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Marine Organisms as Potential Supply for Drug Finding - A Review Study

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Abstract: Oceans are a source of a large group of structurally unique natural products that are mainly found in invertebrates such as sponges, tunicates, bryozoans and molluscs. This diversity has been the source of unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals. In recent years, a significant number of novel metabolites with potent pharmacological properties have been revealed from the marine organisms. At the same time as the marine world offers an extremely well-off source for novel compounds, it also represents a great challenge that requires inputs from various scientific areas to bring the marine chemical diversity up to its therapeutic potential. This review highlights several marine natural products and their synthetic derivatives that are currently undergoing clinical evaluation.

Key words: Drugs · Marine organisms · Invertebrates

INTRODUCTION

The world's oceans, covering more than 70 % of the earth's surface, represent an enormous resource for the discovery of potential chemotherapeutic agents. The greater part of the earth surface is covered by the seas and oceans, which contain about 5, 00,000 species of marine organisms. All but two of the 28 major animal phyla are represented in aquatic environments, with eight being exclusively aquatic, mainly marine [1]. While marine organisms do not have a significant history of use in traditional medicine, the ancient Phoenicians employed a chemical secretion from marine mollusks to produce purple dyes for woollen cloth and seaweeds have long been used to fertilize the soil. First notable discovery of biologically active compounds from marine sources was the serendipitous isolation of the C-nucleosides, spongouridine and spongothymidine, from the Caribbean sponge, *Cryptotheca crypta,* in the early 1950s. These compounds were found to possess antiviral activity and synthetic analog studies eventually led to the development of cytosine arabinoside (Ara-C) as a clinically useful anticancer agent approximately 15 years later [1], together with Ara-A as an antiviral agent. The systematic investigation of marine environments as sources of novel biologically active agents only began in earnest in the mid-1970s. These studies have clearly demonstrated that the marine environment is a rich source of bioactive compounds, many of which belong to totally novel chemical classes not found in terrestrial sources [2]. The interest in nature as a source of potential chemotherapeutic agents continues [3]. The marine microorganisms, seaweeds, soft corals, fungus, sponges, bryozoans, tunicates, annelids, holothurians, molluscs, echinoderms have all been reported to be a source of bioactive molecules (acetogenins, polyketides, terpenes, alkaloids, peptides and many compounds of mixed biosynthesis).

MARINE NATURAL PRODUCTS

Marine life is fascinating and is considered to have great potential for its intrinsic value as well as for the development of new drugs. Earlier studies on chemistry of marine natural products were limited to the isolation, structure elucidation and phytogenetic relationship of specific substances, such as quinonoid pigment and sterol present in various marine organisms. Now this field attracted the attention of not only the natural product chemists, but also those of marine biologists, biochemists,

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pharmacologists etc. The invention of the aqualung and the advent of new technology in the past few decades led to the awareness that the oceans may be a new frontier of biomedical research and key to cure of many dreaded diseases.

The number of natural products isolated from marine organisms increases rapidly and now exceeds 18,000 [4], with hundreds of new compounds being discovered every year [5, 6]. A large proportion of these natural compounds have been extracted from marine invertebrates, especially sponges, ascidians, bryozoans and molluscs and some of them are currently in clinical trials [7]. Research into the pharmacological properties of marine natural products has led to the discovery of many potently active agents considered worthy of clinical application. The marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural/chemical features not found in terrestrial natural products [8]. The sea hare, *Dolabella auricularia* from the Indian Ocean, is the source of more than 15 cytotoxic cyclic and linear peptides, dolastatins. Due to its potency and mechanism of action, dolastatin 10, a linear depsipeptide which was shown to be a tubulin interactive agent, entered Phase I clinical trials in the 1990s and progressed through to Phase II trials as a single agent, but has been dropped due to lack of significant activity. As a result of the synthetic processes, many derivatives of the dolastatins have been synthesized with TZT-1027 (Auristatin PE or Soblidotin) now in Phase II clinical trials in Europe, Japan and the United States [9]. The modern concept for the treatment of human ailments comprises natural products with unusual structures and functions derived from marine plants and animals. The various biodynamic agents isolated from marine origin have been developed in recent years. Some of the isolates, for example Cephalosporin, Cytosine, Saxitoxin, Didemins, Kainic acid etc., are being used clinically. The following brief outline gives an indication about the current developments in marine bioactive substances and drugs.

Drugs from Marine Micro Organism and Phytopplankton: Numerous bioactive compounds of invertebrate origin are in fact microbial metabolites originating from dietary, commensalic or endosymbiotic microorganisms. Istamycin A and B, Isolated from marine *Streptomyces tenjimariensis* against Gram positive and Gram negative bacteria, including those with known resistance to amino glycoside antibiotics. 2, 4-DIBROMO-6 (3, 4 tribromo pyrrole-2yl) Phenol: Highly brominated pyrrole phenol possessing antibiotic properties, from marine Pseudomonas bromoutilis. Cephalosporins: Discovered in the 50's from a marine fungus, *Cephalosporium acremonium*. Modification of the original cephalosporin has led to the life saving antibiotics active against microbes insensitive to penicillin and ampicillin.

Drugs from Marine Sponges: Microbiologists are highly fascinated by sponges, as they are associated with enormous amounts of microorganisms. They can be considered as 'microbial fermenters' that hold a largely untapped potential for therapeutics. Sponges are traditionally a rich source of bioactive compounds in a variety of pharmacological screens [1] and a number of sponge-derived agents are in clinical development as potential anticancer agents [9]. These include the polyhydroxylated lactone, discodermolide, isolated from the Caribbean sponge, *Discodermia dissoluta* [10], HTI-286, a synthetic analog of hemiasterlin [11] originally isolated from a South African sponge, *Hemiasterella minor* [12] and soon thereafter from a Papua New Guinea sponge from *Cymbastela* [13] and a synthetic analog (E7389) of halichondrin B [14], which was originally isolated in 1985 from the Japanese sponge, *Halichondria okadai* and subsequently from Axinella sp. from the Western Pacific, Phakellia carteri from the Eastern Indian Ocean and from *Lissodendoryx sp.* off the east coast of South Island, New Zealand [9]. Girolline isolated from *Pseudaxinyssa cantharella* and LAF-389, a synthetic analog of bengamide A, isolated from Jaspis cf. coraciae, advanced into clinical trials, but was dropped due to lack of efficacy [6, 9]. Avarol and Avarone: Isolated from sponge, *Diced avara*, inhibit immunodeficiency virus, have high therapeutic indices and the ability to cross blood brain barrier, treatment of AIDS. β - CARBOLINE: Isolated from sponges, Eudistoma olivaceum has potent antiviral activity. Manolide a new steroidal lipid from Pacific Ocean sponge is a powerful anti-inflammatory substance and a pain killer. Spongothymidine Isolated from Carribean (West Indies) sponge, *C. crypta* has shown promising anti-tumor and antiviral activities. Spongouridine Isolated from Carribean (West Indies) sponge, *C. crypta* has shown promising anti-tumor and antiviral activities. Zidovudine: sponge derived compounds like Zidovudine (AZT) can fight the AIDS virus and cytosine arabinoside (Ara-C) is used in the treatment of leukaemias and lymphomas [15].

Acyclovir, which was synthetically known as Ara-A, was modelled based on sponge-derived spongothymidine or spongouridine. Ara-A is the first sponge-derived antiviral compound in the market. Polyketide Calyculin A (a selective inhibitor of protein phosphatise 1, isolated from sponge *Discodermia calyx*), Manoalide (a potent anti-inflammatory marine natural product and a direct inactivator of venom phospholipase A2), Okadaic acid, a potent inhibitor of protein phosphatases, especially protein phosphatises 1 and 2, respectively isolated from *Luffariella variabilis* and *Halichondria okadai* has reached the market undergoing from basic research to long phases of clinical study [16, 17].

Drugs from Seaweeds: Despite the fact that extracts of seaweeds *Ulva fasciata* and *Hypnea musciformis* exhibit antiviral activity, that of green mussel, *Perna viridis* exhibit anti-HIV and antiinfluenza activity [18]. Kainic Acid a valuable antihelmintic used clinically in Japan against parasitic roundworm, tapeworm isolated from marine red algae namely *Digenea simplex*. Domoic Acid, Another valuable compound isolated from dried red algae *Chondria armata* effective in expelling ascaris and pinworm without any side effect. Carageenan, Sulfated polysaccharide found to possess non-immune inflammatory response eg. rat paw odema, has also been injected into sinovial fluid of animals to produce anti-inflammatory drugs. Nereistoxin, A number of halogenated compounds isolated from marine red algae, *Plocamium cartilagineum* have insecticidial properties. Caulerpin, A pigment with indole structure isolated from *Caulerpa* species, has plant growth regulatory activity similar to indole auxins.

Drugs from Fish: Squalamine, isolated from the common dogfish shark, *Squalus acanthias,* collected off the New England coast [19]. *Saxitoxin,* Tetradotoxin from the figu fish and shell fish is a deadly toxin. The one isolated from butter clam *Saxidomus giganteus* has marked hypotensive effect which diminishes at lower doses, in addition isolated from liver of puffer fish, possessing cardiovascular activity. Alpha-helical amphipathic peptides are very common in fish as recently reviewed by Smith and Fernandes [20]. The first fish family of AMPs to be discovered was the α-helical pardaxins. These were isolated from the skin glands of Red Sea Moses sole, *Pardachirus marmoratus*, on the basis of their cytotoxic, pore-forming activities [21,22]. Pardaxins were originally described as toxins with anti-predatory function but subsequently they have been found to be active against Gram-positive and Gram-negative bacteria [23]. However, most fish α-helical peptides are members of the piscidin family, which includes the pleurocidins and piscidins [20]. Pleurocidins are 25-residue peptides first isolated from the skin mucus of winter flounder, *Pleuronectes americanus* [24].

Drugs from Echinoderms: Marine-derived compounds currently in clinical trials against cancer include ecteinascidin 743, isolated from the Caribbean ascidian, *Ecteinascidia turbinata* [25], aplidine, the dehydro analog of didemnin B, isolated from the Caribbean tunicate, *Tridemnum solidum* [26], Many cytotoxic compounds of therapeutic interest have been isolated frommarine invertebrates and some of them have been reported to be of microbial origin. Pyridoacridine alkaloids are the main compounds extracted from the ascidian *Cystodytes dellechiajei* [26]. HOLOTHURINS, Toxic triterpenoid glycosides, obtained from sea cucumbers *Actinopyga agassizi* are found to inhibit the growth of sarcoma and adeno carcinoma mice. Recently two cytotoxic saponins rhelothurium A&B, have been isolated and both the glycosides have shown potent anti-tumor activity.

Drugs from Corals: Prostaglandins, (15-epi-PGA2 acetate & 15 S PGA2): The richest natural source of prostaglandins, so far discovered in the soft coral *Plexaura hamomala* found in the Caribbean sea. Some prostaglandins have also been isolated from red algae, *Gracilaria lichenoides* PGE2 which showed anti-tumor activity. Macrocyclic lactone 'Bryostatin 1' from bryozoan sp. *Bugula neritina* and soft coral compounds, diterpene glycoside 'Eleutherobin' and Pyrrole alkaloid alkaloid 'Lamellarin D' anticancer6 while, anti-inflammatory compound 'OAS-100' which is semisynthetic derivative of pseudopterisone A are the hope of new effective therapeutic agents.

Drugs from Molluscs: Kahalalide F, isolated from the Hawaian mollusk, *Elysia rufescens* [27, 28], spisulosine, isolated from the marine clam, *Spisula polynyma* [29], Dolatriol, Isolated from marine mollusc *Dollabella auricularia* has pronounced antileukemic activity. Synthadotin and Soblidotin are two synthetic analogues of Dolastatin isolated from molluscan sp. *D. auricularia* in trials. Alkylamino alcohol 'ES-285' (Spisulosine) isolated from *Mactromeris polynyma* is another compound in preclinical trial, molecular target of this molluscan compound is Rho (GTP-bp).

The high potency of cone snail venoms has inspired pharmacologists to investigate their potential use as adjuncts in anaesthesia, antiepileptic, cardiac and antipsychotic drugs. More than 100 patents and patent applications reflect the strong commercial interest in these molecules. Zinconitide, which is the venom predatory snail, *Conus magnus* is licensed by Elan Pharmaceuticals under the name Prialt and is used for intratracheal treatment for chronic pain. *Lungbya majuscule* was recognized as the source of aplysia toxin found in sea slug Aplysia [30]. Similarly, a serves of highly active antitumor compounds, dollastains insolated from sea slug by pettit's group are considered to be of blue green algal origin.

Drugs from Annelids: Three novel AMPs have been purified from marine worms. Two isoforms of the AMP, arenicin, have been purified from the immune cells of the lugworm, *Arenicola marina* [31]. The arenicins are 21-residue peptides containing 2-stranded β-sheets as well as one disulphide bridge forming an 18-residue ring [31]. Arenicins completely kill *E. coli* within 5 minutes at a concentration of 5 μM probably by membrane permeabilization [32]. A second annelid peptide, named perinerin, has been purified from the clamworm, *Perinereis aibuhitensis* [33]. Finally, the most recent AMP to be isolated from a marine annelid is hedistin purified from the ragworm, *Nereis diversicolor* [34]. It shares no significant similarity with other AMPs [34]. Both native and synthetic hedistins are active against Gram-positive and Gram-negative bacteria.

Drugs from Other Organism: Bryostatins, A group of macrolide known as bryostatins, isolated from *Bugula neritina,* posses pronounced anti-tumor activity. A bioactive molecule from temperate marine diatom, Skeletonema is now used against a non-small-cell bronchopulmonary carcinoma line (NSCLCN6) [35]. Saclike filter feeder tunicates have been reported to be an importent source in drug discovery. Tetrahydroisoquinolone alkaloid 'Ecteinascidin 743' from *Ecteinascidia turbinate*, cyclic depsipeptides 'Dehydrodidemnin B and Didemnin B' from *Tridemnum solidum*, cyclic peptide 'Vitilevuamide' from *Didemnin cucliferum* and 'Diazonamide' from *Diazona angulata* are a few tunicate compounds in anticancer preclinical or clinical trials.

Study of marine organisms is a discipline, which endeavours to identify and decipher the troubles regarding not only sustainable exploitation of marine life for human health and welfare but also for marine ecology [36]. These entities are the sources of new leads for treatment of many diseases such as cancer, AIDS, inflammatory conditions and a large variety of viral, bacterial and fungal diseases [37]. International agencies realized the untapped drug potential of Indian Ocean wealth way back in late 1960s. Such efforts were launched in India only in the last decade with prestigious institutions (National Centre for Ocean Information Services, CMFRI, CDRI, NIO) funding research on marine bioprospecting. Indian drug and pharmaceutical industries have increased their R&D spending by 400% in the past 4 years [24], however, they still spend only one-tenth of their revenues on R&D against 20% by western companies. Based on the potentially large health benefits to society, the governments should encourage and support the search investment on marine biotechnology and marine biomedical field. It is time that our agencies and institutions recognize the magnitude of the problem and the all-too-obvious limitations of our laboratories [38].

In conclusion study of marine organisms for their bioactive potential, being an important part of marine ecosystem, has picked up the rhythm in recent years, with rich biodiversity and vast marine resources along the Indian coast, in the form estuaries, creeks, deep seas and continental shelf is potential useful for research in the area of marine drug development and exciting new frontier of scientific discovery and economic opportunity.

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