Review Article

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IJRAP

# MARINE: THE ULTIMATE SOURCE OF BIOACTIVES AND DRUG METABOLITES

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Received: 12-07-2010; Revised: 24-08-2010; Accepted: 17-09-2010

**ABSTRACT**

Bioactive compounds from marine flora and fauna have extensive past and present use in the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification. Several molecules isolated from various marine organisms (microorganisms, algae, fungi, invertebrates, and vertebrates) are currently under study at an advanced stage of clinical trials, some of them have already been marketed as drugs. This article gives an overview of current trends in screening and the activity analysis of metabolites from marine resources. Although the marine resources have been somewhat limited to date, selected bioactive from marine flora and fauna have already published. This report summarizes the screening for bioactive compounds of marine animals and marine microorganisms. Finally, new approaches for the screening of metabolites from marine resources are discussed. The goal of this article is to expose the new models and mechanisms of action of marine substances to bring new solutions for tackling some of the major public health problems.

**Keywords:** Marine flora and fauna, Secondary metabolites, Clinical trials, Symbionts

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## INTRODUCTION

Pharmaceutical market is growing rapidly and continuously. But, still the demand for new drug discovery is encouraged. The reason behind this motivation can be the growing numbers of drug–resistant infectious disease and more and more upcoming disorders. The terrestrial resources have been greatly explored and thus academic and industry researchers are striving to get lead molecules from the inner space of oceans.

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.[4] Only 10% of over 25,000 plants have been investigated for biological activity. The marine environment may contain over 80% of world's plant and animal species. In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, bryozoans, sea slugs and marine organisms.[5] The marine environment covers a wide thermal, pressure and nutrient ranges and it has extensive photic & non-photic zones. This extensive variability has facilitated extensive specification at all phylogenetic levels, from microorganism to mammals. Despite the fact that the biodiversity in the marine environment for exceeds that of the terrestrial environment, research into the use of marine natural products as pharmaceutical agent is still in its infancy. This may be due to the lack of ethnomedical history and the difficulties involved in the collection of marine organisms.[6] But with the development of new diving techniques, remote operated machines etc, it is possible to collect marine samples and during the past decade, over 4200 novel compounds have been isolated from shallow waters to 900-m depths of the sea.[4]

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 [7, 8, 9].

### Marine chemical weapons for human welfare

To understand the link between marine chemical warfare and human health it is crucial to study chemical ecology in the oceans. Many sessile invertebrates such as sponges, corals and tunicates feed by filtering seawater. Since, seawater contains high concentrations of bacteria; these organisms produce antibiotics to defend themselves from potentially harmful microorganisms. Thus the production of anti-bacterial compounds by filter feeders such as sponges provides a possible link between chemical defense for sponges and antibiotics for use in humans. However, why should a sponge produce anticancer drugs or why a coral should produce a compound useful in the treatment of arthritis? In the scenario of two encrusting sponges

growing together, the sponge that will win the race of competition for space is the one that produces the chemical most effective at killing the rapidly dividing cells of the neighboring sponge. The ability of chemical to kill rapidly dividing cells is the hallmark of chemotherapy. Anticancer drugs often act by killing the rapidly dividing cells of a tumor but generally do not harm 'normal' healthy cells. These ideas provide a connection between marine chemical warfare and the possible application of marine natural products in medicine. Chemical ecology of marine organisms relates very closely to biotechnology by exploring these secondary metabolites to develop drugs to treat various life threatening diseases. Natural products released into the water is rapidly diluted and therefore need to be highly potent to have any effect. For this reason, and because of the immense biological diversity in the sea as a whole chemical entities exist in the ocean with biological activities that may be useful in the quest of finding drugs with greater efficacy and specificity for the treatment of many human diseases [4,10].

It's difficult to summarize the whole ocean wealth of life in one review, thus few major organisms discussed below:

**SPONGES**

Sponges are often studied because of their wealth of metabolites, which display biological activity. This is related to the nutritional physiology of these filter feeding animals, which efficiently filter bacteria from the inhalant water current. The diffusion of antibiotic agents in the living tissues may increase the efficiency of the retention mechanism concerned, and may also provide a defense against microbial infections and/or be used to control symbiotic bacteria populations. Inhibition and promotion of microbial growth by sponge extracts have been illustrated in simple experiments with laboratory and marine cultures of bacteria and of pathogenic fungi. However, their ecological and physiological significance remains largely unknown.[11]

So far an estimated 15,000 species have been described, but the true diversity is probably much higher. Particularly the tropical sponges are known for their colorful appearances and their morphological plasticity, encompassing encrusting, rope, ball and vase shapes ranging in size from a few mm to > 1m. Sponges are diploblast metazoans that lack true tissues or organs. In spite of their simple organization, genome sequencing has revealed genes encoding function that are highly homologus to those of their vertebrate analogs. As sessile filter feeders, they pump large volumes of water through a specialized canal system, termed the aquiferous system. The filtration capacities of sponges are remarkably efficient, leaving the expelled water essentially sterile. There are many bioactives isolated and screened various pharmacological activity. Many of them proved to be good drug molecules with significant results for preclinical and clinical studies. Some of which are discussed below:

Marine sponges belonging to the genus *Ircinia* are known to be a very rich source of terpenoids, several of which have shown a wide variety of biological activities. Since terpenoids containing a tetronic acid moiety showed strong antibiotic activity. Eg: Variabilins, which were polyprenyl – hydroquinones, had analgesic and anti-inflammatory properties.

Among the halogenated alkaloids, bromoalkaloids form the most widely distributed group of natural compounds, which are predominantly found in marine eukaryotes like sponges, are significantly rarer in prokaryotic micro plants and animals.[12]

Components of marine sponges are known to modulate various biological activities and have anti-inflammatory, anti fungal and anticancer effects. These in vitro activities imply that marine products may be potential therapeutic agents.

Polyacetylenenic alcohols, including (35,145)- petrocortyre A, purified from the marine sponge *Petrosia* Sp., are biologically active lipid compound having similar structure to a long carbon chain compounds such as sphingolipids possess cytotoxic activity against a small panel of human solid tumour cell liner by inhibiting DNA replication.[13]

The high biological activity of *Aplysina cavernicola*, a much studied sponge which produces aeroplysinin and aerthionin and other dibromo and dichlorotyrosine derivatives, with some antibiotic activity against *Bacillus subtilis* and *Proteus vulgaris*.

The sponge *Ircinia ramosa* has also been shown to possess antiviral, CNS stimulatory and antialgal properties.[14]

Red Sea Sponges has shown hypoglycemic effect in normal mice. An ethanol extract of *Haliclona virdis* showed a significant hypoglycemic effect lasting for more than 8 hr. after single oral doses of 200 or 500 mg /kg to normal mice.[15]

**TUNICATES**

The Urochordata, sometimes known as the Tunicata, are commonly known as "sea squirts".[16] They are all sessile as adults. The name Tunicates arises from the existence of the tunic.[17] Typically this tunic is attached to the substrate by a small holdfast and stands upright. It has two openings, an inhalant siphon and an exhalent siphon.

The blood of tunicates is normally clear and often contains extremely high quantities of vanadium, a rare element normally occurring in very small quantities in sea water. Nobody yet seems to know why it should collect this vanadium.Tunicates are mostly hermaphroditic, meaning they are both male and female at the same time. Generally they avoid self fertilisation by either having the eggs and sperm chemically designed to reject each other, or by having the eggs and sperm mature at different times. Sperm are released into the sea but the eggs are retained within the body where they are fertilised by sperm brought in with incoming water. The eggs are brooded within the body until they hatch.[18,19]

Many of them are known to be a rich source of chemically diversity secondary metabolites with often remarkable biological activities. In many cases these compound are simple amino acid derivatives or more complex alkaloids. They often exhibit potent anticancer activities, so they are considered unusal cytotoxic metabolites. Perhaps, this property has limited the antimalarial potential of the pyridoacridones, isolated from *Cystodytes dellechiajei*, and of bistramides, isolated from *Lissoclinum bistreatum*, as they possessed very narrow therapeutic indices.[20]

Iejimalides obtained from a marine tunicate *Eudistomacf Rigida* are unique 224-membered polyene macrolides having two methoxy groxy, four dienes units, and an N-formyl-L-serine terminus, and exhibit potent cytotoxic activity in vitro.[21] Aromatic alkaloids possessing polysulfide structures have been isolated from ascidians of the genera Lissoclinum, Eudistoma and Polycitor. These compounds have shown various biological activities like antifungal, antibacterial, cytotoxicity, antimalarial activity, inhibition of protein kinase C.

Three new active polysulfide aromatic alkaloids are found namely lissoclibadins 1,2,3, together with two known dimeric alkaloids, lissodinotoxins E and F.[22]

Halocidin is an antimicrobial peptide isolated from the hemolytes of the tunicate. Among the several known synthetic halocidin analogues, di-19HC has been previously confirmed to have the most profound antibacterial activity against antibiotic – resistant bacteria. This peptide has been considered to be an effective candidate for the development a new type of antibiotic.[23]

**SEAWEEDS**

The term seaweed refers to the large marine algae that grow almost exclusively in the shallow waters at the edge of the world's oceans. They provide home and food for many different sea animals, lend beauty to the underwater landscape, and are directly valuable to man as a food and industrial raw material.

Seaweeds are plants because they use the sun's energy to produce carbohydrates from carbon dioxide and water. They are simpler than the land plants mainly because they absorb the nutrients that they require from the surrounding water and have no need for roots or complex conducting tissues.[24] Many seaweeds have hollow, gas-filled structures called floats or pneumatocysts. These help to keep the photosynthetic structures of the seaweed buoyant so they are able to absorb energy from the sun. The term thallus refers to the entire plant body of a seaweed.[25]

Seaweed draws an extraordinary wealth of mineral elements from the sea which includes sodium, calcium, magnesium, potassium, chlorine, sulfur and phosphorus; the micronutrients include iodine, iron, zinc, copper, selenium, molybdenum, fluoride, manganese, boron, nickel and cobalt. It also contains several

vitamins like carotenes (provitamin A); vitamin C, $B_{12}$ along with higher proportion of essential fatty acids than land plants.

Seaweeds provide a rich source of structurally diverse secondary metabolites which includes terpenes, acetogenins, alkaloids and polyphenolics, with many of these compounds being halogenated. The functions of these secondary metabolites are defense against herbivores, fouling organisms and pathogens; they also play a role in reproduction, protection from UV radiation and as allelopathic agents. Chemical defense mechanisms that inhibit bioflim development are a common occurrence in seaweeds, with many secondary metabolites produced by seaweeds having bacteriocidal or bacteriostatic properties. Physical stress such as desiccation, UV and visible light and nutrient availability are able to alter the secondary metabolites in seaweeds.[26,27]

Some of the active algal specimens are *Laminaria angustata* var langissima, *L.japonica*, *L.Japonica* var. *Ochotencs*, *Ecklonia cava* and *Esienia bicyclis* and the green seaweed *Monostrome nitidum*.[28]

The number and diversity of studies related to toxicity of marine algae are high. The first report on toxicity research are those of Doty and Anguilar-Santos and Aguilar-Santos and Doty, where the biological activity of the compound caulerpicine, isolated from caulerpa species was found to be toxic to mice. Norris and Fenical (1982) suggest that natural compound with biological activity are unusual or unique, generally halogenated or non-hologenated terpenoids synthesized by marine seaweeds alga to high herbivore pressure.[29]

The red alga *Sphaerococcus coronopifolius* was shown to have antibacterial activity; the green alga *Ulva lactuca* was shown to posses an anti-inflammatony compounds and an anti-tumor compound was isolated from *Portieria hornemanii*, *Ulva fasciata* produces a novel sphingosine derivative has been found to have antiviral activity in vivo. A cytotoxic metabolite, Stypoldione, which inhibits microtubule polymerization and thereby presents miotic spindle formation, has been isolated from tropical brown alga, *Stypodium zonale*. *P.Hornemannii* is found to be a novel source of cytotoxic penta halogenated monoterpene, halomon, which exhibited one of the most extreme of differential cytotoxicity in the screening conducted by the National Cancer Institute (NCI), USA. Haloman has been selected for preclinical drug development since this compound shows toxicity to brain, renal and colon tumor cell liner and preliminary in vivo evaluations have been encouraging. An iodinated novel nucleoside has been isolated from *Hyprea volitiae,* which is a potent and specific inhibitor of Adenosine Kinase.[30]

Crude Polysaccharide and Proteins from *Himanthalia elongate* and *Cedium tomentosum* have shown reduction in blood glucose after intravenous administration by 50% and 30% respectively at 5mg /kg dose.[31]

**MARINE MICRO ORGANISMS**

For centuries, higher plants are major sources of drug used in many civilizations since ancient times, although the nature of the compounds in the drug is not exactly known. After the discovery of penicillin, attention has been focused on searching from terrestrial microorganism to look for new sources of drug and many new families of antibiotics are found from these microorganism.

Marine microbes having immense genetic and biochemical diversity look likely to become a rich source of novel effective drugs. Marine bacteria constitute ~ 10% of the living biomass carbon of the biosphere[32] and they represent dramatically different environment than their terrestrial counterpart. These bacteria originate mainly in sediments but also occur in open oceans and associated with the marine organisms. It was surprising to find that many bioactive compounds, reported from marine invertebrates are produced by their microbial symbionts. Competition among microbes for space and nutrients in the marine environment is a driving force behind the production of such precious antibiotics and other useful pharmaceuticals. Interestingly microorganisms associated with marine invertebrates are proved valuable candidates for drug discovery program[33-35].

Like bacteria, marine fungi are also reported to be potential source of bioactive substances. Sorbicilactone-A, novel type alkaloids was reported from sponge (*Ircinia fasciculata)* associated fungus, *Penicillium chrysogenum.* This compound showed therapeutic human trials. Polyketide synthases (PKSs) are a class of enzymes that are involved in the biosynthesis of secondary metabolites such as Erythromycin,

Rapamycin, Tetracycline, Lovastatin and Resveratrol. Polyketide biosynthetic genes from bacteria and fungi have been cloned, sequenced and expressed in heterologous hosts. Some marine sponge associated bacteria with antimicrobial assets are also detected to have polyketide synthases gene cluster and investigation is underway to explore them. Deep-sea hydrothermal vent microorganisms are also reported to produce unusual bioactive metabolites.

**Symbionts**

Sponges are filter feeders, not completely sealed off from the surrounding medium. This may facilitate the formation of various types of associations with other organisms; some of these associations with other organisms; some of these associations may be more permanent than others. They can be intracellular as well as extracellular although fitness effects and the permanence of these relationships remain largely unknown.[27]
The presence of large amounts of micro-organisms within the mesophyl of many demosponges is well documented. Bacteria are probably permanently associated with the host sponge unless they are disturbed by external stress factors. Several recent studies have sought to address the phylogenetic diversity of microbial communication associated with marine sponges by using 16 sRNA gene sequence analysis. A comprehensive analysis showed that sponges from different oceans contain phylogenetically complex, yet highly specific, microbial signatures. In particular, representatives of the poorly characterized phyla chloroflexi, Acidobacteria and Actinobacteria are abundant in gene libraries.[36]

Micro-organisms associated with marine invertebrates are reported to be involved in the production of bioactive molecules. Bioactive compound production in these bacteria could be attributed to the competition among them for space and nutrition. Though these bioactive compounds may be important for epibiotic defense of marine invertebrate hosts, they also have significant medical and industrial applications.[35,37]

Marine sponges and the microbes using within them are important from both an ecological viewpoint sponges are important members of shallow and deep water reef communication with nutrition supplied by photosynthetic symbionts often allowing them to compete with other benthic organisms such as corals. In some cases the active metabolites are produced by the microbes, rather than the sponge itself. Sponges and their associated microorganisms are therefore receiving much attention from pharmaceutical companies.[38]

Convincing evidence for the involvement of micro organisms in natural product synthesis has been complied for the tropical sponges *Dysidea habacea* and *Theonella* swinhoei, in which the producing microbe is a cynobacterium in the former and a bacterium in the latter.[39]

Sponge's harbor a rich diversity of micro organism in their tissues and in some case constitute up to 40% of the biomass, e.g. the Mediterranean sponge *Aplysina aerophoba.*[40,41] Sponge associated bacteria are capable of producing antibacterial metabolites. Surface associated bacteria with sponge *Ircinia ramosa* has shown Antibacterial activity.[14]

Several bacteria activated from tunicate have yielded natural products. An example is andrimid and the moramides A-C from a *Pseudomonas flurescens* strain, Harman previously known from tunicates and was shown also to be synthesized by a tunicate – associated *Enterococeus faecium*. The antifouling agent six bromoindole – 3 – baldehyole and its debromo derivative were isolated from the ascidian *Stomozoa murrayi* and also from an Actinobacter Sp. associated with this animal .[42]

The epibiotic bacteria in seaweed play a protective role by releasing secondary metabolites into the surrounding seawater that help preventing extensive fouling of the surface. Epibiotic bacteria are therefore attracting attention as a source of new natural products.[43]
The proportion of active bacteria associated with marine invertebrates (20%) and seaweeds (11%) is higher than that isolated from seawater (7%) and sediment (5%) [44-45].

**ACKNOWLEDGEMENT**

Authors are thankful to Dr. C.G.Naik, National Institute of Oceanography, Goa for his constant support. Authors are thankful to Hyderabad (Sind) National Collegiate Board and Dr. (Mrs) S.S.Bhalerao, Principal, HSNCB's Dr.L.H.Hiranandani College of Pharmacy, Ulhasnagar for their support.

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Source of support: Nil, Conflict of interest: None Declared