



Review Article

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Marine Actinobacteria: A Potential Avenue to Novel Pharmaceutically Active Compounds

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To Cite This Article: Ahmed Shuikan*. Marine Actinobacteria: A Potential Avenue to Novel Pharmaceutically Active Compounds. Am J Biomed Sci & Res. 2025 25(3) AJBSR.MS.ID.003326, DOI: [10.34297/AJBSR.2025.25.003326](https://doi.org/10.34297/AJBSR.2025.25.003326)

Received: 📅 December 26, 2024; **Published:** 📅 January 16, 2025

Abstract

Bioactive compounds derived from marine actinobacteria enrich the field of pharmaceutical industries. Secondary metabolites of marine actinobacteria have been tested against pathogenic bacteria, fungi, viruses, parasites, different cell lines and as immunomodulatory agents. In the marine environment, different genera of actinobacteria may live free in marine sediments or associated with several invertebrate and vertebrate organisms. Different marine actinobacterial genera have been identified such as *Streptomyces*, *Actinomyces*, *Salinispora*, *Micrococcus*, *Micromonospora*. Of these, *Streptomyces* sp. has received much attention because of its ability to produce an enormous number of secondary metabolites. The potent antimicrobial activities of these compounds make them a promising alternatives to overcome drug resistant microbes. In addition, several marine actinobacteria derived compounds have potent cytotoxic activities against several cell lines. This property has been exploited to secure save and potent anticancer alternative instead of traditional cancer therapies. In the current review, we reviewed the pharmaceutical importance of marine actinobacteria. For this purpose, we collected the most recent data regarding the bioactivities of marine actinobacteria derived compounds. The origin, distribution and diversity of marine actinobacteria are discussed. The data presented in this review emphasize the importance of marine actinobacteria and should draw the attention toward these marvellous bacteria.

Introduction

Actinobacteria are a class of Gram-positive bacteria that possess a number of features such as high genomic G/C content (79-80%), no distinctive cell wall, and the formation exospores in response to harsh conditions [1]. They are usually filamentous with slender non-septate mycelium [2]. Actinobacteria are ubiquitous where they colonize different habitats such as freshwater, marine, and soil. Actinobacteria of terrestrial origin have been extensively investigated since the early 1950s. Marine actinobacteria are among the most active producers of secondary metabolites with potential

applications in pharmaceutical and biotechnological industries [3-6]. They were reported to produce a wide array of secondary metabolites with antibiotics, anticancer, and immunosuppressive activities [7]. In addition, actinobacteria-derived compounds have activities against viruses, fungi, malaria, and parasites [8].

Actinobacteria produce more than 10,000 bioactive secondary metabolites which account for up to 45% of all discovered bioactive compounds [9]. For pharmaceutical purposes, actinobacteria are the main antibiotic producers for several potent antibiotics

such as chloramphenicol, macrolide, and aminoglycosides [9]. In addition, a variety of actinobacteria-derived anticancer compounds have been used clinically such as daunomycin, doxorubicin, neocarzinostatin, carzinophilin, and chalcomycin [10,11]. Such outstanding properties of Actinobacteria attract the attention of researchers around the globe. This creates a state of progression in drug discovery from these microorganisms through i) high-throughput screening and fermentation, ii) genome mining for cryptic pathways, and iii) combinatorial biosynthesis to synthesize novel secondary metabolites [12].

Marine actinobacteria reside in a complex environment in terms of pressure, salinity, and temperature. In such environment, Actinobacteria were reported to form symbiotic relationships with different fishes, seaweeds, molluscs, mangroves and sponges [2,13]. Isolation and identification of marine actinobacteria is the first step to discover new bioactive compounds. In comparison with their corresponding terrestrial partners, marine actinobacteria are difficult to be cultured. This could be attributed to the difference in growth requirements, particularly the halophilic nature of marine actinobacteria [14]. However, several studies have reported the sampling techniques and isolation of actinobacteria from shallow coastal sediments to the deepest sediments [15-17]. In addition, enhancement of the fermentation techniques for the specific bioactive compounds [18,19] genetic engineering of the biosynthesis gene clusters [20] were also reported. In the current review, the following topics will be discussed; i) origin, distribution and diversity of marine actinobacteria, and iii) different biological activities of marine actinobacteria-derived compounds.

Marine Actinobacteria: Origin, Distribution and their Role in the Marine Environment

Oceans cover more 70% of the Earth's surface with a great biological of life than in the terrestrial environment [21]. Geographically, the coastal area of the sea represents only 7-8% and the remaining is for the deep sea [22]. The nature of the marine environment particularly, the deep sea extremely differs from the terrestrial environment. The deep sea has high pressure, low temperature, darkness, and inconstant salt and oxygen concentrations [23]. With such extreme conditions, marine Actinobacteria is expected to possess unique features and consequently secrete different and novel bioactive compounds compared to their terrestrial counterparts [24]. Marine actinobacteria are believed to originate from terrigenous sediments as they are widely distributed in the soil environment. In addition, another fact that support their terrestrial origin is their ability to produce resistant spores. These spores can be transported from the land to the marine environment and can remain dormant for several years [25]. In the marine environment, actinobacteria exist in mangrove swamps, other coastal environments, and even deep ocean sediments and significantly contribute to the diversity of the actinomycetes taxa [26,27].

Actinobacteria form stable populations in different marine

niches and produce novel bioactive compounds with enormous biological activities [11,28,29]. Marine actinobacteria occupies various marine habitats such as different types of sediments; marine sediments [30], Ocean sediments [31], and sediments with moderate to high salt concentrations [32]. In addition, several actinobacterial genera were recovered from seawater [4], and freshwater ecosystems [33]. In addition, marine actinobacteria have been recovered from both swimming and sessile marine vertebrates and invertebrates [34]. Several genera belong to different families such as Micrococceae, Dermatophilaceae and Gordoniaceae, were found to be associated with sponges [18]. The actinobacterium *Nocardiopsis dassonvillei* was isolated from ovaries of the puffer fish [35].

Although the existence of indigenous actinobacteria in the marine environs still elusive, culture-dependent studies revealed several marine indigenous actinobacterial genera. These include *Dietzia*, *Rhodococcus* [36], *Streptomyces*, *Salinispora* [37], *Marinophilus*, *Salinibacterium*, *Aeromicrobium marinum* [38], *Verrucosipora* [39], *Actinomadura*, *Actinosynnema*, *Arthrobacter*, *Blastococcus*, *Brachybacterium*, *Frankia*, *Geodermatophilus*, *Gordonia*, *Kitasatospora*, *Micromonospora*, *Micrococcus*, *Microbacterium*, *Nocardioides*, *Nocardiopsis*, *Psuedonocardia*, *Rhodococcus*, *Saccharopolyspora*, *Serinicoccus*, *Solwaraspora*, *Streptosporangium*, *Tsukamurella*, *Turicella* [34].

Actinobacteria has a significant role in the marine environment where they contribute in the degradation and turnover of numerous materials. Marine actinomycetes were reported to have cellulolytic and chitinolytic activities [40,41]. They also participate in the degradation and recycling of organic compounds [25] and produce a wide array of enzymes of industrial importance [42]. In addition, they have a vital role in mineralization of organic matter, nitrogen fixation and immobilization of mineral nutrients [43]. Most importantly, marine actinobacteria produce enormous numbers of bioactive compounds with a wide array of applications in agricultural, industrial, biotechnology and medical fields [9,24].

Marine Actinobacteria-Derived Secondary Metabolites

The increased rate of antibiotic resistance by pathogenic bacteria and the deleterious consequences of cancer chemotherapies are pushing toward alternative approaches. Actinobacteria have long been considered the prolific producers of a wide array of secondary metabolites with potential activities against viruses, fungi, bacteria, malaria, parasites and cancers [44]. Thousands of bioactive compounds were produced by several actinobacterial genera such as *Streptomyces*, *Actinomyces*, *Corynebacterium*, *Micrococcus*, *Micromonospora* [9,24]. Among members of the actinobacteria, more than 500 species of the genus *Streptomyces* responsible for about 80% of the total actinobacterial secondary metabolites with numerous biological activities [45]. In the subsequent sections, biological activities of actinobacterial-derived secondary metabolites against different pathogens and cancer are discussed.

Actinobacterial-Derived Compounds with Anti-Microbial Activities

Actinobacterial-Derived Compounds with Antibacterial Activities: Mortalities due to Multidrug-Resistant (MDR) organisms has increased dramatically with annual costs 20 billion dollars in the United States alone [46,47]. According to the official reports of the CDC, up to 23,000 people die annually in the USA due to infection with multidrug-resistant organisms. Moreover, global estimation of premature deaths is expected to increase to 300 million by 2050, with economic losses around \$100 trillion [48]. Therefore, searching for alternative drugs with no previous resistance becomes a priority. Numerous bioactive compounds of marine bacteria were found to have good antibacterial activities against several drug resistant pathogenic bacteria. Abyssomicin C, a newly discovered antibiotic, has antibacterial activity against MDR gram-positive bacteria of medical importance. It was first isolated from the marine actinobacterium *Verrucosipora* [39]. Abyssomicin belongs to polycyclicpolyketide group and acts by inhibiting the biosynthesis of folic acid [49].

The marine species of *Streptomyces* produce a number of antibiotics such as bonactin [50], BD21-2, and chlorinated dihydroquinones. Structurally, chlorinated dihydroquinones can be categorized into the napyradiomycin class [51]. The three types were reported to have antibacterial activity against both Gram-positive and Gram-negative bacteria. Other antibacterial compounds produced by the marine *Streptomyces* species include, himalomyins [52], frigocyclinone [53], glyciapyrroles [54], essramycin [55], caboxamycin [56], marinopyrroles [57], and tirandamycin [58]. Some of these compounds are active against Gram-positive bacteria such as frigocyclinone while others have broad activity against both Gram-positive and Gram-negative bacteria such as essramycin.

In addition, antibacterial compounds such as tirandamycin displayed activity against vancomycin-resistant *Enterococcus faecalis* [58] and bisanthraquinone showed *S. aureus* resistant to methicillin and tetracycline [59]. Diazepinomicin and lynamycins are two antibiotics that produced by the marine actinobacteria *Micromonospora* and *Marinispora*, respectively. Lynamycins are chlorinated bisindole pyrroles which have broad spectrum activities against different bacteria. Moreover, lynamycins are active against methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* [60]. Purified extracts of 20 isolates of actinomycetes including *Streptomyces*, *Rubrobacter*, *Actinokineospora*, *Microbacterium*, *Micromonospora*, and *Rhodococcus* were active against clinical isolates of *E. faecalis*, *S. aureus*, *E. coli*, *P. aeruginosa* [61].

Actinobacterial-Derived Compounds with Antifungal Activities: Although numerous types of fungi are being used in several industries, some are pathogenic to human, animals, and plants. They can cause serious human diseases such as candidiasis and others drastically affect several crops. Bioactive compounds extracted from marine actinobacteria displayed activity against both human and plant fungal pathogens. Chitinase, a bioactive

compound from the marine actinobacterium *Streptomyces*, displayed activities against *Aspergillus niger* and *Candida albicans*. This strain of *Streptomyces* was first isolated from South China and was associated with a type of sponge [62]. Since chitin is a predominant component of fungal cell wall, chitinase produced by *Streptomyces* is expected to have a broad spectrum against several fungal species. In addition, chitinase is widely used in several fields such as biomedical, agricultural, food technology and cosmetics [63,64].

In biomedical field, chitinase has been used in wound healings, cartilage tissue engineering, and drug delivery [65,66]. In the agricultural field, antifungal compounds derived from marine actinobacteria have been used as agrochemicals [67,68]. For instance, the marine actinobacterium *Streptomyces rutgersensis* produces a systemic fungicide, Kasugamycin against *Magnaporthe grisea* [Yoshii *et al.*, 2012]. Chandrananimycin A, is a novel compound that's is isolated from *Actinomadura* sp., has a potent antifungal activity against *Mucor miehei* [69]. Another potent antifungal compound produced by *Nocardia dassonvillei* has an activity against *C. albicans*, with a MIC of 64 g/mL [70].

Macrolides produced by sponge-associated *Streptomyces* sp. and *Micromonospora* have activity against *Cryptococcus* and *C. albicans* at a concentration of 10 mg/ml [71,72]. Polyketides and alkaloids (e.g. caerulomycins A and C) are two anticandidal compounds produced by *S. psammoticus* and *A. cyanogriseus*, respectively [73,74]. In addition to these purified and identified compounds, extracts of some *Salinispora* species displayed antifungal activity against *C. albicans* [75]. Similarly, extracts from sponge-endosymbiotic Actinomycete strains were active against several fungal species such as *C. tropicalis*, *A. fumigatus*, and *A. flavus* [76, Vimal *et al.*, 2009]. A novel antifungal protein named SAP was reported to have a broad spectrum activity against several plant fungal pathogens such as *Alternaria alternata*, *A. fumigatus*, *A. versicolor*, *F. graminearum*, *M. circinelloides*, and *Pythium oligandrum* [77]. In a recent study, Buatong *et al.*, [78] identified a new compound with a potent antifungal activity against *Pyricularia oryzae*, a rice blast fungus. Extract of the marine actinobacterium *Streptomyces* sp. had a potent inhibitory effect on the growth of *P. oryzae* strains with MICs values of 8 to 16 µg/ml and minimum fungicidal concentrations values of 16 to 128 µg/ml. The active compound was determined by HPLC/MS as *oligomycin* A. Fortunately, the conditions of the submerged rice fields support the growth the marine *Streptomyces* sp., and thus can be used as biocontrol agent against rice blast fungus *P. oryzae* [78].

Actinobacterial-Derived Compounds with Antiviral Activities: Viruses have long been known to cause disastrous epidemics to the human beings. Millions of deaths were reported due to influenza viruses, human immunodeficiency virus, hepatitis viruses and many others. In fact, viruses are difficult to be treated and many viruses develop resistance to the available antiviral drugs. In this regard, several marine actinobacterial-derived compounds have antiviral activities. Benzastatin C, an alkaloid

produced by *Streptomyces nitrosporeus*, exhibited antiviral activity herpesviruses; herpes simplex virus type 1, herpes simplex virus type 2 and Vesicular Stomatitis Virus (VSV), respectively [79]. Extracts from the marine *Streptomyces* increased the survival rate of shrimps' larvae challenged with White Spot Syndrome Virus [80]. This virus causes great economic losses to the shrimp farmers due to its high mortality rate. Guanine-7-N-oxide purified from a culture of *Streptococcus* sp. was active against fish herpes virus, rhabdovirus, and infectious pancreatic necrovirus [81].

Replication of influenza viruses was found to be affected by bioactive compounds from *Actinomadura* sp [82] and *Streptomyces lavendulae* [83]. Raveh, et al. [84] successfully isolated a potent antiviral compound, antimycin A1a, from the marine *Streptomyces kaviengensis*. Antimycin A1a showed a broad spectrum activity against several viruses including western, eastern, and Venezuelan equine encephalitis viruses (Togaviridae), La Crosse virus (Bunyaviridae), cephalomyocarditis virus (Picornaviridae), vesicular stomatitis virus (Rhabdoviridae), Sendai virus (Paramyxoviridae) and hepatitis C virus (Flaviviridae) [84]. The compound (Z)-1-((1-hydroxypenta-2,4-dien-1-yl) oxy) anthracene-9,10-dione" is produced by *Nocardia alba* and was report to inhibit the replication of Newcastle disease virus and infectious Brucellosis disease virus [85].

It is obvious that marine actinobacterial derived compounds have been extensively tested against bacteria and fungi. But antiviral activities of these compounds still need further investigation. This could be attributed to the high safety levels, laboratory facilities, animal models and costs required to perform viral assays. Actinobacteria of marine origin are rich in a variety of secondary metabolites that may have potent antiviral activities. We believe that screening of bioactive compounds from marine actinobacteria could reveal novel and potent antiviral compounds. This could help to treat diseases caused by these viruses and to control the serious epidemics caused by viruses of medical importance.

Actinobacterial-Derived Compounds with Anticancer Activities

Cancer is a life threatening disease with annual worldwide incidence of 10 million cases [86]. Traditional cancer therapies such as chemotherapy, surgery, and radiotherapy usually associated with serious side effects [87,88]. The deleterious consequences of such traditional therapies push toward searching for alternative approaches. In this regard, marine actinobacteria offer a plenty of bioactive compounds with anti-proliferative activities. Species of marine actinobacteria; *Salinispora*, *Streptomyces*, and *Marinispora* were investigated for their anti-proliferative compounds. Salinosporamide A, a bicyclic beta-lactone gamma-lactam compound, produced by *Salinispora tropica* displayed anti-proliferative activity against different cell lines [89,90]. Salinosporamide A acts by stimulating the apoptosis cascade in malignant cells [91]. The promising results of Salinosporamide A encouraged its use in clinical trials to treat different cancer types [92]. Two species of the marine marine actinobacterium *Salinispora*;

S. arenicola and *S. pacifica* produce a considerable number of polyketide I with anticancer activity against human colorectal cancer cell line [93,94]. *S. pacifica* give rise to four new polyketides, salinipyrone A and B, and pacificanones A and B which were active against human colon cancer cells [94].

Species of *Streptomyces* produce an array of anti-proliferative compounds such caprolactones and chinikomycin, aureoverticillactam, chalcomycin, daryamides, piperazimycins, and mansouramycin. Caprolactones and chinikomycin exhibited activity against different cell lines of human origin such as breast cancer, melanoma and renal cancer [95,96]. Chalcomycin and Daryamide A were active against HeLa cell line [97], and human colon carcinoma cell line [98], respectively. Aureoverticillactam was reported to inhibit the growth of human colorectal adenocarcinoma cell line, Jurkat leukemia and mouse melanoma cell lines [99].

Other genera of actinobacteria such as *Marinispora* sp. and *Thermoactinomyces* sp. produce two potent antitumor compounds marinomycins and mechercharmyn A, respectively [100,101]. Piperazimycins exhibited a good efficacy against human colon carcinoma cell line, leukaemia, melanoma, and prostate cell line [102]. In a similar fashion, mansouramycins displayed significant cytotoxicity to an array of cell lines including lung cancer, breast cancer, melanoma and prostate cancer cells [103]. In a recent study, extract of *Streptomyces bingchenggensis* was cytotoxic to different cell lines of human origin such as human acute myelocytic leukemia (K562), cervical cancer (HeLa), human gastric, breast cancer (MCF-7), and human acute promyelocytic leukemia (HL-60). Purification and structural elucidation of *S. bingchenggensis*'s extract revealed two anticancer compounds; ULDF4 and ULDF5 which are structurally related to staurosporine and kigamicin [104].

Actinobacterial-Derived Compounds with Anti-Parasitic Activities

The activities of actinobacterial bioactive compounds are extended to the parasites of medical importance such as *Trypanosoma* sp., *Leishmania* sp. and *Plasmodium* sp. Trypanosomatids cause three important diseases to humans; the African trypanosomiasis or sleeping sickness caused by *Trypanosoma brucei*, South American trypanosomiasis or Chagas disease, caused by *Trypanosoma cruzi*, and leishmaniasis caused by several species of *Leishmania* [105]. Of these diseases, Chagas disease is a systemic disease (i.e. affect multiple organs) that killed more than 10,000 individuals during the year 2008. It was estimated that *T. cruzi* infected more than 18 million people and about 40 million people are at risk of getting the infection [106]. Similarly, leishmaniasis affects more than 88 countries with around 350 million people are at risk of acquiring infection [107]. Malaria is an endemic disease that affects several countries with high incidence and high mortality rate. The causative agent, *P. falciparum*, infects more than 300 million cases with an estimated 2 million deaths per annum [24].

The available drugs to treat these parasitic diseases are not efficient and some were not effective because of resistance.

In addition, some anti-parasitic synthetic drugs have serious side effects due to prolonged parenteral administration [108]. Benznidazole is specific for the treatment of Chagas disease but is active for the acute phase of the disease with toxic side effects [106]. For the treatment of leishmaniasis, antimony organic compounds are commonly prescribed followed by pentamidine, miltefosine, and amphotericin B [108]. The high mortality rates of such parasitic diseases, side effects of the used drugs and drug resistance necessitate the need for novel and effective therapeutic drugs. Screening of marine actinobacteria yielded several bioactive compounds with anti-parasitic activities.

Maskey et al, reported the high efficiency of Trioxacarcins compounds against *P. falciparum*. The authors purified trioxacarcin

A, B and C from cultures of *Streptomyces ochraceus* and *Streptomyces bottropensis* [109]. Sponge-associated *Streptomyces* produce three compounds with anti-parasitic activity; cyclic depsipeptide valinomycin, indolocarbazole alkaloid staurosporine and butenolide. The three compounds were active against *Leishmania major* and *Trypanosoma brucei brucei* [110]. Actinosporins, a compound produced by the sponge-associated *Actinokineospora* sp. was active against *Trypanosoma brucei brucei* [61]. In a recent study, Santos, et al. [111] successfully isolated eighteen isolates of sponges-associated marine actinomycetes. They tested the extracts of these isolates for their anti-fungal, antibacterial, anti-cancer and anti-parasitic activities. Extracts of some isolates were active against *Trypanosoma cruzi* [111-203] (Table 1).

Table 1: Biological activities of marine antibacterial-derived compounds.

Genus	Bioactive Compounds	Structural Type	Biological Activities	Isolation Source	References
<i>Streptomyces</i> sp.	Antibacterial Activity				
	Glaciapyrroles	Pyrrolosequiterpenes	Antibacterial	Sediment, Alaska	Macherla, et al. [54]
	Strepchazolins	Alkaloids	Antibacterial	Marine sediments	Wu, et al. [191]
	Chloro-dihydroquinones	Isoprenoid	Antibacterial	Ocean sediments, La Jolla	Soria Mercado, et al. [51]
	Lobophorin K	Spirotetronate	Antibacterial	Deep Sea	Yellamanda, et al. [201]
	Lajollamycin	Polyketide/non-ribosomal Peptide	Antibacterial	La Jolla, California	Manam, et al. [162]
	Norresistomycin	Polyketide	Antibacterial	Sediment, Bay of Bengal, India.	Gorajana, et al. [138]
	2-Allyloxyphenol	2-prop-2-enoxyphenol	Antibacterial	Bay of Bengal, India	Arumugam, et al. [113]
	Caboxamycin	Benzoxazole	Antibacterial	Atlantic Ocean deep-sea sediment	Hohmann, et al. [56]
	Bisanthraquinone	Anthraquinone	Antibacterial	La Paragua, Puerto Ric	Socha, et al. [59]
	Tirandamycins C	Dienoyl tetramic acids	Antibacterial	Marine sediments	Carlson, et al. [58]
	Bonactin	Nonactic acid and homononactic acid	Antibacterial	Sediment, Kailua Beach, Oahu, Hawaii	Schumacher, et al. [50]
	Resistoflavin methyl ether	Quinones	Antibacterial	Sediment, Gulf of Mexico	Kock, et al. [154]
	Taxifolin	Dihydroquercetin	Antibacterial	Mangrove- actinobacterium	Gopikrishnan, et al. [137]
	Essramycin	Triazolopyrimidine	Antibacterial	Sediments Mediterranean Sea-Egypt	El-Gendy, et al. [55]
	Marinopyrroles	Bispyrrole	Antibacterial	Sediment, La Jolla	Hughes, et al. [57]
	Glyciapyrroles	Pyrrolosequiterpenes	Antibacterial	Alaskan Marine Sediment	Macherla, et al. [54]
	Himalomycins	Anthracycline	Antibacterial	Sediment, Mauritius	Maskey, et al. [52]
	Caboxamycin	Benzoxazole	Antibacterial	Sediment, Canary Basin	Hohmann, et al. [56]
	Gutingimycin	3-dihydro-1,4-anthraquinone parimycin and trioxacarcins	Antibacterial	Marine	Maskey, et al. [109]

Streptomyces sp.	Antifungal Activity				
	Daryamides	Polyketide	Antifungal	Sediment, San Diego coast	Asolkar, et al. [98]
	Caprolactones	Alkanolide	Antifungal	Mangrove sediment	Stritzke, et al. [95]
	Antiviral Activity				
	Antimycin A1a	bis-lactone	Broad spectrum anti-viral activities	Sediments, Coast of New Ireland, Guinea	Raveh, et al. [84]
	Antitumor Activity				
	Griseorhodin A	Polyketide	Antitumor	Associated with the marine tunicate Aplidium lenticulum	Li, et al. [158]
	Albidopyrone	α -pyrone	Anticancer	Atlantic Ocean sediment	Hohmann, et al. [144]
	ML-449	Macrolactam	Anticancer	Marine sediment	Jørgensen, et al. [151]
	Usabamycins	Anthramycin-analogue	Anticancer	Marine sediments	Sato, et al. [177]
	Mansouramycin C	Isoquinolinequinones	Anticancer	Sediment-Jade Bay	Hawas, et al. [103]
	Piperazimycins	Non-ribosomal peptide	Anticancer	Sediments-Guam	Miller, et al. [102]
	Resistoflavine	Quinone-related	Anticancer	Sediment-Bay of Bengal, India	Gorajana, et al. [139]
	Nonactin	Macrotetrolide	Anticancer	Deep-sea Sediments at Ayu Trough	Jeong, et al. [149]
	Actinofuranones	Polyketide	Anticancer	Sediment -Guam	Cho, et al. [124]
	Manumycins	Polyketide	Anticancer	Sediment Jiaozhou Bay	Chauhan, et al. [91]
	Elaiomycins B and C	Alkylhydrazide	Antitumor	Marine-derived	Helaly, et al. [143]
	Staurosporinone	Sesquiterpene	Antitumor	Jiaozhou Bay of Qindao, China	Wu, et al. [192]
	Methylantraquinone	Anthraquinone	Antitumor	Marine plant, China	Huang, et al. [145]
	Chinikomycins	chlorine-aromatized manumycin derivatives	Anticancer	Sediment-Jiaozhou Bay in China	Li, et al. [156]
	Piericidins	Polyketide	Antitumor	Iwayama Bay	Hayakawa, et al. [142]
	Streptokordin	Methylpyridine	Antitumor	Sediments-Ayu Trough	Jeong, et al. [149]
	Mitomycin C	Methylazirinopyrrolindole-dione	Antitumor	Marine derived	Mao, et al. [164]
	Arenimycin	Benzo- α -naphthacene quinone	Antitumor	Mangrove-Bahama	Asolkar, et al. [98]
	Mechercharmyn A	Cyclic peptide-like with four oxazoles and a thiazol,	Antitumor	Sea mud at Mecherchar in the Republic of Palau	Kanoh, et al. [100]
	Altemicidin	Isoprenoid	Antitumor	Sea mud collected at Gamo, Japan	Takahashi, et al. [187]
	Ammosamides	Pyrroloiminoquinone	Antitumor	Bahamas islands	Hughes, et al. [57]
	Aureoverticillactam	Polyketide	Antitumor	Marine sediment	Mitchell, et al. [99]
	Bohemamines	Pyrrolizidine	Antitumor	Marine sediment	Bugni, et al. [121]
	Chalcomycin	Polyketide	Antitumor	Jiaozhou Bay, China	Wu, et al. [193]
	Chartreusin	Polyketide	Antitumor	Jiaozhou Bay, China	Wu, et al. [192]
	Echinosporins	Acetal-lactone	Antitumor	Jiaozhou Bay, China	Cui, et al. [126]
	Komodoquinones	Polyketide	Antitumor	Marine sediment	Itoh, et al. [147]
	Marineosins	Polypyrrole	Antitumor	Marine sediment, La Jolla, California	Boonlarppradab, et al. [118]
	Marmycins	Polyketide	Antitumor	Marine sediment, Sea of Cortez	Martin, et al. [65]
	Parimycin	Polyketide	Antitumor	Sediment, Laguna de Términos, Mexico	Maskey, et al. [166]

<i>Streptomyces</i> sp.	Rabelomycin	Polyketide	Antitumor	Sandy sediment of Mauritius coastal	Maskey, et al. [52]
	Resitoflavine	Polyketide	Antitumor	Island of Guam	Gorajana, et al. [139]
	Tetracenomycin D	Polyketide	Antitumor	Marine sediment, Bengal Bay, India	Kock, et al. [154]
	T-Muurolol	Isoprenoid	Antitumor	Marine sediment, Jiaozhou Bay, China	Wu, et al. [193]
	Trioxacarcins	Polyketide	Antitumor	Sediment, Laguna de Términos, Mexico	Maskey, et al. [166]
	Antimycin	Alkaloid	Anticancer	Marine sediments from the mangrove zone	Yang, et al. [199]
	Fridamycin D	Polyketide	Antitumor	Mauritius (Indian ocean)	Maskey, et al. [52]
	Somalimycin	Peptide	Weak anticancer	Deep sea marine sediment	Brana, et al. [119]
	Petrocidin A	Dipeptide	Anticancer	Symbiont to sponge	Zhang, et al. [203]
	Succinilenes	Triene Polyol	Anticancer	Marine Sediment	Yang and Sun [200]
	Streptochlorin	Indole	Antitumor, antiangiogenic	Marine Sediment, Ayajin Bay, East Sea of Korea	Shin, et al. [125]
	Marangucycline A	Angucycline	Anticancer	Deep sea sediment	Bekiesch, et al. [117]
	Staurosporins	Indolocarbazole	Antitumor	Marine Sediment	Itoh, et al. [147]
	Streptopyrrolidine	Tetrahydropyrrole	Antitumor	deep-sea sediment, Ayu Trough	Choi, et al. [125]
	Streptokordin	Methylpyridine	Antitumor	Deep-sea sediments at Ayu Trough	Jeong, et al. [149]
	Bonnevillamides	Peptide	Modulate heart growth and cardiac function	Sediment	Li, et al. [157]
	Wailupemycins	Polyketide	α -glucosidase inhibitor	Symbiont to marine algae	García, et al. [135]
<i>Salinispora</i> sp.	Antibacterial Activity				
	Arenjimycin	Quinone	Antibacterial	Bahamas	Asolkar, et al. [115]
	Rifamycins	Polyketides	Antibacterial	Great Barrier Reef, Australia	Kim, et al. [2]
	Thiolactomycin	Thiotetronic acids	Antibacterial	Pacific Ocean sediment	Tang, et al. [188]
	Antitumor Activity				
	Salinosporamide A	Polyketide-Nonribosomal Peptides	Anticancer; antimalarial	Bahamas	Jensen, et al. [148]
	Salinosporamides B & C	Polyketide-Nonribosomal Peptides	Anticancer	Mangrove, Chub Cay, Bahamas	Williams, et al. [90]
	Saliniketal	Polyketide	Cancer chemoprevention	Island of Guam	Jensen, et al. [148]
	Cyanosporaside A	Sporolides	Weak anticancer	Sediment, Palau island	
	Salinipyrones A & B	Polyketide	Mild anticancer activity	Western Pacific Ocean	Oh, et al. [94]
	Pacificanones A & B	Polyketide	Antibacterial	Marine sediment, the Palau island	
	Arenicolides A-C	Polyketide	Mild anticancer activity	Guam	Jensen, et al. [148]
	Salinoquinones	Anthraquinone- γ -pyrones	Anticancer	Deep sea-water Bahamas	Murphy, et al. [170]
	Cyanosporasides	Polyketide	Antitumor	Palau island	Asolkar, et al. [98]
	Saliniketals	Polyketide	Antitumor	Island of Guam	Williams, et al. [93]
	Retimycin	Peptide	Anticancer	Deep sea-water, Bahamas	Duncan, et al. [128]

<i>Salinispora</i> sp.	Arenamides	Non-ribosomal peptides	Antitumor	Astrolab Reef, Kandavu Island chain	<i>Asolkar, et al.</i> [116]
	Cyclomarine	Diketopiperazine dipeptides	Anti-inflammatory	Palau	<i>Schultz, et al.</i> [181]
	Sporolide A	Polyketide	Unknown	Sediment, Bahamas	<i>Jensen, et al.</i> [148]
	Sporolides	Polyketide	Unknown	Marine derived	<i>Buchanan, et al.</i> [90]
	Salinispyrone	Pyrones	Unknown	Marine sediment	<i>Jensen, et al.</i> [148]
<i>Marinispora</i> sp.	Marinomycins	Polyketide	Antimicrobial; anti-cancer	La Jolla, California	<i>Kwon, et al.</i> [101]
	Lynamicins	Indolocarbazole	Antibacterial	Marine sediment, California, USA	<i>McArthur, et al.</i> [60]
<i>Verrucosipora</i> sp.	Proximicins	Non-ribosomal peptide	Antibacterial	Sea of Japan and	<i>Fiedler, et al.</i> [131]
	Abyssomicins	Polyketides	Antibacterial	Sea of Japan	<i>Bister, et al.</i> [49]
	Proximicins A,B,C	Non-ribosomal peptides	Anticancer	Sea of Japan	<i>Schneider, et al.</i> [180]
	Thiocoraline	Non-ribosomal peptide	Anticancer	Sponge-Florida Keys, USA	<i>Wyche, et al.</i> [194]
<i>Thermoactinomyces</i> sp.	Mechercharmucins	Non-ribosomal peptide	Anticancer	Mecherchar in Palau	<i>Kanoh, et al.</i> [100]
<i>Actinomadura</i> sp.	Forazoline A	Polyketide	Antifungal	Florida Keys, USA	<i>Wyche, et al.</i> [196]
	ZHD-0501-Staurosporine analog	Indocarbazoles	Anticancer	Jiaozhou Bay, China	<i>Han, et al.</i> [140]
	JBIR-65	Diterpene	Anti-oxidant	Sponge – Okinawa Prefecture, Japan	<i>Takagi, et al.</i> [186]
	Halomadurone	Chlorinated pyrones	Active against neuro-degenerative diseases	Florida Keys, USA	<i>Wyche, et al.</i> [197]
	Chandrananimycins	Phenoxazin-3-one	Anticancer	Jiaozhou Bay, China	<i>Maskey, et al.</i> [69]
	1,6-phenazinediol	Phenazine	Anticancer	Jiaozhou Bay in China	<i>Lombó, et al.</i> [160]
	IB-0028	Polyketide	Anticancer	Marine-derived	<i>Rodríguez, et al.</i> [174]
	Iodinin	Phenazine	Anticancer	Jiaozhou Bay in China	<i>Tsujibo, et al.</i> [189]
	Questionimycins	Phenoxazin-3-one	Anticancer	Jiaozhou Bay in China	<i>Maskey, et al.</i> [69]
<i>Saccharopolyspora</i> sp.	Undecylprodigiosin	Prodigiosin	Anticancer	Coast of Qingdao, China	<i>Liu, et al.</i> [96]
	PM070747	Benz[α] anthraquinone,	Anticancer	marine sponge near the coast of Tanzania	<i>Perez, et al.</i> [172]
	Tenvermectin	Macrocyclic lactone	Anti-parasitic	Deep-sea sediment from the Atlantic Ocean,	<i>Wan, et al.</i> [190]
	Metacycloprodigiosin	Prodigiosin	Anticancer	Coast of Qingdao, China	<i>Liu, et al.</i> [96]
<i>Micromonospora</i> sp.	Antibacterial Activity				
	Fluostatin	Aromatic polyketides	Antibacterial	Sediment, South China Sea	<i>Zhang, et al.</i> [202]
	Diazaquinomycins H, J	Diazoanthracenes	M. tuberculosis	Marine sediment	<i>Fukuda, et al.</i> [134]
	Micromonohalimanes A, B	Diterpenoid	MRSA	Marine ascidian	<i>Zhu, et al.</i> 2012
	Nenestatin A	Benzo[b]fluorene	Antibacterial	Deep sea	<i>Jiang, et al.</i> [150]
	Antitumor Activity				
	IB-96212	Macrolide	Anticancer	Marine-derived	<i>Cañedo, et al.</i> [122]
	Thiocoraline	Non-ribosomal peptide	Anticancer	Soft coral at the Indian Ocean	<i>Romero, et al.</i> [175]
	Anthracyclinones	Dione	Anticancer	Taiba Beach, Ceará, Brazil	<i>Sousa, et al.</i> [185]
	Thiocoraline	Non-ribosomal peptide	Anticancer	Soft coral at the Indian Ocean	<i>Lombó et al.</i> [160]

<i>Micromonospora</i> sp.	Paulomycin G	Paulomycin derivatives	Anti-tumor	Deep sea marine sediment	<i>Kim, et al.</i> [152]
	Isopimara-2-one-3-ol,15-diene	Terpene	Anticancer	Sediment	<i>Gomez and Bibb</i> [136]
	Lagumycin B	Angucycline	Anticancer	Sediment	<i>Fu and Macmillan</i> [132]
	Anti-Parasitic Activity				
	Lobosamides	Amide	Antitryposomal	Sediment, California, USA	<i>Schulze, et al.</i> [182]
	Manzamine A	Alkaloid	Antimalarial	Symbiont to sponge	<i>Fukuda, et al.</i> [134]
	3-(4-Hydroxyphenyl)-N-methylpropanamide	Peptide	Anti-trypanosomal	Symbiont to Agelas oroides	<i>Muldowney, et al.</i> [169]
	Lobosamides	Amide	Anti-trypanosomal	Sediment	<i>Schulze, et al.</i> [182]
<i>Nocardia</i> sp.	Peptidolipins	Lipopeptides	Antibacterial	Florida Keys, USA	<i>Wyche, et al.</i> [195]
	N-(2-hydroxyphenyl)-2-phenazin-amine	Phenazine	Anticancer, Antifungal	Arctic ocean	<i>Gao, et al.</i> [70]
<i>Nocardiosis</i> sp	Antibacterial Activity				
	Nocarimidazoles	4-aminoimidazole alkaloids	Antibacterial	Sediment, the Coast of southern California,	<i>Leutou, et al.</i> [155]
	Nocardiamides	α - pyrones	Antibacterial	Sediment, La Jolla, California, USA	<i>Wu, et al.</i> 2013
	TP-1161	Thiopeptide	Antibacterial	Sediment, Trondheim Fjord, Norway	<i>Engelhardt, et al.</i> [130]
	4,8-diaza-2,9-dibenzoyl-5,6-diphenyl-2,8-decadienedioic acid diethyl ester	-	Antibacterial	Sediments, Andhra Pradesh, India.	<i>Priyanka, et al.</i> [173]
	Antitumor Activity				
	Lucentamycins	Non-ribosomal peptide	Anticancer	Sediment, Bahamas	<i>Cho, et al.</i> [124]
	Nocapyrones	α - pyrones	Weak Anticancer	Sponge-Baltic Sea, Germany	<i>Schneeman, et al.</i> [178]
	Isomethoxyneihumicin	lactam-lactim tautomers	Antitumor	Sediment, Ogasawara, Japan	<i>Fukuda, et al.</i> [134]
	Nocapyrones	Pyrones	Reduced the pro-inflammatory factor	Sediment, Eastern sea Korea	<i>Kim, et al.</i> [153]
	Fijiolides	Benzodihydropentalene	Anti-inflammatory	Sediment Beqa Lagoon, Fiji	<i>Nam, et al.</i> [171]
	Butenolides	Butenolide	Anticancer	Coast of Taipingjiao, China	<i>Li, et al.</i> [159]
<i>Saccharomonospora</i> sp	Saccharomonopyrones	α -Pyrones	Weak antioxidant	Deep sea sediment	<i>Xie, et al.</i> [198]
<i>Nesterenkonia</i>	Nesterenkoniane	Ether	Anti-allergic	Deep sea water sample	<i>Sarmiento-Vizcaino, et al.</i> [176]
<i>Microbacterium</i> sp	Microindolinone A	Indole	Anticancer	Deep sea marine sediment	<i>Cheng, et al.</i> [123]
<i>Rhodococcus</i> sp	3-Isopropylhexahydro1H-pyrido[1,2-a]pyrazine-1,4(6H)-dione	-	Antibacterial	Marine samples	<i>Mangamuri, et al.</i> [163]
<i>Dermacoccus</i> sp.	Dermacozine	Phenazine alkaloids	Anticancer	Mariana Trench sediment	<i>Abdel Mageed, et al.</i> [112]
<i>Saccharothrix</i> sp.	Saccharothrixones	Polyketide	Anticancer	Sediment	<i>Hassan, et al.</i> [141]
<i>Actinomycetospira</i> sp.	Thiasporine A	Thiazole	Anticancer	Marine sediment, mangrove swamp	<i>Song, et al.</i> [184]
<i>Actinoallomurus</i> sp.	NAI 414 A/B	Spirotetronate	Antibacterial, Anti-cancer	Marine-derived	<i>Mazzetti, et al.</i> [168]

<i>Amycolatopsis</i> sp.	Pyridinium	Aminodecyl	Antimicrobial	Sediment, Bay of Bengal, India	Dasari, et al. [127]
<i>Tsukamurella</i> sp.	Lipocarbazoles	Carbazole moiety	Anticancer	Marine samples	Schneider, et al. [179]
<i>Janibacter</i> sp.	Helquinoline	Tetrahydroquinoline antibiotic	Antibacterial	Marin-derived	Asolkar, et al. [114]
<i>Actinoalloteichus</i> sp.	Caerulomycins	Bipyridines	Antibacterial, Anti-cancer	Marine sediments, the seashore of Weihai, China	Fu, et al. [74]
<i>Solwaraspora</i> sp	Solwaric acids	Trialkyl-substituted aromatic acids	Antibacterial	Symbiont to ascidian, from Florida Keys, USA	Ellis, et al. [129]

Conclusion and Future Perspectives

In the medical field, two serious problems need to be resolved; i) the continual emergence of drug resistant microorganisms which increases the likelihood of life threatening infections, and ii) the deleterious side effects of using traditional cancer therapies. These two important issues challenged the researchers to search for safe and effective alternatives. In this regard, marine actinobacteria is considered a drug treasure house as they offer a tremendous number of secondary metabolites with a wide array of biological activities. Thousands of marine actinobacteria-derived compounds have been tested in *in vitro* for their antimicrobial and anti-proliferative activities. In addition, some compounds were evaluated in pre-clinical and clinical studies. Of the tested compounds, some compounds were of potential activity against MDR bacteria, drug resistant viral strains and several types of cancers. Among the actinobacterial genera, *Streptomyces* sp. is responsible for the largest number of bioactive compounds. Marine actinobacteria occupies different marine niches and can be found associated with several vertebrate and invertebrate species. Although marine actinobacteria is a very important source for discovering novel bioactive compounds, research in this field still necessitates further improvements. Collection of deep sea samples, extraction, purification and identification techniques are needed to be developed.

Acknowledgement

None.

Conflict of Interest

None.

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