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EDITORIAL

Drugs from the sea

The marine environment is one of the most fascinating realm. Marine life with its beauty, mystery and variety has fascinated man since very long time. The ocean covers about 71% of this planet. Beneath this surface, the average depth of ocean is 3.8 km. This gives an approximate volume of 1370×10^8 km^3. This huge water body has innumerable organisms, displaying rich biodiversity. There are extremely diverse species of marine organisms such as plankton, algae, invertebrates and vertebrates. Besides these organisms, most of the Earth's microbial diversity is found in the ocean.

The marine environment is believed to be the original source of life on Earth. Many of the organisms in the aquatic world communicate with each other by way of signaling systems composed of primordial chemical messengers. We have evolved from this environment, our internal signaling pathways, including our endocrine systems, still respond to the primordial exocrine signaling system found today in these ancient marine animals.

Due to the physical and chemical conditions of the marine environment, almost every class of marine organism exhibits variety of molecules with unique structural features, which are not found in terrestrial natural products. Today, researchers have isolated approximately 11,000 marine-derived natural products compared with more than 155,000 natural, terrestrial products. Although, the oceans contain much greater biodiversity than is found on land, efforts to exploit this biodiversity by identifying new chemical compounds have hardly begun. New chemcial compounds mainly have been isolated from algae, sponges, coelenterates such as seafans and soft corals, other representatives such as ascidians, opisthobranch mollusks, echinoderms and bryozoans.

The search for marine drugs dates back to 1950s when Burgmann *et al.* isolated nucleotides, spongothymidine and spongouridine from Carrabean sponge *Tethya crypta* (Tethylidae). These nucleotides contained rare arabinose sugar rather than ribose, which is a quite ubiquitous sugar in nucleosides. This discovery lead researchers to synthesize anlogues, Ara-A and Ara-C which improved antiviral activity. Cytarabine (AraC) is a commercially available chemotherapy drug that is active against leukemia and used routinely when the disease is first diagnosed.

Since the mid-1970s, academic, government, industrial, and private research laboratories have devoted varying levels of effort to the discovery of marine-derived pharmaceuticals. The major emphasis has been on the discovery of anti-cancer compounds, due in large part to the availability of funding to support marine-based drug discovery. Currently, there are 14 small molecule marine natural products in clinical development as anticancer drugs. Although, there are only a few marine derived products currently on the market, several robust new compounds derived from marine natural products are now in the clinical pipeline, with more clinical development.

Didemnin, the first marine compound subjected to phase II clinical trials was proved toxic, hence, it was rejected as a therapeutic drug source. Nevertheless, its development laid the foundation for large-scale cultivation and extraction of marine organisms, which proved essential for development of other drugs from the sea. Didemnin has now been replaced by aplidin, obtained from tunicate *Aplidium albicans*. It is being manufactured by PharmaMar and currently in Phase II of clinical development. US Food and Drug-Administration (FDA) has granted Orphan drug status for the treatment of multiple myeloma and acute lymphoblastic leukemia.

One of the most notable compounds discovered at Harbor Branch Oceanographic Institution (HBOI) is discodermolide, a potent antitumor agent from sponge *Discodermia* spp. This compound has been licensed to Novartis and is in phase I clinical trials for the anticancer treatment. Another compound of interest is ecteinascidian (ET-743), a potent antitumor agent that is in phase III clinical trials. Yondelis or

Ecteinascidian-743 is a tetrahydrosoquinone alkaloid derived from the colonial tunicate *Ecteinascidia turbinata.* It is the first treatment for the soft tissue sarcoma to be released on the market in 30 years and offers an excellent example of the kind of drug that can be developed through marine organism research.

Bryostatin isolated from marine bryozoan *Bugulla neritina* has been licensed to Bristol-Mayers Squibb and is currently in Phase II clinical trials. It has been reported that Bryostatin-1 is not effective in cancer treatment by itself, but it seems to enhance the activity of such chemotherapies as taxol and cisplatin. Dolastatin 10 isolated from the sea hare *Dolabella auricularia* from the Indian Ocean is well-known antitumor agent in phase II clinical trials. It displayed unprecedented potency in experimental antineoplastic and tubulin assembly system.

Kahalalide F is a desipeptide isolated from *Elysia rubefescens* from Hawaii. KF induces cytotoxicity and blocks the cell cycle in G1 Phase in p53-independent manner. This compound is in phase II trial for the detection of prostate cancer.

Manolide isolated from Palauan sponge *Luffariella variabilis*, is a potent analgesic and anti-inflammatory agent. Manoline was licensed by Allergan Pharmaceuticals who took compound through phase I clinical trials for the treatment of psoriasis. Manolide is however commercially available as a standard probe for PLA_2 inhibition. IPL 512602, a synthetic analogue of steroid contignosterol isolated from the sponge *Petrosia contignata* is in phase II clinical trials as a leukocyte suppressive anti-inflammatory drug for the treatment of Asthama.

Sqalamine lactate, a novel antiangiogenic aminosteroid 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 by the FDA.

The high potency of cone snail venoms has inspired pharmacologists to investigate their potential use as adjuncts in anaesthesia, analgesia or as antiepileptic, cardiac and antipshychotic drugs. More than 100 patents and patent applications reflect the strong commercial interest in these molecules. Ziconitide, which is the venom of predatory snail, *Conus magnus* is licensed by Elan Pharmaceuticals under the name Prialt® and is used for intratracheal treatment for chronic pain.

High amounts of long chain polyunsaturated fatty acids (PUFAs) like eicosapentaenoic acid (EPA) and docosahexaenoc acid (DHA) makes fish oil unique compared to other lipid sources. These omega-3 fatty acids have been found to reduce the risk of cardiovascular diseases, hypertension, autoimmune and inflammatory disorders. It has been found to protect against various cancers. Astaxanthin, a strong antioxidant agent from marine algae and crustaceans is gaining importance as a powerful chemopreventive agent.

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. Numerous bioactive compounds of invertebrate origin are in fact microbial metabolites originating from dietary, commensalic or "endosymbiotic" microorganisms. Striking structural similarities that are frequently observed between natural products from marine invertebrates and compounds isolated from microorganisms support this hypothesis. Further, support for this hypothesis comes from molecular biological studies which has led to the isolation and characterization of putative biosynthetic gene clusters from microorganisms, associated with marine invertebrates. This can be well illustrated by didemnin B and dolastatin, which were firstly isolated from marine invertebrates and later discovered to be of bacterial origin.

With the inclusion of the known unique adaptations of microorganisms to high salt environments and high hydrostatic pressure, the immense diversity of the microorganisms in marine habitats becomes apparent. Hence, there is an urgent need to tap this marine resource not only for antibiotic and cancer study, but AIDS, tuberculosis, osteoporosis and infectious diseases as well.

One important application of the many bioactive compounds derived from the marine environment is their use as molecular probes, molecules broadly defined as non-drug substances, which can be used to probe the foundations of important biochemical events. A gene coding for green fluorescent protein (GFP) from the bioluminescent jellyfish *A. Victoria* has been developed for use as a reporter gene in numerous studies on the regulation of gene expression. Due to GFP fluorescence in living tissues, it is now possible to monitor gene expression continuously, a property of particular value in the study of differentiation in both embryos and tissue culture cells. There are many other marine products that have contributed to basic and clinical research including enzymes for molecular biology. A marine

microorganism isolated from the deep-sea hydrothermal vents yielded the Vent DNA polymerase, which is used in high fidelity PCR reactions common to both diagnostic procedures and the gene mapping studies of the Human Genome Project.

As a result of ocean exploration research, genomic libraries of marine organisms can be made which preserve all the genes found in that organism. From genomic libraries, a gene that makes an important biomedical compound can be cloned and expressed as a chemical compound in an artificial system-metagenomics.

Numerous recent developments in the United States have began to increase the interest in bioactive compounds in the sea. Various agencies and programs from United states such as NIH, Environmental Protection Agency (EPA), Biological Oceanography program at NSF and sea grant program at NOAA are funding research for collection, taxonomy and potentially useful chemicals in marine environment.

To boost domestic production of certain indigenously made drugs, government of India is providing funding to 'Drugs from the Sea' program through various agencies. This programme is being carried out successfully under the leadership of Central Drug Research Institute (CDRI), Lucknow and with the participation of 13 other national and state R&D laboratories, including universities. The drugs are being explored for various priority diseases like cancer, HIV, etc. Indian scientists have begun collecting various flora and fauna species from the surrounding ocean for developing new life saving medicines and rare biochemicals. 31 samples with significant antihyperglycaemic, antihyperlipidaemic, anti-fungal, spermicidal, antitubercular, antiviral activities have been discovered to date. Of these, three samples have been identified for product development. Two samples derived from mangrove fruit, CDR-134-D-123 are in Phase I Clinical Trials as an antihyperglycaemic agent, and CDR-134-F-194 as antihyperglycaemic & antihyperlipidaemic agent. A sample derived from puffer fish, CU1-002/004 has shown immense potential as antihyperlipidaemic agent from which IND has been filed.

In summary, the marine world has become an important source of therapeutic agents with novel mechanisms of action. Even though thousands of new molecules are discovered every year only small number of candidates is incorporated in clinical trials. The main problem underlying this is sustainable supply of these compounds from natural sources. To battle this problem various strategies are developed, such as mariculture or aquaculture of source organisms, development of synthetic analogues of active compounds, fermentation of microorganisms producing the compound, etc. Another possible solution is the use of genetic engineering to transfer the genes encoding the synthetic enzymes that produce the desired compound to microorganisms that can be grown in huge quantities. Development of these products and services, as well as the fundamental research from which they must be derived will be enhanced by greater dependence on interdisciplinary sciences such as pharmacology, chemical ecology, molecular biology, genomics, metagenomics, computational and combinatorial chemistry and biology.

The field of marine natural products is passing its discovery phase and moving to the second phase where understanding relationships and processes is driving the research towards novel drugs from the sea. Marine plants, animals and microorganisms will be the basis of new products and services important to technology in the future.

With rich biodiversity and vast marine resources along the Indian coast, in the form of estuaries, creeks, deep seas and continental shelf, the opportunities for research in the area of marine drug development are endless.

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