Review Article

Drugs from Marine Microorganisms

Jigna Kanani*, Madhurima Banerjee, Rajendran N
School of Biosciences and Technology, VIT University, Vellore-632014, India.
***Corresponding author's E-mail:** jigna.knn@gmail.com

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ABSTRACT

For a very long time, drugs from different organisms have been discovered and used to prevent a wide range of diseases. For past few decades, marine microbiologists have identified several microorganisms that produce certain compounds which have potential antibacterial, antifungal, antiviral, antitumor activities etc. Marine environment consists of a diverse range of bacteria, fungi etc. Microbes have been found to be a better source to overcome certain limitations of some of the existing drugs. Based on numerous studies, marine microorganisms represent an underexplored reservoir for the discovery of new drugs and for exploitation in the pharmaceutical industries. Due to the adaptation of marine microorganisms in an extreme environment such as hydrothermal vents and cold seeps, researchers believe that they could serve as a source for a variety of novel products. In this review, existing and currently available drugs from marine microorganisms and the necessity for the discovery of new drugs from microorganisms, ongoing research for new microbial sources and new drugs have been highlighted.

Keywords: Drugs, Marine, Microorganisms.

INTRODUCTION

According to the book "Drug Discovery from Nature" by Grabley and Thiericke, drugs from nature have been known by mankind since thousands of years. Ancient civilization used extracts of plant or animal products as drugs with few inorganic salts. In India where the ayurveda gave access to a large variety of medicines from plants reported since ca. 1000 BC. Moreover, Chinese medicine based on natural products reported since about 500 BC[1]. Ayurveda is a whole medical system that is based on various theories about health and illness and on ways to prevent, manage, or treat health problems [2].

The bioactive compounds from organisms are responsible for effect to cure disease and within a short period, it can act significantly. These bioactive compounds are called drugs. A drug is a substance which can be used as a medicine, performance enhancer or for the other effects when introduce into human body or the body of another organism. In pharmacology, a drug is a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to enhance physical or mental well-being.

Historically, drugs were discovered through identifying the active ingredient from traditional remedies. Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability.

The drugs are either natural substances isolated from plants, animals and microorganisms or they are semi synthetic compounds. But some of the drugs which are already available in market have some side effects and limitations. Some of them can not cure disease completely and they are very expensive. So, it draws our attention to look for new drugs.

Marine microorganisms produce drugs

With the passage of time, majority of the world's population extensively depends on plants for medicines and plants also are able to supply the active ingredients of the traditional natural medical products. Plants are the root source of most of the commercial drugs available today. But it has been later found that medicines can be obtained from many other wide ranges of organisms other than plants. Many organisms both terrestrial and aquatic organisms are able to produce several medicinal products. For the past few decades, marine microorganisms has proved to be extensive source of a wide variety of bioactive compounds that can act as potent anti-inflammatory, antibacterial, antifungal and antimalarial in nature. Some marine epiphytic bacteria produced secondary metabolites. Numerous compounds have been derived from marine fungi used for medicinal purposes. Antioxidant compounds are also derived from some fungi that can be used in cure of diseases like dementia and cancer. It was found that marine cyanobacteria have apoptosis activity against myeloid leukemia cells. The benthic cyanobacteria from the temperate marine environments provided novel drugs against leukemia.[3] Trabectedin is produced from symbiotic bacteria. *Vibrio corallilyticus*[4] and *Aspergillus* sp.[5] exhibit antibacterial activities. *Enhygromyxa salina* [6] exhibit both antibacterial and antibiotic activities. Marine *Thermococcales* produce Thermostable Dna Polymerase.[7] Hyperthermophillic *Archae* is used as model to study DNA replication.[8] *Alteromonas sp.* produces metabolites that are anti-HIV.[9] *Vibrio alginolyticus* produces six proteases, also produces collagenases. [10]

Table 1: Microorganisms, drugs and their uses

Microorganism	Drug	Uses	References
Lyngya sp.	Apratoxin	Cytotoxic activity towards lung cancer cells.	Javed F. et al.(2011)[3]
Micromonospora marina	Thiocoraline	Antitumor activity	Erba et al.(1999)[11]
Brevibacillus laterosporus PNG276	tauramamide	New lipopeptide antibiotic	Bhakuni et al. (2005)[12]
Chaetomium sp	Chaetocyclinone A	Polyketide metabolite	Debbab et al.(2010)[13]
Aspergillus sulphureus	Decumbenones A-C	Stimulators of development of agricultural plants	Mikhail et al.(2012)[14]
Chromobacterium violaceum	Violacein	Antiviral	Andrighetti et al. (2003)[15]

Necessity of new drugs

In spite of the prevalence of many drugs being used for quiet sometime now, there has been a call for new drugs from unexplored sources due to some disadvantages of the existing drugs. Many of the drugs have side effects that necessitate the need for new drugs. Sometimes, resistance has been observed on using some of the drugs. There is the necessity of exploring new cost-effective drugs as many of the existing drugs are very expensive. Many strains of drug resistant organisms have come to existence. Moreover, many pharmaceutical leads based on land based plants and animals sources for drug development are proving less successful with the passage of days. Oceans have turned out to be a major source of various drugs[16]. So, the view has been shifted to the search of organisms from the marine environment as sources for new drugs. The search for new biomedical from marine organisms resulted in the isolation of more or less 10,000 metabolites [17] many of which endowed of pharmacodynamic properties.

Marine environment: source of new drug discovery

Recently, however, there have been diminishing returns from attempts to further exploit terrestrial sources and with the lack of new hits generated from computational approaches, attention has increasingly focused to the marine environment.

A large proportion of the world is occupied by aquatic ecosystems like rivers, lakes, ponds and oceans that provide vast habitable space on earth. Around 97% of the world's aquatic environment is covered by oceans and less than 0.008 % by rivers, lakes and ponds. The fresh water i.e. the rivers and lakes which have salt concentration less than 1% is lesser compared to that in the oceans which is about 3%.

Marine environment is biologically more diverse compared to fresh water environment and even terrestrial environment. Marine environments probably consist of almost 80% of the world's plant and animal species. The sea water exhibits harsh environments that include extremities in temperature, salinity, pressure, different levels of aeration and radiation, overcoming effects of mutations, combating infections, fouling and overgrowth by other organisms. The marine environment is free from desiccation, except during the high tides, and so no highly specialized means is required for conservation of water. Sea water has buffering capacity and is advantageous for the survival of a wide range of marine organisms for two reasons (1) an abundant supply of carbon can be available in the form of carbon dioxide for the use of plants in the synthesis of carbohydrates without disturbance to the animal life that may be sensitive to small changes in *p*H, and (2) in the slightly alkaline habitat the many organisms that construct shells of calcium carbonate (or other calcium salts) can carry on this function much more efficiently than in a neutral solution.

Support is offered to marine organisms by the specific gravity of the surrounding medium which obviates the need of supporting skeletal structures for many forms such as jelly fishes, unarmed mollusks, unarmed dinoflagellates etc. and also the large number of marine mammals with their heavy skeletons. Sea water serves as proper environment for living cells, since it contains most of the chemical elements essential for growth and maintenance of plant and animal protoplasm. Many exotic compounds have been found in majority of the lower life forms present in the sea. Many different marine organisms have been explored for bioactive compounds.[16] Fresh water organisms are in hypotonic solution and require maintaining ion balance. In the comparison the marine organisms are in hypertonic solution and can adapt their inner ion concentration to that in the surrounding water.

Marine microorganisms

The importance of terrestrial bacteria and fungi has proved to be valuable sources of bioactive metabolites. More than 120 medicines used today are from the terrestrial microorganisms (penicillin, cyclosporine A, adriamyccin etc). Microorganisms help in the defense mechanisms. Recently, there has been an extremely developing interest for marine microorganisms because of their high genetic and biochemical diversities. Marine microorganisms inhabit in all the existing niches ranging from polar ice to hydrothermal vents in the deep sea. Microbes also compete for space and nutrients in the marine environments that has lead to the production of drugs so far and in future too. Microbes are present in mangrove areas as well as in oligotrophic open ocean regions.

Today, marine microorganisms have the potential of producing novel metabolites as they move into diverse ecological units. The secondary metabolites obtained from microbes are important for our health and nutrition.

Microbes act as a better resource for getting lead molecules with novel scaffold to overcome limitations of existing drugs. Microorganisms like actinobacteria, myxobacteria etc. have extensive contribution to drug delivery. Microbes can be easily collected in considerable amounts, isolated and cultured in laboratory premises also. Microorganisms are often in mutuality or symbiotic relationships with other organisms in the marine environment like the sponges, coral reefs, echinoderms etc.

"Much of nature's treasure trove of small molecules remains to be unexplored, particularly from the marine and microbial environments."[18]

Marine microbial diversity

It is an established fact that marine microorganisms can live in variations of pressure, temperature and salinity. Evidences are being produced about the fact that microorganisms are the true producers of a number of potent varieties of drugs. This can be explained with some examples: the genes for the biosynthesis of the compound bryostatins (that were first extracted from bryozoans *Bugula sp.)* was extracted from tunicate *Ecteinascidia turbinate* but later its synthesis became difficult and it was found that a bacterial product safracin could be used as the starting product for chemical synthesis. So, it has been found that larger amounts of natural products can be obtained from microorganisms.

Microorganisms associated with marine invertebrates have reported to produce a wide range of bioactive compounds. Mostly it has been found that the active metabolites are produced by the associated microorganisms rather than the organisms they are associated to like sponges, macro algae, bryozoans, corals, sea weeds etc.

Marine Bacteria

Seawater contains high concentrations of bacteria. These organisms produce antibiotics to defend themselves from potentially harmful microorganisms. Marine bacteria are a rich source of secondary metabolites. Marine bacteria are majorly present in the sediments, in open oceans and most often are associated with other marine organisms. Vibronacea strain of bacteria exhibits high antibacterial activity and allows isolation of antibacterial compounds and production of bioactive metabolites. Many halotolerant and halophillic bacteria are able to produce bioactive metabolites due to low water activity. For example, metabolites from *Cladosporium* species have been shown to have antibacterial, antifungal and cytotoxic components inhibit bacterial growth. [19] Myxobacteria are also a good source of antibiotics.[16]

Marine Cyanobacteria

These microorganisms can photosynthesize and form the base level of the food chains. Marine cyanobacteria have the ability to produce structurally diverse and biologically active compounds that can induce cytotoxicity, anti-inflammatory and antibacterial activities.[20] Marine cyanobacteria are popular anticancer agents. For example, Apratoxin D produced by the species *Lyngya* is potently cytotoxic to lung cancer cells in humans.[3]

Marine fungi

Fungi are also potent sources of many bioactive compounds. Marine fungi are prolific sources of many natural products. Compounds like cycloglobosins and halovirs have been isolated from fungi.[17] Sorbicilactone A, a novel alkaloid produced from a sponge (*Ircinia fasciculata*) associated fungus *Penicillium chrysogenum.* Marine Myxobacteria is also a good source of antibiotics.[16]

Ongoing research

Although the number of natural products is increasing day by day, very few compounds find their way to the market because of many factors which may include cytotoxicity that they show on normal human cell lines and/or compound may be unfit for medical supplement. Despite the failure rate, some potential compounds have shown promising results as antitumor agents in preclinical trials and many have made it to different phases of clinical trials. [21]

Table 2: Clinical status and chemical class of marine derived antitumor drugs [21]

Clinical status	Compound name	Marine microorganisms	Chemical class
Phase III	Soblidotin (TZT 1027)	Bacterium	Peptide
Phase II	Tasidotin, Synthadotin (ILX-651)	Bacterium	Peptide
Phase I	Bryostatin 1	Bacterium/ Bryozoa	Polyketide
	Marizomib, Salinosporamide A; NPI-0052)	Bacterium	Beta-lactone-gamma Lactam
Preclinical	LY355703, CRYPTO 52	Cyanobacterium	Cryptophycin
	Depsipeptide (NSC 630176)	Cyanobacterium	Bicyclic peptide

Research on the development of new bioactive compounds depends on the multiple biological processes that these compounds can fulfill efficiently. Bioactive compounds help in increase in microbial interactions. As there is a wide diversity prevailing in the new marine natural products and their producers preferably the microorganisms, the research work on developing new bioactive compounds or natural products is continued in full swing.

Marine microorganisms are surprisingly present in the harsh environments such as in hydrothermal vents where temperature is so high that is up to 113˚C and in deep sea where temperature is below 5 ˚C, pressure is too high and the availability of nutrients is very less. The microorganisms present in cold seeps are also unique.

The microorganisms which can live in extreme environments are called extremophiles for instance thermophiles (high temperature), psychrophiles (cold loving) and barophiles (pressure loving). Many available enzymes do not withstand industrial reaction condition in pharmaceutical industries. As a result, the marine microorganisms from extreme environmental have received great attention and they could be a source of valuable enzymes used in industries. [22]

Many research works are going on to find new medicines from the coldest and deepest places on the planet. For instance, some bacteria from deep sea hydrothermal vents have anti- tuberculosis activity against *Mycobacterium tuberculosis* which causes life threatening disease tuberculosis. [23] Therefore, scientists are focusing to find new drugs from such unexplored environment to find medicine to treat diseases like AIDS and cancer.

CONCLUSION

'Drugs from the sea' is an international ongoing research programme to discover drugs from the marine organisms. Such a research result would helps to identify novel compounds not only from marine microorganisms but also from other macroorganisms.

From the summary, it could be understood that marine microorganisms have a great potential for drugs that should be explored properly and exploited well.

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