

MARINE DRUGS USED IN CARDIOVASCULAR DISEASE

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ABSTRACT

This Article consist of many marine drugs which can be used in the cardiovascular diseases. Many drugs have proven their significance in the treatment of diseases. Many of the species contain toxic compound the marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compound the marine with the potential. Industrial development has pharmaceuticals, cosmetics, nutritional supplements molecular properties, fine chemical and chemicals. Marine toxins were reported to possess an extremely high potency about their pharmacological actions, and, therefore, sometimes collectively referred to as 'toxins'. 1. Circulates oxygen & remove carbon dioxide 2. Provide cells with nutrients 3. Removes the waste products of metabolism to the excretory organs for disposal 4. Protects the body against disease & infection.

Keywords: Marine, Cardiovascular, Ancient, Research, Fungi, Bacteria.

1. INTRODUCTION

Marine Pharmacognosy is the investigation & identification of medically implant or animals in marine environment. It is a sub branch of terrestrial Pharmacognosy generally the drugs are obtained from the marine species of bacteria virus, algae, fungi and sponges. The drugs which are obtained from marine organisms are known as marine drugs. These marine drugs are used since ancient times. chines and Japanese are very famous to use these resources. And interestingly, innumerable products derived from the marine organisms in several 'crude forms' have been widely used across the globe by the traditional practitioners for thousands of years. Many of the species contain toxic compound the marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compound the marine with the potential. Industrial development has pharmaceuticals, cosmetics, nutritional supplements molecular properties, fine chemical and chemicals. Marine toxins were reported to possess an extremely high potency about their pharmacological actions, and, therefore, sometimes collectively referred to as 'toxins' 'the drugs which are obtained from marine organisms are known as marine drugs. These marine drugs are used since ancient times. Chines and Japanese are very famous to use these resources. And interestingly, innumerable products derived from the marine organisms in several 'crude forms' have been widely used across the globe by the traditional practitioners for thousands of years. Many of the species contain toxic compound the marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compound the marine with the potential. Industrial development has pharmaceuticals, cosmetics, nutritional supplements molecular properties, fine chemical and chemicals. Marine toxins were reported to possess an extremely high potency about their pharmacological actions, and, therefore, sometimes collectively referred to as 'toxins'.

The cardiovascular system is sometimes called the blood-vascular or simply the circulatory system. It consists of the heart, which is a muscular pumping device a closed system of vessels called as arteries, veins & capillaries. the cardiovascular system also called known as the circulatory system .it is consisting of heart, blood vessels & blood. these components make up two circulatory systems-the systemic & pulmonary circulatory systems. The cardiac cycle consists of two phases-systole(relaxation)and diastole(contraction)cardiovascular means relating to the heart and blood vessels.

cardiovascular drug, any agent that affects the function of the heart and blood vessels. Drugs that act on the cardiovascular system are among the most widely used in medicine. Examples of disorders in which such drugs may be useful include hypertension (high blood pressure), angina pectoris (chest pain resulting from inadequate blood flow through the coronary arteries to the heart muscle), heart failure (inadequate output of the heart muscle in relation to the needs of the rest of the body), and arrhythmias (disturbances of cardiac rhythm). [1]

2. METHODOLOGY

➤ MARINE NATURAL PRODUCTS –

- Many natural products from these organisms act as chemical weapons and are highly potent inhibitors of physiological processes.
- Several show pharmacological activities and are effective against cancer, AIDS, arthritis

- Variety of molecules show unique structural features and exhibit various types of biological activities
- Marine drugs are highly potent bioactive molecules in recent years a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organism although there are only a few marine drives from marine natural products are now in the clinical pipeline with more clinical development.

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➤ MARINE PHARMACOLOGY IN INDIA -

India has over 8 thousand km of coastline with clusters of marine habitats like inter tidal rocky muddy and sandy shores coral and mangrove forest. the potential of India marine habitats demanded largely unexplored for their potential of new drugs and biotechnology program. Some of the selected institutes such as national institutes of Oceanology, Goa; Central drug Research Institute, Lucknow; Bose Institute, Kolkata; Central Institute of Fisheries Education, Mumbai Regional Research Laboratory, Bhubaneswar of Council for Scientific and Industrial Research are present working for exploration of life saving drugs from marine Sources. Many other Indian institute universities, and pharmaceutical companies have also recognized the significance of these subject.

Marine pharmacology has been reviewed extensively in the past all over the world as well as in India. But still there is a need to review the potential of the oceans as sources for the development of new drugs, considering the advantage of their abundance in nature and large-scale production. At a present, the drug industry is working on screening and isolation of novel molecule with unreported pharmacological properties that can be exploited for the development of new therapeutic agent for commercial use. This review has largely focused on different classes of marine drug currently in use and at the different stages of trials for approval and the marketing in future. The review has also tried to delve into the limitation and future trends of the drug from marine sources.

➤ CLASSIFICATION OF MARINE PHARMACOLOGY –

Marine pharmacology can be classified based on source of the candidate drug.

- 1.genetically engineered marine organisms
- 2.manufacture of pharmaceuticals and nutraceuticals of marine origin
- 3.chemicals produced by or found in marine organisms shown to have a wide variety of applications as pharmaceuticals.

Some of the drugs of marine origin approved for human use in different parts of the world are as follows:

Cytarabine (cytosine arabinoside or arabinosyl cytosine, ara-C)

Cytarabine is a synthetic pyrimidine nucleoside derived from spongothymidine and primarily isolated from a Caribbean sponge species *Tethya crypta*. It is FDA approved and mainly used in different types of leukaemia, including acute myelocytic leukaemia, lymphocytic leukaemia, meningeal leukaemia, and blast crisis phase of chronic myelogenous leukaemia.[2]

Vidarabine (adenine arabinoside, ara-A or arabinofuranosyladenine)

Vidarabine is a synthetic purine nucleoside isolated from the Caribbean sponge *T. crypta* and developed from spongouridine is currently obtained from *Streptomyces antibioticus*. It is approved by FDA for use in recurrent epithelial keratitis caused by HSV) type 1 and 2, acute kerato-conjunctivitis, and also for superficial keratitis.[2]

Ziconotide

Ziconotide is a synthetic molecule, equivalent to a natural 25-amino acid peptide, v-conotoxin MVIIA. It is originally extracted and purified from the venom of marine snail *C. magus*, which is a fish-hunting species. Ziconotide has shown potential as an analgesic with a novel mechanism of action.[2] It is approved as an analgesic by FDA.

Ziconotide is an N-type calcium channel antagonist used to manage patients with severe chronic pain who cannot tolerate, or who have not responded adequately to other treatments such as intrathecal morphine and systemic analgesics.

Brand name- prialt

Genetic name –ziconotide

Synonyms-ziconotida, ziconotide

Background of ziconotide- Ziconotide (also known as SNX-111) is a neurotoxic peptide derived from the cone snail *Conus magus* comprising 25 amino acids with three disulphide bonds. Other such peptides, collectively termed

conotoxins, exist, and some have shown efficacy in binding specific subsets of calcium channels; ziconotide is used in part because it can be synthesized without loss of proper bond formation or structural elements. Ziconotide is used to manage severe chronic pain refractory to other methods, through its ability to inhibit N-type calcium channels involved in nociceptive signalling. Ziconotide was granted FDA approval on December 28, 2004 for marketing by TerSera therapeutics LLC. Under the name Prialt. To date, ziconotide is the only calcium channel blocking peptide approved for use by the FDA.

Associated conditions of severe chronic pain and indication of ziconotide is indicated for management of severe chronic pain in patients refractory to other treatment and for whom intrathecal therapy is warranted.

Contraindications & blackbox warnings- avoid life threatening adverse drug events & improve clinical decision support.

Pharmacodynamics- Ziconotide inhibits N-type calcium channels involved in nociceptive signalling, primarily in the dorsal horn of the spinal cord. 5,7,8,9,12,14,18 Although binding is reversible, careful dosing is required to ensure therapeutic effects while minimizing adverse effects, and ziconotide has been described as possessing a narrow therapeutic window^{13,18}. Patients taking ziconotide may experience cognitive and neuropsychiatric symptoms, reduced levels of consciousness, and elevated serum creatine kinase levels. In addition, ziconotide may increase the risk of infection, including serious cases of meningitis. Patients who withdraw from opiates for ziconotide initiation are advised to taper off the dose. ¹⁸

Mechanism of action- Nociceptive pain signalling is a complex processing pathway involving peripheral nociceptors, primary afferent nerve fibres, and downstream CNS neurons located in the spinal cord. Voltage-gated calcium channels (VGCCs) are important regulatory components of neural signalling and include the N-type (Cav2.2) heteromultimeric high-voltage type calcium channels. Chronic ^{8,14} the release of neurotransmitters substance P (SP), calcitonin gene-related peptide (CGRP), and glutamate, which influence downstream neural activation and pain perception. In addition, SP and CGRP induce inflammation, potentially exacerbating pre-existing inflammatory chronic pain. Ziconotide belongs to the ω -conotoxin class of neurotoxic peptides derived from the cone snail *Conus magus* which are capable of inhibiting N-type VGCCs. Although the exact mechanism is yet to be elucidated, it is thought that ω -conotoxins function through direct occlusion of the ion pore to prevent calcium translocation across the membrane. Additional studies involving expression of chimeric subunits and molecular modelling suggest that insertion of the ziconotide Met residue into a hydrophobic pocket formed by Ile, Phe, and Leu of Cav2.2 increases binding and may be associated with toxic adverse effects

Absorption- Ziconotide administered intrathecally over one hour in doses between 1 and 10 mcg produced calculated AUC values between 83.6-608 ng*h/mL and C between 16.4-132 ng/mL; these values are approximately dose-proportional. Given the intrathecal administration and low membrane permeability due to its size, ziconotide is expected to remain primarily in the CSF; plasma levels, where detected, remain constant up to nine months following administration. ^{max 18}

Volume of distribution- In patients administered 1-10 mcg intrathecal ziconotide over one hour, the apparent volume of distribution was calculated as 155 ± 263 mL; this value is roughly equivalent to the expected CSF volume. Although intravenous administration is not indicated, intravenous administration of between 0.3-10 mcg/kg/day ziconotide resulted in an apparent volume of distribution of $30,460 \pm 6366$ mL. ^{18 18}

Protein binding- Ziconotide is roughly 50% bound to human plasma proteins. ¹⁸

Metabolism -Ziconotide is expected to be processed by various peptidases upon entering systemic circulation; no detailed information on ziconotide metabolism has been reported. ¹⁸

Route of elimination- A small fraction of intravenous ziconotide (< 1%) is recovered in urine. ¹⁸

Half-life- In patients administered 1-10 mcg intrathecal ziconotide over one hour, the elimination half-life was calculated as 4.6 ± 0.9 hr. Although intravenous administration is not indicated, intravenous administration of between 0.3-10 mcg/kg/day ziconotide resulted in an elimination half-life of 1.3 ± 0.3 hr. ¹⁸

Clearance- Ziconotide CSF clearance is 0.38 ± 0.56 mL/min while plasma clearance is 270 ± 44 mL/min. ¹⁸

Adverse Effects -Improve decision support & research outcomes with our structured adverse effects data.

toxicity -Symptoms of overdose include neurological effects such as ataxia, nystagmus, stupor, sedation, speech difficulties, dizziness, nausea, and vomiting, and may also cause other effects such as hypotension; overdose is not associated with respiratory depression. In case of overdose, symptom-related supportive care up to and including hospitalization is recommended. Ziconotide has no known antidote, but the withdrawal of ziconotide generally allows patients to clear the drug and recover within 24 hours. As ziconotide does not bind to opiate receptors, opioid antagonists are not effective at ameliorating overdose effects. ¹⁸

Trabectedin

A marine natural product extracted from a tunicate species *Ecteinascidia turbinata* generally inhabitant of Mediterranean and Caribbean Sea. Trabectedin molecule is an alkaloid of tetrahydroisoquinoline class.

➤ **ASTAXANTHIN: A POTENTIAL THERAPEUTIC AGENTS IN CARDIOVASCULAR DISEASE-**

ASTAXANTHIN – astaxanthin is a xanthophyll carotenoid of predominantly marine origin, with potent antioxidant and anti-inflammatory effects demonstrated on both experimental and human studies. Oxidative stress and inflammation are common pathophysiological features of atherosclerotic cardiovascular disease hence astaxanthin may have a potential therapeutic role in this condition. astaxanthin is a xanthophyll carotenoid present in microalgae, fungi, complex plants, seafood, flamingos and quail. It is an antioxidant with anti-inflammatory properties and as such has potential as a therapeutic agent in atherosclerotic cardiovascular disease.

➤ **Astaxanthin of marine origin**

Astaxanthin is used in nutritional supplements is usually a mixture of configurational isomers produced by *haematococcus pluvialis*, a unicellular microalga

➤ **CARDIOVASCULAR ACTIVE AGENTS-**

During the past three decades a huge number of extracts, fraction and pure isolates from thousands of marine organisms were subjected to thorough cardiovascular screening in various research laboratories around the world. Interestingly, most of these compounds did exhibit cardiovascular activities perhaps as frequently as observed antibiotic and antineoplastic activities. Unfortunately, as on date hardly any compound could surface out and obtain the FDA approval as a potential drug. The cardiovascular active drugs may be broadly classified under the following two categories, namely: (a) cardio tonics (b) hypotensive compounds

▪ **LAMININ:**

Biological source: Laminin is obtained from a marine algae *laminaria angustata*

CHEMICAL STRUCTURE CHARACTERISTIC FEATURES:

- It is the abundant structural component of the basal lamina
- It is critical to the stability of the extracellular matrix and to the adhesion of cells to the basement membrane
- It belongs to the family of HETEROTRIMERIC GLYCOPROTEINS composed of a heavy chain, which are linked by disulphide bonds to form an asymmetrical cross- shaped structure.

USES:

- It shows hypotensive effect.
- It also exhibits diverse biological activities

▪ **ELDOISIN:**

It is a powerful hypotensive compound. it also shows strong vasodilator effects

❖ **Biological source:**

Eldoisin is obtained from the posterior salivary glands of *eledone* spp. [small octopus] *eledone moschata* chemical structure of eldoisin

CHARACTERISTIC FEATURES:

- Eldoisin is obtained as a sesquihydrate powder that gets decomposed at 230 c
- It has specific optical rotation
- It is found to lose its activity gradually when incubated in blood.

❖ **USES:**

1. It is found to stimulate extra vascular smooth muscle.
2. Eldoisin acts as a potent vasodilator and hypotensive agent.
3. It also stimulate lacrimal secretion.
5. It causes salivation and enhances capillary permeability in certain specific species.

▪ **SEPONGOSIN:**

It is chemically nucleoside (methoxy derivative of adenosine) derivative it reduces both the rate and the force of concentration of heart.

Biological source:

It is obtained from the Caribbean sponge *cryptotethia crypta* and with a minor structural modification of the parent isolated nucleoside known as arabinosylnucleoside.

USES:

1. It exhibited various coronary effects resembling to those of adenosine, for instance coronary vasodilation and negative inotropy.
2. It is found to exert more marked and pronounced long- acting effects.
3. It acts as a hypotensive at such as dose level at which adenosine is observed to be absolutely in active.

4. It reduces the rate as well as the force of contraction of heart.

➤ FUNCTION OF THE CARDIOVASCULAT SYSTEM-

1. Circulates oxygen & remove carbon dioxide
2. Provide cells with nutrients
3. Removes the waste products of metabolism to the excretory organs for disposal
4. Protects the body against disease & infection
5. Clotting stops bleeding after injury

➤ THERE ARE FOUR MAIN TYPES OF CVD –

1. Coronary heart disease
2. Stroke
3. Peripheral arterial disease
4. Aortic disease .

➤ THERE ARE 3 TYPES OF BLOOD CIRCULATION-

1. Systemic circulation
2. Coronary circulation
3. Pulmonary circulation

➤ TYPES OF HEART DISEASE-

1. Coronary artery disease or CAD it is the most common form of heart disease
2. Heart attack or myocardial infarction
3. Heart failure, otherwise known as congestive heart failure
4. Heart valve disease
5. Heart muscle disease or cardiomyopathy
6. Abnormal heart rhythms or arrhythmia
7. Heart arrhythmias pericardial disease
8. Pericardial disease
9. Cardiomyopathy (heart muscle disease)
10. Congenital heart disease

• SYMPTOMS-

1. Chest pain
2. Pain, weakness or numb legs& lower arms
3. Breathlessness
4. Very fast or slow heart beat or palpitations
5. feeling dizzy, lightheaded or faint
6. Fatigue
7. Swollen limbs
8. Chest tightness
9. Chest pressure
10. Chest discomfort (angina)
11. Shortness of breath
12. Pain in neck

• TREATMENT –

Treatment plans can vary depending on your symptoms & the type of cardiovascular disease you have cardiovascular disease treatment may include lifestyle changes, medication ,procedure or surgeries ,cardiac rehabilitation ,active surveillance and besides blood tests& a chest x-rays , tests to diagnose heart disease can include Electrocardiogram (ECG OR EKG) an ECG is a quick & painless test that records the electrical signals in the heart it can tell if the heart is

beating too fast or too slowly. Common medical test to diagnose heart conditions –blood test, Electrocardiogram (ECG) echocardiogram(ultrasounds), exercise stress test, magnetic resonance imaging (MRI)

- PREVENTION –

1. Avoiding all tobacco products
2. Achieving & maintaining a healthy weight
3. Eating a diet low in saturated fat and sodium
4. Exercising at least 30&60min per day on most days
5. Reducing & managing stress

➤ EFFECT ON HEART FUNCTION-

Effects on heart functions Drugs affect the function of the heart in three main ways. They can affect the force of contraction of the heart muscle (inotropic effects); they can affect the frequency of the heartbeat, or heart rate (chronotropic effects); or they can affect the regularity of the heartbeat (rhythmic effects).

Contractions-

Inotropic agents are drugs that influence the force of contraction of cardiac muscle and thereby affect cardiac output. Drugs have a positive inotropic effect if they increase the force of the heart's contraction. The cardiac glycosides, substances that occur in the leaves of the foxglove (*Digitalis purpurea*) and other plants, are the most important group of inotropic agents. Although they have been used for many purposes throughout history, the effectiveness of cardiac glycosides in heart disease was established in 1785 by English physician William Withering, who successfully used an extract of foxglove leaves to treat heart failure. The two compounds most often used therapeutically are digoxin and digitoxin. Cardiac glycosides, however, have disadvantageous side effects. These include a tendency to block conduction of the electrical impulse that causes contraction as it passes from the atria to the ventricles of the heart (heart block). Cardiac glycosides also tend to produce an abnormal cardiac rhythm by causing electrical impulses to be generated at points in the heart other than the normal pacemaker region, the cells that rhythmically maintain the heartbeat. These irregular impulses result in ectopic heartbeats, which are out of sequence with the normal cardiac rhythm Occasional ectopic beats are harmless but if this process continues

Related Topics:

nitro-glycerine

- quinidine
- chronotropic agent
- squill
- inotropic agent rhythm.

Occasional ectopic beats are harmless, but if this process continues to a complete disorganization of the cardiac rhythm (ventricular fibrillation), the pumping action of the heart is stopped, and death occurs within minutes unless resuscitation is performed. Because the margin of safety between the therapeutic and the toxic doses of glycosides is relatively narrow, they must be used carefully. Cardiac glycosides are believed to increase the force of cardiac muscle contraction by binding to and inhibiting the action of a membrane enzyme that extrudes sodium ions from the cell interior. These drugs also enhance the release of calcium from internal stores, resulting in a rise in intracellular calcium. This subsequently increases the force of contraction, since intracellular calcium ions are responsible for initiating the shortening of muscle cells. The disturbances of rhythm that may be caused by cardiac glycosides result partly from the depolarization and partly from the increase in intracellular calcium. Because these rhythm disturbances are caused by the same underlying mechanism that causes the beneficial effect, there is no likelihood of finding a cardiac glycoside with a significantly better margin of safety. Apart from their cardiac actions, these glycosides tend to cause nausea and loss of appetite. Because digoxin and digitoxin have long plasma half-lives (two and seven days, respectively), they are liable to accumulate in the body. Treatment with either of these drugs must involve careful monitoring to avoid the adverse effects that may result from the second type of inotropic agents that increase the force of cardiac muscle contraction includes dobutamine. Administered intravenously in moderate doses, dobutamine will increase contractility without affecting blood pressure or heart rate.

➤ Drugs affecting the blood vessels-

Drugs affect blood vessels by altering the state of contraction of the smooth muscle in the vessel wall, altering its diameter and thereby regulating the volume of blood flow. Such drugs are classified as vasoconstrictors when they cause the smooth muscle lining to contract and vasodilators when they cause it to relax. Drugs may act directly on the smooth muscle cells, or they may act indirectly—for example, by altering the activity of nerves of the autonomic nervous system

that regulate vasoconstriction or vasodilation. Another type of indirect mechanism is the action of vasodilator substances that work by releasing a smooth muscle relaxant substance from the cells lining the interior of the vessel. Some drugs mainly affect arteries, which control the resistance to blood flow in the vascular system, an important determinant of the arterial blood pressure; others mainly affect the veins, which control the pressure of blood flowing back to the heart and hence the cardiac output (i.e., the volume of blood pumped out by the heart per minute). Apart from the actions of the autonomic nervous system, several other physiological mechanisms regulate vascular smooth muscle. Of pharmacological importance is the renin-angiotensin system and locally acting vasodilator substances, such as histamine, bradykinin, prostaglandins, and nitric oxide. Renin is an enzyme that is released into the bloodstream by the kidney when the blood pressure falls. It acts on a plasma protein to produce a peptide, angiotensin I, which consists of a chain of 10 amino acids. This in turn is acted on by angiotensin converting enzyme (ACE) to produce an eight-amino-acid peptide, angiotensin II (a potent vasoconstrictor), which in turn ACE inhibits raises the blood pressure. ACE inhibitors, which block the formation of angiotensin II, are used in treating hypertension, which is produced by excessive constriction of the small arteries. Drugs that block the binding of angiotensin II to its receptor can also be used.

➤ THERE ARE FOUR MAIN TYPE OF CVD-

1. coronary artery disease
2. Stroke
3. Peripheral arterial disease
4. Aortic disease

❖ CORONARY ARTERY DISEASE-

Coronary artery disease is the major cause of mortality worldwide, especially in low- and middle-income earners. To not only reduce angina symptoms and exercise-induced ischemia but also prevent cardiovascular events, pharmacological intervention strategies, including antiplatelet drugs, anticoagulant drugs, statins, and other lipid-lowering drugs, and renin-angiotensin-aldosterone system blockers, are conducted. However, the existing drugs for coronary artery disease are incomprehensive and have some adverse reactions. Thus, it is necessary to look for new drug research and development. Marine natural products have been considered a valuable source for drug discovery because of their chemical diversity and biological activities. The experiments and investigations indicated that several marine natural products, such as organic small molecules, polysaccharides, proteins, and bioactive peptides, and lipids were effective for treating coronary artery disease. Here, we particularly discussed the functions and mechanisms of active substances in coronary artery disease, including antiplatelet, anticoagulant, lipid-lowering, anti-inflammatory, and antioxidant activities.

Cardiovascular disease (CVD), especially coronary heart disease (CHD) and stroke, is the leading killer in Western Society and its prevalence is increasing dramatically in developing nations [1]. Atherothrombotic disease is the consequence of conventional risk factors such as smoking, hypertension, hyperlipidaemia, insulin resistance and diabetes, and vaping, lack of physical activity, over use of alcohol chronic kidney disease, obesity. Novel risk factors include highly sensitive C-reactive protein (hs-CRP) and other markers of inflammation, homocysteine, and lipoprotein (a) [2]. Along with genetic factors and age, lifestyle and diet are also considered important risk factors. Reduction in dietary consumption of animal fat, cholesterol, and sodium should be the mainstay of population-wide CHD prevention [3]. Dietary interventions should be the initial step in the treatment of CVD. A group of phytochemical substances in carotenoids which is responsible for the colour of food play an important role in the prevention of human diseases and the maintenance of good health [4]

Coronary artery disease (CAD) mostly results from atherosclerosis, which may cause arteries to be narrowed or clogged by cholesterol and fat deposits (1). Furthermore, atherosclerosis can result in myocardial ischemia and hypoxia. CAD can be divided into acute coronary syndromes and chronic coronary syndromes (1). Acute coronary syndromes attack when a portion of the heart is completely cut off by total blockage of a coronary. This is usually due to a sudden closure from a blood clot forming on top of a previous narrowing. Chronic coronary syndrome always accompanies chest pain because of the lack of oxygenated blood supply. It was demonstrated that CAD had been considered the primary hazard to adults in all age groups in the US. In addition, it could lead to a destructive influence on younger generations and their relatives (2). CAD is also referred to as the most popular angio cardiopathy and a significant risk regarding public hygiene (3). Another investigation also indicated that CAD was the major reason for mortality in the world, especially in low- and middle-income earners (4). In conclusion, CAD is a harmful disease that is worthy of more attention. CAD has several risk factors, including family history, age, obesity, smoking, passive smoking, physical activity, dyslipidaemia, diabetes, hypertension, H-type hypertension, sleep, and so on (3). Hence, to not only reduce angina symptoms and exercise-induced ischemia but also prevent cardiovascular events, pharmacological intervention

strategies, including antiplatelet drugs, anticoagulant drugs, statins and other lipid-lowering drugs, and renin–angiotensin–aldosterone (ACE) system blockers, are conducted.

ORGANIC SMALL MOLECULES-

Fucoxanthin-

Fucoxanthin is a carotenoid containing oxygen that is extracted from brown algae (6). Recent studies have suggested that fucoxanthin prevented lipids from overoxidation and restrained the accumulation of lipids. In addition, fucoxanthin downregulated transcription factors related to adipogenesis, such as sterol regulatory element-binding protein 1c and peroxisome proliferator-activated receptor. Meanwhile, fucoxanthin not only decreased the expression of fatty acid synthase but also increased adipose triglyceride lipase and the phosphorylation of the production of lipase sensitivity to the hormone that is used for lipolysis (7). fucoxanthin remarkably reduced the blood glucose level by increasing the expression of glucokinase (GCK) mRNA and restrained the expression of phosphoenolpyruvate carboxykinase mRNA. In skeletal muscle, fucoxanthin elevated the glycogen content and GLUT4 and GSY protein expression as well as suppressed glycogen synthase kinase (GSK)3 β protein expression. Consequently, glycogen synthesis could be promoted. Finally, fucoxanthin promoted the protein expression of PPAR α , p-ACC, and carnitine palmitoyl-transferase (CPT)-1 and restrained FAS protein expression in the liver to reduce blood lipid levels. Mechanistic investigations demonstrated that insulin receptor substrate (IRS)-1/phosphatidylinositol 3-kinase (PI3K)/kinase B phosphorylation (AKT) and AMP-activated protein kinase (AMPK) signalling protein expression were observably increased with the use of fucoxanthin (11).

SAPONINS -

Saponins Sea cucumber saponins (SCSs) can be defined as secondary metabolites coming from sea cucumbers, and SCSs are a group of glycosides, the aglycones of which are triterpene or spirostan compounds (12). Studies have demonstrated that SCSs could be competent for antiatherosclerosis activity. To explain the mechanism, reasons can be divided into two sides. On the one hand, it might be the function of SCSs to regulate lipid metabolism and glycometabolism. Recent studies have indicated that SCS treatment dose dependently decreases the levels of lipids in serum in rats fed a cholesterol-rich diet. In particular, ApoE $^{-/-}$ mice accelerated the disappearance of plaques by 56.9% with an 8-week treatment of 0.07% SCSs (13). Further research showed that adiponectin, which is released by sea cucumber saponins, is the main functional ingredient to ameliorate the metabolism of lipids and glucose. Studies have suggested that adiponectin promotes sirtuin 1 (SIRT1) expression. Due to the activation of SIRT1, sterol regulatory element-binding protein (SREBP)-1c, stearoyl-CoA desaturase (SCD)-1, and fatty acid synthase (FAS) expression could be restrained not only at the mRNA level but also at the protein level.

Astaxanthin-

Astaxanthin is a natural compound with bioactivity, which is classified as xanthophyll, existing in microalgae and marine natural products. Notably, astaxanthin possessed strong antioxidant activities because of its characteristic molecular structure, which could result in the quenching of oxygen in the singlet state and the elimination of free radicals. An increasing number of studies have demonstrated that astaxanthin can ameliorate oxidative stress, reduce inflammation, and decrease lipids and glucose.

Some findings suggested that astaxanthin prevented the VEGFR2-p-Tyr397-focal adhesion kinase (FAK) signalling axis from being activated, which was induced by homocysteine (Hcy), to suppress endothelial cell dysfunction. If Hcy levels in plasma increase, blood vessel endothelial cells are seriously destroyed (21). Another study indicated that astaxanthin restrained mitochondrial dysfunction and oxidative damage to block the cardiotoxicity induced by Hcy both in vivo and in vitro (22). Further studies investigated whether astaxanthin suppressed the activation of macrophages (23) and promoted the ability of neutrophil granulocytes to phagocytose and sterilize. Consequently, both lipids and proteins sustained less oxidative damage due to astaxanthin (24)

Xyloketal B-

Xyloketal B is a new-style compound that has an extraordinary chemical structure and is extracted from *Xylaria* sp. (12). Previous studies have shown that xyloketal B protects against oxidative injury in endothelial cells induced by oxLDL by suppressing NADPH oxidase-derived ROS generation, facilitating the production of NO, and recovering the expression of Bcl-2 (25). Another study showed that in high-fat diet-fed ApoE $^{-/-}$ mice, xyloketal B reduced the atherosclerotic plaque area not only in the aortic sinus but also all over the aorta by relying on the dose. Moreover, oxidative endothelial dysfunction as well as the reduction in the bioavailability of NO are principal for CAD development. Recent studies have indicated that xyloketal B is effective in suppressing vascular oxidative stress levels and improving the integrity of the injured endothelium as well as the vasorelaxation of NO-dependent aortas in atherosclerotic mice. In addition, xyloketal B outstandingly transformed both eNOS and Akt phosphorylation levels but

did not change total eNOS and Akt expression in cultured human umbilical vein endothelial cells (26). Several findings demonstrated that xyloketal B reduced lipids through the lipid-regulated activation of the SREBP-1c pathway. Xyloketal B promoted CPT1A expression and suppressed SREBP-1c expression, and the downstream targeting enzymes of SREBP-1c, such as ACC1, ACL, and FAS, were also inhibited. Xyloketal B was reported to decrease the accumulation of lipids in HepG2 cells treated with FFAs (27)

DSW-

Recent studies demonstrated that DSW could suppress the increase in cellular cholesterol levels induced by high glucose or FFA/glucose by promoting the transcription of LDLR and ApoA1 and restraining the expression of PCSK9 mRNA in HepG2 hepatic cells. Furthermore, it is key to determine whether 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) expression and/or AMPK phosphorylation take part in the hypocholesterolemia functions of DSW and the proportion of Mg in DSW (28). The findings also indicated that DSW markedly suppressed the activity of intracellular triglycerides and glycerol-3-phosphate dehydrogenase in 3T3-L1 adipocytes. DSW also restrained adipocyte differentiation, lipogenesis, and adipocytokine gene levels as well as elevated lipolysis and fatty acid oxidation gene levels (29). Additionally, DSW was reported to decrease serum lipids by inhibiting the levels of TG and TC in serum and suppressing AMPK, PPAR α , CPT-1, and ACO expression (6). Another investigation also indicated that DSW inhibited HMGCR and PCSK9 expression, promoted the phosphorylation of AMPK, and elevated LDLR, SREBP-1 α , and SREBP-2 expression (6).

Terpenes-

Terpenes are isolated from marine products and have been demonstrated to have anti-inflammatory, antimicrobial, and antiangiogenic functions (30). Previous studies indicated that dichotomous could suppress the gathering of platelet-rich plasma induced by adenosine diphosphate or collagen, but pachydictyol A and isopachydictyol A could not. Meanwhile, dichotomous was incapable of restraining washed platelets. Nevertheless, pachydictyol A and isopachydictyol A could suppress the accumulation of collagen- or thrombin-induced WP. The diterpenes mentioned above could restrain coagulation and thrombin catalysis (31). According to recent molecular mechanism research, compared with pachydictyol A and isopachydictyol A, the lowest electronic density of dichotomous tended to have a better activity to suppress the catalytic activity of thrombin (32). Recent investigations indicated that frondoside A, which is a marine-derived triterpenoid, could suppress the PI3K pathway in platelets to inhibit the formation of thrombi (33).

Benzoic Acid Derivatives-

It was proven that one novel anthranilic acid derivative, which was extracted from a Philippine sponge, could inhibit proinflammatory cytokines by restraining JNK, ERK, activator protein-1, and NF- κ B as well as promoting the ATF-3 signalling pathway (34). Another investigation found that R-/S-HPABA, which was extracted from marine natural products, had an anti-inflammatory function. An in vitro experiment indicated that R-/S-HPABA strongly suppressed more aggregation of platelets, which was induced by ADP, collagen, and arachidonic acid, in rabbit plasma enriched with platelets than in the control group. Regarding the extent that the aggregation of platelets was inhibited, we could conclude that it was like that of aspirin. Significantly, R-/S-HPABA inhibited the thromboxane B2 level and elevated F1 α generation. In addition, R-/S-HPABA could lower the weight of carotid thrombosis (35)

Sponge Extract-

SR-B1 is one type of HDL receptor significant for AS. HDL could combine SR-B1 with the purpose of regulating the transport of cholesterol so that AS might be regulated (12). Compounds purified from tetracyclic mero sesquiterpene, which was extracted from the sponge Hyrtios digitatus in Australia, promoted SR-B1 activity in HepG2 cells in a dose-dependent manner, which upregulated the activity of SR-B1 in HepG2 cells (36). Investigations have also indicated that sponge extracts might z antiatherosclerosis effects by upregulating PPAR response elements and SR-B1 expression (12).

Asperlin

Asperlin was extracted from marine natural products and has been demonstrated to have antifungal and anti-inflammatory activities in vitro. Recently, we found that asperlin significantly inhibited the formation of foam cells induced by LPS. Meanwhile, it elevated the external flow of cholesterol in RAW264.7 macrophages. It was also reported that if asperlin was added, proinflammatory divisors induced by LPS could be inhibited in RAW264.7 macrophages, iNOS, IL-1 β , and TNF α expression might be restrained, and IL-10 and IL-4 expression could be promoted. Consequently, macrophage polarization had an outstanding transformation. In ApoE $^{-/-}$ mice fed a high-fat diet, it was shown that taking asperlin orally could markedly lower the formation of aortic atherosclerotic plaques in vivo by inhibiting the dilatation of the aorta and diminishing the proportion of atherosclerotic lesions (37). Furthermore, asperlin lowered proinflammatory cytokine levels in serum, such as MCP1, TNF- α , and IL-6, based on unaltered lipid profiles (12).

3. CONCLUSION

This article will give you an overview on which marine drugs can be used in treatment of cardiovascular disease. And what side effects can be observed in while the treatment. Asperlin, Astaxanthin, Benzoic Acid Derivatives, Terpenes, Fucoxanthin, SAPONINS was extracted from marine naturals product & has been demonstrated to have antifungal & anti-inflammatory effect. As these drugs obtained from the marine origin, they do not have any side effects. They have less adulteration with the products they do not have drug-drug interactions. They have a major effect on the cardiovascular disease but do not show interactions with food & drugs.

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