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Review Article

Marine Organisms as Source of Anticancer Agents: A Review

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ABSTRACT

Oceans cover more than 70% of the earth surface and the marine environment is highly diverse. Marine floras are taxonomically diverse, largely productive, biologically active and chemically unique offering a great scope for discovery of new anticancer drugs. The marine floras are rich in medicinally potent chemicals predominantly belonging to polyphenols and sulphated polysaccharides. The various active anticancer agents are derived from plants and terrestrial microorganisms and the isolation of C-nucleosides from the Caribbean sponge, Cryptothecacrypta, four decades ago, provided the basis for the synthesis of cytarabine that is the first marine derived anticancer agent to be developed for clinical use. Gemcitabine, one of its fluorinated derivatives that has also been approved for use in patients with pancreatic, breast, bladder, and non-small-cell lung cancer. ET-743, Aplidin R and Kahalalide F, has shown to show a positive therapeutic index and activity in resistant solid tumors that supports the ongoing clinical phase II/III trials. ET-743 represents as the first active agent against tumors developed in the past 25 years and has demonstrated a therapeutic potential in pretreated ovarian cancer. In recent times, a 44-member Dilactone macrolide swinholide J, epoxide of swinholide A, a known cytotoxic compound that was reported from the Red Sea sponge *Theonellas winhoei* and their cytotoxic properties indicated this compound to be less potent against oral carcinoma cell lines. This review revolves around the latest examinations and affirmations the colossal force of marine life frame as anticancer biomolecule sources

Keywords: Sponges, Bacteria, Fungi, Cytotoxicity, Bryostatsins, Aplidine

INTRODUCTION

Cancer, it is a highly dreadful human disease which is increasing with changing life style. Cancer treatments do not have much efficacious medicine, as the currently available drugs are causing side effects in some cases. In this context, the natural products obtained from medicinal plants has attained significance in the treatment of cancer and according to the WHO about 80% of the world's population primarily those of developing countries rely on plant-based medicines for the health care system [1]. Natural products and their derivatives represent more than 50% of all the drugs in clinical use of the world and most of higher plants contribute not less than 25% of the total. Among all the anticancer drugs approximately 60% are of natural origin. Fruits and vegetables are the principal sources of vitamins (C, B, E), carotenoids, and fibers, and these contribute towards the apparent cancer-protective effects of the foods. An increase in dietary intake of natural antioxidants results in reduced coronary heart diseases, cancer mortality, as well as longevity[2,3].As we go back few decades, there has been a lot of interest among researchers in exploring of new herbal used drugs. This process has opened up new ways to produce significantly a diverse range of over 1,39,000 natural products, containing medicinally useful alkaloids, terpenoid derivatives, glycosides, steroids, polyphenolics and many more to the list. As per data from The National Cancer Institute (NCI) of the United States of America (USA), researchers have screened about 1,14,000 extracts from an approximately 35,000 plant samples against a number of tumor systems[4]. Of the 92 anti-cancer drugs commercially available prior to 1983 in the USA and approved world-wide between 1983 and 1994, approximately 62% can be related to natural origin[5]. Some examples include vinblastine and vincristine (Catharanthus roseus), paclitaxel (Taxusbaccata, T. brevifolia, T. canadensis), camptothecin (Camptothecaacuminata), homoharringtonine (Cephalotaxusharringtonia var. drupacea), elliptinium (Bleekeriavitensis), epipodophyllotoxin, an isomer of podophyllotoxin (Podophyllumpeltatum roots), flavopiridol (Dysoxylumbinectariferum), and ipomeanol (Ipomoea batatas). The two medicinal products, paclitaxel and camptothecin were estimated to have nearly one third of the global anticancer market, respectively in the year 2002[6] Numerous types of bioactive compounds have been isolated from plant sources. The utilization of herbal drug formulations in the management and treatment of cancer is emerging since the last thirty years. Moreover, the focus on natural sources for potential chemotherapeutic agents is still underway. Many of them are currently undergoing clinical trials or preclinical trials or under further investigation.

Among the natural drugs, the drugs from the marine sources are still in the infancy state despite of 95% of the

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Table 1: Cytotoxic agents developed from natural sources[7]

Herbal Moeity	Anti-cancer use	Herbal Source
Etoposide	Testicular tumors, small-cell lung cancer	Podophyllumpeltatum, Podophyllumemodi
Cytarabine	Leukemia and non- Hodgkin lymphomas	Cryptothecacrypta
Vinblastine	Hodgkin's disease, non-Hodgkin, lymphoma, germ-cell tumors, Kaposi's sarcoma and breast cancer	Catharanthus roseus
Vincristine	Acute leukemia, Hodgkin's disease, non Hodgkins Lymphoma	Catharanthusroseus
Gemcitabine	Pancreatic, bladder, breast and non-small-cell lung cancer	Cryptothecacrypta
Vinorelbine	Activity in breast and non-Small cell and lung cancer	Catharanthusroseus

biosphere belongs to oceans. Recently, significant efforts have been made, by both pharmaceutical organizations and scholarly foundations, to segregate and distinguish new marine-determined particularly from faunal species. Regarding advancement and biodiversity, the ocean gives off an impression of being better than the earthly environment. As marine species contain around a half of the aggregate biodiversity, they are putting forth a tremendous source from which helpful therapeutics can be found. Over the previous decade, marine life forms have been perceived as an undiscovered asset for novel bioactive mixes. Marine verdures have been utilized for restorative purposes in India, China, the Near East and Europe, since old time. Chinese pharmacopeia suggests ocean growth based formulas for various physiological issues, for example, torment, abscesses, menstrual troubles and disease.[8] Marine inferred biomolecules, for example, peptides, catalysts, chemical inhibitors, lipids has potential for the counteractive action and treatment for tumor growth. Refined peptides from these sources have been appeared to effectively affect a few human malignancies, for example, pancreatic, bosom, bladder and lung tumor.

Marine Floras Sources for Anticancer Agents

Bacteria and cynacobacteria

Marine microorganisms are a rich wellspring of new qualities, exploration of which prompt the revelation of new medications and remedial methodologies. The auxiliary metabolites created by marine microscopic organisms yielded numerous pharmaceutical items like novel mitigating specialists (e.g., Seudopterosins, Topsentins, Scytonemin and Manoalide), anticancer operators (e.g., Bryostatins, Discodermolide, Eleutherobin and Sarcodictyin) and anti-infection agents (e.g., Marinone). Hostile to Parasitic compound Valinomycin is acquired from Streptomyces sp. strains of Mediterranean Sea.[11.]

Bryostatin, specifically obtained from the Bryozoan, *Bugula neritina*, although some of types have been leached out from sponges and tunicates. Sorbicillin-derived alkaloids sorbicillactone A and its 2', 3'-dihydro analog sorbicillactone-B has indicated activity against leukemia cells free from any imperative cytotoxicity. Sorbicillactone-B has been derived from a salt-water culture of a bacterial strain *Penicillium chrysogenum* which has been derived from a sponge *Ircinia fasciculata*, a Mediterranean sponge species.[12]

Table 2: Therapeutically significant bio-molecules from marine organisms[9, 10]

Organism	Agent	Bioactivity
Bacteria	Valinomycin	Anti-Parasitic
Cyanobacteria	Calothrixin A and B	Antimalarial
Cyanobacteria	Curacao extracts	Anti-proliferative
Fungi	Cephalosporin	Antibiotic
Fungi	Atherosclerosis	Antioxidants
Soft coral	Methanol extracts	Anticancer
Sponge	Kuanoniamines	Growth-inhibitors
Sponge	Steroid	Inflammation, asthma
Sponge	Ara-c	Antiviral
Cone snail	Conotoxins	Chronicpain

Cyanocobacteria

The cyanobacteria populace includes 150 genera and around 2000 types of extensive decent variety and the strength of marine cyanobacteria as anticancer specialists is most investigated among all marine determined chemicals. Other than cytotoxicity in tumor cell lines, a few mixes have risen as guide for the advancement of new anticancer medications e.g. cyanobacteria species incorporates Nostoc, Calothrix, Lyngbya, Symposia and so on.[13]

Fungi

Marine inferred growths give a lot of fundamentally and organically dynamic one of a kind optional metabolites in which Anthracenedione subordinates act like intense anticancer operators screened from the mangrove endophytic parasite Halorosellinia sp.. Moreover, Guignardia sp. for instance, Cytarabine, a hostile to leukemic medication and Trabectedin, a specialist for treating delicate tissue sarcoma that are created from growths sources. In addition, marine-determined parasites are additionally known to be a wellspring of against oxidative normal items, for example, Acremonin A from Acremonium sp. Xanthone subsidiary from Wardomycesanomalus. Cell reinforcements delay or anticipate oxidative harm and in this manner they might be valuable as therapeutics or nourishment added substances and distinctive kinds of Cephalosporin are confined from marine parasites which are utilized as anti-infection [14].

Table 3: Some of the marine floral derivatives, peptides and their anticancer activities

Marine flora	Chemical agent	Biological activity
	Microbial flora	
Microcystisaeruginosa[23,24]	MicroviridinToxin BE-4, Siatoxin	Antibiotic, anticancer
Streptomyces peucetius[25]	Daunorubicin	Myeloid Leukemia and acute Leukemia
	Algal flora	
Nostocspongiaforme[26]	Cryptophycin8	Greater therapeutic efficiency and lower toxicity than cryptophycin 14 in vivo
Cyanobacteria Nostoclinckia and Nostovspongiaeforme[27]	Borophycin	Cytotoxicty against human epidermoid carcinomavartenue
Cyanobacteria[28]	Apratoxins	Inhibit a variety of cancer cell lines
Nostoclinckia[29]	Cyptophycin 1	Cytotoxicity-against human tumor cell and human solid tumors
Stylopodium sp.[30]	Stypoldione	Cytotoxic
Chondria sp[31]	Condriamide A	Cytotoxicity
Caulerpa sp.[32,33,34]	Caulerpenyne	Cytotoxicity, anticancer, anti-proliferating activity
Acanthophoraspicifera[35,36]	Crude	Tumoricidal activity on Ehrlich's ascites carcinoma
Stigonema sp.[37]	Scytonemin	Antiproliferative and Antinflammatoryactivities cells developed in mice
Leptolyngbya sp[38,39]	CoibamideA	Cytotoxicity against NCIH460 lung and mouseneuro 2a cell

Sponge

In excess of 10,000 sponges have been discovered worldwide and the greater part of them live in marine situations and marine sponges have yielded more than 70 novel mixes to date that show huge inhibitory movement towards a scope of protein kinases. A scope of bioactive mixes has been found in excess of 11 spoges genera. Three of these genera (Haliclona, Petrosia and Discodemia) create compelling anticancer and calming specialists and these mixes have a wide range of organic exercises. Be that as it may, it's hard to disengage them in adequate amount for pharmacological testing [15].

Table 4: Compounds with their chemistry and mechanism of action [40, 41]

S.No.	Compound	Organism	Chemistry	Mechanism of action
1.	Aaptamine[42,43,44]	Sponge	Alkaloid	Induction of p21 and G2/M cell cycle arrest
2.	Cortistatin A[45]	Sponge	Alkaloid	Selective inhibition of angiogenesis
3.	Aplidine[46-53]	Ascidian	Depsipeptide	Oxidation and inactivation of low molecular weight-protein tyrosine phosphatase activity
4.	Bastadine 6[54]	Sponge	Alkaloid	Inhibition of angiogenesis in vitro and in vivo involves apoptosis
5.	Fucoxanthinol[55]	Ascidian	Carotenoid	Induction of apoptosis
6.	Lamellarin D[56]	Mollusk	Alkaloid	ErbB3 protein and PI3K- Akt pathway involved in necrosis induction
7.	Clavulone II[57]	Soft coral	Prostanoid	G1 cell cycle arrest and apoptosis
8.	Geodiamolides	Sponge	Peptide	Ineffectiveness of actin filaments
9.	Ircinin-1	Sponge	Sesterterpene	G1 phase inhibition and apoptosis induction
10.	Laxaphycins A and B	Bacterium	Cyclic peptides	Amplified polyploidy by putative topoisomerase II alterations
11.	Leptosins C and F	Fungus	Alkaloid	DNA topoisomerase I and II inhibition and apoptosis induction
12.	Onnamide A	Sponge	Polyketide	Protein synthesis inhibition
13.	Philinopside A	Sea cucumber	Saponin	Inhibition of angiogenesis and receptor tyrosine kinases

14.	Variolin B	Sponge	Alkaloid	Inhibition of cyclin-dependent and apoptosis induction kinases
15.	Aplidine[46-53]	Ascidian	Depsipeptide	Induction of apoptosis with concomitant G1 arrest and G2 blockage
16.	Asciddidemin	Ascidian	Alkaloid	Direct iminoquinone reduction and reactive oxygen species generation
17.	Cammbrescidin 800	Sponge	Alkaloid	Induction of eythroid differentiation and cell cycle arrest
18.	Dideoxypetrosynol A	Sponge	Fatty acid	Induction of apoptosis via mitochondrial signaling pathway
19.	Dolastatin 10[58-64]	Mollusk	Peptide	Binds to amino-terminal peptide of β tubulin containing cysteine
20.	Girolline	Sponge	Alkaloid	Induction of G2/M cell cycle arrest and p53 proteasome recruitment
21.	Halichondrin B	Sponge	Macrolide	Induction of mitotic blockage and derivative apoptosis
22.	Lissoclinolide	Ascidian	Fatty acid	G2/M cell cycle arrest
23.	Neoamphimedine	Sponge	Alkaloid	Induction of topoisomerase II α mediated catenation of DNA
24.	Psammaplin A	Sponge	Alkaloid	Inhibition of amino peptidase N and suppression of angiogenesis in vitro
25.	Alkylpyridinium	Sponge	Alkaloid	Induction of apoptosis and reduced cell adhesion
26.	Aeroplysinin	Sponge	Alkaloid	Induction of apoptosis on proliferating endothelial cells
27.	Bryostatin-1[65-70]	Bryozoan	Macrolide	Potentiation of ara-C induced apoptosis by PKC-dependent release of TNF-α
28.	Cephaiostatin	Worm	Steroid	Apoptosis and increased mitochondrial matrix density
29.	Chondropsin A	Sponge	Macrolide	In Vitro inhibition of V-ATPase enzyme
30.	Dehydrothrysiferol	Algae	Triterpene	Enhanced apoptosis induction in estrogen receptor negative breast cancer cells
31.	Diazonamide-A	Ascidian	Peptide	Disruption of mitosis and cellular microtubules with inhibition of GTPhydrolysis
32.	Dictyostatin	Sponge	Polyketides	Induction of tubulin polymerization
33.	Dolastatin 11[71-77]	Mollusk	Peptide	F-actin stabilization by connection between two long-pitch strands
34.	Ecteinascidin- 743[78-85]	Ascidian	Isoquinoline	Telomere dysfunction increases susceptibility to ET-743
35.	GA3 polysaccharide	Alga	Polysaccharide	Inhibition of topoisomerase I and II
36.	Hemiasterlin	Sponge	Tripeptide	Induction of microtubule depolymerisation
37.	Kahalalide F [86-92]	Mollusk	Depsipeptide	Potent cytotoxicity and induction of necrosis
38.	Lamellarin D	Mollusk	Alkaloid	Potent inhibition of topoisomer- ase I and II
39.	omega-3	fatty acids	Fish Fatty acid	--

Compounds Isolated from Sponges

Jaspamide

It is a cyclic depsipeptide confined from sponges of the family Jaspis and Hemiastrella. It has a 15-carbon macrocyclic ring which contains three amino corrosive buildups. It has been demonstrated this is a bioactive compound initiating apoptosis in human promyelocytic leukemia cell line and T cells in mind tumor by Caspase-3 actuation and diminishing in Bcl-2 protein articulation.

Hemiasterlins are oligopeptides secluded from two unmistakable genera (Auletta; Siphonochalina) of wipe. There are three diverse Hemiasterlins with medicate improvement potential (Hemiasterlin, Hemiasterlin A, Hemiasterlin C) display cytotoxic and antitubulin movement. Mitotic restraint happens through authoritative to tubulin at the peptide locale in a way like Dolastatin [16].

Discodermintetradecapeptides

These are another gathering of cytotoxic peptides got from sponges of the variety Discodermia sp. containing 13– 14 referred to and uncommon amino acids as a chain, with a macrocyclic ring constituted by lactonization of a threonine unit with the carboxy terminal. Discodermins A–H is being tried against human lung cell line indicating cytotoxicity. Papuamides A– D are confined from sponges of the variety Theonella, are the main marine-determined peptides answered to restrain the disease of human T-lymphoblastoid cells by HIV-1 in vitro.[17,18]

Mollusk

Mollusks are species that have an extensive variety of uses in pharmacology. Different sorts of straight, cyclic and conjugated peptides are found as restoratively intense anticancer biomolecules from the cone snail and other shelled creatures, for example, Kahalalides, Dolastatins, Ziconotide, Bursatellanin, Keenamides etc[19]

Anti-cancer Peptides from Marine Organisms

Today, more than 60% of the anticancer drugs commercially available are of natural origin. The relevance of the sea as a tool to discover novel anticancer compounds was validated by the discovery, development and marketing approval of isolated marine derived bioactive compounds. The available results clearly anticipated the potential of the marine ecosystem in cancer therapy[20]. During the last decade about 2500 new metabolites with anti-proliferative activity have been reported. A recent review has discussed 68 new marine derived anticancer chemical entities, most of them with undetermined modes of action[21]. The identification of new targets for therapeutic intervention in cancer is instrumental to improve the physiological condition of cancer patients. The clinical results generated with a number of marine derived compounds such as the Dolastatins, Didemnin B, Aplidine have been recently reviewed. Most of the natural products of interest to the pharmaceutical industry are secondary metabolites, but there is a growing interest in products of primary metabolites such as various marine lipids, enzymes complex hetero polysaccharides and different types of peptides[22]. Although different types of anticancer bio-molecules are obtained from various types of marine organism this manuscript critically summarizes the developmental status of marine derived peptides from different micro and macro organism.

Beside these there are number of compounds obtained from marine as potential anti-cancer agents included in Table 4.1 and 4.2.

DISCUSSION AND CONCLUSIONS

The above examples illustrate the intense excitement which surrounds the past decade's achievements in the area of new anticancer leads from marine organisms. The combination of novel structures and for some, novel mechanisms of action, is translating into new methods by which to treat cancer, and ultimately, improved outcomes, particularly for patients with solid tumors of the lung, breast, colon or prostate. The last decade has seen an ever evolving strategy for the screening and discovery of new anticancer leads from nature, and this is proving effective. Structures of compounds discussed in text, includingEcteinascidin 743 (ET-743), a tetrahydroisoquinolone alkaloid currently in clinical trials for treatment of various cancers. Evaluation of crude extracts by in vivo screens to current evaluation of peak or pre fractionated libraries in mechanism-based assays, the level of sophistication and success has steadily improved. Screening strategies are continuing to evolve, probing new ideas and knowledge of cancer, introducing high throughput screening and new analytic methodologies. In part, the need for this continuing evolution has been stimulated by a desire to develop novel and less toxic therapies for cancer treatment. High throughput screening methods have both enabled more sophisticated mechanism based screening, and subsequently required the move to pre fractionation and peak library generation. These ''prior-to-screening'' purifications have the consequence of reducing the complexity of screening materials, increasing the titer of low abundance components, segregating nuisance substances into discrete fractions, and generally speeding up the time line from detection of a primary screening hit to identification of a molecular structure for the active substance. It can generally be concluded that contemporary screening protocols in natural products chemistry are using chromatographic purification steps, sometimes producing pure compounds, before biological or enzymatic bioassay. Coupled to these more effective paradigms for screening are new assays that evaluate natural products in more detailed, refined, and novel ways. For example, detailed knowledge of the cellular mechanisms controlling proliferation has yielded numerous targets for mechanism-based anticancer screens. A long-standing and perplexing question in marine natural products chemistry has been the identification of the metabolite producing organism or potentially metabolite bio transforming organism, in systems involving an invertebrate host and symbiotic microorganisms. This has been a surprisingly difficult issue to satisfactorily answer except in a very few cases, largely because of the difficulty of growing various microorganisms separately from their hosts. An alternative approach that has met with some success has been to isolate the various cell populations by centrifugation, sieving, or fluorescence-activated cell sorting, and then chemically analyze these samples for metabolites of interest. For example, in the case of the sponge Dysideaherbacea and its symbiotic cyanobacterium Oscillatoria spongellae, this has been accomplished on a couple of occasions and generally supports metabolic trends observed from working with pure strains of cyanobacteria. The cyanobacterial cells were found to contain a series of highly distinctive chlorinated peptides, previously isolated from work with the intact sponge, and which have strong structural precedence in metabolites isolated from the free-living cyanobacteriumLyngbyamajuscula. Alternatively, a similar approach with the tunicate Lissoclinum patella, which harbors an abundance of the cyanobacteriumProchloron spp., yielded equivocal results for a series of distinctive cyclic peptides which were found to be associated with both the cyanobacterial and tunicate cells. In general, the approach of associating a specific

natural product with an isolated cell type is potentially flawed as it is conceivable, and even possibly expected with microbial populations, that metabolites will be secreted and become associated with cell types other that those responsible for their production. Hence, new approaches are needed which truly show the genetic and biochemical ability of a particular cell type to synthesize a metabolite of interest. A genetic approach has also been applied to this latter symbiosis which showed that Prochloron spp. do possess non ribosomal peptide synthetases.

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