Marine Microbial Pharmacognosy: Prospects and Perspectives

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Abstract

Modern scientific advancements and research on marine microbes has revealed their significance as producers of therapeutic products useful in treating various human diseases. Microbes in marine habitat have evolved to adapt to the harsh condition that prevails in the ocean. Their struggle to compete for space and nutrients has paved way for the synthesis of different novel enzymes possessing distinctive characteristics. Thus, marine habitat hosts many remarkable microorganisms that offer unique biologically active compounds, enzymes endowed with astonishing properties, and mechanism to survive in extreme environmental conditions. The utilization of marine biotic resources grows at an extraordinary growth rate of 12% per annum and is evident from about 4900 patents filed connected with marine genetic resources and 18,000 natural compounds. This concern has boosted research all over the world to explore the untapped potential hidden in marine microbes, which has lot of biotechnological
applications that includes bioactive compounds (metabolites) for therapeutics, novel enzymes, cosmetics, and nutraceuticals. This book chapter will meticulously deliberate the utilization of marine resources by biotechnological applications for therapeutics like antibiotics, chemical compounds, biopolymer, enzymes, and various microbial biomedical purposes such as drug delivery and tissue engineering from marine biota (bacteria, fungi, and algae).

**Keywords**

Microbial Pharmacognosy · Bioactive compounds · Biomedical application

### 5.1 Introduction

The ocean engulfs about 70% of the area on planet earth whereas the aquatic ecosystem houses nearly 80% of living organisms on the whole biosphere. The marine environment hosts 178,000 different species of microorganisms (34 phyla) as reported by the United Nations Environment Programme on Global Biodiversity Assessment (UEPA 2006). The marine unicellular organisms play a crucial role in the conservation and sustainability of the marine ecosystem. The marine microbes are competent in enduring from volcanic eruptions to Antarctic glacier, and they possess numerous distinctive adaptations compared to the terrestrial microbes. Marine microbes adapt to environmental variations like high salt concentration, extreme temperature, low or higher concentrations of organic matter, high hydrostatic pressure, and other external physiochemical factors. Due to their continued exposure to various environmental changes, they have developed unique defense and survival mechanisms employing secondary metabolites that can sense, adopt, and protect them from such harsh conditions.

Microbes are the modern day marvel, whose potential has not been fully explored, yet they offer extensive application in diverse fields like heavy metal bioremediation (Rainbow 1995), antibiotics and enzyme production (Okami 1986), biodegradation and bioremediation of hydrocarbons (Mohanrasu et al. 2018), biosurfactant production (Maneerat and Phetrong 2007), degradation of plastic debris (Mohanrasu et al. 2018), anti-biofilm activity (Jiang et al. 2011), and polyhydroxybutyrate (bioplastics) synthesis (Arun et al. 2006). Recently, researchers have discovered a number of novel metabolites from marine bioresources including macro or micro algae, bacteria, and fungi that are used as antimicrobial, anti-obesity, antitumorous, antidiabetic, immunological, and therapeutic potential biomolecules. For example, the *Pseudomonas* genus serves as a wellspring of bioactive compounds such as andrimid, bushrin, moiramides, phthalate, pseudopeptide, phloroglucinol, phenazine, pyrroles, pyrrolidinedione, phenanthrene, quinolone, and zafrin for the treatment of many diseases (Romanenko et al. 2008).

The marine microbial biosphere delivers a variety of biomolecules that cater diverse novel biologically active compounds for pharmaceutical applications. This
chapter exclusively focuses on biologically active compounds synthesized by marine microbes for pharmaceutical applications; we highlight the varieties of biological compounds from marine-based algae, bacteria, and fungi (Fig. 5.1 and Table 5.1).

5.2 Past, Present of Marine Microbial Pharmacognosy

In today’s modern world, with increasing population and demanding food industry, marine habitat acts as a crucial food source that caters around 90 million tons of food per year. Due to the huge biodiversity, marine environment offers a variety of biologically active compounds that could be efficiently employed to treat new diseases. Emerging infectious diseases with newly emerging drug-resistant microbial strains demand pristine compounds that would be tailored by marine microbes as researchers have shifted their interest toward the quest for bioactives from marine
Table 5.1 Novel bioactive compounds produced by marine microbes

| Source                        | Compound                        | Activity                        | Literature                  |
|-------------------------------|---------------------------------|---------------------------------|-----------------------------|
| Micromonospora sp.             | Thiocoraline                    | Antitumor, antimicrobial        | Romero et al. (1997)        |
| Streptomyces sp.               | Salinamides                     | Anti-inflammatory               | Moore et al. (1999)         |
| Streptomyces sp.               | Himalomycins                    | Antibacterial                   | Maskey et al. (2003)        |
| Streptomyces sp. KS3           | Komodoquinone A                 | Neuritogenic                    | Itoh et al. (2003)          |
| Streptomyces sp. BD21-2        | Bonactin                        | Antimicrobial                   | Schumacher et al. (2003)    |
| Salinispora tropica            | Salinosporamide A               | Anticancer                      | Feling et al. (2003)        |
| Streptomyces sp. B8652         | Complex compounds               | Anticancer, antimalarial        | Maskey et al. (2004)        |
| Verrucosispora                 | Abyssomicin C                   | Antibacterial                   | Riedlinger et al. (2004)    |
| Verrucosispora sp.             | Abyssomicins                    | Antibacterial                   | Riedlinger et al. (2004)    |
| Streptomyces aureovercillatus  | Aureovercillactam               | Antitumor                       | Mitchell et al. (2004)      |
| Verrucosispora maris           | Abyssomicin C                   | Antibacterial                   | Bister et al. (2004)        |
| Streptomyces sp. M045          | Chinikomycins                   | Antitumor                       | Li et al. (2005)            |
| Streptomyces sp.               | Glyciapyrroles                  | Antibacterial                   | Macherla et al. (2005)      |
| Streptomyces sp.               | 10α,11-dihydroxyamorph-4-ene, 10α,15-dihydroxyamorph-4-en-3-one, and 5α,10α,11-trihydroxyamorph-3-one | Antitumor | Macherla et al. (2005) |
| Thermoactinomyces sp.          | Mechercharmycins                | Antitumor                       | Kanoh et al. (2005)         |
| Streptomyces sp. CNQ-085       | Daryamides                      | Antitumor, antifungal           | Asolkar et al. (2008)       |
| Streptomyces CNQ766            | Actinofuranones                 | Cytotoxic                       | Cho et al. (2006)           |
| Streptomyces sp. KORDI-3238    | Streptokordin                   | Anticancer                      | Jeong et al. (2006)         |
| Streptomyces corchorusii AUBN1/7 | Tetracenomycin D              | Cytotoxic                       | Adinaryan et al. (2006)     |
| Streptomyces sp. QD518         | Selina-4(14),7(11)-dien-8,9-dio | Anticancer                      | Wu et al. (2006)            |
| Streptovercillium              | Butenolides                     | Cytotoxic                       | Li et al. (2006)            |
| Streptomyces sp. NTK 937       | Caboxamycin                     | Anticancer                      | Hohmann et al. (2009c)      |
| Streptomyces sp.               | Piericidins                     | Anticancer                      | Hayakawa et al. (2007)      |
| Source             | Compound                                                                 | Activity          | Literature                        |
|--------------------|---------------------------------------------------------------------------|-------------------|-----------------------------------|
| Nocardopsis lucentensis | Lucentamycins                                                            | Cytotoxic          | Cho et al. (2007)                |
| Streptomyces sp.    | Essramycin                                                               | Antibacterial     | El-Gendy et al. (2008a, b)        |
| Marinispora sp.     | Lynamicins                                                               | Antibacterial     | McArthur et al. (2008)            |
| Salinispora arenicola | Saliniketals                                                             | Anticancer        |                                   |
| Salinispora arenicola | Arenicolides                                                             | Antitumor         | Williams et al. (2007)            |
| Brevibacillus laterosporus | 2-alkylidene-5-alkyl-4-oxazolidinones, lipoxazolidinone A, lipoxazolidinone B | Antimicrobial     | Macherla et al. (2007)            |
| Salinispora pacifica CNS-237 | Pacificanones                                                           | Cytotoxic         | Oh et al. (2008)                  |
| Salinispora pacifica CNS-237 | Pseudomonas stutzeri                                                     | antimicrobial     | Uzair et al. (2008)               |
| Streptomyces sp.    | Piperazimycins                                                            | Cytotoxic         | Miller et al. (2007)              |
| Marinispora sp. (NPS12745) | Lyncamicins B, Lyncamicins C                                              | Antimicrobial     | McArthur et al. (2008)            |
| Salinispora arenicola | Arenamides                                                               | Cytotoxic         | Asolkar et al. (2008)             |
| Streptomyces sp.    | Cyclomarines                                                             | Anti-inflammatory | Schultz et al. (2008)             |
| Pseudomonas stutzeri | Zafrin                                                                   | antimicrobial     |                                   |
| Nocardia sp.        | Ayamycin                                                                  | Antifungal        | El-Gendy et al. (2008a, b)        |
| Streptomyces sannurensis | Marinopyrroles A, Marinopyrroles B                                      | Cytotoxic & MRSA  | Hughes et al. (2008)              |
| Verrucosispora sp.  | Proximincis                                                              | Cytostatic        | Fiedler et al. (2008)             |
| Streptomyces sp. CNQ-418 | Marinopyrroles                                                          | Antibacterial     | Hughes et al. (2008)              |
| Streptomyces sp. Merv8102 | Essramycin                                                              | Antibacterial     | El-Gendy et al. (2008a, b)        |
| Streptomyces sp.    | Mansouramycins                                                           | Cytotoxic         | Hawas et al. (2009)               |
| Streptomyces sp.    | Albidopyrone                                                             | Cytotoxic         | Hohmann et al. (2009a)            |
| Streptomyces sp.    | Carboxamycin                                                             | Antibacterial, cytotoxic | Hohmann et al. (2009b)          |
| Streptomyces sp.    | 2-Allyloxyphenol                                                         | Antimicrobial, antioxidant | Arumugam et al. (2010)          |
| Dermacoccus sp.     | Dermacozines                                                             | Cytotoxic, radical scavenging | Abdel-Mageed et al. (2010) |
| Streptomyces sp.    | ML-449                                                                   | Cytotoxic         | Jørgensen et al. (2010)           |
sources. Though terrestrial plants and microbes have severed as an important source in last couple of decades for biomedical drug discovery and health, the untapped potentials of marine microbes have emerged as widespread resources. 1940s penicillin was discovered by Alexander Fleming whereas the in same decade penicillinase (resistant to penicillin antibiotic) produced by *Staphylococcus aureus* was reported similarly in 1950. To counter this drug resistance, modern pharmaceutical industry has ventured the use of marine environments to foster the next generation of antibiotics. Scientists have isolated in the 1950s the first marine bioactive compounds (spongouridine and spongothymidine) from *Cryptotheca crypta* (Caribbean sponge) and demonstrated its significant anti-cancer and anti-viral properties (Leary et al. 2009). Since, the discovery of marine bioactive metabolites, several interesting molecules were isolated from marine environment, which was evident from accelerated research that resulted in a diverse array of applications like pharmacology, biology, biochemistry, organic chemistry, and ecology (Leary et al. 2009).

| Source                  | Compound                  | Activity                                      | Literature                  |
|-------------------------|---------------------------|-----------------------------------------------|-----------------------------|
| *Nocardiopsis sp.*      | TP-1161                   | Antibacterial                                 | Engelhardt et al. (2010)    |
| *Actinomadura sp.*      | Halomadurones A–D         | Potent Nrf2-ARE activation                    | Wyche et al. (2014)         |
| *Nocardiopsis sp.*      | Nocapyrones H–J           | Pro-inflammatory factor, stronger inhibitory effect on nitric oxide | Kim et al. (2014)           |
| *Micrococcus sp.*       | Microluside A             | Antibacterial activity                        | Eltamany et al. (2014)      |
| *Micromonospora sp.*    | MBJ-0003                  | Moderate cytotoxicity                         | Kawahara et al. (2014)      |
| *Actinomycetospora chlora* | Thiasporines A–C       | Cytotoxicity                                  | Fu and MacMillan (2015)     |
| *Nocardiopsis sp.*      | Diketopiperazine 1        | Sterol O-acyltransferase inhibitor            | Kobayashi et al. (2015)     |
| *Verrucosispora sp.*    | Glycerol 1-hydroxy-2,5-dimethyl benzoate | Anti-MRSA activity                             | Huang et al. (2016)         |
| *Micromonospora sp.*    | Quinoline alkaloid        | Antibacterial activity                        | Thi et al. (2016)           |
| *Pseudonocardia carboxydivorans* | Branimycins B and C     | Antibacterial activities                      | Braña et al. (2017)         |
| *Nocardiopsis sp.*      | Nocazines F and G         | Excellent cytotoxicity                         | Sun et al. (2017)           |
The marine diversity has immense untapped potential, awaits for researchers to unravel it, recently more than 1277 new compounds has been published in 432 papers during 2016 alone and a peak 17% rise in research output during 2018 compared to latter 1490 novel compounds from 477 papers (Blunt et al. 2018). The enormous evolution of technologies in the field of marine biotechnology leads to tremendous therapeutic potent compound breakthroughs from the marine ecosystem. Scientists have found numerous deleterious components possess astonishing therapeutic novel value compounds that are castoff as predator defense mechanisms by marine microbes. Many marine microorganisms have been rigorously investigated over the past 50 years from which 270,000 natural products and 30,000 compounds have been isolated among which 9 compounds have been approved as medical drugs (Blunt et al. 2011; Gerwick and Moore 2012; Rangel and Falkenberg 2015).

5.3 Pharmacological Potential Biomaterials from Marine Algae

Humans had utilized algae mainly for nutrients (protein) produced by Spirulina (Chlorophyta). Marine microalgae are mainly classified into three types based on the pigmentation as red (Khan et al. 2015). With the development of improved technologies, a diverse array of application for algae has been recognized from health care, cosmetics, and pharmaceutical. Polyunsaturated fatty acids (PUFAs) from microalgae have started gaining commercial value (Roy and Pal 2015). There are several compounds isolated from algae that are promising bio alternatives to the existing drug, which exhibits higher efficacy, with nearly less side-effects, and some of them are briefly discussed. The primary producers of marine algae n-3 PUFA have several health benefits such as in treating cardiovascular diseases, brain development, function and as healing for inflammatory conditions. Awad (2000) segregated 3–0-β-D-glucopyranosyl stigmasta-5,25-diene compound from green alga Ulva lactuca, which have potential anti-inflammatory activity. The bioactive compound, Isorawsonol have been isolated by Chen et al. (1994) from tropical green alga Arrainvill arawsonii that exhibited potential anticancer and immunosuppressive effects (Chen et al. 1994).

Cycloeudesmol isolated from marine alga Chondria oppositclada exhibited potent antibiotic activity against Staphylococcus aureus (Fenical and Sims 1974). Ascosalipyrolidinones A and B isolated from green alga Ulva spp. presented potential antiplasmodial activity against Plasmodium falciparum strains NF-54 and K1 (Osterhage et al. 2000). Halitunal compound isolated from Halimeda tuna displays antiviral toward murine coronavirus A59 in in vitro condition (Koehn et al. 1991). Two new compounds, Capisterones A and B, are triterpene sulfate esters isolated from green alga Penicillus capitatus, which shows antifungal activity against marine algal pathogen Lindra thallasiae (Puglisi et al. 2004).

The brown algae color is mainly due to the presence of xanthophyll and fucoxanthin pigments, which mask the presence of other pigments (chlorophyll a and c, β carotenes). Currently there are 1200 compounds reported from brown algae (Phaeophyceae). Leptosins K, K1, and K2 compounds from Sargassum tortile
exhibited antitumor activity against sarcoma 180 as cites and cytotoxicity against cultured P388 cells (Takahashi et al. 1995). The compound Stypoldione from *Stypopodium zonale* brown alga is found to possess ichthyotoxic effect (Gerwicket al. 1979). Cis-dihydroxy tetrahydrofuran isolated from brown alga *Notheia anomala* found in southern coast of Australia showed nematocidal activity against parasitic nematodes such as *Trichostrongylus scolubriformis* and *Haemonchus contortus* (Capon et al. 1998). Lobophorolide isolated from brown alga *Lobophora variegata* possesses potent anti-fungal activity against *C. albicans* and is highly specific against *Dendrobothia salina* and *Lindra thalassiae* (Kubanek et al. 2003).

Lopophorins A and B compounds from brown alga *Lobophora variegata* compound illustrated good anti-inflammatory activity (Jiang et al. 1999). *Dictyota paffii* isolated compound displayed strong anti-human syncytial virus (HSV)-1 activity and moderate activity against human immunodeficiency virus (HIV)-1 reverse transcriptase (Pereira et al. 2004); *Dictyota dichotoma* obtained compounds such as diterpenes, dictyolactone, and sanadaol that showed algicidal activity against dinoflagellate *Alexandrium catanella* (Finer et al. 1979); Ecklonia cava derived 8,8‴- bieckol (Fukuyama et al. 1989); and 8,4‴- bieckol showed activity against HIV-I and fucosterol from *Pelvetia siliquosa* that displayed antidiabetic activity (Lee et al. 2004).

In red algae, the presence of pigments phycoerythrin and phycocyanin are responsible for red coloration, whereas those compounds suppress other pigments xanthophylls, β- carotene, and chlorophyll a and thus are termed as red algae (Bold and Wynne 1985). The red algae *Portieria hornemanii* produced halmon (polyhalogenated monoterpane) and showed antitumor activity in in vitro condition (Fuller et al. 1992). The red algae *Gigartina tenella* compounds Sulquinovosyl diacylglycerol, sulfolipid KM043, and KM043 are a class of 6-sulf-α-D-quinovopyranosyl-(1→3)-1,2 diacylglycerol (SQDG) compounds and have potential antiviral activity against HIV-I reverse transcriptase (Ohata et al. 1998). Chondriamide C and 3- indol acrylamide were isolated from red algae *Chondria atropurpurea* and displayed antiviral activity against HIV-1 and fucosterol from *Pelvetia siliquosa* that displayed antidiabetic activity (Lee et al. 2004).

The red alga *Symphyocladia latiuscula* produce cyclohexanone shown free radical scavenging activity (Choi et al. 2000). *Digenea simplex* derived amino acid (α-alkokainic acid) shown potent neurophysiological activity in mammals (Biscoe et al. 1975; Ferkany and Coyle 1985). *Laurencia pinnata* synthesized compound Laurepinacine and isolaurepinacin showed insecticidal activity (Fukuzawa and Masamune 1981). *Laurencia brongniarti* derived four polybrominated indoles has a potential antimicrobial activity against *Saccharomyces cerevisiae* and *Bacillus subtilis* (Carter et al. 1978). *Tichocarpus crinitus* red algae obtained tichocarpols A and B showed antioxidant activity against *Stronglylocentrotus intermedius* (Ishii et al. 2004).

Fucoxanthin is a member of carotenoid present in various species of brown algae exhibited different pharmaceutical applications such as antioxidant activity,
anticancer, anti-inflammatory, antiobesity, neuroprotective effect, antiangiogenic, and skin protective effect (Kim and Pangestuti 2011). The marine algae–derived sulfated polysaccharides are the source for numerous health beneficial activities such as antioxidant, anticoagulant, anti-allergic, anti-human immunodeficiency virus, immunomodulating activities, and anticancer activities (Ngo and Kim 2013).

### 5.4 Marine Bacteria: A Promising Resource for Biomedical Application

Ever since the inception of mankind, nature has been nourishing us with valuable resources for the sustainability of humans by providing necessity for survival like food, shelter, and protection. Extensive screening of marine actinobacteria was started from early 1969 to formulate antagonistic compounds (Weyland 1969). Early evidence shows members of actinomycetes like *Aeromicrobium marinum*, *Dietzia*, *Marinophilus*, *Rhodococcus*, *Salinibacterium*, *Salinispora*, *Solwaraspora*, *Streptomyces*, *Verrucosispora*, *Arthrobacter*, *Streptomyces*, *Corynebacterium*, *Frankia*, *Micrococcus*, and *Micromonospora* synthesize numerous important compounds that have a huge variety of pharmaceutical applications (Solanki et al. 2008).

Marine actinobacteria are the main source for novel secondary metabolites, around the 1970s there were only 11 genera of actinomycetes reported and then in 2005 the number rose to 100 whereas in 2010 the numbers doubled to around 220. The reason behind such a sharp increase in genera is the advancements in sequencing techniques that revealed novel actinomycetes (Subramani and Aalbersberg 2013). Actinobacteria are filamentous, Gram-positive bacteria belonging to the Actinomycetaceae family. *Streptomyces* are known for their unsurpassed amount of secondary metabolite productions that account for 80% actinobacterial natural products (Manivasagan et al. 2014a, b). The marine actinobacteria are found in diverse biological sources (seawater and sediment, sponges, seaweeds, fish, mollusks, and mangroves) and several reports indicated that marine actinobacteria have several biotechnological applications such as antitumor agents, antibiotics, enzyme, immunosuppressive agents, and pigments (Fenical and Jensen 2006; Bull and Stach 2007; Dharmaraj 2010; Mayer et al. 2011).

The extensive search of bioactive compounds from microorganisms has led to the discovery of 23,000 antibiotics, and several reports have been published related to marine actinobacteria that are biologically active molecules (Lam 2006; Solanki et al. 2008; Zotchev 2012; Manivasagan et al. 2014a, b; Subramani and Sipkema 2019) Apparently, only minor fraction of marine actinomycetes natural products were discovered, but with recent sophisticated techniques made accessibility for isolation and identification of numerous bioactive compounds, which are in pipelines for antimicrobial, anticancer, anti-inflammatory and neuromodulating drugs.
5.4.1 Antibacterial Activity

Typically, antibacterial activity implies any element that kills the bacteria or inhibits bacterial growth or it will help to inhibit or kill the infectious diseases causing antibiotic-resistant microorganisms. Riedlinger et al. (2004) isolated novel polycyclic polyketide (Abyssomicin C) antibiotic from *Verrucosispora* sp., a potent inhibitor of p-aminobenzoic acid biosynthesis that will lead to inhibition of folic acid biosynthesis, an earlier stage inhibition than the well-known synthetic sulfa drugs. Abyssomicin C has potential antibacterial activity against vancomycin-resistant, against Gram-positive bacteria and multi-drug resistant *Staphylococcus aureus*. A novel compound, bonactin displays antimicrobial activity against both Gram-positive and Gram-negative bacteria that are obtained from the liquid culture of *Streptomyces* sp. BD21–2, the culture was accumulated from Kailua Beach, Oahu, Hawaii (Schumacher et al. 2003).

El-Gendy et al. (2008a, b) isolated *Streptomyces* sp. Merv8102 from sediments of the Mediterranean Sea at the Egyptian Coast and extracted Essramycin (triazolopyrimidine) antibiotic. The compounds shown antibacterial activities against Gram-positive, Gram-negative bacteria like as *Bacillus subtilis* (ATCC 6051), *Escherichia coli* (ATCC 10536), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 10145), and *Micrococcus luteus* (ATCC 9341). Hughes et al. (2008) isolated *Streptomyces* sp. CNQ-418 from La Jolla, California, and extracted densely halogenated and axially chiral metabolites of marinopyrroles A that contain uncommon bispyrrole structure. The marinopyrroles have potential antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Caboxamycin is a new antibiotic (benzoxazole) produced by *Streptomyces* sp., are isolated from deep-sea sediments of Canary Basin has inhibitory activity against Gram-positive bacteria (Hohmann et al. 2009a, b, c).

5.4.2 Antifungal Activity

Several unique structural features of bioactive compounds were obtained from a variety of marine actinomycetes, yet research is conducted to find the novel antibiotics against pathogenic fungi (Subramani and Sipkema 2019). The common saprophytic nature *Streptomyces* species are significant to produce complex antibiotics and biopolymers (Wanner 2009). In south China, the sponge (*Craniella australiensis*) associated Marine *Streptomyces* sp. DA11 was found to produce chitinase enzyme that exhibited antifungal activities against *Candida albicans* and *Aspergillus niger* (Han et al. 2009).

Daryamides are a novel antifungal compound isolated from marine sediment *Streptomyces* strain, CNQ-085, that shows antifungal activities against *Candida albicans* with moderate or weak cytotoxicity against human colon carcinoma cell line HCT-116 (Asolkar et al. 2008). The antibiotic N-(2-hydroxyphenyl)-2-phenazinamine (NHP) was obtained from *Nocardia dassonvillei*, which has antifungal activity against *C. albicans* (Gao et al. 2012). Numerous compounds revealed
antifungal activity such as Trioxacarcins, Bonactin, Aureoverticillactam, Rapamycin, FK520 Ascomycin, and Jinggangmycin against some clinically important pathogens like *Aspergillus flavus*, *Trichoderma ressei*, *C. albicans*, *Aspergillus niger*, and *Alternaria alternate*.

### 5.4.3 Anticancer Activity

In recent years, cancer has been the second leading disease with high fatality of about 9.6 million death in 2018. Thus a huge urge for anticancer compounds have raised, result in diverse avenue of researchers extending further pursuit in finding novel anticancer compounds from actinobacteria. Cancer is one of the leading human health problems, breast cancer is responsible for second most causes of deaths in women (Ravikumar et al. 2010). Several therapeutic treatments are available to counter cancer, which includes immunotherapy, radiotherapy, and chemotherapy even though cancer could not be defeated till date as a major issue for mankind (Gillet et al. 2007). Salinosporamide A has shown inhibitory effects against various malignant cell types that were isolated from *Salinispora tropica* in oceanic sediments (Prudhomme et al. 2008). Salinosporamide A is a proteasome inhibitor which leads to apoptosis in multiple myeloma cells, subsequently entered to phase I of human trials for solid tumors, multiple myeloma and lymphoma (Jensen et al. 2007; Feling et al. 2003). Stritzke et al. (2004) isolated *Streptomyces* sp. B6007 from mangrove sediment in Papua New Guinea, acquired caprolactones, which showed moderate cytotoxicity and low cytotoxicity against cancer cells. Miller et al. (2007) isolated *Streptomyces* sp. CNQ-593 from marine sediments in Guam, and piperazimycins A-C (cyclic hexadepsipeptides) were extracted from the fermentation broth of a *Streptomyces* sp. with cytotoxic activities against the human colon carcinoma HCT-116 cell line with cytotoxicity of GI50 of 76 ng/mL for each. Piperazimycin A also exhibits potent vitro biological activity against multiple (60) cancer cell lines. *Nocardiopsis lucentensis* strain CNR-712 produced Lucentamycins 3-methyl-4-ethyldene proline-containing peptides and Lucentamycins showed cytotoxicity against HCT-116 cell line (IC50 values of 0.20 and 11 μM) (Cho et al. 2007).

### 5.4.4 Cytotoxic and Cytostatic Activity

Salinosporamide A has shown potential cytotoxicity against HCT-116 human colon carcinoma, MDA-MB-435 breast cancer, SF-539 CNS cancer, NCI-H226 non-small cell lung cancer, and SK-MEL-28 melanoma cells (Feling et al. 2003). Two new polyketides furanones A and B have been isolated from fermentation broth of *Streptomyces* CNQ766, found in the marine sediments displayed weak in vitro cytotoxicity against macrophages and splenocyte T-cells (Cho et al. 2006). *Nocardiopsis lucentensis* strain CNR-712 isolated from the sediment of saline pond in Bahamas exhibits Lucentamycins compound (3-methyl-4-
ethylidene-proline-containing peptides) that showed cytotoxicity against colon carcinoma HCT-116 cell line (IC50 values of 0.20 and 11 μM) (Cho et al. 2007). Arenamides A is a cyclohexa depsipeptide, isolated from the fermented broth of actinobacterial *S. arenicola* CNT-088 strain obtained from a depth of 20 m marine sediments in Kandavu Island chain, Fiji. Arenamides A possess weak in vitro cytotoxicity against human colon carcinoma HCT-116 (IC50 values of 13.2 and 19.2 g/mL) (Asolkar et al. 2008). The cyclic hexadepsipeptides, Piperazimycins were obtained from *Streptomyces* sp. CNQ-593 fermentation broth, exhibited in vitro cytotoxic against human colon carcinoma HCT-116 cell line melanoma (average LC50 of 0.3 μM), leukemia cell line (average LC50 of 31.4 μM), prostate cell lines (average LC50 of 0.6 μM), and central nervous system (average LC50 of 0.4 μM), respectively. Proximicins A, B, and C produced by *Verrucosispora* strain MG-37, *Verrucosispora maris* AB-18-032, displayed strong cyostatic effect against various human tumor cell lines such as hepatocellular carcinoma Hep G2 (GI50 of 0.82, 9.5, and 0.78 μM), adenocarcinoma AGS (GI50 of 0.6, 1.5 and 0.25 μM), and hepatocellular carcinoma Hep G2 (GI50 of 0.82, 9.5, and 0.78 μM, respectively) (Schneider et al. 2008).

**5.4.5 Anti-Inflammatory and Anti-Parasitic Activity**

One of the major challenges faced by developing tropical countries are infectious diseases that is one of the foremost causes of death. About 335 infectious diseases were reported between 1940 to 2004 (Jones et al. 2008). The prominent new discovery of effective bioactive compounds from marine environment has started countering the burden of infectious disease. Abdelmohsen et al. (2010) reported 90 actinomycetes from 11 different species with anti-infective activities against clinically potential organisms such as Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*), Gram-positive (*E. faecalis, S. aureus*) bacteria, human parasites (*Leishmania major, Trypanosoma brucei*), and fungi (*C. albicans*). Globally, the parasitic disease is one of the major health problems to humans, and it is responsible for one million deaths every year and it is almost close to the number of deaths caused by AIDS (Antoszczak et al. 2019; Bhatti et al. 2016). The tropical disease caused by parasitic protozoa *Leishmania*, the species are *Leishmania major, L. amazonensis, Leishmania aethiopica, L. tropica, Leishmania mexicana, Leishmania braziliensis, Leishmania donovani*, and *Leishmania Mexicana*. Pimentel-Elardo et al. (2010) obtained secondary metabolites form marine sponge associated *Streptomyces* sp. that showed antiparasitic activities against *T. brucei* (staurosporine IC500.022 μM; valinomycin IC500.032 μM; butenolide IC5031.77 μM) and *L. major* (staurosporine IC505.30 μM; valinomycin IC50 < 0.11 μM;).
5.4.6 Antimalarial and Antiviral Activity

Malaria remains one of the devastating infectious diseases globally caused by protozoan parasites of the *Plasmodium* genus, and its species include *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* that are together responsible for two million deaths with 300 million clinical cases annually. The global prevalence evidently showed that *P. falciparum* causes higher mortality rates compared to other species of *Plasmodium* (World Health Organisation 2014). The potential peptide from *Streptomyces* sp. LK3 (JF710608) was isolated from a Nicobar marine sediment sample that exhibited antiplasmodial activity with IC50: 25.78 mg/ml (Karthik et al. 2014). Marinacarbolines (A – D) compounds are produced by *Marinactinospora thermotolerans* SCSIO 00652 which belongs to *Nocardiopsacea* family, exhibited antiplasmodial activity against *Plasmodium falciparum* with IC50 values ranging from 1.92 to 36.03 μM (Huang et al. 2011). Marine actinobacteria *Streptomyces nitrosporeus* derived compound benzastatin exhibits antiviral activity against simplex virus type 1 (HSV-1), *Vesicular stomatitis virus* (VSV), *Herpes simplex* virus type 2 (HSV-2) with EC50 values of 1.92, 1.99, and 0.53 μg/mL (Lee et al. 2007).

5.4.7 Antioxidant and Anti-Angiogenesis

Antioxidant compounds retard or prevent the oxidation of lipid. The marine isolate *Nocardiopsis alba* produced (Z)-1-((1-hydroxypenta-2,4-dien-1-yl)oxy) anthracene-9,10-dione compound showed significant in vitro antioxidant capacity (Janardhan et al. 2014). The *Streptomyces VITSVK5* spp. was isolated by marine sediment at the Marakkanam coast in the Bay of Bengal, India, with a compound 5-(2,4-dimethylbenzyl)pyrrolidin-2-one (DMBPO), which exhibited significant antioxidant activity (50.10% at 5 μg/ml DMBPO) (Saurav and Kannabiran 2012). Secondary metabolites, Dermacozines A-G (phenazine compounds) were obtained from *Dermacoccus*, which shows significant antioxidant properties (Pathom-Aree et al. 2006). Angiogenesis is an essential step for the formation of new blood vessels from pre-existing vessels and it is a vital step for tumor cell proliferation (Risau 1997). *Streptomyces* sp. isolated from the deep-sea sediment at Ayu Trough exhibit Streptopyrrolidine compounds with significant anti-angiogenesis activity (Shin et al. 2008). The compound Cyclo-(L-Pro-L-Met) was isolated from fermentation broth of a marine-derived actinomycete *Nocardiopsis* sp. 03 N67 showed anti-angiogenesis activity against human umbilical vein endothelial cells (HUVECs) (Shin et al. 2010).

5.4.8 Exopolysaccharides (EPSs)

Polysaccharides are high molecular weight polymers that are vital material for synthesizing microbial and plant cell walls, and they can be produced as both intracellular or extracellular polysaccharides (EPSs) during extreme environmental
conditions. These natural polysaccharides have an exceptional physical characteristic that has extensive applications in the pharmaceutical field. Okutani (1984, 1992) reported polysaccharides from *Vibrio* and *Pseudomonas* with antitumor, antiviral, and immunostimulant activities. *A. infernus* produced exopolysaccharide displaying anticoagulant property (Senni et al. 2011).

**5.4.9 Biosurfactants**

Biosurfactants or biological surfactants are microbial compounds with a wide range of structural variety (fatty acids, glycolipids, lipopeptides, phospholipids and neutral lipids, polysaccharide-protein complexes) produced by bacteria, yeast, and fungi (Mnif and Ghribi 2015). Initially, biosurfactants are used in pollution remediation and some surface-active compounds are used as anti-adhesive agents against several pathogens, anti-biofilm against human multi-drug resistant pathogens, antibacterial, antifungal, antiviral, and anti-cancer activities (Singh and Cameotra 2004).

**5.4.10 Microbial Biopolymers**

The microbial origin naturally occurring biopolymers are produced by variety of microorganisms, most of them are of bacterial sourced biopolymers. Bacterial polyhydroxyalkanoates (PHAs) are polyesters synthesized by a wide variety of 300 Gram-positive and Gram-negative species as a carbon/energy storage material (Rehm 2003). Due to its microbial origin, PHB is gaining more interest in medical applications. The unique properties of these polymers are utilized as drug carriers, biocontrol agents, antibacterials, tissue engineering, biodegradable implants, anticancer agents, and also as memory enhancers (Ray and Kalia 2017).

**5.5 Pharmacological Effects of Marine Fungi-Derived Biomaterials**

Marine fungi are rich in diversity of species, phylogenetic distribution and natural products (NPs) whereas in recent years extensive research has provided thorough data about marine resources (Richards et al. 2012; Imhoff 2016; Rämä et al. 2016; Taylor and Cunliffe 2016). The diverse physical and chemical growth conditions of fungi are the prime reason for the production of novel drugs whereas certain marine fungal metabolic pathways are entirely distinct from terrestrial fungi (Kijjoa and Sawangwong 2004; Abdel-Lateff 2008). Marine Fungi are a potential producer of secondary metabolites like peptides, alkaloids, terpenes, and mixed biosynthesis compounds. Two new indole alkaloids, (2–3, 3- dimethylprop-1- ene)-epicostaclavine and (2–3, 3-dimethylprop-1-ene)-costaclavine, are known compounds of costaclavine, fumgaclavine with antibacterial activity obtained from *Aspergillus fumigates* (Kossuga et al. 2012).
Several marine fungi such as *Trimmatostroma salinum*, *Phaeotheca triangularis*, *Aureobasidium pullulans*, *Hortaea werneckii*, and *Cryptococcus liquefaciens* produce photo-protective compounds (mycosporines). These compounds absorb UV in the range of 310–320 nm (Kogej et al. 2006). Zopfiellamide A is a pyrrolidinone derivative; it was obtained from marine fungi *Zopfiella latipes*, which inhibits the growth of Gram-negative *Acinetobacter calcoaceticus* and Gram-positive *Bacillus subtilis*, *Bacillus brevis*, *Corynebacterium insidiosum*, *B. licheniformis*, *Micrococcus luteus*, *Corynebacterium insidiosum*, *Arthrobacter citreus*, *Mycobacterium phlei*, and *Streptomyces* sp. (Daferner et al. 2002). Marine fungal antiviral compounds such as phomasetin, equisetin, and integric acid showed significant anti-HIV activities based on bioassay experiments, and Sansalvamide A compound obtained from *Fusarium* sp. was found against pathogenic poxvirus *Molluscum contagiosum* (MCV) (IC50 = 124 μM) (Hwang et al. 1999).

5.6 Conclusion

This chapter provides firsthand information of marine microbial products and its marine genetic resources of commercial interest. The marine microbes possess potentially untapped resources, and if utilized properly they will lead to the discovery of novel compounds that can revolutionize the pharmaceutical industry. In recent years, a number of patents and scientific publications have demonstrated the importance of marine genetic resources to the scientific community. The remarkable new methodologies of underwater exploration, bioassays, recent technology in cultivation of marine microorganisms combined with proteomics, genomics, DNA shuffling, combinatorial chemistry, bioinformatics, and DNA shuffling are used to rapidly screen the bioactive compounds from marine microbes. Marine microbes can produce chemically unique secondary metabolites, will have greatest impact on marine natural products (MNP), and will eventually lead to revealing unexplored pharmaceutical significant bioactive compounds. As a result of improved methodologies in marine microbes and bioactive metabolites isolation has led to successful pipelines in pharmaceutical fields, Carrol et al. (2019) clearly elucidated that in last 10 years there is about 41% jump in discoveries of MNP was observed.

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