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# Marine Actinomycetes the Past, the Present and the Future

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## Abstract

In the field of exploring new natural sources for biologically active products with economic importance, the marine environment draws particular attention due to the noticeable diversity and extreme conditions; it is well known that the marine environment is a valuable source of biological and therapeutic compounds with great value. The marine environment represents a novel source for the discovery of new secondary metabolites including antibiotic, antiviral, antitumor, antifouling agents, as well as enzymes. Marine actinomycetes are widely distributed through the marine environment from shallow to sea sediments. The secondary metabolites obtained from such marine actinomycetes have proved their value in different industries due to their unique properties and structures. This review focuses on the importance of marine actinomycetes as well as their secondary metabolites. The development of new technologies for marine actinomycetes bioprospection is very promising, leading to the discovery of high-quality value products with biotechnological and medical applications.

**Keywords:** Marine Actinomycetes; Bioactive Compounds; Biological Activities; Commercial Use

## Introduction

Actinomycetes are groups of Gram-positive bacteria that are characterized by having high G+C content (>55%) in their DNA [1,2]. Actinomycetes exhibit high economical and biotechnological priceless importance. They play a major role in the production of many novel metabolites such as enzymes, anti-parasitic agents, herbicides, pesticides, immune-modifiers, antitumour agents, enzyme inhibitors, and vitamins as well as many other biologically active products [3-6]. Moreover, actinomycetes play a vital role in the degradation of various organic wastes due to the ability of actinomycetes to produce various enzymes such as ligninase, xylans, chitinase, and pectinase, etc [5]. The majority of actinomycetes have been isolated from different terrestrial sources, however, recently the scientists focus on the isolation of different marine actinomycetes as well as studying the production of potential metabolites from these marine strains [7,8]. More than 70% of the earth's surface has been covered by oceans that represent a suitable environment for microbial diversity including actinomycetes. Marine organisms have shown their capacity to produce a wide variety of novel bioproducts with unique structures and functional features due to the occurrence of these organisms in extreme environmental conditions such as salinity, pressure, temperature, as well as many other conditions [9,10]. The marine environments are completely different from those of the terrestrial ones, thus marine actinomycetes are expected to provide a potential source of novel compounds that differs from those produced by the terrestrial actinomycetes [11,12]. Little is known about the versatility of the marine organisms' bioactive metabolites. This could be attributed to the difficulty of the isolation of such microorganisms. However, recently with the aid of the

new technologies, the existence of actinomycetes and their biosynthesis gene clusters as well as their occurrence in various marine ecosystems have been proved [13,14].

## Marine Actinomycetes Bioactive Secondary Metabolites

Among 23,000 bioactive secondary metabolites produced by microorganisms, about 1,000 are produced by actinomycetes, which represent about 45% of all discovered bioactive microbial metabolites [15]. The genus Streptomyces members produce approximately 7,600 compounds [15]. Between 1969 and 1999, nearly 300 patents on marine bioactive products were issued [16,17].

Actinomycetes are well known for the production of bioactive compounds with high industrial importance [18,19]. Several actinomycetes play important roles in environmental protection, mineralization of organic matter, nitrogen fixation, and immobilization of mineral nutrients, etc [20]. Among these actinomycetes, several genera have been reported from the marine environment. Many of these marine strains produce many metabolites with biological activities and which can be developed as therapeutic and pharmaceutical agents [21]. Among these biologically active compounds are peptides, polyketides, isoprenoids, sterols, and phenazines as well as others [22, 23].

### Antimicrobial Agents

Secondary metabolites with potent antimicrobial properties including antibacterial and antifungal properties have been widely used against various infectious diseases (Table1 and Table2). Thus, antibiotic-producing actinomycetes have gained great importance in the pharmaceutical industry [15]. Early in 1940, 1942, and 1943, actinomycin and streptothricin, and streptomycin produced by actinomycetes were reported respectively as effective sources of antibiotics [24, 25]. Antibiotics obtained from actinomycetes have been used in various fields including agriculture, veterinary, and pharmaceutical industries, etc [26-29].

| Compound | Source | References |
|---|---|---|
| Amphotericin B | Streptomyces nodosus | Hartsel and Bolard [30] |
| Antimycin | Streptomyces sp. SCSIO 1635 | Su-Mei, et al. [31] |
| Bonactin | Streptomyces sp. BD21-2 | Schumacher, et al. [32] |
| Daryamides | Streptomyces sp. CNQ-085 | Asolkar, et al. [33] |
| Natamycin | Streptomyces natalensis | Pedersen [34] |
| Nystatin | Streptomyces noursei ATCC 11455 | Zotchev, et al. [35] |
| Urauchimycins (member of antimycin class)<br>Urauchimycins A and B-from marine sponge Ni-80<br>Urauchimycin C-from marine sediment | Streptomyces sp. | Sharma, et al. [36] |

*Most of the antifungal agents derived from *Streptomyces* species are macrolide polyenes.
**Table 1:** Examples for antifungal metabolites produced by marine actinobacteria.

| Compound | Source | References |
|---|---|---|
| Bonactin | Streptomyces sp. BD21-2 | (Schumacher, et al. [32] |
| Chandrananimycins | Actinomadura sp. | Maskey, et al. [37] |
| Diazepinomicin (ECO-4601) | Micromonosproa sp. | Charan, et al. [38] |
| Frigocyclinone | Streptomyces griseus | Bruntner, et al. [39] |
| Glaciapyrroles A, B and C | Streptomyces sp. NPS008187 | Macherla, et al. [40] |
| Helquinoline | Janibacter limosus | Asolkar, et al. [33] |
| Lajollamycin | Streptomyces nodosus | Mann [41] |
| Marinomycins | Marinispora | Kwon, et al. [26] |
| Rifamycin | Streptomyces arenicola | Floss and Yu [42] |
| Tetracenomycin D | Streptomyces corchorusii | Adinarayana, et al. [43] |

**Table 2:** Examples for antibacterial metabolites produced by marine actinobacteria.

**Antiviral Agents:** Some marine actinomycetes have shown their ability to produce some antiviral agents that show various applications in various fields such as biological control of human viral infections, also it can be used in chemotherapy of humans viral diseases. Additionally, these antiviral compounds can be applied in the treatment of sewage-polluted waters. Benzastatin C produced by *Streptomyces nitrosporeus* has been used as a potent antiviral agent [44]. Another study reported a marine actinomycetes strain named *Streptomyces kaviengensis*, produced a novel metabolite "antimycin A" that showed potent antiviral activity. Antimycin A derivative was very effective against the Western equine encephalitis virus where the $IC_{50}$ value was less than 4 nM. It was also revealed that Antimycin A exerts its antifungal activity via disrupting the mitochondrial electron transport and pyrimidine biosynthesis [45]. *Streptomyces* sp. HK18 isolated from the soil of a Korean solar saltern also produced biologically active metabolites "xiamycins C-E" with antiviral properties. Among these, xiamycin D showed the maximum antiviral effect against porcine epidemic diarrhea virus (PEDV) replication with of $EC_{50}$ value equals to 0.93 μM [46].

**Antitumor Compounds:** Cancer is a serious health problem that requires a great attention. Besides the antimicrobial properties exhibited by marine actinomycetes they also show cytotoxicity against many tumor cells. Many compounds isolated from marine actinobacteria gained great importance as antitumor compounds. These actinomycetes derived antitumor drugs belong to various structural classes [47,48], these include:

- Antimetabolites: Carzinophilin and pentostatin;
- Aureolic acids: chromomycin A3 and mithramycin;
- Enediynes: neocarzinostatin;
- Heterocyclic quinones: mitomycin C;
- Indolocarbazoles: rebeccamycin and staurosporine;
- Polyketides: anthracyclines, daunomycin, elloramycin, geldanamycin, oviedomycin, etc.

The Antitumor compounds obtained from marine actinomycetes function via various processes. These include mitochondria permeabilization, DNA cleavage process that can be mediated by topoisomerase I or II inhibition, inhibition of vital enzymes like proteases that are involved in signal transduction, and even by the inhibition of tumor-induced angiogenesis [48].

Moreover, the family Micromonosporaceae that belongs to marine actinomycetes produce potent bioactive compounds. These strains are reported to target proteasome and hence found success in pharmaceuticals [16]. *Streptomyces chartreusis* that is first isolated from by Leach, et al., produces chartreusin that exhibits antibacterial activity as well as potent antitumor activity against various human cell lines [49]. Another marine actinomycete designated MAR4 that belongs to the family Streptomycetaceae were also reported to produce a host of meroterpenoids belonging to the class of napyradiomycin [50-52]. These napyradiomycins were first reported for their antimicrobial activity, however, they have also been reported to inhibit gastric ($H^+$-$K^+$) ATPases and act as antagonists for estrogen receptors. These properties allow napyradiomycins to be effective in the treatment of cancer, however, more studies are needed to define their mechanisms of action in cancer cells.

**Enzymes Production**

Actinomycetes are well-known producers of enzymes. Marine actinomycetes are reported to produce many enzymes with industrial importance and that have more stability and unique substrate specificities. The availability of the natural product in marine environments may rely on the ratio of enzyme produced by marine microorganisms [53]. Among the enzymes produced by marine actinomycetes are Proteases and α-Amylases, cellulases, chitinases, xylanases, ribonucleases, etc. Proteases isolated from marine actinomycetes have been purified as well as characterized [54]. Proteases have great commercial importance that is utilized in various industries, such as detergents, brewery, cheese-making, meat tenderization, and baking, etc [55]. Also, alkaline proteases have been extensively applied in other industries including textile, leather, wastewater treatment, etc. On the other side, *Streptomyces* species are well known as potent produced of amylolytic enzymes [56]. Amylases are widely applied in fermentation, food, textile, and paper industries.

Cellulase producers have been reported in the actinomycetes. These cellulolytic enzymes are applied in several industries such as cellulosic biomass pretreatment to improve its nutritional quality, pretreatment of industrial wastes, color extraction from juices, and detergents for color brightening [57,58]. Chitinases have been also reported to be produced by actinobacteria [59]. Chitinase finds a great application as a potent antifungal agent due to its ability to degrade chitin [60]. Xylanase has been applied widely in the pulp and paper industry due to the ability of xylanases to disrupt the cell wall structure of xylan at elevated temperatures. Actinobacteria have shown their capacity to produce xylanases [61]. Ribonuclease which is also known as RNase plays an important role in many biological processes, including self-incompatibility in flowering plants and angiogenesis. Several prokaryotic toxin-antitoxin systems have been reported to have RNase activity. Thus, various enzymes are being produced by marine actinomycetes and which show great industrial importance. These enzymes produced are used as pharmaceuticals, fine chemicals and food industries [62, 63].

**Enzyme Inhibitors:** Enzyme inhibitors are molecules that can bind to enzymes and as a results decreases or inhibit their activities. Some drugs can act as enzyme inhibitors by blocking the enzyme's activity and which in turn can correct a metabolic imbalance or even kill a pathogen. Also, they can be applied to many pesticides. The discovery and improvement of enzyme inhibitors are areas of interest in the pharmacology and biochemistry fields [64-70]. Also Some marine actinomycetes showed their ability to produce enzyme inhibitors.

### Future Prospects and Scope

Future efforts in this field should include deep comprehension of microbial physiology, systematics, and metabolism. Exploring the sequencing of various actinomycete genomes as well as studying the secondary metabolite pathways found in actinomycetes are required. More effort should be directed towards the development of more techniques that help easier and more efficient isolation various novel compounds should be exerted.

## Conclusion

Exploring the biotechnological and therapeutical active metabolites from marine actinomycetes has gained attention recently. Nevertheless, more effort should be done to address the exact pharmaceutical potency of various marine actinomycetes. The marine ecosystem is not completely unexplored for its potential compounds despite their vast resources. Actinomycetes are well known as producers of many novel compounds with pharmaceutical and clinical importance. Traditional and innovative techniques and strategies have been developed to characterize the marine actinomycete diversity as well as studying the relationship between the marine environment and the secondary metabolite produced by marine microbes. Altogether, this will help increasing our ability to understand their systematics, as well as clarify their evolution and ecology. Actinomycetes have shown their ability to produce various potent secondary metabolites that are required in several important industries such as pharmaceutical, cosmetic, medical, and food industries. More effort is needed to explore the potential of marine microorganisms especially marine actinomycetes as producers of novel drugs of natural sources. Many studies worldwide have lined up the points towards the research on marine actinomycetes for searching of drug lead or new drugs.

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