Acta Oceanol. Sin., 2019, Vol. 38, No. 6, P. 1–17
https://doi.org/10.1007/s13131-018-1340-z
http://www.hyxb.org.cn
E-mail: hyxbe@263.net

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

Swati Sharma[1*†], Abhay B. Fulke[2*†], Asha Chaubey[3]

[1] CSIR-Indian Institute of Integrative Medicine (CSIR-IIIM), CSIR-Innovation Centre, Mumbai 400053, India

[2] Regional Centre, CSIR-National Institute of Oceanography (CSIR-NIO), Mumbai 400053, India

[3] CSIR-Indian Institute of Integrative Medicine, Jammu180001, India

Received 13 January 2018; accepted 3 July 2018

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 de?ning a new era for bioactive compounds with medical and biotechnological applications.

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

Citation: Sharma Swati, Fulke Abhay B., Chaubey Asha. 2019. Bioprospection of marine actinomycetes: recent advances, challenges and future perspectives. Acta Oceanologica Sinica, 38(6): 1–17, doi: 10.1007/s13131-018-1340-z

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 secret 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

Foundation item: The CSIR-NIO contribution number 6263.

*Corresponding author, E-mail: afulke@nio.org; abhay_fulke@yahoo.co.in

†These authors contributed equally to this work.

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-

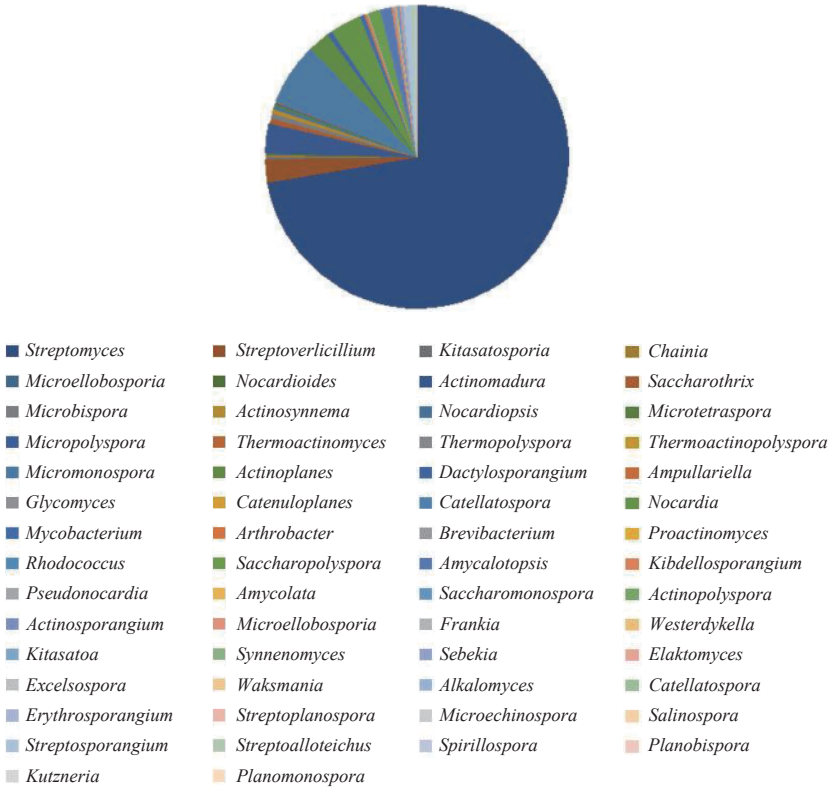

Fig. 1. Number and species of bioactive metabolites producing actinomycetales (adapted and reconstructed from Sharma et al., 2014).

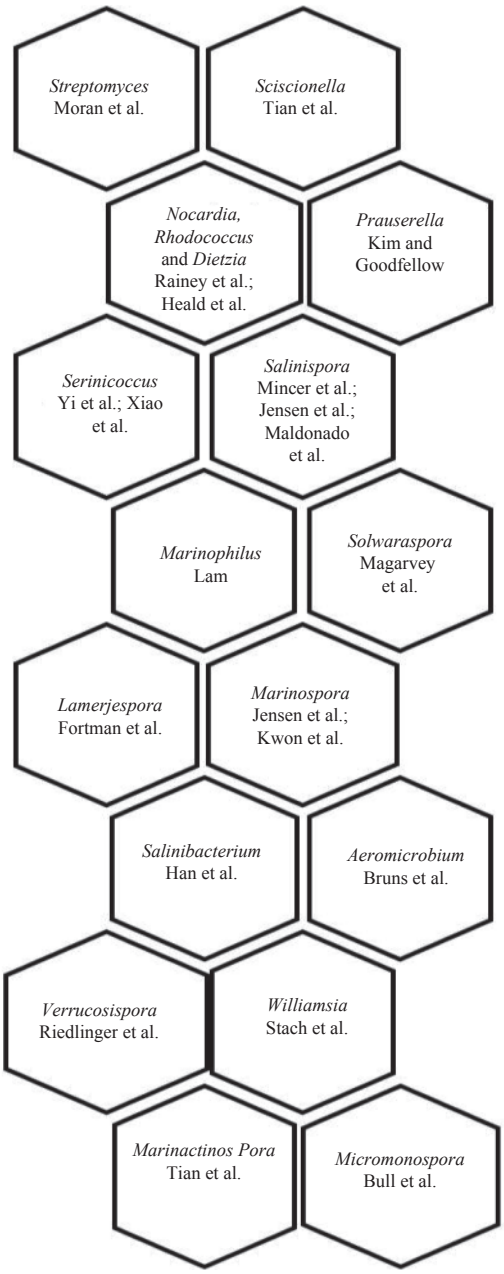

Fig. 2. Representative genera of actinomycetes reported from marine environment.

pensable for the treatment of a variety of microbial infections. Report of actinomycin in 1940 and subsequent reports of streptothricin 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, oviedomycin, 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	*S. noursei ATCC 11455*	Zotchev et al. (2000)
Amphotericin B	*S. nodosus*	Hartse and Bolard (1996)
Natamycin	*S. natalensis*	Pedersen (1992)
Antimycin	*Streptomyces* sp. *SCSIO 1635*	Li et al. (2011)
Urauchimycins (member of antimycin class) Urauchimycins A and B-from marine sponge Ni-80 Urauchimycin C-from marine sediment	*Streptomyces* sp.	Sharma et al. (2014)
Daryamides	*Streptomyces* sp. *CNQ-085*	Asolkar et al. (2006)
Bonactin	*Streptomyces* sp. *BD21-2*	Schumacher et al. (2003)
Chandrananimycins	*Actinomadura* sp.	Maskey et al. (2003b)
Antibacterial agents		
Glaciapyrroles A, B and C	*Streptomyces* sp. *NPS008187*	Macherla et al. (2005)
Abyssomicin C	*Verrucosispora*	Bister et al. (2004)
SBR-22	*Steptomyces psommoticus BT408*	Sujatha et al. (2005)
Thiocoraline	*Micromonospora*	Romero et al. (1997)
Salinamides A and B	*Streptomyces* sp.	Moore et al. (1999)
IB-00208	*Actinomadura*	Malet et al. (2003)
Tetracenomycin D	*Streptomyces corchorusii AUBN(1)/7*	Adinarayana et al. (2006)
Resistoflavine	*Streptomyces chibaensis AUBN(1)*	Gorajana et al. (2007), Kock et al. (2005)
Himalomycins A and B	*Streptomyces* sp. *B6921*	Maskey et al. (2004)
Helquinoline	*Janibacter limosus*	Asolkar et al. (2004)
Chlorinated dihydroquinones	*CNQ-525*	Mercado et al. (2005)
Arenicolide A	*Salinispora arenicola*	William et al. (2007)
Marinomycins	*Marinispora*	Kwon et al. (2006)
Bonactin	*Streptomyces* sp. *BD21-2*	Schumacher et al. (2003)
Chandrananimycins	*Actinomadura* sp.	Maskey et al. (2003b)
Diazepinomicin (ECO-4601)	*Micromonosproa* sp.	Charan et al. (2004)
Frigocyclinone	*Streptomyces griseus*	Bruntner et al. (2005)
Gutingimycin	*Streptomyces* sp.	Maskey et al. (2003a)
Lajollamycin	*Streptomyces nodosus*	Mann (2001)
Rifamycin	*S. arenicola*	Floss and Yu (2005)
β-indomycinone	*Streptomyces* sp.	Biabani et al. (1997)
Essramycin	*Streptomyces* sp.	El-Gendy et al. (2008)
Lynamicins	*Marinispora* sp.	McArthur et al. (2008)
1, 4-Dihydroxy-2-(3-hydroxybutyl)-9, 10-anthraquinone 9, 10-anthrac	*Streptomyces* sp.	Ravikumar et al. (2012)
Bisanthraquinone	*Streptomyces* sp.	Socha et al. (2006)
Antiviral agents: Antiviral activity of marine actinomycetes have 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	*Streptomyces nitrosporeus*	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	*Streptomyces* sp.	Pimentel-Elardo et al. (2010)
Avermectins	*Streptomyces avermitilis*	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	*Streptomyces* 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	*Streptomyces* sp.	Lam (2006)
Salinosporamide A (NPI-0052)	*Salinispora tropica*	Prudhomme et al. (2008)
Cytotoxic agents		
Manumycins	*Streptomyces* sp.	Chauhan et al. (2005)
Salinipyrones	*Salinispora pacifica*	Oh et al. (2008)
Pacificanones	*Salinispora pacifica*	Oh et al. (2008)
Actinofuranones	*Streptomyces* sp.	Cho et al. (2006)

to be continued

Continued from Table 1

Compound	Source	Reference
Nonactin	*Streptomyces* sp.	Jeong et al. (2006)
Resistoflavine	*Streptomyces chibaensis*	Gorajana et al. (2007)
Neomarinones	*Actinomycetales*	Hardt et al. (2000)
Piericidins	*Streptomyces* sp.	Hayakawa et al. (2007)
Lucentamycins	*Nocardiopsis lucentensis*	Cho et al. (2007)
Arenamides	*Salinipora arenicola*	Asolkar et al. (2006)
Piperazimycins	*Streptomyces* sp.	Miller et al. (2007)
Mansouramycin C	*Streptomyces* sp.	Hawas et al. (2009)
Usabamycins	*Streptomyces* sp.	Sato et al. (2011)
Pyridinium	*Amycolatopsis alba*	Dasari et al. (2012)
ML-449(macrolactam)	*Streptomyces* sp.	Jørgensen et al. (2010)
Salinosporamide B & C	*Salinipora tropica*	Williams et al. (2005)
Albidopyrone	*Streptomyces* 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 fiveyear originate from Streptomyces. 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.		
–	*Streptomyces* sp. and *Streptosporangium* sp.	Vijayakumar et al. (2010)
–	*Streptomyces* 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	*Actinomadura* sp.	Maskey et al. (2003b)
Extracellular antialgalsubstance	*Streptomyces neyagawaensis*	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.		
–	*Streptomyces lunalinharesii*	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 *Streptomyces* 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	*Streptomyces pilosus*	Balagurunathan and Radhakrishnan (2007)
Anti-angiogenesis activity: Inhibiting angiogenesis has been considered as an important anticancer strategy to suppress tumor growth and metastasis.		
Streptopyrrolidine	*Streptomyces* sp.	Shin et al. (2008)
Cyclo-(l-Pro-l-Met)	*Nocardiopsis* 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	*Streptomyces* sp.	Renner et al. (1999)
Diazepinomicin (ECO-4601)	*Micromonosproa* sp.	Charan et al. (2004)
Antioxidant agents: In its commercial use as a food additive, the fermenting sponge associated *Streptomyces* isolate (AQBMM35) produced carotenoids namely phytoene which has antioxidant activity (Dharmaraj, 2011).		
Dermacozines A-G	*Dermacoccus*	Abdel-Mageed et al. (2010)
Lipocarbazoles	*Tsukamurella pseudospumae*	Schneider et al. (2009)
2-Allyloxyphenol	*Streptomyces* 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)	*Streptomyces hygroscopoicus*	Chapman and Perry (2004)
Toxin producers: Actinomycetes are also known to produce toxins.		
Tetrodotoxin (TTX)	*Streptomyces* 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	*Streptomyces* sp.	Romero et al. (2012)
Diketopiperazines	*Streptomyces fungicidicus*	Li et al. (2006)
–	*Streptomyces praecox 291-11* *Streptomyces albus*	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 produced 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	*Nocardiopsis* sp.	Stamford et al. (2001)
	Alpha-amylase	*Actinobacterium* (*A-19*)	
		Streptomyces sp. *D1*	
		Streptomyces gulbargensis DAS 131	
2	Protease	*Streptomyces* sp. *MML1614*	Jeyadharshan (2013)
3	Cellulase	*Streptomyces ruber*	Chandramohan et al. (1972)
4	Thrombinase	*Streptomyces venezuelae*	Naveena et al. (2012)
5	L-asparaginase	*Streptomyces* sp. *PDK2*	Dhevagi and Poorani (2006)
		Streptomyces noursei MTCC 10469	
6	Novel extracellular phospholipase C	*Streptomyces* sp.	Mo et al. (2009)
7	New exocytoplasmic, nutritionally controlled endodeoxyribonuclease	*Streptomyces antibioticus*	Cal et al. (1995)
8	Two exocellular nucleases	*Streptomyces antibioticus*	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 (Mukhopadyay 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; Pecznska-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—*Nocardiopsis*, *Nocardia* and *Pseudonocardia* spp.;

(2) SHF (super-high frequency) irradiation—*Streptosporangium* and *Rhodococcus* species;

(3) EHF (extremely high frequency) irradiation—*Nocardiopsis*, *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).

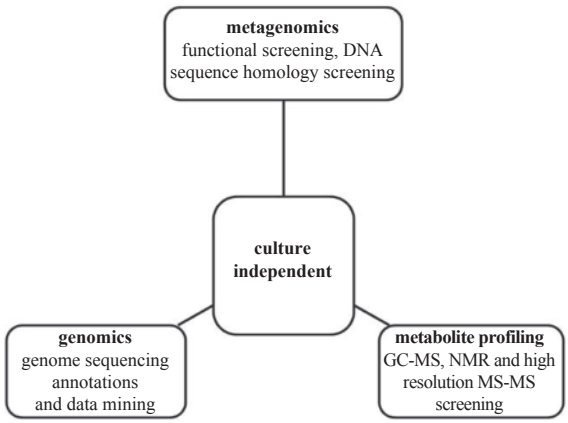

Fig. 3. Culture independent approaches—stage for progression in marine natural product bioprospecting.

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 requiremnets like *Aeromicrobium marinum* (Bruns 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*, *Streptomycetaceae*, *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 (Garcia-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 aslso 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-

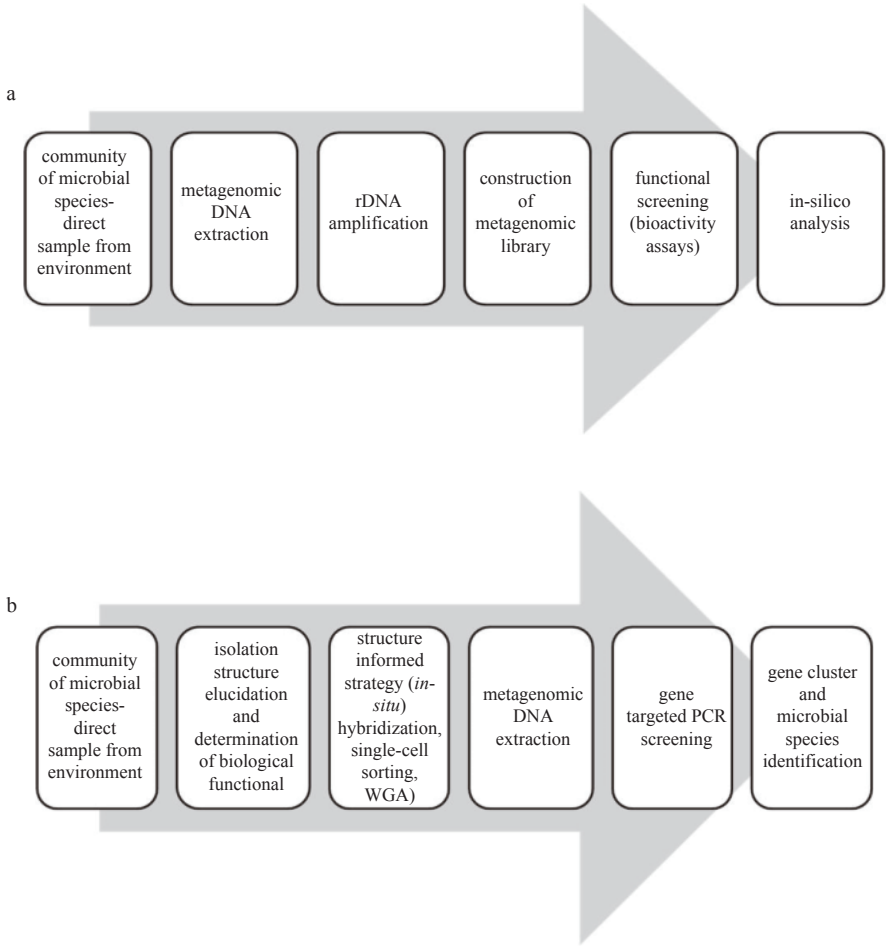

Fig. 4. Traditional functional metagenomic based screening (a) and moderntargeted and function-guided screening (b).

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 factorsconfining 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 perceptive 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 ecophysiological 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 perceptive 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 linedup the points towards the research on marine actinomycetes for searching of new drugs or drug leads.

Acknowledgements

We are grateful to the encouragement from the Director of CSIR-Indian Institute of Integrative Medicine (CSIR-IIIM), and the Director of CSIR-National Institute of Oceanography (CSIR-NIO), Goa and Scientist-in-Charge, CSIR-NIO, Regional Centre, Mumbai.

References

Abdel-Mageed W M, Milne B F, Wagner M, et al. 2010. Dermacozines, a new phenazine family from deep-sea dermacocci isolated from a Mariana Trench sediment. Organic & Biomolecular Chemistry, 8(10): 2352–2362

Adinarayana G, Venkateshan M R, Bapiraju V V, et al. 2006. Cytotoxic compounds from the marine actinobacterium. Bioorganicheskaia Khimiia, 32(3): 328–334

Akondi K B, Lakshmi V V. 2013. Emerging trends in genomic approaches for microbial bioprospecting. OMICS: A Journal of Integrative Biology, 17(2): 61–70, doi: 10.1089/omi.2012.0082

Anzai K, Ohno M, Nakashima T, et al. 2008. Taxonomic distribution of Streptomyces species capable of producing bioactive compounds among strains preserved at NITE/NBRC. Applied Microbiology and Biotechnology, 80(2): 287–295, doi: 10.1007/s00253-008-1510-6

Arbat A B, Zodpe S N. 2014. Biodiversity of *Actinomycetes* species isolated from saline belt of Akola district. Indian Journal of Applied Research, 4(7): 450–452

Arumugam M, Mitra A, Jaisankar P, et al. 2010. Isolation of an unusual metabolite 2-allyloxyphenol from a marine actinobacterium, its biological activities and applications. Applied Microbiology and Biotechnology, 86(1): 109–117, doi: 10.1007/s00253-009-2311-2

Asolkar R N, Jensen P R, Kauffman C A, et al. 2006. Daryamides A-C, weakly cytotoxic polyketides from a marine-derived actinomycete of the genus *Streptomyces* strain CNQ-085. Journal of Natural Products, 69(12): 1756–1759, doi: 10.1021/np0603828

Asolkar R N, Schröder D, Heckmann R, et al. 2004. Helquinoline, a new tetrahydroquinoline antibiotic from *Janibacter limosus* Hel. The Journal of Antibiotics, 57(1): 17–23, doi: 10.7164/antibiotics.57.17

Atta H M. 2007. Production of vitamin B_{12} by *Streptomyces fulvissimus*. Egyptian Journal of Biomedical Sciences, 23(1): 166–184

Balagurunathan R, Radhakrishnan M. 2007. Microbial siderophores-gateway for iron removal. Envis Centre Newsletter, 5: 7–9

Baltz R H. 2008. Renaissance in antibacterial discovery from actinomycetes. Current Opinion in Pharmacology, 8(5): 557–563, doi: 10.1016/j.coph.2008.04.008

Barcina I, Iriberri J, Egea L. 1987. Enumeration, isolation and some physiological properties of actinomycetes from sea water and sediment. Systematic and Applied Microbiology, 10(1): 85–91, doi: 10.1016/S0723-2020(87)80016-4

Bérdy J. 2005. Bioactive microbial metabolites. The Journal of Antibiotics, 58(1): 1–26, doi: 10.1038/ja.2005.1

Bertsch A, Coello N. 2005. A biotechnological process for treatment and recycling poultry feathers as a feed ingredient. Bioresource Technology, 96(15): 1703–1708, doi: 10.1016/j.biortech.2004.12.026

Bhat M K. 2000. Cellulases and related enzymes in biotechnology. Biotechnology Advances, 18(5): 355–383, doi: 10.1016/S0734-9750(00)00041-0

Biabani M A F, Laatsch H, Helmke E, et al. 1997. δ-Indomycinone: a new member of pluramycin class of antibiotics isolated from marine *Streptomyces* sp. The Journal of Antibiotics, 50(10): 874–877, doi: 10.7164/antibiotics.50.874

Binayke A, Ghorbel S, Hmidet N, et al. 2018. Analysis of diversity of actinomycetes from arid and saline soils at Rajasthan, India. Environmental Sustainability, 1(1): 61–70, doi: 10.1007/s42398-018-0003-5

Bister B, Bischoff D, Ströbele M, et al. 2004. Abyssomicin C—A polycyclic antibiotic from a marine *Verrucosispora* strain as an inhibitor of the *p*-aminobenzoic acid/tetrahydrofolate biosynthesis pathway. Angewandte Chemie International Edition, 43(9): 2574–2576

Blin K, Medema M H, Kazempour D, et al. 2013. antiSMASH 2.0—a versatile platform for genome mining of secondary metabolite producers. Nucleic Acids Research, 41(W1): W204–W212, doi: 10.1093/nar/gkt449

Böckle B, Galunsky B, Müller R. 1995. Characterization of a keratinolytic serine proteinase from *Streptomyces pactum* DSM 40530. Applied & Environmental Microbiology, 61(10): 3705–3710

Bode W, Huber R. 1992. Natural protein proteinase inhibitors and their interaction with proteinases. European Journal of Biochemistry, 204(2): 433–451, doi: 10.1111/ejb.1992.204.issue-2

Bredholdt H, Galatenko O A, Engelhardt K, et al. 2007. Rare actinomycete bacteria from the shallow water sediments of the Trondheim fjord, Norway: isolation, diversity and biological activity. Environmental Microbiology, 9(11): 2756–2764, doi: 10.1111/emi.2007.9.issue-11

Brinkhoff T, Santegoeds C M, Sahm K, et al. 1998. A polyphasic approach to study the diversity and vertical distribution of sulfur-oxidizing *Thiomicrospira* species in coastal sediments of the German Wadden sea. Applied and Environmental Microbiology, 64(12): 4650–4657

Bruns A, Philipp H, Cypionka H, et al. 2003. *Aeromicrobium marinum* sp. nov., an abundant pelagic bacterium isolated from the German Wadden sea. International Journal of Systematic and Evolutionary Microbiology, 53(6): 1917–1923, doi: 10.1099/ijs.0.02735-0

Bruntner C, Binder T, Pathom-Aree W, et al. 2005. Frigocyclinone, a novel angucyclinone antibiotic produced by a *Streptomyces griseus* strain from Antarctica. The Journal of Antibiotics, 58(5): 346–349, doi: 10.1038/ja.2005.43

Bull A T, Stach J E M, Ward A C, et al. 2005. Marine actinobacteria: perspectives, challenges, future directions. Antonie van Leeuwenhoek, 87(1): 65–79, doi: 10.1007/s10482-004-6562-8

Burg R W, Miller B M, Baker E E, et al. 1979. Avermectins, new family of potent anthelmintic agents: producing organism and fermentation. Antimicrobial Agents and Chemotherapy, 15(3): 361–367, doi: 10.1128/AAC.15.3.361

Burkholder P R, Pfister R M, Leitz F H. 1966. Production of a pyrrole antibiotic by a marine bacterium. Applied Microbiology, 14(4): 649–653

Butler M S. 2004. The role of natural product chemistry in drug discovery. Journal of Natural Products, 67(12): 2141–2153, doi: 10.1021/np040106y

Cal S, Aparicio J F, De Los Reyes-Gavilan C G, et al. 1995. A novel exocytoplasmic endonuclease from *Streptomyces antibioticus*. Biochemical Journal, 306: 93–100, doi: 10.1042/bj3060093

Carlson J C, Li Shengying, Burr D A, et al. 2009. Isolation and characterization of tirandamycins from a marine-derived *Streptomyces* sp. Journal of Natural Products, 72(11): 2076–2079, doi: 10.1021/np9005597

Castillo U, Myers S, Browne L, et al. 2005. Scanning electron microscopy of some endophytic streptomycetes in snakevine-*Kennedia nigricans*. Scanning, 27(6): 305–311, doi: 10.1002/sca.4950270606

Challis G L. 2008. Genome mining for novel natural product discovery. Journal of Medicinal Chemistry, 51(9): 2618–2628, doi: 10.1021/jm700948z

Chandramohan D, Ramu S, Natarajan R C. 1972. Cellulolytic activity of marine *Streptomycetes*. Current Science, 41: 245–246

Chapman T M, Perry C M. 2004. Everolimus. Drugs, 64(8): 861–872, doi: 10.2165/00003495-200464080-00005

Charan R D, Schlingmann G, Janso J, et al. 2004. Diazepinomicin, a new antimicrobial alkaloid from a marine *Micromonospora* sp. Journal of Natural Products, 67(8): 1431–1433, doi: 10.1021/np040042r

Charusanti P, Fong N L, Nagarajan H, et al. 2012. Exploiting adaptive laboratory evolution of *Streptomyces clavuligerus* for antibiotic discovery and overproduction. PLoS One, 7(3): e33727, doi: 10.1371/journal.pone.0033727

Chater K F. 2006. *Streptomyces* inside-out: a new perspective on the bacteria that provide us with antibiotics. Philosophical Transactions of the Royal Society B: Biological Sciences, 361(1469): 761–768, doi: 10.1098/rstb.2005.1758

Chauhan D, Catley L, Li Guilan, et al. 2005. A novel orally active proteasome inhibitor induces apoptosis in multiple myeloma cells with mechanisms distinct from Bortezomib. Cancer Cell, 8(5): 407–419, doi: 10.1016/j.ccr.2005.10.013

Chen Yunqiu, Ntai I, Ju K S, et al. 2012. A proteomic survey of nonribosomal peptide and polyketide biosynthesis in actinobacteria. Journal of Proteome Research, 11(1): 85–94, doi: 10.1021/pr2009115

Cheng Yuanbin, Jensen P R, Fenical W. 2013. Cytotoxic and antimicrobial napyradiomycins from two marine-derived *Streptomyces* strains. European Journal of Organic Chemistry, 2013(18): 3751–3757, doi: 10.1002/ejoc.201300349

Cho J Y, Kwon H C, Williams P G, et al. 2006. Actinofuranones A and B, polyketides from a marine-derived bacterium related to the genus *Streptomyces* (Actinomycetales). Journal of Natural Products, 69(3): 425–428, doi: 10.1021/np050402q

Cho J Y, Williams P G, Kwon H C, et al. 2007. Lucentamycins A-D, cytotoxic peptides from the marine-derived actinomycete *Nocardiopsis lucentensis*. Journal of Natural Products, 70(8): 1321–1328, doi: 10.1021/np070101b

Choi H J, Kim B H, Kim J D, et al. 2005. *Streptomyces neyagawaensis* as a control for the hazardous biomass of *Microcystis aeruginosa* (Cyanobacteria) in eutrophic freshwaters. Biological Control, 33(3): 335–343, doi: 10.1016/j.biocontrol.2005.03.007

Comroe J H Jr. 1978. Pay dirt: the story of streptomycin. Part I. from waksman to waksman. The American Review of Respiratory Disease, 117(4): 773–781

Corre C, Challis G L. 2009. New natural product biosynthetic chemistry discovered by genome mining. Natural Product Reports, 26(8): 977–986, doi: 10.1039/b713024b

Cuesta C, García-de-la-Fuente R, Abad M, et al. 2012. Isolation and identification of actinomycetes from a compost-amended soil with potential as biocontrol agents. Journal of Environmental Management, 95(S1): S280–S284

Cundliffe E. 1989. How antibiotic-producing organisms avoid suicide. Annual Review of Microbiology, 43: 207–233, doi: 10.1146/annurev.mi.43.100189.001231

Das S, Lyla P S, Khan S A. 2008. Distribution and generic composition of culturable marine actinomycetes from the sediments of Indian continental slope of Bay of Bengal. Chinese Journal of Oceanology and Limnology, 26(2): 166–177, doi: 10.1007/s00343-008-0166-5

Das M, Royer T V, Leff L G. 2007. Diversity of fungi, bacteria, and actinomycetes on leaves decomposing in a stream. Applied and Environmental Microbiology, 73(3): 756–767, doi: 10.1128/AEM.01170-06

Dasari V R R K, Muthyala M K K, Nikku M Y, et al. 2012. Novel Pyridinium compound from marine actinomycete, *Amycolatopsis alba* var. nov. DVR D4 showing antimicrobial and cytotoxic activities *in vitro*. Microbiological Research, 167(6): 346–351, doi: 10.1016/j.micres.2011.12.003

Dharmaraj S. 2011. Study of L-asparaginase production by *Streptomyces noursei* MTCC 10469, isolated from marine sponge *Callyspongia diffusa*. Iranian Journal of Biotechnology, 90(2): 12–108

Dhevagi P, Poorani E. 2006. Isolation and characterization of L-asparaginase from marine actinomycetes. Indian Journal of Biotechnology, 5: 514–520

Dionisi H M, Lozada M, Olivera N L. 2012. Bioprospection of marine microorganisms: Biotechnological applications and methods. Revista Argentina de Microbiologia, 44(1): 49–60

Dixit V S, Pant A. 2000. Hydrocarbon degradation and protease production by *Nocardiopsis* sp. NCIM 5124. Letters in Applied Microbiology, 30(1): 67–69, doi: 10.1046/j.1472-765x.2000.00665.x

Donadio S, Monciardini P, Alduina R, et al. 2002. Microbial technologies for the discovery of novel bioactive metabolites. Journal of Biotechnology, 99(3): 187–198, doi: 10.1016/S0168-1656(02)00209-2

El-Gendy M M A, Shaaban M, Shaaban K A, et al. 2008. Essramycin: a first triazolopyrimidine antibiotic isolated from nature. The Journal of Antibiotics, 61(3): 149–157, doi: 10.1038/ja.2008.124

Ferrer M, Beloqui A, Timmis K N, et al. 2009. Metagenomics for mining new genetic resources of microbial communities. Journal of Molecular Microbiology and Biotechnology, 16(1–2): 109–123

Fiedler H P, Bruntner C, Bull A T, et al. 2005. Marine actinomycetes as a source of novel secondary metabolites. Antonie van Leeuwenhoek, 87(1): 37–42, doi: 10.1007/s10482-004-6538-8

Fischbach M A, Walsh C T. 2006. Assembly-line enzymology for polyketide and nonribosomal peptide antibiotics: logic, machinery, and mechanisms. Chemical Reviews, 106(8): 3468–3496, doi: 10.1021/cr0503097

Floss H G, Yu T W. 2005. Rifamycin-mode of action, resistance, and biosynthesis. Chemical Reviews, 105(2): 621–632, doi: 10.1021/cr030112j

Gallagher K A, Fenical W, Jensen P R. 2010. Hybrid isoprenoid secondary metabolite production in terrestrial and marine actinomycetes. Current Opinion in Biotechnology, 21(6): 794–800, doi: 10.1016/j.copbio.2010.09.010

Garcia-Fernández L F, Reyes F, Sánchez-Puelles J M. 2002. The marine pharmacy: new antitumoral compounds from the sea. Pharmaceut News, 9: 495–501

Goodfellow M, Haynes J A. 1984. Actinomycetes in marine sediments. In: Ortiz-Ortiz L, Bojalil LF, Yakoleff V, eds. Biological, Biochemical, and Biomedical Aspects of Actinomycetes. Orlando: Academic Press, 453–472

Goodfellow M, Williams S T. 1983. Ecology of actinomycetes. Annual Review of Microbiology, 37: 189–216, doi: 10.1146/annurev.mi.37.100183.001201

Gorajana A, Venkatesan M, Vinjamuri S, et al. 2007. Resistoflavine, cytotoxic compound from a marine actinomycete, *Streptomyces chibaensis* AUBN$_1$/7. Microbiological Research, 162(4): 322–327, doi: 10.1016/j.micres.2006.01.012

Haefner B. 2003. Drugs from the deep: marine natural products as

drug candidates. Drug Discovery Today, 8(12): 536–544, doi: 10.1016/S1359-6446(03)02713-2

Hameş-Kocabaş E E, Uzel A. 2012. Isolation strategies of marine-derived actinomycetes from sponge and sediment samples. Journal of Microbiological Methods, 88(3): 342–347, doi: 10.1016/j.mimet.2012.01.010

Han S K, Nedashkovskaya O I, Mikhailov V V, et al. 2003. *Salinibacterium amurskyense* gen. nov., sp. nov., a novel genus of the family *Microbacteriaceae* from the marine environment. International Journal of Systematic and Evolutionary Microbiology, 53(6): 2061–2066, doi: 10.1099/ijs.0.02627-0

Handelsman J. 2004. Metagenomics: application of genomics to uncultured microorganisms. Microbiology and Molecular Biology Reviews, 68(4): 669–685, doi: 10.1128/MMBR.68.4.669-685.2004

Hardt I H, Jensen P R, Fenical W. 2000. Neomarinone, and new cytotoxic marinone derivatives, produced by a marine filamentous bacterium (actinomycetales). Tetrahedron Letters, 41(13): 2073–2076, doi: 10.1016/S0040-4039(00)00117-9

Harmsen H, Prieur D, Jeanthon C. 1997. Distribution of microorganisms in deep-sea hydrothermal vent chimneys investigated by whole-cell hybridization and enrichment culture of thermophilic subpopulations. Applied and Environmental Microbiology, 63(7): 2876–2883

Hartsel S, Bolard J. 1996. Amphotericin B: new life for an old drug. Trends in Pharmacological Sciences, 17(12): 445–449, doi: 10.1016/S0165-6147(96)01012-7

Hawas U W, Shaaban M, Shaaban K A, et al. 2009. Mansouramycins A-D, cytotoxic isoquinolinequinones from a marine *Streptomycete*. Journal of Natural Products, 72(12): 2120–2124, doi: 10.1021/np900160g

Hayakawa M. 2008. Studies on the isolation and distribution of rare actinomycetes in soil. Actinomycetologica, 22(1): 12–19, doi: 10.3209/saj.SAJ220103

Hayakawa Y, Shirasaki S, Kawasaki T, et al. 2007. Structures of new cytotoxic antibiotics, piericidins C_7 and C_8. The Journal of Antibiotics, 60(3): 201–203, doi: 10.1038/ja.2007.23

Helfrich E J N, Reiter S, Piel J. 2014. Recent advances in genome-based polyketide discovery. Current Opinion in Biotechnology, 29: 107–115, doi: 10.1016/j.copbio.2014.03.004

Hertweck C. 2009. The biosynthetic logic of polyketide diversity. Angewandte Chemie International Edition, 48(26): 4688–4716, doi: 10.1002/anie.v48:26

Higginbotham S J, Murphy C D. 2010. Identification and characterisation of a *Streptomyces* sp. isolate exhibiting activity against methicillin-resistant *Staphylococcus aureus*. Microbiological Research, 165(1): 82–86, doi: 10.1016/j.micres.2008.12.004

Hohmann C, Schneider K, Bruntner C, et al. 2009a. Albidopyrone, a new α-pyrone-containing metabolite from marine-derived *Streptomyces* sp. NTK 227. The Journal of Antibiotics, 62(2): 75–79, doi: 10.1038/ja.2008.15

Hohmann C, Schneider K, Bruntner C, et al. 2009b. Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep-sea strain *Streptomyces* sp. NTK 937. The Journal of Antibiotics, 62(2): 99–104, doi: 10.1038/ja.2008.24

Hong Kui, Gao Anhui, Xie Qingyi, et al. 2009. Actinomycetes for marine drug discovery isolated from mangrove soils and plants in China. Marine Drugs, 7(1): 24–44, doi: 10.3390/md7010024

Hough D W, Danson M J. 1999. Extremozymes. Current Opinion in Chemical Biology, 3(1): 39–46, doi: 10.1016/S1367-5931(99)80008-8

Hwang K S, Kim H U, Charusanti P, et al. 2014. Systems biology and biotechnology of *Streptomyces* species for the production of secondary metabolites. Biotechnology Advances, 32(2): 255–268, doi: 10.1016/j.biotechadv.2013.10.008

Imada C. 2005. Enzyme inhibitors and other bioactive compounds from marine actinomycetes. Antonie van Leeuwenhoek, 87(1): 59–63, doi: 10.1007/s10482-004-6544-x

Janssen P H, Yates P S, Grinton B E, et al. 2002. Improved culturability of soil bacteria and isolation in pure culture of novel members of the divisions *Acidobacteria*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Applied and Environmental Microbiology, 68(5): 2391–2396, doi: 10.1128/AEM.68.5.2391-2396.2002

Jensen P R. 2010. Linking species concepts to natural product discovery in the post-genomic era. Journal of Industrial Microbiology & Biotechnology, 37(3): 219–224

Jensen P R, Gontang E, Mafnas C, et al. 2005a. Culturable marine actinomycete diversity from tropical Pacific Ocean sediments. Environmental Microbiology, 7(7): 1039–1048, doi: 10.1111/emi.2005.7.issue-7

Jensen P R, Mafnas C. 2006. Biogeography of the marine actinomycete *Salinispora*. Environmental Microbiology, 8(11): 1881–1888, doi: 10.1111/emi.2006.8.issue-11

Jensen P R, Mincer T J, Williams P G, et al. 2005b. Marine actinomycete diversity and natural product discovery. Antonie van Leeuwenhoek, 87(1): 43–48, doi: 10.1007/s10482-004-6540-1

Jensen P R, Williams P G, Oh D C, et al. 2007. Species-specific secondary metabolite production in marine actinomycetes of the genus *Salinispora*. Applied and Environmental Microbiology, 73(4): 1146–1152, doi: 10.1128/AEM.01891-06

Jeong S Y, Shin H J, Kim T S, et al. 2006. Streptokordin, a new cytotoxic compound of the methylpyridine class from a marine-derived *Streptomyces* sp. KORDI-3238. The Journal of Antibiotics, 59(4): 234–240, doi: 10.1038/ja.2006.33

Jeyadharshan V N. 2013. Production and partial purification of protease by actinomyces species. International Journal of Scientific and Research Publications, 3(4): 1–3

Jørgensen H, Degnes K F, Dikiy A, et al. 2010. Insights into the evolution of macrolactam biosynthesis through cloning and comparative analysis of the biosynthetic gene cluster for a novel macrocyclic lactam, ML-449. Applied and Environmental Microbiology, 76(1): 283–293, doi: 10.1128/AEM.00744-09

Kaeberlein T, Lewis K, Epstein S S. 2002. Isolating "uncultivable" microorganisms in pure culture in a simulated natural environment. Science, 296(5570): 1127–1129, doi: 10.1126/science.1070633

Kalisz H M. 1988. Microbial proteinases. Advances in Biochemical Engineering/Biotechnology, 36: 1–65, doi: 10.1007/BFb0047943

Kathiresan K. 2015. Bioprospecting of marine organisms for novel bioactive compounds. Scientific Transactions in Environment and Technovation, 1(3): 107–120

Kathiresan K, Balagurunathan R, Masilamani S M. 2005. Fungicidal activity of marine actinomycetes against phytopathogenic fungi. Indian Journal of Biotechnology, 4: 271–276

Kellenberger E, Hofmann A, Quinn R J. 2011. Similar interactions of natural products with biosynthetic enzymes and therapeutic targets could explain why nature produces such a large proportion of existing drugs. Natural Product Reports, 28(9): 1483–1492, doi: 10.1039/c1np00026h

Kennedy J, Flemer B, Jackson S A, et al. 2010. Marine metagenomics: new tools for the study and exploitation of marine microbial metabolism. Marine Drugs, 8(3): 608–628, doi: 10.3390/md8030608

Kersten R D, Yang Yuliang, Xu Yuquan, et al. 2011. A mass spectrometry-guided genome mining approach for natural product peptidogenomics. Nature Chemical Biology, 7(11): 794–802, doi: 10.1038/nchembio.684

Kersten R D, Ziemert N, Gonzalez D J, et al. 2013. Glycogenomics as a mass spectrometry-guided genome-mining method for microbial glycosylated molecules. Proceedings of the National Academy of Sciences of the United States of America, 110(47): E4407–E4416, doi: 10.1073/pnas.1315492110

Kieser T, Bibb M J, Buttner M J, et al. 2000. Preparation and analysis of genomic and plasmid DNA. In: Kieser J, Bibb M J, Buttner M J, et al., eds. Practical *Streptomyces* Genetics. Norwich, UK: The John Innes Foundation, 162–170

Kim T K, Fuerst J A. 2006. Diversity of polyketide synthase genes from bacteria associated with the marine sponge *Pseudoceratina clavata*: culture-dependent and culture-independent approaches. Environmental Microbiology, 8(8): 1460–1470, doi: 10.1111/emi.2006.8.issue-8

Kock I, Maskey R P, Biabani M A F, et al. 2005. 1-hydroxy-1-norresist-

omycin and resistoflavin methyl ether: new antibiotics from marine-derived *Streptomycetes*. The Journal of Antibiotics, 58(8): 530–534, doi: 10.1038/ja.2005.73

Komaki H, Sakurai K, Hosoyama A, et al. 2018. Diversity of nonribosomal peptide synthetase and polyketide synthase gene clusters among taxonomically close *Streptomyces* strains. Scientific Reports, 8(1): 6888, doi: 10.1038/s41598-018-24921-y

Krug D, Müller R. 2014. Secondary metabolomics: the impact of mass spectrometry-based approaches on the discovery and characterization of microbial natural products. Natural Product Reports, 31(6): 768–783, doi: 10.1039/c3np70127a

Kumar C G, Takagi H. 1999. Microbial alkaline proteases: from a bioindustrial viewpoint. Biotechnology Advances, 17(7): 561–594, doi: 10.1016/S0734-9750(99)00027-0

Kunz C, Ludwig A, Bertheau Y, et al. 1992. Evaluation of the antifungal activity of the purified chitinase 1 from the filamentous fungus *Aphanocladium album*. FEMS Microbiology Letters, 90(2): 105–109, doi: 10.1111/fml.1992.90.issue-2

Kurtböke D İ. 2012. Biodiscovery from rare actinomycetes: an ecotaxonomical perspective. Applied Microbiology and Biotechnology, 93(5): 1843–1852, doi: 10.1007/s00253-012-3898-2

Kwon H C, Kauffman C A, Jensen P R, et al. 2006. Marinomycins A-D, antitumor-antibiotics of a new structure class from a marine actinomycete of the recently discovered genus "*Marinispora*". Journal of the American Chemical Society, 128(5): 1622–1632, doi: 10.1021/ja0558948

Lam K S. 2006. Discovery of novel metabolites from marine actinomycetes. Current Opinion in Microbiology, 9(3): 245–251, doi: 10.1016/j.mib.2006.03.004

Leach B E, Calhoun K M, Johnson L E, et al. 1953. Chartreusin, a new antibiotic produced by *Streptomyces chartreusis*, a new species. Journal of the American Chemical Society, 75(16): 4011–4012, doi: 10.1021/ja01112a040

Lee S Y, Kim H U, Park J H, et al. 2009. Metabolic engineering of microorganisms: general strategies and drug production. Drug Discovery Today, 14(1–2): 78–88

Lee J G, Yoo I D, Kim W G. 2007. Differential antiviral activity of benzastatin C and its dechlorinated derivative from *Streptomyces nitrosporeus*. Biological & Pharmaceutical Bulletin, 30(4): 795–797

Li Xiancui, Dobretsov S, Xu Ying, et al. 2006. Antifouling diketopiperazines produced by a deep-sea bacterium, *Streptomyces fungicidicus*. Biofouling, 22(3): 187–194, doi: 10.1080/08927010600780771

Li Sumei, Tian Xinpeng, Niu Siwen, et al. 2011. Antimycins from marine *Streptomyces* sp. SCSIO 1635 from the South China Sea. Natural Product Research and Development, 23(1): 10–14

Macherla V R, Liu J, Bellows C, et al. 2005. Glaciapyrroles A, B, and C, pyrrolosesquiterpenes from a *Streptomyces* sp. isolated from an Alaskan marine sediment. Journal of Natural Products, 68(5): 780–783, doi: 10.1021/np049597c

MacLean D, Jones J D G, Studholme D J. 2009. Application of 'next-generation' sequencing technologies to microbial genetics. Nature Reviews Microbiology, 7(4): 287–296

Magarvey N A, Keller J M, Bernan V, et al. 2004. Isolation and characterization of novel marine-derived actinomycete taxa rich in bioactive metabolites. Applied and Environmental Microbiology, 70(12): 7520–7529, doi: 10.1128/AEM.70.12.7520-7529.2004

Maldonado L A, Fenical W, Jensen P R, et al. 2005. *Salinispora arenicola* gen. nov., sp. nov. and Salinispora tropica sp. nov., obligate marine actinomycetes belonging to the family *Micromonosporaceae*. International Journal of Systematic and Evolutionary Microbiology, 55(5): 1759–1766, doi: 10.1099/ijs.0.63625-0

Malet-Cascón L, Romero F, Espliego-Vázquez F, et al. 2003. IB-00208, a new cytotoxic polycyclic xanthone produced by a marine derived *Actinomadura*. I. Isolation of the strain, taxonomy and biological activities. The Journal of Antibiotics, 56: 219–225, doi: 10.7164/antibiotics.56.219

Mann J. 2001. Natural products as immunosuppressive agents. Natural Product Reports, 18(4): 417–430, doi: 10.1039/b001720p

Maskey R P, Helmke E, Laatsch H. 2003a. Himalomycin A and B: isolation and structure elucidation of new fridamycin type antibiotics from a marine *Streptomyces* isolate. The Journal of Antibiotics, 56(11): 942–949, doi: 10.7164/antibiotics.56.942

Maskey R P, Li F C, Qin Song, et al. 2003b. Chandrananimycins A-C: production of novel anticancer antibiotics from a marine *Actinomadura* sp. isolate M048 by variation of medium composition and growth conditions. The Journal of antibiotics, 56(7): 622–629, doi: 10.7164/antibiotics.56.622

Maskey R P, Sevvana M, Usón I, et al. 2004. Gutingimycin: a highly complex metabolite from a marine *Streptomycete*. Angewandte Chemie Internation Edition, 43(10): 1281–1283, doi: 10.1002/(ISSN)1521-3773

McArthur K A, Mitchell S S, Tsueng G, et al. 2008. Lynamicins A-E, chlorinated bisindole pyrrole antibiotics from a novel marine actinomycete. Journal of Natural Products, 71(10): 1732–1737, doi: 10.1021/np800286d

Miller E D, Kauffman C A, Jensen P R, et al. 2007. Piperazimycins: cytotoxic hexadepsipeptides from a marine-derived bacterium of the genus *Streptomyces*. The Journal of Organic Chemistry, 72(2): 323–330, doi: 10.1021/jo061064g

Mincer T J, Fenical W, Jensen P R. 2005. Culture-dependent and culture-independent diversity within the obligate marine actinomycete genus *Salinispora*. Applied and Environmental Microbiology, 71(11): 7019–7028, doi: 10.1128/AEM.71.11.7019-7028.2005

Mincer T J, Jensen P R, Kauffman C A, et al. 2002. Widespread and persistent populations of a major new marine actinomycete taxon in ocean sediments. Applied and Environmental Microbiology, 68(10): 5005–5011, doi: 10.1128/AEM.68.10.5005-5011.2002

Mo S, Kim J H, Cho K W. 2009. Enzymatic properties of an extracellular phospholipase C purified from a marine *Streptomycete*. Bioscience, Biotechnology, and Biochemistry, 73(9): 2136–2137, doi: 10.1271/bbb.90323

Monciardini P, Sosio M, Cavaletti L, et al. 2002. New PCR primers for the selective amplification of 16S rDNA from different groups of actinomycetes. FEMS Microbiology Ecology, 42(3): 419–429

Moore B S, Trischman J A, Seng D, et al. 1999. Salinamides, antiinflammatory depsipeptides from a marine *Streptomycete*. Journal of Organic Chemistry, 64(4): 1145–1150, doi: 10.1021/jo9814391

Moran M A, Rutherford L T, Hodson R E. 1995. Evidence for indigenous *Streptomyces* populations in a marine environment determined with a 16S rRNA probe. Applied and Environmental Microbiology, 61(10): 3695–3700

Mukhopadyay R P, Chandra A L. 1993. Protease of keratinolytic *Streptomycetes* to unhair goat skin. Indian Journal of Experimental Biology, 31: 557–558

Muyzer G. 1999. DGGE/TGGE a method for identifying genes from natural ecosystems. Current Opinion in Microbiology, 2(3): 317–322, doi: 10.1016/S1369-5274(99)80055-1

Nachtigall J, Kulik A, Helaly S, et al. 2011. Atacamycins A–C, 22-membered antitumor macrolactones produced by *Streptomyces* sp. C38. The Journal of Antibiotics, 64(12): 775–780, doi: 10.1038/ja.2011.96

Naveena P, Sakthiselvan P, Elaiyaraju P, et al. 2012. Ultrasound induced production of thrombinase by marine actinomycetes: Kinetic and optimization studies. Biochemical Engineering Journal, 61: 34–42, doi: 10.1016/j.bej.2011.12.007

Newman D J, Cragg G M. 2007. Natural products as sources of new drugs over the last 25 years. Journal of Natural Products, 70(3): 461–477, doi: 10.1021/np068054v

Nichols D, Lewis K, Orjala J, et al. 2008. Short peptide induces an "uncultivable" microorganism to grow in vitro. Applied and Environmental Microbiology, 74(15): 4889–4897, doi: 10.1128/AEM.00393-08

Nicieza R G, Huergo J, Connolly B A, et al. 1999. Purification, characterization, and role of nucleases and serine proteases in *Streptomyces* differentiation. The Journal of Biological Chemistry, 274(29): 20366–20375, doi: 10.1074/jbc.274.29.20366

Niehaus F, Bertoldo C, Kähler M, et al. 1999. Extremophiles as a

source of novel enzymes for industrial application. Applied Microbiology and Biotechnology, 51(6): 711–729, doi: 10.1007/s002530051456

Nimnoi P, Pongsilp N, Lumyong S. 2010. Genetic diversity and community of endophytic actinomycetes within the roots of *Aquilaria crassna* Pierre ex Lec assessed by *Actinomycetes*-specific PCR and PCR-DGGE of 16S rRNA gene. Biochemical Systematics and Ecology, 38(4): 595–601, doi: 10.1016/j.bse.2010.07.005

Niu Xuemei, Li Shenghong, Görls H, et al. 2007. Abyssomicin E, a highly functionalized polycyclic metabolite from *Streptomyces* species. Organic Letters, 9(13): 2437–2440, doi: 10.1021/ol0705999

Noval J J, Nickerson W J. 1959. Decomposition of native keratin by *Streptomyces fradiae*. Journal of Bacteriology, 77(3): 251–263

Ochi K, Hosaka T. 2013. New strategies for drug discovery: activation of silent or weakly expressed microbial gene clusters. Applied Microbiology and Biotechnology, 97(1): 87–98, doi: 10.1007/s00253-012-4551-9

Oh D C, Gontang E A, Kauffman C A, et al. 2008. Salinipyrones and pacificanones, mixed-precursor polyketides from the marine actinomycete *Salinispora pacifica*. Journal of Natural Products, 71(4): 570–575, doi: 10.1021/np0705155

Okami Y, Hotta K. 1988. Search and discovery of new antibiotics. In: Goodfellow M, Williams S T, Mordarski M, eds. Actinomycetes in Biotechnology. San Diego: Academic Press, 33–67

Olano C, Méndez C, Salas J A. 2009. Antitumor compounds from marine actinomycetes. Marine Drugs, 7(2): 210–248, doi: 10.3390/md7020210

Oldfield C, Wood N T, Gilbert S C, et al. 1998. Desulphurisation of benzothiophene and dibenzothiophene by actinomycete organisms belonging to the genus *Rhodococcus*, and related taxa. Antonie van Leeuwenhoek, 74(1–3): 119–132

Olsen G J, Lane D J, Giovannoni S J, et al. 1986. Microbial ecology and evolution: a ribosomal RNA approach. Annual Review of Microbiology, 40: 337–365, doi: 10.1146/annurev.mi.40.100186.002005

Pace N R, Stahl D A, Lane D J, et al. 1986. The analysis of natural microbial populations by ribosomal RNA sequences. In: Marshall K C, ed. Advances in Microbial Ecology. Boston, MA: Springer, 1–55

Pacheco da Rosa J, Korenblum E, Franco-Cirigliano M N, et al. 2013. *Streptomyces lunalinharesii* Strain 235 shows the potential to inhibit bacteria involved in biocorrosion processes. BioMed Research International, 2013: 309769

Pathom-Aree W, Stach J E M, Ward A C, et al. 2006. Diversity of actinomycetes isolated from Challenger Deep sediment (10,898 m) from the Mariana Trench. Extremophiles, 10(3): 181–189, doi: 10.1007/s00792-005-0482-z

Payne D J, Gwynn M N, Holmes D J, et al. 2007. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery, 6(1): 29–40, doi: 10.1038/nrd2201

Pecznska-Czoch W, Mordarski M. 1988. Actinomycete enzymes. In: Goodfellow M, Williams S T, Mordarski M, eds. Actinomycetes in Biotechnology. London: Academic Press, 219–283

Pedersen J C. 1992. Natamycin as a fungicide in agar media. Applied and Environmental Microbiology, 58(3): 1064–1066

Pfleiderer E, Reiner R. 1988. Microorganisms in processing of leather. In: Rehm H J, Reed G, eds. Biotechnology. Germany: VCH Verlagsgesellschaft, 729–743

Piel J. 2004. Metabolites from symbiotic bacteria. Natural Product Reports, 21(4): 519–538, doi: 10.1039/b310175b

Pimentel-Elardo S M, Kozytska S, Bugni T S, et al. 2010. Anti-parasitic compounds from *Streptomyces* sp. strains isolated from Mediterranean sponges. Marine Drugs, 8(2): 373–380

Pisano M A, Sommer M J, Taras L. 1992. Bioactivity of chitinolytic actinomycetes of marine origin. Applied Microbiology and Biotechnology, 36(4): 553–555

Prudhomme J, McDaniel E, Ponts N, et al. 2008. Marine actinomycetes: a new source of compounds against the human malaria parasite. PLoS One, 3(6): e2335, doi: 10.1371/journal.pone.0002335

Qiu Danheng, Ruan Jisheng, Huang Ying. 2008. Selective isolation and rapid identification of members of the genus *Micromonospora*. Applied and Environmental Microbiology, 74(17): 5593–5597, doi: 10.1128/AEM.00303-08

Rahman H, Austin B, Mitchell W J, et al. 2010. Novel anti-infective compounds from marine bacteria. Marine Drugs, 8(3): 498–518, doi: 10.3390/md8030498

Ramesh S, Jayaprakashvel M, Mathivanan N. 2006. Microbial status in seawater and coastal sediments during pre- and post-tsunami periods in the Bay of Bengal, India. Marine Ecology, 27(3): 198–203, doi: 10.1111/mae.2006.27.issue-3

Ramesh S, Mathivanan N. 2009. Screening of marine actinomycetes isolated from the Bay of Bengal, India for antimicrobial activity and industrial enzymes. World Journal of Microbiology and Biotechnology, 25(12): 2103–2111, doi: 10.1007/s11274-009-0113-4

Rashad F M, Fathy H M, El-Zayat A S, et al. 2015. Isolation and characterization of multifunctional *Streptomyces* species with antimicrobial, nematicidal and phytohormone activities from marine environments in Egypt. Microbiological Research, 175: 34–47, doi: 10.1016/j.micres.2015.03.002

Rath C M, Janto B, Earl J, et al. 2011. Meta-omic characterization of the marine invertebrate microbial consortium that produces the chemotherapeutic natural product ET-743. ACS Chemical Biology, 6(11): 1244–1256, doi: 10.1021/cb200244t

Ravikumar S, Gnanadesigan M, Saravanan A, et al. 2012. Antagonistic properties of seagrass associated *Streptomyces* sp. RAUACT-1: a source for anthraquinone rich compound. Asian Pacific Journal of Tropical Medicine, 5(11): 887–890, doi: 10.1016/S1995-7645(12)60165-5

Reen F J, Gutiérrez-Barranquero J A, Dobson A D W, et al. 2015. Emerging concepts promising new horizons for marine biodiscovery and synthetic biology. Marine Drugs, 13(5): 2924–2954, doi: 10.3390/md13052924

Renner M K, Shen Y C, Cheng X C, et al. 1999. Cyclomarins A-C, new antiinflammatory cyclic peptides produced by a marine bacterium (*Streptomyces* sp.). Journal of the American Chemical Society, 121(49): 11273–11276, doi: 10.1021/ja992482o

Riedlinger J, Reicke A, Zähner H, et al. 2004. Abyssomicins, inhibitors of the *para*-aminobenzoic acid pathway produced by the marine *Verrucosispora* strain AB-18-032. The Journal of Antibiotics, 57(4): 271–279, doi: 10.7164/antibiotics.57.271

Riesenfeld C S, Schloss P D, Handelsman J. 2004. Metagenomics: genomic analysis of microbial communities. Annual Review of Genetics, 38: 525–552, doi: 10.1146/annurev.genet.38.072902.091216

Romero F, Espliego F, Pérez Baz J, et al. 1997. Thiocoraline, a new depsipeptide with antitumor activity produced by a marine *Micromonospora*. I. Taxonomy, fermentation, isolation, and biological activities. The Journal of Antibiotics, 50(9): 734–737, doi: 10.7164/antibiotics.50.734

Romero F, Fernández-Chimeno R I, de la Fuente J L, et al. 2012. Selection and taxonomic identification of carotenoid–producing marine actinomycetes. In: Barredo J L, ed. Microbial Carotenoids from Bacteria and Microalgae: Methods and Protocols. Totowa, NJ: Humana Press, 13–20

Sato S, Iwata F, Yamada S, et al. 2011. Usabamycins A–C: new anthramycin-type analogues from a marine-derived actinomycete. Bioorganic & Medicinal Chemistry Letters, 21(23): 7099–7101

Schneider K, Nachtigall J, Hänchen A, et al. 2009. Lipocarbazoles, secondary metabolites from *Tsukamurella pseudospumae* Acta 1857 with antioxidative activity. Journal of Natural Products, 72(10): 1768–1772, doi: 10.1021/np9002178

Schumacher R W, Talmage S C, Miller S A, et al. 2003. Isolation and structure determination of an antimicrobial ester from a marine sediment-derived bacterium. Journal of Natural Products, 66(9): 1291–1293, doi: 10.1021/np020594e

Sharma M, Dangi P, Choudhary M. 2014. Actinomycetes: source, identification, and their applications. International Journal of Current Microbiology and Applied Sciences, 3(2): 801–832

Shin H J, Kim T S, Lee H S, et al. 2008. Streptopyrrolidine, an an-

giogenesis inhibitor from a marine-derived *Streptomyces* sp. KORDI-3973. Phytochemistry, 69(12): 2363–2366, doi: 10.1016/j.phytochem.2008.05.020

Shin H J, Mondol M A M, Yu T K, et al. 2010. An angiogenesis inhibitor isolated from a marine-derived actinomycete, *Nocardiopsis* sp. 03N67. Phytochemistry Letters, 3(4): 194–197, doi: 10.1016/j.phytol.2010.07.005

Shiomi K, Iinuma H, Naganawa H, et al. 1987. Biosynthesis of napyradiomycins. The Journal of Antibiotics, 40(12): 1740–1745, doi: 10.7164/antibiotics.40.1740

Shiomi K, Nakamura H, Iinuma H, et al. 1986. Structures of new antibiotics napyradiomycins. The Journal of Antibiotics, 39(4): 494–501, doi: 10.7164/antibiotics.39.494

Sithranga Boopathy N, Kathiresan K. 2010. Anticancer drugs from marine flora: an overview. Journal of Oncology, 2010: 214186

Sivakumar K, Sahu M K, Thangaradjou T, et al. 2007. Research on marine actinobacteria in India. Indian Journal of Microbiology, 47(3): 186–196, doi: 10.1007/s12088-007-0039-1

Socha A M, LaPlante K L, Rowley D C. 2006. New bisanthraquinone antibiotics and semi-synthetic derivatives with potent activity against clinical *Staphylococcus aureus* and *Enterococcus faecium* isolates. Bioorganic & Medicinal Chemistry, 14(24): 8446–8454

Soria-Mercado I E, Prieto-Davo A, Jensen P R, et al. 2005. Antibiotic terpenoid chloro-dihydroquinones from a new marine actinomycete. Journal of Natural Products, 68(6): 904–910, doi: 10.1021/np058011z

Srinivasan M C, Laxman R S, Deshpande M V. 1991. Physiology and nutritional aspects of actinomycetes: an overview. World Journal of Microbiology and Biotechnology, 7(2): 171–184, doi: 10.1007/BF00328987

Stach J E M, Maldonado L A, Ward A C, et al. 2003. New primers for the class *Actinobacteria*: application to marine and terrestrial environments. Environmental Microbiology, 5(10): 828–841, doi: 10.1046/j.1462-2920.2003.00483.x

Stach J E M, Maldonado L A, Ward A C, et al. 2004. *Williamsia maris* sp. nov., a novel actinomycete isolated from the sea of Japan. International Journal of Systematic and Evolutionary Microbiology, 54(1): 191–194, doi: 10.1099/ijs.0.02767-0

Stamford T L M, Stamford N P, Coelho L C B B, et al. 2001. Production and characterization of a thermostable α-amylase from *Nocardiopsis* sp. endophyte of yam bean. Bioresource Technology, 76(2): 137–141, doi: 10.1016/S0960-8524(00)00089-4

Sujatha P, Bapi Raju KV V S N, Ramana T. 2005. Studies on a new marine *Streptomycete* BT-408 producing polyketide antibiotic SBR-22 effective against methicillin resistant *Staphylococcus aureus*. Microbiological Research, 160(2): 119–126, doi: 10.1016/j.micres.2004.10.006

Sun Wei, Dai Shikun, Jiang Shumei, et al. 2010. Culture-dependent and culture-independent diversity of *Actinobacteria* associated with the marine sponge *Hymeniacidon perleve* from the South China Sea. Antonie van Leeuwenhoek, 98(1): 65–75, doi: 10.1007/s10482-010-9430-8

Takizawa M, Colwell R R, Hill R T. 1993. Isolation and diversity of actinomycetes in the Chesapeake bay. Applied and Environmental Microbiology, 59(4): 997–1002

Tamehiro N, Hosaka T, Xu Jun, et al. 2003. Innovative approach for improvement of an antibiotic-overproducing industrial strain of *Streptomyces albus*. Applied and Environmental Microbiology, 69(11): 6412–6417, doi: 10.1128/AEM.69.11.6412-6417.2003

Thornburg C C, Zabriskie T M, McPhail K L. 2010. Deep-sea hydrothermal vents: potential hot spots for natural products discovery?. Journal of Natural Products, 73(3): 489–499, doi: 10.1021/np900662k

Trindade M, van Zyl L J, Navarro-Fernández J, et al. 2015. Targeted metagenomics as a tool to tap into marine natural product diversity for the discovery and production of drug candidates. Frontiers in Microbiology, 6: 890

Uchiyama T, Miyazaki K. 2009. Functional metagenomics for enzyme discovery: challenges to efficient screening. Current Opinion in Biotechnology, 20(6): 616–622, doi: 10.1016/j.copbio.2009.09.010

Udwary D W, Zeigler L, Asolkar R N, et al. 2007. Genome sequencing reveals complex secondary metabolome in the marine actinomycete *Salinispora tropica*. Proceedings of the National Academy of Sciences of the United States of America, 104(25): 10376–10381, doi: 10.1073/pnas.0700962104

ul Hassan S S, Anjum K, Abbas S Q, et al. 2017. Emerging biopharmaceuticals from marine actinobacteria. Environmental Toxicology and Pharmacology, 49: 34–47, doi: 10.1016/j.etap.2016.11.015

van Lanen S G, Shen Ben. 2006. Microbial genomics for the improvement of natural product discovery. Current Opinion in Microbiology, 9(3): 252–260, doi: 10.1016/j.mib.2006.04.002

Venter J C, Remington K, Heidelberg J F, et al. 2004. Environmental genome shotgun sequencing of the Sargasso sea. Science, 304(5667): 66–74, doi: 10.1126/science.1093857

Vigal T, Gil J A, Daza A, et al. 1991. Cloning, characterization and expression of an α-amylase gene from *Streptomyces griseus* IMRU3570. Molecular and General Genetics MGG, 225(2): 278–288, doi: 10.1007/BF00269860

Vijayakumar R, Murugesan S, Cholarajan A, et al. 2010. Larvicidal potentiality of marine actinomycetes isolated from Muthupet mangrove, Tamilnadu, India. International Journal of Microbiological Research, 1(3): 179–183

Waksman S A. 1943. Production and activity of streptothricin. Journal of Bacteriology, 46(3): 299–310

Waksman S A, Woodruff H B. 1940. Bacteriostatic and bactericidal substances produced by a soil actinomyces. Proceedings of the Society for Experimental Biology and Medicine, 45(2): 609–614, doi: 10.3181/00379727-45-11768

Walsh C T, Fischbach M A. 2010. Natural products version 2.0: connecting genes to molecules. Journal of the American Chemical Society, 132(8): 2469–2493, doi: 10.1021/ja909118a

Wawrik B, Kerkhof L, Zylstra G J, et al. 2005. Identification of unique type II polyketide synthase genes in soil. Applied and Environmental Microbiology, 71(5): 2232–2238, doi: 10.1128/AEM.71.5.2232-2238.2005

Weber T. 2014. In silico tools for the analysis of antibiotic biosynthetic pathways. International Journal of Medical Microbiology, 304(3–4): 230–235

Weber T, Charusanti P, Musiol-Kroll E M, et al. 2015. Metabolic engineering of antibiotic factories: new tools for antibiotic production in actinomycetes. Trends in Biotechnology, 33(1): 15–26, doi: 10.1016/j.tibtech.2014.10.009

Wenzel S C, Müller R. 2009. The impact of genomics on the exploitation of the myxobacterial secondary metabolome. Natural Product Reports, 26(11): 1385–1407, doi: 10.1039/b817073h

Williams P G, Buchanan G O, Feling R H, et al. 2005. New cytotoxic salinosporamides from the marine actinomycete *Salinispora tropica*. The Journal of Organic Chemistry, 70(16): 6196–6203, doi: 10.1021/jo050511+

Williams P G, Miller E D, Asolkar R N, et al. 2007. Arenicolides A-C, 26-membered ring macrolides from the marine actinomycete *Salinispora arenicola*. The Journal of Organic Chemistry, 72(14): 5025–5034, doi: 10.1021/jo061878x

Wommack K E, Bhavsar J, Ravel J. 2008. Metagenomics: read length matters. Applied and Environmental Microbiology, 74(5): 1453–1463, doi: 10.1128/AEM.02181-07

Xiao Jing, Luo Yingxue, Xie Shujie, et al. 2011. *Serinicoccus profundi* sp. nov., an actinomycete isolated fromdeep-sea sediment, and emended description of the genus *Serinicoccus*. International Journal of Systematic and Evolutionary Microbiology, 61(1): 16–19, doi: 10.1099/ijs.0.019976-0

Xiong L, Li J, Kong F. 2004. *Streptomyces* sp. 173, an insecticidal micro-organism from marine. Letters in Applied Microbiology, 38(1): 32–37, doi: 10.1046/j.1472-765X.2003.01437.x

Xu Ying, He Hongping, Schulz S, et al. 2010. Potent antifouling compounds produced by marine *Streptomyces*. Bioresource Technology, 101(4): 1331–1336, doi: 10.1016/j.biortech.2009.09.046

You Jianlan, Xue Xiaoli, Cao Lixiang, et al. 2007. Inhibition of *Vibrio*

biofilm formation by a marine actinomycete strain A66. Applied Microbiology and Biotechnology, 76(5): 1137–1144, doi: 10.1007/s00253-007-1074-x

Zengler K, Toledo G, Rappé M, et al. 2002. Cultivating the uncultured. Proceedings of the National Academy of Sciences of the United States of America, 99(24): 15681–15686, doi: 10.1073/pnas.252630999

Zengler K, Walcher M, Clark G, et al. 2005. High-throughput cultivation of microorganisms using microcapsules. Methods in Enzymology, 397: 124–130, doi: 10.1016/S0076-6879(05)97007-9

Zhang Jinhua, Zhang Liping. 2011. Improvement of an isolation medium for actinomycetes. Modern Applied Science, 5(2): 124–127

Zhang Haitao, Zhang Wei, Jin Yan, et al. 2008. A comparative study on the phylogenetic diversity of culturable actinobacteria isolated from five marine sponge species. Antonie van Leeuwenhoek, 93(3): 241–248, doi: 10.1007/s10482-007-9196-9

Zhou Meiying, Zheng Zhicheng. 1998. Identification of marine actinomycetes S-216 strain and its biosynthetic conditions of antifungal antibiotic. Journal of Xiamen University (Natural Science) (in Chinese), 37(1): 109–114

Zotchev S, Haugan K, Sekurova O, et al. 2000. Identification of a gene cluster for antibacterial polyketide-derived antibiotic biosynthesis in the nystatin producer *Streptomyces noursei* ATCC 11455. Microbiology, 146(3): 611–619, doi: 10.1099/00221287-146-3-611