

Marine Biotherapeutics: Delving Into The Vast Untapped Resource Of Therapeutic Molecules Showing Better Outcomes Against Diseases

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ABSTRACT

The planet earth is covered with 97% water, which is largely found in the seas and oceans of the planet. Marine diversity can become a huge scope for sources of chemical drugs/compounds that are naturally obtained from a variety of marine population from microorganisms to phytoplanktons and animals like fish and mollusks. Such naturally extracted molecules are researched and studied for their efficacy to work against serious health issues like cancer, HIV etc.

1. INTRODUCTION

In recent years, many research and discoveries have been done on marine biotherapeutics. Discoveries of many antimicrobial, antiviral, anticancerous Marine Natural Products (MNPs) have been done as well as studied. MNPs include secondary metabolites, bioactive compounds, cytotoxic compounds, also compounds useful as nutraceuticals and for drug discovery and key role in drug resistance. In this review paper, we would like to introduce few very important and effective roles of marine extracted products or compounds. FDA (Food and Drug Administration) and EU (European Union) has also recently approved MNPs (Begum & Hemalatha, 2022) such as Cytarabine, which was clinically approved as a potential drug in 1969 as Ara-C type of compound which is effective against leukaemia and has saved many lives and is till date widely used for the treatment of the disease. Later, in the year 1976, a compound called Vidarabine, isolated from sponge *Tethya crypta*, which is Ara-A type of compound that encompasses antiviral bioactivity (Sagar et al., 2010). Vidarabine was used as antiviral agent against *Herpes simplex* virus but for a short period of time as it was less successful (Dyshlovoy & Honecker, 2020). Ziconotide is a non-opioid drug used in the treatment of severe chronic pain and 1st FDA approved analgesic drug used for the treatment of pain. Ziconotide is isolated from marine snail, *Conus magus* (Mcgivern, 2007), omega 3 fatty acid is an essential component required regularly by the human body. The best direct source can be Cod fish liver oil capsules. A study showed the relationship between consumption of omega 3 fatty acid supplement usage and inflammation. The relationship showed that after and before exercising the CRP levels induced showed the absorption of omega 3 fatty acids resulting in less inflammation in the body. Basal CRP levels were reduced and the exercise-induced CRP response was attenuated in those individuals who regularly had omega 3 fatty acid supplement (Hansen et al., 2021). Trabectedin, approved as anticancer drug in 2007 which was isolated from Caribbean marine tunicate *Ecteinascidia turbinata* (Senthilkumar & Kim, 2013) and Plitidepsin have grabbed the attention for cancer treatment. These drugs are of marine origin that have a positive effect working as an antitumour agent by not only targeting the tumour cells but also the tumour environment (Galmarini et al., 2014), Eribulin Mesylate (2010), Brentunimab vedotin (2011) and Iota-carrageenan are some other studied MNPs (Begum & Hemalatha, 2022). MNPs have been isolated from various resources have demonstrated a wide range of pharmacological properties including antibacterial, antiviral, analgesic, anticancer, apoptotic, antiangiogenic and antioxidant properties (Begum & Hemalatha, 2022). Marine *Bacillus* species have been studied that produce Mixirins that possess cytotoxic activity against colon cancerous cells in humans. Other than this, *Bacillus* also produces polypeptides, lipopeptides, fatty acids, polyketides, macrolactones and isocoumarins. All of these variety of compounds of *Bacillus* hold antimicrobial, antialgal and anticancer properties (Mondol et al., 2013). Marine bioactive

peptides have potential effects as anticoagulant, antifungal, antihypersensitive, antidiabetic, antiobesity and involves calcium – binding bioactivities (Giordano et al., 2018). Fucoidans are sulphated polysaccharides that are extracted from brown algae, *Fucus evanescens* having multiple bioactivities such as anti-angiogenesis, anti-inflammatory and possess key roles in successful bone regeneration (Ohmes et al., 2022). Cancer being a major public health concern as it has become the second most leading cause of death in humans (Pradhan et al., 2023), irrespective of age and gender. Apart from treatments like chemotherapy, radiotherapy, immunotherapy which can be a matter of financial crisis too for a family having a cancer patient, we need to focus on natural and also affordable treatment options for saving people. *Ulva*, a green seaweed produces a cell wall polysaccharide called *Ulvan* having anticancerous property. *Ulva* is a phytoplankton that produces a cell wall polysaccharide called ulvan upto 9-36% of dry weight in composition and 45% in total dry weight along with other uronic acids such as glucouronic acid, iduronic acid, sulphated rhamnase and xylose (Pradhan et al., 2023). Isolation of Ara-C (1-beta-D-arabinofuranosylcytosine) and Ara-A (1-beta-D-arabinosefuranosyladenine) from marine sponges of Florida coast (Singh et al., 2020) (Sumit Mehrotra et al., 2008). Algal species named *Sphaerococcus coronopifolius* produces anticancerous, antitumor and cytotoxic compounds that have effective ability to be used as drugs (Alves et al., 2018). The recently emerged SARS-CoV-2 which had become a world threat to human lives, for robust and effective therapeutic, it has recently been studied that some specific molecules derived from algae can be used to produce antibodies and vaccines against the virus (Ahmed et al., 2021). There are many MNPs discovered and used as drugs for the treatment of various health issues. Yet still many compounds of marine origin are undiscovered or are undergoing research. This review article throws a light on some very important, researched MNPs that are effective against cancer, viral infections and inflammation. Thus, we think that this review article can help for further research in the vast and novel field of marine biotherapeutics for developing drugs that can be both natural and effective for people.

2. METHODS AND MATERIALS

2.1 Source of MNPs:

Various areas of marine environment have been selected and studied for obtaining phytochemical compounds from various species of phytoplankton and from marine microbes as well as from higher order marine species. Following list gives details of these geographical regions opted by the researchers (Table 1):

Table 1: Geographical regions and species opted for the isolation of biotherapeutic compounds

GEOGRAPHICAL REGIONS	SPECIES SELECTED
Arctic	<i>Bacillus</i> sp.
Coasts of Florida	Shallow water sponges
Indian ocean, Pacific islands, Asia-Pacific regions, New Zealand, etc.	<i>Ulva</i>
Antarctic	<i>Desmarestia menziesii</i>
Mediterranean sea nearby Sardinia	<i>Acremonium chrysogenum</i>
Caribbean sea	<i>Ecteinascidia turbinate</i>
Jiao Zhou Bay, China	<i>Streptomyces</i>
Qingdao Coast, China	<i>Actinomyces</i>
New Zealand Peninsula	<i>Lindgomycetacea</i>
Far Eastern seas of Russia	<i>Fucus evanescens</i>

2.2 Extraction of MNPs:

The methods commonly employed for the extraction of the MNPs include hydrogel preparation, characterization, detection, isolation and cultivation (Ohmes et al., 2022). The antioxidant ability of these species was evaluated by using DPPH (2,2-diphenyl-1-picrylhydrazyl) method. Ara-C (1-beta-D-arabinofuranosylcytosine) was isolated from agarose hydrogels using layer by layer assembly. Ara-C is chemotherapeutic agent medically used for treatment of acute leukaemia (Sumit et al., 2013). *Desmarestia menziesii* was selected for the isolation of 9'HSQ compound. The compound was isolated from the brown algae, followed by cell culture experiments and viability assays to confirm the effect of 9'HSQ on non-neoplastic cells. Effect of 9'HSQ was then studied on lymphoid neoplastic cells for 18 hours (to check mitochondrial membrane potential) and for 24 hours (to check cell cycle). Further, ex-vivo analysis for the effect of 9'HSQ were done on the neoplastic cells (Santos-Pirath et al., 2020). Vidarabine was firstly isolated from uridine phosphorylase enzyme from *Clostridium perfringens* and then purified. The techniques such as Flow chemistry technologies along with biocatalysis is used (Tamborini et al., 2020). Cytarabine is synthesized and formulated with the help of TINPs, the drug content analysis was performed using HPLC technique including other physiochemical characterization by FTIR, PXRD (Powder X-Ray Diffractometry), cell viability assays and anticancer activity tests (Fule et al., 2023).

3.RESULT

Many MNPs have been proven to be effective as anticancer drugs/compounds (Table 2). Some of which are used clinically as a part of the treatment for cancer. Cytarabine, derived from marine sponge is widely used as anticancer drug that has positive actions against leukaemia. Fucoidans have multiple actions such as antiosteogenesis, antiangiogenesis and anti-inflammatory. Fucoidans are delivered using injectable, thermosensitive chitosan-collagen hydrogels that temporarily immobilize the polysaccharide at the site of injury. The need of omega 3 fatty acid as supplement to the body is fulfilled by cod fish liver oil which is commercialized in the form of capsules since many years. Sharks, rays and skates produce heavy chain antibody IgNAR that are helpful in the making of nanobodies as therapeutics for autoimmune diseases like rheumatoid arthritis. Ulvan, a polysaccharide has anticancer and antioxidant properties. 9' HSQ is useful in lymphoid neoplasm treatment. Mixirins have resulted into cytotoxic activity against colon cancer in human body. Polyketides from *Aspergillus sp.* that produce antibacterial agent against MRSA and MDRSA. This also involves *Lindgomycin* that synthesizes antibacterial polyketide. *Vibrio sp.* yield pigmentary antioxidants. Indian marine sponge *Petrosia similis* was found to produce 2-bis-quinolizidine alkaloids Petrosins which have anti HIV activity. Targeted cytotoxic drugs obtained from *Dolabella auricularia* has shown anticancer activity.

Table 2: Comprehensive list of the marine biotherapeutic molecules including their medicinal use, source (species) and citations.

Serial No.	SOURCE	MOLECULE	USE	Literary source
1.	<i>Fucus evanescens</i> (brown algae)	Fucoidans	Antioosteogenesis, antiangiogenesis, anti-inflammatory	(Menshova et al., 2016) (Ohmes et al., 2022)
2.	<i>Ulva</i> species	Ulvan	Anticancer, antioxidant	(Pradhan et al., 2023)
3.	<i>Tethya crypta</i> (shallow water sponge)	Vidarabine (Ara-A) and Cytarabine (Ara-C)	Ara-A being antiviral, Ara-C being anticancer, effective in acute leukaemia	(Singh et al., 2020) (Sumit et all., 2013)
4.	<i>Desmarestia menziesii</i> (brown algae)	Plastoquinone 9' hydroxysargaquinone (9'HSQ)	Useful for lymphoid neoplasm treatment	(Santos-Pirath et al., 2020)
5.	Sharks (from indoor shark farming systems)	Shark Immunoglobulins (Igs) IgNARs, consists of one variable domain (V _{NAR}) and five constant domains	Effective in autoimmune diseases, like in treatment for rheumatoid arthritis	(Tanaka et al., 2022)
6.	<i>Sphaerococcus coronopifolius</i>	Cytotoxic compounds	Useful as anticancer, antitumor drugs	(Alves et al., 2018)
7.	Cod Fish (liver oil)	Omega-3-fatty acid	Useful as a nutraceutical-enriched in Vit. A, Vit.D & Vit.E, has anti-inflammatory property	(Hansen et al., 2021)
8.	<i>Acremonium chrysogenum</i> (marine fungus)	Cephalosporin C	Useful and effective as antimicrobial agent	(Sruthi et al., 2020)

9.	<i>Bacillus</i> species	Mixirins	The compound has cytotoxicity activity against human colon cancer cells	(Kemp, 2011) (Mondol et al., 2013)
10.	<i>Aspergillus</i> species	The polyketides (+)-epoxydon, gentisyl alcohol, 3-chlorogentisylalcohol and methylhydroquinone isolated from a marine-derived <i>Aspergillus</i> species.	Found as potent antibacterial agents against MRSA and multi-drug-resistant <i>Staphylococcus aureus</i> (MDRSA)	(Kim et al., 2007)
11.	<i>Lindgomycetacea</i>	Lindgomycin	Antibacterial polyketide	Untraced
12.	<i>Cryptotheca crypta</i> (Caribbean sponge)	C-nucleotides	Used as the basis for the synthesis of Cytarabine, currently used in the routine treatment of patients with leukaemia and lymphoma cancers.	(El-Demerdash et al., 2018)
13.	<i>Bryozoan bugula neritina</i> (common-global fouling organism)	Cytostatic compound	Complex polyketide Bryostatin	Untraced
14.	<i>Ramalina terebrata</i> (lichen)	Ramalin	Antioxidant	Untraced
15.	<i>Synoicum adareanum</i> (tunicate)	Palmerolide A and D-G (macrolides)	Potent V-ATPase inhibitory and anti-melanoma(sub-micro molar)	Untraced
16.	<i>Vibrio Spp.</i> (Strain PIGB 184)	Phenol 2,4- bis(1,1-dimethylethyl) & pyrrolo(1,2-a) pyrazine-1,4- dione, hexahydro-3-(2-methylpropyl)	Produce pigmentary antioxidants	(Pawar et al., 2016)
17.	<i>Streptomyces</i> species	Yields chlorine containing Manumycin derivatives, Chinikomycins A and B	Both the compounds displayed antitumour activity against a number of human cancer cell lines	Untraced
18.	<i>Actinomycete saccharopolyspora sp.</i> Associated with the sponge <i>Mycale plumose</i>	Metacyclo-prodigiosin	Has significant cytotoxicity and anticancer activity against five cancer human cell lines	Untraced
19.	Indian marine sponge <i>Petrosia similis</i>	2- bis-quinolizidine alkaloids petrosins	Exhibits anti-HIV property	Untraced
20.	<i>Dolabella auricularia</i> (mollusc)	Brentuximab vedotin (Adcetris) – Targeted cytotoxic drugs.	pronounced anticancer activity	Untraced

4. DISCUSSION

The present review article is an attempt to highlight the plethora of marine molecules with medicinal use. As has been illustrated earlier, the isolated molecules from marine sources have activity against a wide range of diseases like cancer, infection and inflammations, neoplasms etc. Though majority of MNPs are observed as per the studies have been found to be effective as therapeutic drugs to treat cancer and viral infections (Fig 1). The species targeted for the isolation of the therapeutic molecules also is quite diverse ranging from microorganisms e.g. bacteria and fungi to sponges, algae and higher animals like tunicates, different fishes and sharks. This highlights the diversity of the species targeted for the isolation of the molecules. Among the various diseases targeted, majority of the molecules discovered so far haven been found to have anticancer effect (Fig 2).

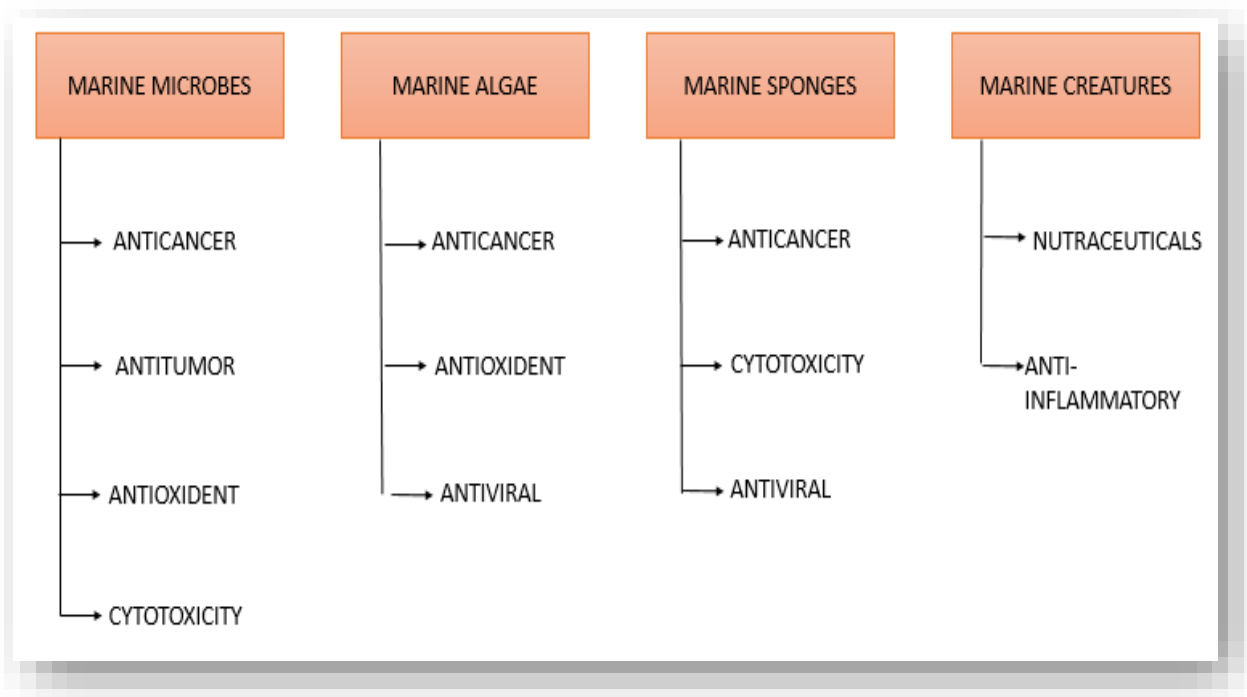


Fig 1: Characterization of the action against specific diseases, as exhibited by the marine biotherapeutic molecules isolated from diverse sources.

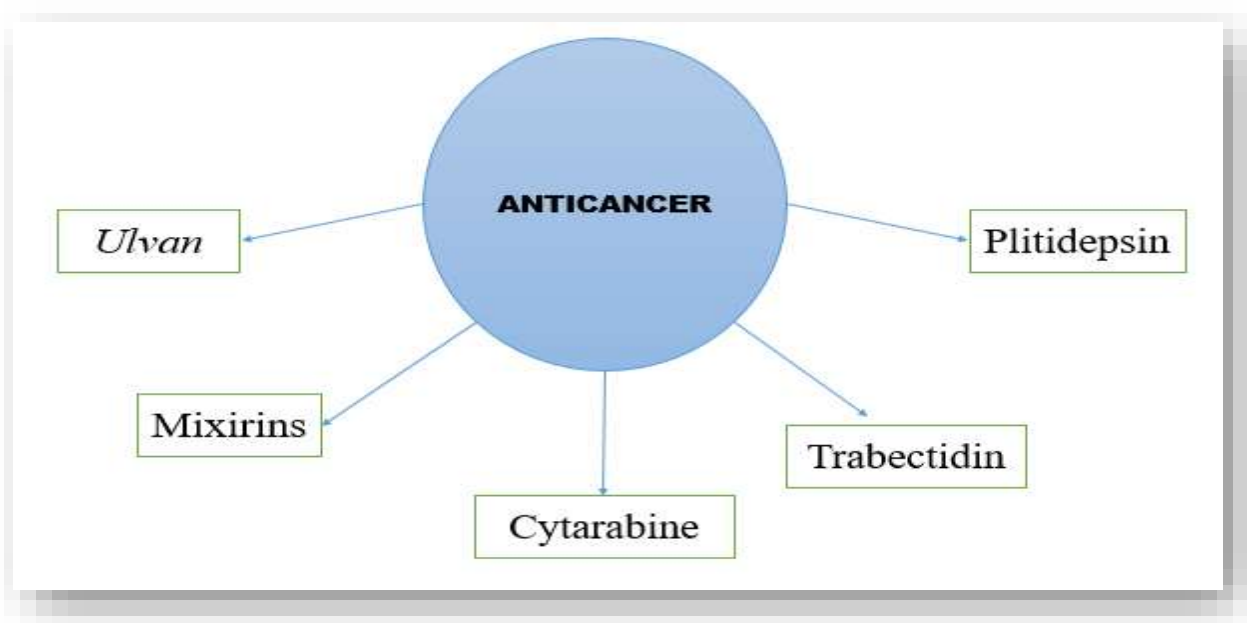


Fig 2: Different therapeutic molecules isolated from marine source with anti-cancer effect.

5. CONCLUSION

This review paper concludes that marine sources are of great help for the humanity. There are yet many unexplored regions of marine environment that remain as a wider scope for extensive studies and research. All the naturally obtained compounds of marine origin that have been studied and are also utilized for various purposes have shown better results rather than the artificial drugs made. Not only these compounds have aided in the betterment of the human health but also worked efficiently as supplements along with allopathic treatments. We have compiled a number of marine compounds researched over past recent years.

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