A Review on Anticancer Drug from Marine

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ABSTRACT

The marine environment is a rich source of both biological and chemical diversity. It is very much likely that marine organisms would be wonderful source of biologically active molecules. The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphrastic, analgesic and anticancer agent from bacteria, cyanobacteria, fungi, sponge. This review focuses on the latest studies and critical research in this field and evidences the immense potential of marine organisms as sources of bioactive peptides and other anticancer biomolecules. Various anticancer compounds like Aplidine, Bryostatin-1, Didemin B, Dolastation, Ecteinascididine with diverse modes of action, such as, anti-proliferative, antioxidant, anti-microtubule have been isolated from marine sources. Traditional chemotherapeutic agents have a range of side effects like fatigue, gastrointestinal distress and depression of immune system which introduces that these sources have been shown to have antioxidant activity and cytotoxic effect on several human cancers such as leukemia, lymphoma, ovarian, melanoma, breast, bladder, neuroendocrine, prostatic, colon and non-small cell lung cancer very potently.

Keywords: Marine Organisms, Bryostatin-1, Dolastation, Human Cancers

I. INTRODUCTION

Over the past few years, about 3000 new compounds like anti-tumor, anti-microtubule, anti-proliferative, photoprotective, antibiotic and anti-infective discovered from various marine sources have entered clinical trials. This activity has been largely due to improvements in the technologies involved in deep-sea sample collection and large-scale drug production through aquaculture and drug synthesis which took place in the 1980s. These developments suggest that, in the future, the oceans will become an important source of novel chemical classes not found in the terrestrial environment.

II. METHODS AND MATERIAL

Therapeutic Agents from Marine Sources

Bacteria
Marine microorganisms are a rich source of new genes, exploitation of which is likely to lead to the discovery of new drugs and therapeutic approaches. Only a few marine bacteria can be isolated under laboratory conditions and there is an urgent need to develop new culture techniques to isolate slow-growing bacteria and also to isolate the bacteria that are unique in production of novel natural products. (e.g. Seudopterosins, Topsentins, Scytonemin and Manoalide), anticancer agents (e.g. Bryostatins, Discodermolide, Eleutherobin and Sarcodictyin) and antibiotics (e.g. Marinone). Anti-Parasitic compound Valinomycin is isolated from Streptomyces sp. strains of Mediterranean Cyanobacteria

The cyanobacteria population comprises 150 genera and about 2000 species of considerable diversity. The potency of marine cyanobacteria as anticancer agents is the most explored among all marine derived chemicals. Besides cytotoxicity in tumor cell lines, several compounds have emerged as templates for the development of new anticancer drugs. Well studied species of marine cyanobacteria includes Nostoc, Calothrix, Lyngbya, Symploca

Fungi
Marine derived fungi provide plenty of structurally unique and biologically active secondary metabolites. The Anthracenedione derivatives acting as the potent
anticancer agents screened from the mangrove endophytic fungus Halorosellinia sp. and Guignardia sp. Fore example, Cytarabine, an antileukemic drug and Trabectedin, an agent for treating soft tissue sarcoma are developed from marine fungi sources [8]. Besides, marine-derived fungi are known to be a source of antioxidative natural products such as Acremonin A from Acremonium sp. and Xanthone derivative from Wardomyces anomalous [9].

Sponge

Approximately 10,000 sponges have been found worldwide [11] and most of them live in marine environments [12]. Marine sponges have yielded over 70 novel compounds to date that exhibit significant inhibitory activity towards a range of protein kinases. A range of bioactive compounds has been found in about 11 sponge genera. Three of these genera (Haliclona, Petrosia and Discodemia) produce influential anticancer and anti-inflammatory agents [13].

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>COMPOUND</th>
<th>BIOACTIVITY</th>
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<tbody>
<tr>
<td>Bacteria</td>
<td>Valinomycin</td>
<td>Anti-Parasitic</td>
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<tr>
<td>Cyanobacteria</td>
<td>Calothrixin A and B</td>
<td>Antimalarial</td>
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<td>Cyanobacteria</td>
<td>Curacao extracts</td>
<td>Antiproliferative</td>
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<td>Fungi</td>
<td>Cephalosporins</td>
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<td>Fungi</td>
<td>Antioxidants</td>
<td>Atherosclerosis, dementia</td>
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<td>Soft coral</td>
<td>Methanol extracts</td>
<td>Anticancer</td>
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<td>Sponge</td>
<td>Kuanoniamines</td>
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<tr>
<td>Sponge</td>
<td>Steroid</td>
<td>Inflammation, asthma</td>
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<td>Sponge</td>
<td>Ara-c</td>
<td>Antiviral</td>
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**BRYOSTATIN-1**

![Bryostatin-1](image)

**Source organism: Bugula neritina (Bryozon)**

Bryostatin-1 is a macrocyclic natural lactone isolated from the marine Bryozoan, Bugulaneritina (Fig.1). It has shown both antitumour as well as immunomodulatory effects [1,2]. It is a potent activator of the protein kinase C (PKC) family, lacking tumour-promoting activity and with antagonistic effects on tumour-promoting phorbol esters. This effect is probably related to down-regulation of PKC or by specific isoform activation. It also stimulates cytokine production, bone marrow progenitor cells and neutrophils [3,4]. In vitro, bryostatin-1 has cytotoxic activity against various leukaemia and solid tumour cell lines. It has also in vivo antitumour activity in various murine models, including leukemia, lymphoma, ovarian cancer and melanoma. It was shown to enhance the antitumour effects of various anticancer agents, such as vincristine, cytosine arabinoside, cisplatin, melphalan, paclitaxel and others. These effects may be schedule-dependent [1,2,5]. This agent was studied in phase I trials at different infusion schedules. The recommended doses for phase II trials were 25-35 M-g/m2 when administered over one hour for three of every four weeks; 25 u.g/m2 given as a weekly 24 hour infusion. Myalgia was the DLT in all trials. Other toxicities were joint aches and a transient decrease in platelet counts [6,7]. Notably, partial responses were reported in patients with melanoma, ovarian cancer and. Phase II trials of bryostatin-1 are being conducted at various infusion regimens in a large number of tumour types in both solid and haematological malignancies. In addition, phase I trials of brystatin-1 in combination with other agents, such as cisplatin, paclitaxel, fludarabine, vincristine, cytosine arabinoside and 2-CDA are also being conducted.

**Figure 1.** The Bryozoan Bugula neritina
APLIDINE

**Figure 2.** The tunicate Aplidium albicans

Source Organism: *Aplidium albicans* (tunicate)

Aplidine was obtained from a Mediterranean colonial tunicate, *Aplidium albicans*. It has a pyruvyl group replacing the lactyl group in DB and its synthesis has been achieved. It appears more active than DB in preclinical models and apparently not cardiotoxic. Aplidine entered clinical trials in 1999 both in Europe and in the US under the sponsorship of the Spanish company Pharma Mar. It is appeared that these cancer cells are sensitive to low concentrations of this compound. *Aplidine*’s mode of action involves several pathways; that’s why Aplidine is described as multifactorial apoptosis inducer. The compound induces rapid cell cycle arrest at G1-G2 and inhibition of protein synthesis, thus introduce apoptosis of cancer cells [9]. Aplidine also inhibits the expression of the vascular endothelial growth factor gene, having antiangiogenic effects [10]. However, Aplidine appeared as more active than Didemnin in preclinical models and so far has not shown evidence of life threatening neuromuscular toxicity [8,9,4].

**Figure 3.** Dolabella auricularia

Source Organism: Dolabella auricular

The dolastatins are cytotoxic peptides, which can be cyclic or linear, derived from the sea hare, *Dolabella auricularia*, an mollusc from the Indian Ocean. Dolastatin 10 and 15 are small peptides that were shown to interact with tubulin. Dolastatin was selected for initial clinical development because of its more favourable preclinical profile. It is extremely potent in vitro and it was shown to inhibit microtubule assembly, tubulin-dependent guanosine triphosphate (GTP) binding and inhibit vincristine and vinblastine binding to tubulin. It causes cells to accumulate in metaphase arrest and is modulated by the MDR gene product [14,15]. Dolastatin has in vitro activity against several human leukaemia, lymphoma and solid tumour cell lines.

![Aplidine](image1.png)

The dose limiting toxicity with the protracted schedule is muscular with a remarkable lack of haematological toxicity in spite of the cytotoxicity noted at low concentrations in leukemic blasts explanted from patients [11,12]. Consistent evidence of activity has been noted in pretreated neuroendocrine tumors [13] and other tumor types. Phase II studies are now ongoing with an every other week schedule giving APL as a protracted or 3 hours intravenous infusion at a dose of 5 mg/m².

DOLASTATINS

**Figure 3.** Dolabella auricularia

Source Organism: Dolabella auricular

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![Dolastatins](image2.png)

It has documented antitumour activity in various human solid tumour models, such as LOX#IMVI melanoma,
OVCA3 ovarian carcinoma and NCI-H522 NSCLC cell lines. In animal toxicology studies, myelo suppression was the dose-limiting toxicity. This agent is highly bound to plasma proteins and pharmacokinetic studies in animals showed a rapid degradation probably by hepatic metabolism [16,17]. This agent entered phase I trials as an i.v. bolus injection every 3 weeks. The maximum tolerated dose (MTD) was 300 mg/m2 for heavily pretreated patients, while 400 mg/m2 appears to be the MTD for minimally pre-treated patients. The dose-limiting toxicity (DLT) was myelo suppression, and local irritation and phlebitis, and mild peripheral neuropathy were also observed. Phase II trials are being initiated in breast, colon, lung, ovarian and prostate cancer, as well as lymphomas and leukemias [18, 19]. Side effects observed were peripheral sensory neuropathies, pain, swelling, and erythematous at the injection site. Complexity and low yield of chemical synthesis of Dolastatins together with low water solubility

ECTEINASCIDINS (ETS)

**Figure 4.** The tunicate Ecteinascidiaturbaninata

**Source Organism: Ecteinascidiaturbaninata**

The ecteinascidins (Ets) are derived from the Caribbean tunicate Ecteinascidiaturbaninata. Following a period of supply problems, enough amounts of this compound could be obtained from aquaculture and synthesis. The derivative Ecteinascidin 743 (ET 743) showed promising activity in murine and human tumour models, and is currently in early clinical development. It is a tetrahydro isoquinoline alkaloid that alkylates selectively guanine N2 from the DNA minor groove, and this alkylation is reversed by DNA denaturation. Therefore, it differs from other DNA alkylating agents so far used in the clinic.

Recent mechanistic data demonstrates that ET-743 induces a broad inhibition of activated transcription with no effect on the constitutive transcription [20,21,22]: ET-743 inhibits the activation of the multidrug resistant pathway [23] that is considered to be the main mechanism of primary and acquired resistance of cancer cells to natural drugs such doxorubicin and taxanes. ET-743 is the only known anticancer entity for which there is an inverse correlation between the DNA repair efficiency and the sensitivity/resistance pattern [24,25]; such evidence offered a rationale to Marine Drugs 2004, 2 18 implement combinations studies with platin salts [26] and to seek for correlations in patients between the DNA efficiency and the response to ET-743 [27] An extensive phase I program assessing different schedules of administration was completed[28,29,30]: The dose limiting toxicities were bone marrow toxicity and fatigue. As predicted in the preclinical toxicology, transaminitis is noted in the majority of the patients but such a drug induced effect is transient/reversible and non cumulative and therefore does not represent a limiting factor for long-term therapy.

Consistent evidence of antitumor activity in patients bearing resistant disease was reported in the phase I program. In fact, objective remissions in breast cancer, melanoma and mesothelioma were observed together with a consistent evidence of antitumor activity in patients with advanced resistant sarcoma. Such evidence was the starting point for a fast track pivotal phase II program in patients with advanced soft tissue sarcoma resistant or relapsed to conventional therapies. Long-term results from such studies have clearly confirmed a significant therapeutic impact in this disease setting [36,
37, 38, 39, and 40]. In these studies ET-743 has been given as a 24 hours intravenous infusion every 3 weeks at a dose of 1.5 mg/m2.

**DIDEMMIN B**

**Figure 5. Trididemnum Solidum**

Source Organism: Trididemnum Solidum

Different types of tunicates and ascidia are inhabitants of sea floor. They produce complex antitumor compounds that are estimated as more effective than any other cancer medicine now in use. One of these potent compounds is Didemnin which was isolated first from Caribbean tunicate Trididemnum solidum[41]. But later has also been extracted from other species of the same genus [42]. Among various Didemnin, Didemnin B has the most potent antitumor and antiproliferative activity against human prostatic cancer cell lines [41]. Didemnin B is the first marine peptide to enter into clinical trial as a potent anticancer drug [43]. This is acyclic depsipeptide which exerts antitumor activity via protein synthesis inhibition [44]. However, high toxicity, poor solubility and short life span led to the discontinuation of clinical trials of Didemnin B [43]. It has shown impressive antitumour activity in human tumour models in vitro as well as in tumours growing in athymic mice. In initial clinical trials, patients with various solid tumours or non-Hodgkin lymphoma were given a short intravenous infusion of didemnin B every 3 weeks, and antitumour effects were observed. However, severe neuromuscular and cardiotoxic effects led to the discontinuation of clinical trials.11,12

**III. CONCLUSION**

The marine environment is a rich source of both biological and chemical diversity. It is very much likely that marine organisms would be a wonderful source of biologically active molecules. The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphratric, analgesic and anticancer agent from bacteria, cyanobacteria, tunicae, fungi, sponge. This review focuses on the latest studies and critical research in this field and evidences the immense potential of marine organisms as sources of bioactive peptides and other anticancer biomolecules. Various anticancer compounds like Aplidine, Bryostatin-1, Didemin B, Dolastation, Ecteinascidin with diverse modes of action, such as, anti-proliferative, antioxidant, anti-microtubule have been isolated from marine sources. Traditional chemotherapeutic agents have a range of side effects like fatigue, gastrointestinal distress and depression of immune system which introduces the these sources have been shown to have antioxidant activity and cytotoxic effect on several human cancers such as leukemia, lymphoma, ovarian, melanoma, breast, bladder, neuroendocrine, prostatic, colon and non-smallcell lung cancer very potently..

**IV. REFERENCES**


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