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REVIEW PAPER-MARINE MICROBIAL BIOACTIVE COMPOUNDS

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ABSTRACT

Oceans have borne most of the biological activities on our planet. A number of biologically active compounds with varying degrees of action, such as anti-tumor, anti-cancer, anti-microtubule, anti-proliferative, cytotoxic, photo protective, as well as antibiotic and antifouling properties, have been isolated to date from marine sources. The marine environment also represents a largely unexplored source for isolation of new microbes (bacteria, fungi, actinomycetes, microalgae-cyanobacteria and diatoms) that are potent producers of bioactive secondary metabolites. Extensive research has been done to unveil the bioactive potential of marine microbes (free living and symbiotic) and the results are amazingly diverse and productive. 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. Recent years have seen the introduction into clinical trials of new classes of chemotherapeutic agents, which are derived from marine sources and have novel mechanisms of action. Among other biological activities, the marine ecosystem is increasingly being acknowledged as a source of potential antimicrobial agents. Available treatments for many infectious diseases caused by bacteria, fungi and viruses are limited. Research on new antimicrobial substances must therefore be continued and all possible strategies should be explored. In this review, we will present the structures and antimicrobial activity of natural compounds isolated from marine sources

KEYWORDS: Marine environment, Secondary metabolites, Biological activities.

INTRODUCTION

Infectious diseases caused by bacteria, fungi and viruses are still a major threat to public health, despite the tremendous progress in human medicine. Their impact is particularly large in developing countries due to the relative unavailability of medicines and the emergence of widespread drug resistance. As a result of the continuous evolution of microbial pathogens towards antibiotic-resistance, there have been demands for the development of new and effective antimicrobial compounds. The molecular architectures of the β-lactams (penicillins, cephalosporins, carbapenems, monobactams), polyketides (tetracycline), phenylpropanoid (chloramphenicol), aminoglycosides (streptomycin), macrolides (erythromycin), glycopeptides (vancomycin), streptogramins (pristinamycin) and, most recently, the lipopeptides (daptomycin) and glycylcyclines (tegicycline) are borrowed from natural products. The other three classes, the sulfonamides, quinolones (ciprofloxacin) and oxazolidinones (linezolid), have no precedent in Nature. Following the discovery of most antimicrobial classes in the 1940s to 1960s, the so-called “Golden Age” of antimicrobial research, the arsenal of compounds for the treatment of microbial infections in humans was deemed sufficient.

In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, bryozoans, sea slugs and marine organisms. 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. (Rajeev Kumar Jha and

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Xuzi-rong (2004) 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. (Proksch *et al*., 2002) It is noteworthy that marine sources have also demonstrated tremendous abilities as producers of anti-cancer compounds and secondary metabolites which act against infectious diseases and inflammation. Blunt *et al.* (2004) listed that in marine environment sponges (37%), coelenterates (21%) and microorganisms (18%), are major sources of biomedical compounds, followed by algae (9%), echinoderms (6%), tunicates (6%), molluscs (2%) bryozoans (1%), *etc.* (Smith *et al*., 2010). However, marine microorganisms have not been given the attention they deserve and a very limited insight into the capabilities and bioactive potential of marine microorganisms is available in literature to date. There is still scope for a higher magnitude of research and investigation to explore the potential of both marine organisms and marine microorganisms as producers of novel drugs. Marine fungi have been explored to a much lesser ex-tent than their terrestrial counterparts, such as those for use in treatment of human diseases as well as several others in biotechnological applications (Aline *et al*., 2008). Hence, we tried to review the research carried out so far regarding marine fungi and their bioactive compounds. Previous literature shows that marine-derived fungi have been recognized as one of the tapped sources for new biologically active secondary metabolites including anti-tumor, antibacterial, antiviral, antifungal, anti- inflamma-tory and anticancer activities and enzyme inhibitor com-pounds. Clodepsipeptide(1) isolated from the marine fungus, *Clonostachys* sp. is having anti cancer activity (Samuel *et al*., 2011). Until 1991, only 321 species of obligate marine fungi had been described, of which 11 belong to the class Ascomycete, which are found in shal-low waters. Facultative marine fungi have been explored to a lesser extent, and only 56 species have been des-cribed until 1999 (Aline *et al*., 2008). Between 2000 and 2005, approximately 100 marine fungal metabolites were described and between 2006 and 2010, a total of 690 natural products were reported as being isolated from fungi in marine habitats (Katia *et al*., 2012). Marine fungi have attracted great attention as considerable resources from only few decades. Recent investigations on marine filamentous fungi looking for biologically active secondary metabolites indicate their tremendous potential as a source of new medicines even at low concentrations of their secondary metabolites (Swathi *et al*., 2013).

MARINE MICROORGANISMS AS PRODUCERS OF BIOACTIVE COMPOUNDS

Most of the developed and underdeveloped countries have since shifted their focus to the marine habitat and new marine oriented programs are emerging worldwide. Major classes of microbes like bacteria and fungi are now the target of biomedical study and intriguing novel metabolites are being produced. Coastal bacterial samples grown under saline conditions have been reported to yield new antibiotics, antitumor, and anti-inflammatory compounds (Pathirana *et al*., 1992; Trischman *et al.*, 1994a; Trischman *et al.*, 1994b;) In fact, the symbiotic microbial consortia also prove to be a source of bioactive compounds with pharmaceutical potential. Bacteria and fungi have been sampled from the surfaces of marine plants and the internal tissues of invertebrates and, in particular, marine fungi seem to be of increasing interest (Numata *et al.*, 1992; *Cheng et al*., 1994; Kakeya *et al*., 1995; Takahashi et al., 1995; Belofsky *et al*., 1998)

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. More than 5,300 different products are known from sponges and their associated microorganisms, and more than 200 new metabolites from sponges are reported each year. The chemical diversity of sponge products is remarkable. In addition to the unusual nucleosides, bioactive terpenes, sterols, peptides, alkaloids, fatty acids, peroxides and amino acid derivatives (all of them frequently halogenated) have been described from sponges. Their early appearance in evolution has given them considerable time for the development of an advanced chemical defence system. It is interesting to note that the synthesis of secondary metabolites is regulated according to the conditions that the sponge experiences. The huge number of different secondary metabolites discovered in marine sponges and the complexity of the compounds and their biosynthetic pathways can be regarded as an indication of their importance for survival. As infectious microorganisms evolve and develop resistance to existing pharmaceuticals, marine sponges provide novel leads against bacterial, fungal and viral diseases (Laport *et al*., 2009; Sagar *et al.*,2010).

Algae

Algae are very simple chlorophyll-containing organisms composed of one cell, grouped together in colonies or asorganisms with many cells, sometimes collaborating together as simple tissues. They are found everywhere on

earth: in the sea, rivers and lakes, on soil and walls, in animal and plants (as symbionts-partners collaborating together); in fact just about everywhere where there is a light to carry out photosynthesis. 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.(Strik *et al*., 2006; Dharmananda *et al*., 2007) 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*. (Maruyama *et al*., 1984) 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.(Lara Isassi *et al*., 2000). Marine algae produce a cocktail of metabolites with interesting biological activities (antiinfective, antiinflammatory, antiproliferative,…) and with potential commercial value (Cardozo *et al*., 2007; Nair *et al*., 2007; El Gamal *et al*., 2010; Nunnery *et al.*, 2010) . Structures exhibited by these compounds range from acyclic entities with a linear chain to complex polycyclic molecules and included bioactive terpenes, phenolic compounds, alkaloids, polysaccharides and fatty acids. Their medical and pharmaceutical application has been investigated for several decades. Many of these secondary metabolites are halogenated, reflecting the availability of chloride and bromide ions in seawater (Cabrita *et al*., 2010).

Microorganisms

Marine bacteria: Bacteria produce some secondary metabolites for their defense against other microorganisms and these secondary metabolites serve as a source of bioactive compounds for use in human therapies. Marine bacteria are prolific producers of such secondary metabolites as they thrive in harsh oceanic climates. *Pseudomonas* are gram-negative Gammaproteobacteria dwelling on lithosphere as well as in a marine environment. Compared to terrestrial isolates, the marine isolates are not well explored and only a limited number have been reported as producers of bioactive compounds. Marine *Pseudomonas* derived bioactive substances are diverse, including pyrroles, pseudopeptide pyrrolidinedione, phloroglucinol, phenazine, benzaldehyde, quinoline, quinolone, phenanthren, phthalate, andrimid, moiramides, zafrin and bushrin (Romanenko *et al*., 2008a). Some of these bioactive compounds are antimicrobial agents, and dibutyl phthalate and di-(2-ethylhexyl) phthalate have been reported to be cathepsin B inhibitors (Isnansetyo *et al*., 2009a). Bacteria not only produce secondary metabolites against other organisms, but they also produce certain compounds which help in cleaning their environment. Certain marine bacterial species are known as prolific producers of biosurfactants, bioemulsifiers and exopolysaccharides. Das *et al.* (2008) studied the degradation of a model polyaromatic hydrocarbon, anthracene, an organic pollutant, by a marine *Bacillus circulans* strain. In addition, the produced biosurfactant depicted a high degree of emulsification of various hydrocarbons. It was observed that this bacterium utilized anthracene as a carbon substrate for the production of biosurfactant (Das *et al*., 2008). This group also investigated another biosurfactant producing marine bacterium with an ability to remove metal from solutions with efficiency dependent on the concentration of the metal as well as on the biosurfactant (Das *et al*., 2009).

Marine fungi:

Marine derived fungi have been widely studied for their bioactive metabolites and have proven to be a rich and promising source of novel anticancer, antibacterial, antiplasmodial, anti-inflammatory and antiviral agents (Bhadury *et al*.,2006; Newman *et al*., 2006) . Some marine fungi have unique new carbon frameworks which are exceptional in nature. Compounds produced by such fungi are of interest as new lead structures for medicine as well as for plant protection. Responding to the great demand for natural compounds from marine derived fungi, Kjer *et al.* (2010) have defined a detailed protocol for their isolation and cultivation from various marine organisms (sponges, algae and mangrove plants) in order to characterize and elucidate the structure of secondary metabolites produced by these fungi (Kjer *et al.* (2010) . A couple of years ago, Du *et al.* (2007) isolated a novel anthraquinone derivative with naphtho[1,2,3-de]chromene-2,7-dione skeleton, and named it aspergiolide A. It was isolated from a marine filamentous fungus, *Aspergillus glaucus* in the Fujian province of China, and was found to exhibit cytotoxicity against K562 and P388 cell lines (Du *et al.* (2007). The same group has recently worked

on the antitumor activities of alkaloids isolated from a *Penicillium sp.* derived from deep ocean sediment. They isolated two new meleagrin analogs, meleagrin D and E, and two new diketopiperazines, roquefortine H and I which showed weak cytotoxicity as compared to the previously reported meleagrin B and meleagrin that induced HL-60 cell apoptosis or arrested the cell cycle through G2/M phase, respectively. They proposed that the distinct substitutions on the imidazole ring could have a significant influence on the cytotoxicity of these alkaloids (Du et al., 2010). A number of novel compounds and metabolites with bioactive potential continue to be isolated and characterized from marine derived fungi, which are capable of producing not only antimicrobial but also antifouling compounds. In 2006, a bioassay-guided isolation and purification procedure was used to obtain a novel antifouling and antimicrobial compound from a marine-derived fungus *Ampelomyces sp*. The isolate, 3-chloro-2,5-dihydroxybenzyl alcohol effectively inhibited larval settlement of the tubeworm *Hydroides elegans* and of cyprids of the barnacle *Balanus amphitrite* and was non-toxic; suggestive of a potent antifoulant and/or antibiotic activity(Kwong *et al*., 2006).

Marine fungi have also been reported to have a nematicidal effect, for example, nematicidal and antimicrobial metabolites were reported previously from marine ascomycete *Lachnum papyraceum* (Karst.) Karst III and the production of novel isocoumarin derivatives was achieved under halogenated conditions (Stadler *et al*., 1995). Inspired by this work, Nenkep *et al.* (2010) recently reported the isolation of halogenated benzoquinones (bromochlorogentisylquinones A and B), with significant radical scavenging activity against DPPH, from a marine derived *Phoma herbarum* strain (Nenkep *et al.* (2010).

Actinomycetes

Actinomycetes from natural sources are widely recognized to produce secondary metabolites, including many antimicrobials such as streptomycin, erythromycin, and tetracycline, with original and ingenious structures and potent biological activities (Takahashi *et al*., 2003).Therefore, actinomycetes are considered to be a potent resource for new lead compounds in drug development. Many marine isolates of actinomycetes have been reported to be producers of novel antitumor (Olano *et al*.,2009), antimalarial and antimicrobial agents. In the exploration of marine derived actinomycetes as a source of antitumor compounds, Cho *et al.* (2007) isolated four new 3-methyl-4-ethylideneproline-containing peptides, Lucentamycins A-D from the fermentation broth of a marine derived actinomycete, *Nocardiopsis lucentensis* (strain CNR-712). Out of the four compounds, Lucentamycins A and B were observed to have significant *in vitro* cytotoxicity against HCT-116 human colon carcinoma (Cho *et al*., 2007).In a report published last year, five isoquinoline quinones, four new derivatives, Mansouramycin A-D, and the known 3-methyl-7- (methylamino)-5,8-isoquinolinedione were isolated from the ethyl acetate extract from the marine derived Mei37 isolate of *Streptomyces* sp. These isolated compounds, when subjected to cytotoxicity analysis against 36 tumor cell lines, indicated significant cytotoxicity with great degree of selectivity for non-small cell lung cancer, breast cancer, melanoma, and prostate cancer cells (Hawas *et al*., 2009). Suggesting their potential as anticancer drugs.

Marine actinomycetes are not only known for their anti-tumor and anti-cancerous potential, they are well documented as antimicrobial agents too. A California based study was successful in isolating a series of chlorinated bisindole pyrroles, Lynamicins A–E from a novel strain of a marine actinomycete, *Marinispora*. This isolate from marine sediment collected off the coast of San Diego (California) demonstrated broad-spectrum activity against both Gram-positive and Gram-negative organisms. When tested for their antimicrobial spectrum against a panel of 11 pathogens, these compounds showed activity against drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* (McArthur *et al*., 2008). Carlson *et al.* (2009) have reported the isolation of novel dienoyl tetramic acids tirandamycin C and tirandamycin D with activity against vancomycin-resistant *Enterococcus faecalis*, from the marine environmental isolate *Streptomyces* sp. 307-9. These compounds were structurally similar to the previously identified compounds Tirandamycins A and B with a slight variation in the pattern of pendant oxygenation on the bicyclic ketal system (Carlson *et al*., 2009).

ANTI-INFECTIVE COMPOUNDS

Terpenoids : Amongst the vast array of marine natural products, the terpenoids are one of the more commonly reported and discovered to date. During the formation of terpenoids, the isoprene units are usually linked in a head-to-tail manner, and the number of units incorporated into a particular unsaturated hydrocarbon terpenoid serves as a basis for the classification of these compounds: monoterpenoids (C10), sesquiterpenoids (C15), diterpenoids (C20), sesterterpenoids (C25), meroterpenoids (C26),… A survey of current available chemical data suggest that sesterterpenoids, sesquiterpenoids and meroterpenoids are the main classes of antimicrobial and

antiviral terpenoids found in the marine environment. Marine sesterterpenoids are frequently occurring, particularly in marine sponges, and they show prominent bioactivities, including antimicrobial and antiviral properties (Ebada *et al*., 2010). Lee *et al.*2008 isolated seven sesterterpenes sulphates from the tropical sponge *Dysidea* sp., and investigated their inhibitory activities against isocitrate lyase from *Candida albicans*. Most of the compounds were found to be strong isocitrate lyase inhibitors, and also showed potent antibacterial effect against *Bacillus subtilis* and*Proteus vulgaris*. Another bioactive sesterterpenoid is hyrtiosal, isolated from the marine sponge *Hyrtios erectus*, which inhibits HIV integrase (IN) binding to viral DNA by a new inhibitor binding site (Du *et al*., 2008). Molecular dynamic analysis correlated with a site-directed mutagenesis approach further revealed that such hyrtiosal-induced viral DNA/IN binding inhibition was caused by the fact that hyrtiosal could bind HIV N-terminal domain at Ser17, Trp19 and Lys34. As hyrtiosal was recently discovered as a protein tyrosine phosphatase 1B inhibitor, this work might also supply multipletarget information for this marine natural product. Reports of other antimicrobial terpenoids isolated from marine sponges also included meroterpenoids. During an investigation aimed at discovering new antimicrobial agents from marine organisms, Zhang *et al.* isolated fascioquinols A-F as bioactive meroterpenes from a deep-water southern Austalian marine sponge *Fasciospongia* sp. Fascioquinols B, C and D are a series of new acid mediated hydrolysis/cyclization products of fascioquinol A. Two of these compounds, fascioquinol A and B displayed promising Gram (+) selective antibacterial activity against *Staphylococcus aureus* (inhibitory concentration 50 IC50 0.9-2.5 μM) and *Bacillus subtilis* (IC50 0.3-7 μM). Four new meroterpenes, alisiaquinones A-C and alisiaquinol were isolated from a New Caledonian deep water sponge (Desoubzdanne et al.,2008) The compounds displayed μM range activity on two enzymatic targets of importance for the control of malaria, the plasmodial kinase Pfnek-1 and a protein farnesyl transferase, as well as on different chloroquine-sensitive and –resistant strains of *Plasmodium falciparum*. Examples of another antimicrobial terpenoid of marine sponge origin also included diterpene and diterpene isonitriles from the tropical marine sponge *Cymbastela hooperi* (Wright *et al*., 2011).

Steroids: Steroid glycosides are a class of widespread natural products having either terrestrial or marine origins. Several cardiac glycosides are used therapeutically in the treatment of cardiac failure and atrial arrhytmias, and many glycoside compounds, belonging to other structural groups, show cytotoxic, antimicrobial, hypocholesterolemic and other biological activities. Most marine steroid glycosides were isolated not from pants, but from invertebrates such as echinoderms, sponges and soft corals, and are one of the most important chemical constituents of microalgae (Ivanchina *et al*., 2011) Phytochemical and pharmacological studies have been undertaken in order to reveal the presence of steroids with antimicrobial activity. These reports mainly concerned their antifungal activity. Eurysterols A and B are two new steroidal sulphates isolated from an undescribed marine sponge of the genus *Euryspongia* collected in Palau (Boonlarppradab *et al*., 2007) The compound exhibited antifungal activity against amphotericin B-resistant and wild-type strains of *Candida albicans*, with MIC values in turn of 15.6 and 62.5 μg/ml. Bioassay-guided fractionation of the extract of *Topsentia* sp. led to the identification of two new sulphated sterols, geodisterol-3-*O*-sulphite and 29-demethylgeodisterol-3-*O*-sulphite, as active constituents reversing efflux pumpmediated fluconazole resistance (Digirolamo et al., 2009)Both compounds enhanced the activity of fluconazole in a *Saccharomyces cerevisiae* strain overexpressing the *Candida albicans* efflux pump MDR1, as well as in a fluconazole-resistant *Candida albicans* clinical isolate known to overexpress MDR1.

Phenolic compounds: Phenols probably constitute the largest group of plant secondary metabolites. Widespread in nature, and found in most classes of natural compounds having aromatic moieties, they range from simple structures with one aromatic ring to highly complex polymeric substances. Phenolic compounds, occasionally incorporating halogen, occur frequently in marine environment. In recent years, a large number of studies have been performed concerning the antimicrobial activity of phenolic compounds isolated from marine sponges, mainly antibacterial activity. 2-(2',4'-dibromophenoxy)-4,6-dibromophenol isolated from the marine sponge *Dysidea granulosa* collected off the coast of Lakshadweep Islands, Indian Ocean, exhibited potent and broad spectrum *in vitro* antibacterial activity, especially against methicillin-resistant and –sensitive *Staphylococcus aureus*, vancomycin-resistant and –sensitive *Enterococci* and *Bacillus* sp (Shridhar *et al*., 2009). From another *Dysidea* species collected from the Federated States of Micronesia, a new polybrominated diphenyl ether was isolated (Zhang *et al*., 2008).These compounds exhibited inhibitory activities against *Streptomyces* 85E in the hyphae formation inhibition assay. These type of compounds were also isolated from the Indonesian sponge *Lamellodysidea herbacea* (Hanif *et al*., 2007). These metabolites showed potent antimicrobial activity against *Bacillus subtilis*. For the studies of structure-activity relationships, it can be deduced that the presence of two phenolic hydroxyl groups and bromines at C-2 and/or C-5 is important for the exhibition of antibacterial activity. These type of compounds have also been reported from marine bacteria, such as 4,4',6-tribromo-2,2'-biphenol

isolated from an extract of a marine *Pseudoalteromonas* sp. CMMED 290, which displayed significant antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (Feher *et al*., 2010).From another *Pseudoalteromonas* species, the marine bacterium *Pseudoalteromonas phenolica* O-BC30T, Isnansetyo and Kamei (Isnansetyo *et al*., 2009).isolated 2,2',3-tribromo-biphenyl-4,4'- dicarboxylic acid. The compound exhibited anti-methicillin-resistant *Staphylococcus aureus* activity against all ten clinical isolates of these microorganisms, with MIC values between 1 and 4 µg/ml. The compound was also highly active against *Bacillus subtilis* and *Enterococcus serolicida*, but was inactive against Gram (-) bacteria and fungi. Reports of other antimicrobial phenolic compounds isolated from the marine environment also included anthraquinones, coumarins and flavonoids. Some of these compounds have been isolated by bioassay-guided fractionation after previously detecting activity on the marine extracts. As part of an ongoing search for bioactive metabolites from the fungus *Arpergillus versicolor* derived from a marine sponge *Petrosia* sp., five anthraquinones were isolated by bioactivity-guided fractionation. Some of these compounds exhibited antibacterial activity against several clinically isolated Gram (+) strains with MIC values of 0.78-6.25 µg/ml. From another *Aspergillus* species, the marine-derived fungus *Aspergillus* sp. strain 05F16 collected at the coral reef of Manado, Indonesia, two new hexahydroanthrones, tetrahydrobostrycin and 1-deoxytetrahydrobostrycin were isolated (Xu *et al*., 2008) Tetrahydrobostrycin showed weak antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, and 1-deoxytetrahydrobostrycin against *Staphylococcus aureus*.

Alkaloids: Alkaloids represents a group of natural products that has had a major impact throughout history on the economic, medical, political and social affairs of humans. Alkaloids are difficult to define because they do not represent a homogeneous group of compounds from either the chemical, biochemical or physiological viewpoint. Consequently, except for the fact that they are all nitrogenous compounds with a limited distribution in nature, reservations must be appended to any general definition. Marine organisms and microorganisms are known to be a rich source of alkaloids with unique chemical feature and pronounced chemical activities, all of which suggests their potential value as lead structures for the development of new pharmaceuticals. Many of these compounds have potential pharmacological effects, including antimicrobial and antiviral properties. Marine sponges are proving to be productive sources of many interesting antimicrobial active nitrogen-containing heterocyclic compounds, including alkylpiperidine, bromopyrrole and pyrroloiminoquinone alkaloids. In the search for antimicrobial agents against dormant *Mycobacterium tuberculosis*, halicyclamine A was re-discovered as a lead for anti-tuberculosis agent from a marine sponge of *Haliclona* sp. on the guidance of the constructed bioassay (Arai *et al*., 2008) Halicyclamine A showed growth inhibition against *Mycobacterium smegmatis*, *Mycobacterium bovis* and *Mycobacterium tuberculosis*, with MIC in the range of 1-5 µg/ml under both aerobic condition and hypoxic condition inducing dormant state. The growth-inhibitory activity of halicyclamine A was bactericidal and did not exhibit crossresistance with the currently used anti-tuberculosis drugs of isoniazid, ethambutol, rifampicin and streptomycin. More recently, this sponge yielded a new tetracyclic alkylpiperidine alkaloid, 22-hydroxyhaliclonacyclamine B, together with two known alkaloids, haliclonacyclamine A and B as anti-dormant mycobacterial substances (Arai *et al*., 2009).For the studies of structure-activity relationships, it can be deduced that the 22-hydroxy group in position 1 was found to reduce antimycobacterial activity, because 22-hydroxyhaliclonacyclamine B exhibited weaker antimicrobial activities against *Mycobacterium tuberculosis*. Examples of other antimicrobial alkaloids from *Haliclona* sp. also included haliclonin A, which exhibited antibacterial activity against diverse microbial strains (Jang *et al*., 2009).

Polyketides: Polyketides are an important class of secondary metabolites with an enormous impact in the pharmaceutical industry due to their high commercial value. The macrolide antibiotics amphotericin, nystatin and rapamycin are famous examples of this class of natural products employed in human therapy as immunosuppressant, antibiotics and antifungals. Phytochemical studies showed the ability of marine sponges to produce and store polyketide as polycyclic ether macrolides and open-chain polyketides. Some of these compounds showed strong antimicrobial and antiviral activities, and have been isolated by bioassay-guided fractionation after previously detecting activity on the sponge extracts. Bioassay-directed fractionation of South Pacific marine sponges of the genus *Xestospongia*, has led to the isolation of a number of halenaquinone-type polyketides, including two new derivatives named xestosaprol C methylacetal 7 and orholquinone 8 (Longeon *et al*., 2010) Orholquinone 8 displayed a significant inhibition of both human and yeast farnesyl transferase enzymes, with IC50 value of 0.40 µM, and was a moderate growth inhibitor of *Plasmodium falciparum*. A new marinederived macrolide designated neopeltolide, has been isolated from a deep-water sponge of the family Neopeltidae (Wright *et al*., 2007). The compound inhibited the growth of the fungal pathogen *Candida albicans*, with a MIC of 0.62 µg/ml. Other antifungal polyketides are 7-*O*-methylkoninginin D and trichodermaketones A-D isolated from the marine-derived fungus *Trichoderma koningii*, which showed synergistic antifungal activity

against *Candida albicans*, with 0.05 µg/mlketoconazole **(**Song *et al*., 2010).Trichodermaketones A and B are unprecedented polyketides with a bistetrafuran-containing tricyclic skeleton. A new 24-membered macrolide, macrolactin T, and a new polyene δ-lactone, macrolactin U, along with macrolactins A, B, D, O and S were isolated from the cultured broth of the bacterium *Bacillus marinus*, which was isolated from Suaeda salsa collected on the coastline of Bohai sea of China.

FUTURE PERSPECTIVES AND CONCLUDING REMARKS

As evidenced from past and ongoing research, microbial consortium has an excellent plethora of bioactivity. A number of past reviews have focused the attention of researchers on this tremendous treasure of the marine microbial environment But there is still a long way to go. Although a diversified range *viz.*, antibiotic, antifungal, cytotoxic, neurotoxic, antimitotic, antiviral, antineoplastic and antiprotozoal activity is known, extensive studies are still needed in the field of AIDS, immunosuppression, anti-inflammation, Alzheimer disease and ageing processes (Kelecom *et al*., 2002). Efforts are needed to expand the marine microbes derived drug discovery to include other diseases, which need extensive and urgent attention in terms of new therapies. The approach needs to be more focused and organized to combat multi drug resistance and a serious threat of re-emerging infectious diseases, which is a growing concern in the medical fraternity. Advances have begun in the field of marine microbial biotechnology but a more extensive and focused approach is needed to investigate what else the marine microbes have to offer. A recent report suggested the production of bioactive peptides from marine yeast *Aureobasidium pullulans* HN2-3. The peptides produced from single-cell protein of marine yeast strain G7a had good angiotensin-converting enzyme inhibitory activity (Ni *et al*., 2009). Thorough research in the field of bioactive peptides from marine microbes may open the gates for many future implications in the field of biomedical sciences. In fact, microbial biofilms also have a number of technological applications which could be looked into. Many signal transduction pathways involved in the production of marine microbial antifouling compounds can be worked out through a more specific research on biofilms. It is believed that once genetic regulation of the colonization process is better understood, chemicals can be identified and applied that will directly interfere with genetic transcription itself or inhibit or foster any step along the signal transduction pathway (Qian *et al.*, 2007). As any other chemical reaction or metabolic process, production of secondary metabolites also depends upon certain physico-chemical factors *viz*., amount of oxygen available, optimum temperature and pH. The appropriate maintenance of these parameters may enhance metabolite production. Moreover, the pharmaceutical industry is now concentrating on traditional mutagenesis programs for strain and product yield improvement. Genetic engineering could prove to be a boon for improvement in the yield of bioactive metabolites as the biosynthetic pathways can now be manipulated through recombinant DNA technology. It is worth giving serious consideration to the exploitation of marine microbial life and the associated secondary metabolites, aided by genomic analyses, applying metabolic approach and employing combined biomedical and biotechnological efforts, which would lead to discovery of some novel, lead compounds of a varied degree of bioactivity. The novel bioactive metabolites isolated and characterized from marine microbes would be useful in controlling human diseases and protecting human health by solving tribulations associated with antibiotic resistance. Certain bioactive metabolites may also be beneficial in ensuring environmental hygiene (antifouling compounds). The development of more automated and more affordable techniques for isolating and characterizing marine microbial bioactive metabolites would definitely make marine microbial natural product extracts more accessible to natural products‟ chemists and make life more disease free and worth living for mankind.

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