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DIVERSITY IN BIOACTIVE METABOLITES FROMMARINE FUNGI

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ABSTRACT

Microorganisms from marine environments have high diversity with millions of varied species in producing naturally bioactive metabolites like terpenes, quinones, xanthones, coumarins and isocoumarins, chromones, aflatoxins and alkaloids. In point of ecological and biotechnological view current research is sighting in to development of new drugs from marine region which is still attracting the researchers. Fungi are heterotrophic eukaryotes play an ecological role in the decomposition of plants and to a less extent on animal tissues that leads to the release of nutrients back into the ecosystem. The fungal isolates from marine environments are a source of novel and potential bioactive secondary metabolites, which are life-saving like antibacterial, antifungal, antiviral, antiprotozoal and anticytological compounds playing a possible role in disease suppression. More than 23,000 secondary bioactive metabolites are reported out of 17,000 antibiotics were discovered from microorganisms. This review focuses mainly on Marine fungi and its natural products in drug discovery and various isolating techniques to carry out production of potential bioactive compounds.

INTRODUCTION

The oceanic region occupies more than 70% of the Earth's surface, with an incomparable biological diversity, accounting about 95% of the whole biosphere (Qasim, 1999). Among these wide-ranging biological diversities, microbial diversity from marine region constitutes an infinite pool of novel chemistry, to make a valuable source for innovative biotechnology (Berdy 2005 ;Fenical and Jensen,2006 and JensenMafnas 2006). Earth's surface has been scratched so far but the recent studies suggest that culturing of microorganisms from marine sediments (0.25%) (Jones 1977 and Amann *et al.*, 1995), especially from marine water (0.001-0.10%) (Amann *et al.*, 1995and Kogure *et al.*, 1979 and 1980 and Ferguson *et al.*, 1984) is considerably lower compared to soil (0.30%) (Amann *et al.*, 1995 and Torsvik *et al.*, 1990). Wide number of valuable antibiotics and secondary metabolites were derived from terrestrial microorganisms, even though the efforts in this area have been being diminished due to exhaustive studies during late 1980s (Zahner and Fiedler,1995). In this respect, researchers switched over to new environments like marine atmosphere for novel pharmaceutical compounds against human pathogens that cause contagious diseases by bacteria, fungi and viruses and these novel antibacterial compounds from marine region used as a medicine in developing countries. So there is a demand for development of new drugs against pathogens and effective antimicrobial compounds towards antibiotic resistance bacteria.

Microorganisms from the marine environment produce new metabolites with potential biological activities along with antiviral and anti-microbial properties (Lu *et al.*, 2010 and Rahman *et al.*,2010). Microorganisms that produce bioactive compounds from marine environment exists in a traumatic habitat, under bitter, lightless and high pressure conditions resulting exceptional metabolisms to produce metabolites that holds opposing views from the terrestrial ones. Marine fungal bioactive compounds are also derived from tunicates, molluscs, corals, sponges, non algal plants and grass sediments to produce metabolites against pathogenic microorganisms.

Fungi is a heterotrophic eukaryote plays a biological role in decomposition of dead plant (cellulose and lignin) and to a less extent on animal (keratin and chitin) tissues that leads to the release of nutrients back into the ecosystem. Fungi can also produce secondary metabolites which are not directly involved in the growth, development and reproduction of any organism.

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During the last 50 years about 23,000 bioactive secondary metabolites were reported from the microorganisms out of these 17,000 were discovered as antibiotics. Among these antibiotics fungi has structural diversity, rich source of medicinal compounds due to their pharmaceutical and toxicological properties and it has a special feature that it can grow, sporulate and germinates in marine environments.

Unique features of Marine fungi

Unique properties of fungi that exist in marine environments are important for marine biotechnology basing on several reasons:

1. Accepting of the ecosystem helps in prospecting of novel genes.
2. Recombinant process influence special adaptations of organisms.
3. Physical factors like low water potential, high concentrations, salinity and p^H, hydrostatic pressure are different parameters which are mostly seen in the deep sea sediments.

Basically Salinity in the oceans are about 33-35ppt when compared to fresh water (0.05% salts (0.5ppt) where marine salinity is about 50 to 100ppt it is considered as hyper saline and mostly observed in Dead sea. In hyper saline environments osmotic pressure inhibit the growth of microorganisms, so marine fungi accumulates osmolytes like glycerol, mannitol, polyol and trehalose which are unique characteristic features for their existence to reduce the osmotic pressure(Blomberg and Adler,1992). A high level of sodium concentrations in the marine water microbial cells is a unique property; though these high levels of sodium concentrations are toxic to the living things in terrestrial and fresh water organisms. Marine fungi reduce the toxicity of sodium in vacuoles and sequester them (Jennings 1983) with efficient ATPase and sodium efflux (Benito *et al.*, 2002). Some marine fungi like straminipilan fungi, thraustochytrids and labyrinthulids requires sodium levels for their growth and sporulation (Jennings 1986). At optimum levels sodium get shifted to upward and increases the incubation period and temperature during production of novel bioactive metabolites. These crucial characters are indicated as tools to understand the physiology of growth and production of enzymes in presence of sodium. Marine fungi produce extra cellular enzymes at pH 7-8 where terrestrial fungi at pH 4.5-6. (Damare *et al.*,2006).Consequently, pharmacologists and biochemists en route marine secondary metabolites from marine fungi have become a pivotal tool to develop new drugs and to know cellular process at biochemical level.

Distribution of marine fungi

Recently oceanic floor has been demonstrated that marine ecosystem has many unique forms of fungi and among those distributions existence of marine fungi has been reported based on their chemical investigations. Although this will provide a general bias that many marine mycological reports will not be included, this sort of analysis will hopefully reveal about the areas that have not been adequately investigated, that represent valuable resources for unexplored marine fungal habitats and discovery of new secondary metabolites. The distribution of marine fungi will be categorized based on the source of the fungus linking with biosynthetic diversity.

The distribution of fungi has been summarized based on the number of distinct genera from marine environment. According to previous studies it is clear that sponges have yielded the greatest taxonomical diversity though sponge derived fungal hyphae enters in to dormant stage during unfavourable conditions. 70% of Fungi obtained from either sponges, algae, or wood substrates account for the majority of chemistry described. Interestingly sponge-derived fungi account for the largest number (33%) of total compounds in the literature.

Algae derived fungi are accounting about 24% of the total number of compounds, and also represent as slightly higher percentage than other metabolites with the ratio of (3:2) as compared to sponge-derived fungi. Unfortunately, unknown compounds were reported about 8%. A tunicate-derived fungus accounts about 5% of the total number of reported compounds of the novel compounds.

Novel microorganisms may produce new metabolites by rational selection to increase the marine fungal isolates which has great medicinal values.

Different activities of Marine derived fungal Compounds:

Antimicrobial Activity: The antibiotics like polyketides 14 and 15-secocurvularin (2) has mild effect on *Bacillus subtilis than the tetracycline.* It can be isolated from the salt water culture of unidentified marine fungi derived from the marine sponges.

Anticoagulant activity: The pharmacology of the fucoidansderived from the marine algae (Drozd *et al.*,2006). Such as Fucus*e vanescens* and *Laminariacichorioides,* acts as ntithrombin and factor Xa due to the presence of sulphated polysaccharides with high potency.

Antifungal activity: Fluconazole and Capisterones A and B are derived from marine algae like *Penicilluscapitatus* enhances antifungal activity (Li *et al.*, 2006). Phenolic compound derivedfrom the marine sponge *Dysideaherbacea*acts against the human fungal pathogens like *Candidaalbicans* and *Aspergillusfumigates* (Sionov *et al.*,2005).The Symbiotic feature among marine microorganisms is an excellent phenomenon for the production of biologically active compounds like xestolactone B, isolated from marine fungus *Penicillium cf. montanense* associated with the sponge *Xestospongiaexigua* (Vivek and Bajpai2016)

Antiinflammatory activity*:* Marine terpenes from marine sponges like *Dysidea*sp. and *Petrosaspongianigra* inhibit inflammatory bowel disease in humans with drugs like bolinaquinoneand petrosiaspongiolide M (Busserolles *et al.*, 2005).

Antiprotozoal activity*:* Ent-plakortide P derived from marine sponge *Plakortis*sp inhibited the proliferation of *Leishmania Mexicana* but less potent than the ketoconazole (Lim *et al.*, 2006). The novel compound like karatungiol A derived from marine dinoflagellate *Amphidinium*sp, done observation against *Trichomonas foetus* to know the antiprotozoal activity (Washida *et al.*, 2006).

Antituberculosis activity*:* (+)-8-hydroxymanzamine A and manzamine F -types of alkaloids that inhibit *M. Tuberculosis* derived from marine metabolites and nifamycin (Rao *et al.*, 2006) is a first-line antituberculosis drug. (+)-fistularin -3, 11-deoxy-fistularin-3 are isolated from Brazilian sponge

Aplysinacauliformis acts against the *Mycobacterium tuberculosis* H37Rv (de Oliveira *et al.*, 2006).

Antiviral Activities: Three galactanpolysaccharide fractions (Rodriguez *et al.*, 2005) from Argentinean marine algae *Callophyllisvariegate* which are HSV-1, HSV-2 and dengue type 2) plastoquinones are anti-human cytomegalovirus drug. Diterpenes (HIV-1) reverse transcriptase enzyme (de Souza *et al.*, 2005).

Cardiovascular activity: Lepadiformines A and B which are isolated from marine alkaloids from the tunicate *Clavelinamoluccensis* dose-dependently inhibit inward rectify K^+current by blocking the cardiac muscle k^+channel and putatively interacting with "one of the negatively charged aminoacids located in the inner Vicinity of the narrow K^+ selectivity filter, candidates being residues D172, E224 or E229 (Sauviat *et al.*,2006).The isolates of marine dinoflagellate *Symbiodinium*sp also enhances vasoconstrictive to rat blood vessels (Onodera *et al.*,2005).

Immunological activity: The novel drug derived from marine hydroid *Garveiaannulata*is indoleamine 2,3-dioxygenase (INDO)inhibitor agent that prevents immunological rejection of tumors(Pereira *et al.*,2006). A new α-galactoglycosphingolipid, damicoside, isolated from the marine sponge *Axinelladamicornis*. In graded concentration exhibited reliant stimulatory activity in a murine spleen proliferation assay (Costantino *et al.*, 2005). These bioactive glycosphingolipids compounds also showed the antiapoptotic activity of laminarin polysaccharidesisolated from the alga *Laminariajaponica* (Kim *et al.*, 2006) it suppress mouse thymocyte apoptosis and significantly induced upregulation of 33 immunomodulatory genes from a total of 7,410 genes when examined using a cDNA microarray.

Neurogenesis activity: Pharmacological studies using marine compounds affect the nervous system through stimulation of Neurogenesis, targeting of receptors, and other miscellaneous activities of the nervous system. Biologically active molecules derived from marine environment plays a key role in stimulating neurogenesis, rescue damaged neuronal cells and helps in therapeutic strategies to treat neurodegenerative diseases (Tsang *et al.*, 2005). A novel drug from the skin of the blue shark *Prionaceglauca*which exhibited neurogenic activity of both an axonic and a dendritic nature is70-kDa chondroitin sulfate/dermatan and also as binding activities for various growth factors (Nandini *et al.*, 2005). New steroid glycosides are Linckosidesisolated from the Okinawan sea star *Linckialaevigata* enhances the neurogenic activity (Han *et al.*, 2006) and innovative polyketides like himalactone Aisolated from the marine-derived fungus *Emericellavariecolor*GF10 induce neurogenesis in a neuroblastoma Neuro2A cell line at 10μg/mL by an undetermined mechanism (Wei H *et al.*, 2005). To detect novel secondary metabolites chemical epigenetic induction is maximized as a routine part of our screening program involving the exploration of marine derived fungi (Xiaofan 2017)

Role of Fungi in the marine ecosystem

Though the marine fungi existence is known from early times, their significance as active in marine ecological processes has been overlooked (Kohlmeyer J and Kohlmeyer E, 1979 and Hughes Kohlmeyer and Kohlmeyer, 2003) and stated that marine fungi cannot be defined strictly only on physiological criteria, but they need broad ecological spectrum of definition to classify them into obligate and facultative forms. Fungi has a diverse existence biologically and biochemically and utilizes substrates (Bugni and Ireland 2004) such as wood, soil sediments and, algae, corals, calcareous tubes of molluscs, decaying leaves of mangroves, grasses and crustaceans (Kohlmeyer and Kohlmeyer,1979) of marine environment and also lives on estuarine, coastal and oceanic waters without a specific substratum to produce natural potent bioactive metabolites.

Role of secondary metabolites

Bioactive metabolites from marine Fungi have been exhibiting a great potentiality in the field of pharmacology. The biological activity of marine fungi is gaining lot of interest in researchers due to their antibiotic production (TidaDethoupand LekaManoch, 2009). Secondary metabolites produced from marine fungi also exhibit various types of biological activities, and these metabolites have incredible array of chemical structures results in the different biological activities like antioxidants, anti- malarial, antidiabetic, anticancer, antimicrobial properties (Arora and Chandra, 2010).

Secondary metabolites from different species of marine fungi

Aigialus sp.: The species of *Aigialus*produce secondary metabolites from marine ecosystem against pathogenic bacteria, fungi, protozoa and Cytotoxic effects by producing Aigialomycin D (Isaka *et al.*,2002).

Alternaria sp. :The genus of *Alternaria* is known as a source of secondary metabolites found on various kinds of organic material under damp conditions, and is isolated from marine sources (Freeman1966) till date more than 161 compounds have been reported from fungi belonging to this genus likedjalonenol, dibenzo-α-pyrone-djalonensone (Onocha *et al.*,1995 and zinniol (Gamboa-Angulo *et al.*,2000).

Sporormiella sp.: Sporormiella species are coprophilous fungi, mainly isolated from marine sources. The genus *Sporormiella* is noted for its ability to produce bioactive secondary metabolites, e.g. similins A and B isolated from *S. similes* (Weber *et al.*,1992), australi fungi reported from *S. australis* (Mandala *et al.*,1995), terezines A-D isolated from *S. teretispora* (Wangand Gloer1995) and sporovexins A-C from *S. vexans* (JS 306).

*Microsphaeropsis*sp.: These are derived from marine fungi act as a Protein kinases inhibitor by producing bioactive metabolites like 2-betaenone derivatives, 3-tetrahydroxyanthraquinone.

Myrioconium sp.: *Myrioconium sp*. isolated from Fucusvesiculosus, collected by divers around Cuxhaven, North Sea, showed prominent antimicrobial activity.

Diaporthe sp.: Diaporthelactone 7-methoxy-4,6-dimethyl-Antimicrobial 3H-isobenzofuran-1-one and Mycoepoxydiene is a secondary metabolite acts against cancer cells (Lin X *et al.*, 2005).

Penicilliumsp. : Marine fungal secondary metabolite Epolactaene from Pencillium sp. against Neuritogenic(Kakeya *et al.*,1995).

Periconia sp.: Pericosines A and B, Macrosphelides E-H an Anti-tumor agents (Numata *et al.*,1997).

Keissleriellasp. :*Keissleriellasp* (EPS2 Antioxidant) YS4108 (exopolysaccharide) acting against peroxide hydrogen (Sun *et al.*,2005).

Zopfiellasp. :*Zopfiella* is a marine fungi produce a natural products like Zopfiellamides A and B (Daferner *et al.*,2002).

Various compounds from marine fungi with their Chemical structures

Techniques

The secondary metabolites from marine fungi are considered as outstanding sources for cytotoxic effects. According to Strongman (Miller *and* Savard1989) a secondary metabolite like antibiotics, anticancerous agents produced for defensive purpose survive in the environment. The orientation of secondary metabolite from fungi can be initiated by stress or by altering the physico-chemical environment.

Table 1 Antibacterial compounds isolated fungi from marinesource

S.No	Secondary Metabolite	Class of Compound	Source	Activity against bacterial pathogen
1	Guisinol	Depside	*Emericella unguis* (obtained from a mollusc	*Staphylococcus aureus* (Nielsen *et al.*,1999)
2	Varixanthone		*Emericellavariecolor* (sponge derived)	*E. coli, B. subtilis,S. aureus , Enterococcus Faecalis*(Malstrom*et al.*,2002)
3	Sumiki's acid, acetyl Sumiki's acid	Furan carboxylic acid	*Cladosporiumherbarum*(derived from the sponge *Callyspongiaaerizusa*)	*B. subtilis, S. aureus* (Jadulco *et al.*, 2001)
4	Aspergillitine	Chromone derivative	*Aspergillusversicolor* (isolated from the sponge *Xestospongiaexigua*)	*B. subtili*(Lin *et al.*,2003)
5	Phomadecalins A–D, Phomadecalin A, B, D		*Phomasp* (isolated from the stromata of *Hypoxylonsp*)	*B. subtilis S. aureus (*Che *et al.*, 2002)
6	Seragikinone A	Anthracycline related pentacyclic compound	Unidentified marine-derived Fungus	*B. subtilis S. aureus M. luteus Corynebacteriumxerosis*(Shigemori*et al.*,1999)
7	Neomangicol B	Sesterterpenes	*Fusariumsp.*	*B. subtilis* (Renner*et al.*,1998)

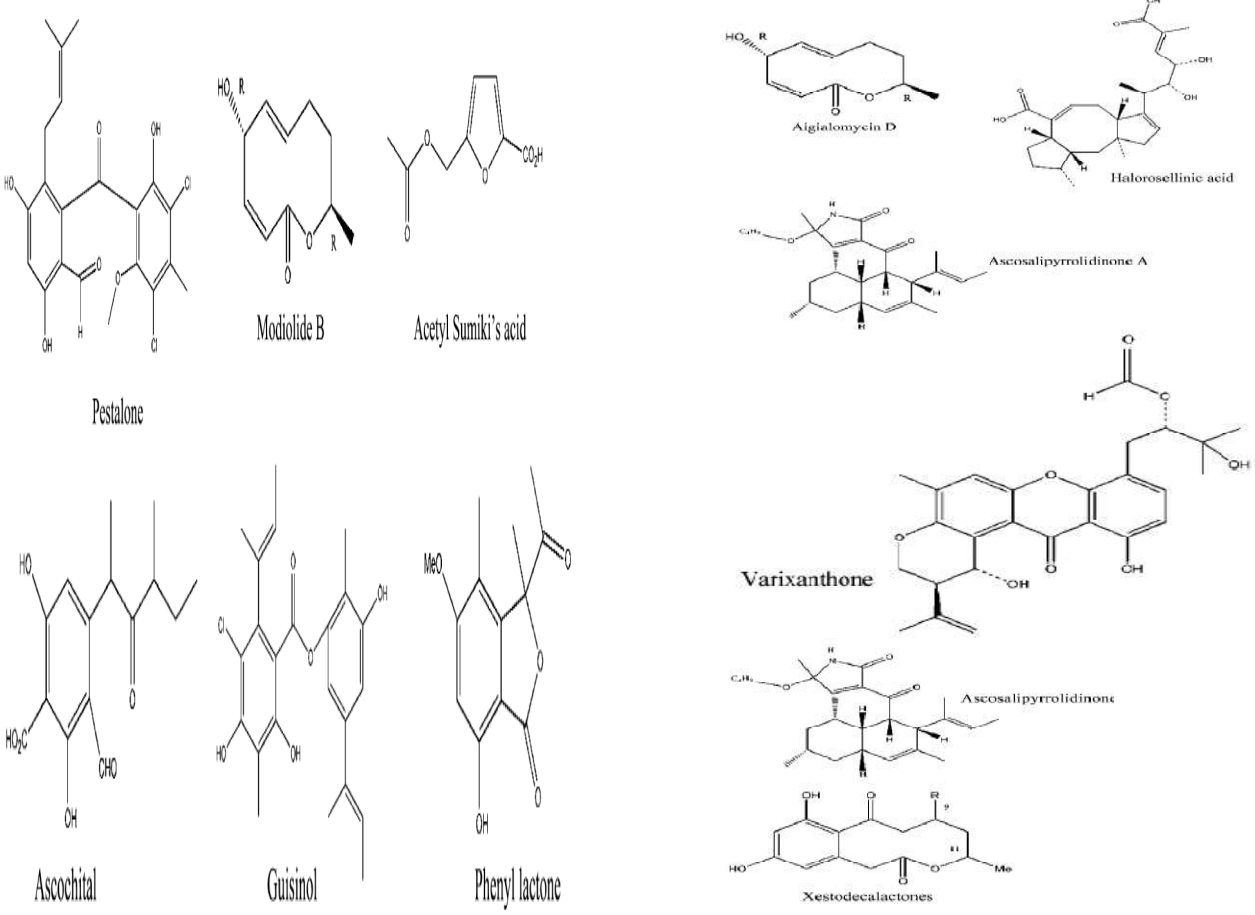

Table 2 Antiprotozoan compounds isolated fungi from marine source

S.No	Secondary Metabolites	Class of Compound	Source	Activityagainst bacterial pathogen
1	Ascosalipyrrolidinone-A	tetramic acid	*Ascochytasalicorniae* Found in association with a marine green alga *Ulva*sp.	*P. falciparum, namelyK1(resistant,t ochloroquinone and pyrimethamine) and NF54* (Osterhage *et al.*, 2000)
2	Aigialomycin D,	resorcyclic macrolide	*Aigialusparvus*	*P.* falciparum (Chinworrungsee *et al.*, 2001)
3	halorosellinic acid	Cytochalasin Q	*Halorosselliniaoceanica*	*P. falciparum*(Edrada *et al.*, 2002)

Table 3 Anti fungal compounds isolated fungi from marine source

S.No	Secondary Metabolite	Class of Compound	Source	Activity against microbial pathogen
1	Xestodecalactone B		*Penicilliumcf. montanense* (derived from the sponge *X. exigua*)	*Candidaalbicans*(Shigemori*et al.*,1999)
2	Seragikinone A	Anthracycline related pentacyclic compound	Unidentified marine fungus (derived from the Rhodophyte *Ceratodictyonspongiosum*)	Weak antifungal activity against *C. albicans*(Tsuda *et al.*,2003)
3	Modiolides A-B	Macrolide	*Paraphaeosphaeriasp*	*Neurosporacrassa* (Liu *et al.*,2002)
4	AscosalipyrrolidinoneA 2,3-Dihydro-2-hydroxy-2, 4-dimethyl-5-transpropenyfuran-3-one	Alkaloid	*Ascochytasalicorniae*	*Mycotyphamicrosporum, Microbotryum violaceum, M. violaceum, Eurotiumrepens*(Daferner *et al.*,2002)
5	3,6,8-trihydroxy-3-[3, 5-dimethyl-2-oxo-3 (E)-heptenyl]-2, 3-dihydronaphthalen-1(4H)-one		*Keissleriellasp.*	*C. albicans, T. rubrum and A. niger*(Holler1999)
6	Zopfiellamides A and B	Pyrrolidinone Derivative	*Zopfiellalatipes*	*Nematosporacoryli and Saccharomyces cerevisiae*(Strongman *et al.*,1987)
7	Microsphaeropsin	Microsphaeropsissp. derived fromspongeMyxillaincrustans	Microsphaeropsis, sp(derived from spongMyxillaincrustans)	Antifungal activity against *Ustilago Violacea*, *Mycotyphamicrospora*(Miller and Blackwell 1986)

Macro nutrients (Nitrogen, carbon and oxygen) are the limiting factors for the *in vitro* conditions to induce marine fungal secondary metabolites. The available reports for the induction of metabolites by limited factors like carbon, oxygen and phosphate (Miller and Blackwell 1986; Miller *and* Savard, 1989andMiller *et al.*,1994).Trace elements (zinc, copper) are also applicable and necessary to understand the structure of the chemical compound involved in it. The main role behind the chemical investigation is to isolate pure and biologically active metabolites from fungal culture extracts is to attain industrially applicable novel bioactive compounds, selected strains from marine environments to be cultured in large-scale, are extracted and these crude extracts have to be separated using various types of techniques like chromatography and spectroscopy. Some of the characteristically employed techniques for the identification of bioactive compounds involve Thin Layer Chromatography (TLC), High Performance Liquid Chromatography (HPLC), Gas Liquid Chromatography (GLC), Gas Chromatography-Mass Spectrometry (GC-MS), NMR spectroscopy, IR spectroscopy, Liquid Chromatography-Mass Spectrometry (LC-MS) and X-ray crystallography. From these techniques new compounds of interest are detected, the reproducibility has to be checked and reported as a novel metabolite after characterization and testing biological activities like anti-microbial, anti-cancerous, anti-inflammatory and anti-oxidants. The chemical investigations get completed through physical characterization and structural elucidation of the isolated metabolites from marine fungi.

CONCLUSION

In the view of immense biological diversity of an ocean as a whole, it is increasingly recognized as a large number of novel chemical entities exist in marine environment. As marine microorganisms, particularly fungi have been evolved with the greatest metabolic diversity as a source of novel secondary metabolite. A beneficiary fungus that exists in oceans is widely distributed in different marine ecosystems. Exploitation of marine fungi as a source for novel secondary metabolites is an infancy. The discovery rate of novel secondary metabolites from marine fungi has recently surpassed the terrestrial counterparts, which is evident by the isolation of many new chemical entities. In this respect, future success relies on our ability to isolate novel fungal species from the marine environments. Some progress has been recently made in this area using enrichment techniques and new selection methods, media and recent culture-independent studies have shown that marine environment still contains a high diversity of rare fungi. The distribution of marine fungi, adaptation of more efficient techniques to screen new chemical compounds in the marine ecosystem and understanding the fungal ecology, taxonomy and chemical biology combined with the help of polyphasic taxonomy including advanced techniques will provide detailed information on the taxonomy, ecology and chemical characteristics of uncultivable or rare marine fungi. Budding of uncultivable or rare marine fungi would represent a unique and promising source for the discovery of novel secondary metabolites. It is clear from the analysis of low or rare diversity marine fungi taxon that patterns of secondary metabolite

production are highly complex and that molecular studies can improve the drug discovery process.

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