



## A review on Actinomycetes distribution, isolation, and their medical applications

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### Abstract

Actinomycetes (Actinobacteria) are Gram-positive bacteria that grow in a variety of environments and have a filamentous shape similar to fungi. The actinomycetes distinguish themselves morphologically by forming a layer of hyphae that carry chains of spores. The aim of this study was to update the recent developments related to the actinomycetes. *Streptomyces*; as an actinomycete, is known for producing a number of bioactive secondary metabolites, including anti-tumour agents; antibiotics, antifungals, antivirals, anti-hypertension drugs, and immunosuppressives. In order to compete with other microorganisms, including those of the same genera, *Streptomyces* species produce several secondary metabolites. However, despite the discovery of antibiotics, the infectious diseases remain the second-leading cause of death worldwide. Each year, around 17 million people die from bacterial infections; mainly children and the elderly. In addition to the overuse of antibiotics, a key factor contributing to antibiotic resistance is self-medication, which reduces the lifespan of antibiotics.

**Keywords:** *Streptomyces* spp., Methods of isolation, Distribution, Antibacterial activity, Secondary metabolites, Antibiotics



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## 1. Introduction

The continuous need to protect human life has accelerated the research on antibiotics that can ensure human safety. Actinomycetes form hyphae-like branches both on the top of and below the agar surface when grown on it. These branched hyphae that grow above the surface of the substrate are called aerial hyphae, while those that grow below it are called substrate hyphae. Increasing the numbers of antibiotic-

resistant pathogens poses a major threat to the global health, which has prompted extensive researches on novel antibiotic-producing actinomycete strains, in order to combat this growing problem. Human treatment claims still require natural health products. According to the US Food and Drug Administration (FDA), the chemical drugs account for 65 % of the 1211 small molecule drugs that have been prescribed

from 1981 to 2020 ([Newman and Cragg, 2020](#)). In 1942, penicillin has been discovered and became the first antibiotic to save millions of lives. Over the last few decades, the number of new antibiotics has dramatically decreased. The lack of new antibiotics and multiple resistance to the existing ones can lead to millions of deaths worldwide ([Mast and Stegmann, 2019](#); [Farda \*et al.\*, 2022](#)).

The actinomycetes have long been thought to have antimicrobial activity. Actinomycetes are filamentous; saprophytic, spore-forming bacteria that produce over 20,000 natural products, which are widely used in pharmaceuticals; veterinary medicine, and agrochemicals. They are found in both of the aquatic and terrestrial environments ([Al-ansari \*et al.\*, 2019](#); [Jagannathan \*et al.\*, 2021](#)). The majority of the known natural products are produced by actinomycetes; however, the *Streptomyces* spp. in particular are prolific and produce a wide range of primary and secondary metabolites, including antibiotics; fungicides, herbicides, pesticides, anti-tumours and those with immunosuppressive activity, in addition to the enzymes ([Takahashi and Nakashima, 2018](#)). A total of 23,000 bioactive microbial metabolites have been produced by the actinomycetes, which account for 45 % of all discovered bioactive metabolites ([Kalyani \*et al.\*, 2019](#)).

Actinomycetes have branched networks of hyphae that are reminiscent of fungi. They have been once considered as intermediate forms between bacteria and fungi. Unlike the fungi, actinomycetes have peptidoglycan cell walls; prokaryotic nuclei, and have the ability to resist the antibacterial agents. Nevertheless, actinomycetes and fungi share a number of similarities. It has been shown that most bacteria are aerobic and they obtain their nutrients through either a heterotrophic or chemoautotrophic metabolism ([Schmidt \*et al.\*, 2019](#)).

Under certain conditions, septa can be seen in the actinomycetes, which usually form threads or rods called hyphae. The sporulating mycelium may be branching or non-branching, straight or spiral. As for

the shape of actinomycetes' spores, they may be oval, spherical, or cylindrical. Initially, filamentous microcolonies are produced, which break up after 24 to 48 h into diphtheroid colonies; short chain colonies, and coccobacillus colonies. Despite the high osmotic pressure, actinomycetes maintain the integrity of their cell shape, due to the rigidity of their cell wall ([Barka \*et al.\*, 2016](#)). There are three components of the actinomycetes cell wall, including peptidoglycan; teichoic and teichuronic acids, and polysaccharides. In addition to N-acetylglucosamine, N-acetylmuramic acid also influences the peptidoglycan structure. A covalent bond is formed between teichoic acids and teichuronic acids when they are attached to peptidoglycan. There is no difference in the cell wall structure between the Gram-positive bacteria and actinomycetes; however, the actinomycetes display distinctive hyphae and cultural patterns ([Mohammad and Dehhaghi, 2017](#)).

As the ocean is the world's largest water body and is a place to over 87 % of the living organisms, it is considered as a rich source of rare microorganisms and new natural products. It is possible that the rare marine actinomycetes can provide a rich source of chemically distinct secondary metabolites as well as novel therapeutic compounds ([Subramani and Sipkema, 2019](#)).

Since the conventional cultivation studies yield fewer rare actinomycetes than the streptomycete strains, the metagenomic high-throughput sequencing has enabled the researchers to uncover novel actinomycetes that have not been previously known. Recent researches on actinomycetes have revealed the differences in their physiological; chemical, and structural characteristics, which allow for their selective isolation media to be adopted ([Mast and Stegmann, 2019](#)).

Up to 2010, a total of 13,700 bioactive metabolites have been produced by the actinomycetes, where 10,400 of them have been isolated from the streptomycetes and 3300 from the rare actinomycetes. The numbers of active actinomycetes metabolites'

have increased in 1980, 1984, 1988, 2005, and 2010, when compared with 1974 ([Subramani and Sipkema, 2019](#)), where about 279 novel secondary metabolites have been discovered from 121 actinomycetes spp. ([Donald \*et al.\*, 2022](#)).

## 2. Actinomycetes distribution

Actinomycetes can live in a variety of environments and are widely distributed in the natural ecosystems. Based on their morphological and chemical criteria; actinomycetes have been classified into several distinct genera. Because of its importance in medical research; ecology, and biotechnology, *Streptomyces* sp. is the most widely isolated genus of the order Actinomycetales ([Olanrewaju and Babalola, 2019](#)). The most prevalent microbial inhabitants of the soil have been identified as actinomycetes. However, it has been reported that only 10 % of the actinomycetes have been isolated from their natural environments. As a result, the researchers must screen additional undiscovered actinomycetes that are capable of producing novel antibiotics against the bacterial spp., which are resistant to the current antibiotic treatments ([Selim \*et al.\*, 2021](#)). These actinobacteria are living in terrestrial, aquatic, and in extreme environments as presented in Table (1).

In addition, the different groups of actinomycetes are stable in the bulk soil and in the rhizosphere of most plants. Accordingly, the actinomycetes are essential to many plants. The rhizospheric streptomycetes, for example; can prevent the plant roots from becoming infected with fungi through the production of antifungal drugs. Actinomycetes are also excellent sources of lytic enzymes; antibiotics, and other bioactive compounds, due to their metabolic diversities ([Vurukonda \*et al.\*, 2018](#)). It has been reported that actinomycetes spores can be present in the air. Moreover, it has been suggested that the airborne actinomycetes; such as *Nocardia* spp., have antibacterial activity. Several unique bioactive microbial compounds have been produced by the symbiotic and transitory bacteria in the insect digestive tracts, which include streptanoate; alpinamide A,

alteramides A and B, coproporphyrin III, deferoxamine, demethylenocardamine, dihydropicromycin, nocardamine, picromycin, surugamides A, B, C, D, and E, tirandamycins A and B, and valinomycin ([Santamaría \*et al.\*, 2020](#)).

According to the recent study conducted [Ambikapathy \*et al.\*, \(2022\)](#) the insect gut microbiota greatly contribute to the nutrition of the termites; cockroaches, and aphids. *Apis mellifera*; the honeybee, has a complex digestive tract, which makes it an interesting model for studying the gut bacteria. Occasionally, *Streptomyces* spp. can dominate the bee stomach. The bee guts have also been recorded to contain *Nocardiopsis* sp., which expresses an antibiotic biosynthesis gene. The *Bacillus* strains natives to the bees and two of the other drug-resistant Gram-positive pathogens have been selectively killed by the actinomycetes. The rare actinomycete *Nocardiopsis alba* has been detected in the guts of honeybees.

In earthworms casting, the actinomycetes and industrial enzymes have rarely been studied. The casting action of *Actinomyces* sp. nourishes and enriches the soil. By burrowing and eating; the earthworms redistribute the organic materials in the soil, increase the soil's permeability that improves the exchange of gases with the atmosphere, and increase the microbial activity. A number of medicinal applications can be recognized for the casting actinomycetes in the animal and human medicines ([Salcedo-Porras \*et al.\*, 2020](#)). The majority of actinobacteria are environmental residents; as opposed to the obligate pathogens. Actinobacteria play vital roles in the life and reproduction of many insects. The streptomycetes protect the European bee wolf pups against the microbial pathogens infection. *Oerskovia* and *Nocardiopsis* spp. are the major bacterial spp. detected in the goat feces, which generate more antifungal agents than the antibacterial agents. Antibiotics from *Streptomyces* spp.; such as monensin and flavomycin, have been utilized to promote the growth rate of cattle ([Selim \*et al.\*, 2021](#)).

**Table 1:** Ecological distribution of the Actinobacteria adopted from [Goel \*et al.\*, \(2021\)](#)

Habitats	Area	Bacterial strains	References
Terrestrial	Soil	<i>Streptomyces</i> sp. <i>Nocardia</i> sp. <i>Streptoverticillium</i> sp. <i>Nocardioopsis</i> sp. <i>Amycolatopsis</i> sp. <i>Micromonospora</i> sp. <i>Actinomadura</i> sp	<a href="#">Al-Mahdi, (2016)</a>
	Freshwater	<i>Actinoplanes</i> sp. <i>Micromonospora</i> sp. <i>Rhodococcus</i> sp. <i>Streptomyces</i> sp.	<a href="#">Jagannathan <i>et al.</i>, (2021)</a>
Aquatic	Marine	<i>Dietzia</i> sp. <i>Agrococcus</i> sp. <i>Arthrobacter</i> sp. <i>Gordonia</i> sp. <i>Mycobacterium</i> sp. <i>Pseudonocardia</i> sp. <i>Rhodococci</i> sp. <i>Streptomyces</i> sp.	
	Extreme environment	<i>Saccharomonospora</i> sp. <i>Georgenia</i> sp. <i>Thermotunica</i> sp. <i>Thermobifida</i> sp. <i>Amycolatopsis</i> sp. <i>Rubrobacter</i> sp.	<a href="#">Shivlata and Satyanarayana, (2015)</a>

An endophyte is a microorganism that lives entirely or in part inside the plant's tissues. The long-standing relationship between the endophytic bacteria and their host plants has led to an increase in their numbers. The actinomycete-derived bioactive compounds have been used to control the silver scurf sickness caused by *Helminthosporium solani* in potatoes ([Gao \*et al.\*, 2021](#)). Significant antifungal properties have been demonstrated in the bioactive compounds that are derived from the Streptomyces spp. *Amycolatopsis* CP2808, which belongs to the *Pseudonocardiaceae* family, has been characterized

for its production of ansacarbamitocins antibiotics. Among the ansamycin antibiotics; ansamitocin has anticancer properties. *Nocardia* sp.; is an endophytic actinomycete that produces ansamitocin ([Selim \*et al.\*, 2021](#)).

[Chen \*et al.\*, \(2021\)](#) study has highlighted that marine actinomycetes interact with a wide variety of aquatic creatures, such as sponges; corals, echinoderms, and puffer fish. The secondary metabolic pathways may evolve as a result of these interactions; thus promoting the diversity of chemical compounds

produced by the marine actinomycetes, as these interactions can have important ecological and biotechnological implications. These compounds may have novel biological activities, including antimicrobial; antitumor, and/or antiviral ones.

In addition to the interaction with the other species of the marine organisms; the marine actinomycetes may thrive in both of the planktonic and the biofilm habitats, and most of these actinomycetes strains have been identified in the sediments ([Schmidt \*et al.\*, 2019](#)). It is not yet known what factors encourage and result in actinomycetes adoption to one of these life choices. In general, the planktonic and biofilm-forming bacteria have diverse species compositions. Several physicochemical factors, including temperature; pH, pressure, total organic carbon, and salinity affect the numbers of actinomycetes population in the ocean sediment; where the optimum conditions vary according to the location. *Streptomyces*, *Micromonospora*, and *Actinomyces* strains have been discovered at depths up to 500 meters ([Jagannathan \*et al.\*, 2021](#)). For instance, *Micromonospora* sp. may be more abundant at 450 m than at lower levels. Furthermore, several investigations have demonstrated that the actinomycetes samples taken from the coastal sediments are more heat resistant than those collected from the salt water; suggesting that the heat-resistant spore forms of the actinomycetes dominate the sediments over their vegetative forms ([Jagannathan \*et al.\*, 2021](#)).

### 3. Methods of isolation of the actinomycetes

#### 3.1. Isolation of the soil actinomycetes

Actinomycetes are Gram-positive bacteria that can live on a wide range of substrates; both the simple and complex ones. Several general bacterial isolation procedures can be used to isolate the actinomycetes, including serial dilution; pouring plates, streaking, and centrifugation ([Majhi, 2018](#)). In the soil samples, centrifugation followed by repeated dilutions can enhance the growth of actinomycetes. However, none of these techniques can specifically separate the

actinomycetes; making the purification of actinomycetes more challenging ([Shivabai and Gutte, 2019](#)).

A pure culture of non-actinomycete bacterium can inhibit the growth of actinomycetes. Therefore, six methods have been developed for selective isolation of the soil actinomycetes; mainly (i) nutritional selection; in which the media contain nutritional components that the actinomycetes preferentially consume, (ii) selective inhibition; in which the growth inhibitors such as antifungal drugs and antibiotics are included to prevent growth of the non-actinomycete bacteria, (iii) physical or chemical sample pre-treatments; in order to limit the non-actinomycete bacteria, (iv) enrichment approaches; where the nutritional medium can be supplemented with extra nutrients, which favor growth of the actinomycetes, and/or inhibit the growth of the other microorganisms, (v) the membrane filter method, which does not require pre-treatment, specific medium, and/or antibiotics; and (vi) the integrated method that can use combinations of various procedures ([Kumar and Jadeja, 2016](#)). Pre-treatment of the soil can either increase the actinomycetes growth or remove most of the unwanted Gram-negative bacteria. There are several pre-treatment methods that have been developed for the different actinomycetes taxonomy. Under natural settings; the streptomycetes play a significant role in the actinomycetes population. As a result; physical pre-treatment can facilitate isolation of the streptomycetes, while chemical pre-treatment and/or combination of physical and chemical pre-treatments may facilitate isolation of the other bacteria ([Ezeobiora \*et al.\*, 2022](#)).

#### 3.2. Isolation of the marine actinomycetes

The phylum Actinobacteria adapts to and colonizes a wide variety of harsh ecosystems, including those in the deep sea; in addition, their metabolic capacity; morphology, and metabolism are extremely diverse. The growth conditions for the uncommon marine actinomycetes are generally different from those for the terrestrial actinomycetes ([Subramani and Sipkema, 2019](#)). A considerable proportion of the bacteria in



underexplored habitats are viable but not culturable; since only around 1 % of these bacteria can form colonies on the isolation media using the standard techniques. For this reason; the high-throughput molecular methods such as metagenomics, are becoming increasingly popular for studying the microbial communities in the environment; where the culture-based approaches are largely ineffective (Gutleben *et al.*, 2018). Furthermore, the culture-independent studies on the actinomycetes functional features have led to the development of improved methods for growing and cultivating the previously uncultivable actinobacteria (Kumar and Jadeja, 2016).

The actinomycetes' taxonomy, physiology, and environmental parameters, including pH; culture temperature, oxygen, and nutritional requirements must be understood and controlled in order to isolate the undiscovered and/or the uncommon actinomycetes. The growth media should normally have osmotic values similar to those of the seawater, since sodium ( $\text{Na}^+$ ) is one of the most critical medium components that are essential for development of the marine microorganisms such as *Salinispora* spp. Furthermore, different carbon sources (i.e., soluble starch; glucose, dextrose, maltose, trehalose, mannitol, raffinose, fucose, chitin, glycerol, and oatmeal), and combined carbon-nitrogen sources (i.e., peptone; yeast extract, casein, malt extract, meat extract, beef extract, and tryptone) should be added to the isolation media. Furthermore, sediment extracts; sponge extracts, and genuine saltwater should be introduced either alone or as supplements to simulate the marine natural growth conditions (Subramani and Sipkema, 2019).

Prior to isolation of the uncommon actinomycetes; marine materials particularly sediments, may be added to eliminate the common terrestrial actinomycetes and the undesirable microorganisms. Isolation of the rare actinomycetes from the marine samples is commonly done through diluting and mixing the samples with sterile natural and/or artificial seawater; deionized/dist. water with NaCl, multi-salts, vitamin B mixtures, Ringer's solution, and/or saline solution. The marine actinomycetes have been preferentially isolated using a

variety of pre-treatment procedures; most commonly the environmental sample is to be dried within a laminar air flow cabinet and then diluted with seawater or saline before it is heated (Siro *et al.*, 2022).

Due to their resistance to desiccation and heat, the actinomycetes spores can be used to select against the other Gram-positive bacteria. The actinomycetes spores are resistant to a variety of substances, including benzethonium chloride; chlorhexidine gluconate, phenol, sodium dodecyl sulfate, and several antibiotics. Selective separation of the actinomycete taxa has been achieved using these substances. These substances kill or inhibit the aerobic Gram-negative bacteria; endospore-forming bacteria, and pseudomonads within 30 min., thus increasing the possibility of selective isolation of the actinomycetes while reducing the other forms of bacteria. Moreover, the ultrasonic waves can disperse the actinobacterial propagules from the soil particles; thereby increasing the actinobacterial strains and lowering those of the undesirable bacteria (Rasuk *et al.*, 2017).

#### 4. Secondary metabolites production by the actinomycetes

Metabolomics is the systematic, qualitative, and quantitative investigation of biologically active compounds in microorganisms; biological fluids, plants, and food matrices (Stuart *et al.*, 2020). The field of metabolomics consists of identifying and quantifying the small-molecule of metabolites in the metabolome of biological samples using high-throughput methods. A metabolomics study collects all the molecules of metabolites discovered in a cell, organ, or a microorganism. These molecules include peptides; amino acids, nucleic acids, carbohydrates, organic acids, vitamins, medicines, food additives, phytochemicals, and toxins. There are two types of metabolites; mainly primary and secondary metabolites (Ahmad *et al.*, 2017). In the course of the microorganism's development and energy metabolism, the primary metabolites are frequently produced. In addition to glucose; protein, amino acids, and fatty acids, these main metabolites are essential for the cell

growth, development, and reproduction. In contrast, the secondary metabolites are formed from the primary metabolites under specific conditions, and they play a major role in the pathogen defence ([Thirumurugan \*et al.\*, 2018](#)). These low-molecular-weight metabolites are a highly valuable class of compounds that can be used in a wide range of applications, including drugs (e.g., antibiotics, antitumour agents); agrochemicals (e.g., pesticides); biofuels (e.g., oleoresin), and food additives (e.g., essential oils). Several secondary metabolites that are produced by fungi and bacteria are found useful for use as antibacterial agents, such as the phenazine produced by *Streptomyces kebangsaanensis* ([Ahmad \*et al.\*, 2017](#)). Generally, the metabolomics can be used to discover and optimize the synthesis of secondary metabolites. The metabolism data can be used to construct culture and manufacturing procedures on a small scale, which will then be scaled up to a fermenter system ([Devi \*et al.\*, 2020](#)).

Gas chromatography-mass spectrometry (GC-MS) is a useful technology for the separation of various components found in the secondary metabolites. Many chemicals such as lipids; drug metabolites, and environmental pollutants, in addition to forensic science have been investigated using gas chromatography coupled to mass spectrometry (GC-MS). A benefit of GC-MS is that a microbial species can be identified based on its retention time and mass spectrum (i.e., a compound's fragmentation pattern). Typical electron voltages of -70 eV are used to ionize the compounds, which produce repeatable fragmentation patterns. Therefore, GC-MS fragmentation spectra are not instrument-dependent and allow for the establishment of databases and data exchange among the users, which makes this approach very useful. In addition, GC-MS enables quantitative identification of the analytes ([Mustafa \*et al.\*, 2017](#)).

It is well known that actinomycetes; especially *Streptomyces* spp., produce a wide variety of secondary metabolites such as antibiotics. Despite of this, little systematic research has been conducted on the volatile organic compounds produced by these microorganisms. Nevertheless, they received much

attention for producing off-odor; musty, and odor compounds, including 2-methylisoborneol, which negatively affects the freshwater sources and aqua cultured fish. Despite of the concurrent use of the existing antibiotics and the search for new potent ones to control these resistant pathogens; however the antibiotic resistance is still increasing ([Siro \*et al.\*, 2022](#)).

From the marine sources, several potent antibacterial metabolites have been discovered. *Streptomyces* spp. produce a wide range of physiologically active secondary metabolites, including the antibiotics. The secondary metabolites derived from the marine *Streptomyces* spp. are unique in that they create novel natural antimicrobials. Most of the antibiotics known to man are produced by *Streptomyces* spp. In addition, *Streptomyces* spp. produce around 75 % of the world's effective antibiotics ([Salvatore \*et al.\*, 2018](#)). In 1981, it has been discovered that trioxacarcins are complex antibiotics. In the marine streptomycetes; trioxacarcins A, B, C, and D have been identified. As antiplasmodial agents, trioxacarcins A and D have exceptionally high IC<sub>50</sub> values ( $1.6 \pm 0.1$  ng/ml and  $2.3 \pm 0.2$  ng/ml, respectively), which are equivalent to an antimalarial drug named artemisinin (0.7 ng/ml to 0.1 ng/ml). Compared with trioxacarcins A and D, trioxacarcin B has about 100 times lower antiplasmodial activity, while trioxacarcin C is essentially inactive (IC<sub>50</sub> value is > 5000 ng/ml) ([Ahmad \*et al.\*, 2017](#)).

Coronamycin is a new type of peptide antibiotic that is discovered in 2004. This chemical has been isolated from an endophytic *Streptomyces* sp. named *Monstera* sp., which is found in Peru's upper Amazon area. With an IC<sub>50</sub> of 9.0 ng/ml, coronamycin has an antiplasmodial activity against *Plasmodium falciparum*. Coronamycin has no anticancer effect against the BT20 breast cancer cells; however, its cytotoxicity against the HMEC; a human mammary epithelial cell line, is similar to Taxol, which is an anticancer chemotherapy medication. Another bioactive molecule with antimalarial properties is Gancidin-W, which has been isolated from

*Streptomyces* sp. *In vivo* testing of Gancidin-W effect on *Plasmodium berghei* NK 65-infected mice revealed 80 % of the parasite suppression at concentrations of 6.25 and 3.125 g\ kg body weights on the penultimate day of the test. Furthermore, 50 % of the mice treated with Gancidin-W at a dosage of 3.125 g\ kg body weight have survived for 11 months post inoculation ([Ezra \*et al.\*, 2004](#)).

## 5. Medical applications of the actinomycetes

### 5.1. As sources of antibiotics

The majority of antibiotics currently used in medicine are derived from the actinobacteria; with *Streptomyces* spp. composing 50 % of them. As a result of the phylum's extensive ability to produce antibiotics; the actinobacterial strains are able to produce between 10 and 20 types of secondary metabolites. Tetracyclines are classified under the macrolide and macropeptide categories, while aminoglycosides are categorized under the aminoglycoside category. Neomycin; streptomycin, kanamycin, cephamycin, vancomycin, erythromycin, and tylosin are among the antibiotics recently developed from actinomycetes ([Mast and Stegmann, 2019](#)).

Most of the human microbial infections have been treated with antibiotics based on the novel secondary actinobacterial metabolites. Rifampicin and cycloserine are used to treat *Mycobacterium tuberculosis*, while erythromycin derived from *Saccharopolyspora erythraea*, is used to combat the Legionnaires' disease. Tetracycline targets the bacterial ribosomes, which is produced by *Streptomyces aureofaciens*. The vancomycin-resistant and methicillin-resistant *Staphylococcus aureus* (MRSA) are treated by the daptomycin antibiotic, which has been developed by *Streptomyces roseosporus*. Chloramphenicol inhibits the protein synthesis in *Streptomyces venezuelae* ([Fatahi-Bafghi, 2019](#)). There are several strains of *Staphylococcus aureus*; *Streptococcus* spp., and *Pseudomonas* spp. that are chloramphenicol-susceptible. The antibiotic

gentamicin that is derived from *Micromonospora purpurea* is used to treat the Gram-positive and Gram-negative bacterial infections. *Streptomyces cinnamomensis* produces monensin, which is used for treating the Gram-positive bacteria that are resistant to several antibiotics ([Schneider, 2021](#)).

Numerous novel therapeutic antibiotics can still be developed through isolating the novel actinomycete drugs. In the marine sponge-derived *Nocardiopsis* sp., about 3 novel angucycline and nocardiosistins antibiotics have been discovered that have anti-MRSA activity. Thirteen strains of actinomycetes that are isolated from the Andaman Islands' mangrove habitat have shown broad spectrum activity against the Gram-positive and Gram-negative bacteria. A single unique *Streptomyces* sp. has developed bioactive compounds with broad-spectrum activities against fish; poultry, and fungal diseases ([Bergeijk \*et al.\*, 2020](#)).

Even though hundreds of antibiotics are currently available; however, novel antimicrobials are still needed. Despite the "Golden Age" of antibiotic discovery has been in the period of 1950s and 1960s; however, the Food and Drug Administration (FDA)-approved antibiotics have declined; emphasizing the need for innovative antibiotics. Unfortunately, the development of new antibiotics is a time-consuming procedure, which generally takes about 10 to 15 years from the discovery of the first chemical to the development of the final pharmaceutical product. In addition, only one out of every 1000 prospective drugs makes it to the clinical trials, and 90 % of them fail to pass the human testing. For more profit of the pharmaceutical companies, they must heavily invest for new drug development ([Goel \*et al.\*, 2021](#)).

More than 70 % of bacterial pathogens are resistant to at least one of the currently available antibiotics; accordingly, the need for new medicines or alternative approaches to combat the antibiotic resistance is increasing. One of the medicines greatest concerns is the antibiotic-resistant bacterial ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter*



*baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) (Mancuso *et al.*, 2021). By 2050, it is predicted that the multidrug-resistant (MDR) infections will overtake the cancer as the leading cause of death. In order to treat the MDR strains of bacteria, new sources of antibiotics are being under investigation (Tenebro *et al.*, 2021).

New antibiotic development is significantly challenged by MDR Gram-negative bacteria, due to their wide resistance mechanisms that are not exclusive to certain antibiotic classes. There are several strains of *Streptomyces* spp. that exist on the terrestrial surfaces, and produce bioactive chemicals against ESKAPE infections. A wide range of MDR bacteria can be treated with antibiotics produced by the marine actinomycetes that have been isolated from the ocean sediments, including Gram-negative bacteria such as carbapenem-resistant *Enterobacteria*, and Gram-positive bacteria, such as the methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterobacteria* (Davies-bolorunduro *et al.*, 2021). *Nonomuraea* sp. as a marine actinomycete works as a source of several antibiotics; where *Nonomuraea* sp. has not only killed the carbapenem-resistant *Enterobacteria* and the Gram-positive bacteria, but it also generated several anti-human immunodeficiency virus products. In their fight against MDR infectious pathogens, the marine actinomycetes are promising sources of antibiotic discoveries (Bertrand and Munoz-Garay, 2019).

## 5.2. Anti-cancerous agents

Actinomycetes have the potential to treat cancer; especially those whose products have fewer side effects than the traditional chemotherapy, such as salinosporamide A. Adriamycin; is a medication isolated from *Streptomyces peucetius*, which inhibits DNA replication and is therefore considered as an anticancer medication. Other potent cancer chemotherapeutics (mitomycin C), include actinomycin D; bleomycin, anthracyclines (daunorubicin), and mitosanes. These medicines are produced by *Streptomyces verticillus*; *Streptomyces*

*peucetius*, *Streptomyces caespitosus*, and other intragenic isolates. Furthermore, the marine actins includes streptochlorin; aureoverticillactam, chalocomycin B, cyanosporasides, komodoquinones, nonactin, resitoflavine, sporelides, tetracenomycin D, thiocoraline, t-muurolol, butenolides, echinosporins, and streptokordin. As secondary metabolites derived from the marine actinomycetes; streptochlorin, lynamicins, marizomib, and thiocoraline are all anti-cancerous compounds (Zou and Kwok, 2021).

## 5.3. Biopesticides

To naturally control the insects, microorganisms that are detrimental to them have been used. Actinomycetes produce insecticidal active substances that are used to control the house fly (*Musca domestica*). After applying an actinomycete pesticide, about 90 % of the larval and pupal stages have died. *Culex quinquefasciatus* has been effectively suppressed by the actinomycetes (Yandigeri, 2021).

## 5.4. Plant growth hormone

Actinomycetes produce several plant growth hormones such as auxins and gibberellin-like substances, which boost the plant development. The major form of auxin that is produced by the actinomycetes is Indole-3-acetic acid (IAA); where this molecule is essential for cell proliferation; elongation, and differentiation (Meena *et al.*, 2017).

## 5.5. Antiviral agents

*Streptomyces lavendulae* synthesizes peptides called estatins, which failed to demonstrate inhibitory efficacy against the human immunodeficiency virus (HIV). However, these peptides bind to the HIV cell receptors and block HIV-1 adsorption (Akilandeswari and Pradeep, 2017).

Selim *et al.*, (2021) previous study has shown that culture supernatants of *Streptomyces chromofuscus* include a protease inhibitor drug (PISC-2002), which is effective against influenza virus A/Rostock/34 (H7N7). Pimprinine; is an extracellular alkaloid

generated by *Streptomyces* spp., which has antiviral properties against *Enterovirus 71* (EV71), in addition to its antibacterial and anticonvulsant activities.

### 5.6. As sources of pigments

Actinomycetes produce pigments under natural and artificial conditions, where the most common colors for these pigments are blue; violet, red, rose, yellow, green, brown, and black. There is a possibility that these pigments will permeate the media and/or may be retained in the actinomycete mycelium. Several antibiotics are manufactured by the actinomycetes, which have a variety of colors. The use of melanin in pharmaceuticals and cosmetics is common. *Streptomyces hygroscopicus*; is an actinomycete that produces pigments, which have antibacterial properties against several MDR strains, including methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Staphylococcus aureus* (VRSA), and extended-spectrum  $\beta$ -lactamases (ESBL). Other *Streptomyces* spp. produce a yellowish substance that kills the pathogenic bacteria ([Kazi et al., 2022](#)).

### 5.7. Commercial enzymes

The values of the commercial enzymes have recently grown significantly as a result of their various applications in the pharmaceutical; food, and detergent industries. Actinomycetes contain unique active enzymes that may catalyse many biochemical processes. The important enzymes generated by *Streptomyces* spp. include amylase; protease, and cellulases, which have several economic uses in the various industries. Furthermore, L-glutaminase; L-asparaginase, and L-galactosidase play important roles in the bio-cycling of C and N in natural water and sediments. In addition, l-glutaminase and L-asparaginase, which are generated by the marine streptomycetes, have anticancer properties ([Selim et al., 2021](#)).

### 5.8. Enzyme inhibitors

A previous study reported by [Sivakumar et al., \(2007\)](#) that the enzyme inhibitors are gaining

popularity as helpful tools for studying the enzyme structures and reaction processes, in addition to their prospective use in the pharmaceutical sector. Generally, the marine actinomycetes are promising sources for synthesis of enzyme inhibitors, including N-acetyl-D-glucosaminidase; pyroglutamyl peptidase, and amylase. The amylase inhibitors are starch blockers; as they include chemicals that prevent the body from consuming the dietary starch.

### 5.9. As anti-inflammatory compounds

Saphenic acid and lipomycin are anti-inflammatory compounds produced by the marine actinomycetes. *Micromonospora* sp. has also been shown to produce anti-inflammatory and antibacterial bioactive substances. Cyclomarin A and C are two anti-inflammatory metabolites produced by another *Streptomyces* spp.; with cyclomarin A has anti-tuberculosis and anti-malarial activities. Furthermore, the inflammation is reduced when cyclomarin A has been administered topically or intraperitoneally ([Pandey, 2019](#)).

### 5.10. Biosurfactants

A biosurfactant is a surface-active chemical that is mostly generated by microorganisms, and affects the surfaces. Due to their selectivity; biodegradability, and low toxicity, the biosurfactants offer various advantages. Also, these biosurfactants' have the ability to act under high temperature; pH, and salinity conditions. Actinomycetes are essential in the generation of emulsifiers. Trehalose dimycolates are formed by several actinomycetes such as *Nocardia* spp. Numerous biosurfactants have been also generated by *Streptomyces griseoflavus* and *Nocardioopsis A17* ([Selim et al., 2021](#)).

## Conclusion

The use of antibiotics needs to be regulated in order to encourage the pharmaceutical companies to develop new antibiotics. The key challenge remains to finding a regulatory solution that ensures the commercial viability of the developing antibiotics. In

addition to reducing the number of competing research and developing groups, the merge of these pharmaceutical companies has an immediate impact. However, this makes it more difficult to develop new antibiotics when the other areas are more lucrative commercially to these pharmaceutical companies. A new technology has evolved (i.e., functional genomics), which allows us to evaluate the interaction between the mechanisms of action of the target antibiotic and the development of specific antibiotic resistant bacteria. Despite the recent advances in the sequencing technology and the identification of new targets for treating the pathogenic microorganisms; however, there is still a limited success in developing an effective treatment.

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### Conflict of interest

The authors have no conflicts of interest to declare.

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None applicable.

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