Review Article

The Oceans – Unlocking the Treasured Drugs

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ABSTRACT

The health of human population requires a wide variety of chemical and physical support from both local and global ecosystems. Ocean exploration often led to new theories, ideas and discoveries, including new medicine. The identification of medically useful compounds produced by marine organisms has reached not only to vitally important drug development opportunities but also to increase in preserving ocean habitats for research. The ocean is the key source of organisms that are beginning to yield new and potent drugs for the treatment of human diseases as well as new products for use in biotechnology.

The ocean is a treasure chest of unique Prokaryotes (Bacteria), Archea, Eukaryotes (Plants, Animals, Fungi, and Algae). This provides a vast store house of chemical compounds unknown on land. The potential of oceans as treasured medicine depends largely in the realm of survey and experimentation. Most of the bioactive products have been isolated from marine resources which have taken and edge to cure deadly disease like AIDS, Cancer, Arthritis, diabetes etc. Man must adhere to limitations for unearthing the living resources from ocean in order to ensure pathogen free environs. The main objective of this review is to emphasize by exploring the promises of ocean science, while also unchanging the danger to human health found in this new exploration making a major contribution to improve human health in the 21st century and beyond with regard to coral reef ecosystems.

Keywords: Bioactive Products, Environs, Marine Biotechnology, Metabolites and Coral Reef Ecosystems.

INTRODUCTION

Oceans cover about 70% of the Earth surface. Oceans are the mother of origin of life. Societies rely heavily on the ocean for many of their needs. Most of the diverse system on Earth exists in the oceans. Novel marine biodiversity is concentrated in four areas: 1.Coral Reefs, 2. Ocean / Seamounts, 3. Hydrothermal Vents and 4. Abyssal Slopes and Plains. Compounds with uncommon and exciting biological activity have been discovered in marine environment. The ocean is the key source of organisms that are beginning to yield new and potent drugs for treatment of human disease, as well as new products for use in biotechnology. The ocean is the most promising frontier for sources of drugs and marine organisms by providing models for understanding human biology. The uses of marine-derived compounds are varied, but the most stimulating potential lies in the medical realm.

Marine organisms are used fully or partial for making or modifying products, for specific uses with the help of marine pharmacology. With the aid of different molecular, cellular and biotechnological techniques, mankind has been able to expose many biological techniques which are applicable for aquatic organisms. Harvey et al[1], have examined 10% amongst 25,000 plants for the biological activity. A search[2] for new pharmaceutical drugs from marine organisms are covered by 80% flora and fauna taxons which are from marine environs. The ability to procure the marine life forms is fundamental, to turn a natural compound or a synthetic counterpart into a safe and effective pharmaceutical product. Most of the bioactive products have been isolated[3] from marine invertebrates such as Sponges, Tunicates, Corals, Molluscs, Bryozoans etc as well as from marine microorganism such as Bacteria and Fungi.

The looks for new metabolites from marine organisms have resulted in extraction[4] of almost 10,000 metabolites till date, out of which many are gifted, with pharmacodynamic properties. Secondary metabolites produced by marine bacteria and invertebrates have yielded medicinal products such as novel Anti-inflammatory agents (pseudopterosins, topsentins, scytonemin, manoalide), Antibiotics (marinone), Anti-cancer agents (sarcodictyin, bryostatins, eleutherobin, discodermolide). By merging the potential of microbial genetics with biological and chemical

diversity, apts a bright future for marine natural product drug discovery[5] and related compounds which have taken an edge for future clinical and advanced preclinical trials[6]. Deep water glass sponges from silica based structures may improve the function of fiber-optic cables[7] and these provide an insight into bone regeneration. Most of these derived compounds are used in a variety of consumer products like skin creams, hair treatments and cosmetics.

Most of the drugs in use today have come from nature. Raising the scientific awareness is now being focused on the potential medical uses of the benthic organisms. These organisms have developed unique adaptations to survive in cold, dark and highly pressurized environments. Metabolites with novel and chemical structures belong to diversified classes and been characterized from Mangrove and Mangal associates. Many chemicals like amino acids, carbohydrates, fats and proteins are products of primary metabolism which are vital for maintaining life processes. Some secondary metabolites like alkaloids, steroids, and terpenoids are classified into secondary metabolites which have pharmacological, toxicological and ecological significance. Biomedical compounds extracted from marine organisms[8] regulate by understanding the molecular basis of cellular reproduction and development.

Marine Pharmaceutical Resources

Marine natural products discovery, an area of research has made a considerable progress in recent years by fulfilling a meaningful role in championing the cause of ocean conservation. The identification of medically useful compounds produced by marine organisms has led to drug development opportunities. During the last 30 years around 24,500 samples were isolated, identified and screened for biological activities such as antidiarrhoeal, antimicrobial, antiviral, antimalarial, antidiabetic, anti-hyperlipidaemic etc. Most of them exhibited remarkable biological behavior with new novel chemical structures like amino acids, fatty alcohol esters, glycosides, terpenoids, alkaloids etc.

Because of its enormous biodiversity, the oceans offer huge potential for the discovery of new drugs with the increase in antibiotic-resistant microbes, it is increasingly important for new compounds to be obtained and the oceans offer exceptional opportunities for new pharmaceuticals. Most of the marine environs cover photic and aphotic zones, covering wide thermal (below freezing temperature to about 350°C in hydothermal vents), pressure (1-1000 atm) and nutrient ranges (eutrophic to oligotrophic).

Sources of Bioactive Compounds

There are many number of changes that took place during the adaptation to the terrestrial environment, but the identification of medically useful compounds produced by marine organisms has led not only to vitally important drug development opportunities[9,10] but also increased interest in preserving ocean habitat for research. Furthermore, it has fueled the development of new thechniques[11] for generating synthetic versions of natural compounds in order to prevent the unnecessary harvesting of organisms from their natural habitats. The scientific study of marine animals is an endeavor defined by unpredictable and serendipitous discoveries. The ability to procure the marine life forms[12] is fundamental to turn a natural compound or a synthetic counterpart into a safe and effective pharmaceutical product.

Metabolites from Bryozoans

The bioactive extracted compounds in Bryozoans are mostly alkaloids[13]. A sample of *Flustra foliacea* yielded deformylflustrabromine, displaying moderate cytotoxicity against the HCT-116 cell-line[14]. The marine Bryozoan, *Amathia convoluta* collected from the east coast of Tasmania, produced tribrominated alkaloids namely convolutamine-H and convolutindole-A,displaying a potent and selective activity against *Haemonchus contortus*, a parasitic nematode of ruminants[15]. *Watersipora subtorquata* from Tsutsumi Island, Japan, was the source of bryoanthrathiophene. This compound exhibited potent anti-angiogenic activity on bovine aorta endothelial cell (BAEC) proliferation[16]. *Amathia wilsoni* produced amathamide A and B alkaloids[17], by accomplishing with the starting material from 3-hydroxybenzaldehyde[18]. Bryostatin, a potent anti-cancer compound from *Bugula neritina*[17, 19] showed remarkable selectivity against human leukemia, renal cancer, melanoma, and non-small cell lung and cancer cell-lines. The major metabolite convolutamide-A exhibits in vitro cytotoxicity against L-1210 murine leukemia cells and KB human epidermoid carcinoma cells[20]. *Cribricellina cribreria* has yielded β-carboline alkaloid, which exhibited cytotoxic, antibacterial, antifungal, antimicrobial and antiviral activities[21, 22].

Metabolites from Fish, Sea Snakes and Marine Mammals

Various fish species are used to extract fish oil, rich in ω-3 fatty acids, used for the remedy of arthritis in human beings. The most vital substance of pharmacological importance extracted from fish is Tetradotoxin (TTX / zombie powder), a potent[23] neurotoxin, and specifically blocking voltage-gated sodium channels on the surface of nerve membranes. Other toxins isolated include ciguatoxin from electric rays, which is served as a potent antidote for pesticide poisoning[24].A new class of water-soluble broad-spectrum antibiotics; squalamines has been isolated from the stomach extracts of *Squalus acanthias* (mud shark, or piked dogfish) [25]. From the sea snakes, an anticancerous drug, namely "Fu-anntai", which has antiblastic effects on cervical carcinoma, stomach cancer, rhinocarnoma and leukemia cells, has been extracted[26].

Metabolites from Echinoderms

Glycosylated ceramides and saponins are the major classes of metabolites identified in Echinoderms. Due to cell lysis[27], Sea Stars and Sea Cucumbers[28] are extensively studied. Isolation and characterization of hedathiosulphonic acids A and B were isolated from *Echinocardium cordatum*[29, 30]. Benzyltetrahydroisoquinolone alkaloid is isolated from *Dermasterias imbricata*[27]. A range of sterol sulphates and steroidal glycosides were isolated from the starfish *Diplopteraster multipes*[31] and *Lysastrosoma anthosticta*[32] in the Sea of Japan. Ten new saponins, certonardosides (A–J) [33] were isolated from the starfish *Certonardoa semiregularis* collected off the Coast of Komun Island, Korea. Linckosides A and B, neuritogenic steroidal glycosides, were reported from an Okinawa collection of the starfish *Linckia laevigata*[34]. Two triterpene glycosides were isolated from the Sea Cucumber *Telenata ananas* as antagonists of the chemokine receptor subtype-5 (CCR5)[35]. Ceramide sex pheromone isolated from the female Hair Crab, *Erimacrus isenbeckii*[36,37] while squaric acid ester derivatives[38] was used in a new synthesis of echinochrome-A, a polyhydroxylated napthoquinone pigment commonly isolated from sea urchin spines.

Metabolites from Molluscs

Up to date around 3000 scientific studies led to the contribution of toxins extracted from cone snails, out of which around 115 have potential toxins which were analyzed[39]. Molluscs fall in the first category regarding the pharmacological actions. Conotoxin[40] is a valuable probe in physiological and pharmacological studies isolated from *Conus* species. Neosurugatoxin isolated from *Babylonia japonica* is useful in characterizing two classes of acetylcholine receptors[41]. Dolastatin, isolated from *Dolabella auricularia* is having antineoplastic[42] action. Ulapualide-A and B[43], a sponge-derived macrolide isolated from *Hexabranchus sanguineus* exhibits cytotoxic activity against L 1210 murine leukemia cells and antifungal activity. Chromodorolide-A[44] isolated from *Chromocloris cavae* exhibits in vitro antimicrobial and cytotoxic activities. Onchidal isolated from *Onchidella bieyi* helped in contributing to the binding sites and hydrolysis of acetyl cholinesterase. New polypropionates[45, 46] from the skin of the Mediterranean mollusk *Pleurobranchus membranaceus* have majorly played in stereochemistry. Siphonarin-B[47], [48] was isolated from the molluscs *Siphonaria zelandica* and *Siphonaria atra* which were useful in absolute stereochemistry. Bursatellanin-P, a 60-kDa protein was purified from the purple ink of the sea hare *Bursatella leachii*[49].

Metabolites from Microorganisms

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from microorganisms, many based on their use in traditional medicine. With the discovery of penicillin, a new enzyme, Taq DNA polymerase obtained from *Thermus aquaticus* led to the discovery and isolation of around 50,000 natural products. In spite of such successes in drug discovery from microorganisms, marine microorganisms have received very little attention. The difficulty in the search of metabolites from marine bacteria is mainly due to the non-culturability of the majority (over 99%) [50]. The studies made by the scientists at the Scripps Institution of Oceanography show that marine bacteria are capable of producing unusual bioactive compounds that are not observed in terrestrial sources[51, 52]. In most of the bacterial and archaeal hyperthermophilic[53] marine microorganisms, thermo-stable proteases, lipases, esterase's, and starch and xylan degrading enzymes have been actively isolated. The microlactins, a novel class of antiviral and cytotoxic macrolides[54] from deep-sea marine bacterium has been isolated.

This major metabolite, macrolactin A inhibits B16-F10 murine melanoma cells in *in vitro* assays, showing significant inhibition of mammalian herpes simplex virus (type I and II) and protecting T lymphocytes against HIV

replication. Marine toxins [55-58] such as tetrodotoxin, saxitoxin, ciguatoxins and brevetoxins are potent and specific sodium channel blockers, and pharmacological studies with these toxins have played a major role in developing the concept of sodium channels in general and membrane channels and voltage–gated sodium channels. These toxins are useful in neurophysiological and neuropharmacological studies, and marine bacteria could be an important source of these valuable molecules. Some anti-HIV actions have been identified in compounds extracted from *Lyngbya lagerhaimanni* and *Phormidium tenue*. *Fusarium chlamydosporum* isolated from the marine red algae is the source of Fusaperazines A & B. Lyngbyatoxin-A and Debromoaplysiatoxin are two highly inflammatory but structurally different metabolites[59] isolated from toxic strains of *Lyngbya mausculata*. Four new epipolysulphanyldioxopiperazines were isolated from fungus *Eptosphaeria* spp originating from the brown algae *Sargassum tortile*[60]. A series of noval antibiotics agents have been isolated from dianoflagellates, antifungal agents from *Gambierdiscus toxicus*[61, 62] and brevitoxins from *Ptychodiscus brevis*. As they depolarize the excitable membranes and their binding sites on sodium channel the mechanism seems to be different from that of other activators. Okadaic acid, a polyether fatty acid produced by Prorocentrum spp., has been a key molecule in studying[63] signal transduction pathways in eukaryotic cells since it is a selective protein phosphatase inhibitor.

Metabolites from Seaweeds

Seaweeds are abundant in the inter-tidal zones and in clear tropical waters. There are many numbers of seaweeds with economic potential[64] and these will be of great significance if these species could be the major role players in drug development. 720 species of marine algae belong to Rhodophyta, Phaeophyta, Chlorophyta were identified in both inter-tidal and deep water zones. The bioactive compounds found in seaweeds are a major breakthrough for an array of medical applications. The red alga *Sphaerococcus coronopifolius* was shown to have antibacterial activity[65]. The green alga *Ulva lactuca* was shown to possess an anti-inflammatory compound and an anti-tumor compound isolated from *Portieria hornemannii*[66]. *Ulva fasciata* produces a novel sphingosine derivative which was found to have antiviral activity *in vivo*. A cytotoxic metabolite, stypoldione[67, 68], which inhibits microtubule polymerization and thereby prevents mitotic spindle formation, has been isolated from tropical brown alga, *Stypodium zonale*. An iodinated novel nucleoside[69] has been isolated from *Hypnea valitiae*, which is a potent and specific inhibitor of adenosine kinase. It can be used in the studies of adenosine receptors in a variety of systems, and in studies on nucleotide metabolism and regulation. The green alga *Codium iyengarii* has been found as the source of a steroid, iyengadione and two new steroidal glycosides, iyengarosides A and B. Iyengaroside-A displayed moderate activity[70] against a range of bacteria.

Metabolites from Tunicates

Didemnin-B from the Caribbean tunicate *Tridemnum solidum* was the first marine compound[27, 71] to enter human cancer clinical trial as a purified natural product. Two drugs namely Ecteinascidin and Phthalascidian interacting with DNA and unknown proteins in cancer cells help in preventing the disease. Besides, the inhibitor of Matrix Metalloproteinase (MMP2) from an ascidian of the family Polyclinidae collected from Western Japan was identified as sodium1- (12-hydroxy) octadecanyl sulphate[72]. Ecteinascidin isolated from *Ectenascidia turbinata* shows potent activity[73] *in vivo* against a variety of mouse tumor cells. A study of the Thai ascidian *Ecteinascidia thurstoni*[74], using a KCN-pretreatment, identified the known two alkaloids ecteinascidins and the two novel analogues ecteinascidins. The identified ecteinascidins exhibited potent cytotoxicity towards tumor cell-lines and growth inhibition of *Mycobacterium tuberculosis* H37Ra. *Lissoclinum bistratum* produces bristratene[75] that makes PKC, and a useful tool for analyzing molecular mechanisms of cell growth, differentiation by enhancing its phospholipid activity.

Conclusion and Future Prospective

The Oceans, which is called the ‘Storehouse of unexplored treasured medicine” have structural unique natural products that are mainly accumulated in living organisms. Several of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily useful for many diseases and ailments. The life-saving drugs are mainly found abundantly in microorganisms, algae and invertebrates, while they are scarce in vertebrates. In the future, marine ecosystems could represent an increasingly important source of medical

treatments, nutritional supplements, pesticides, cosmetics and other commercial products. Drugs from the ocean are without question one of the most promising new directions of marine science today. Modern technologies have opened vast areas of research for the extraction of biomedical compounds and important metabolites, whose exploration has just begun.

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