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Anticancer drugs from marine organisms: A review

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Abstract
Cancer has become one of the common occurrences in the modern population and is currently the second paramount cause of mortality worldwide. Most cancer medications and therapies (Chemotherapy/hormonal) used around the world have been reported to have associated side effects. These associated side effects have attracted researchers around the globe towards unearthing molecules from natural sources, with minimal to least side effects. Marine oceans are rich in biodiversity of organisms and their metabolites are unusual from most terrestrial ones due to extreme oceanic conditions. Currently, very few plants and animal-based molecules are used in cancer treatment. This review highlights various recently discovered metabolites and molecules from marine organisms like marine sponges, algae, bacteria, and fungi as potent anti-cancer targets and their potential mechanism of action. These natural molecules for cancer therapy may reduce the predicted and unpredicted side effects caused by most chemical agents used today and point out some potent agents against various cancer types.

Keywords: Anti-cancer, marine drugs, fucoidan, inhibition

1. Introduction
Humans face potential death every day. We could catch a deadly virus/bacterium or a life-threatening condition like cancer. Our immune system tries to fight these critical conditions with an army of specialized cells to eliminate the invading pathogen up to a certain degree. Lethal conditions like cancer, however, try and weaken the immune system and start spreading to different body parts including bone marrow after reaching the metastatic phase. Cancer is one of the leading causes of death worldwide, with around 10 million reported deaths worldwide in 2020 [1]. Despite the advancements in medicine over the last few decades, which include radiation, chemotherapy, and surgical excision, they are still accompanied by side effects such as high toxicity or drug resistance. Therefore, there is a need for the discovery of novel, pharmacologically safe, and efficient anticancer drugs. Currently, about 80% of the chemotherapeutic medicines being researched for the treatment of cancer are based on natural products [2]. Researchers have spent a large amount of time scouring the seas and oceans seeking marine animals that are blended with substances with the potential of having clinical and therapeutic benefits. These add to a diverse range of aquatic life forms that includes a variety of mollusks, delicate chordates, microorganisms, robust seaweed, and permeable sponges [3]. Persistently, sea-based living things have obtained the capacity to communicate designed mixtures of what more or less may be cytotoxic, contemplating how these organisms have made sense of how to survive in typically undesired and undermining settings of the marine environment that is characterized by higher levels of salt and pressure, a shortage of oxygen for cellular respiration and availability of light, as well as extremely intense sets of shifting marine temperatures [4].
To stop the growth and spread of malignancies, researchers are still actively looking for innovative therapeutic compounds derived from marine organisms that target certain molecular signaling pathways. Several clinically approved marine-derived drugs, the majority of which are derived from marine microbes or invertebrates, demonstrate their huge

potential for bioprospecting. A large number of additional compounds are currently undergoing clinical research or are in the preclinical stage.

2. Anti-cancer Molecules from marine bacteria and fungi

Marine fungi have been reported to produce a plethora of compounds with distinctive chemical structures in marine environments, making them excellent leads against various cancers. These compounds include alkaloids, polyphenols, peptides, polysaccharides, etc., which have been studied against cancer target proteins and environment using *in-silico, in-vitro,* and *in-vivo studies.* Apratoxin A is a peptide isolated from marine cyanobacterium *Lyngbya boulloni,* which has been reported to inhibit the cell cycle in the cervical cancer cell line (HeLa) [5]. Recently, polyketide analogs have been reported to selectively target human breast cancer cells via the HER2 signaling pathway. HER2 is reportedly considered an important target for selective cancer therapy and is associated with approximately 30% of human breast cancers with drug-resistant and more aggressive tumors [6]. Polyketides like Sulochrin, *Monochloro Sulochan*, and Diorcinol, obtained from *Aspergillus falconensis* from the red sea in Egypt, have been found to inhibit Matrix metalloproteinase-13 (MMP-13) and cyclin-dependent kinase 2 (CDK2) pathway, suggesting anti-cancer properties in MDA-MB 231 breast cancer cells via inhibition of migration at a concentration of 70 µM [7]. MMP-13 is also considered an excellent target for the treatment of osteoarthritis, therefore, these polyketides can further be tested as potent molecules against various targets in osteoarthritis. Diorcinol and Sulochrin are further reported to inhibit Human DNA topoisomerase II, which is responsible for the promotion of cell proliferation as well as DNA replication, and were able to show comparable binding scores to the anti-proliferative, anti-cancer standard drug available in the market (Doxorubicin), thereby confirming their anti-cancer potential [8].

Demethoxyfumitremorgin C, a secondary metabolite from the fungus *Aspergillus fumigatus* have been found to reported to exert cytotoxicity by inducing apoptosis via activation of activated caspase-3, 8, and 9, leading to PARP pathway through blocking of mitochondrial electron transport chain and subsequent disruption of mitochondrial membrane potential in Human prostate cancer cell line PC3 [9]. Moreover, an endophytic fungus, *Penicillium chrysogenum* isolated from the green algae *Chaetomorpha antennina* produces bioactive molecules that possess anticancer properties.

Anti-cancer molecules from marine algae

Codium decorticatum is a green seaweed found along south-east coat of India. The extracts of *Codium decorticatum* have been reported to have cytotoxic effects against five cancer cell lines, viz. HeLa (cervical cancer), SKBR-3 (breast cancer), HT-29 (colorectal adenocarcinoma), PC3 (prostate cancer), and MIA PaCa-2 (pancreatic cancer) cells, exhibiting an IC50 values ranging 72.88-97.32 µg/mL with the dichloromethane extract at 48 hours. Glycoprotein (GLP) from *C. decorticatum* has significant cytotoxic activity against the MCF-7 breast cancer cell line, Siha cervical cancer cell line, and A549 lung cancer cell line, the increasing GLP concentrations in MDA-MB 231, were found to increase the percentage of cells in the G2/M phase as compared to the control cells, thereby concluding that GLP induces cell cycle arrest at the G2/M phase in the MDA MB 231 cells keading to apoptosis [10].

Fucoidans are naturally derived sulfated polysaccharide molecules that have been reported to possess anti-oxidant nature. Fucoidan isolated from brown algae *Turbinaria conoides* by hot water extraction showed cytotoxic activity and inhibited the pancreatic epithelial cancer cell line MiaPaCA-2 and PANC-1 cells. Moreover, upon fucoidan treatment (5 µg/ml, 24h), 300% increase in the protein levels of caspase 3, 8, and 9, and the case of PANC-1 cells, the levels of caspase 3, 8 were increased by 200% and caspase 9 increased by 400% as compared to the untreated cells [11]. Results clearly showed that fucoidan fraction induces apoptosis in pancreatic cancer cells as a potent marine drug macromolecule.

Bioactive molecules from sponge for cancer

Sponge (phylum Porifera) growth rates range greatly amongst various families and appear to be relatively stable and long-lived. Marine sponges are mostly found in saltwater and have been around for a very long time and had been used even by ancient Romans for medical purposes such as wound healing, infectious disease and even tumor treatments [12]. Although these marine creatures create secondary metabolites in very small quantities, they assist them to compete with sessile species and ward off predators [13]. When it comes to the variety of their secondary metabolites, marine sponges are a "gold mine," as has been revealed over the past fifty years.

Nucleosides, bioactive terpenes, cyclic peptides, alkaloids, fatty acids, sterols, peroxides, and amino acid derivatives (Often halogenated) are all present in marine sponges. A number of the identified compounds and their analogs have entered clinical trials, including Eribulin mesylate, which entered phase I and II cancer clinical trials for the treatment of metastatic breast cancer [12]. A brominated tyrosine derivative known as Bastadin 6 was discovered in the marine sponge *Ianthella sp.* Bastadin 6 when exposed to Human umbilical vein endothelial cells (HUVECs) exhibited decreased vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF)-dependent proliferation (IC50 = 0.052M). Additionally, it also prevented HUVECs from forming tubules in response to VEGF or bFGF or migrating in response to VEGF [14]. Aaptamine, a marine sponge alkaloid, has anticancer properties against HepG 2 human liver carcinoma cell line (IC50 = 75 g/mL) [15]. Table 1, lists a few marine derived anticancer molecules in clinical trials.

Table 1: Marine-derived anticancer molecules in clinical trials

S. No	Compound	Source organism	Effects	Ref.
1.	Enzastaurin	*Streptomyces staurosporeus*	Inhibits Phosphatidylinositol 3 kinase	(Ning *et al*., 2018)
2.	Lestaurtinib	*Streptomyces staurosporeus*	Inhibits tyrosine kinase 3	(Wang *et al*., 2019)
3.	Depatuxizumab mafodotin	*Caldora penicillata*	Inhibits tubulin polymerization	(Pereira *et al*., 2019)
4.	Brentuximab vedotin	*Dollabella auricularia*	Blocks cell cycle progression from step G2 to M	(Pereira *et al*., 2019)
5.	Cytarabine	*Cryptotheca crypta*	Hampers DNA production	(Pereira *et al*., 2019)
6.	Eribulin mesylate	*Halichondria okadai*	Synthetic microtubule inhibitor	(Pereira *et al*., 2019)

Challenges and Future Prospects

We have come a long way in technological advancements in drug discovery pipeline in the past decade. There still lies a challenge though in isolating these molecules in large quantities, while preserving the quality and structural integrity, while going through a series of purification steps. However, the recent innovations and discoveries in science have made it easier to screen for potent drug molecules from sea sources. A hight throughput screening approach along with conventional experimental and pharmaceutical sciences can help solve the lag between the preclinical studies and medicinal market. Advanced nano-biotechnology based formulations can be further used to enhance the pharmaceutical activity and drug delivery and absorption potential of naturally discovered molecules.

Conclusion

Ocean based natural products are promising pool for drug molecules of high structural diversity. These molecules have been linked to various anticancer bioactivities and can be developed or used as initiation point in the discovery and optimization of novel cancer drugs. This review highlights and encourages making contributions in natural molecule research to achieve better human health and longevity.

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