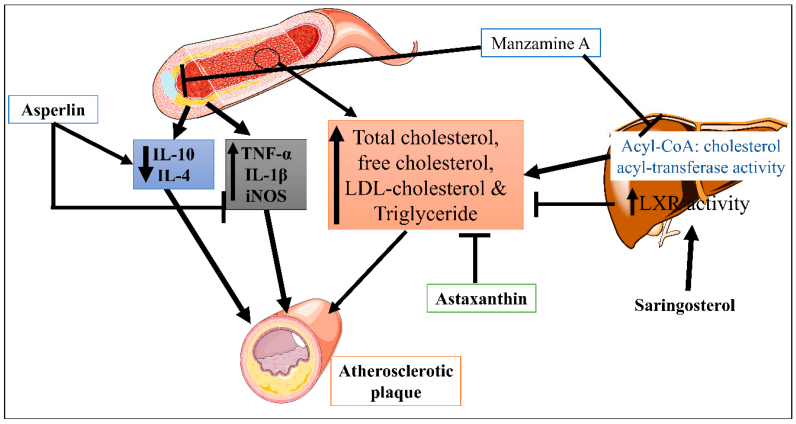

Figure 2. Mechanisms of Manzamine A, Astaxanthin, and Asperlin in CVDs.

Moreover, there are several major causes of atherosclerosis. However, thermo-inflmation plays a crucial role in atherosclerosis pathogenesis via influencing the plague formation. Thrombo-inflammation refers to the complex cascading interaction between the blood coagulation process and inflammation in the pathogenesis of CVDs [38]. The formation of arterial thrombosis is mostly caused by platelet adhesion under high shear stress, which arises in stenotic atherosclerotic arteries [39]. Meanwhile, platelet-activating factor (PAF) is a powerful lipid mediator that acts through PAF/PAF-R pathways and is a key player in inflammation by recruiting neutrophils and activating platelets in the development of atherosclerosis [40].

Several marine-derived drugs have been investigated to inhibit thrombo-inflammation in CVDs. Fascaplysin is a Fijian marine sponge derived from the genus *Fascaplysinopsis* [41], which is a kinase inhibitor with anti-thrombotic properties via inhibiting GPIIb/IIIa activation, platelet aggregation, and thrombus formation [23]. Another cyclodepsipeptide marine compound Isaridin E derived from the *Amphichorda feline* (*Beauveria feline*) fungus [42], demonstrated the dose-dependent inhibition of platelet activation, aggregation, and secretion. However, it does not have any effect against thrombin- or collagen-induced platelet aggregation. Isaridin E also showed an antithrombotic effect without increasing bleeding time in a dose-dependent manner against the $FeCl_3$-induced carotid mouse model [24]. F-fucoidan (FD) is a polysaccharide compound derived from the brown alga *Laminaria japonica* that also shows an antithrombotic effect through shortening the blood lysis time, H2O2 expression stimulation, and H2O2 released after induction of PGI2 production and might be effective in CVDs' patients [43]. The anti-thrombotic and anti-atherosclerotic properties of marine-derived omega 3 polyunsaturated fatty acids (n-3 PUFA) may help to reduce heart failure by lowering the risk of ischemic heart disease. It is known that n-3 PUFA enhances plasminogen activator inhibitor-1 by lowering fibrinogen and decreasing platelet-derived thromboxane A2 (TXA2), which increases platelet aggregation and vasoconstriction [44]. Therefore, So, overall, it seems like marine-based drugs could be used to treat atherosclerosis, but a more detailed mechanistic study is still needed.

3. Myocardial Infarction (MI)

MI occurs due to the occlusion of the coronary artery, leads to a shortage in oxygen and nutrients, and causes irreversible necrosis and death of cardiomyocytes [45]. It is the major cause of death and disability among other CVDs worldwide [46]. Using marine-derived metal nanoparticles, a novel method for treating thrombus dissolution and myocyte healing in infarcted areas (myocardial infarction) [47]. The anti-myocardial infarction activity of the gold nanoparticles (GNPs) was an innovative method in which cyanobacterial extract, GNP solution, and a combination of both were developed [25]. Omega-3 polyunsaturated fatty acids (PUFA), a marine compound, have shown beneficial benefits on myocardial infarction by reducing MI size in experimental and clinical research (**Figure 2**) [44]. Docosahexaenoic acid (DHA) is a long-chain omega-3 PUFA obtained from the marine source that has shown a protective effect against myocardial infarction [27]. An in vivo study of DHA in a rat model showed a protective effect against MI at 5 g/kg [48]. There are few marine-derived compounds in MI that have been investigated until now. Thus, in addition, a more detailed mechanistic study is needed.

4. Ischemic Heart Disease (IHD)

IHD is an inadequate blood supply of the coronary artery to the myocardium. Endothelial dysfunction is the main involvement in the mechanism of IHD [49]. It is the main cause of morbidity and mortality among all CVDs globally [50]. A 2016 report states it is responsible for 9 million deaths worldwide [51]. Marine-derived drugs are better than synthetic drugs to treat IHD due to their affective action and better results [44]. Histochrome, a sodium salt of echinochrome A, is a marine drug found as a common sea urchin pigment. It is a powerful and biosafe cell-priming agent that prevents cardiac progenitor cells (CPCs) from cellular apoptosis via the downregulation of BCL2-associated X (Bax) cleaved caspase-3, and phosphorylated histone, whereas upregulation of Bcl-xL and B-cell lymphoma 2 (Bcl-2) proteins, utilizing patient-derived human CPCs in treating heart disease [52]. In vitro study of echinochrome A (Ech A), a naturally occurring pigment from sea urchins, showed marine anti-thrombotics, especially sulfated polysaccharides, are relevant due to their distinct

modes of action and absence of bleeding. Their distinct modes of action as an antithrombotic are due to the high negative charge that sulfation imparts, which enables them to interact with proteins and molecules involved in vital biological processes such as coagulation [53]. In addition, both polysaccharides Enteromorpha prolifera polysaccharides (EPPs), produced from green algae, and fucoidan, extracted from brown algae, have anti-oxidant, lipid-lowering, and antiangiogenic properties [54]. Alginate (ALG), mostly derived from brown seaweed, can lower TC, TG, and LDL-C serum levels and upregulate HDL-C concentrations, making it an effective treatment for coronary artery disease [55].

5. Cardiac Stroke

Cardiac stroke is the most severe complication of CVDs, causing sudden death. CVDs are mostly caused by cardiac arrest or stroke in individuals with elevated blood pressure, high cholesterol, obesity, increased blood glucose levels, and weight gain [56]. Natural compounds derived from marine sources have already been regarded as lead molecules for treating CVDs and cardiac arrest due to their varied chemical compositions and pharmacological characteristics [57]. A carotenoid molecule called fucoxanthin, obtained from brown algae, prevents lipids' oxidation and buildup [58]. Fucoxanthin protects against cardiac stroke by regulating metabolic syndrome [59]. Another carotenoid, astaxanthin, showed a positive effect in cardiac stroke via the modulating number of biological processes, including the reduction in inflammation, augmentation of oxidative stress, enhancement of antioxidants, and the modification of lipid and glucose concentrations via suppressing TLR4/NF-κB/ROS signaling pathway [60]. A new type of unique structure called Xyloketal B contains a marine component derived from *Xylaria* species. Xyloketal B can benefit cardiac stroke due to its protective effect in the two-clip stroke-prone hypertensive model [61].

6. Cardiac Arrhythmia

Cardiac arrhythmias account for 10%–15% of fatalities, making them a substantial reason for morbidity and mortality worldwide [62]. Tetrodotoxin (TTX) is a marine compound obtained from the actinomycetes of marine sediments and has a beneficial effect on cardiac arrhythmia. It is also known as the puffer fish toxin that prevents sodium channels in excitable neurons [63]. It has also shown an antiarrhythmic effect in combinatorial therapy with lidocaine [64].

Many toxins, including tetrodotoxin, saxitoxin, brevetoxins, antillatoxin, conotoxins, and cnidarians, are found in marine species such as pufferfish, shellfish, sea anemones, and cone snails, are voltage-gated sodium channels (VGSCs) blockers, and show protective effects against cardiac arrhythmia [65]. Other marine drugs, omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, have shown antiarrhythmic effects against various arrhythmic disturbances, including atrial fibrillation and ventricular arrhythmia [66]. Eicosapentaenoic acid shows antiarrhythmic activity when added to the superfusate before adding the toxins, including ouabain, lysophosphatidylcholine, high Ca^{2+}, acylcarnitine, β-adrenergic agonist, and the Ca^{2+} ionophore [30]. Botulinum toxin is obtained from the marine source *Clostridium botulinum*. *Clostridium botulinum* is a Gram-positive anaerobic spore-forming bacterium found in marine environments [67]. The botulinum toxin (BoNT/A1)–chitosan nanoparticles (BTN) formulation inhibits arrhythmia caused by sodium, calcium, and potassium channel activation [29].

7. Cardiac Dysfunction

Chronic cardiac dysfunction is caused by contractility overload on the heart myocardium. Different etiologies may favor existing compensatory mechanisms such as excentric (dilatation) and concentric hypertrophy. Chronic left ventricular dysfunction is the most prevalent complication of MI. Chronic cardiac dysfunction worsens left ventricular ejection fraction and stroke volume as dilatation progresses, eventually leading to heart failure [68]. Retinoid receptors play a crucial role in several diseases, including diabetes [69], cancer [70], and CVDs [71]. A research study reported that the retinoid receptor is essential for heart function. Moreover, tamoxifen-induced myocardial specific RARα deletion (RARαKO) mice showed significant diastolic dysfunction, increased intracellular ROS, NOX2 (NADPH oxidase 2), NOX4 and decreased antioxidant level (SOD1 and SOD2). This effect is reversed by overexpression of retinoid receptors [72]. In addition, Guleria RS et al. also demonstrated that retinoid receptors play a role in diabetic-induced cardiomyopathy [73]. In the same way, zeaxanthin heneicosylate (ZH) extracted from microalgae *Dunaliella salina* significantly reduced plasma biochemical alteration (AST, ALT, urea, and creatinine level), pro-inflammatory level (IL-6, NF-κB, and iNOS), antioxidant level (SOD), and histological changes in D-galactose-induced cardiac dysfunction rats through stimulating the retinoid receptors [32]. There are only a few studies on cardiac dysfunction; thus, detailed mechanistic studies are needed.

8. Heart Valve Disease or Valvular Heart Disease

Valvular heart disease (VHD) is a cluster of frequent cardiovascular disorders that account for 10–20% of all cardiac surgical operations in the United States. Heart valve problems include regurgitation (valve flaps do not close properly), stenosis (narrowed valve opening), and atresia (valve does not have a proper opening). Fucoxanthin is a marine carotenoid obtained from the seaweed microalgae *Phaeodactylum tricornutum* and possesses antioxidant and anti-inflammatory properties [74]. A report by Chiang et al. demonstrated the protective potential of heart valves in heart valve interstitial cells and dogs. Results showed that fucoxanthin treatment significantly reduced H_2O_2-induced ROS level, DNA damage, cell survival, and protein-related apoptosis and calcification expression via modulating the Akt/ERK pathway. In

addition, long-term (0.5 to 2 years) supplementation to the dog also improved the left atrium to aortic (LA/AO) dimension ratio and E/e value (indicate mitral valve inflow, mitral valve leakage, and left ventricular diastolic dysfunction) [31]. This suggests that marine-derived compounds hold a diverse therapeutic potential. In addition, marine drugs which hold biological effects in CVDs tubulated in **Table 2**.

Table 2. Marine drugs class, source, and their biological effects in CVDs.

Class	Marine Drugs	Marine Source	Biological Effects	References
Pigments (Xanthophyll carotenoid)	Astaxanthin	Microalgae (*Haematococcus pluvialis, Chlorella zofingiensis,* and *Chlorococcum* sp.), fungi (red yeast *Phaffia rhodozyma*) crustacean, Shrimp, lobster, trout, krill, salmon, fungi, complex plants, seafood, flamingos, and quail	Cardioprotective (atherosclerosis protective), antidepressant, antioxidant, anti-inflammatory, neuroprotective, anticancer, antidiabetic, gastrointestinal protective, and hepatoprotective.	[75][76][77][78][79]
Soluble dietary fibers	Fucoxanthin	Macroalgae (*Undaria pinnatifida, Hijikia fusiformis* and *Sargassum fulvelum*)	Cardioprotective, Antioxidant, thermogenesis, stroke prevention, anti-inflammatory, anticancer, and improved blood pressure and liver function.	[59]
	Alginate/Alginic acid	Brown macroalgae (*Pseudomonas* and *Azotobacter, Pseudomonas aeruginosa, Azotobacter chroococcum*)	Cardioprotective (used in myocardial infarction), antimicrobial, anti-inflammatory, anticancer, and antidiabetic.	[79][80][81][82]
	Carrageenan	Red macroalgae *Chondrus armatus* (Gigartinaceae), *Eucheuma, Betaphycus, Kappaphycus,* and *Chondrus crispus*	Cardioprotective (used for ischemic heart disease), immunomodulator, anti-hypercholesterolaemic, anti-inflammatory, anticancer, and antivirus properties.	[83]
	Agar	*Gelidium, Pterocladia*, and *Gracilaria gracilis* (Rhodophyta)	Cardioprotective, anticoagulant, antiviral, antioxidative, anticancer, and immune-modulating activities.	[79][80][84]
	Fucoidans	*Fucus vesiculosus and L. japonica*	Cardioprotective, coagulant activity.	
	Ulvans	*Ulva pertusua*	Anti-oxidant activity.	
Peptides	Leu-Lys-Gln-Glu-Leu-Glu-Asp-Leu-Leu-Glu-Lys-Gln-Glu	*Crassostrea gigas*	Anticancer, antihypertensive, anti-thrombosis, antioxidant, and anticoagulant properties.	[79][80]
	Pepsin-hydrolyzed peptide (VECYGPNRPQF)	Seaweed (*Chlorella vulgaris*)	Potent antioxidant, anticancer, opioid agonists or antagonists, immunomodulatory, antithrombotic, anti-atherosclerotic, and antimicrobial activities.	[85]
	Antitumor polypeptide Y2	*Spirulina platensis*		
	Phycobili protein byproduct	*Porphyra columbina*	Immunosuppressive effects through increasing IL-10 production and preventing the production of IFN-γ and TNF-α.	[86]
	Leu-Trp, Val-Tyr, Ile-Tyr, Phe-Tyr, and Ile-Tyr	*U. pinnatifida*	Antihypertensive effects.	[8]
	α and β subunits of phycoerythrin	Red seaweed (*P. palmate*)	ACE inhibition activity.	[87]
	Ile-Leu-Ala-Pro, Leu-Leu-Ala-Pro, and Met-Ala-Gly-Val-Asp-His-Ile	Macroalga (*Palmaria palmata*)	Inhibited DPP-IV (ischemic cardiovascular disease marker).	[88]
	Ile-Pro and Ala-Phe-Leu	*Chlorophyta U. rigida*	ACE inhibition activity.	[16]
Phlorotannins (phenolic compounds)	Phloroglucinol	*Hyaleucerea fusiformis*	Potent antioxidant effects, anti-inflammatory and anticancer effects, inhibit the hyaluronidase enzyme.	[79][80][89]
	Phlorofucofuroeckol A	*Eisenia bicyclis, Ecklonia cava* (brown algae)	Antidiabetic, antihypertensive, antioxidant activity.	

Class	Marine Drugs	Marine Source	Biological Effects	References
Minerals	Na, K, Mg, P, I, Zn, and Fe	Microalgae (*Chlorococcum humicola* and *Chlorella vulgaris*)	Used for the prevention and treatment of CVDs.	[79][80]
	Na^+/K^+ ratio, Mg		Controls blood pressure, prevent metabolic syndrome and atherosclerosis.	
	NaCl		Increases arterial constriction and peripheral vascular resistance, increased blood pressure.	
	K^+		Decreases the blood pressure, preventing problems associated with high blood pressure.	
Lipids	Eicosapentanoic acid	Microalga *Nannochloropsis gaditana* (NG)	Reduced inflammatory genes expression and inhibits platelets.	[80][90]
	Arachidonic acid	*Mortierella alpina* (saprophytic, oleaginous soil fungus)	Activates the immune functions, pro-inflammatory properties, maintaining homeostasis, anticancer, cardioprotective, anti-psoriasis, anti-arteriosclerosis, and antiulcer properties.	[80][91]
Sulphated fucans	Fucoidan	Brown seaweeds (*Sargassum ilicifolium* and *Sargassum angustifolium*)	Reduces lipid deposition in atherosclerosis, hypolipidemic effect controls obesity. CVDs	[92][93]
Marine Neurotoxins	Tetrodotoxin (TTX)	Sea-slug *Pleurobranchaea maculata* and pufferfish *Takifugu niphobles*	Visceral analgesic, local anesthetic, controls cardiac contractions.	[65][94][95][96]
Non-peptide neurotoxin	Saxitoxin (STX)	Dinoflagellates species from the genera *Alexandrium, Gymnodinium, Centrodinium* and *Pyrodinium*	Wound healing, corneal analgesic, controls myocardial impulse generation.	[65][96][97]
Fungus	Xyloketal B	Mangrove fungus *xylaria* species		[98]

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