REVIEW ARTICLE

Marine Bioactives in Cancer Prevention and Treatment

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ABSTRACT

The twice high incidence risk of cancer in men was the reason for over a million new cases and deaths recorded globally in 2018. The two most frequent cancer-related fatalities are lung and breast cancer. Novel therapies have been made possible by developments in immunotherapy, biology, and pharmaceutical design. Novel cancer prevention and therapy elements are being made possible by technological advancements and studies on marine natural resources. The creation of innovative anticancer medications is utilizing marine-derived natural products (MNPs). Biologically active polyketides, high molecular weight organic sugars, terpenes, bioengineered alkaloids, and marine animal peptides are some examples of these MNPs. Anticancer drugs are also developed with the help of plants, animals, invertebrates, and microbes found on land. The National Cancer Institute is exploring the potential of nutrition and food in cancer prevention despite the absence of preclinical and clinical data. Marine organisms contain bioactive compounds that have potential anticancer effects. Polyphenols, polysaccharides, and alkaloids are some of the active components found in marine species. Polyphenols, found in edible seaweeds like *Palmaria palmata*, can lower cancer cell division and proliferation, while polysaccharides trigger the innate immune system, causing apoptosis in pancreatic islet cancer and human leukemia cells. Alkaloids, derived from marine sources, can inhibit cancer cell development. Peptides, found in various plant species, have shown cytotoxic effects on several human cell lines, including pancreatic, breast, lung, and bladder cancers. Marine drug approval faces challenges like the possibility of a resurgence of different metabolites due to environmental conditions and limited lead compound availability.

Keywords: Marine, Plants, Cancer, Organisms, Drugs, Natural products.

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INTRODUCTION

With 10 million fatalities and 18 million new examples recorded globally in 2018, cancer is still a deadly illness. Global estimates place the number of new cases and deaths at above 1,000,000, with males having an incidence rate that is twice as high. In North America, Australia, and New Zealand, the most prevalent type of cancer to be diagnosed is nonmelanoma skin cancer. Age and bad lifestyles are linked to the greatest incidence rates.[1] The two most common cancer-related deaths in both men and women are lung and breast cancer. There are two types of predisposition factors for cancer: internal (genetic predispositions, immunological disorders) and external (tobacco, chemicals, radiation, infectious organisms). Thanks to developments in immunotherapy, biology, and contemporary medication design, it is now possible to find a cure for cancer.[2] Numerous cancers in humans have previously been cured, extending their lives. Chemotherapy, however, has a number of negative consequences, which has led researchers to look for more potent treatments with fewer side effects. With more than half of all pharmaceuticals and 80% of authorized chemotherapeutic treatments being based on bioactive natural ingredients, Novel drugs can be derived from natural ingredients.[3] Marine-derived metabolites have anticancer properties, and naturally occurring bioactive compounds target macromolecules that are expressed by cancer cells.[4] Recent technological and research advancements in marine natural resources are paving the way for the evaluation of new anticancer medications in clinical trials.[5] There are many promises in marine resources for finding novel cancer-prevention and -treatment entities. Since its inception in the late 1800s, medication development has become the primary focus of marine biotechnology.[6] Marine natural product scaffolds are a prospective source of chemicals for cancer therapy due to their complexity and variety. With the use of cutting-edge instruments, this continuous study provides a chance to assess novel modes of action and new chemical families of anticancer drugs.[7,8]

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Natural Products Derived from the Marine and their Categories

Marine organisms are driving the innovation of new anticancer treatments by utilizing huge oceanic resources and marine chemicals for improved therapeutic techniques and extensive chemical component research.[9] Unexplored sources of anticancer medicinal medicines include marine sources. The best MNPs are bioengineered alkaloids, various terpenes, marine animal peptides, biologically active polyketides, and organic sugars high molecular weight. These MNPs' inherent ability to fend off deadly infections makes them essential in anticancer drugs.[10]

Nature and cancer chemotherapy

Natural compounds made from marine plants and microorganisms have demonstrated advantages in the management and treatment of cancer during the past 50 years. Marine-based medications are used to treat leukemia, soft tissue sarcoma, ovarian cancer, and metastatic breast cancer.[11] These medications include, among others, cytarabine, brentuximab vedotin, eribulin mesylate, and trabectidine. Terrestrial bacteria, invertebrates, mammals, and plants are additional sources of anticancer medications. The active ingredients in vinca herb and taxol, an antineoplastic medication derived through the Western Yew tree's bark, have been shown to be beneficial against choriocarcinoma, Hodgkin's disease, and juvenile leukemia.[12] Although there hasn't been much research done on cancer chemoprevention utilizing marine natural substances, the National Cancer Institute is trying to understand the impact that nutrition and diet have in preventing cancer. There is still a lack of preclinical and clinical evidence for this approach despite its compelling chemical justification. Thirteen of the natural compounds having anticancer qualities that have been identified from microorganisms, plants, and marine life have undergone clinical testing. A targeted, combinatorial strategy could hasten the creation of novel marine resource-based anticancer medications.[13]

Marine Organism and Cancer Chemotherapy

Around 500 × 106 prokaryotic and eukaryotic creatures make up the global biodiversity of the oceans, which encompass 70% of the planet. There are around 250,000 species known to exist in the marine environment, making it an incredibly diversified wellspring of life.[14] There are 3.7 × 1030 microorganisms in marine species, of which 99% are bacteria that cannot be grown but can produce natural compounds that may lead to new drugs.[15] Europe, the Near East, China, and India have long utilized marine plants for therapeutic purposes. But just 5% of the deep water has been looked into, and only 0.01% of the deep-sea bottom has undergone detailed sampling. The first marine creature to be studied chemically was the Caribbean sponge, and other marine species have been investigated for their potential to cancer prevention. Clinical studies have assessed bioactive compounds against different forms of cancer. Novel techniques for cancer research have been made possible by developments in marine chemistry.[16,17]

Marine Resources and Anticancer Drug Origins

Marine microorganisms, such as sponges, algae, corals, marine bacteria, and marine fungi produce novel secondary metabolites (NSMs) with a variety of chemical compositions. These SMs can be crucial for the development of anticancer medications. Prokaryotes, algae, mangroves, and other marine organisms are the sources of these medications. Ninety percent of sea biomass is composed of the diverse marine microflora and microalgae found across the world's seas. MNPs have been found as a possible route for creating novel cancer therapy medications or therapeutic leads, despite their varied bioactivities.[18]

Bacteria

Marine microorganisms are essential for creating novel therapeutic targets. Sarcodictyin, eleutherobin, discodermolide, and bryostatins are anticancer isolates that have been created from secondary primary metabolites from marine minute living forms. Pathogenic living organisms control probiotic microorganisms such as *lactobacilli* and *bibidobacteria* through anticancer combinations. The nutritional benefits of lactobacilli are lowering the risk of colon cancer; macrolactin-A suppresses the growth of B16-F10 murine melanoma cancer cells; and *Streptomyces spinoverrucosal,* dibohemamines B and C may be able to influence the lineage of lung cancer cells. The mollusc *Elysia rubefescens* generates a depsipeptide known as Kahalalide F (KF), which has demonstrated action against solid tumors, including prostate cancer cell lines, both in vitro and *in-vivo*[19] Additionally, *in-vivo* study suggests that it is involved in breast and colon cancers. An indole microbial anticancer drug called trisindolal 38 is also effective against melanoma and breast carcinoma cell lines. A rich supply of anticancer drugs may be found in marine actinomycetes, especially coraline, which has the ability to cytotoxically treat lung and colon cancer by inhibiting RNA construction. Through the p53 immune system, thiocoraline exerts antiproliferative effects on the growth of colon cancer. The marine-derived bacteria *Poseidonocella sedimentorum* KMM 9023T inhibits the growth of human cancer cells in the colony and has no cytotoxicity.[20,21]

Fungi

Though their study is less extensive than that of their terrestrial counterparts, marine fungi are significant sources of novel anticancer drugs taken from deep-sea sediments, algae, sponges, and endophytic mangroves. It has been discovered that marine-associated fungi have both growth-inhibitory and cytotoxic anticancer activities when grown on cancer cell lines. These include marine sediment-derived fungus like *Neosartorya fischeri*, sponge-associated fungi like *Arthrinium arundinis*, mangrove endophytic fungi like Pestalotiopsis microspore, and deep-sea fungal species like *Simplicillium obclavatum*.[22] Isolated marine fungus may be useful as pharmaceuticals since they produce anticancer chemicals. None, however, have made it onto the market because of restrictions on the recognition of anticancer discoveries,

Table 1: List of compounds obtained from marine sources having possible anticancer effects

Brugine /Alkaloid,	*Extracted from Bruguiera sexangular plant*	*Tested on Sarcoma 180 and Lewis cell*	*No specific result*	26
Apratoxin A/Peptide	Derived from *Lyngbya boulloni* bacteria	In Cervical cancer	Cell cycle inhibition IC_{50} value 2.2 nM	27
Fucoidan/Polysaccharides	Isolated from *Ascophyllum nodosum* algae	In Colon cancer	Prevent the growth of arterial smooth muscle cells at concentrations between 80 and 100 µg/mL.	28
Lyngbyabellin B/p Peptide	Obtained from *Lyngbya majuscule* bacteria	Effective against Burkitt lymphoma cancer	Inhibit of cell growth IC50 value 0.02 µM	29
Sansalvamide A/Peptide	Sourced from Marine fungi	Impede in pancreatic, colon, breast, and prostate cancers.	Inhibits protein complex formation	30
Phloroglucinol/polyphenol	Extracted from Brown seaweed	In Colon cancer	At 80–100 µg/mL, shown to prevent arterial smooth muscle cells.	31
Actinomycin/Peptide	Derived from *Streptomyces parvullus*, *Streptomyces* sp. ZZ338 Actinomyces	Childhood cancer, Wilms tumor	By Inhibiting of RNA polymerase	32

taxonomic analyses, biological targets, and interaction modalities. To resolve concerns with clinical effectiveness, more research is required.[23]

Microalgae

It has been discovered that the Japanese Okeania species' cytotoxin, *cyanobactin wewakazole* B, is cytotoxic to human cancer cells. Curacao samples from *Lyngbya majuscula* are used to make curacin-A, a powerful anticancer medication. In nanomolar structures, a family of cyanobacterial chemicals called aprotoxins inhibits potentially fatal malignancies. Adenocarcinoma cytotoxicity is demonstrated by a parental chemical called apatoxin A, which was isolated from *Lyngbya bouillonii*. In human unfavorable tumor cell lines, GSV 224, a combination of *Gracilaria* sp. and galaxamide analogs, showed genuine cytotoxicity and directed drug affectability action against tumor cells deadly to human drug-resistant and stable tumor cells. Additional substances with antimetastatic, anticancer, antitumor, and fibrinolytic properties include cyanobacteria and fucoidans.[24]

Sponges

30% of all-natural products found have been obtained from marine sponges, which have prompted the creation of medications like spongothymidine and spongouridine. Thanks to synthetic analogs, AraC, a therapeutically effective anticancer drug, and eribulin, a synthetic variant of halichondrin B, have been developed.[25]

Marketing and FDA approval of anticancer medications produced from marine sources

Despite the 20 to 30 year lead disclosure period, four FDA-approved marine pharmaceuticals are presently under development, making marine nanoparticles (MNPs) an important bioactive knowledge indicator. Marine-derived anticancer drugs are being developed in hematology and oncology. Adcetris, a drug approved by the FDA in 2011, is based on dolastatin 10 and ADCs. It is the world's leading drug in the 7 MM sectors and has been a significant contributor to the market development of hematological and oncological cancers.[33] The FDA approved cytarabine in 1969, and it is the best treatment for myeloid leukemia, nHL, and meningeal leukemia. Upjohn originally used the brand name Cytosar-U to promote it in the United States. Nevertheless, cytarabine's function in the brain is limited by its inability to pass through the blood-brain barrier. The FDA authorized Halaven, a medication for metastatic breast cancer, in 2010. Halaven is consolidated with a new cancer infrastructure at Eisai Research Institute. Johnson and Johnson medication research and innovation have approved the use of trametin, an antineoplastic alkaloid derived from the Caribbean Sea Squirt *Ecteinascidia turbinata*, to treat soft tissue sarcoma.[34]

Marine derived drugs in clinical trials

Four marine medications have been licensed for use as anticancer treatments for more than 50 years, and a small number of additional compounds are undergoing Phase I, II, and III clinical studies. The four primary stages of a successful study are preclinical, post-clinical, and post-clinical. Further examination is carried out to ascertain marketability, including detrimental trends, medication potency, formulation and manufacturing obstacles, copyright authenticity, market circumstances, and plausible competition. After then, the medication enters the following stage.[35] Potential treatments for malignancies that may be challenging to cure are provided by the intricate pharmaceutical development pipeline of anticancer medicines originating from marine sources. Many medications are being tested in clinical trials right now to treat cancer. Among the medications undergoing phase III trials are depatuxizumab mafodotin, enfortumab vedotin, lurbinectedin, marizomib, plinabulin, polatuzumab vedotin, enzastaurin, and lestaurtinib. GSK2857916, Aplidin®, ladiratuzumab vedotin, PM060184, tisotumab vedotin, indusatumab vedotin,

and glembatumumab vedotin are among the trials that are in phase II. A phase I clinical trial is presently ongoing for the medication Midostaurin (Rydapt®).[36]

Bioactive constituents of marine organism

Marine species include a high concentration of physiologically strong, highly active anticancer chemicals called polyphenols, polysaccharides, and alkaloids.

Polyphenol

It is well known that polyphenols, which include tannins, flavonoids, phenolic acids, and other substances, lower the amounts of cellular proteins required for cancer cell division and proliferation as well as the mitotic index. They also show inhibitory effects on human platelet aggregation, antiviral, and anti-inflammatory qualities. The edible seaweed *Palmaria palmata* has a wealth of polyphenols that may have antioxidant and anticancer effects because they block the enzymes that break down xenobiotics, causing disruption to cell division and changes to mitotic processes.[37]

Polysaccharides

Polysaccharides, which are mostly present in marine species such as carrageenans, agar, and alginates, have a cytotoxic impact because they trigger the innate immune system. This stimulates the generation of tumoricidal cytokines by natural killer cells and macrophages at the target site. It has been discovered that sulfated polysaccharides cause pancreatic islet cancer and human leukemia cells to undergo apoptosis. Glycosaminoglycans have the ability to cause apoptosis in melanoma cells in mice. Fucoidan is a sulfated polysaccharide derived from brown algae that functions by downregulating the kinase pathway and activating caspase-3 to control angiogenesis, metastasis, and atherosclerosis.[38]

Alkaloids

Marine habitats are the source of three different kinds of alkaloids: halogenated indoles, other alkaloids, and phenylethylamines. *Acanthus illicifolius, Bruguiera sexangula*, and *Kandelia candel* contain other alkaloids, including brugine, benzoquinones, and acanthicifolin. In the meantime, Lophocladia species is the source of ophlocladine A and B. It has been demonstrated that the main alkaloid found in the leaves of *Rhizophora mucronata* and *Rhizophora stylosa*, rhizophorine, inhibits the growth of cancer cells.[39]

Peptides

The cytotoxic effects of peptides on human cell lines, including those from malignancies of the lung, pancreas, breast, and bladder, have been demonstrated. It has been discovered that cyclic depsipeptides, such as apatoxin A, coibamide A, and lyngbyabellin B, suppress the cell cycle. Antiproliferative qualities are found in active peptides derived from the Lyngbya and Nostoc species. Proscolaride A and B, two novel cyclodepsipeptides, have dramatically slowed the growth of colon and pancreatic tumors. Sansalvamide A, a brand-new cyclic depsipeptide, has demonstrated promise as an anticancer treatment lead.[1]

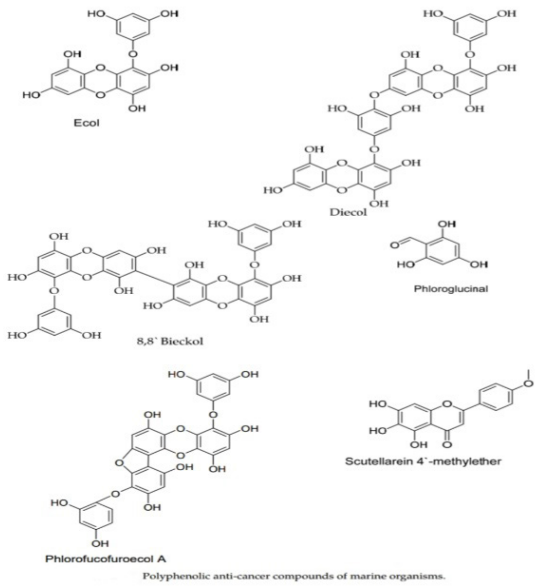

Figure 1: Polyphenolic compounds from marine organisms.[31]

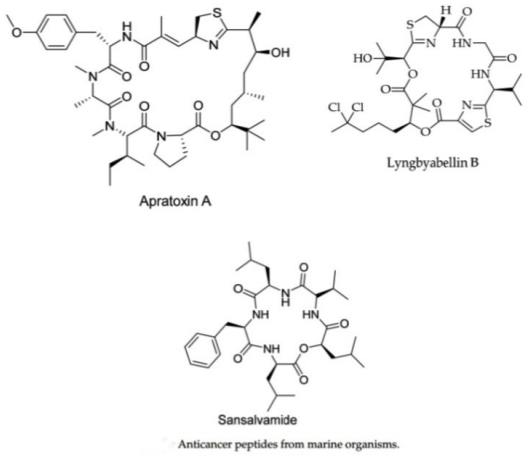

Figure 2: Peptides from marine organisms.[30,32]

Barriers and Restrictions in the Authorization of Marine Drugs

Various metabolites originating from the same organism might arise again depending on the environmental circumstances. Microorganisms found in aquatic animals, not their marine invertebrate hosts, are the ones that produce bioactive substances. The activities of their host influence the growth of microorganisms in symbiotic partnerships. In this context, metagenome research is becoming more and more important as it provides direct contact with microbial populations and uncultivable bacteria. Another difficulty is maintaining a sustainable supply of extracted lead compounds since they are areolating and only available in small quantities.[40] One of the main obstacles to the development of marine drugs is the lack of molecules with sustainable availability. Creating easier synthesis techniques or synthesizing analog derivatives

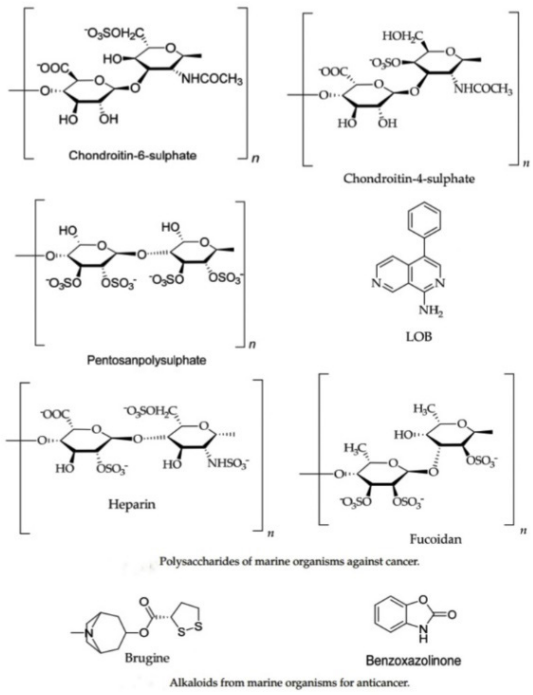

Figure 3: Polysaccharides, Alkaloids compounds from marine organisms[28,41]

are two attempts to overcome the issue. On the other hand, poor yields and the complexity of marine compounds might result in improper chemical configuration and formula. It is advised to control the use of natural resources and to raise aquatic animals in their native environments. Drugs obtained from marine sources must meet the same market entrance requirements as medications generated from land, which can lead to problems, harmful side effects, and unsustainable accessibility.[9] Chemical variety in drug development can be enhanced via co-cultivation, the OSMAC method, and epigenetic processes. Simplified structures can be designed with an increased understanding of chemical production and structural constituents. Cell-based cytotoxicity screening may be improved by high-content techniques and specific targets, which will help to categorize potential treatment candidates intelligently. Although it damages the marine ecology, the manufacture of drugs from marine animals depends on a steady supply of chemicals and organisms. Supply management that is both environmentally and economically feasible is essential for market potential. Improvements in marine biotechnology and sampling techniques can help with supply problems.[13]

CONCLUSION

With over 1,000,000 new cases and fatalities from the disease globally in 2018, cancer is still a dangerous illness, with a twice-high incidence rate in men. In Australia, New Zealand, and North America, nonmelanoma skin cancer is the most prevalent kind. Lung and breast cancer are the most common causes of cancer-related death. Because of advancements in immunotherapy, biology, and pharmaceutical design, new treatments have been created. Metabolites produced from marine environments have anticancer capabilities by targeting macromolecules expressed by cancerous cells. Innovations in technology and scientific study on marine resources are opening doors for new organizations focused on cancer prevention and treatment. Innovative anticancer treatments, such as polyketides, organic sugars, terpenes, alkaloids, and marine animal peptides, are being developed using marine-derived natural products (MNPs). Many drugs have shown promise in the past 50 years for the prevention and treatment of cancer. The National Cancer Institute is looking into how food and nutrition can help prevent cancer. Bioactive substances found in marine species include alkaloids, polyphenols, and polysaccharides that may have anticancer properties. However, there are obstacles to the approval of marine medications, including the availability of extracted lead compounds and environmental circumstances. The bacteria present in aquatic animals are used in the development of marine medications because they produce bioactive compounds. Understanding microbial communities and uncultivable microorganisms requires research on the metagenome. Sustainable lead compound extraction is a challenge, though. It is necessary to manage natural resources and raise animals in their natural habitats in order to develop marine medications. Drug development can be improved by increasing chemical variety through co-cultivation, the OSMAC approach, and epigenetic mechanisms. Market potential depends on supply management, and advancements in sampling methods and marine biotechnology can help with supply-related problems.

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