

Bioprospection of marine actinomycetes: recent advances, challenges and future perspectives

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Abstract

In exploring new sources for economically important products, marine environment draws particular attention because of its remarkable diversity and extreme conditions; it is known to produce metabolic products of great value. It represents untapped source for the discovery of novel secondary metabolites with varying potential such as antibiotic, anti-tumor, antifouling and cytotoxic properties. Marine actinomycetes distributed throughout the marine environment from shallow to deep sea sediments have proved to be a finest source for this discovery. Secondary metabolites derived from marine actinomycetes have proved their worth in industries based on the research on their properties and wide range applications. Spotlight of the review is range of marine based actinomycetes products and significant research in this field. This shows the capability of marine actinomycetes as bioactive metabolite producers. Additionally, the present review addresses some effective and novel approaches of procuring marine microbial compounds utilizing the latest screening strategies of drug discovery from which traditional resources such as marine actinobacteria has decreased due to declining yields. The aim is in the context of promoting fruitful and profitable results in the near future. The recent surfacing of new technologies for bioprospection of marine actinomycetes are very promising, resulting in high quality value added products, and will be defining a new era for bioactive compounds with medical and biotechnological applications.

Key words: marine actinomycetes, bioprospection, commercial use, bioactive compounds, genome mining

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1 Introduction

Actinomycetes are one of the ubiquitous dominant groups of gram positive bacteria having high G+C (>55%) content in their DNA (Chater, 2006; Das et al., 2008). Actinomycetes are the most economically and biotechnologically priceless prokaryotes. They have been commercially exploited as they play a major role in production of novel pharmaceuticals, enzymes, antitumour agents, enzyme inhibitors, immune-modifiers, anti-parasitic, herbicides, pesticides and vitamins (Rashad et al., 2015; Arbat and Zodpe, 2014; Butler, 2004; Atta, 2007). Also, their role in organic waste degradation has been significant due to its ability to secrete extracellular enzymes viz. chitinase, ligninase, xylans and pectinase (Arbat and Zodpe, 2014). Their role on recycling organic matter is the point to be considered (Srinivasan et al., 1991).

So far actinomycetes have been isolated from terrestrial sources. However, potential marine actinomycetes offer a great scope for the discovery of potential metabolites chemically and biologically because of their diversity (Kurtböke, 2012; Komaki et al., 2018). Ocean covers more than 70% of the earth surface and represents a less explored environment for microbial diversity which is a suitable source for isolation of actinomycetes. They are far and wide throughout the ocean, including intertidal zones (Goodfellow and Williams, 1983), marine and estuarine sediments (Takizawa et al., 1993; Moran et al., 1995; Mincer et al.,

2002; Jensen et al., 2005a; Thornburg et al., 2010; Xiao et al., 2011; Bull et al., 2005), seawater (Ramesh et al., 2006; Ramesh and Mathivanan, 2009), in symbiosis with different marine invertebrates, e.g., with sponges (Piel, 2004; Kim and Fuerst, 2006; Zhang et al., 2008; Sun et al., 2010), animals (Maldonado et al., 2005) and plants (Castillo et al., 2005). It is already known that large number of natural products and novel chemical entities found in ocean are with unique biological activities and potential for treatment of human diseases (Haefner, 2003).

Marine organisms are capable of producing novel chemicals with unique structural and functional features as they prevail in the extreme environment of pressure, salinity, temperature, etc. (Kathiresan, 2015). The sea environments are entirely different from the terrestrial conditions and actinomycetes are potential source of novel compounds (Piel, 2004; Zhou and Zheng, 1998), e.g., rare actinomycetes that require sea water for their growth, a kind of unique adaptation (Thornburg et al., 2010; Kim and Fuerst, 2006; Jensen and Mafnas, 2006; Jensen et al., 2007; Janssen et al., 2002). Existence of marine microbes was questioned many times due to the difficulty in isolating these microorganisms from marine environment and the versatility of their bioactive metabolites has not been fully explored. With the advent of new technologies and approaches, existence of actinomycetes and the biosynthesis gene clusters they harbor in the

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oceans and their distribution in different marine ecosystems have been proved (Janssen et al., 2002; Donadio et al., 2002). It has now been recovered from the deepest known ocean trench (Pathom-Aree et al., 2006).

Marine environment is a prolific but underexploited source for the discovery of actinomycetes (Barcina et al., 1987) and novel secondary metabolites (Bull et al., 2005; Stach et al., 2003; Jensen et al., 2005b; Fiedler et al., 2005; Magarvey et al., 2004). Due to challenges in the field there is reduced research interest and commercial investment. This review clearly shows that actinomycetes indeed exist in the oceans and are an important source of secondary metabolites. A lot has been reported about marine actinomycetes and their products but in this review we will address latest screening strategies and focus on recent advancement in this field. There is still scope for advanced research and investigation to explore the potential of marine actinomycetes as producers of bioactive secondary metabolites.

2 Marine actinomycetes: fruitful source of bioactive secondary metabolites

From 23 000 bioactive secondary metabolites produced by microorganisms 10 000 are produced by actinomycetes, representing 45% of all bioactive microbial metabolites discovered (Bérdy, 2005). The species belong to the genus *Streptomyces* constitute approximately 7 600 compounds (Bérdy, 2005). About 300 patents on bioactive marine natural products were issued between 1969 and 1999 (Kathiresan et al., 2005; Sithranga and Kathiresan, 2010). Representative genera of actinomycetes *Streptomyces*, *Saccharopolyspora*, *Amycolatopsis*, *Micromonospora* and *Actinoplanes* are the major producers of commercially important biomolecules. There are number of actinomycetales species, including all the rare actinos, known to produce bioactive

metabolites (Fig. 1).

Actinomycetes are well known for production of bioactive compounds and hence they are characterized as industrially important (Tamehiro et al., 2003; Higginbotham and Murphy, 2010). Various starring role of actinomycetes like improvement of physical parameters and environmental protection, nitrogen fixation, mineralization of organic matter, immobilization of mineral nutrients have been described (Goodfellow and Haynes, 1984). Different genera of actinomycetes have been reported from marine environment (Fig. 2). Many of their metabolites possess biological activities and have the potential to be developed as therapeutic agents (Cundliffe, 1989; Kieser et al., 2000). The marine actinobacteria has also been found to synthesize various compounds like polyketides, peptides, isoprenoids, phenazines and sterols which serve as potential drugs for treatment of HIV, cancer, etc. (ul Hassan et al., 2017; Binayke et al., 2018). They also contribute to the breakdown and recycling of organic compounds (Goodfellow and Haynes, 1984) and for production of agriculturally important compounds (Okami and Hotta, 1988). They are well known for their remarkable ability to produce range biologically active compounds (Table 1).

Among the secondary metabolites produced by actinomycetes, these have been the most significant and so far growing continuously for development.

2.1 Antibiotics

Bioactive secondary metabolites with strong antibacterial and antifungal activities are being intensely used as potent antibiotics and are effective against infectious diseases. As a result, antibiotic-producing actinomycetes are exploited by the pharmaceutical industry (Bérdy, 2005). Among the large number and variety of antibiotics, one produced by actinomycetes is indis-

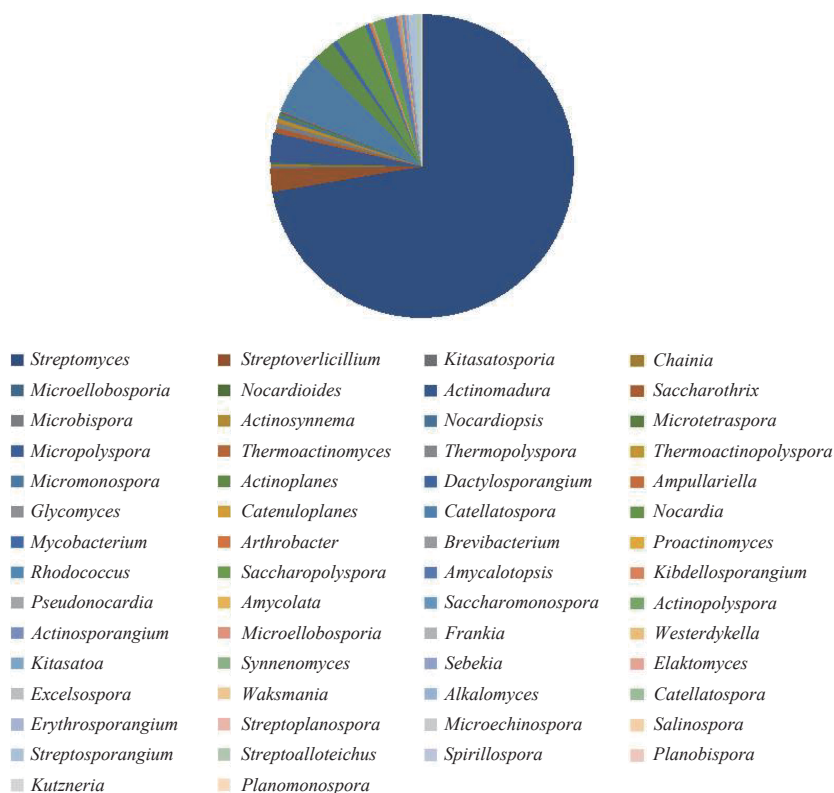


Fig. 1. Number and species of bioactive metabolites producing actinomycetales (adapted and reconstructed from Sharma et al., 2014).

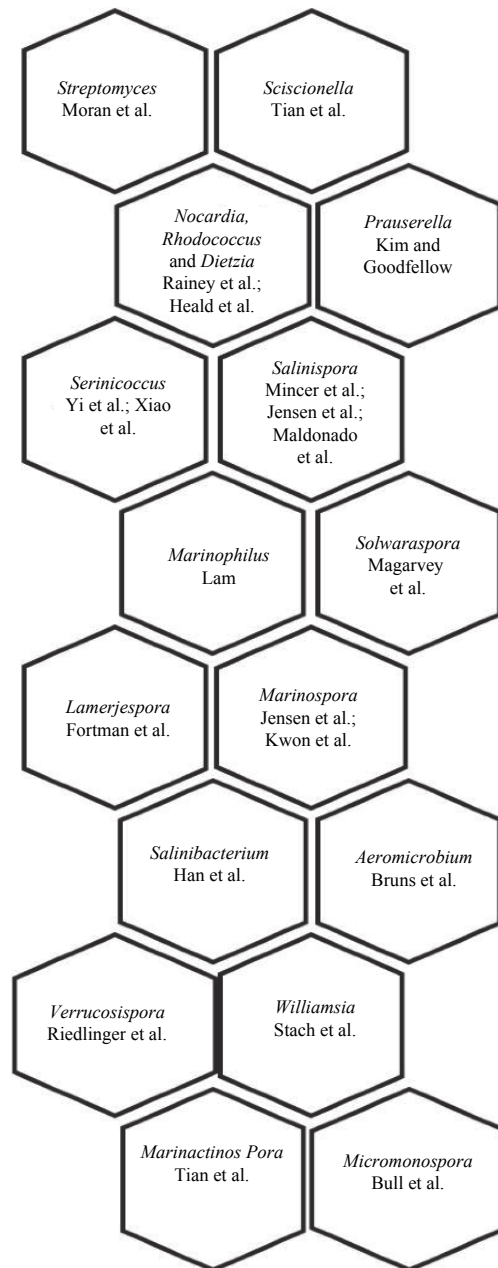


Fig. 2. Representative genera of actinomycetes reported from marine environment.

pensable for the treatment of a variety of microbial infections. Report of actinomycin in 1940 and subsequent reports of streptomycin in 1942 and streptomycin in 1943 introduced the actinomycetes as source of antibiotics (Waksman, 1943; Waksman and Woodruff, 1940; Comroe, 1978).

Actinomycetes are known to produce clinically relevant antibiotics and are used in many fields including agriculture, veterinary, and pharmaceutical industry (Lam, 2006; Niu et al., 2007; Anzai et al., 2008; Arumugam et al., 2010; Hohmann et al., 2009b; Carlson et al., 2009; Hong et al., 2009; Rahman et al., 2010; Pimentel-Elardo et al., 2010; Xu et al., 2010).

2.2 Anti-tumor compounds

Cancer is the most serious health problem that needs attention. Many of the compounds from marine actinobacteria play an important role as anti-tumor compounds. List of clinically useful

antitumor drugs produced by actinomycetes belong to several structural classes such as (Newman and Cragg, 2007; Olano et al., 2009):

Polyketides—anthracyclines, daunomycin, elloramycin, geldanamycin, thiocoraline, ovidomycin, steffimycin and doxorubicin;

Aureolic acids—mithramycin and chromomycin A3;

Mixed polyketide/non-ribosomal peptides—glycopeptide bleomycin, glycopeptide actinomycin D, rapamycin, salinosporamide;

Heterocyclic quinones—mitomycin C;

Indolocarbazoles—staurosporine, rebeccamycin;

Enediynes—neocarzinostatin;

Antimetabolites—pentostatin, Carzinophilin.

Antitumor compounds function by processes like apoptosis through DNA cleavage mediated by topoisomerase I or II inhibi-

Table 1. Representative metabolites from marine actinobacteria

Compound	Source	Reference
Antifungal agents: Antifungal agents derived from streptomyces tend to be macrolide polyenes (large ring structure with lots of conjugated carbon-carbon double bonds).		
Nystatin	<i>S. noursei</i> ATCC 11455	Zotchev et al. (2000)
Amphotericin B	<i>S. nodosus</i>	Hartse and Bolard (1996)
Natamycin	<i>S. natalensis</i>	Pedersen (1992)
Antimycin	<i>Streptomyces</i> sp. SCSIO 1635	Li et al. (2011)
Urauchimycins (member of antimycin class)	<i>Streptomyces</i> sp.	Sharma et al. (2014)
Urauchimycins A and B-from marine sponge Ni-80		
Urauchimycin C-from marine sediment		
Daryamides	<i>Streptomyces</i> sp. CNQ-085	Asolkar et al. (2006)
Bonactin	<i>Streptomyces</i> sp. BD21-2	Schumacher et al. (2003)
Chandrananimycins	<i>Actinomadura</i> sp.	Maskey et al. (2003b)
Antibacterial agents		
Glaciapyrroles A, B and C	<i>Streptomyces</i> sp. NPS008187	Macherla et al. (2005)
Abyssomicin C	<i>Verrucosipora</i>	Bister et al. (2004)
SBR-22	<i>Streptomyces psommatocis</i> BT408	Sujatha et al. (2005)
Thiocoraline	<i>Micromonospora</i>	Romero et al. (1997)
Salinamides A and B	<i>Streptomyces</i> sp.	Moore et al. (1999)
IB-00208	<i>Actinomadura</i>	Malet et al. (2003)
Tetracenomyacin D	<i>Streptomyces corchorusii</i> AUBN(1)/7	Adinarayana et al. (2006)
Resistoflavine	<i>Streptomyces chibaensis</i> AUBN(1)	Gorajana et al. (2007), Kock et al. (2005)
Himalomycins A and B	<i>Streptomyces</i> sp. B6921	Maskey et al. (2004)
Helquinoline	<i>Janibacter limosus</i>	Asolkar et al. (2004)
Chlorinated dihydroquinones	CNQ-525	Mercado et al. (2005)
Arenicolide A	<i>Salinispora arenicola</i>	William et al. (2007)
Marinomycins	<i>Marinispora</i>	Kwon et al. (2006)
Bonactin	<i>Streptomyces</i> sp. BD21-2	Schumacher et al. (2003)
Chandrananimycins	<i>Actinomadura</i> sp.	Maskey et al. (2003b)
Diazepinomicin (ECO-4601)	<i>Micromonospora</i> sp.	Charan et al. (2004)
Frigocyclinone	<i>Streptomyces griseus</i>	Bruntner et al. (2005)
Gutingimycin	<i>Streptomyces</i> sp.	Maskey et al. (2003a)
Lajollamycin	<i>Streptomyces nodosus</i>	Mann (2001)
Rifamycin	<i>S. arenicola</i>	Floss and Yu (2005)
β -indomycinone	<i>Streptomyces</i> sp.	Biabani et al. (1997)
Essramycin	<i>Streptomyces</i> sp.	El-Gendy et al. (2008)
Lynamycins	<i>Marinispora</i> sp.	McArthur et al. (2008)
1, 4-Dihydroxy-2-(3-hydroxybutyl)-9, 10-anthraquinone 9, 10-anthrac	<i>Streptomyces</i> sp.	Ravikumar et al. (2012)
Bisanthraquinone	<i>Streptomyces</i> sp.	Socha et al. (2006)
Antiviral agents: Antiviral activity of marine actinomycetes has application in biological control of human enteropathogenic virus contamination and disease transmission in sewage-polluted waters and in chemotherapy of viral diseases of humans and lower animals.		
Benzastatin C	<i>Streptomyces nitrosporeus</i>	Lee et al. (2007)
Antiparasitic agents: Alarming death rate caused by the parasites and the emergence of antibiotic resistance underline the need for new and effective drugs. Marine actinomycetes have a potential to produce antiparasitic compounds that fulfills this.		
Valinomycin	<i>Streptomyces</i> sp.	Pimentel-Elardo et al. (2010)
Avermectins	<i>Streptomyces avermitilis</i>	Burg et al. (1979)
Anti-infective agents: Anti-infectives has their importance against antibiotic-resistant infectious diseases and mainly involves recalcitrant and nosocomial infections. Potential of marine actinomycetes to produce bioactive compounds can be exploited for novel anti-infective activities (Rahman et al., 2010).		
Tirandamycins A and B	<i>Streptomyces</i> sp. (Strain 307-9)	Carlson et al. (2009)
Antimalarial agents: Malaria continues to be a devastating parasitic disease; new chemotherapeutic strategies are urgently needed to combat malarial disease. Some novel activities of actinomycetes with biomedical importance involve antimalarial activity.		
Trioxacarcins	<i>Streptomyces</i> sp.	Lam (2006)
Salinosporamide A (NPI-0052)	<i>Salinispora tropica</i>	Prudhomme et al. (2008)
Cytotoxic agents		
Manumycins	<i>Streptomyces</i> sp.	Chauhan et al. (2005)
Salinopyrones	<i>Salinispora pacifica</i>	Oh et al. (2008)
Pacificanones	<i>Salinispora pacifica</i>	Oh et al. (2008)
Actinofuranones	<i>Streptomyces</i> sp.	Cho et al. (2006)

to be continued

Continued from Table 1

Compound	Source	Reference
Nonactin	<i>Streptomyces</i> sp.	Jeong et al. (2006)
Resistoflavine	<i>Streptomyces chibaensis</i>	Gorajana et al. (2007)
Neomarinones	<i>Actinomycetales</i>	Hardt et al. (2000)
Piericidins	<i>Streptomyces</i> sp.	Hayakawa et al. (2007)
Lucentamycins	<i>Nocardiopsis lucentensis</i>	Cho et al. (2007)
Arenamides	<i>Salinipora arenicola</i>	Asolkar et al. (2006)
Piperazimycins	<i>Streptomyces</i> sp.	Miller et al. (2007)
Mansouramycin C	<i>Streptomyces</i> sp.	Hawas et al. (2009)
Usabamycins	<i>Streptomyces</i> sp.	Sato et al. (2011)
Pyridinium	<i>Amycolatopsis alba</i>	Dasari et al. (2012)
ML-449(macrolactam)	<i>Streptomyces</i> sp.	Jørgensen et al. (2010)
Salinosporamide B & C	<i>Salinipora tropica</i>	Williams et al. (2005)
Albidopyrone	<i>Streptomyces</i> sp.	Hohmann et al. (2009a)
Biopesticide agents: Biopesticide agents produced by actinomycetes are environmentally safer and more potent than their synthetic counterparts.		
-	marine actinomycetes	Haefner (2003)
Insecticidal agents: Range of new insecticides and herbicides (about 60%) reported in the past five year originate from <i>Streptomyces</i> . The alarming death rate caused by disease transmitted through insects is a major problem need to be tackled. Control of such diseases is becoming increasingly difficult due to the emergence of antibiotic resistance. An approach of using actinomycetes as potential producer of insecticidal metabolites is a brilliant way out.		
-	<i>Streptomyces</i> sp. and <i>Streptosporangium</i> sp.	Vijayakumar et al. (2010)
-	<i>Streptomyces</i> sp.173	Xiong et al. (2004)
Antialgal compounds: Blooms of algae are widespread in lakes and reservoirs and cause many problems of toxicity and unpleasant odours.		
Chandrananimycins	<i>Actinomadura</i> sp.	Maskey et al. (2003b)
Extracellular antialgal substance	<i>Streptomyces neyagawaensis</i>	Choi et al. (2005)
Biocorrosive agents: Biocorrosion is a very problematic phenomenon which causes billions of dollars of losses in monitoring and control every year. Some bacteria are involved in biofilm formation and biocorrosion, inhibition of these bacteria by compounds from marine actinomycetes offers a more effective, environmental friendly and long term method of corrosion controls.		
-	<i>Streptomyces lunalinhaensis</i>	Pacheco da Rosa et al. (2013)
Role as siderophores: Role of siderophores to scavenge iron from the environment and to make the mineral, which is almost always essential, available to the microbial cell. Siderophores effectively increase the solubility of iron in sea water and support more microbes by making more iron available for essential biological processes and thus have applications in environmental, clinical and agricultural. The potency of common antibiotics has been elevated by binding in to the iron binding functional groups of siderophores. Sideromycin is an iron chelating antibiotic produced by <i>Streptomyces</i> species showed good antimicrobial activity. Siderophores have potential ability to resolve various environmental problems like biofouling, bioleaching, rust removal, dye degradation and sewage treatment.		
Desfarrioxamine B	<i>Streptomyces pilosus</i>	Balagurunathan and Radhakrishnan (2007)
Anti-angiogenesis activity: Inhibiting angiogenesis has been considered as an important anticancer strategy to suppress tumor growth and metastasis.		
Streptopyrolidine	<i>Streptomyces</i> sp.	Shin et al. (2008)
Cyclo-(l-Pro-l-Met)	<i>Nocardiopsis</i> sp.	Shin et al. (2010)
Anti-inflammatory agents: Inflammation if being untreated may lead to onset of diseases. Because of side effects, economy and potency, current drugs are not of great significance.		
Cyclomarin A	<i>Streptomyces</i> sp.	Renner et al. (1999)
Diazepinomicin (ECO-4601)	<i>Micromonospora</i> sp.	Charan et al. (2004)
Antioxidant agents: In its commercial use as a food additive, the fermenting sponge associated <i>Streptomyces</i> isolate (AQBMM35) produced carotenoids namely phytoene which has antioxidant activity (Dharmaraj, 2011).		
Dermacozines A-G	<i>Dermacoccus</i>	Abdel-Mageed et al. (2010)
Lipocarbazoles	<i>Tsukamurella pseudospumae</i>	Schneider et al. (2009)
2-Allyloxyphenol	<i>Streptomyces</i> sp.	Arumugam et al. (2010)
Immunosuppressive agents: Actinomycetes are known to produce a class of compounds that are potential immunosuppressive agents.		
Everolimus (derivative of Rapamycin)	<i>Streptomyces hygroscopicus</i>	Chapman and Perry (2004)
Toxin producers: Actinomycetes are also known to produce toxins.		
Tetrodotxin (TTX)	<i>Streptomyces</i> sp.	Imada (2005)
Nutraceuticals: Nutraceuticals have received considerable interest in health community due to its multiple therapeutic effects. Compounds from actinomycetes considered great nutraceuticals due to its reduced risk of side effects. Carotenoids synthesized by marine actinomycetes are used as colorants, feed supplements, and nutraceuticals in the food, medical, and cosmetic industries.		
Carotenoid	marine actinomycetes	Imada (2005)
Antifouling agents: More environmentally friendly and effective ways of reducing biofouling.		
Five structurally similar compounds	<i>Streptomyces</i> sp.	Romero et al. (2012)
Diketopiperazines	<i>Streptomyces fungicidicus</i>	Li et al. (2006)
-	<i>Streptomyces praecox</i> 291-11	
-	<i>Streptomyces albus</i>	You et al. (2007)

tion, mitochondria permeabilization, inhibition of key enzymes involved in signal transduction like proteases, or cellular metabolism and in some cases by inhibiting tumor-induced angiogenesis (Olano et al., 2009). Many antitumor compounds are pro-

duced by marine actinomycetes (Table 2). Whereas, Nachtigall et al. (2011) studied Atacamycins A–C, 22-membered antitumor macrolactones produced by *Streptomyces* sp. C38 (Nachtigall et al., 2011).

Table 2. Examples of industrially important enzymes from marine actinomycetes

Sample No.	Enzyme	Source	Reference
1	Amylase Alpha-amylase	<i>Nocardioopsis</i> sp. <i>Actinobacterium</i> (A-19) <i>Streptomyces</i> sp. D1 <i>Streptomyces gulbargensis</i> DAS 131	Stamford et al. (2001)
2	Protease	<i>Streptomyces</i> sp. MML1614	Jeyadharshan (2013)
3	Cellulase	<i>Streptomyces ruber</i>	Chandramohan et al. (1972)
4	Thrombinase	<i>Streptomyces venezuelae</i>	Naveena et al. (2012)
5	L-asparaginase	<i>Streptomyces</i> sp. PDK2 <i>Streptomyces noursei</i> MTCC 10469	Dhevagi and Poorani (2006)
6	Novel extracellular phospholipase C	<i>Streptomyces</i> sp.	Mo et al. (2009)
7	New exocyttoplasmic, nutritionally controlled endodeoxyribonuclease	<i>Streptomyces antibioticus</i>	Cal et al. (1995)
8	Two exocellular nucleases	<i>Streptomyces antibioticus</i>	Nicieza et al. (1999)

Marine actinomycetes in the family *Micromonosporaceae* are very potent producers. These microbes target proteasome and thus have huge success in pharmaceuticals (Kathiresan et al., 2005). Chartreusin (1a) is not only antibacterially active, but also shows a very promising antitumor-activity against different human cell lines, it was first isolated from *Streptomyces chartreusis* by Leach et al. (1953). A largely marine actinomycete taxon, tentatively designated MAR4 (family Streptomycetaceae), was found to produce a host of meroterpenoids of the napyradiomycin class (Soria-Mercado et al., 2005; Gallagher et al., 2010; Cheng et al., 2013). The napyradiomycins were first discovered from cultures of the actinomycete *Chainia rubra* isolated in Japan in 1986 (Shiomi et al., 1986, 1987). The napyradiomycins were initially characterized for their antimicrobial activity, but have since been found to inhibit gastric (H⁺-K⁺) ATPases and to behave as estrogen receptor antagonists. An examination of the biological potential of these molecules in the treatment of cancer, however, has not been reported, and specific information defining their interactions with targets in cancer cells is unknown.

2.3 Enzymes

Actinomycetes are profound harbingers of enzymes in the marine environment. Enzymes produced by actinomycetes are industrially important and have unique substrate specificities and a higher stability, including temperature stability. It has been assumed that availability of natural product and condition of marine environment may depend on the ratio of enzyme producing microorganism (Ramesh and Mathivanan, 2009).

Among the most important enzymes produced by actinomycetes strains includes:

α-Amylase—Amylases are of great significance in the present-day biotechnology with applications in food, fermentation, textile, and paper industries. *Streptomyces* are known to be a potential source of amylolytic enzymes (Vigal et al., 1991).

Proteases—Proteases are important commercial enzymes and are utilized extensively in a variety of industries, including detergents, meat tenderization, cheese-making, dehairing, baking, and brewery, in the production of digestive aids, and in the recovery of silver from photographic film. Alkaline proteases have extensive utilization in other industrial sectors such as leather, textile, organic synthesis, and wastewater treatment

(Kalisz, 1988; Kumar and Takagi, 1999). Protease from marine actinomycetes has been purified and characterized (Dixit and Pant, 2000).

Cellulases—In industrial processes, cellulolytic enzymes are employed in the color extraction from juices, detergents for color brightening and softening, biostoning of jeans, pretreatment of biomass that contains cellulose to improve nutritional quality of forage, and pretreatment of industrial wastes (Niehaus et al., 1999; Bhat, 2000). Cellulase producers have mainly been found in the actinomycetes (Chandramohan et al., 1972).

Chitinase—Chitinase is a potential antifungal agent because of its chitin degradation activity (Kunz et al., 1992). Actinobacteria is studied for characterization of chitinase gene (Pisano et al., 1992).

Keratinase—Keratinase is a specific protease and hydrolyzing keratin which is a protein found in feathers, wool, and hair. Specific keratinases have been found in some species of actinobacteria (Böckle et al., 1995; Noval and Nickerson, 1959). It is used as an attractive alternative method for efficient bioconversion and improving the nutritional value of keratin by hydrolyzing keratin-containing wastes by microorganisms possessing keratinolytic activity. Keratinolytic proteinases play an important role in biotechnological applications like enzymatic improvement of feather meal and production of amino acids or peptides from high molecular weight substrates or in the leather industry (Pfleiderer and Reiner, 1988; Bertsch and Coello, 2005). Also, keratinases can be used for wastewater treatment, textile, medicine, cosmetic, and feed and poultry processing industries, as well as leather industry (Mukhopadhyay and Chandra, 1993).

Xylanases—Xylanase at elevated temperatures disrupts the cell wall structure of xylan. It has a great application in the pulp and paper industry. Actinobacteria have been reported to produce xylanases (Bode and Huber, 1992).

Ribonucleases—Ribonucleases (commonly abbreviated RNase) play a critical role in many biological processes, including angiogenesis and self-incompatibility in flowering plants (angiosperms). Many stress-response toxins of prokaryotic toxin-antitoxin systems have been shown to have RNase activity and homology.

Enzymes produced are used as pharmaceuticals, food additives, and fine chemicals (Burkholder et al., 1966; Hough and

Danson, 1999; Harmsen et al., 1997). Various enzymes of industrial importance are being produced by marine actinomycetes. Application of various enzymes and their products in biotechnological industries and biomedical fields from actinomycetes has been reported (Oldfield et al., 1998; Peczniska-Czoch and Mordarski, 1988).

2.4 Enzyme inhibitors

An enzyme inhibitor is a molecule that binds to an enzyme and decreases its activity. Drugs acts as enzyme inhibitors by blocking an enzyme's activity which can kill a pathogen or correct a metabolic imbalance. They are also used in pesticides. Many drug molecules are enzyme inhibitors, so their discovery and improvement are active areas of research in biochemistry and pharmacology. Marine actinobacteria are the potential source for production of enzyme inhibitors (Imada, 2005; Garcia-Fernández et al., 2002).

3 Biodiscovery from marine actinomycetes: a commercial approach

Actinomycetes are lucrative and inexhaustible resource for prospecting novel bioactive molecules. Due to the complexity and dynamic nature of the marine environments, characterizing them has been especially challenging. In contrast to previously thought to be “uncultivable” microbes, now they are isolated and purified from the ocean by both conventional and innovative isolation methods. Recent progress on drug discovery from actinomycetes by using high-throughput screening and fermentation, mining genomes for cryptic pathways, and combinatorial biosynthesis to generate new secondary metabolites has made actinomycetes a great source of new compounds (Garcia-Fernández et al., 2002). Still a fully untapped source, biodiscovery of actinomycetes depends on: (1) the improved understanding of their ecology and biogeography, (2) the effective selective recovery of bioactive ones from environmental sources, (3) the rapid and reliable identification techniques, and (4) the effective screening strategies to assess the value of their bioactive compounds for pharmaceutical and biotechnological applications (Kurtböke, 2012). There are choices of current approaches available to explore biodiversity and bioprospection of actinomycetes.

Conventional isolation techniques include choice of screening source, selective medium, culture conditions, and recognition of candidate colonies in the primary isolation. The classical approach for the discovery of bioactive secondary metabolites typically involves screening of crude extracts, followed by series of bioassay-guided fractionation or chemical screening and finally structure elucidation. Using traditional plate culture methods, microorganisms from marine samples can be isolated but it has its own limitations (Akondi and Lakshmi, 2013).

Culture enrichment techniques by providing selective conditions enhance the possibility of isolating organisms. Employment of pretreatments by drying and heating or by adding chemicals such as phenol to sediments are some selective techniques. Specialized growth media with macromolecules such as casein, chitin, hair hydrolysate, and humic acid that are carbon and nitrogen sources have been developed to isolate specific actinomycete genera (Qiu et al., 2008; Bredholdt et al., 2007; Zhang and Zhang, 2011; Cuesta et al., 2012). Several antibiotic molecules are also used in selective media to inhibit unwanted microbes, including fast-growing bacteria and fungi (Lam, 2006; Hayakawa, 2008; Bredholdt et al., 2007). Treatment with chemo-attractants xylose, chloride, collidine, bromide and vanillin leads to selection of *Actinoplanes*, *Dactylosporangium* and *Catenuloplanes*

(Hayakawa, 2008); while chloramine treatment leads to selection of genera *Herbidospora*, *Microbispora*, *Microtetraspora* and *Streptosporangium* (Hong et al., 2009). Different kinds of radiation support isolation of specific actinomycetes such as (Bredholdt et al., 2007):

- (1) UV-irradiation—*Nocardioopsis*, *Nocardia* and *Pseudonocardia* spp.;
- (2) SHF (super-high frequency) irradiation—*Streptosporangium* and *Rhodococcus* species;
- (3) EHF (extremely high frequency) irradiation—*Nocardioopsis*, *Nocardia* and *Streptosporangium* spp.

A high throughput method on the other hand allows isolation of novel organisms of biological interest by screening wide range of conditions.

Although traditional methods are important in discovering high number of metabolites (Xu et al., 2010), reoccurrence of metabolites and isolation of <1% of microbes and leaving bulk of microorganism and their biochemical pathway unapproachable have been the drawbacks (Kennedy et al., 2010; Rath et al., 2011). That is when the culture independent approaches came into action which involves isolation of DNA and generation of genomic or metagenomic libraries to explore the vast diversity of uncultivable, as well as cultivable, organisms and right of entry to study their biochemical pathways (Fig. 3). These libraries can be further screened for novel bioactive molecules and functional characteristics (Riesenfeld et al., 2004; Venter et al., 2004).

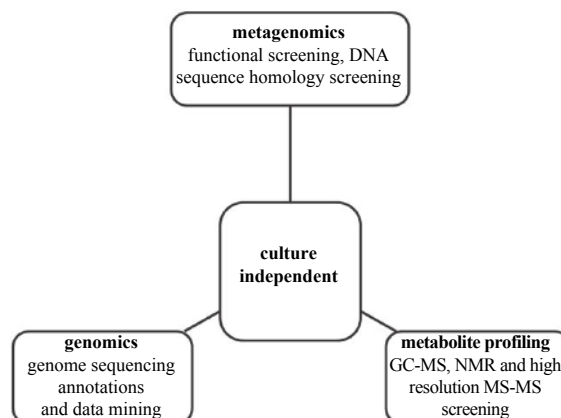


Fig. 3. Culture independent approaches—stage for progression in marine natural product bioprospecting.

4 Culture-independent methods: potential approach to biodiscovery

This budding approach has proved that indigenous marine actinomycetes do exist in marine environment (Maldonado et al., 2005; Monciardini et al., 2002; Das et al., 2007). Also actinomycetes with specific requirements like *Aeromicrobium marinum* (Brunns et al., 2003), has an obligate requirement for salt, and *Salinibacterium*, can tolerate up to 10% NaCl but does not have a salt requirement for growth (Han et al., 2003), which are also reported with the help of these advanced techniques.

These nucleic acid-based molecular methods have been developed to bypass the culture-dependent techniques, the difficulties and limitations associated with these techniques are triumphed over (Mincer et al., 2005). It involves PCR amplification of the DNA or cDNA from RNA extract of environmental sample. Now to identify and enumerated actinomycetes these amplified molecules are analysed (community fingerprinting), cloned and

sequenced (Barcina et al., 1987; Stach et al., 2004; Riedlinger et al., 2004). Specific set of primers for *Actinomycetales* families *Micromonosporaceae*, *Streptomyetaceae*, *Streptosporangiaceae* and *Thermomonosporaceae*, and from the genus *Dactylosporangium* are already developed (Monciardini et al., 2002). Molecular ecology via direct analysis of rRNA gene sequences has undoubtedly revealed diversity of actinomycetes which cannot be cultured via conventional methods (Rath et al., 2011; Brinkhoff et al., 1998; Olsen et al., 1986; Pace et al., 1986). 16S rRNA typing also allows comparison of microorganisms among different samples, in addition to quantifying the relative abundance of each taxonomic group. Being robust and versatile this technique brings out phylogenetic inferences and gains insights into the metabolic diversity of microorganisms. This technique has provided the most convincing evidence of the vastness of microbial diversity (García-Fernández et al., 2002).

A cutting edge approach includes combination of three technologies, i.e., comparative genomics/RFLP, PCR and electrophoresis (Wawrik et al., 2005). It also involves separation of sequences electrophoretically using denaturing gradient gel electrophoresis (DGGE) and TGGE (thermal-GGE) to determine the diversity and community of actinomycetes in environmental samples (Venter et al., 2004; Brinkhoff et al., 1998; Muyzer, 1999; Nimnoi et al., 2010). Akondi and Lakshmi explained taxonomical and functional tool that involves techniques such as DNA microarrays, real-time PCR and PCR-independent amplification techniques that are widely used for genome and proteome analysis of mixed microbial communities (Akondi and Lakshmi, 2013). Genome-guided fermentation studies are now replacing classical approaches and thus facilitating novel biodiscoveries (Udwary et al., 2007). Sustained development in the field of genome mining is a potentially invaluable resource for the discovery of new chemical entities. Identifying gene clusters by facilitating genetic manipulation result in the discovery of new enzyme pathways and unusual chemical conversions (van Lanen and Shen, 2006). Also, greater challenge lies in assigning functions at the biochemical level to the newly identified genes. Three different types of function-driven approaches, phenotypic detection of gene activity, heterologous complementation of host strains and induced gene expression, are the perfect solution to the problem (Akondi and Lakshmi, 2013; Rath et al., 2011).

So far approaches involving culture-independent methods focus on the genetic complement of single organism. However, approach of metagenomics focuses on microbial community profiling and transcends the limitation of studying individual organisms. The metagenomic approach maximizes the diversity of libraries of marine natural product extracts by studying the DNA directly from marine samples (Kennedy et al., 2010; Venter et al., 2004; Riedlinger et al., 2004; Handelsman, 2004). The approach of metagenomics employs use of whole metagenome shotgun sequencing for the cloning and sequencing of microbial DNA from marine environments (Kennedy et al., 2010). This technique has the advantages of (1) overcoming limitations occurring due to direct DNA cloning; (2) minimizing improper representations of the microbial community; (3) by-passing the major limitations of classical approaches in microbiology; (4) extensive application to explore biosynthetic diversity of microorganisms from extreme environments; (5) high probability of reconstructing the metabolic pathways; and (6) dominant approach to gene, genome, protein and metabolic pathway discovery.

Range of compounds and their biosynthetic gene clusters have been reported with the use of traditional metagenomic approach (Fig. 4a). However, rate of compounds with therapeutic

potential is very low and this is where the classical approach takes a step back. Compelling need for improvement leads our way towards the targeted and function-guided metagenomic screening (Fig. 4b). This modern strategy is the centre for discovery of many compounds of therapeutic importance.

Being a cost effective technique and gaining popularity as next generation sequencing method for genome sequencing involves pyrosequencing (Kennedy et al., 2010; MacLean et al., 2009). As there are benefits there are also certain limitation to the method which is lower read lengths between 200 and 300 bp (Wommack et al., 2008) and thus is suitable for the simplest of consortia. Advances in molecular field have brought new and innovative approaches to the field of biodiscovery such as developing genetic engineering biosynthetic pathways. Better understanding of naturally occurring combinatorial biosynthesis also can lead a way to discover novel antimicrobials. It speeds up the process of generation of derivatives of antibiotics and other secondary metabolites that would be difficult or impossible to generate by medicinal chemistry (Baltz, 2008). In view of current advances in the field of chemical biology, protein folding topology correlations now disclose information on the natural product's ability to recognize biology space and further represent a potential tool for drug design (Kellenberger et al., 2011).

In the field of genome mining, identification of novel natural products by activation of silent clusters through the manipulation of pathway-specific regulatory genes can also be useful (Challis, 2008). Genomics-derived target-based approach is very helpful in screening for new classes of drugs with novel modes of action (Payne et al., 2007). In an effort to enhance cultivability of more microbial types, techniques based on mimicking the natural habitat in which the microorganisms of interest grow and thrive are being developed. Some of these techniques which are effective in cultivation of marine microorganism in low-nutrient media include dilution-to-extinction, culturing in arrays, diffusion chambers and micro-droplet encapsulation (Kaeberlein et al., 2002; Zengler et al., 2002, 2005; Nichols et al., 2008; Dionisi et al., 2012).

Helfrich reported recent progress in pathway engineering, chemical analytics and bioinformatics. It digs out the information regarding genome based polyketide discovery in a more systematic fashion (Helfrich et al., 2014). These methods include bioinformatic tools to predict polyketide core structures, strategies for genetic and metabolic engineering to allocate biosynthetic gene clusters, and analytical tools for detection and structure elucidation. Metabolic engineering of antibiotic now includes novel methods to identify the secondary metabolite biosynthetic gene clusters by genome mining, to clone them, and to express them in heterologous hosts in much higher throughput than before. These technologies now enable metabolic engineering approaches to optimize production yields and to directly manipulate the pathways to generate modified products (Weber, 2014).

It is therefore necessary to assess the past accomplishment of marine actinomycetes natural products and to observe future possibilities that arise from both conventional and new technologies to further explore the biodiversity of marine actinomycetes and their associated secondary metabolites. With their biotechnological and pharmaceutical applications, these bioactive compounds isolated using the above strategies has also increased our understanding of the diversity of marine microbes with their environment and the exploitable resources. A novel approach should include targeting potential gene clusters and use of genome mining strategies in activating these clusters as they are si-

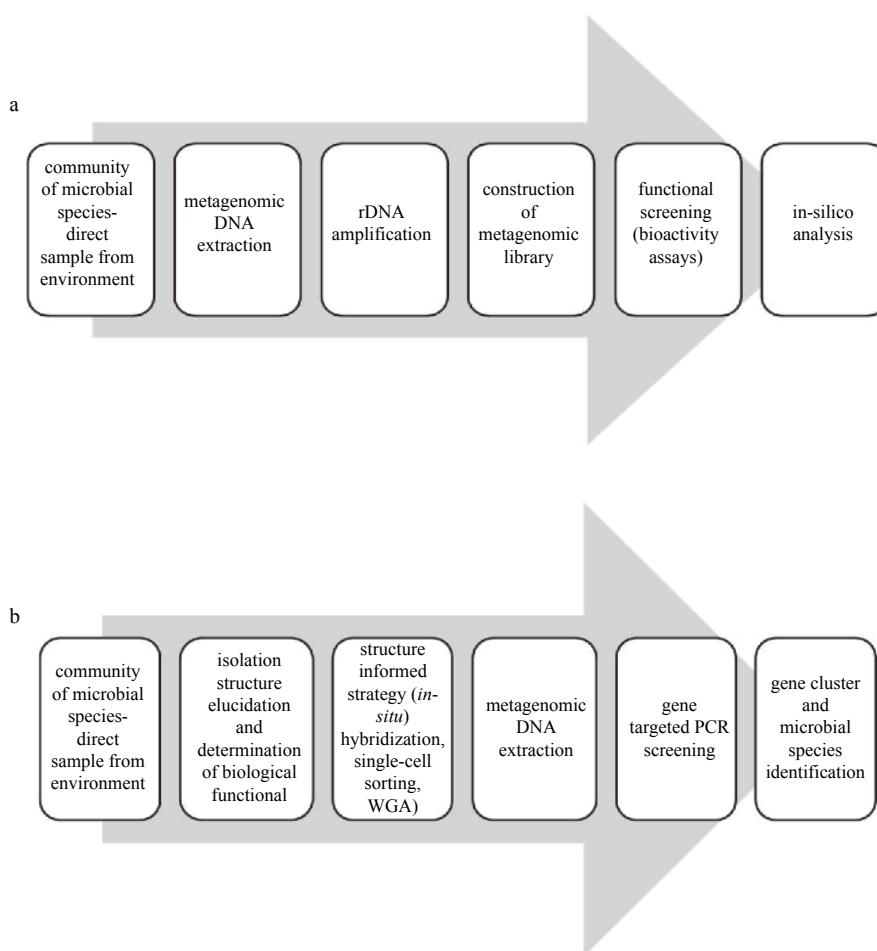


Fig. 4. Traditional functional metagenomic based screening (a) and modern targeted and function-guided screening (b).

lent under typical laboratory conditions.

5 Innovation in the field: genome mining as a tool for detection of secondary metabolites biosynthetic gene clusters

Due to pressing need of new agents for commercial and medicinal uses, there has been a significant improvement in development of new technologies. As an important part of this review, improvement in genomics based strategies and identification of secondary metabolites gene clusters by genome mining are put into light. Also cloning them and expressing them in heterologous host has been in its high rise. So far metabolic engineering manage to over produce secondary metabolites that are important to us (Lee et al., 2009; Corre and Challis, 2009).

Genome mining offers a powerful new pathway generating increased understanding of the chemical or environmental signal that is required for the expression of biological activity. In the presence of effective molecular approaches there is greater than ever genome sequence data that indicate a pool of natural-products. These large volumes of genetic data have been exploited for the whole-genome sequence mining to uncover biosynthetic pathways for previously undetected metabolites. Analysis of full genome sequence of bacteria has shown that the genes governing the biosynthesis of bioactive secondary metabolites tend to be clustered together. Also, these organisms possess more potential secondary metabolic biosynthetic clusters than already reported metabolites (Wenzel and Müller, 2009; Walsh and Fischbach, 2010; Weber et al., 2015; Blin et al., 2013;

Krug and Müller, 2014; Fischbach and Walsh, 2006). Usually under standard fermentation conditions these cryptic or silent pathways are overlooked. Apart from new secondary metabolites discovery, these pathways also contain genes coding for the multidomain and multimodular polyketide synthases (PKS) and nonribosomal peptide synthetases (NRPS) which leads to biosynthesis of various commercially important therapeutic agents (Walsh and Fischbach, 2010). Similarly, distinct gene clusters are encoded within the genome of bacteria that are responsible for biosynthesis of secondary metabolites. The work here is to identify these clusters through genome mining (Hwang et al., 2014).

Advancement in sequencing technologies and novel mass spectrometry (MS) detection tools has generated vast amount of biological information, which can be incorporated into various databases and software tools for prediction of gene cluster and their corresponding secondary metabolite pathway (Weber et al., 2015). Example of one such software is antibiotics and secondary metabolites analysis shell (antiSMASH) which includes rule based as well as statistics based algorithms to identify secondary metabolite biosynthetic gene clusters (Blin et al., 2013). Proteome and metabolome analysis in combination with MS is a link between target secondary metabolite and its biosynthetic gene cluster (Helfrich et al., 2014; Krug and Müller, 2014). There is conserved biochemical reasoning for every class of secondary metabolite biosynthesis and matching this data with the genes in the genome is the logic behind (Fischbach and Walsh, 2006; Hertweck, 2009). The success of MS-based genome mining tech-

niques is governed by availability of two factors: high quality genome annotation data and sensitive mass spectrometers.

Approaches work in the following way:

There are specific fragment pattern in the analytical data generated by MS that contain aminoacyl and glycosyl tags. Now, there is conserved biochemical logic for ribosomal and non-ribosomal peptides which can be used to search these tags against amino acid building blocks predicted from the genome of the target (Kersten et al., 2011, 2013; Chen et al., 2012). Same way glycosyl tags can be used to link to their biosynthetic genes among all the glycosylation genes which are initially characterized by genome mining. Examples of novel metabolites from peptidogenomics and glycogenomics are the discovery of arenimycin B from the marine actinobacterium *Salinispora arenicola* CNB-527, which is effective against multidrug-resistant *Staphylococcus aureus* (Kersten et al., 2011).

Unlike the many advances in genomes mining, however, relatively few genome mining cases are available in rare actinomycetes. Hence, whole genome sequencing techniques represent new opportunities for secondary metabolites discovery. Number of examples shows that these techniques have been successful in unveiling new metabolites that were often overlooked under standard fermentation and detection conditions.

Various methods have been developed that nonspecifically trigger the expression of such “silent gene clusters” in actinomycetes including:

(1) Inducing mutations in ribosomal proteins or RNA polymerase.

(2) Supplementing the fermentation broth with chemicals such as rare earth elements, antibiotics, N-acetyl glucosamine, or particular synthetic compounds having positive effects on the expression of SMBGCs and the yield of their resulting compounds (Ochi and Hosaka, 2013).

(3) Co-culturing producer microorganism with other microorganisms (Charusanti et al., 2012).

So, they are valuable as far as new natural products from underexplored organisms possessing unprecedented structural features as well as novel modes of action can be isolated via these methods. However, to work efficiently in the future and to gain access to therapeutically important compounds, new measures need to be taken for the difficulty faced during cultivation and genetic manipulation of these organisms. Emerging advances in genome mining methods may help overcome these difficulties.

6 Challenges in research on marine actinomycetes

Widespread distribution in marine environments makes actinomycetes one of the most fruitful sources of commercially important compounds. Many factors including the use of enrichment and pre-treatment techniques, selection of growth media and antibiotic supplements should be taken into account for the isolation of actinomycetes from marine environments. High-throughput cultivation is an innovative technique that mimics nature and facilitates the growth of slow-growing actinomycetes by eliminating undesired, fast-growing bacteria. But today culture-dependent methods used in the laboratories are grossly insufficient. A review by Hameş-Kocabaş and Uzel comprehensively evaluates the traditional and innovative strategies used for the isolation of actinomycetes from marine sponge and sediment samples (Hameş-Kocabaş and Uzel, 2012).

Biotechnological and therapeutic potentials of actinomycetes are yet to be fully explored (Sivakumar et al., 2007). Thus, culturing of marine actinomycetes and their bioactivity evaluation are two major challenges in marine actinomycetes research. These

limitations necessitated the culture independent studies and new high throughput screening methods to enhance the pace of research in this area. Even the use of classical approaches of genome mining has its own limitations. Heterologous gene expression is one of factors confining the strength of metagenomics to fully access metabolic profile (Ferrer et al., 2009; Uchiyama and Miyazaki, 2009; Reen et al., 2015). The reasons are (Trindade et al., 2015): (1) Exceedingly different marine factors are difficult to replicate in functional screening. Expression of these marine biota and their associations in simple expression system are challenging. (2) Even if heterologous expression is possible, the product may not be the one that is required. These limitations can be overcome by the use and development of alternative bacterial hosts, expression systems, and multi-host shuttle vectors. (3) Functional screening of metagenomic libraries is constrained by need for the entire cluster to be recovered on a single clone and hence they undersell the true diversity. (4) Due to negative selection in the heterologous system sometimes activities identified from extracts are lost even before structure elucidation. (5) A large proportion of activities which may be toxic to heterologous host can never be represented in metagenomic libraries.

Continuous efforts to characterize marine actinomycete diversity and how adaptations to the marine environment affect secondary metabolite production will create a better perspective of the usefulness of these bacteria as a source of products for biotechnological applications (Jensen, 2010; Binayke et al., 2018).

7 Future prospects and scope

The future efforts in this field should include sound understanding of microbial physiology, metabolism and systematics, as well as taking the knowledge of sequencing of multiple actinomycete genomes and variety of secondary metabolite pathways present in actinomycetes to further extent.

Some points well described by Kurtböke (2012) include: (1) Amplified data of microbial ecology and physiology with an eco-physiological perspective (e.g., characteristics of environmental substrates which would influence microbial growth). (2) Development of more intentional, less conventional isolation procedures, taking into consideration functional diversity and physiological characteristics of indigenous organisms. Design of media or simulation of natural environments. (3) Increased interest in study of extreme or unexplored habitats. (4) Prerequisite for more efficient identification systems like MALDI-TOF Mass Spectrometry. (5) Utilization of new advances (e.g., bioinformatics, gene disruption and heterologous). (6) Exploitation of taxon-chemistry and taxon property so that the molecules that are directly involved in the biosynthesis of secondary metabolites can be used to gain information about the biodiversity of antibiotic production indifferent actinomycetes. (7) Advance in the field to develop new methodology for rapid small scale investigation of natural product extracts and effective dereplication. (8) Design of high throughput effective screening strategies. (9) Screening of known compounds for novel targets and bringing in current understanding of antibiotic action for discovery of new drugs. (10) A new perspective of polyphasic approach and generation of effective computational cluster analysis based on genomic information will no doubt provide significant knowledge to reveal the location as well as taxonomical and chemical identities of previously undetected bioactive actinomycetes. This will surely lead to discoveries and new uses of secondary metabolites with substantial contributions.

Hence more efficient techniques to isolate novel compounds and better understanding biology, taxonomy and ecology of mar-

ine actinomycetes, with the pooled approach including advanced molecular techniques, promise fruitful results in the near future (Jensen et al., 2005a; Rath et al., 2011).

8 Conclusions

The vast scope of exploring biotechnological important and therapeutically active biomolecules from marine actinomycetes has been comprehended recently. However, the exact pharmaceutical potential of marine actinomycetes is yet to be addressed. In spite of vast resources, the marine ecosystem is largely unexplored for potential substances. However actinomycetes always fulfill our expectations to provide novel lead compounds of clinical and pharmaceutical importance and will be there in a long run. Development in traditional and innovative techniques and strategies, continued efforts to characterize marine actinomycete diversity and how adaptations to the marine environment affect secondary metabolite production will greatly increase our capacity to clarify their systematics, to understand their ecology and evolution, and to inform bioprospecting programs. So far as a matter of fact actinomycetes are well known producers of secondary metabolites which indicate the potential for pharmaceutical, food, cosmetic and medical use. Hence, it is of great economic importance and can be exploited to its new horizons for both its industrial and academic interests. There is still scope for a higher magnitude to explore the potential of both marine organisms and marine microorganisms as producers of novel drugs. There is a need for research programs focusing on actinomycetes at the levels of individuals, species, metapopulations and communities. Many studies worldwide have lined up the points towards the research on marine actinomycetes for searching of new drugs or drug leads.

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