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Marine-Derived Pharmaceuticals: Unlocking the Ocean's Potential for Human Health

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Abstract

The ocean, covering 70% of the Earth's surface, is a rich source of unique bioactive compounds with potential therapeutic applications. This review aims to highlight the significance of marine-derived pharmaceuticals in human health, focusing on clinically approved and commercially available medications. The review covers various marine-derived compounds, their structural features, modes of action, and applications in treating diseases, such as cancer, diabetes, and neurodegenerative disorders. The review identifies several marine-derived medications, including, cytarabine (ara-C) for leukemia and lymphoma, vidarabine (ara-A) for viral infections, ziconotide for pain management, trabectedin for cancer treatment, eribulin mesylate for breast cancer. Additionally, the review discusses the potential of marine-derived compounds in managing diabetes and neurodegenerative diseases, such as Alzheimer's and Parkinson's.

Keywords: Marine-derived pharmaceuticals, bioactive compounds, cancer, diabetes, neurodegenerative diseases, clinically approved medications

INTRODUCTION

This review includes pharmaceuticals that are licensed for clinical use and that are commercially accessible that are derived from marine compounds or compounds that are inspired by marine natural products. This review's objective is to enlighten readers on the significance of marine goods for human health, as this information is expected to address more widespread disease-related difficulties down the road. Not only does this review provide information about marine medications, but it also covers their structural features and modes of action that help to alleviate pathological disorders. We intend to bring drug design researchers – particularly those who are influenced by marine natural resources – to our notice [1]. The seas, which make up over 70% of the Earth's surface, are home to a diverse range of marine organisms with high levels of activity and efficacy. These animals have unique and inventive characteristics that are not found on land. Since the National Cancer Institute (NCI) started looking into marine resources for anti-cancer activity in 1968, research on marine pharmaceuticals has grown into its own expertise [2].

Since ancient times, people have taken advantage of the vast natural resources found in the sea, using fish and other marine animals as well as algal concoctions as sources of medicinal remedies. The traditional example of a marine-derived substance that has been used for aeons is fish oils. A subfield

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of pharmaceutical sciences called marine pharmacology studies the compounds that have active pharmacological characteristics that are found in marine plant and animal species. With structural and chemical characteristics that are typically absent from natural goods found on land, the marine environment offers an amazing repository of novel bioactive natural compounds. In addition, marine life offers a wealth of nutraceuticals that may be used to cure a variety of illnesses in humans. Microbes are the focus of marine pharmacotherapy nowadays [3].

An abundant supply of these naturally occurring chemicals with a variety of bioactivities, including photoprotective properties, may be found in the ocean, several modes of action, including antihelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, antiviral, and others [4, 5]. Marine pharmaceutics has been an emerging area in the realm of anticancer medication development for the last 20 years. Marine life, such as sponges, microbe-sponge symbiotic relationships, and soft coral have been extensively investigated for their possible anticancer agents [6–8]. Between 1981 and 2008, over 68% of all anti-infection medications (such as antibacterial, antiviral, antiparasitic, and antifungal substances) and 63% of anti-cancer medications were obtained from natural sources [9].

The current review is on the pharmacological characteristics and marine provenance of medications that the FDA and/or EMA approved for sale, as well as on current clinical trials involving molecules derived from the sea [10].

BIODIVERSITY OF MARINE ENVIRONMENT

Over 80% of the world's unique plant and animal species can be found in its oceans. Marine organisms including sponges, tunicates, fish, soft corals, nudibranchs, sea hares, opisthobranchs molluscs, echinoderms, bryozoans, prawns, shells, sea slugs, and marine microbes contain bioactive substances, such as oils and cosmetics [11]. The first biologically active marine natural product was formally reported in late 1950 by Bergmann [12]. The genetic and biochemical uniqueness of maritime plants and animals was demonstrated in late 1970. Thirty percent of these unusual natural compounds – roughly fifteen thousand—have been isolated from sponges [13]. Additionally, it was found that people can tolerate molecules of a marine origin with little to no modification [14].75 bacterial strains from four species of sea sponges were found in the investigation; 21% of these isolates had strong antibacterial activity, and several of them demonstrated species specificity [15].

MARINE PHARMACOLOGY IN INDIA

India boasts more than 8000 km of coastline that is home to diverse marine environments, including mangrove forests, coral reefs, and intertidal rocky, muddy, and sandy shorelines. The potential of the Indian maritime ecosystem for the development of novel medications and biotechnological initiatives has not received much attention. The Central Drug Research Institute in Lucknow, the Bose Institute in Kolkata, the Central Institute of Fisheries Education in Mumbai, the Regional Research Laboratory of the Council for Scientific and Industrial Research in Bhubaneswar, the National Institute of Oceanology in Goa, and others are currently researching life-saving drugs made from marine sources. Numerous other Indian organizations, academic institutions, and pharmaceutical businesses have acknowledged the importance of this topic as well [16].

CLASSIFICATION OF MARINE PHARMACOLOGY

Based on the source of the prospective medicine, marine pharmacology can be categorized as follows:

- Marine creatures that have undergone genetic engineering.
- Production of marine-derived medications and nutraceuticals.
- Substances generated by or present in marine life that have been demonstrated to have a broad range of uses as medicines (Figure 1) [17–20].

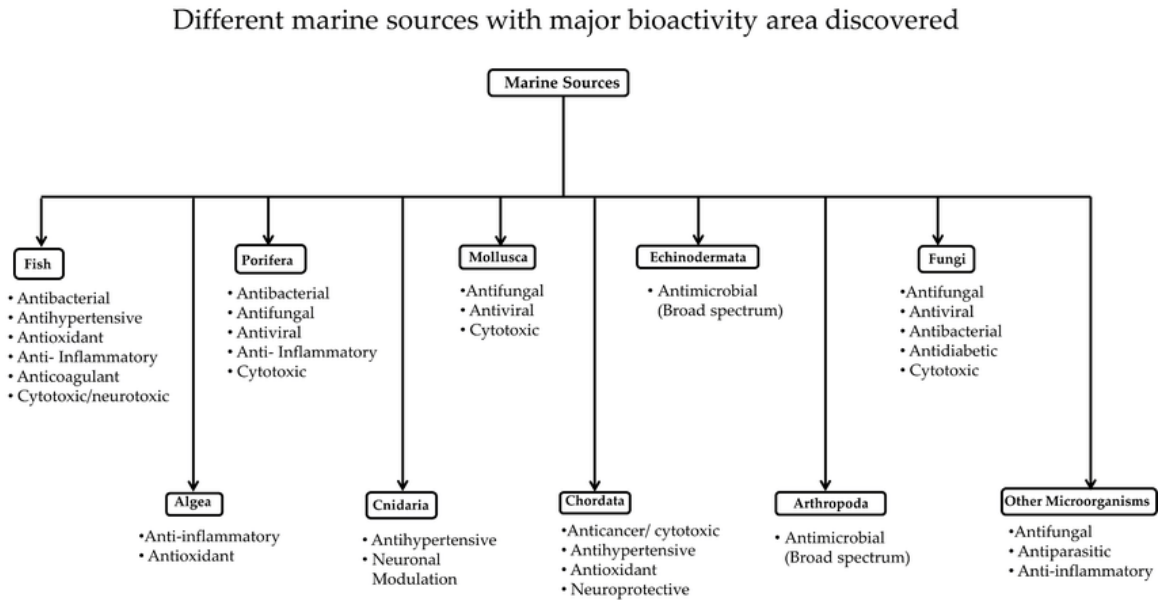

Figure 1. Different marine sources with major bioactivity area discovered [21].

CLASSIFICATION OF DRUG MOLECULE OF MARINE ORGANISM

Anti-Bacterial

One polyunsaturated fatty acid that is shielded from the marine diatom is eicosapentaenoic acid. Tricornutum Phaeodactylum. It shows interest against a variety of Gram-positive and Gram-negative bacteria, including a type of staphylococcus arcus that is resistant to multiple drugs.

Anti-Inflammatory

The rat version of the carrageenan-made paw oedema assay uses extracts and many different concentrations of the Mediterranean sponge species, *Spongia officinalis*, which has anti-inflammatory properties.

Anti-Viral Agents

Higher molecular weight exopolysaccharides isolated from the French marine sponge *Celtodoryx giradae* have been shown to exhibit anti-herpes simplex virus-1 (HSV) action, along with signs of related symbiotic bacteria.

Anti-Microbial

One well-known antimicrobial agent of marine origin is cephalosporin. First, cephalosporin C was isolated from a marine fungus, and then cephalosporin acremonium was purified from the same marine fungus.

Anti-Parasitic

Tunisian sponge is valued because of its sarcophagus species extracts, which are available in dichloromethane. Through the showing of the associated morphological alternation or changes within the promastigotes of Leishmania major, the in-vitro anti-leishmanial strategy has been created.

Anti-Cancer

The enormous and distant bryozoan bryostatin is derived from *Buegula neritina*. Additional paperwork had been taken out of sponges and tunicates. The sorbicillactone, an offshoot alkaloids and their analogue 2', 3'-dihydro sorbicillactone B have demonstrated their efficacy in inhibiting leukemia cells that are freed from cytotoxicity. The bacterial stress penicillium chrysogenum's saltwater lifestyle is the source of sorbicillactone-B. Penicillium chrysogenum is protected from a mediterranean sponge species called *Ircinia fasciculata*. An alternative anti-cancer medication called keyhole limpet

hemocyanin is employed as an immunotherapeutic treatment. KLH is an extracellular respiratory protein that contains copper. In *Megathura crenulata*, it exists. *Megathura crenulata* is a marine gastropod species that is commonly seen in vast quantities along the Pacific coast of Mexico and California.

KLH has two isoforms: KLH1 and KLH2. KLH is employed as an immunotherapeutic agent and in experimental immunology due to its immunostimulatory qualities in a variety of experimental animals and people. Treatment for bladder cancer involves KLH. Its effectiveness stems from the epitode of cross-reacting carbohydrates.

Neuroprotective

Using the extracts of South Indian inexperienced seaweed, such as ulva reticulata, provides neuroprotection. It moves with the help of acetyl and butyrylcholinesterase inhibitors. The effectiveness is currently accredited for the treatment of Alzheimer's disease and shares characteristics with retailers [17–20].

MARINE BIOACTIVE INGREDIENTS SOLD IN THE MARKET

CYTARABINE, ara-C [1, 21]

The marine sponge was kept away from cytarabine (also known as Ara-C and Cytasar-U). It kills cancer cells by preventing DNA polymerase from doing its job. Cytarabine, often referred to as cytosine arabinoside, is a chemotherapeutic medication used to treat acute myeloid leukemia, chronic myelogenous leukemia, and non-Hodgkin's lymphoma (Figure 2).

- *(DrugBank ID):* (DB00987).
- *Source Organism: Cryptotethia crypta* (sponge).
- *Molar Mass:* 243.217 G/Mol.
- *Formula:* C9H13N3O.
- *Brand Name (Company):* CYTOSAR-U® (Pfizer, New York City, NY, USA) and DEPOCYT® (Pacira Pharma, San Diego, CA, USA; Bedford Lab, Seattle, WA, USA, Enzon Pharmaceuticals, Piscataway, NJ, USA.
- *Class:* Anti metabolites.
- *Protein Binding:* 13%.
- *Routes of Administration:* Injectable (Intravenous or infusion or intrathecal or subcutaneous).
- *Metabolism:* Liver.
- *Excretion:* Kidney.
- *MOA:* Within the cell, it is changed into the triphosphate form and completed with cytidine to produce DNA. Cytarabine's sugar moiety interferes with the DNA molecule's ability to rotate.
- *Dosing:* When starting induction therapy for acute non-lymphocytic leukemia, the standard dosage of Cytarabine in conjunction with other anti-cancer medication is 100 mg/m2 IV every 12 hours (days 1–7) or 100 mg/m2 IV every day (days 1–7).
- *Side Effects:* Leukopenia, thrombocytopenia, anemia, bone marrow suppression, nausea, vomiting, diarrhea, and stomach pain.

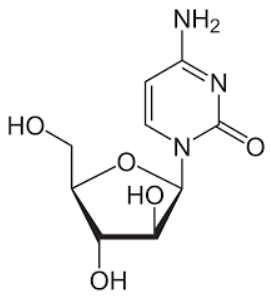

Figure 2. Chemical structure of Cytarabine [21].

Vidarabine, ara-A [1, 21]

The most significant known antiviral lead of marine origin is nucleoside ara-A (vidarabine), which is extracted from the sponge *Tethya crypta*. Vidarabine is an antiviral agent that exhibits activity against several RNA cancer viruses, rhabdoviruses, hepadnaviruses, herpes virus, and pox virus. Treatment for recurrent superficial keratitis and acute keratoconjunctivitis caused by HSV-1 and HSV-2 involves the administration of 3% ophthalmic vira-A (Figure 3).

- *(Drug Bank ID):* (DB00194).
- *Source Organism: Cryptotethia crypta* (sponge).
- *Molar Mass:* 267.24.
- *Formula:* C10H13N5O4.
- *Brand Name (Company):* VIRA-A® (King Pharmaceuticals, Bristol, FL, USA).
- *Route of Administration:* Eyes.
- *Excretion:* Kidney.
- *Protein Binding:* 24–38%.
- *MOA:* Artificial spongonucleoside analogue that inhibits herpes virus DNA replication.
- *Side Effects:* Burning, pain, irritation, itching, redness, swelling, blurred vision.

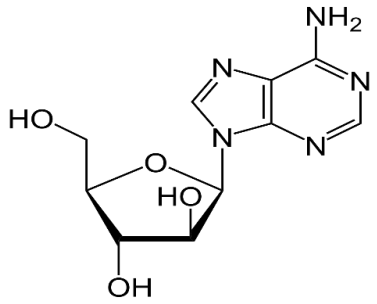

Figure 3. Chemical structure of Vidarabine [21].

Ziconotide [1, 21]

Another name for ziconoide is SNX-111. It is an analgesic that isn't an opioid. It is conotoxin MVIIA in a synthesized form. The venom of the fish-eating marine snail Conus magus contains a peptide called conotoxin. Due to its poor capacity to pass the blood-brain barrier, patients get intrathecal administration of it. When administered intrathecally, ziconotide can quickly achieve its maximum local concentration, promoting the fast onset of analgesia (Figure 4).

- *(Drug Bank ID):* (DB06283).
- *Source Organism: Conus magus* (marine snail).
- *Molar Mass:* 2639.14.
- *Formula:* C102H172N36O32S7.
- *Brand Name (Company):* PRIALT® (Azur Pharma, Dublin, Ireland).
- *Route of Administration:* Intra thecal.
- *Excretion:* <1% urine.
- *MOA:* By blocking N-type calcium channels, it prevents the primary afferent nerve terminal from releasing excitatory neurotransmitters and causes antinociception.
- *Side Effects:* Dizziness, drowsiness, nausea, headache, weakness.

Trabectedin [1, 21]

Beneath the Yodelis brand, Trabectedin is a reliable product. It is a Caribbean tunicate-derived alkylating cytostatic medication. When surgery is not an option for treating liposarcoma that has spread to other body areas and the patient has already received chemotherapy treatment, intrathecal succededin injection is performed (Figure 5).

- *(Drug Bank ID):* ET-743 (DB05109).

- *Source Organism: Ecteinascidia turbinate* (tunicate).
- *Molar Mass:* 761.84 g/mol.
- *Formula:* C39H43N3O11S.
- *Brand Name (Company):* YONDELIS® (PharmaMar SA, Madrid, Spain).
- *Metabolism:* Liver.
- *Protein Binding:* 94–98%.
- *MOA:* Binds to the DNA minor groove that interacts with the machinery responsible for DNA repair, genetic transcription, and cell division.
- *Side Effects:* Headache, weakness, fatigue, diarrhea, constipation, body aches, darkening of the skin, or difficulty falling asleep.

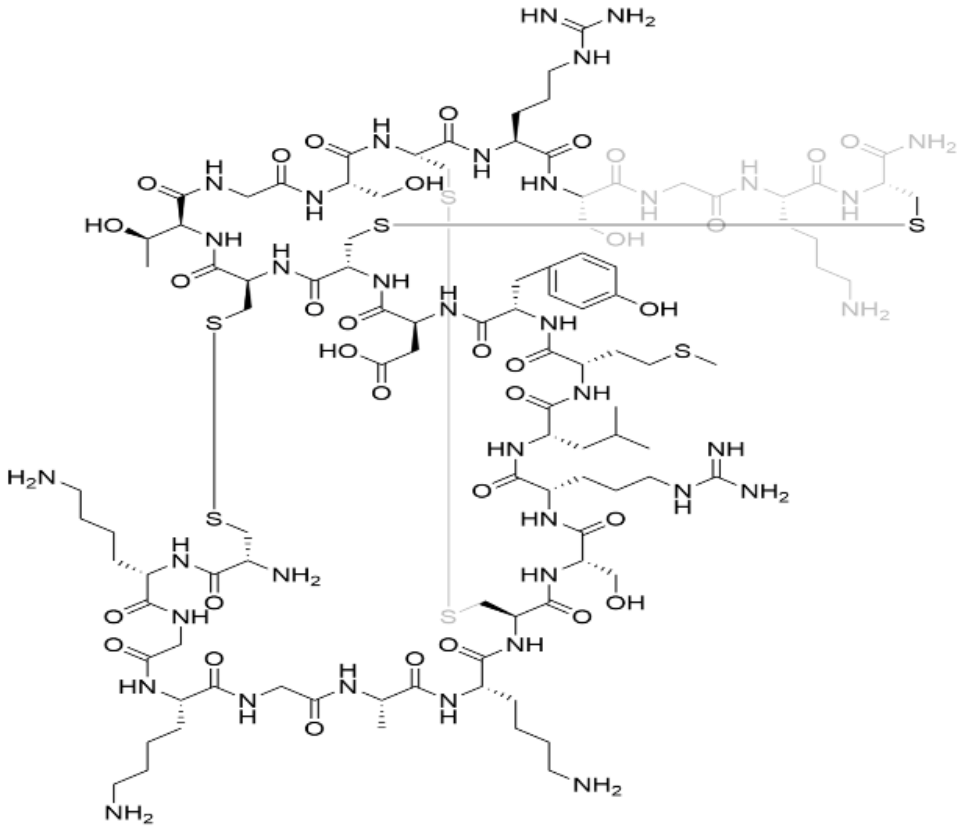

Figure 4. Chemical structure of Ziconotide [21].

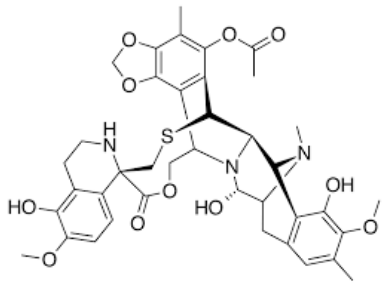

Figure 5. Chemical structure of Trabectedin [21].

Eribulin Mesylate (E7389) [1, 21]

Eribulin is an anticancer medication that is used to treat solid tumors, including breast cancer. The synthetic counterpart of halichondrin B, eribulin mesylate, is a bulky polyether macrolide that is generated from a naturally occurring inhibitor of mitotic tubules (Figure 6).

- *(Drug Bank ID):* (DB08871).
- *Source Organism: Halichondria okadai* (sponge).
- *Brand Name (Company):* HALAVEN® (Eisai, Bunkyo, Japan).
- *Molar Mass:* 826.0 g/mol.
- *Formula:* C14H69NO14S.
- *Class:* Anti- neoplastic drug.
- *MOA:* suppression of the microtubule growth phase in the absence of a matching suppression of the shortening phase.
- *Side Effect:* Nausea, constipation, loss of appetite, weight loss, headache, weakness, tiredness, bone-back pain or joint pain.

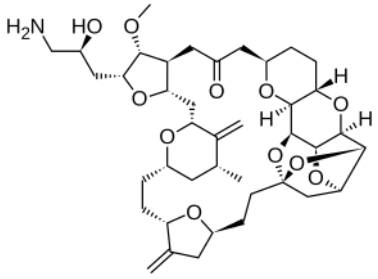

Figure 6. Chemical structure of Eribulin Mesylate [21].

Soblidotin [21]

Dolastatin 10 is a tetrapeptide derivative that is known as soblidotin. It is a strong anti-tumor agent that inhibits tubulin polymerization. It functions as an apoptosis inducer, an antineoplastic, and a microtubule destabilizing agent. It shares a functional correlation with L-valine and phenylethylamine (Figure 7).

- *Molar Mass:* 702.0 g/mol.
- *Formula:* C39H67N5O6.
- *MOA:* prevents tubulin from polymerizing, which causes cell cycle arrest and apoptosis to be induced.
- *Side Effects:* Severe cumulative neuropathy, neutropenia and fatigue, alopecia, diarrhea and nausea.

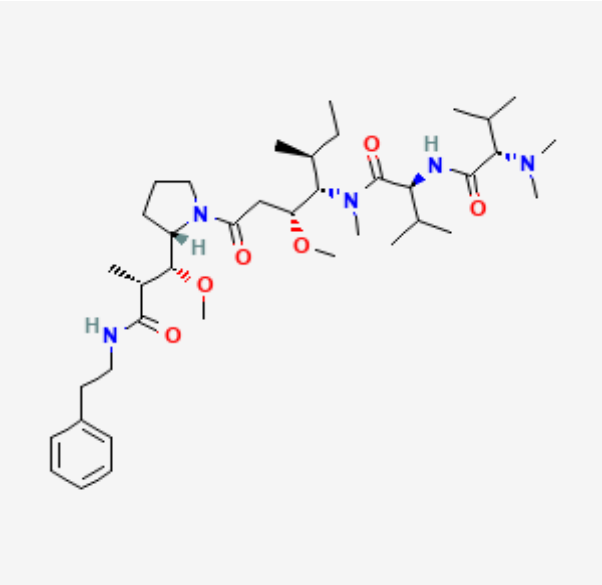

Figure 7. Chemical structure of Soblidotin [21].

MARINE DRUGS IN THE MANAGEMENT OF DIABETES MELLITUS

The main symptoms of diabetes mellitus, a chronic metabolic disorder, are high blood sugar levels and abnormal sugar metabolism. It is a major cause of death and morbidity in both developed and developing countries, including India. A malfunction in the secretion and location of action of insulin is a component of this condition. The devastation of various microstructures, including neurons, nephrons, and retinas, illustrates the disease's severity and emphasizes how it affects the kidneys, eyes, and nerves. Food provides a significant amount of energy in the form of sugar, which is needed to keep the body's millions of cells operating physiologically. By using two ways to move sugar across the cell membrane – a receptor that functions as a door and insulin that targets the receptors – the body regulates sugar. Type 2 diabetes is primarily characterized by elevated blood sugar levels, primarily because of a receptor malfunction. A hyperglycemic condition caused by an insulin malfunction is known as type 1 diabetes [22]. Type 2 diabetes is more prevalent globally than type 1 diabetes. An estimated 20 million individuals globally have been diagnosed with type 1 diabetes, and in certain countries, an annual increase of 2% to 5% is projected. However, 90% to 95% of instances of diabetes worldwide are caused by type 2 diabetes. Over 280 million individuals were predicted to have type 2 diabetes in 2011, and by 2030, that figure is expected to increase to as high as 500 million [23].

The anti-glucosidase and anti-amylase properties of over 500 freshwater and marine cyanobacteria have been investigated; 38 intriguing candidates have also been shown to be beneficial in the treatment of diabetes [24]. It has been discovered that the marine sponge-related bacterium Coralliphaga is very active in the breakdown of polysaccharides and the processing of glycolipids and glycoproteins. Because it produces several glucosidase inhibitors, it is a promising candidate for development as a treatment for obesity and diabetes. Streptomyces bacteria strains, including Streptomyces corchorusii subspecies rhodomarinus, demonstrated intriguing anti-diabetic properties by inhibiting the activity of the enzyme amylase, while other species of a similar strain produced Pyrostatins A and B, two novel compounds with N-acetyl-glucosaminidase inhibition properties [25].

It has also been demonstrated that photosynthetic eukaryotic microalgae, which make up a large portion of freshwater and marine phytoplankton, have a crucial role in the control of diabetes mellitus [26, 27]. Three strains of microalgae, *Chlorella protothecoides*, *Chlorella zofingiensis*, and the diatom *N. laevis*, have been evaluated to have protective action against the exogenous and endogenous AGEs in an ARPE-19 cell-based model due to their nutritional components, which include carotenoids and omega 3 fatty acids. These microalgae can be used as a dietary supplement to prevent and treat diabetic retinopathy since they contain carotenoids and omega-3 fatty acids. They also inhibit the development of cataracts and further macular degeneration by reducing the levels of mRNA expression of VEGF and MMP-2, which are important factors in the etiology of diabetes-induced retinopathy [28]. Corals, sea grasses, fish, shark fusion proteins, sea anemones, salmon skin, and even fish and shellfish wastes have all been examined for their ability to prevent diabetes throughout the last 15 years. Due to their advantageous qualities, they are now consumed only as extracts or whole meals in several nations that have chosen them as a healthy lifestyle option [29].

MARINE DRUGS IN NEURODEGENERATION

Researchers in the 21st century are facing their biggest medical challenge: neurodegenerative diseases. These are a collection of diverse late-onset illnesses that result in altered mobility and cognitive impairment because of the increasing malfunction and death of neuronal cells. Neurodegenerative disorders are becoming increasingly widespread as people age, and they are more prevalent in the older patient population. Aging is the primary factor linked to the neurodegenerative process [30, 31]. These disorders are primarily characterized by a decline in neuronal function and the development of misfolded proteins, which are then followed by extracellular intracellular deposits, aggregation of the proteins, and death of the neurons. Overproduction of reactive oxygen species (ROS) and neuroinflammation are major factors in the pathogenesis of various neurodegenerative illnesses and are a direct result of disruptions in the central nervous system's (CNS) homeostasis [32]. To manage age-related deterioration and foster stability in patients, effective treatments are being investigated. The

quality of life is only partially improved by the treatments used to treat neurodegenerative diseases. As a result, the area demands research and development that investigates and finds new, safer lead compounds with unique mechanisms of action that target specific physiological pathways and enhance patient outcomes. The sea, which has the highest diversity of flora and fauna and is the least studied, draws more attention as interest in natural products grows. As a result, some of the intriguing substances found in the water are listed below, along with information on how to use them as adjunctive treatments for arole in the management and prevention of neurodegenerative diseases [33, 34].

An additional marine substance known as conotoxins functions as a CNS receptor antagonist and plays a vital role in several physiological processes, including learning, memory, and attention. The following is a list of some of the popular marine medications used to treat neurodegenerative diseases.

Fucoidan

This substance effectively reduces motor impairment and has a protective impact in the treatment of Parkinson's disease due to its interaction with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Additionally, the chemical effectively prevented the striatal region's dopaminergic neurones from being depleted. Treatment with this chemical resulted in increased mitochondrial activity while maintaining the shape of neuronal cells. Though the exact pharmacological mechanism behind this protective function is unknown, its antioxidant activity is known to be responsible for preventing the production of reactive oxygen species and other mechanisms including anti-inflammation [35].

Seaweeds

Because it is an antioxidant, seaweed is another marine component that is thought to have extraordinary bioactive characteristics. After testing various seaweed extracts, it was determined that their anti-apoptotic mechanism was responsible for their neuroprotective effects. It was discovered that the extracts significantly reduced dopaminergic neurotoxicity and increased cell viability, which led to its application in the treatment of Parkinson's disease. Only present in brown seaweeds, phenoltannins are the cause of this compound's antioxidant properties. A promising neuroprotective seaweed with anti-oxidative and anti-genotoxic qualities is Codium tomentosum. The material readily scavenges both nitrogen and oxygen free radical species and contains a variety of organic acids, such as malic acid, aconitic acid, oxalic acid, fumaric and malonic acids, phenolic compounds, and secondary metabolites [36, 37].

MARINE DRUGS IN THE MANAGEMENT OF CANCER

Cancer is a chronic illness that affects practically all creatures with many cells. The illness is closely linked to aging because, as a person ages, somatic cell mutations multiply and encourage the unchecked proliferation and invasion of unhealthy cells, which alters bodily functioning and is detrimental to the organism's health. This disease is characterized by uncontrolled cell proliferation, tumor-derived inflammation, metastasis, genetic instability, longevity of replication, resistance to cell death, onset of angiogenesis, reprogramming of energy metabolism, and immune destruction prevention [38–40]. The development of more innovative and sophisticated diagnostic methods as well as treatment drugs has improved the clinical results of cancer patients by combining cutting-edge research and technology with attempts to identify and comprehend the characteristics of the disease. Cancer treatments can be broadly classified into two classes: those derived from natural compounds and those derived from synthetic compounds. These can be further separated into two categories: biologics, or high molecular weight substances, such as ribonucleic acid (RNA) or monoclonal antibodies, and small molecules, or low molecular weight compounds, which readily penetrate cells and cause biological responses. antibodies, which enter cells with the aid of delivery systems [41]. Most cancer therapy medications are sourced from natural sources. For example, the taxanes plant is the source of the two most widely used chemotherapeutic medications for the treatment of breast, prostate, and other cancers: paclitaxel and docetaxel. Another naturally occurring anticancer substance, cabacitaxel, was produced by chemically diversifying taxanes [42].

The unique living dweller of marine sources is thought to offer treasurable medicinal potential, which is why the ocean is being researched for its hidden potential. It is interesting that compounds obtained from the ocean have a high potency, operate via several molecular pathways, and can target various cancer hallmarks in combination [43]. More than a thousand compounds derived from marine sources have been identified and are undergoing preclinical research to assess their efficacy; 23 compounds derived from marine sources are undergoing phase I–III clinical trials, and seven have been given the go-ahead for commercialization. Of all the substances obtained from marine sources, four are now being employed in clinical settings for their anticancer properties: brentuximab vedotin, a conjugated antibody, eribulin mesylate, cytarabine, and trabectedin.

CONCLUSIONS

Marine-derived pharmaceuticals offer a promising avenue for discovering new medications with unique mechanisms of action. With several compounds already clinically approved and commercially available, continued research in this field is expected to yield innovative treatments for various diseases.

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