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Marine Organism: A Rich Source of Bioactive Metabolites

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Abstract

Natural products have proved to be a rich source of therapeutic agents. Plant extracts have been used for thousands of years in the treatment of human diseases. It is somewhat contradictory to note that most of them obtained either by synthesis or from terrestrial organism. The present study is a compilation of some of the marine biologicals with proven chemical nature and pharmacological actions and their separation and isolation techniques. This review summarizes the screening for bioactive compounds of marine animals and marine micro-organism; finally, new approaches for the screening of metabolites from marine resources are discussed. The goal of this article is to expose the marine substances to bring new solutions for tackling some of the major public health problems.

Key words: Bioactive, Marine, Metabolites, Screening

Introduction

The marine resources are nowadays widely studied because of numerous reasons. One of the reason is as the oceans cover more than 70% of the world surface and among 36 known living phyla, 34 of them are found in marine environments with more than 300000+ known species of fauna and flora [1-3]. The rationale of searching for drugs from marine environment stem from the fact that marine plants and animals have adapted to all sorts of marine environments and these creatures are constantly under tremendous selection pressure including space competition, predation, surface fouling and reproduction. The attention of finding drug from sea had started from 1970s. For instance, about 300 patents on bioactive marine natural product have been issued between 1969 and 1999. So far, more than 10,000 compounds have been isolated from marine organisms. Marine microbes live in a biologically competitive environment with unique conditions of pH, temperature, pressure, oxygen, light, nutrients and salinity, which is especially rich in chlorine and bromine elements. There is no wonder that marine microbial metabolites exhibit special biological activities compared with 'terrestrial' bacteria.[5-6]

The discovery of new bioactive compounds necessarily involves previously diversity studies, because by knowing the type of microorganisms that reside in a certain environment, it is possible to design cultivation techniques adapted for all the microbial communities present in a certain ambience. That is why it is very important to identify the organisms that produce bioactive secondary metabolites, and to be able to structure a plan of use and preservation of those species that represent a potential source for new drug development, especially those obtained from bacteria, because of their own cultivation characteristics, have attracted attention on either a big quantity of investigators on a global scale in the search of new natural products with anticancer and antibiotic activity principally.[7]

About 5 lakh species of marine organisms are antimicrobial, antiviral, antibiotic, anticancer/cytotoxic, anti-inflammatory, prostaglandins, neuro-physiological and cardiovascular agents.[8] Many of the species contain cardiovascular compounds. Several marine organisms are sessile and soft bodied, then the question will arise; how do these delicate looking simple sea creatures protect themselves from predators and pathogens in the marine environment. The answer to this inquest is the defense mechanism of the marine organism. The chemical compounds (like secondary metabolites) which are produced or obtained from micro organism. By the marine flora and fauna are very potent and biological active.

The potency of bioactive from marine life is mainly due to the intensive ecology pressure and from the stronger and /or predators. Investigations in their chemical ecology have revealed that the secondary metabolites not only play various roles in the metabolism of the producer but also in their strategies in the given environment. The study on

marine chemical compounds produced by different organisms; showed the strategies for their use for human benefit.[9-11] Marine organisms not only elaborate pharmaceutically useful compounds but also produce toxic substances. One of the most important societal contribution of marine natural products chemists has been the isolation and identification of toxins responsible for seafood poisoning.[12] Outbreaks of seafood poisoning are usually sporadic and unpredictable because toxic fish or shellfish do not produce the toxins themselves, but concentrate them from organisms that they eat. Most marine toxins are produced by microorganisms such as dinoflagellates or marine bacteria and may pass through several levels of the food chain. The identification of marine toxins has been one of the most challenging areas of marine natural products chemistry.

The major occupation of marine natural products chemists for the past two decades has been the search for potential pharmaceuticals. It is difficult to single out a particular bioactive molecule that is destined to find a place in medicine. However, many compounds have shown promise. Marine organisms produce some of the most cytotoxic compounds ever discovered, but the yields of these compounds are invariably so small that natural sources are unlikely to provide enough material for drug development studies. The art by which marine organisms elaborate bioactive molecules is fascinating.[13-18] Marine environment provides different biosynthetic conditions to organisms that live in it. Marine organisms generally live in symbiotic association. The pathway of transfer of nutrients between symbiotic partners is of much importance and raises questions about the real origin of metabolites produced by association. A recent trend in marine natural products chemistry is the study of symbiosis. [19]

Marine natural products chemistry has passed through several phases of development. The scuba diving made the collection of materials from deep seas easy. Effective methods of isolation provided many potent compounds in pure form. Advancement in instrumentation methods such as nuclear magnetic resonance, mass spectrometric techniques and X-ray diffraction have helped to solve many intricate structural and stereochemical problems. The present text is an effort to fill up the void in bioactive marine natural products. It would be inappropriate to claim that a complete coverage of all bioactive compounds has been made. Attempts have nevertheless been made not to leave out any of the major class of bioactive compounds. [20-22] The chemistry and biology of the bioactive metabolites of marine algae, fungi and bacteria and of marine invertebrates; separation and isolation techniques; biological, toxicological and clinical evaluation; bioactivity of marine organisms; biosynthesis of bioactive metabolites of marine organisms; bioactive marine toxins; bioactive marine nucleosides; bioactive marine alkaloids, bioactive marine peptides; and marine prostaglandins have drawn organic, medicinal and bioorganic chemists, pharmacologists activity.[23] It's difficult to summarize the whole ocean wealth of life in one review, thus few major bioactive metabolites are discussed below:

Marine natural products and drug discovery

Unlike the long-standing historical medical uses of terrestrial plants, marine organisms have a shorter history of utilization in the treatment and/or prevention of human disease. Among the first bioactive compounds from marine sources, spongouridine and spongothymidine from the Caribbean sponge (*Cryptotheca crypta*), were isolated serendipitously in the early 1950s.[24] They were approved as an anticancer drug (cytosine arabinoside, Ara-C) and an antiviral drug (adenine arabinoside, Ara-A), respectively, 15 years later.[25] However, it was only in middle of the 20th century that scientists began to systematically probe oceans for medicines. So far, more than 10,000 bioactive molecules have been discovered from marine sources, with hundreds of new compounds still being discovered every year.[26] .

However, in marine environment, this leading position is taken by invertebrates such as sponges, molluscs, bryozoans, tunicates, etc. They not only produce a great number of marine natural products currently known but also show the largest chemical diversity of natural products, including alkaloids, peptides, terpenes, polyketides, etc. Interestingly, out of 13 marine natural products (or analogues derived from them) that are currently in clinical trials as new drug candidates, 12 are derived from invertebrates.[27] Consider the fact that many marine organisms have soft bodies and lead a sedentary lifestyle, making a chemical system of defense almost essential for survival. Marine organisms have evolved the ability to synthesize such toxic compounds or extract or convert pertinent compounds from other marine microorganisms.

Natural products from marine organisms are released into the water and therefore are rapidly diluted; accordingly they must be very potent materials to have the desired end effect. The richly available marine biodiversity that is available to us has to this point only been explored to an extremely limited extent. Furthermore, the primary chemical diversity available from marine organisms is most likely capable of delivering an even greater abundance of secondary metabolites for research use. Drug discovery research from marine organisms has been accelerating and now involves interdisciplinary research including biochemistry, biology, ecology, organic chemistry, and pharmacology. For all of these reasons it is believed that the natural products that are available from the seas and oceans provide a tremendous opportunity for the discovery of novel therapeutic agents.[28-30]

Cytotoxic (Anticancer Compound)

Cancer is one such disease that has many naturally-derived therapies and for which tools are necessary to elucidate its complex progression pathways. Improvements in the area of cancer therapy are vital, considering that cancer is forecasted to be the major cause of death in the 21st century.[31] Marine-derived anticancer therapeutics exhibit their activity through several mechanisms of action on a diverse range of biological targets. In a recent assessment of the cytotoxic and antitumor properties of 150 marine natural products isolated from 2003-2004 it was noted that only 31 of the structurally defined marine natural products had known mechanisms of action, while the other 119 remained unknown.[32] Common anticancer targets include signal transduction, angiogenesis, apoptosis, cell cycle, DNA synthesis, mitochondrial respiration, mitosis and multidrug efflux, among others.[33-35]

Future efforts in the area of marine natural products as anticancer agents are concentrated on the development of new technologies. Genetic engineering is one such technology, which allows for the production of a desired metabolite in a heterologous host.[36-38] Several clinically useful drugs, investigational drug candidates, and pharmacological tools have already resulted from these marine-product discovery programmes. anticancer drugs commercially available are of naturally origin derived antiproliferative drugs such as doxorubicin, daunomicin, bleomycin, mytomicin C, vincristine and vinblastine play an important role in curative cancer chemotherapy in a number of solid tumors and haematological malignancies and the most important recent incorporations to the clinical armamentarium in oncology, taxanes and campthothecins, are also naturally derived compounds.[39-40]

The marine environment is a rich source of both biological and chemical diversity. 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 agro chemicals.[41] The new classes of anticancer drugs that have been isolated from marine organisms have been shown to possess cytotoxic activity against multiple tumor types.[42-44] Most of these compounds were identified during the 1980s following great improvements in deep-sea sample collection and in technologies that allowed the production of drugs on a large scale through aquaculture and synthesis.[45]

Table 1 Cytotoxic Acitvity

ORGANISM	COMPOUND	ACTIVITY	CHEMISTRY
Sponge	Aaptamine	antiproliferative	Alkaloid
Sponge	Agosterol A	Potent cytotoxic	Steroid
Sponge	Alkylpyridinim salts	Haemolytic,cytotoxic	Alkaloid
Ascidian	Ascididemin	antileukemic activity	Alkaloid
Sea hare	Aplyronine A	antitumor	Macrolide
Ascidian	Aplidine	antitumor	Depsipeptide
Bryozoan	Bryostatin-1	Antitumor,antidepressant	Macrolide
Sponge	Bastadin 6	anti-angiogenic	Alkaloid
Ascidian	Bistramide A	anticancer	Polyketide
Soft coral	Bromovulone III	antitumor	Prostanoid
Tube worm	Cephalostatin 1	apoptosis-resistant	Steroid
Sponge	Cortistatin A	antiangiogenic activity	Alkaloid
Sponge	Dictyostatin-1	anticancer	Macrolide
Sponge	Discodermolide	antitumor	Polyketide
Ascidian	Ecteinascidin-743	antitumor	Isoquinoline alkaloid
Ascidian	Fucoxanthinol	antineoplastic	Carotenoid
Mollusk	Kahalalide F	antitumor	Depsipeptide
Sponge	Onnamide A	antitumor	Polyketide
Sponge	Peloruside A	Antimitotic agent	Macrolide

Marine Toxins

The marine products like insecticides, anthelmintics, anticoagulants and compounds act as potent bioactive compounds. Some of the microorganism from the sea which are autotropic, also act as a source of toxins. These toxins are both ectocrine or external metabolites and endotoxins. Such endotoxins are some of the most potent materials. Various species of algae can produce marine toxins under certain circumstances. These toxins can then accumulate in shellfish such as mussels, oysters and scallops. When these contaminated shellfish species are consumed severe intoxication can occur.[46]

Table. 2 Marine toxin group and their responsible algae

	Toxin group	Syndrome	Genus	Species
Hydrophilic toxins	Domoic acid	ASP	Pseudo-nitzschia	australis, calliantha, cuspidata, delicatissima, fraudulenta, galaxiae, multiseries, multistriata, pseudodelicatissima, pungens, seriata, turgidula
	Saxitoxins	PSP	Alexandrium	angustitabulatum, catenella, fundyense, lusitanicum, minutum, tamarense, tamiyavanichii
			Gymnodinium	catenatum
			Pyrodinium	bahamense
Lipophilic toxins	Brevetoxins	NSP	Karenia	brevis, brevisulcata, mikimotoi, seliformis, papilionacea
			Chatonella	cf. verruculosa
	Okadaic acid and dinophysistoxins and pectenotoxins [1]	DSP	Phalacroma	rotundatum
			Prorocentrum	arenarium, belizeanum, concavem, lima
			Dinophysis	acuminata, acuta, arenarium, caudate, fortii, mitra, norvegica, ovum, rotundata, sacculus, tripos
	Yessotoxins		Protoceratium	reticulatum
			Lingulodinium	polyedrum
			Gonyaulax	polyhedra
	Azaspiracids	AZP	Azadinium	spinosum
	Spirolides	–	Alexandrium	ostenfeldii, peruvianum
	Gymnodimines	–	Karenia	seliforme
			Gymnodium	mikimotoi

*ASP Amnesic shellfish poisioning
*PSP Paralytic shellfish poisioning
*NSP Neurologic shellfish poisioning
*DSP Diarrhetic shellfish poisioning
*AZP Azaspiracid shellfish poisioning

Other Compounds

1) Cardiovascular Active substances
2) Antifungal
3) Antituberculosis
4) AntiviralS
5) Antiprotozoal
6) Antibacterial
7) Anthelmintic

Cardiovascular Active substances

These drugs are obtained from marine organism which are being conventionally used and constitute an important group of marine drugs.

DRUG CLASS	COMPOUND	ORGANISM	CHEMISTRY	MMOA
Cardiovascular	Sapogenins	Seastar	Sterol And Saponin	Ca^+ Influx
Cardiovascuar	Zooxanthellotoxin-B	Dinoflag	Macrolide	Ca^+ Influx
Cardiovascular	B-90063	Bacterium	Pyridine	Endot. Inhib.
Antihistamine	Verongamine Analogs	Synthtet	Imidazole	Histam. Antag
Antiinflammatory	Decatetraenoic Acids	Alga	Fatty Acid Metabolism	Eicos. Inhib
Anti-Inflammatory	Pseudopterosins	Coral	Diterpene	Eicos. Inhib
Anti-Inflammatory	Prenyl Hydoquinones	Synthtet	Terpenene	Eicos. Inhib
Immunosupressant	Palau'amine	Sponge	Guanidine	Eicosa Inhib
Immunosupressant	Pateamine A	Sponge	Macrolide	Il-2 Inhib

Table 3. Marine compounds with Cardiovascular Activity

COMPOUND	SOURCE	ACITVITY
Anthopleurins	Coelenterates	Cardiotonic effect
Eptatretin	Eptatretus stoutii	Potent cardiac stimulant
Laminine	Laminaria angustata	Hypotensive effect
D (-) octopamine	Octopus macropus	Adrenergic and cardiovascular response
Saxitoxin	Saxidomus giganteus	Hypotensive effect
Autonomium	Verongia fistularis	CNS stimulant
Eledosin	Cephalopodeledone moschata	Vasodilatory actions
Spongosine	Crypotethia crypta	Muscle relaxant
Eledosin	Eledone moschata	Vasodilator effect

Table.4**.** Summarizes the current status of representative compounds isolated from marine sources. The marine natural products are classified in the following categories: antiparasitic drugs, antinematodal drugs, antituberculosis agents, antiviral leads and antifungal agents.[47] They include aureol, puupehenone, sarcophine, palinurin and manzamine alkaloids.[48] As we can see from the table, sponges, together with other marine organisms such as corals, are an important source of biologically active natural products. Several microbes isolated from sponges and from other marine animals produced the same compounds in the laboratory as those originally isolated from their hosts. Because the majority of marine invertebrates have no methods of physical defense against predators, it is reasonable to hypothesize that symbiotic marine microorganisms are the original producers of these bioactive compounds.[49,50]

Representative marine metabolites with different therapeutic activities		
Compound	Type	Source
Antifungal activity		
Aurantoside B	Polyketide	Siliquariaspon. japonica sponge
Phorboxazole A	Macrolide	Phorbas sp. Sponge
Halishigamide A	Macrolide	Halichondria sp. Sponge
Halichondramide	Macrolide	Halichondria sp. sponge
Fascaplysin	Bis (indole) alkaloid	Fascaplysinopsis sp. sponge
Meridine	Polycyclic alkaloid	Corticium sp. sponge
Bengazole A	Oxazole- fatty-acid ester	Jaspis sp. sponge
Ptilomycalin A	Polycyclic	Ptilocaulis spiculifer guanidine alkaloid sponge
Antituberculosis activity		

Alkaloid	(+)-8-hydroxymanzamine Heterocyclic ring system attached to a carboline moiety	Pachypellina sp. sponge and Petrosiidae genus
Axisonitrile-3	Cyanosesquiterpene	
Litosterol	C-19 hydroxysteroid	Acanthella klethra sponge
Puupehenones	Shikimate-sesquiterpene	Okinawan soft coral Litophyton viridis Sponges
Antiviral activity		
Papuamides A	Cyclic depsipeptides	Theonella mirabilis,T. swinhoei
Avarone	Sesquiterpene hydroquinone	Dysidea avara sponge
Gymnochrome D	Brominated phenanthroperylenequinone	Fossil crinoid Gymnocrinus richeri pigments
Microspinosamide		
Solenolide A	Cyclic depsipeptide	Sidonops microspinosa sponge
Hennoxazole A	Diterpene lactone	Gorgonian of the genus Solenopodium
Thyrsiferol	Oxazole-containing alkaloid	
Spongiadiol	Triterpene Tetracyclic furanoditerpene	Polyfibrospongia sp. sponge Red alga Laurencia venusta Deep-water Spongia sp
Antibacterial activity		
Squalamine	Aminosterol	Dogfish shark Squalus acanthias
Cribrostatin 3	Isoquinolines	Cribrochalina sp. sponge
Bromosphaerone	Bromoditerpenes	Sphaerococcus coronopifolius red alga
Pestalone	Chlorinated benzophenone	
Jorumycin	Dimeric isoquinoline alkaloid	Rosenvingea sp. brown alga Jorunna funebris
Antiprotozoal activity		
Cyclic peroxides	Peroxide	Plakortis aff angulospiculatus sponge
Sigmosceptrellin- B	Alkaloid	
Plakortide	Cyclic peroxylactone	Diacarnus erythraeanus red sea sponge
Ascochyta Salicorniae	Fungus	Plakinastrella onkodes sponge Ulva sp. green alga
Anthelmintic activity		
Dihydroxytetrahydrofuran	Tetrahydrofuran	Notheia anomala south Australian marine brown alga
Amphilactams		Amphimedon sp. sponge
Geodin A magnesium salt lactam tetramic acid	Macrocyclic polyketide	Geodia sp. sponge

Conclusion

The past three years have seen an explosion of information in the field of novel bioactive compounds that have been isolated from marine microbes. It is therefore timely to review the past successes of marine microbial natural products as medicines and to examine future possibilities that arise from both conventional and new technologies to further explore the biodiversity of marine microbes and their associated secondary metabolites. It can generally be concluded that contemporary screening protocols in natural products chemistry are using chromatographic purification steps, sometimes producing pure compounds, before biological or enzymatic bioassay. Coupled to these more effective paradigms for screening are new assays that evaluate natural products in more detailed, refined, and novel ways. For example, detailed knowledge of the cellular mechanisms controlling proliferation has yielded numerous targets for. Mechanism-based anticancer screens. The productivity of the past decade in terms of discovery of new clinical anticancer leads from diverse marine life should translate into a number of new treatments for cancer in the decade to come. In turn, these successes should rekindle serious efforts to evaluate marine life for useful leads with anticancer properties. Although this review has mainly focused on recent developments in the preclinical pharmacology of marine natural products, and development of novel pharmaceutical agents.

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