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Research on Marine derived Biomolecules in Cancer Management

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Abstract : Research into the pharmacological properties of marine natural products has led to the discovery of many potently active agents considered worthy of clinical application. Nature has been instrumental as a source of therapeutics. Since the oceans cover more than 70% of the earth surface and the marine environment is highly diverse, it is very much likely that marine organisms would be a wonderful source of biologically active molecules. Over the past decade, several new therapeutic agents derived from marine sources have entered preclinical and clinical trials. This field has expanded significantly as a result of improvements in the technology of deep-sea collection, extraction and large-scale production through aquaculture and synthesis. The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphrastic, analgesic and anticancer activity. Various active anticancer agents are derived from plants and terrestrial microorganisms. The isolation of C-nucleosides from the Caribbean sponge, Cryptotheca crypta, four decades ago, provided the basis for the synthesis of Cytarabine, the first marine derived anticancer agent to be developed for clinical use. Cytarabine is currently used in the routine treatment of patients with leukemia and lymphoma. Gemcitabine, one of its fluorinated derivatives, has also been approved for use in patients with pancreatic, breast, bladder, and non-small-cell lung cancer. Traditional chemotherapeutic agents have a range of side effects like fatigue, gastrointestinal distress and depression of immune system which introduces the necessity of natural anticancer drug discovery. 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.
Key Words : Marine source; aquaculture; therapeutic agents; bioactive peptides; anticancer biomolecules.

Introduction

Cancer is a dreadful human disease, increasing with changing life style, nutrition, and global warming. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances. In this context, the natural products derived from medicinal plants have gained significance in the treatment of cancer **[1].**

Nature has been playing an important role in providing therapeutic entities since ancient time for treating and preventing human disease. The vast source of nature includes terrestrial and marine plant, microorganism, vertebrates and invertebrates etc. it is important to consider that the major anti-infective, anticancer, analgesics and immunosuppressive compounds are of natural origin in terms of evolution and

biodiversity the sea appears to be superior to the terrestrial ecosystem as marine species comprise approximately a half of the total biodiversity, they are offering a vast source from which useful therapeutics can be discovered. Over the past decade, marine organisms have been recognized as an untapped resource for novel bioactive compounds. Marine floras have been used for medicinal purposes in India, China, the Near East and Europe, since ancient time. During the last 25 years, natural products derived from marine organism have been the focus of many investigations, especially for cancer. Marine derived biomolecules such as peptides, enzymes, enzyme inhibitors, lipids has potential for the prevention and treatment for cancer and they might be useful as molecular models in drug research **[2]**. This importance of natural products in the field of therapeutics may be attributed to their high affinity to the target, little loss of entropy when they bind to a protein and their bioavailability. Almost 60% of drugs approved for cancer treatment are of natural origin. Vincristine, irinotecan, etoposide, taxanes and camptothecines are all examples of plant-derived compounds. Dactinomicine, anthracyclines, mitomycin and bleomycin are anticancer agents derived from microbial sources. The development of marine compounds as therapeutic agents is still in its infancy due to the lack of an analogous ethno-medical history as compared with terrestrial habitats, together with the relative technical difficulties in collecting marine organisms. Over the last few decades significant efforts have been made, by both pharmaceutical companies and academic institutions, to isolate and identify new marine-derived, natural products. These initiatives have been accompanied by funding support from governmental agencies. Specific programs directed towards the collection and characterization of marine natural products and evaluation of their biological activity has been established **[3].**

Marine drugs: Major Players in Cancer

Marine organisms are rich source of chemical products. In recent years, a renaissance has occurred in marine pharmacology. Emerging evidence suggests that marine natural products, specially the secondary metabolites from marine organisms, are far more likely to yield potential anticancer drugs than terrestrial sources.

1. Compounds Targeting Enzymes

Protein serine/threonine kinase inhibitors

Bryostatins

The bryostatins are macrocyclic lactones **(Fig.1)** isolated from the marine bryozoan Bugula neritina (Bugulidae). Bryostatin 1 is one of the most abundant and best studied compounds of this series. It was originally described on the basis of inhibiting growth in murine P388 lymphocytic leukemia cells at sub nanomolar concentrations. A range of properties have subsequently been described including activation of T-cells, immunomodulation and stimulation of hematopoietic progenitor cells. However, only many years after its discovery was the molecular site of action of this compound identified. Bryostatin 1 was found to bind to protein kinase C with high affinity, which may be the mechanistic basis for both observed anticancer and immune stimulating activities **[4].**

Bryostatin-1 has been granted Orphan Drug status by the FDA and has been designated an Orphan Medicinal Product in Europe for esophageal cancer in combination with paclitaxel.

Side effects

The main toxic effects in initial clinical trials were myalgia, local phlebitis, fatigue, nausea and vomiting, and thrombocytopenia. However, it was shown to induce cell differentiation in patients with refractory chronic lymphocytic leukemia.

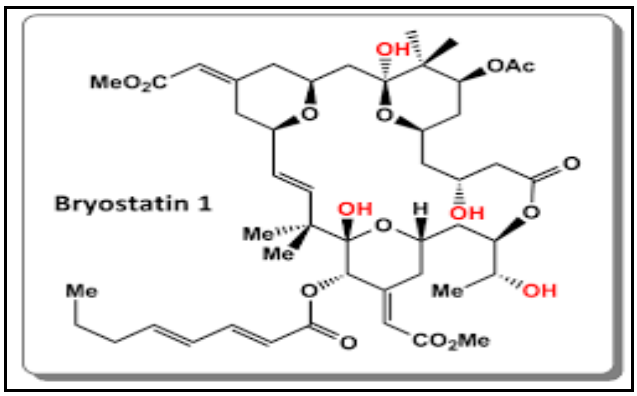


Fig. 1- Chemical Structure of Bryostatin 1

Scytonemin

Scytonemin is a protein serine/threonine kinase inhibitor referred to as a marine natural product, but the molecule was in fact isolated for structural analysis and pharmacological characterization from the *Cyanobacterium stigonema sp.* collected from Waldo Lake, Oregon. The compound is a yellow-green ultraviolet sunscreen pigment present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. It has a unique symmetrical dimeric ring structure (Fig. 1). The monomeric subunit is closely related to nostodione A **(Fig. 2)**, a mitotic spindle poison from the terrestrial blue-green alga *Nostoc commune*. Scytonemin was found to inhibit human pololike kinase (IC50=2 μM), which has an important role in the regulation of mitotic spindle formation as well as other kinases involved in cell cycle control, including checkpoint kinase 1 and CDK1, with similar potency **[5].**

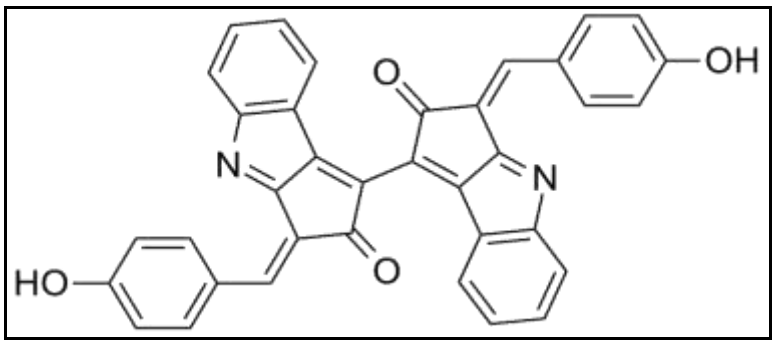


Fig. 2- Chemical Structure of Scytonemin

Methionine Aminopeptidase Inhibitors

LAF389

LAF389 is a synthetic analogue of Bengamide B **(Fig. 3)**, a natural product isolated from Jaspidae sponges. LAF389 has both antiproliferative and antiangiogenetic properties, and preclinical investigation showed a broad antitumor activity **[6].**

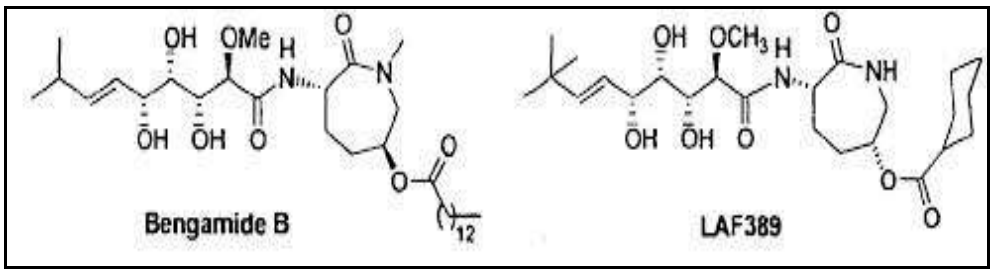
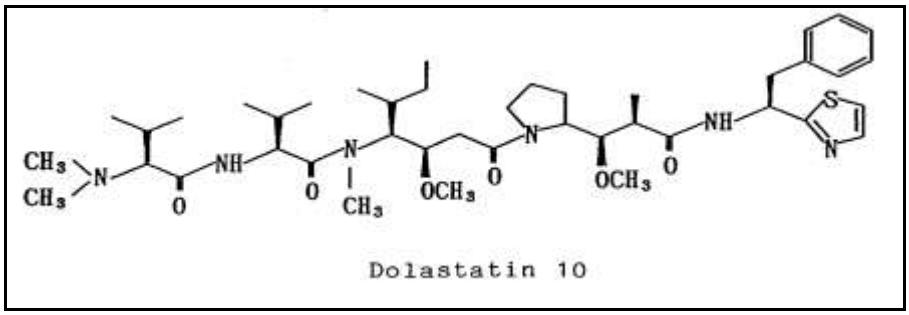


Fig. 3: Chemical Structure of Bengamide B & LAF389

2. Microtubule-interfering agents

The development of resistance in tumours to the microtubule-stabilizing taxanes has prompted the search for novel microtubule-interfering agents in the hope of finding a way to circumvent this problem. Marine organisms have yielded the largest number of such compounds **[7]:**

- **Discodermolide**, a polyketide, purified from the sponge *Discodermia dissolute*;
- **Eleutherobin**, a diterpenoid, from the soft coral *Eleutherobia* sp;
- **Sarcodictyins**, diterpenoids, from the Mediterranean coral *Sarcodictyon roseum*;
- **Dolastatins**, short peptides containing unique amino acids, from the sea hare *Dolabella auricularia*, a nudibranch snail and, later, from marine cyanobacteria. Dolastatin 10 and 15 **(Fig. 4)** are small peptides; Dolastatin 10 was selected for clinical trials because of its more favorable preclinical profile. It inhibits microtubule assembly, causing cells to accumulate in metaphase and is extremely potent *in vitro*. Dolastatin 10 caused bone-marrow toxicity in initial clinical trials, as well as local irritation at the injection site and mild peripheral neuropathy **[8].**



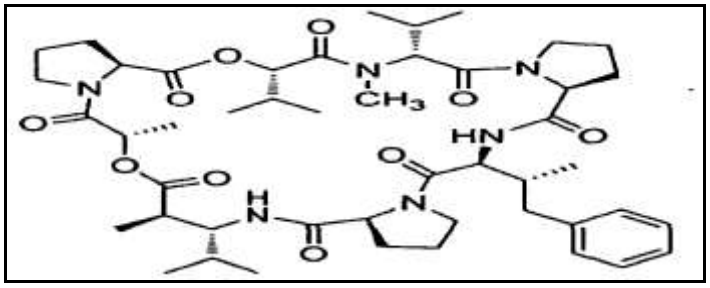


Fig. 4: Chemical Structure of Dolastatin 10 & Dolastatin 15

- **Halichondrin B**, a polyether macrolide from the sponge *Halichondria okadai* and has shown *in vivo* activity in melanoma and leukaemia models. It can also be obtained from the deep-water sponge *Lissodendoryx*, which is found in New Zealand. This compound is also active in various human tumour-cell models *in vitro* and *in vivo* **[9].**
- **Laulimalide**, as well as its rearrangement product isolaulimalide, which are 18-membered macrocyclic lactones, from the sponge *Cacospongia mycofijiensis* **[10].**
- **Peloruside** A, related to Bryostatin 1, from the sponge *Mycale* sp **[11].**
- **Hemiasterlin**s, tripeptides from the sponges *Auletta* sp. and *Siphonochalina* sp **[12].**
- **Vitilevuamide**, a bicyclic marine peptide, from the ascidians *Didemnum cuculiferum* and *Polysyncraton* **[13].**

All of these compounds have been reported to have general cytotoxic activity and to kill cancer cells *in vitro* but only dolastatin 10, dolastatin 15, analogues ILX651 and cemadotin, discodermolide and the hemiasterlin analogue HTI286 have so far reached clinical development. The laulimalides and discodermolide are of special interest to anticancer drug discovery researchers because they have been shown to remain active in cells over expressing multidrug-resistant P-glycoprotein**.**

3. **DNA- Interactive agents**

Several established anticancer drugs are DNA-interactive agents. These compounds, including the platinum drugs cisplatin and carboplatin, are characterized by strong cytotoxic activity, but they also show a total lack of specificity for cancer versus normal cells.

ET-743 (Trabectedin, YondelisTM)

ET-743 **(Fig.5)** is a tetrahydroisoquinoline alkaloid produced by the colonial tunicate *Ecteinascidia turbinate*. ET-743 is a novel DNA interactive agent that has shown *in vivo* activity in nude mice harbouring human resistant xenografted tumors **[14, 15].** ET743 was shown to cause a prolonged cell cycle blockade in G2/M and to inhibit induced gene transcription of several genes including HSP70 and p21 while having little effect on basal gene expression. Moreover, ET743 can enhance the activities of other chemotherapeutic agents by inhibiting multidrug resistant MDR1 gene expression upon co-administration. Cells in the G1 phase of the cell cycle, and of these soft tissue sarcoma cells in particular, are extremely sensitive to ET743-induced cell killing. Other cancer cells that have shown sensitivity towards ET743 are cell lines and xenografts derived from tumours of the breast, kidney, lung, ovaries and prostate as well as from glioblastomas and melanomas. The cytotoxic effects of ET743 are entirely dependent on the presence of functional transcription-coupled nucleotide excision repair (TC-NER) in the treated cells but independent of wild-type p53 tumour suppressor protein function. Interference with this DNA repair pathway is, therefore, thought to be at the heart of the unique mode of action of ET743 **[16].**

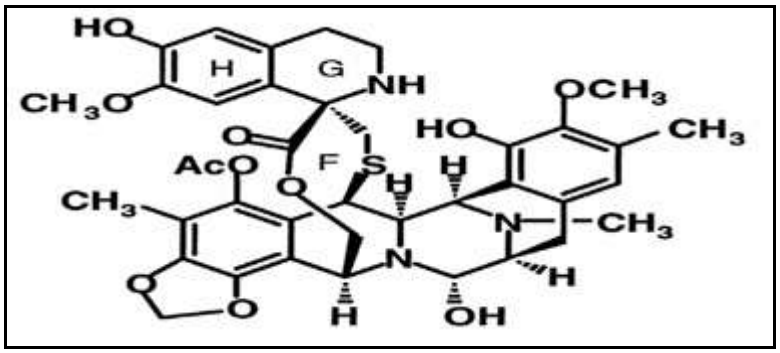


Fig. 5- Chemical Structure of ET743

4. Oxidative stress inducer

APL (dehydrodidemnin B, Aplidin™)

APL (dehydrodidemnin B, Aplidin™)a cyclic depsipeptides **[17] (Fig.6)** derived from *Aplidium albicans*. The compound triggers rapid and persistent activation of the apoptotic process as a consequence of the induction of oxidative stress and the sustained activation of the protein kinases Jun Nterminal kinase, p38 stress-activated protein kinase, EGF receptor and Src .At present, more than 200 patients have been treated with APL in phase I clinical trial for cancer. The phase I program has investigated the feasibility of dose dense schedules and have confirmed a positive therapeutic index in patients harbouring pretreated solid tumors and lymphoma**.**

Didemnins

The didemnins are a family of cyclic depsipeptides **(Fig.6)** obtained from the Caribbean tunicate *Tridemnun solidum.* Didemnin B (DB) was the most potent didemnin in the antitumor screening system that was selected for clinical development. DB inhibits the synthesis of RNA6, DNA and proteins and binds noncompetitively to palmitoyl protein thioesterase. It showed antitumor activity against a variety of models and has been investigated in phase II clinical trials for the treatment of breast, ovarian, cervical, myeloma, glioblastoma/astrocytoma, and lung cancers. Despite a variety of treatment protocols and testing against many different cancer types, the compound was simply too toxic for use, which led to the termination of trials by the National Cancer Institute in 1990. The experience gained from these trials led to the synthesis of related molecules, such as aplidine **[3].**

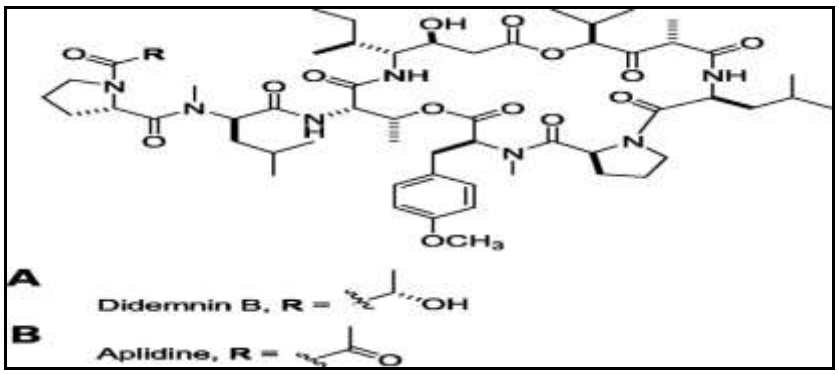


Fig. 6: Chemical Structure of Didemnin B & Aplidine.

5. Lysosomotropic compounds

Kahalalide F (KF)

Kahalalide F is one of a family of dehydro aminobutyric containing cyclic peptides **(Fig.7)** isolated from the Hawaiian mollusk *E. Rufencens* **[18, 19].** The compound has shown antitumor activity, probably by interfering with lysosome function in prostate, colorectal and lung cancer cell lines as well as in animal models of lung and breast cancer. It is currently in phase I trials for prostate cancer and other solid tumors.

The dose limiting toxicity is acute transaminitis that precluded the administration of the compound in a weekly fashion, with a remarkable absence of bone marrow suppression, alopecia and other organ toxicities; such early data suggests lack of cumulative toxicities that may allow chronic therapy. The pharmacokinetic profile demonstrates a short terminal half-life, a finding supporting additional studies with longer infusional schedules.

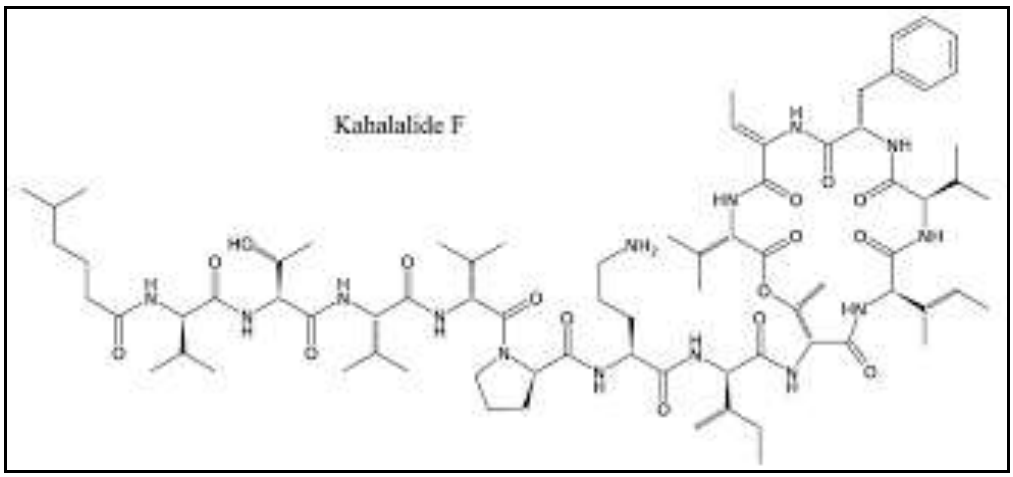


Fig. 7- Chemical Structure of Kahalalide F

6. Immunostimulatory agents

KRN7000

KRN7000, a novel α-galactosylceramide derived from agelasphin-9b **(Fig.8)**, which, in turn, was isolated from the sponge *Agelas mauritianus*, for the potential treatment of cancer and other diseases. KRN7000 has been shown to have immunostimulatory and antimetastatic activity possibly by enhancing antigenpresenting cell function. Phase I clinical trials for solid tumours showed no drug-related toxicity, no signs of accumulation or saturation and an increase in interferon-γ, interleukin-4, interleukin-12 and granulocyte macrophage colony-stimulating factor levels, as well as natural killer cell activity at least in some of the patients **[20].**

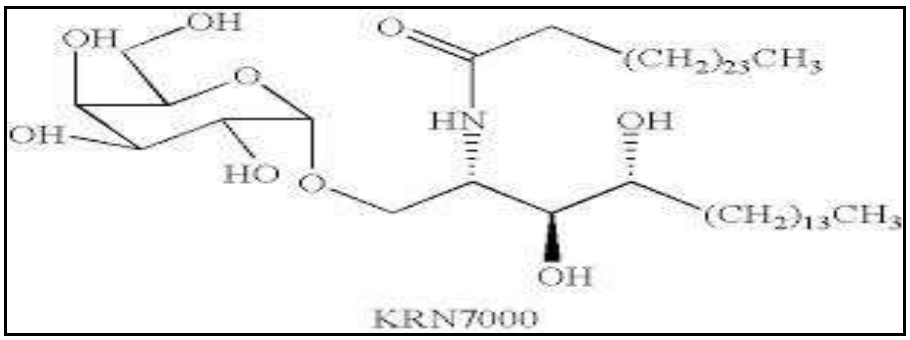


Fig. 8- Chemical Structure of KRN7000

7. Calcium-binding protein antagonists

Squalamine lactate

Squalamine lactate, a novel antiangiogenic amino steroid **(Fig.9)** from the dogfish shark *Squalus acanthias* is currently in phase II clinical trials for ovarian and non-small cell lung cancer and was granted orphan drug status for the treatment of ovarian cancer by the FDA. Reported objective response rates were around 30% for one or more cycles of treatment in combination with standard chemotherapy. The compound is thought to act by sequestration of calmodulin, resulting in the inhibition of a sodium/proton antiport regulating intracellular pH and, consequently, in reduced cell proliferation in endothelial cells **[21].**

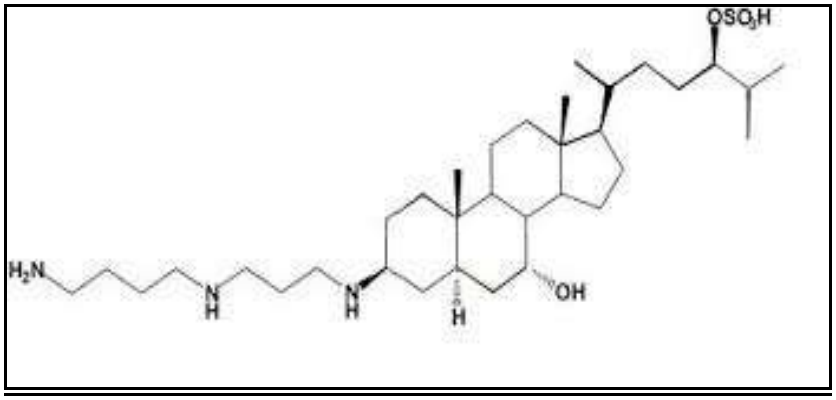


Fig. 9- Chemical Structure of Squalamine lactate

Challenges in marine drug research

Although much development has been achieved in the fields of biomedicine and pharmaceutical sciences, still very few natural products have found their way to the market till date. There are ample reasons that may be affecting this shortfall, including; lack of sufficient amount of natural product, difficulties in accessing the source of the samples, problems associated with harvesting of the product, troubles in synthesizing the necessary amounts of the compound, difficulties in isolation and purification procedures, high toxicity of the active compound, ecological considerations, government policies, lack of infrastructure and insufficient capital investment **[22].**

A number of marine microorganisms are difficult to culture and lack of literature on the isolation procedures and standardized culture conditions makes the situation even worse, with less numbers of academics undertaking such studies. For instance, despite the fact that the marine actinomycetes may be a storehouse of novel bioactive molecules, different from terrestrial counterparts, they are an underexploited source for the discovery of novel secondary metabolites, the main reason being the lack of efforts spent in exploring them. In addition, the fact that the terrestrial actinomycetes produce resistant spores which get transported from land to oceans, where they can remain available but dormant for many years, has made researchers more skeptical for the existence of indigenous populations of marine actinomycetes. Thus, the myth prevails that marine

actinomycetes are originally terrestrial. This lack of knowledge prevents uncovering of the vast potential of marine actinomycetes.

A lack of understanding of cancer biomarkers (major players in carcinogenesis and tumor progression) is also a major shortfall in harnessing the marine environment for specific tumor targeting drugs. Despite a vast array of technologies in cancer research with unprecedented depths of analyses, the complexity of cancer proteomics and the underlying altered signaling pathways pose a great challenge for marine antitumor drug research. There is an imperative need for extensive, integrative and collaborative endeavors to explicate proteome alterations in cancer. Moreover, even after knowing the targets and the development of novel marine drugs against the same, fewer and fewer breakthrough ideas find their way out of research institutions and into the hands of experienced clinicians and medical product development teams as the promising research and innovation are not being translated into new treatments. The increasing drug resistant mutations in cancer causing microbial agents, further leads to the lesser number of antitumor drugs in the market.

Prevailing threats to global marine biodiversity including overfishing, habitat loss, invasive species and pollution, rising water temperatures and ocean acidification are further making marine antitumor drug research more and more difficult.

Alternative approaches

A semisynthetic approach could be one of the alternatives to enhance the yield of lead natural compounds. It can be achieved by modifying the functional groups of existing natural compounds. This would lead to the generation of structural analogues with greater pharmacological activity and with fewer side effects. For example, studies on the marine HIF inhibitor Laurenditerpenol were hindered by a lack of compound supply. However, a recently completed total synthesis has resolved the absolute configuration of Lauren diterpenol. A more integrated approach comprising high-throughput screening methods, computational biology and bioinformatics may be useful in producing compounds that are more efficient than the ones that are prevalent today **[22].**

It can be generally 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 cellular mechanisms controlling proliferation has yielded numerous targets for mechanism-based anticancer screens **[23].**

Conclusion

Nature has supplied several active anticancer agents (eg the vinca alkaloids, anthracyclines, epipodophyllotoxins, and taxanes), which have significantly improved the management of many types of human cancers. These marine-derived compounds are extremely potent in culture, with inhibitory concentrations generally in the nanogram range. Thus the marine ecosystem offers a huge potential in the naturally based pharmacopoeia of this century. However, an unfavorable balance between discovery and the very small number of candidates incorporated for clinical evaluation exists. So it appears that a better and more pragmatic approach is urgently needed in order to translate innovative discoveries into active clinical therapeutics. Although it is very difficult to predict the final outcome of such a scheme of drug discovery, it can be assured that a focused approach and combined efforts would definitely accelerate the development of new marine anticancer drugs to be discovered with increased efficiency.

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