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Novel Bioactive Compounds from Marine Sources as a Tool for Drug Development

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Abstract

The marine environment is a relatively unexplored source of functional ingredients that can be used in food processing, storage, and fortification in a variety of ways. Marine microorganisms are a possible source of novel bioactive chemicals with potential human utility. Some of these microbes can live in the harsh marine environments, resulting in complex compounds with unique biological properties that can be used in several industrial and biotechnological applications. So far, several marine microorganisms (fungi, myxomycetes, bacteria, and microalgae) have been isolated that produce antioxidant, antibacterial, apoptotic, antitumoral, and antiviral chemicals. Furthermore, it emphasizes the enormous potential for marine microbes to produce very important bioactive chemicals. They are used for new drug developments extensively across the world. Marine pharmacology offers the scope for research on these drugs of marine origin. Few institutes in India offer such opportunities which can help us in the quest for new drugs. This is an extensive review of the drugs developed and the potential new drug candidates from marine origin along with the opportunities for research on marine derived products. It also gives the information about the institutes in India which offer marine pharmacology related courses.

Keywords: Anticancer, Bryostatin, Cytarabine, Keyhole limpet hemocyanin, Mariculture, Sponge, Ziconotide

Introduction

A significant portion of the Earth's biodiversity (an estimated 25% of the total number of species on Earth) is comprised of marine species[1]. These have evolved mechanisms to survive in an extremely different and hostile environment compared with land in terms of light, salinity and pressure. This is reflected by the myriad of secondary metabolites (or natural products) that they produce to defend themselves against predators, to locate mates and to out-compete competitors for limited resources. Many of these compounds have no terrestrial analogues and are unique in terms of chemical structure and biological activity. What makes these products interesting for humans are their potential applications as pharmaceuticals for the treatment of numerous diseases or as templates for medicinal chemistry. Humans have been trying to understand and use ocean resources for medicinal purposes since ancient times. The Chinese and Japanese were eating a variety of iodine-rich seaweeds already in 1400 BC that accounted for their low incidence of goiter[2]. In Ireland, the red algae Chondrus crispus and Mastocarpus stellatus were used as a folk cure for colds, sore throats, chest infections and bronchitis for several centuries[3]. In the early 20th century cod liver oil was an important nutritional supplement in many northern European countries. However it was only after the 1950s, with the advent of scuba diving and new sampling technologies that scientists began to systematically probe the oceans for useful therapeutics. The number of potential compounds isolated from marine organisms now exceeds 28,000 with hundreds of new compounds being discovered every year[4]. However, despite the number of compounds isolated from marine organisms and the biological activities attributed to many of these, those that have either been marketed or are under development are relatively few. There are several reasons for this including the time and cost it takes to reach the market, difficulties in harvesting the organism, low titres of natural product in producing organisms, difficulties in isolation and purification procedures, problems in obtaining a sustainable supply of the compound, high toxicity of the active compound, ecological impact on natural populations, and insufficient investment by pharmaceutical companies[5]. However, notwithstanding these difficulties there has been a 'renaissance' in marine drug discovery in the last decade due to technological developments that have accelerated structural elucidation and screening, and the use of marine microbial genomics to provide biosynthetic pathways for the production of marine natural products[6]. The development of emerging 'omics' tools such direct sequencing of eDNA, next generation sequencing technologies, meta proteomic and synthetic biology, heterologous expression and bioinformatics tools will improve the discovery and production of these compounds and facilitate the study of biosynthetic pathways of organisms previously inaccessible by traditional methods[7] . This is coupled with the fact that alternative technologies such as combinatorial chemistry have failed to provide the pharmaceutical industry with the

chemical diversity necessary to significantly increase the number of new drug-like leads. Here we discuss the current state of art of marine compounds approved, developed or in clinical trials for treating various diseases, or marketed as nutraceuticals and cosmeceuticals. Several excellent reviews already exist on marine drug discovery so this paper does not attempt to provide a comprehensive overview, but rather to illustrate some examples of the recent advances in this field. We also discuss the ambitions and efforts of an on-going EU project to find new molecules from microorganisms for the treatment of bacterial and viral infections, and inflammatory and neurodegenerative diseases. With a focus on under-exploited marine phyla of cultivable microorganisms, essentially photo- and chemosynthetic bacteria together with fungi and microalgae, this project aims to achieve optimized and sustainable production of relevant biomass and high added-value compounds for pharmaceutical, nutraceutical and cosmeceuticals applications, and to overcome some of the major bottlenecks in the drug discovery pipeline.

Biodiversity of marine environment

Marine environment is a natural habitat for a broad variety of living organisms having different physiology and capacity to adapt their environment. Out of over 33 animal phyla known today, a total of 32 phyla are embodied in the marine environment out of which 15 varieties are exclusively present in the marine environment[8]. Such genetic diversity renders chemical diversity which is promising for new drug development. Oceans contain more than 80% of diverse plant and animal species in the world. Marine organisms such as sponges, tunicates, fishes, soft corals, nudibranchs, sea hares, opisthobranch Molluscs, echinoderms, bryozoans, prawns, shells, sea slugs, and marine microorganisms are sources of bioactive compounds (viz. oils and cosmetics) [9]. The first biologically active marine natural product was formally reported in late 1950 by Bergmann[10]. In late 1970, it was established that marine plants and animals are genetically and biochemically unique. Around 15,000 such unique natural compounds have been described and out of them 30% products have been isolated from sponges[11]. The remarkable discovery of unusual arabino-or ribo-pentosyl nucleosides in marine sponges was the first illustration that is naturally occurring nucleosides could contain sugars other than ribose and deoxyribose[12]. It was also observed that molecules of marine origin can be accepted by humans with minimal manipulation[13].There are some reports on the characterization of the antimicrobial activity of marine macroorganisms collected from the Indian coastline have appeared. Streptomyces sp. has been the most widely studied microbial species from the Indian coastal waters as a source of antibiotics[14]. In a study, 75 bacterial strains from 4 species of marine sponges were isolated, out of which 21% of the isolates have shown good antibacterial activity, with some of the strains showing species specificity[14]. The study indicated the diversity of antibiotic producing marine bacteria and also established that sponges are a rich source of bacteria capable of producing novel pharmacologically active molecules

Marine pharmacology in India

India has over 8000 km of coastline with clusters of marine habitats like inter-tidal rocky, muddy and sandy shores, coral reefs, and mangrove forests. The potential of Indian marine habitat has remained largely unexplored for their potential of new drugs and biotechnological programs. Some of the selected institutes such as National Institute of Oceanology, Goa; Central

Drug Research Institute, Lucknow; Bose Institute, Kolkata; Central Institute of Fisheries Education, Mumbai; Regional Research Laboratory, Bhubaneswar of Council for Scientific and Industrial Research are presently working for exploration of life saving drugs from marine sources. Many other Indian institutes, universities, and pharmaceutical companies have also recognized the significance of this subject[15]. Marine pharmacology has been reviewed extensively in the past all over the world as well as in India, but still there is a need to review the potential of the oceans as source for the development of new drugs, considering the advantage of their abundance in nature and large scale production. At present, the drug industry is working on screening and isolation of novel molecules with unreported pharmacological properties that can be exploited for the development of new therapeutic agents for commercial use. This review has largely focused on different classes of marine drugs currently in use and at different stages of trials for approval and marketing in future. The review has also tried to delve into the limitations and future trends of the drugs from marine sources.

Classification of marine pharmacology

Marine pharmacology can be classified on the basis of source of the candidate drug[11]

- Genetically engineered marine organisms
- Manufacture of pharmaceuticals and nutraceuticals of marine origin
- Chemicals produced by or found in marine organisms shown to have a wide variety of applications as pharmaceuticals.

Marine drugs can be broadly classified based on their actions as follows:

Antibacterial

Eicosapentaenoic acid, a polyunsaturated fatty acid, isolated from a diatom of marine origin *Phaeodactylum tricornutum* which has shown activity against an array of Gram-positive and Gram-negative bacteria, which also includes a multidrug-resistant variety of Staphylococcus aureus[16].

Anti-inflammatory

The anti-inflammatory function of extracts and other parts of a Mediterranean sponge species Spongia officinalis in the in vivo study on rat model of carrageenan-induced paw edema assay[17].

Neuroprotective

The extracts of South Indian green seaweed *Ulva reticulata* has shown neuroprotection by inhibiting acetyl-and butyryl-cholinesterases, efficacy comparable to agents currently approved for Alzheimer's disease treatment[18].

Antiparasitic

Extracts of *Sarcotragus* sp. known as Tunisian sponge prepared in dichloromethane has demonstrated in-vitro anti-leishmanial activity by demonstrating the associated morphological alterations in promastigotes of leishmania major[19].

Antiviral agents

Anti-herpes simplex virus-1 (HSV) activity found in high molecular weight exo-polysaccharides extracted from the *Celtodoryx girardae* (French marine sponge) and its associated symbiotic bacteria has been reported[20].

Anticancer

Bryostatin, primarily obtained from the Bryozoan, *Bugula neritina*, although some forms have been extracted from

sponges and tunicates. Sorbicillin-derived alkaloids sorbicillactone A and

its 2', 3'-dihydro analog sorbicillactone-B has shown activity against leukemia cells free from any noteworthy cytotoxicity. Sorbicillactone-B has been derived from a salt-water culture of a bacterial strain *Penicillium chrysogenum* which has been isolated from a sponge *Ircinia fasciculata*, a Mediterranean sponge specimen[21]. Another promising anticancer drug used as an immunotherapeutic agent is keyhole limpet hemocyanin (KLH). KLH is a copper containing extracellular respiratory protein present in *Megathura crenulata*, a marine Gastropod species found in large numbers at the Pacific coast of California and Mexico. KLH is found in two isoforms KLH1 and KLH2[22]. KLH is reported to possess remarkable immunostimulatory properties in experimental animals and human, used in experimental immunology and also clinically as an immunotherapeutic agent[23]. KLH is specifically used in clinical setup for the treatment of bladder carcinoma, and its efficacy is perhaps due to a cross-reacting carbohydrate epitope. KLH may also have significant potential for the treatment of other types of cancers, particularly the adenocarciomas derived from the epithelium, by using it as a carrier for gangliosides of carcinoma and mucin-like epitopes[22]. KLH is intravesically administered to patients with bladder carcinoma. Its clinical success in carcinoma patients is attributed to the presence of the disaccharide epitope Gal (β1-3), Ga1NAc[24]. This epitope of KLH is believed to be cross-reactive with an equivalent epitope on the urinary bladder tumor cell surface. The cumulative cellular and humoral immunological responses to KLH can result in a cytolytic reduction of tumor growth[22]. In addition to tumor immunotherapy, KLH is also prescribed in the following conditions[22]:

i. As a generalized vaccine component for antigen presentation, alone or in adjuvant cocktail

ii. For diagnosis of schistosomiasis because of cross-reactivity to one of the epitopes on larval schistosomes

iii. In drug assays

iv. Treatment of drug addiction by immunoassay for abused drugs

v. For immune competence testing

vi. Assessment of stress and inflammation.

Analgesic

Ziconotide was the first drug of marine origin to obtain approval from the U.S. Food and Drug Administration (USFDA) in 2004 to treat pain. It is also known as Prialt, and it was originally extracted from the marine snail Conus magus. Results from animal studies suggested the role of ziconotide in blocking of N-type calcium channels on the primary nociceptive nerves of the spinal cord[22].

Antimicrobial

The cephalosporins are well-known antimicrobial agents with a marine source of origin. Cephalosporin C was firstly extracted and purified from a marine fungus, *Cephalosporium acremonium*[9].

Antimalarial activity

Isonitrile containing antimalarial molecules have been extracted from the *Acanthella* sp., a Japanese sponge. The isolated molecules belong to kalihinane diterpenoids class, which also contains antifungal, anthelmintic, and antifouling compounds[23].

Evolution of marine pharmacology

The recent global marine, pharmaceutical pipeline consists of only 3 USFDA approved drugs, and one European Union (EU) registered drug. Currently, marine drugs in the clinical lineup have 13 compounds that are at different stages of clinical trials, with a very large number of marine-derived compounds/ molecules in the preclinical testing pipeline as well[25]. The three Food and Drug Administration (FDA) approved the marine-derived drugs currently used in the United States are, cytarabine (Cytosar-UW, DepocytW), vidarabine (Vira-AW), and ziconotide (PrialtW).

Approved drugs of marine origin

Some of the drugs of marine origin approved for human use in different parts of the world are as follows:

Cytarabine (cytosine arabinoside or arabinosyl cytosine, ara-C)

Cytarabine is a synthetic pyrimidine nucleoside derived from spongothymidine and primarily isolated from a Caribbean sponge species Tethya crypta. It is FDA approved and mainly used in different types of leukemia, including acute myelocytic leukemia, lymphocytic leukemia, meningeal leukemia, and blast crisis phase of chronic myelogenous leukemia[25].

Vidarabine (adenine arabinoside, ara-A or arabinofuranosyladenine)

Vidarabine is a synthetic purine nucleoside isolated from the Caribbean sponge T. crypta and developed from spongouridine is currently obtained from Streptomyces antibioticus. It is approved by FDA for use in recurrent epithelial keratitis caused by HSV) type 1 and 2, acute kerato-conjunctivitis, and also for superficial keratitis[25].

Ziconotide

Ziconotide is a synthetic molecule, equivalent to a natural 25-amino acid peptide, v-conotoxin MVIIA. Itis originally extracted and purified from the venom of marine snail C. magus, which is a fish-hunting species. Ziconotide has shown potential as an analgesic with a novel mechanism of action[25]. It is approved as an analgesic by FDA.

Trabectedin

A marine natural product extracted from a tunicate species *Ecteinascidia turbinata* generally inhabitant of Mediterranean and Caribbean Sea. Trabectedin molecule is an alkaloid of tetrahydroisoquinoline class, and it was the first anticancer molecule of marine origin got approval in EU for use in the treatment of soft-tissue sarcoma and in relapsed cases of platinum-sensitive ovarian cancer[25].

New drugs in development

Currently there are about 26 natural products in Phase I to Phase III clinical trials, 23 as anticancer cancer agents, two for schizophrenia and Alzheimer's, and one for chronic pain (http://marinepharmacology.midwestern.edu/clinPipeline.htm). Thus, the pipeline of promising marine derived compounds is very strong, and several of these agents are likely to reach the market in the coming years[25]. Some of these new marine drugs are discussed briefly in the next section.

Anticancer

Aplidine (dehydrodidemnin B), a depsipeptide dehydrodidemnin isolated from the Mediterranean tunicate Aplidium albicans has antiproliferative activity by blocking the cell cycle and inducing apoptosis, with strong activity against multiple myeloma cells. PharmaMar is currently developing Aplidin for the treatment of multiple myeloma (phase III of

clinical trials), and for solid and haematological malignant neoplasias, like T-cell lymphoma (phase II of clinical trials) (http://www.pharmamar.com/aplidin.aspx). Plinabulin is a synthetic analogue of a natural product isolated from a marine fungus (Aspergillus sp.) that inhibits tubulin polymerization, leading to the disruption of the vascular endothelial architecture of the tumour. BeyondSpring

Pharmaceuticals is developing plinabulin and announced the start of phase III clinical trials in patients with non-small cell lung cancer in 2015 (http://www.beyondspringpharma.com/press-release-plinabulin-phase-3-trial/).
Salinosporamide A[26] is a novel, potent proteasome inhibitor from the marine actinomycete, Salinispora tropica, that induces apoptosis by a caspase-8 dependent mechanism in multiple myeloma and leukaemia cells. Currently, combination therapies of salinosporamide A with other drugs are under investigation in phase I clinical trials. Further examples of anticancer drugs of marine origin in clinical development are discussed by Newman and Cragg[27].

Alzheimer's disease

Bryostatin 1, a macrolide lactone isolated from the bryozoans species, Bugula neritina, is a potent modulator of protein kinase C that is currently in phase II clinical trials for the treatment of Alzheimer's disease by Neurotrope Bioscience (http://www.neurotropebioscience.com/). The drug has shown pre-clinical efficacy to not only treat Alzheimer's disease symptoms, but also its underlying causes. Bryostatin was originally intended for anti-cancer chemotherapy, but was then discovered to potentially arrest Alzheimer's disease[28]. Pre-clinical testing revealed that it reduced the toxic Alzheimer's disease protein amyloid-b and the deposits of amyloid-b called amyloid plaques, restored lost synapses, and protected against the loss of memory functions. DMXBA, a synthetic analogue of the toxic alkaloid produced by several nemertinean worm species, such as Paranemertes peregrine and Amphiporus lactifloreus, improves cognition and sensory deficit in several animal models, and has shown neuroprotective effects in vitro and in vivo. Phase I and II clinical trials showed a significant cognitive improvement in healthy young adults and in schizophrenic patients[29]. Comentis Inc. is developing the drug for treatment for Alzheimer's disease and schizophrenia (http://comentis.com/).

Analgesics

The guanidine alkaloid tetrodotoxin (TTX), a blocker of voltage dependent sodium channels isolated from fish, algae and bacteria, has shown therapeutic efficacy as an analgesic in cancer patients. Two formulations are currently under evaluation in phases II and III of clinical trials by the Canadian WEX Pharmaceuticals Inc.: the first formulation is in phase III, indicated for the treatment of neuropathic pain in cancer patients; the second one is in phase II of clinical trials, for peripheral pain and cancer-related pain (http://www.wextech.ca/clinical trials.asp?m=1&s=0&p=0; http://www.clinicaltrials.gov).

Antibacterials

Despite the urgent need for new antibiotics, particularly to tackle the rise of antibiotic-resistant bacteria, new antibiotic development has moved slowly and there are few compounds in the antibiotic development pipeline. This lack of activity reflects market failure as the risk–reward ratio has been considered unattractive for pharmaceutical companies. Mayer et al. 2013[30] lists 23 antibacterial compounds in preclinical pharmacological research. An interesting example is Anthracimycin, a polyketide antibiotic discovered in 2013, derived from marine actinobacteria that has shown significant activity against Bacillus anthracis, the bacteria that causes anthrax[31-33].

Challenges and future trends

There are certain major challenges to derive the drugs from marine sources. The variable environmental conditions could result in the production of different metabolite every time from the same organism. A major challenge sometimes faced is that the microorganisms residing in the marine animal and not the invertebrate marine hosts actually produces the bioactive molecules[34]. Sustainable supply of isolated and identified lead compounds sometimes pose a problem because the lead compound is present only in low quantity and/or technically it becomes very difficult to isolate such compound[35]. For any of intended use (drug, cosmetic, etc.,) of the compound, the required quantity may vary from few grams needed for preclinical drug development and safety studies in different setup; to quantities in kilogram required for clinical study in different phases and many of tons of cosmetics[34]. And the availability of lead compound in such abundance can be a key issue. Lack of sustainable supply of the candidate compound has sometimes held back further research and development of many extremely potent marine novel compounds. Attempts have been made to beat this hurdle by increased development of synthetic or hemi synthetic analogues derivatives with desired and customized properties, or designing a pharmacophore of lower complexity with easier synthesis method[36] . Identification of a bioactive compound synthesized or hemi synthesized must be done with the reference to the compound derived from the biological source. The structural complexity of the isolated compound and meager yield which is generally faced with marine compounds, may lead to wrong assignment of chemical formula of the compound, its real constitution (planar connectivity), configuration of intramolecular bonds, configuration entirity, and incorrectly assigned one or multiple stereocenters [37]. To overcome the issue of regular supply, the use of natural resources should be under control and need to favor the growth of marine organisms in its natural environment by farming which is also known as Mariculture[37,38]. Another option is to culture the marine organisms under artificial conditions by the process called as aquaculture[37, 38] . Martins et al. has very well elucidated the commercial and market issues that are relevant and mostly overlooked in the developmental process of new natural products[34]. Some of the points that need to be addressed from the very early development phase are as follows: (i) What are the potential industrial use of the product and need of that particular activity of the compound in the market? (ii) What will be the final cost per kg for the final bioactive material? (iii) The desired formulation and preferred route of administration of the compound; (iv) What process of manufacture is being used and whether the supply is sustainable? and finally (v) How will the product reach the market chain? Some limitations of the marine drug development includes the development of universal expression systems for biosynthesis of small molecules with high-yield, development of genetic tools to access the in vivo potential of cultured marine microorganisms, and the regulatory arousing of silent biosynthetic pathways for small molecule discovery[38]. The subsequent levels of development of drugs comprises in vivo evaluations of safety and efficacy in animal models, determination of the mechanism and site of action, development of structure-activity relationships, formulation and characterization of pharmacokinetics parameters and pharmaceutical properties including improvements through the use of medicinal chemistry[38]. Initial efforts in marine natural products chemistry have largely focused on collecting metabolites from most easily collected species[39]. Minor metabolites present in very small

quantities are a challenge for analytical and biological evaluations. In silico screening programs can be useful to understand the natural scaffolding of these minor drug candidates better[39]. Scientists are making efforts to improve the access to minor metabolites through technological advancements, such as increasingly widespread use of NMR microcryogenic and capillary flow-probes, biological assays in increasingly smaller volumes such as in 384- and 1534-well plate formats and enhancements of the methods as well as informatics and logistics associated with mass spectrometry[40-43] . Another area of improvement in marine drug discovery programs is the biological assay methods of extracts, fractions, and pure compounds. Assay-based isolation design for marine natural products has the potential for automation that may result in dramatic improvement in the way by which different classes of natural products are discovered in nature [38]. Looking at the vast potential and leads, there are several Institutes in India as well as all over the world, concentrating on research and training in marine pharmacology field. Most of the research institutes are concentrating on the discovery of potential novel compounds from marine organisms, extraction/ isolation, their safety and efficacy assessment and large-scale commercial production.

Conclusions

Marine environment has become a promising source of natural products, molecules, and drugs of therapeutic use. Having enormous varieties with a great diversity of organism and virgin areas of marine life, the prospects of yielding more novel products from the sea is enormous. The curiosity of science and industry has established the oceans as a prospective source for new potential drug leads. Scientists have come up with drugs of various categories out of which anticancer, anti-inflammatory, analgesics, and antivirals are the most important to mention.

These lead molecules are in different stages of preclinical and clinical testing stages around the world. Many drugs from marine sources have a promising effect on several chronic and unbeatable diseases like cancer. They may prove to open up a new chapter of making the treatment of chronic diseases cheaper and successful. After identification, extraction, and large scale production of promising marine natural products of therapeutic uses, their marketing and commercial exploitation of potential is dependent on the results of preclinical and clinical data.

The current screening for active natural products should be increased along with a large and rapid random screening method. Several research institutes and universities are working in this field to develop new moieties and train people to work in this area. The technology should be targeted optimally for drug research, approvals, and launches. The medical pharmacologist from India should consider taking up the further research in marine pharmacology to help our country in new drug developments.

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