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Review Paper

Bioprospecting of marine organisms for novel bioactive compounds

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Abstract

The best sources of pharmacologically active compounds from the sea are mostly invertebrates (sponges, soft corals, gorgonians, sea hares, nudibranchs, bryozoans, and tunicates), microbes (bacteria, fungi and actinomycetes), algae and mangroves. The bioactive compounds are produced either by the marine organisms or the microbes associated with them. These compounds are mostly novel ones with potent bioactivity, but still in their preclinical or early clinical stage of development as drugs.

Keywords : bioprospecting, bioactive compounds, marine invertebrates, marine microbes, mangroves

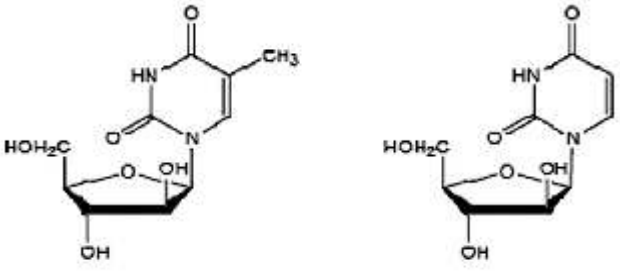
INTRODUCTION

Occupying 70% of the world's surface, accommodating the world's most productive ecosystems such as mangroves, coral reefs *etc*., containing 34 known living phyla with more than 0.3 million known species of fauna and flora (Faulkner, 2001), the ocean has a vast potential for a huge number of novel chemicals that may be useful for finding drugs with greater efficacy and specificity for the treatment of many human diseases (Bergmann and Feeney, 1951; Faulkner, 2001). The marine organisms have to withstand extreme variations in pressure, salinity, temperature *etc*. and these environmental variables have facilitated the organisms to produce varied chemicals of unique features. Among biological species found in the oceans, the best sources of pharmacologically active compounds are mostly invertebrates (sponges, soft corals, gorgonians, sea hares, nudibranchs, bryozoans, and tunicates), microbes (bacteria, fungi and actinomycetes), algae, and mangroves; about which, this article compiles recently available information.

STATUS OF DRUGS FROM THE SEA

Bioprospecting of marine organisms as sources of bioactive metabolites that may be directly utilized as drugs or serve as lead structures for drug development started in the late 1960s. The systematic investigation began in the mid-1970s. The earliest discovery is of the sponge-derived nucleosides spongothymidine and spongouridine (Fig. 1) (Bergmann and Feeney, 1951). During the decade from 1977 to 1987, about 2500 new metabolites were reported from a variety of marine organisms. These studies have clearly demonstrated that the marine environment is an excellent source of novel chemicals, not found in terrestrial sources (Carte, 1996).

So far, more than 10,000 compounds have been isolated from marine organisms (Proksch *et al.*, 2002). With hundreds of new compounds still being discovered every year (Proksch *et al.*, 2002), about 300 patents on bioactive marine natural products have been issued between 1969 and 1999. Most of these molecules are still in preclinical or early clinical development but few are already on the market, such as cytarabin-e, or are predicted to be approved soon, such as ET743 *Yondelis* (Burkhard, 2003). Table 1 summarizes the marine compounds that have been patented in recent years.



spongothymidine **spongouridine**
from the sponge *Cryptotethya crypta*

Figure 1. Anti-viral nucleosides from sponges

MARINE MICROBES

More recently, marine-derived microorganisms, which have immense genetic and biochemical diversity, have received attention for marine drug prospecting. The microbial secondary metabolites can be brought in use in three different ways: (i) the bioactive molecule can be produced directly by fermentation; or (ii) the fermentation product can be used as starting material for subsequent chemical modification; or (iii) the molecules can be used as lead compounds for a chemical synthesis. But there also exist major weaknesses in the technology for conducting drug screens and industrial fermentation with marine microorganisms as it is estimated that at least 99% of marine bacterial species do not survive on laboratory media. Furthermore, available commercial fermentation equipments are not optimal for use in saline conditions, or under high pressure (Lene, 1996).

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Table 1. Some of the recently patented marine compounds (compiled from Ocean Drug Alert, Lucknow, New Delhi, Vols. 10- 17)

Organism	Compound	Activity	Assignee	Year
Sea cucumber	crude extract	Anti-inflammatory	Coastide Bioresource,	1998
Sea cucumber	Fucosylated chondroitin sulfate	Inhibits complementary pathway	-do-	1999
Sponge, *Crambe crambe*	Crambescidin	Anti-viral and cytotoxic	-do-	1999
Cyanobacterium, *Nostoc ellipsosporum*	crude extract	Anti-viral protein and peptide	-do-	1999
Gorgonium, *Psuedopterogorgia elisabethae*	Psuedopeterosine	Anti-inflammatory	Suzannah, K, USA	1999
Sea cucumber	crude extract	Against Malignant tumor	Coastide Bioresources	1999
Sponge, *Discodermia dissolute*	Discodermolide	Anti-mammalian cell cancer	-do-	2000
Clam, *Spisula polynyma*	Spisulosines	Anti-lymphocytic leukemia	-do-	2000
Sponge *Batzella* sp.	Discorhadbin	Anti-tumor and Immuno modulatory	-do-	2000
Gastropod *Lamellaria* sp.	Heparin	Multi drug resistance	-do-	2000
Sponge, *Raspialia* sp.	Asmarin A and B	Cytotoxic	Instituto of biomaro SA, Spain	2001
Brown seaweed, *Padina pavonnica*	crude extract	Calciotropic activity	Texinfine SA	2001
Blue green algae	crude extract	Trafficking or homing of stem cells	-do-	2001
Brown seaweeds, *Laminaria onvolut* *Undaria pinnatifida* *Kjellmaniella crassifolia*	Sulfated fucose containing polysacharides	Anti-cancer and Anti-carcinostatic	Takaro Shuzo Co; Ltd., Japan	2001
Sponge, *Agelas* sp.	Agelagalastatin	Cancer cell growth inhibitor	Arizona Board of Regents, Arizona	2001
Bacterium, *Alcaligenes faecalis*	crude extract	Anti-bacterial agent	University of South Corolina	2001

Table 1 Contd.,

Organism	Compound	Activity	Assignee	Year
Brown seaweed *Cladosighon okamuranus*	Fucoidans	Anti-ulcer	University of South Corolina	2001
Green alga, *Chlorella* sp.	Glutamic acid	Antagonist growth inhibitor	Yakult Honsha Co ltd.	2001
Brown seaweed, *Laminaria* sp.	crude extract	Osmo protectors, Anti-oxidant	Mekideche	2001
Sandy tree species, *Salvadora persica*	crude extract	Tocolytic agent	CSIR, India	2001
Sponge *Erylus formosus*	Eryloside F	Thrombin receptor antagonist and human platelet aggregation	Harbor Branch Oceanographic Institution, Great Britain	2002
Sponge, *Cribrochalina* sp.	Cribrostanin 3,4,5	NaCl human konvolut panel inhibitor	Arizona Board of Regent, Arizona	2002
Sponge, *Adocia* sp.	crude extract	Kinesin motor modulator	The Regents of University of California, Oakland, USA	2002
Eucaryotic algae	Lipo polysacharide	Inhibits innate immune response	Board of Regents of University of Nebraska	2002
krill	crude extract	Treating Cardiovascular disorders, Skin cancer, diabetes	Neptune technologies and bioress; Sampalis Tina, California	2002
Sea cucumber	Carotenoid lipid	Anti-inflammatory, auto immune	-do-	2002
Brown seaweed, *Ascophyllum nodusum*	crude extract	Anti-obesity	Riken Vitamin Co. Ltd., Japan.	2002
Tunicate, *Cystodytes violatinetus*	Pyrido acridines shernilamide D	Anti-tumor	Instituto of bio marino science SA, Spain	2002
Red alga, *Pophyra sp*	crude extract	Stress protein inducing	Larena 13, Avenue De –Segur F-75007, France.	2003
Marine Sponge and Sea Cucumber	Fucosylated Acidic Glycans	Immunostimulants in Anti-cancer and Anti-viral Treatments	-do-	2003

Table 1 Contd.,

Organism	Compound	Activity	Assignee	Year
Marine yeast	β -1 3, Glucan	Anti-cancer	Orient Cancer therapy	2003
Bryozoan, *Bugula neritina*	Bryostatin	Anti-cancer	The University of North Corolina, U.S.A.	2003
Sea cucumber	penta peptide	Anti-cancer Anti-inflammatory	Coastiside Bio Resource	2004
Sponge	Polymeric-1 3- alkylpyridinium	Toxins	Aberdeen University, UK	2004
Seaweeds	Mixed extracts of brown, red and green algae	Anti-diabetic	Endomatrix Inc., U.S.A.	2004
Marine actinomycetes	Indole Carbozole alkaloids	Mammalian cancer cell lines	Institute of bio marine SA Spain.	2005
Sponges *Aplsinia cavernicola, Aplysina fulva, Oeanapia sp*	A spiro hetro cyclic unit connected through a linker of certain length to another spiro cycle, an imidezole ring or an amide group	Against connitive and neuro-degenerative disorders	Neuropharma S.A.; Madrid, Spain.	2005
Microbes-parasites on seaweeds	Isochroman compound pseudodeflectusin	Anti – Cancer	Nippon Kayaku Kabushiki Kaisha, Tokyo, Japan	2005
Marine Actinomycetes	Certain fermentation products	Anti-neoplastic agents	The Regents of University California, U.S.A.	2005
Marine Actinomycetes	Certain fermentation products	Anti-neoplastic agents	The Regents of University California, U.S.A.	2005
Seaweed *Codium fragile* and *Sargassum hornei*	Extract	Anti-coagulant	Cheju National University, South Korea	2007
Fish, Shrimp, Krill, algae, Zooplankton, Phytoplankton or a mixture	Extract Marine lecithin	Against *Psoriasis*	Dupont Paul	2007

Table 2. Bioactive microbes derived from marine sources

Species and source	Bioactivity and compounds	Reference
Lyngbya majuscula	Curacin A, has anti-tumor activity *in vitro* by inhibiting microtubule assembly by binding at the colchicines site; the compound is yet to be successfully formulated for use *in vivo*	Gerwick *et al.* (1994)
Lyngbya majuscula	An immunosuppressive linear peptide microcolin-A, which at nanomolar concentrations suppresses the two way murine mixed lymphocyte reaction	Koehn *et al.* (1992)
Lyngbya majuscula	Lyngbyatoxin-A and debromoaplysiatoxin; both are highly anti-inflammatory	Cardillina *et al.* (1979)
Prorocentrum spp.	Okadaic acid, a polyether fatty acid which is a key molecule in studying signal transduction pathways in eukaryotic cells since it is a selective protein phosphatase inhibitor	Cohen *et al.* (1990)
Marine cyanobacteria	Scytonemin is a sheath pigment that has recently been patented as an anti-inflammatory agent.	Proteau *et al.* (1993)
Marine Actinomycete *Micromonospora marina*	Thiocuraline-Anti-tumor	Baz *et al.* (1997)

Table 3. Bioactive compounds derived from marine algal sources

Species and source	Bioactivity and compounds	Reference
The green alga *Ulva lactuca* and *Portieria hornemannii*	Anti-inflammatory activity	Faulkner, (2002)
The green alga *Ulva fasciata*	A novel sphingosine derivative to have anti-viral activity *in vivo*	Garg *et al.* (1992)
The green alga *Codium iyengarii* from the Karachi coast of the Arabian Sea.	A steroid, iyengadione and two new steroidal glycosides, iyengarosides A and B. Iyengaroside-A displayed moderate activity against a range of bacteria	Ali *et al.* (2002)
The brown algae *Dictyota dichotoma* from Karachi coast in the Arabian Sea	Two compounds (i)Three C-16 oxidised *seco*-dolastanes, and (ii) dichotenols A–C, showing strong anti-HSV-1 activity *in vitro* but little inhibition of HIV-1 reverse transcriptase	Ali *et al.* (2004)
Ecklonia kurone, a very common alga in Pacific-coast Japanese species	One new phloroglucinol derivative and two known phloroglucinols, eckol and dieckol. All three compounds inhibited glycation and α-amylase, so may have an effect on complications of diabetes.	Fukuyama *et al.* (1989)
The red alga *Sphaerococcus coronopifolius*	Anti-bacterial activity	Donia *et al.* (2003)

Recently our research team has successfully extracted agricultural fungicides (Kathiresan *et al.,* 2005), biofertilizers (Ravikumar *et al.,* 2004; Kathiresan and Masilamaniselvam 2005), shrimp feed supplement (Palaniselvam and Kathiresan 1998) from marine microbes. All these researches are limited to those marine microbes which are easily cultured in laboratory. The genome sequencing makes it possible to visualize potential metabolic and biochemical capabilities of even non-culturable marine microbes. One of the future research trends will be focused on bioactive substances derived from non-culturable marine microorganisms. A list of bioactive microbes is given in Table 2.

Bacteria

Even though it is estimated that only a few per cent of marine bacteria are amenable to culture, some interesting new metabolites have been reported in the past 5 years. There is an urgent need to develop new culture techniques to isolate slow-growing bacteria and those bacteria that are unique in production of novel natural products (Jensen *et al.,* 1996).

Most of the marine phyla produce toxins and some studies show that these marine toxins may be produced by marine bacteria [Kodama *et al.,* 1988; Kodama *et al.,* 1990; Simudu *et al.,* 1990]. These toxins are useful in neurophysiological and neuropharmacological studies. The major metabolite, macrolactin-A inhibits B16-F10 murine melanoma cells *in vitro* assays, showing significant inhibition of mammalian herpes simplex virus (type I and II) and protecting T lymphocytes against human immuno-deficiency virus (HIV) replication (Carte, 1996).

Fungi

Among this group of marine organisms the richest profile of biologically active metabolites is described from filamentous fungi (making up about 20%) the vast majority coming from just three genera: *Penicillium*, *Aspergillus* and *Fusarium* (Lene , 1996). However, only a small fraction has been examined for metabolite profile. Recently, more interest has been generated around studying biologically active metabolites from higher fungi (Basidiomycetes), endophytic fungi and filamentous fungi from marine habitats, the symbiotic lichens *etc.*

In one study, the lignicolous fungus *Leptosphaeria oraemaris* (Pleosporaceae) yielded leptosphaerin (Pallenberg and White, 1986; Schiehser *et al*., 1986). A further study of the same fungal species yielded none of the previously found metabolites, but the polyketides, leptosphaerolide, its *o*-dihydroquinone derivative and leptosphaerodione (Guerriero *et al*., 1991). This leads to a conclusion that the production of secondary metabolites might be highly dependent on the culture conditions and the origin of the strains. To produce these metabolites and to maximize the potential chemical diversity, they need to be grown in various nutrient-limited media. For example, media for *Penicillium* spp. that are deficient in carbon have been used to produce penicillins, those that are phosphorus-limited produce cephalosphorins and vancomycin, and those that are nitrogen-limited can produce carbapenems (Lawrence, 1999).

Marine-derived fungi are known to be a source of anti-oxidative natural products, such as Acremonin A from *Acremonium* sp. (Abdel-Lateff *et al.,* 2002), Xanthone derivative from *Wardomyces anomalus* (Abdel-Lateff *et al.,* 2003). Reactions of free radicals such as super-oxide radical, hydroxyl radical, peroxyl radical and other reactive oxygen and nitrogen species are associated with diseases such as atherosclerosis, dementia, and cancer. Anti-oxidants delay or prevent oxidative damage. They may thus be useful as therapeutics or food additives.

Marine Actinomycetes

For more than 50 years, soil-derived actinomycetes of terrestrial origin provided a major pharmaceutical resource for the discovery of antibiotics and related bioactive compounds. However, marine actinomycetes received very recent attention. Gutingimycin is a highly polar trioxacarcin derivative from a *Streptomyces* species isolated from sediment of the Laguna de Terminos, Gulf of Mexico (Maskey *et al.,* 2002). The same *Streptomyces* species also yielded trioxacarcins D–F 3–5, in addition to the known trioxacarcins A–C (Maskey *et al.*, 2002). Among the antibiotic-producing microbes, marine actinomycetes within the family Micromonosporaceae are very promising. These microbes are found to be a potent source of anti-cancer agents that target proteasome function and their industrial potentials have been validated by several pharmaceuticals. A cytotoxic compound. *S. chibaensis* AUBN1/7 is produced from *Streptomyces chibaensis*. It showed a potent cytotoxic activity against cell lines *viz.* Gastric adenocarcinoma and Hepatic carcinoma *in vitro* and also exhibited weak anti-bacterial activities against Gram-positive and Gram-negative bacteria (Gorajana, *et al.,* 2007).

Algae

It is exciting to note that many algae can convert simple polyunsaturated fatty acids such as arachidonic acids into complex eicosanoids and related oxylipids (Gerwick *et al.,* 1994). Derivatives of arachidonic acids are important in maintaining homeostasis in mammalian systems and aberrant production of metabolites of this class occurs in diseases such as psoriasis, asthma, arteriosclerosis, heart disease, ulcers and cancer (Carte, 1996). A list of pharmacologicaly important compounds

from algae is given in Table 3.

INVERTEBRATES

It is generally accepted that sessile, soft-bodied marine invertebrates (sponges, corals, tunicates *etc*.,) which lack physical defenses, produce toxic chemicals to protect themselves in a very hostile environment and the chemical defenses have been developing in the oceans for thousands of years and has resulted in nature's most toxic chemicals. Therefore, they are prime candidates to possess bioactive metabolites because the targets of the chemical defenses, primary metabolites such as enzymes and receptors, are highly conserved compared with secondary metabolites. A list of marine invertebrate-derived bioactive compounds is given Table 4.

Sponges

A range of bioactive metabolites has been found in about 11 sponge genera. Three of these genera (*Haliclona*, *Petrosia* and *Discodemia*) produce powerful anti-cancer, anti-inflammatory agents, but their cultivation has not been studied (Blunt *et al.,* 2004). Actual research on sponge natural products was systematically started in 1951 by Bergmann and Feeney who isolated three nucleosides from the Caribbean sponge *Cryptotethya crypta*. Anti-viral properties of these nucleosides were demonstrated later and initiated the synthesis of analogues which led to the first anti-viral compound Ara-A (active against Herpes Simplex virus) and anti-tumour compound, Ara-C (effective in acute lymphoid leukaemia). The compounds Ara-A and Ara-C are the only marine invertebrate-related compounds in clinical use.

Recently three new spiculoic acids 1–3 and two members of a new closely related family of natural products named zyggomphic acids 4 and 5 were isolated from the very little studied marine sponge *Plakortis zyggompha*. These polyketides posses preliminary structures of anti-tumoral and anti-mycobaterial agents. (Berrue, *et al.,* 2007). The compound Ircinamine B was isolated from the marine sponge *Dactylia* sp., showed moderate activity against the murine leukemia cell line P388 (Sato *et al.,* 2006.) Marine sponge, *Biemna laboutei*, was found to be cytotoxic to a series of human tumor cells. (Sorek *et al.,* 2006). The Mediterranean sponge *Axinella verrucosa* has been investigated for its alkaloid composition and has been found to produce a complex mixture of bromopyrrole alkaloids that display neuroprotective activity against the agonists serotonin and glutamate *in vitro* (Aiello, 2006).

Echinoderms

Physiologically active saponins have been studied extensively from sea stars and sea cucumbers (Dubois *et al.,* 1988), but not as useful as drugs because of their tendency to cause cell lysis (Carte, 1996). Even then, glycosylated ceramides and saponins continue to be the major classes of metabolites identified in echinoderms.

A full account of the isolation and characterization of hedathiosulphonic acids A and B, isolated from a deep-sea urchin *Echinocardium cordatum* (Takada *et al.,* 2001) has been reported(Kita *et al.,* 2002) . Imbricatine from the sea star *Dermasterias imbricata* is the first benzyltetrahydroisoquinolone alkaloid from a non-plant source (Carte, 1996). A study of the starfish *Diplopteraster multipes* indicated a range of sterol sulphates (Levina *et al.,* 2002). Lysastroside-A, a new steroidal glycoside was isolated from the starfish *Lysastrosoma anthosticta* collected in the Sea of Japan (Levina *et al.,* 2002).

Cnidarians

This group of organisms consists of soft corals, gorgonians, jellyfish, anemones, and related species. The discovery of prostaglandin in corals in the late 1960s contributed greatly to the rapid developments in the field of marine natural products (Carte, 1996). New examples of cadinene-skeleton sesquiterpenes, xenitorins A–F, have been isolated from *Xenia puerto-galerae* (Duh *et al.,* 2002).

Tunicates

Ecteinascidin is a new anti-cancer agent isolated from "the mangrove tunicate" found in the Florida as well as other areas of the Caribbean. This drug is in human trials for breast and ovarian cancers and is one of the most promising new treatments under development for solid tumors. Ecteinascidin-743 or ET-743 is a tetrahydroisoquinoline alkaloid derived from the colonial tunicate *Ecteinascidia turbinata*, a sea squirt that lives in clusters in the Caribbean and Mediterranean seas. The compound was also demonstrated for very potent activity against a broad spectrum of tumour types in animal models (Rinehart, 2000).

Tunicates of the genus *Eudistoma* produce an important series of compounds known as eudistomins. *Eudistoma olivaceum*, a Caribbean tunicate species, produces specific oxathiazepine-bearing eudistomins that act as powerful anti-viral agents; but study of these compounds has been hindered by low availability.

Mollusks

More than 2600 scientific studies over the last 20 years testify to the important contribution of toxins extracted from the cone snails to medicine and cellular biology (Pickrell, 2003). Conotoxins are obtained from the venom ducts of predatory snails of the genus *Conus* found mainly in tropical waters (Duda *et al.,* 2001). The venom of each *Conus* species is known to contain between 50 and 200 peptide components. The *Conus* species have evolved deadly nerve toxins and small, conformationally constrained peptides of 10-30 amino acids. These highly

Table 4. Bioactive compounds derived from marine invertebrates

Species and source	Bioactive compounds and activity	Reference
The Palauan sponge *Luffariella variabilis*	Manoalide , a potent anti-biotic	de Silva and Scheuer, (1980)
The Carribean sponge *Batzella* spp.	Batzelladine A & B, novel polycyclic guanidine alkaloids exhibiting potent inhibition to the binding of HIV glycoprotein, on CD4 receptors of T cells	Carte, (1996)
Marine sponge, *Phakellia onvolute* was first described as a source of metabolite (Sharma *et al.* 1980) from the Great Barrier Reef and was later rediscovered as a metabolite of *Hymeniacidon aldis*	Debromohymenialdisine (DBH, **7**); DBH has been patented as a Protein Kinase C inhibitor and more recently as a treatment for osteoarthritis.	Kitagawa *et al.* (1983)
Marine sponge, *Hymeniacidon aldis.*	Hymenialdisine is a sponge alkaloid. The compound inhibited the *in vitro* phosphorylation of human microtubule-associated protein, which is implicated in the pathogenesis of Alzheimer's disease, and in Sf9 cells expressing the protein	Williams and Faulkner, (1996)
The Indian Ocean sponge *Cribrochalina* spp.	Isoquinolinequinone metabolite, cribostatin shows selective activity against all nine human melanoma cells	Pettit *et al.* (1992)
Sea hare, *Dollabella auricularia* from the Indian Ocean	Dolastatin 10 is a linear peptide isolated and is a well known anti-tumour agent with ED50 = 0.046 ng/ml against P 388 cells. It displayed unprecedented potency in experimental anti-neoplastic and tubulin assembly systems. Dolastatin 10 is in Phase I clinical trials as anti-cancer agent for use in the treatment of breast and liver cancers, solid tumours and leukemia	Yamada *et al.* (2000)
A starfish *Lysastrosoma anthosticta* collected in the Sea of Japan	Lysastroside-A, a new steroidal glycoside	Levina *et al.* (2002)
Cnidarians, a soft coral, *Lobophytum crassum*	Ceramideas, a moderately anti-bacterial component	Vanisree and Subbaraju, (2002)
Cnidarians–gorgonians of the genus *Pseudopterogorgia*	Pseudopetrocin-E, a tricyclic diterpene pentoside shows anti-inflammatory and analgesic activities equal in potency to industrial standard indomethicine	Carte, (1996)
The Caribbean tunicate, *Trididerunum solidum*	Didemnin B is perhaps the most studied of marine natural products. This cyclic peptide is anti-viral and immuno-suppressive as an effective agent for the treatment of leukemia and melanoma.	Rinehart *et al.* (1981)

Table 4 Contd.,

Species and source	Bioactive compounds and activity	Reference
An ascidian, *Didemnum* spp. collected from Stanley Reef, the Great Barrier Reef	Lepadins D with an unidentified counterion, lepadins E and lepadins F showing anti-plasmodial and anti-trypanosomal activities	Wright *et al.* (2002)
An unidentified ascidian collected at the Three Kings Islands, New Zealand	Coproverdine, a cytotoxic alkaloid isolated	Urban *et al.* (2002)
Tunicate, *Ectenascidia onvolute*	Ecteinascidin with potent activity *in vivo* against a variety of mouse tumour cells	Sakai *et al.* (1992)
Spanish collection of the ascidian *Synoicum blochmanni*	Cytotoxicity towards a variety of murine and human tumour cell-lines. Rubrolide-M-recently isolated was synthesised using palladium catalysed coupling methodology	Ortega *et al.* (2000); Bellina *et al.* (2002)
Tunicate, *Eudistoma* spp.	Eudistomins with potent anti-viral activity	Rinehart *et al.* (1993)
Tunicate, *Eudistoma* spp.	Besides eudistomins, a number of potent PKC inhibitors have been isolated which includes staurosporine aglycone, 11-hydroxy staurosporine, trithianes and pentathiepins	Kinnel and Scheuer, (1992); Carte *et al.* (1994) and Horton *et al.* (1994)
Tunicate, *Lissoclinum bistratum*	The compound bistratene enhances the phosholipid-dependent activity of PKC and may be a useful probe for studying molecular mechanisms of cell growth and differentiation as well as anti-cancerous drugs	Foster *et al.* (1992)
A mollusk, *Elysia rufescens* in Hawaii.	Kahalaide F is a depsipeptide, causing a disruption of lysosomal membranes and consequently the formation of large vacuoles. This mechanism is unique among anti-cancer agents and may cause increasing acidification of the intra-cellular space, a stimulatory event that initiates a pathway for apoptosis	Hamann *et al.* (1993)
Mollusk, *Babylonia* sp.	Neosurugatoxin isolated is useful in characterizing two classes of acetylcholine receptors	Ireland *et al.* (1993)
Bryozoan, *Flustra foliacea* from the southern North Sea	Deformylflustrabromine, Which displayed moderate cytotoxicity against the HCT-116 cell-line	Lysek *et al.* (2002)
The marine bryozoan *Amathia convoluta* collected from the east coast of Tasmania	Tribrominated alkaloids convolutamine-H and convolutindole-A. The compounds displayed potent and selective activity against *Haemonchus contortus*, a parasitic nematode of ruminants.	Narkowicz *et al.* (2002)
Sea anemone *Actineria villosa*	Hemolytic toxin Avt-I	Uechi *et al.* (2005)

constrained sulphur rich components or conotoxins (Adams *et al.*, 1999; McIntosh and Jones, 2001) represent a unique arsenal of neuropharmacologically active peptides (Bingham *et al.*, 1996; Heading, 2002) that can also be used as research tools to target voltage-gated and ligand-gated ion channels (McIntosh *et al.*, 1999). Some of the conotoxins block channels regulating the flow of potassium or sodium across the membranes of nerve or muscle cells; others bind to N-methyl-D-aspartate receptors to allow calcium ions into nerve cells; and some are specific antagonists of acetylcholine receptors responsible for muscle contraction. Thus, conotoxin are valuable probes in physiological and pharmacological studies (Myers *et al.*, 1993).

A novel anti-HIV protein (Bursatellanin-P) with molecular weight of 60 kDa has been purified from the purple fluid of the Sea Hare, *Bursatella leachii*, which inhibits the reverse transcriptase (RNA- dependent DNA polymerase) (Rajaganapathi *et al.*, 2002).

Bryozoa

Most of the extracted products from bryozoans are alkaloids but comparatively less in quantity. The first isolation and structure determination of a bryostatin was performed by George Pettit in the 1980s. One particular bryozoan, *Bugula neritina* is the source of a family of protein kinase-C inhibitors called bryostatins currently in clinical trials for cancer.

COASTAL MARINE MANGROVES

Mangroves have long been used in fisher-folk medicine to treat diseases (Bandaranayake, 1998; Kathiresan, 2000). Sixteen plants are the possible source of anti-cancer drugs, based on traditional knowledge and preliminary scientific work (Kathiresan *et al.*, 2006). Mangrove extracts have been proved to kill mosquito larvae and also to have repellent activity against adult mosquitoes (Thangam and Kathiresan, 1988, 1989, 1992a, 1992b, 1993a, 1993b, 1994 and 1997; Thangam *et al.*, 1992).

A few mangrove species, especially those belong to the botanical family – Rhizophoraceae – are known to have high anti-viral activity (Premanathan *et al.*, 1992: Kathiresan *et al.*, 1995). The extracts have proven activity against human, animal and plant pathogenic viruses including, HIV (Premanathan *et al.*, 1996), Semliki forest virus (Premanathan *et al.*, 1995), Tobacco Mosaic Virus (Padmakumar and Ayyakkannu, 1997), Vaccinia virus (Premanathan *et al.*, 1994a), Encephalomyocarditis virus (Premanathan *et al.*, 1994b), New castle disease virus (Premanathan *et al.*, 1993), and hepatitis B viruses (Premanathan *et al.*, 1992). Acid polysaccharides extracted from *Rhizophora mucronata* are active at a very low concentration to suppress the drug- resistant HIV strains (Premanathan *et al.*, 1999a and 1999b). These compounds do prevent human blood to clot (Kathiresan *et al.*, 2006). These properties of mangrove polysaccharides are advantageous in development of drugs. Lignins extracted from mangrove leaves of *Ceriops decandra* have been shown to protect mice from lethal infection by human pathogenic *E. coli* and this activity was attributed to antioxidant property of the lignins (Sakagami *et al.*, 1998).

DRUGS FROM THE SEA – WHO ARE THE PRODUCERS?

It is assumed that microorganisms associated with the marine invertebrates in particular sponges produce the bioactive substances as a chemical defense mechanism against predatory animals and pathogenic bacteria. Unfortunately, it appears that many obligate marine symbiotic microbes cannot at present be cultured.

Marine invertebrates harbor microorganisms within their tissues where they reside in the extra- and intra-cellular space (Vacelet and Donadey, 1977; Wilkinson, 1992). The associated microorganisms may constitute up to 40% of the biomass in sponges such as the Mediterranean *Aplysina aerophoba* (Vacelet, 1975; Friedrich *et al.*, 1999). Many invertebrates are filter feeders and consume microorganisms from the inhaled seawater by phagocytosis.

The structures of pharmacologically active natural products isolated from sponges, tunicates and other marine invertebrates exhibit striking chemical similarities to known microbial metabolite. For instance, the structural features of ET-743 from the tunicate *E. turbinata* reveal striking similarities to safracin B, a metabolite of *Pseudomonas fluorescens* (Ikeda *et al.*, 1983). Scytonemin is a protein serine/threonine kinase inhibitor referred to as a marine natural product (Lene, 1996), but the molecule was in fact isolated from the cyanobacterium, *Stigonema* sp. The bryostatins, which are produced from bryozoans, are actually synthesized by symbiotic bacterium *Candidatus Endobugula sertula* (Davidson *et al.*, 2001).

Another example is symplostatin 1, a close structural analogue of dolastatin 10 isolated from the marine mollusk *Dolabella auricularia* and currently in phase II clinical trials, is a metabolite of the blue-green alga *Symploca hydnoides* (Harrigan *et al.*, 1998). Further evidence for a dietary origin of dolastatins in *Dolabella auricularia* was provided when the same dolastatin derivatives that had previously been isolated from the sea hare were detected in free-living cyanobacteria, such as dolastatin 10 detected in the marine cyanobacterium *Symploca* species VP642 38 (Luesch *et al.*, 2001).

Involvement of microorganisms in natural product synthesis has recently been evidenced for the tropical sponges *Dysidea herbacea* and *Theonella swinhoei*. Specimens of *Dherbacea* from the Great Barrier Reef in

Australia contain the sesquiterpenes spirodysin and herbadysidolide as well as the chlorinated amino acid derivative 13-demethylisodysidenin (Unson and Faulkner, 1993). The sponge tissue is furthermore loaded with the cyanobacterial symbiont, *Oscillatoria spongeliae* (Berthold *et al.*, 1982) which comprises close to 50% of the cellular volume (Bewley and Faulkner, 1998).

However, there is no strong correlation between chemical class of secondary metabolites and the taxonomic position of the producing organism exists. Both bacteria and fungi have been found to produce similar class of compounds both in complexity, size and activity. It is found surprisingly that even complicated molecules *e.g.* the methoxyacrylates are produced by a very diverse selection of microorganisms (representing both white and brown spored Basidiomycetes as well as bacteria).

CONCLUSION

There is a great promise for development of novel drugs from the sea for the human diseases, which lack potential drugs to treat. In spite of the advances in computer-assisted drug design, in molecular biology and gene therapy, there is still a dire need for new drugs to treat many serious diseases like cancer and AIDS. It is necessary to have increased input from marine biology, microbiology and molecular biology in order to generate sound knowledge about the biochemical and genetic mechanisms that are underlying the synthesis of natural products. With this knowledge, sufficient quantities of "drugs from the sea" without destroying natural resources may be achieved.

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REFERENCES

Abdel-Lateff, A., Klemke, C., Konig, G.M. and Wright, A.D. 2003. Two new Xanthone Derivatives from the Algicolous Fungus *Wardomyces anomalus*. *J. Nat. Prod.* 66: 706-708.

Abdel-Lateff, A., Konig, G.M., Fisch, K.M., Holler, U., Jones, P.G. and Wright, A.D. 2002. New Antioxidant Hydrochinone Derivatives from the Algicolous Marine Fungus *Acremonium* sp. *J. Nat. Prod.* 65: 1605-1611.

Adams, D.J., Alewood, P.F., Craik, D.J., Drinkwater, R. and Lewis, R.J.1999. Conotoxin and their potential pharmaceutical applications. *Drugs Devel. Res.* 46: 219-234.

Aiello, A., Esposito, M.D., Fattorusso, E., Menna, M., Muller, W.E.G., Perovi-Ottstadt, S. and Schroder, H.C., 2006. Novel bioactive bromopyrrole alkaloids from the Mediterranean sponge *Axinella verrucosa. Bioorg. Med. Chem.* 14: 17–24.

Ali, M.S., Pervez, M.K., Ahmed, F. and Saleem, M. 2004. Dichotenol-A, B and C: The C-16 oxidized seco-dolastanes from the marine brown alga *Dictyota dichotoma* (Huds.) Lamour. *Nat. Prod. Res*. 18: 543-549.

Ali, M.S., Saleem, M., Yamdagni, R. and Ali, M.A. 2002. Steroid and antibacterial steroidal glycosides from marine green alga *Codium iyengarii* Borgesen. *Nat. Prod. Lett.* 16: 407- 413.

Bandaranayake, W.M. 1998. Traditional medicinal uses of mangroves: mangrove and salt marshes, *Wett. Ecol. Manag.* 2: 133-148.

Baz, J.P., Canedo, L.M., Puentes, J.L.F. and Silva Elipe, M.V. 1997. Thiocoraline, a novel depsipeptide with antitumor activity produced by a marine *Micromonospora* II: Physico-chemical properties and structure determination. *J. Antibiot*. 50: 738–741.

Bellina, F., Anselmi, C. and Rossi, R. 2002. Total synthesis of rubrolide M and some of its unnatural congeners. *Tetrahedron Lett.* 43: 2023-2027.

Bergmann, W. and Feeney, R. 1951. Contribution to the study of marine sponges. *J. Org. Chem.* 16: 981-987.

Berrue, F., Thomas, O.P., Laville, R., Prado, R.L.S., Golebiowski, J., Fernandez, R. and Amade, P. 2007. The marine sponge *Plakortis zyggompha*: a source of original bioactive polyketides. *Tetrahedron* 63: 2328–2334.

Berthold, R.J., Borowitzka, M.A. and Mackay, M.A. 1982. The ultrastructure of *Oscillatoria spongeliae*, the blue-green algal endosymbiont of the sponge *Dysidea herbacea*. *Phycologia* 21: 327–335.

Bewley, C.A. and Faulkner, D.J. 1998. Lithistid sponges: Star performers or hosts to the stars? *Angew Chem. Int. Ed.* 37: 2162–2178.

Bingham, J.P., Jones, A., Lewis, R.J., Andrews, P.R. and Alewood, P.F. 1996. *Conus* venom peptides (Conopeptides): Inter-species, intra-species and with in individual variations revealed by ion spray mass spectrometry. Chapter 2, *In: Biochemical Aspects of Marine Pharmacology*. Lazarovici P, Spira ME, Zlotkin E, (Ed.) Alaken Inc., Fort Collins, Coloralo P. 13-27.

Blunt, J.W., Copp, B.R., Munro, M.H.G., Northcote, P.T. and Prinsep, M.R. 2004. Marine Natural products. *Nat. Prod. Rep*. 21: 1-49.

Burkhard, H. 2003. Drugs from deep: marine natural products as drug candidate. *Drug Dis.Tod.* 8: 536-544.

Cardillina, J.H., Marner, F.J. and Moore, R.E. 1979. Seaweed dermatitis: structure of lyngbyatoxin A. *Science* 204: 193-195.

Carte, B.K. 1996. Biomedical potential of marine natural products. *BioScience* 46: 271-286.

Carte, B.K., Chan, G., Freyer, A., Hemling, M.E., Hofmann, G.A., Mattern, M.R., Compagone, R.S. and Faulkner, D.J. 1994. Pentatheipins and trithianes from two *Lissoclinum* species and a *Eudistoma* sp.: inhibitors of protein kinase C. *Tetrahedron* 50: 12785-12792.

Cohen, P., Holmes, C. and Tsukitani, Y. 1990. Okadaic acid: a new probe for the study of cellular regulation. T*rends Biochem. Sci.* 15: 98-102.

Davidson, S.K., Allen, S.W., Lim, G.E., Anderson, C.M. and Haygood, M.G. 2001. Evidence for the biosynthesis of bryostatins by the bacterial symbiont "*Candidatus Endobugala sertula*" of the bryozoan *Bugula neritina*. *Appl. Environ. Microbiol.* 67: 4531-4537.

De Silva, E.D. and Scheuer, P.J. 1980. Manoalide, an antibiotic sesterterpenoid from the marine sponge *Luffariella variabilis* (Polejaeff). *Tetrahedron Lett.* 21: 1611–1614.

Donia, M. and Hamann, M.T. 2003. Marine natural products and their potential applications as antiinfective agents. *The Lancet.* 3: 338-348.

Dubois, M.A., Higuchi, R., Komori, T. and.Sasaki, T. 1988. Structure of two new oligoglycoside sulfates, pectinoside E and F, and biological activities of 6 new pectinosides. *Liegbig's Annalen der Chemis.* 845-850.

Duda, T.F., Kohn, A.J. and Palumbi, S.R. 2001. Origins of diverse feeding ecologies within Conus, a genus of venomous marine gastropods. *Bio. J. Linn. Soci.* 73: 391-409.

Duh, C.Y., Chien, S.C., Song, P.Y., Wang, S.K., El-Gamal, A.A.H. and Dai, C.F. 2002. New cadinene sesquiterpenoids from the Formosan soft coral *Xenia puerto-galerae*. *J. Nat. Prod.* 65: 1853-1856.

Faulkner, D.J. 2001. Marine natural products. *Nat. Prod. Rep.* 18: 1-49.

Faulkner, D.J. 2002. Marine natural products. *Nat. Prod. Rep.* 19: 1-48.

Foster, M.P., Mayne, C.L., Dunkel, R., Pugmire, R.J., Grant, D.M., Kornprobst, J., Verbist, J., Biard, J. and Ireland, C.M. 1992. Revised structure of bistramide A (bistratene A): application for a program for the analysis of 2D INADEQUATE spectra. *J. Am. Chem. Soc*. 114: 1110-1111.

Friedrich, A.B., Merkert, H., Fendert, Hacker, J., Proksch, P. and Hentschel, U. 1999. Microbial diversity in the marine sponge *Aplysina cavernicola* (formerly *Verongia cavernicola*) analyzed by fluorescence in situ hybridization (FISH). *Mar. Biol.* 134: 461–470.

Fukuyama, Y., Kodama, M., Miura, I., Kinzyo, Z., Kido, M., Mori, H., Nakayama, Y. and Takahashi, M. 1989. Structure of an anti-plasmin inhibitor, eckol, isolated from the brown alga *Ecklonia kurome* Okamura and inhibitory activities of its derivatives on plasma plasmin inhibitors. *Chem. Pharm. Bull.* 37: 349.

Garg, H.S., Sharma, T., Bhakuni, D.S., Pramanik, B.N. and Bose, A.K.1992. An antiviral sphingosine derivative from green alga *Ulva fasciata*. *Tetrahedron lett.* 33: 1641-1644.

Gerwick, W.H., Proteau, P.J., Nagle, D.G., Hamel, E., Blokhin, A. and Slate, D.L. 1994. Structure of curacin A, a novel antimitotic, antiproliferative,and brine shrimp toxic natural product from the marine cyanobacterium *Lyngbya majuscula*. *J. Org. Chem.* 59: 243–1245.

Gorajana, A., Venkatesan, M., Vinjamuri, S., Kurada, B.V.V.S.N., Peela, S., Jangam, P., Poluri, E. and Zeeck, A. 2007. Resistoflavine, cytotoxic compound AUBN1/7 from a marine actinomycete *Streptomyces chibaensis*. *Microbiol. Res.* (Article in press).

Guerriero, A., D'Amrosio, M., Cuomo,V. and Pietra, F. 1991. A novel, degraded polyketidic lactone, leptosphaerolide, and its likely diketone precursor, leptosphaerodione, Isolation from cultures of the marine ascomycete *Leptosphaeria oeaemaris* (Linder), *Helv. Chim. Acta.* 74: 1445.

Hamann, M.T., Scheuer, P.J. and Kahalide, F. 1993, A Bioactive Depsipeptide from the Sacoglossan Mollusk *Elisia refescens* and the Green Alga *Bryopsis sp*. *J. Am. Chem. Soc.* 115: 5825-5826.

Harrigan, G.G., Luesch, H., Yoshida, W.Y., Moore, R.E., Nagle, D.G, Paul, V.J., Mooberry, S.L., Corbett, T.H. and Valeriote, F.A. 1998. Symplostatin 1. A dolastatin 10 analogue from marine cyanobacterium *Symploca hydnoides*. *J. Nat. Prod.* 61: 1075–1077.

Heading, C.E. 2002. Conus peptides and neuroprotection. *Curr. Opin. Investig. Drugs* 3: 915-920.

Horton, P.A., Longly, R.E., McConnel O.J. and Ballas, L.M. 1994. Staurosporine aglycone (K252-c) and acryriaflavin - A from the marine ascidian *Eudistoma* sp. *Experientia* 50: 843-845.

Ikeda, Y., Matsuki, H., Ogawa, T. and Munakata, T. 1983. Safracins, new antitumor antibiotics. II. Physicochemical properties and chemical structures. *J. Antibiot.* 36: 1284–1289.

Ireland, C., Copp, B., Foster, M., McDonald, L., Radisky, D. and Swersey, J. 1993. Biomedical potential of marine natural products. *In: Marine Biology*. Attaway D, Zeborsky O, Ed.) Vol I, Plenum Press, New York. P.1-43.

Jensen, P.R., Kauffman, C. and Fenical, W. 1996. High recovery of culturable bacteria from the surfaces of marine algae. *Mar. Biol.* 126: 1–7.

Kathiresan, K. 2000. A review of studies on pichavaram mangroves, southeast India. *Hydrobiologia* 430: 185-205.

Kathiresan, K., Boopathy, N.S. and Kavitha, S. 2006. Coastal vegetation–An under-explored source of anticancer drugs. *Nat. Pro. Rad.* 5: 115-119.

Kathiresan, K., Ravindran, V.S. and Muruganantham, A. 2006. Mangrove extracts prevent the blood coagulate! *Ind. J. Biotech.* 5: 252-254.

Kathiresan, K., Thangam, T.S. and Premanathan, M. 1995. Mangrove halophytes: potential source of medicines. *In:* Khan, M.A. and Ungar, I.A. (Eds), *Biology of Salt Tolerant Plants*. University of Karachi, Pakistan. p. 361-370.

Kathiresan, K., Balagurunathan, R. and Masilamaniselvam, M. 2005. Fungicidal activity of marine actinomycetes against phytopathogenic fungi. *Ind. J. Biotech.* 4: 271-276

Kathiresan, K. and Masilamaniselvam, M. 2005. Evaluation of beneficial bacteria from mangrove soil. *Bot. Mar.* 49: 86-88.

Kinnel, R. and Scheuer, P. 1992. 11 hydroxy-staurosporine: a highlycytotoxic, powerful protein kinase C inhibitor from a tunicate. *J. Org. Chem.* 57: 6327-6329.

Kita, M., Watanabe, M., Takada, N., Suenaga, K., Yamada, K. and Uemura, D. 2002. Hedathiosulfonic acids A and B, novel thiosulfonic acids from the deep-sea urchin *Echinocardium cordatum*. *Tetrahedron* 58: 6405-6412.

Kitagawa, I., Kobayashi, M., Kitanaka, K., Kido, M. and Kyogoku. 1983. Marine natural products. XII. On the chemical constituents of the Okinawan marine sponge *Hymeniacidon aldis*. *Chem. Pharm. Bull.* 31: 2321–2328.

Kodama, M., Ogata, T. and Sato, S. 1988. Bacterial production of saxitoxin. *Agric. Biol. Chem.* 52: 1075-1077.

Kodama, M., Ogata, T., Sato, T. and Sakamoto, S. 1990. Possible association of marine bacteria with paralytic shellfish toxicity of bivalves. *Mar. Ecol. Prog. Ser.* 61: 203-206.

Koehn, F.E., Longley, R.E. and Reed, J.K. 1992. Microcolin A and B, new immunosuppressive peptides from the blue green alga *Lyngbya majuscula*. *J. Nat. Prod.* 55: 613-619.

Lawrence, R.N. 1999. Rediscovering natural product biodiversity. *Drug Dis.Tod.* 4**:** 449-451.

Lene, L. 1996. Microbial metabolites-an infinite source of novel Chemistry. *Pure Appl. Chern.* 68: 745-748.

Levina, E.V., Andriyashchenko, P.V., Kalinovsky, A.I., Dmitrenok, P.S. and Stonik, V.A. 2002. Steroid Compounds from the Far Eastern Starfish *Diplopteraster multiples. Russ. J. Bioorg. Chem.* 28: 189-193.

Levina, E.V., Andriyashchenko, P.V., Kalinovsky, A.I., Dmitrenok, P.S., Stonik, V.A. and Prokof'eva, N.G. 2002. Steroid compounds from the starfish *Lysastrosoma anthosticta* collected in the Sea of Japan. *Russ. Chem. Bull.* 51: 535-539.

Luesch, H., Moore, R.E., Paul, V.J., Mooberry, S.L. and Corbett, T.H. 2001. Isolation of dolastatin 10 from the marine cyanobacterium *Symploca* species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1. *J. Nat. Prod.* 64: 907–910.

Lysek, N., Rachor, E., and Lindel, T. 2002. Isolation and Structure Elucidation of Deformylflustrabromine from the North Sea Bryozoan *Flustra foliacea*. *BioSciences* 57: 1056-1061.

Maskey, R.P., Sevvana, M.M., Us´on, I., Helmke, E. and Laatsch, H. 2002. Gutingimycin: A Highly Complex Metabolite from a Marine Streptomycete. *J. Antibiot.* 55: 1031.

McIntosh, J.M. and Jones, R.M., 2001. Cone venom – from accidental stings to deliberate injection. *Toxicon.* 39: 1447–1451.

McIntosh, J.M. Olivera, B.M. and Cruz, L. 1999. Conus peptides as probes for ion channels. *Meth. Enzymol.* 294: 605-624.

Myers, P.A., Cruz, L.Z., Rivier, J.E. and Olivera, B.M. 1993. Conus peptides as chemical probes for receptors and ion channels. *Chem Rev.* 93: 1923-1936.

Narkowicz, C.K., Blackman, A.J., Lacey, E. and Gill, J.H. 2002. Heiland, K Convolutindole A and convolutamine H, new nematocidal brominated alkaloids from the marine bryozoan *Amathia convoluta*. *J. Nat. Prod.* 65: 938-941.

Ortega, M.J., Zubía, E., Ocana, J.M., Naranjo, S. and Salva, J. 2000. New rubrolides from the ascidian *Synoicum blochmanni*. *Tetrahedron* 56: 3963-3967.

Padmakumar, K. andAyyakannu, K. 1997. Antiviral activity of marine plants. *Ind. J. Vir.* 1: 33-36.

Palaniselvam, V. and Kathiresan, K. 1998. Potential of a marine cyanobacterium *Phormidium tenue* (Menegh.) Gomont as a shrimp feed supplement. *Sea. Res. Uti.* 20: 75-78.

Pallenberg, A.J. and White, J.D. 1986. The synthesis and absolute configuration of (+) - leptosphaerin, *Tetrahedron Lett.* 27: 5591-5594.

Patil, A.D., Freyer, A.J., Killmer, L., Hofmann, G. and Johnson, R.K. 1997. Z-Axinohydantoin and debromo-Z-axinohydantoin from the sponge *Stylotella aurantium*: inhibitors of protein kinase C. *Nat. Prod. Lett.* 9: 201–207.

Pettit, G.R., Collins, J.C., Herald, D.L., Doubek, D.L., Boyd, M.R., Schmidt, J.M., Hooper, D.L. and Tackett, L.P. 1992. Isolation and structure of cribostatins1 and 2 from blue marine sponge, *Cribrochalina* sp. *Can. J. Chem.* 70: 1170-1175.

Pettit, G.R., Singh, S.B., Hogan, F., Lloyd-Williams, P., Herald, C.L., Burbett, D.D. and Clewlow, P.J. 1989. The absolute configuration and synthesis of natural (-)-dolostatin10. *J. Am. Chem. Soc.* 70: 5463-5465.

Pickrell, J. 2003. "Wonder Drug" snails face threats, Expert warning. National Geographic News 1-2.

Premanathan, M., Chandra, K., Bajpai, S.K., and Kathiresan, K. 1992. A survey of some Indian marine plants for antiviral activity. *Bot. Mar.* 35: 321-324.

Premanathan, M., Kathiresan, K., Chandra, K. and Bajpai, S.K. 1993. Antiviral activity of marine plants against Newcastle disease virus. *Trop. Biomed.* 10: 31-33.

Premanathan, M., Kathiresan, K. and Chandra, K. 1994a. *In vitro* anti-vaccinia virus activity of some marine plants. *Ind. J. Med. Res.* 99: 236-238.

Premanathan, M., Kathiresan, K., and Chandra, K. 1994b. Anti-viral activity of marine and coastal plants from India. *Inter.J. Pharma.* 32: 330-336.

Premanathan, M., Kathiresan, K. and Chandra, K. 1995. Antiviral evaluation of some marine plants against Semliki forest virus. *Inter. J. Pharma.* 33: 75-77.

Premanathan, M., Nakashima, H., Kathiresan, K., Rajendran, N. and Yamamoto, N. 1996. *In vitro* anti-human immuno deficiency virus activity of mangrove plants. *Ind. J. Med. Res.* 130: 276-279.

Premanathan, M., Kathiresan, K. and Nakashima, H. 1999a. Mangrove halophytes: A source of antiviral substances. *S. Paci. Stu.* 19: 49-57.

Premanathan, M., Arakaki, R., Izumi, H., Kathiresan, K., Nakano, M., Yamamoto, N. and Nakashima, H., 1999b. Antiviral properties of a mangrove plant, *Rhizophora apiculata* Blume, against human immunodeficiency virus. *Antiviral Res.* 44: 113-122.

Proksch, P., Edrada, R.A. and Ebel, R. 2002. Drugs from the seas—current status and microbiological implications. A*ppl. Microbiol. Biotechnol.* 59: 125-134.

Proteau, P.J., Gerwick, W.H., Garcia-Pichel, F. and Castenholz, R.W. 1993. The structure of scytonemin, an ultraviolet sunscreen pigment from the sheaths of cyanobacteria. *Experientia* 49: 825–829.

Rajaganapathi, J., Kathiresan, K. and Singh, T.P. 2002. Purification of Anti-HIV Protein from purple fluid of Sea Hare *Bursatella leachii* de Blainville. *Mar. Bio. Tech.* 4: 447-453.

Ravikumar, S., Kathiresan**,** K., Ignatiammal, S.T.M.,.Selvam, M.B and Shanthy, S. 2004. Nitrogen-fixing azotobacters from mangrove habitat and their utility as marine biofertilizers. *J. Exp. Mar. Bio. Eco.* 312: 5-17.

Rinehart, K.L., 2000. Antitumor Compounds from Tunicates. *Med. Res. Rev.* 20: 1-27.

Rinehart, K.L., Jr, Gloer, J.B., Hughes, R.G.,. Jr, Renis, H.E., McGovren, J.P., Swynenberg, E.B., Stringfellow, D.A., Kuentzel, S.L. and Li, L.H. 1981. Didemnins: antiviral and antitumor depsipeptides from a Caribbean tunicate. *Science* 212: 933–935.

Rinehart, K.L., Shield, L.S. and Cohen-Parsonsm, M. 1993. Antiviral substances *In*: Attaway, D. and Zaborsky, O., (Ed.), *Marine Biotechnology*. II, Plenum Press, New York. P. 309-342.

Sakagami, H., Kashimata, M., Toguchi, M., Satoh, Odanaka, Y., Ida, Y., Premanathan, M. Arakaki, R., Kathiresan, K., Nakashima, H., Komatsu, N., Fujimaki, M. and Yoshihara, M. 1998. Radical Modulation activity of lignins from a mangrove plant *Ceriops decandra* (Griff.) Ding Hou. *In vivo* (Japan) 12: 327-332.

Sakai, R., Rinehart, K.L., Guan, Y. and Wang, A.H.J. 1992. Seven new didemnins from the marine tunicate *Tridemnin solidum*. *Proc. Nat. Acad. Sci. USA.* 89: 11456-11460.

Sato, S., Kuramoto, M. and Ono, N. 2006. Ircinamine B, bioactive alkaloid from marine sponge *Dactylia* sp. *Tetrahedron Lett.* 47: 7871–7873.

Schiehser, G.A., White, J.D., Matsumoto, G., Pezzanite, J.O. and Clardy, J. 1986. The structure of leptosphaerin, *Tetrahedron Lett.* 27: 5587-5594.

Simudu, U., Kita-Tsukamoto, K., Yasumoto, T. and Yotsu, M. 1990. Taxonomy of four marine bacterial strains that produce tetrodotoxin. *Int. Syst. Bacteriol.* 40: 331-336.

Sorek, H., Rudi, A., Gueta, S., Reyes, F., Martin, M.J., Aknin, M., Gaydou, E., Vacelet, J. and Kashmana, Y. 2006. Netamines A–G: seven new tricyclic guanidine alkaloids from the marine sponge *Biemna laboutei. Tetrahedron* 62: 8838–8843.

Takada, N., Watanabe, M., Suenaga, K., Yamada, K., Kita, M. and Uemura, D. 2001. Isolation and structures of hedathiosulfonic acids A and B, novel thiosulfonic acids from the deep-sea urchin *Echinocardium cordatum*. *Tetrahedron Lett.* 42: 6557-6560.

Thangam, T.S. and Kathiresan, K. 1988. Toxic effect of mangrove plant extracts on mosquito larvae *Anopheles stephensi L. Curr. Sci.* 47: 914-915.

Thangam, T.S. and Kathiresan, K. 1989. Larvicidal effect of marine plant extracts on mosquito *Culex tritaeniorhynchus. J. Mar. Bio. Asso. Ind.* 31: 306-307.

Thangam, T. S. and Kathiresan, K. 1992a. Mosquito larvicidal activity of mangrove plant extract against *Aedes aegypti. Inter. Pest Cont.* 4: 116-119.

Thangam, T. S. and Kathiresan, K. 1992b. Smoke repellency and killing effect of marine plants against *Culex quinquefasciatus. Trop. Biomed.* 9: 35-38.

Thangam, T.S. and Kathiresan, K. 1993a. Repellency of marine plant extracts against *Aedes aegypti. Inter. J. Pharma.* 31: 321-323.

Thangam, T.S. and Kathiresan, K. 1993b. The mosquito composition and seasonal distribution of *Culex quinquefasciatus* in a coastal town of south India. *Trop. Bio.* 10: 175-177.

Thangam, T.S. and Kathiresan, K. 1994. Mosquito larvicidal activity of *Rhizophora apiculata* Blume. *Inter. J. Pharma.* 32: 33-36.

Thangam, T.S. and Kathiresan, K. 1997. Mosquito larvicidal activity of mangrove plant extracts and synergistic activity of *Rhizophora apiculata* with pyrethrum against *Culex quinquefasciatus. Inter. J. Pharma.* 35: 1-3.

Thangam, T.S. Srinivasan, K. and Kathiresan, K. 1992. Smoke repellency and killing effect of mangrove plants against the mosquito *Aedes aegypti* Linnaeus. *Trop. Biomed.* 10: 125-128.

Uechi, G., Toma, H., Arakaw, T. and Sato, Y. 2005. Biochemical and physiological analyses of a hemolytic toxin isolated from a sea anemone *Actineria villosa. Toxicon*. 45: 761–766.

Unson, M.D. and Faulkner, D.J. 1993. Cyanobacterial symbiont biosynthesis of chlorinated metabolites from *Dysidea herbacea* (Porifera). *Experientia* 49: 349-353.

Urban, S., Blunt, J.W. and Munro, M.H.G. 2002. Coproverdine, a novel, cytotoxic marine alkaloid from a New Zealand ascidian. *J. Nat. Prod.* 65: 1371-1373.

Vacelet, J. 1975. Etude en microscopie électronique de l'association entre bactéries et spongiaires du genre *Verongia* (Dictyoceratida). *J. Micro. Biol. Cell.* 23: 271–288.

Vacelet, J. and Donadey, C. 1977. Electron microscope study of the association between some sponges and bacteria. *J. Exp. Mar. Ecol.* 30: 301–314.

Vanisree, M. and Subbaraju, G.V. 2002. Alcyonacean Metabolites VIII: Antibacterial metabolites from *Labophytum crassum* of the Indian Ocean. *Asian. J. Chem.* 14: 957-960.

Wilkinson, C.R. 1992. Symbiotic interactions between marine sponges and algae *In*: Reisser, W. (Ed.) *Algae and Symbioses Biopress.* Bristol. P. 112–151.

Williams, D.H. and Faulkner, D.J. 1996. Isomers and tautomers of hymenialdisine and debromohymenialdisine. *Nat. Prod. Lett.* 9: 57–64.

Wright, A.D., Goclik, E., Konig, G.M. and Kaminsky, R., 2002. Lepadins D-F: Antiplasmodial and antitrypanosomal decahydroquinoline derivatives from the tropical marine tunicate *Didemnum* sp. *J. Med. Chem.* 45: 3067-3072.

Yamada, K., Okija, M., Kigoshi, H. and Suenaga, K. 2000. Cytotoxic Substances from Opisthobranch Molluscs, *In*: Fusetan, N, Karger, A.G., (Ed.). *Drugs from the Sea*. Basel P. 59-73.