



Marine Actinomycetes: A Therapeutic Approach

S. Justin Raj^{1*}, Mary Essolin. S²

1. Assistant Professor and Research Guide, Department of Biotechnology, Malankara Catholic College, Mariagiri, Kaliyakavilai, Tamil Nadu, India.

2. Research Scholar, M.S. University, Tirunelveli, Tamil Nadu, India.

*Corresponding author's E-mail: rajstephy6@gmail.com

Received: 10-05-2024; Revised: 26-07-2024; Accepted: 08-08-2024; Published on: 15-08-2024.

ABSTRACT

Actinomycetes are potential antibiotic producers. Marine environments in India are less explored for their bioactive compounds. Marine actinomycetes produce diverse groups of secondary metabolites and provide scope for pharmaceutical and other industries. The marine ecosystem in India is less explored than the global average. New Metabolites are being discovered from actinomycetes from different marine sources in India. They are important from the economic and industrial point of view. The study of new metabolites is a growing field in the country. 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 antibiotics, antiviral, antitumor, antifouling agents, as well as enzymes. The secondary metabolites obtained from such marine actinomycetes have proved their value in different industries due to their unique properties and structures. These organisms have proved to be important, both biotechnologically and economically considering their global presence. With the rapid advancement in the study of actinomycetes from different marine sources in India, new metabolites are being discovered which have an important role from the economic and industrial point of view. As the world is witnessing newer diseases such as Sars-Cov 2 and the pandemic due to its demands drugs and other metabolites are increasing day by day. Therefore, the necessity for the quest for unique and rare marine actinomycetes is enhancing too. This review focuses on the therapeutic potential of less explored actinomycetes from extreme environments that can be utilized for industries, agriculture and allied sectors as sustainable herald for green biotechnology.

Keywords: Actinomycetes, Marine ecosystem, Bioactive metabolites, Antifouling agents, Green biotechnology.

INTRODUCTION

Actinomycetes have been characterized as the most important group of microorganisms in the field of biotechnology, as producers of bioactive secondary metabolites with medical, industrial and agricultural applications. However, until now, only less than 1% of the actinomycetes have been identified, investigated and documented.¹ Actinomycetales is an order of Gram-positive bacteria composed of both benign and pathogenic bacteria belonging to the phylum Actinobacteria. Actinobacteria are a well-defined group of Gram positive, free-living, saprophytic bacteria with high G+C content in their DNA. The genus *Streptomyces* was described for the first time by Waksman and Henrici in the year 1943. Historically actinobacteria have been described as having a higher GC content in their DNA,² though several members of the species such as freshwater and marine organisms were recently identified with comparatively low GC contents.³ Members of this order are often distinguished by their mycelial morphology with branched hyphae and the ability to form spores, although not all actinomycetes are sporulating.⁴ They exhibit great diversity in a variety of characteristics including moisture tolerance, habitat, optimal pH, and thermophilicity.⁵ Actinomycetes are often found at moderate pH levels though some acidophilic and alkaliphilic species are known.^{6,7} While some thermophilic actinomycetes have been recorded, most species appear to prefer moderate temperatures.⁸⁻¹⁰ Actinobacteria was

originally considered as an intermediate group between bacteria and fungi, but later it attained a distinct position.¹¹ *Streptomyces* are filamentous, aerobic spore formers and omnipresent.^{12,13} They are the largest antibiotic producing genus and about 70% of the antibiotics have been isolated from them.¹⁴ They also produce other types of compounds that are deleterious to competing microbes apart from a wide array of natural bioactive compounds such as antifungal, antiviral, anti-hypersensitivity, antitumor.¹⁵⁻¹⁷ Bioactive substances resulting from *Streptomyces* do not just treat disease in humans and animals, they are also used as biological control agents.¹⁸ They are also known producers of industrial enzymes, agrochemical and pharmaceutical products.¹⁹ They play an important role in carbon recycling, degradation of organic matter and enhance soil fertility.²⁰ Development of antibiotic resistance microbes to the commonly available antibiotics and antifungal agents has necessitated the requirement of new compounds and the members of the genus *Streptomyces* offer promising lead compounds.²¹

The biodiversity of marine environment proved to be an important resource for isolation of potent microorganisms to produce biologically active secondary metabolites.²² The marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compounds with the potential for industrial development such as pharmaceuticals, cosmetics, nutritional supplements, molecular probes,



enzymes, fine chemicals and agrochemicals. Each of these classes of marine bio-products has a potential multibillion dollar market value. So far, several bioactive molecules have been discovered from marine sources, with many more compounds still being discovered every year.²³ Antibiotics have been defined as substances produced by microorganisms that are antagonistic to the growth or life of other microbes. Thousands of marine organisms are known to contain antibiotic substances and only a very minimal quantity has been examined for their pharmacological activity.²⁴ The recent estimates suggest that the cultivability of microorganisms in marine sediments (0.25%) and especially seawater (0.001–0.10%) is considerably lower compared to soil (0.30%).²⁵⁻³⁰ A few valuable antibiotics and metabolites have been derived from terrestrial microorganisms (99% of the known microbial compounds) Since environmental conditions of the sea are extremely different from terrestrial conditions, it is felt that marine actinomycetes may have different characteristics from terrestrial actinomycetes and therefore might produce novel bioactive compounds and new antibiotics.³¹⁻³³

BIONOMICS OF ACTINOMYCETES

Actinomycetes are found in a wide range of environments and habitats, including as freshwater soil, marine environments, animals, plants, insects, and fertilizer.^{34, 35} They are saprophytes that live freely in environments like soil pores or endophytes that reside in plants.³⁶ Actinomycete members include pathogens that affect plants, animals, or soil (*Corynebacterium*, *Mycobacterium*, or *Nocardia* species); they also include plant symbionts (*Frankia* spp.); and dwellers of soil or aquatic environments (*Streptomyces*, *Micromonospora*, *Rhodococcus*, and *Salinispora* species).³⁷⁻³⁹ They can also be found in harsh settings, particularly in psychrophilic areas like the terra of Antarctica and deserts soil.⁴⁰⁻⁴²

Soil Actinomycetes

Actinomycete populations are highest and decrease with depth because of their necessity for oxygen. The estimated values of these are 104 to 108 cells in a gram of soil. They are sensitive to acidity/low pH (optimum pH range is 6.5–8.0) and waterlogged soil conditions. These organisms thrive at temperatures ranging from 25 °C and 30 °C, and they mainly are mesophilic. The species actinomycetes have an important ecological role as saprophytes, active participation in biological processes such as recycling of organic waste, bioremediation and promotion of plant growth.^{43,44}

Endophytic Actinomycetes

Excellent sources of potential new bioactive compounds are endophytic actinomycetes that can be found in the inner tissue of healthy plants, and which have no adverse effect on the host plant. From a variety of plants, including crops, medicinal plants, halophytes and some woody species, endophytic strains have been isolated. Examples of endophytic actinomycetes include *Actinoallomurus*,

Actinoplanes, *Allonocardiopsis*, *Amycolatopsis*, *Blastococcus*, *Glycomyces*, *Kibdelosporangium*, *Micrococcus*, *Micromonospora*, *Rothia*, *Saccharopolyspora*, *Solirubrobacter*, *Sphaerisporangium*, *Streptomyces*, *Streptosporangium*, *Wangella*, and *Xiangella*.⁴⁵

According to some of the results, unusual actinomycetes—that is, non-*Streptomyces*-dominate in plant samples. Fast-growing *Streptomyces* strains typically prevent or impede irregular and infrequently occurring actinomycetes from emerging from soil samples. On the other hand, where the ratio of *Streptomyces* is low, this is not the case in plant roots. Thus, it makes sense to think of plant roots as a great potential source of uncommon actinomycetes and, most likely, novel intermediate metabolites.⁴⁶

ROLE OF ACTINOMYCETES IN COMPOSTING

Microorganisms (bacteria, actinomycetes, and fungus) are essential to the breakdown of organic matter during the composting process because they create carbon dioxide, water, heat, and humus as byproducts, as well as the relatively stable organic product.⁴⁷ In general, the composting process consists of three main phases: i.e. the mesophilic phase, II. the thermophilic phase, III. the cooling and maturation phase. In compost, actinomycetes are typically present in the thermophilic and curing stages. High temperatures hasten the breakdown of organic compounds like proteins, lipids, and complex carbohydrates in plant-like lignin, hemicellulose, and cellulose during the thermophilic phase. The temperature of the compost gradually drops as these complex chemicals are depleted and mesophilic microbes once again dominate the last stage of "curing" or maturing the residual organic matter. In ecosystems where organic matter decomposes at high temperatures and aerobic conditions (such as inadequately stored hay, cereal grains, manure, straw, and other composts), thermophilic actinomycetes—well-known components of the microflora of composts—play a crucial role. Many genera of actinomycetes, including *Saccharomonospora*, *Saccharopolyspora*, *Streptomyces*, *Thermoactinomyces*, *Thermobifida*, and *Thermomonospora*, are known to be thermophilic.^{48,49}

ACTINOMYCETES IN MARINE ENVIRONMENT

Different from other aquatic environments, marine ecosystems are characterized by several unique characteristics. It has a composition of different salts and minerals that produce about 85% of the solids in seawater. The salinity of the water varies between 33 and 37 ppt in addition to extreme conditions such as high temperatures, pressures and pH differences between acids and alkalines. Most marine life cannot adapt to significant changes in the salinity of its environment. This makes it possible for microorganisms to produce different bioactive compounds than their terrestrial counterparts. They can evolve in these difficult environments by the production of



compatible solutes, such as polyol, amino acids and increased concentration of cytol ions.

An extensive wellspring of variety and for the most part undistinguishable actinomycetes can be tracked down in marine natural surroundings. Waterfront, remote ocean residue, seawater and mangrove backwoods are living spaces in the marine climate. Mangrove backwoods, which cover 75 % of the world's heat and humidity, are profoundly unique environments, and the variety of mangrove creatures is less known. Mangrove woods are special in that they differ in saltiness and flowing variances, which favor the improvement of surprising metabolites by their life forms. A significant wellspring of the disconnection of novel Actinomycetes strains to create their extraordinary metabolites is marine residue, surface waters, tidal pond beds, swamps, salty estuaries and collections of marine creatures like wipes, corals, mollusks and fish.⁵⁰

From the late 19th century, reports were emerging on marine actinomycetes. Studying marine microorganisms in various uses, such as drug development and biotechnology has initially provided guidance since 1980.⁵¹ In 2005, the first seawater-obligate marine actinomycetes genus, *Salinispora*, was described. The new species found in the family micromonosporaceae are *Salinispora tropica* and *Salinispora arenicola*. Studied marine actinomycete genera includes *Dietzia*, *Rhodococcus*, *Streptomyces*, *Salinispora*, and *Micromonospora*. Traditional bacterial enumeration in marine ecosystems, including seawater⁵³, coral reefs⁵⁴⁻⁵⁶ and mangroves⁵⁷⁻⁶⁰, has been studied. In mangrove residue, different kinds of organisms, for example, Pseudomonadota, Actinomycete and parasites can be found. Both *Streptomyces* and *Micromonospora* from marine living spaces are great contender for segregating strong development repressing mixtures and antitumor specialists. Its optional metabolites show different bioactivities, like antifungal, antitumor and antibacterial.⁶¹⁻⁶³

A CRUCIAL SECONDARY METABOLITE PRODUCER

Actinomycetes are evaluated to be the fundamental creator of neutralizing agents poisons among all microorganisms and produce ~55% of each and every spread out enemy of contamination. Generally 75% of these were found from *Streptomyces*, and the extra 25% from non-*Streptomyces* species. Of the 22,000 known microbial helper metabolites, 70% are conveyed by actinomycetes, 20% by parasites, 7% by *Bacillus* spp., and 1-2% by various microorganisms.⁶⁴ The discretionary metabolites of marine actinomycetes can be set up considering their substance structure as alkaloids, peptides, polyketides, caprolactones, butanolides, polycyclic xanthenes, trioxacarcins, and others.⁶⁵⁻⁶⁷

BIOTECHNOLOGICAL CAPABILITY OF ACTINOMYCETES

The auxiliary metabolites which are delivered by organisms have been getting a lot of consideration, particularly in the valuable impacts of human wellbeing, because of their

helpful natural exercises. Actinomycetes have different synthetic designs and natural exercises by which they are assuming a significant part in the medications and clinical businesses by their auxiliary metabolites creating limit. Numerous bioactive metabolites have been disengaged and portrayed and large numbers of them have been formed into drugs for treatment of numerous sicknesses in human, veterinary, and farming areas. Therefore, actinobacteria are the most potential source of secondary metabolites, antibiotics, enzymes and other bioactive compounds. It is well recognized that each actinobacterial strain has genetic potential ability to produce 10-20 secondary metabolites.^{68,69} The vast majority of actinobacteria can produce many biologically active compounds, i.e. antibacterial, antiviral and antifungal agents. Actinomycetes, particularly from the genus *Streptomyces*, has been widely known as antibiotic producers, such as streptomycin (*Streptomyces griseus*), erythromycin (*Streptomyces erythrus*), chloramphenicol (*Streptomyces venezuelae*) and tetracycline (*Streptomyces aureofaciens*).⁷⁰ There are many secondary metabolites of bioactive substances that are produced by actinomycetes, and these metabolites are known to possess antibacterial, antifungal, antioxidant, anti-cancer, anti-algal, anthelmintic, anti-malarial and anti-inflammatory.^{71,72}

Numerous specialists are engaged with the investigation of the bioactivities and modern uses of actinobacteria as it is an alluring wellspring of novel bioactive mixtures. The scientists are giving a lot of consideration on actinomycetes since they can deliver a ton of normal medications, bioactive metabolites, including anti-infection agents, proteins, catalyst inhibitors, antimicrobial substances, immunomodifiers, and development advancing substances, and so on for plants and creatures.⁷³⁻⁷⁶

ACTINOMYCETES AS SOURCE OF ANTIBIOTICS

The antibiotics production of different actinomycete strains can vary enormously as some actinomycete species produce a single antibiotic, whereas some produce a wide-range of different compounds and compound classes. Several of the antibiotics currently in use are natural products or analogs of natural products from actinomycetes.⁷⁷ Because of the decrease in the quantity of new substance platforms and rediscovery of known atoms, the advancement in anti-toxin improvement has dialed back. The investigation of option taxa, which have not been recently developed, could lighten earnest necessities connected with obstruction against as of now utilized anti-microbials. Thus, uncommon actinomycetes are turning into an undeniably significant focal point of examination in the quest for novel normal items since they possess an ineffectively investigated ordered and natural space, which lessens the probability of replication of revelation, and the phylum Actinobacteria is a rich wellspring of bioactive optional metabolites that can be anticipated to yield novel substance platforms for the improvement of new anti-toxins.⁷⁸



Antibiotic Resistance

Drug development is costly and requires substantial investment before pharmaceutical companies can make a profit. The expense in research and development and the long timelines needed for pipelines to produce final products raise increasing concerns about the prospects of fighting antibiotic resistance. Despite the hundreds of antibiotics currently available, there is still potential and demand for the discovery of new antimicrobials.⁷⁹ Unfortunately, the development of new antibiotics is a slow process. Pharmaceuticals typically take 10 to 15 years to progress from initial molecule discovery to final drug development. Additionally, only 1 in 1000 potential drugs make it to the clinical trials, with 90% failing the human-testing phase.^{80,81} More than 70% of bacterial pathogens are resistant to at least one current antibiotic treatment.⁸² Thus, the need for novel antibiotics or other methods to combat antibiotic resistance is becoming increasingly more dire. Antibiotic-resistant bacterial infections, especially those caused by ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*), are one of the biggest threats in medicine.⁸³ Drug-resistant pathogens are projected to surpass cancer as the annual leading cause of death by the end of 2050.⁸⁴ New sources of antibiotics are sought to treat multidrug-resistant (MDR) strains. Through the increase and misuse of antibiotics, antibiotic resistance has been selected for otherwise easily treatable pathogens. Terrestrial *Streptomyces* strains have been isolated that produce bioactive compounds against multiple ESKAPE pathogens.⁸⁵ Marine actinomycetes isolated from ocean sediments have been shown to produce antibiotics that are active against a multitude of multidrug-resistant (MDR) bacteria ranging from Gram-negative bacteria, such as carbapenem-resistant *Enterobacteria* (CRE), to Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).^{86,87} Purified DOPA melanin produced by *Streptomyces* sp. isolated from the coast of Mumbai, India showed strong antibacterial activity against various fish and human *Vibrio* pathogens, including *V. fluvialis*, *V. splendidus*, and *V. parahaemolyticus*.⁸⁸

Anticancer Activity

Marine actinobacteria are known for creating primarily unique and organically dynamic optional metabolites that can go about as powerful medications, which can't be delivered by any earthbound creatures. A large portion of the anticancer mixtures come from marine sources, particularly actinomycetes, and these metabolites act as a significant hotspot for drug enterprises. There is eminent anticancer restorative potential for actinomycetes, particularly those whose items are related with insignificant incidental effects contrasted with customary chemotherapy, for example the compound salinosporamide A. Adriamycin, isolated from

Streptomyces peucetius, inhibits DNA replication and is an anticancer drug. Other effective products for cancer chemotherapeutics are actinomycin D, bleomycin, anthracyclines (daunorubicin), and mitosanes (mitomycin C). These drugs were obtained from *Streptomyces verticillus*, *Streptomyces peucetius*, *Streptomyces caespitosus*, and other intrageneric isolates.⁸⁹ Marine actinomycin compounds with antitumor potential include streptochlorin, actinofuranones, aureoverticillactam, chalocomycin B, cyanosporasides, komodoquinones, nonactin, resitoflavine, sporolides, tetracenomycin D, thiocoraline, t-muurolol, butenolides, echinosporins, and streptokordin. Important secondary metabolites from marine actinomycetes with antitumor potential include streptopyrrolidine, cyclo-(L-Pro-L-Met), streptochlorin, lynamycins, marizomib, and thiocoraline.⁹⁰ Two instances of novel anticancer metabolites are the compound concentrates ULDF4 and ULDF5 got from *Streptomyces* strains found at Lagos. ULDF4 and ULDF5 show cytotoxicity against human intense myelocytic leukemia, cervical carcinoma, human gastric carcinoma, bosom adenocarcinoma, and human intense promyelocytic leukemia.⁹¹ Ketomycin is another planned antitumor compound. Ketomycin stifled cell relocation and intrusion in bosom carcinoma cells, restrained NF- κ B action utilized in upstream announcing upsetting the autophosphorylation of IKK- α /IKK- β , and limited the 3D-attack of bosom carcinoma cells at nontoxic concentrations.⁹² Subsequently, ketomycin isn't just a successful anti-infection, yet in addition a fundamentally straightforward antitumor specialist for mammalian cells.

Antifungal Activity

Among the various kinds of medications available, antifungal anti-toxins, which play a significant part in controlling contagious contaminations, are generally little however critical gatherings of medications. Antifungal specialists are broadly applied in people, medication, horticulture, and veterinary medication. There are five significant classes of antifungal mixtures: (i) polyene anti-toxins, (ii) allylamines and thiocarbamates, (iii) azole subsidiaries, (iv) morpholines, and (v) nucleoside analogs. Polyene antifungal mixtures, for example, amphotericin B are the standard treatment for parasitic diseases. Latest antifungal metabolites were distinguished from *Streptomyces*. The excess was tracked down in uncommon actinomycetes from the genera *Actinomadura*, *Amycolatopsis*, *Actinokineospora*, *Norcardia*, *Pseudonocardia*, *Saccharothrix*, and *Umezawae*.⁹³

Antiviral Activity

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 human viral diseases. The flare-ups of the flu An infection (IAV), serious intense respiratory condition Covid (SARS-CoV), Center East respiratory disorder Covid, and, as of late, SARS-CoV-2 feature the requirement for finding



successful antiviral medications against respiratory RNA infection. To be sure, the Covid infection 2019 caused a worldwide pandemic with high death rates around the world. Regular items got from microbial sources are as yet an amazing underlying theme for finding new therapeutics, including antiviral specialists.⁹⁴

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.⁹⁵ Another study reported a marine actinomycetes strain named *Streptomyces kaviengensis*, produced a novel metabolite “antimycin A”. Antimycin A derivative was very effective against the Western equine encephalitis virus where the IC50 value was less than 4 nM.⁹⁶ *Streptomyces* sp. HK18 isolated from the soil of a Korean solar saltern also produced biologically active metabolites “xiamycins C-E” with antiviral properties.⁹⁷

Immunosuppressive Activity

Immunosuppressants are fundamental medications that essentially decline the dangers of dismissing a relocated organ. Moreover, immunosuppressant drugs are additionally used to treat numerous immune system problems, like Crohn's illness (ongoing aggravation of the gastrointestinal system), rheumatoid joint inflammation, and sketchy going bald (alopecia areata). Different immunosuppressant medicates initially detached as antifungal anti-microbials are delivered by microorganisms, for example, ascomycin from *Streptomyces hygrosopicus* and tacrolimus from *Streptomyces tsukubaensis*.⁹⁸ Immunosuppressive specialists, for example, FR-900506 announced by Fujisawa Drug Organization, delivered by *Streptomyces tsukubaensis* shows more grounded restraint against interleukin-2 creation, blended lymphocyte response, interferon, cytotoxic White blood cells and platelet enacting factor-C induction.^{99,100} In regards to their method of activity, immunosuppressant drugs act by restricting to immunophilin, which is engaged with White blood cell initiation and proliferation.¹⁰¹

ACTINOMYCETES IN ENZYMES PRODUCTION

Marine actinomycetes are reported to produce many enzymes with industrial importance and that have more stability and unique substrate specificities. The availability of natural products in marine environments may rely on the ratio of enzyme produced by marine microorganisms. 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.¹⁰² Proteases have great commercial importance that is utilized in various industries, such as detergents, brewery, cheese-making, meat tenderization, and baking, etc.¹⁰³ 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.¹⁰⁴ Amylases are widely applied in fermentation, food, textile, and paper industries. Chitinases have been also reported to be produced by actinobacteria.¹⁰⁵ Chitinase finds a great application as a potent antifungal agent due to its ability to degrade chitin.¹⁰⁶ 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 ability to create xylanases.¹⁰⁷ Ribonuclease, which is otherwise called RNase assumes a significant part in numerous organic cycles, remembering self-contrariness for blossoming plants and angiogenesis. A few prokaryotic poison counteragent frameworks have been accounted for to have RNase movement. Consequently, different chemicals are being created by marine actinomycetes which show extraordinary modern significance. These catalysts delivered are utilized as drugs, fine synthetic compounds and food ventures.^{108,109}

ACTINOMYCETES AS ENZYME INHIBITORS

Actinomycetes also synthesize various enzyme inhibitors of low molecular weight. The first low molecular weight enzyme inhibitor was produced by a *Streptomyces* strain.¹¹⁰ Since then, more than 60 enzyme inhibitors have been reported which includes leuprptins, antipain (inhibit papain), plasmin, trypsin, chymotrypsin, and cathepsin B. In the treatment of cancer, the enzyme inhibitors are finding possible role like streptonigrin, retrostatin and revistin from *Streptomyces* species that inhibit reverse transcriptase. Alistragin is found in culture filtrates of *Streptomyces roseoviridis* which inhibits carboxypeptidase B. Phosphoramiden, inhibits metallo proteases and is produced by *S. tanashiensi*.¹¹¹

BIOCONTROL AGENTS

Streptomyces give off an impression of being a promptly accessible regular decision for tracking down better approaches to battle plant microbes and show considerable biocontrol activity against different phytopathogens. Be that as it may, a couple have been created as business items for plant applications in farming. Actinomycetes are known for further developing fertilizer quality and expanding its supplement content. They additionally increment the Oduor of fertilizer since they can totally process the natural matter present in manure.¹¹² It has been shown that the thermophilic Actinomycetota *Streptomyces* sp. and *Micromonospora* sp. can completely degrade yeast debris and sanitise the compost. In addition, *Streptomyces thermodiastaticus* was found to produce various extracellular enzymes involved in pathogenic yeast cell lysis, such as *Candida albicans*. Some thermophilic Actinomycetota can suppress plant diseases and thereby promote good crop plant health, increasing crop yields. Therefore, these thermotolerant Actinomycetota could be used as an alternative to commercial pesticides.^{113,114}



ACTINOMYCETES IN BIOREMEDIATION

Several species of Actinobacteria have been found to use pesticides as carbon sources, degrading them completely and returning them to nontoxic base elements and compounds. Better systems are needed for the cleanup of pesticides, metals, and mixed pollution. Currently, methods for the removal of pesticides and other toxic chemical substances from soil and water exist but are not always effective, particularly with inorganic compounds.^{115,116} For instance, a few types of *Streptomyces* (counting *Streptomyces spinosus*) have been found to create tyrosinase proteins, which are instrumental in the expulsion of phenols, a part of numerous pesticides that dirty water sources. Tyrosinase confined from these microbes was more powerful than regularly utilized tyrosinase, which was recently disengaged from different mushrooms. Albeit this is only one model, it shows the way that Actinobacteria can perform bioremediation in culture and produce synthetics that can be utilized independently for the evacuation of explicit contaminations.¹¹⁷

Marine *Streptomyces* such as *S. albus* subsp. *chlorinus*, have even been found to have properties that allow for effective pesticide/herbicide activity without causing environmental damage.¹¹⁸⁻¹²¹ In one study, *Streptomyces* species such as *S. lividans* were shown to absorb metals such as Cu (II) and Cd (II).¹²² In another review, both *Streptomyces* and *Amycolatopsis* species had the option to bioaccumulate Pb, Cd, Cr, and Zn.¹²³ The request Actinomycetales has areas of strength for a to metabolically deal with weighty metals, an imperative but underexplored region that warrants further examination and application. At long last, another underexplored area of bioremediation research is the use of actinomycetes in the cleanup of radioactive squanders. In an investigation of marine actinobacteria around a thermal energy station in India, a types of *Nocardiopsis* was found that had the option to adsorb huge measures of radioactive cesium. Moreover, *Streptomyces sporoverrucosus* was found to adsorb uranium by collecting it on cell walls in high amount.¹²⁴

CONCLUSION

Actinomycetes assume a main part in the age of various novel metabolites that have drug and other modern applications. Various actinomycetes separated from earthbound sources are likewise fit for delivering different optional metabolites; truth be told, most anti-infection agents come from these sources. However, various microorganisms are acquiring opposition towards the antimicrobials that are usually utilized. Thus, there is a crisis in drug improvement to restrain the development of these microorganisms. An expansive scope of anti-infection agents in the market was gotten from actinomycetes which can really debase an immense scope of xenobiotic compounds and can likewise change them into natural mixtures of high business esteem. Taking into account the tremendous natural assortment of the ocean, it is turning

out to be progressively evident that the oceans incorporate a significant number of remarkable therapeutic substances. Future endeavors in this field ought to incorporate profound cognizance of microbial physiology, systematics, and digestion. Investigating the sequencing of different actinomycete genomes as well as concentrating on the optional metabolite pathways found in actinomycetes are required. More exertion should be coordinated towards the improvement of additional procedures that help simpler and more proficient disengagement of different novel mixtures ought to be applied.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

- Berdy, J. Thoughts and facts about antibiotics: Where we are now and where we are heading. *J. Antibiot.* 2012; 65: 385–395.
- Barka, EA, Vatsa, P, Sanchez, L, Gaveau-Vaillant, N, Jacquard, C, Meier-Kolthoff, JP, Klenk, HP, Clément, C, Ouhdouch, Y, van Wezel, GP. Taxonomy, physiology, and natural products of actinobacteria. *Microbiol. Mol. Biol. Rev.* 2015; 80:1–43.
- Kavagutti, VS, Andrei, AS, Mehrshad, M, Salcher, M.M, Ghai, R. Phage centric ecological interactions in aquatic ecosystems revealed through ultra-deep metagenomics. *Microbiome.* 2019; 7:135.
- Embley, T.M, Stackebrandt, E. The molecular phylogeny and systematics of actinomycetes. *Annu. Rev. Microbiol.* 1994; 48: 257–289.
- Zenova, G.M. Manucharova, N.A, Zvyagintsev, D.G. Extremophilic and extremotolerant actinomycetes in different soil types. *Eurasian Soil Sci.* 2011; 44: 417–436.
- Basavaraj, K.N, Chandrashekhara, S, Shamarez, A.M, Goudanavar, P.S, Manvi, F.V. Isolation and morphological characterization of antibiotic producing actinomycetes. *Trop. J. Pharm. Res.* 2010; 9: 231–236.
- Ramesh, S, Mathivanan, N. Screening of marine actinomycetes isolated from the Bay of Bengal, India for antimicrobial activity and industrial enzymes. *World J. Microbiol. Biotechnol.* 2009; 25: 2103–2111.
- Kurapova, A.I, Zenova, G.M, Sudnitsyn, I.I, Kizilova, A.K, Manucharova, N.A, Norovsuren, Z.; Zvyagintsev, D.G. Thermotolerant and thermophilic actinomycetes from soils of Mongolia desert steppe zone. *Microbiology.* 2012; 81: 98–108.
- Saito, S, Kato, W, Ikeda, H, Katsuyama, Y, Ohnishi, Y, Imoto, M. Discovery of “heat shock metabolites” produced by thermotolerant actinomycetes in high temperature culture. *J. Antibiot.* 2020; 73: 203–210.
- Song, Q, Huang, Y, Yang, H. Optimization of fermentation conditions for antibiotic production by actinomycetes yj1 strain against *Sclerotinia sclerotiorum*. *J. Agric. Sci.* 2012; 4: 95–102.
- Pandey B, Ghimire P, Agrawal VP. Studies on the antimicrobial activity of actinomycetes isolated from Khumbu region of Nepal. PhD dissertation, Tribhuvan University, Kathmandu, Nepal. 2004.
- Kim HJ, Lee SC, Hwang BK. *Streptomyces cheonanensis* sp. nov., a novel streptomycete with antifungal activity. *Int J Syst Evol Microbiol.* 2006; 56: 471- 475.
- Watve MG, Tickoo R, Jog MM, Bhole BD. How many antibiotics are produced by the genus *Streptomyces*? *Arch Microbiol.* 2001; 176: 386-390.



14. Adil A El Hussein, Rihab EM Alhasan, Suhair A Abdelwahab, et al. Isolation and Identification of *Streptomyces rochei* Strain Active against Phytopathogenic Fungi. *British Microbiology Research Journal*. 2014; 4(10):1057–1068.
15. Laskaris P, Tolba S, Calvo-Bado L, Wellington L. Coevolution of antibiotic production and counter-resistance in soil bacteria. *Environ Microbiol*. 2010; 12(3):783–796.
16. Bhuneshwari S, Roymon MG, (2017). Review of current techniques in isolation and characterization of *Streptomyces* from soil. *Ind J Sci Res.*;13(2):226–232.
17. Ogundare AO, Ekundayo FO, Banji Onisile F. Antimicrobial Activities of *Streptomyces* Species Isolated From Various Soil Samples in Federal University of Technology, Akure Environment. *OSR-JPBS*. 2015; 10(4):22–30.
18. Jones GH. Actinomycin production persists in a strain of *Streptomyces antibioticus* phenoxazinone synthase. *Antimicrob Agents Chemother*. 2000; 44(5):1322–1327.
19. Abdelhalem A Hamza, Hiba A Ali, Benjamin R Clark. Optimization of fermentation conditions for Actinomycin D production by a newly isolated *Streptomyces* sp. AH 11.4. *J Biotechnol Pharm Res*. 2013; 4(2):29–34.
20. Abdelhalim A Hamza, Mutaz N Hassan, Mona E Elyass. Isolation and characterization of *Streptomyces* isolates as a source of bioactive secondary metabolites in Sudan. *Journal of Global Biosciences*. 2015; 4(7):2649–2661.
21. Jayapradha Ramakrishnan, Murugesh Shunmugasundaram, Mahesh Narayanan. *Streptomyces* sp. SCBT isolated from rhizosphere soil of medicinal plants is antagonistic to pathogenic bacteria. *Iranian J Biotechnol*. 2009; 7(2):75–81.
22. Bhaskaran R, Vijayakumar R and Mohan PM. Enrichment method for the isolation of bioactive actinomycetes from mangrove sediments of Andaman Islands, India. *Malaysian Journal of Microbiology*. 2011; 7(1): pp. 26-32.
23. Proksh P, Edrada RA and Ebel R. Drugs from the sea Current status and microbiological implications, *Appl Microbiol Biotechnol*. 2002; 59: 125-134.
24. Halstead GW. *Poisonous and Venomous Marine Animals of the World*, US Govt. Printing Office, Washington D C, 1965. p. 994.
25. Jones JG. The effect of environmental factors on estimated viable and total populations of planktonic bacteria in lakes and experimental enclosures. *Freshw Biol*. 1977; 7:67–91.
26. Amann RI, Ludwig W, Schleifer KH. Phylogenetic identification and in situ detection of individual microbial cells without cultivation. *Microbiol Rev*. 1995; 59:143–69.
27. Kogure K, Simidu U, Taga N. A tentative direct microscopic method for counting living marine bacteria. *Can J Microbiol*. 1979; 25:415–20.
28. Kogure K, Simidu U, Taga N. Distribution of viable marine bacteria in neritic seawater around Japan. *Can J Microbiol* 1980; 26:318–23.
29. Ferguson RL, Buckley EN, Palumbo AV. Response of marine bacterioplankton to differential filtration and confinement. *Appl Environ Microbiol* 1984; 47: 49–55.
30. Torsvik V, Goksoyr J, Daae FL. High diversity of DNA of soil bacteria. *Appl Environ Microbiol* 1990; 56:782–7.
31. Carte BK. Biomedical potential of marine natural products. *Biosciences* 1996; 46:271–86.
32. Kijjoa A, Sawangwong P. Drugs and cosmetics from the sea. *Mar Drugs* 2004; 2:73–82.
33. Ellaiah P, Reddy APC. Isolation of actinomycetes from marine sediments off Visakhapatnam, east coast of India. *Indian J Mar Sci*. 1987; 16:34–135.
34. Goodfellow, M, Williams, S.T. Ecology of actinomycetes. *Annu. Rev. Microbiol*. 1983;37:189–216.
35. van der Meij, A, Worsley, S.F, Hutchings, M.I., van Wezel, G.P. Chemical ecology of antibiotic production by actinomycetes. *FEMS Microbiol. Rev*. 2017;41:392–416.
36. Matsumoto, A, Takahashi, Y. Endophytic actinomycetes: Promising source of novel bioactive compounds. *J. Ant.* 2017;70:514–519.
37. Barka, E.A, Vatsa, P, Sanchez, L, Gaveau-Vaillant, N, Jacquard, Klenk, H.P, Clement, C, Ouhdouch, Y, van Wezel, G.P. Taxonomy, Physiology, and Natural Products of Actinobacteria. *Microbiol. Mol. Biol. Rev*. 2016; 80: 1–43.
38. Helmke, E, Weyland, H. *Rhodococcus marinonascens* sp. nov., an actinomycete from the sea. *Int. J. Syst. Bacteriol*. 1984; 34: 127–138.
39. Masand, M Jose, P.A, Menghani, E, Jebakumar, S.R.D. Continuing hunt for endophytic actinomycetes as a source of novel biologically active metabolites. *World J. Microbiol*. 2015; 31: 1863–1875.
40. Kumar, S, Solanki, D.S, Parihar, K, Tak, A, Gehlot, P, Pathak, R, Singh, S.K. Actinomycetes isolates of arid zone of Indian Thar Desert and efficacy of their bioactive compounds against human pathogenic bacteria. *Biol. Futur*. 2021; 72: 431–440.
41. Mohammadipanah, F.; Wink, J. Actinobacteria from arid and desert habitats: Diversity and biological activity. *Front. Microbiol*. 2016; 6:1541.
42. Silva, L.J, Crevelin, E.J, Souza, D.T Lacerda-Júnior, G.V.; de Oliveira, V.M.; Ruiz, A.L.T.G.; Rosa, L.H.; Moraes, L.A.B.; Melo, I.S. Actinobacteria from Antarctica as a source for anticancer discovery. *Sci. Rep*. 2020; 10: 13870.
43. Zenova, G.M, Manucharova, N.A, Zvyagintsev, D.G. Extremophilic and extremotolerant actinomycetes in different soil types. *Eurasian Soil Sci*. 2011; 44: 417–436.
44. Bhatti, A.A, Haq, S, Bhat, R.A. Actinomycetes benefaction role in soil and plant health. *Microb. Pathog*. 2017; 111: 458–467.
45. Rungin, S, Indananda, C, Suttiviriya, P, Kruasuwan, W, Jaemsang, R.; Thamchaipenet, A. Plant growth enhancing effects by a siderophore-producing endophytic streptomycete isolated from a Thai jasmine rice plant (*Oryza sativa* L. cv. KDML105). *Antonie van Leeuwenhoek* 2012; 102: 463–472.
46. Hayakawa M. Studies on the isolation and distribution of rare actinomycetes in soil. *Actinomycetologica*. 2008; 22: 12–19.
47. Hemati A, Nazari M, Asgari Lajayer B, Smith DL, Astatkie T. Lignocellulosics in plant cell wall and their potential biological degradation. *Folia Microbiol*. 2022; 67: 671–681.
48. De Gannes, V, Eudoxie, G, Hickey, W.J. Prokaryotic successions and diversity in composts as revealed by 454-pyrosequencing. *Bioresour. Technol*. 2013; 133: 573–580.
49. Takaku, H, Kodaira, S, Kimoto, A, Nashimoto, M, Takagi, M. Microbial communities in the garbage composting with rice hull as an amendment revealed by culture-dependent and -independent approaches. *J. Biosci. Bioeng*. 2006; 101: 42–50.
50. Gargi Sarkar.K. Suthindhram. Diversity and Biotechnological Potential of Marine Actinomycetes from India. *Indian J Microbiol*. 2022; 62(4):475-493.
51. Khalifa, S.A.M, Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.E.F.; Moustafa, M.S.; El-Wahed, A.A.; Al-Mousawi, S.M.; Musharraf, S.G.; et al. Marine Natural Products: A Source of Novel Anticancer Drugs. *Mar. Drugs*. 2019; 17: 491.
52. Jensen, P.R, Dwight, R, Fenical, W. Distribution of actinomycetes in near-shore tropical marine sediments. *Appl. Environ. Microbiol*. 1991; 57:1102–1108.
53. Bienhold, C, Zinger, L, Boetius, A, Ramette, A. Diversity and Biogeography of Bathyal and Abyssal Seafloor Bacteria. *PLoS ONE*. 2016; 11, e0148016.
54. Betancur, L.A, Naranjo-Gaybor, S.J, Vinchira-Villarraga, D.M, Moreno-Sarmiento, N.C, Maldonado, L.A, Suarez-Moreno, Z.R, Acosta-González, A, Padilla-Gonzalez, G.F, Puyana, M, Castellanos, L, et al. Marine Actinobacteria as a source of compounds for phytopathogen control: An integrative metabolic-profiling/bioactivity and taxonomical approach. *PLoS ONE*. 2017; 12, e0170148.
55. Mahmoud, H.M, Kalendar, A.A. Coral-associated Actinobacteria: Diversity, abundance, and biotechnological potentials. *Front. Microb*. 2016; 7: 204.



56. Sarmiento-Vizcaíno, A.; González, V.; Braña, A.F.; Palacios, J.J.; Otero, L.; Fernández, J.; Molina, A.; Kulik, A.; Vázquez, F.; Acuña, J.L.; et al. Pharmacological Potential of Phylogenetically Diverse Actinobacteria Isolated from Deep-Sea Coral Ecosystems of the Submarine Avilés Canyon in the Cantabrian Sea. *Microb. Ecol.* 2017; 73: 338–352.
57. Jensen, P.R., Mafnas, C. Biogeography of the marine actinomycete *Salinispora*. *Environ. Microbiol.* 2006; 8: 1881–1888.
58. Chen, C, Ye, Y, Wang, R, Zhang, Y, Wu, C, Debnath, S.C, Ma, Z, Wang, J, Wu, M. *Streptomyces nigra* sp. nov. Is a Novel Actinobacterium Isolated From Mangrove Soil and Exerts a Potent Antitumor Activity in Vitro. *Front. Microbiol.* 2018; 9: 1587.
59. Kemung, H.M, Tan, L.T.H, Chan, K.G, Ser, H.L, Law, J.W.F, Lee, L.H, Goh, B.H. *Streptomyces* sp. Strain MUSC 125 from Mangrove Soil in Malaysia with Anti-MRSA, Anti-Biofilm and Antioxidant Activities. *Molecules.* 2020; 25: 3545.
60. Lin X, Hetharua B, Lin L, Xu H, Zheng T, He Z, Tian Y. Mangrove Sediment Microbiome: Adaptive Microbial Assemblages and Their Routed Biogeochemical Processes in Yunxiao Mangrove National Nature Reserve, China. *Microb. Ecol.* 2019; 78: 57–69.
61. Xu, D, Han, L, Li, C, Cao, Q, Zhu, D, Barrett, N.H, Harmody, D, Chen, J, Zhu, H, McCarthy, P.J, et al. Bioprospecting deep-sea actinobacteria for novel anti-infective natural products. *Front. Microbiol.* 2018; 9: 787.
62. Olano, C, Méndez, C, Salas, J.A. Antitumor compounds from marine actinomycetes. *Mar. Drugs.* 2009; 7: 210–248.
63. Subramani, R, Aalbersberg, W. Marine actinomycetes: An ongoing source of novel bioactive metabolites. *Microbiol. Res.* 2012; 167: 571–580.
64. Bérdy, J. Thoughts and facts about antibiotics: Where we are now and where we are heading? *J. Antibiot.* 2012; 65: 385–395.
65. Bentley S D, Chater K F, Cerdeño-Tárraga A M, Challis G L, Thomson N R et al, Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3, *Nature.* 2002; 417: 141-7.
66. Sosio M, Bossi E, Bianchi A & Donadio S. Multiple peptide synthetase gene clusters in actinomycetes, *Mol Gen Genet*, 2000; 264: 213-221.
67. Hamaki T, Suzuki M, Fudou R, Jojima Y, Kajiura T et al. Isolation of novel bacteria and actinomycetes using soil extract agar medium, *J Biosci Bioeng*, 2005; 99 : 485-492.
68. Hopwood D A, *Streptomyces* in nature and medicine: the antibiotic makers, Oxford University Press. 2007.
69. Kekuda T P, Onkarappa R, Gautham S A, Mesta S C & Raghavendra H L, Antimicrobial, antioxidant and cytotoxic activity of *Streptomyces* species from Western Ghat soils of Karnataka, India, *Science, Technology and Arts Research Journal.* 2015; 4: 164-180.
70. Savi D C, Haminiuk C W I, Sora G T S, Adamoski D M, Kenski J et al. Antitumor, antioxidant and antibacterial activities of secondary metabolites extracted by endophytic actinomycetes isolated from *Vochysia divergens*, *Int J Pharm Chem Biol Sci.* 2015; 5:347.
71. Passari A K, Mishra V K, Saikia R, Gupta V K & Singh B P, Isolation, abundance and phylogenetic affiliation of endophytic actinomycetes associated with medicinal plants and screening for their in vitro antimicrobial biosynthetic potential, *Frontiers in Microbiology*, 2015; 6 : 273.
72. Singh R & Dubey A K, Endophytic actinomycetes as emerging source for therapeutic compounds, *Indo Global J Pharm Sci.* 2015; 5: 106-116.
73. Collins C H, Collins and Lyne's microbiological methods (Vol. 493), Oxford: Butterworth-Heinemann (1995).
74. He J, Magarvey N, Pirae M & Vining L C, The gene cluster for chloramphenicol biosynthesis in *Streptomyces venezuelae* ISP5230 includes novel shikimate pathway homologues and a monomodular non-ribosomal peptide synthetase gene, *Microbiology*, 2001; 147 : 2817-2829.
75. Huang F, Haydock S F, Mironenko T, Spittler D, Li Y et al, The neomycin biosynthetic gene cluster of *Streptomyces fradiae* NCIMB 8233: Characterisation of an amino transferase involved in the formation of 2- deoxystreptamine, *Organic & Biomolecular Chemistry*, 2005; 3 :1410-1418.
76. Ohnishi Y, Ishikawa J, Hara H, Suzuki H, Ikenoya M et al, Genome sequence of the streptomycin producing microorganism *Streptomyces griseus* IFO 13350, *J Bacteriol*, 2008; 190 : 4050-4060.
77. Genilloud, O. Actinomycetes: Still a source of novel antibiotics. *Nat. Prod. Rep.* 2017; 34: 1203–1232.
78. Fenical, W.; Jensen, P.R. Developing a new resource for drug discovery: Marine actinomycete bacteria. *Nat. Chem. Biol.* 2006; 2: 666–673.
79. Takahashi, Y, Nakashima, T. Actinomycetes, an inexhaustible source of naturally occurring antibiotics. *Antibiotics.* 2018; 7: 45.
80. Van Norman, G.A. Drugs, Devices, and the FDA: Part 1. *JACC Basic Transl. Sci.* 2016; 1: 170–179.
81. DiMasi, J.A.; Grabowski, H.G.; Hansen, R.W. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J. Health Econ.* 2016; 47: 20–33.
82. Sharma, P, Dutta, J, Thakur, D. Future prospects of actinobacteria in health and industry. In *New and Future Developments in Microbial Biotechnology and Bioengineering: Actinobacteria: Diversity and Biotechnological Applications*; Singh, B.P., Gupta, V.K., Passari, A.K., Eds.; Elsevier: Amsterdam, The Netherlands, 2018.
83. Wright, G.D. Antibiotics: A new hope. *Chem. Biol.* 2012; 19: 3–10.
84. Gupta, A, Mumtaz, S, Li, C.-H, Hussain, I, Rotello, V.M. Combatting antibiotic-resistant bacteria using nanomaterials. *Chem. Soc. Rev.* 2019; 48: 415–427.
85. Zhu, H, Swierstra, J, Wu, C, Girard, G, Choi, Y.H, van Wamel, W, Sandiford, S.K, van Wezel, G.P.Y. Eliciting antibiotics active against the ESKAPE pathogens in a collection of actinomycetes isolated from mountain soils. *Microbiology.* 2014; 160: 1714–1725.
86. Igarashi, M, Sawa, R, Umekita, M, Hatano, M, Arisaka, R, Hayashi, C, Ishizaki, Y, Suzuki, M, Kato, C. Sealutomicins, new enediynes antibiotics from the deep-sea actinomycete *Nonomuraea* sp. MM565M-173N2. *J. Antibiot.* 2021; 74: 291–299.
87. Norouzi, H, Danesh, A, Mohseni, M, Khorasgani, M.R. Marine actinomycetes with probiotic potential and bioactivity against multidrug-resistant bacteria. *Int. J. Mol. Cell. Med.* 2018; 7: 44–52.
88. Sivaperumal, P, Kamala, K, Rajaram, R. Bioactive DOPA melanin isolated and characterised from a marine actinobacterium *Streptomyces* sp. MVCS6 from Versova coast. *Nat. Prod. Res.* 2014; 29: 2117–2121.
89. Feling, R.H, Buchanan, G.O, Mincer, T.J, Kauffman, C.A, Jensen, P.R, Fenical, W. Salinosporamide A: A highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus *Salinispora*. *Angew. Chem. Int. Ed.* 2003; 42: 355–357.
90. Nathan, J, Kannan, R.R. Antiangiogenic molecules from marine actinomycetes and the importance of using zebrafish model in cancer research. *Heliyon.* 2020; 6, e05662.
91. Davies-Bolorunduro, O.F, Adeleye, I.A, Akinleye, M.O, Wang, P.G. Anticancer potential of metabolic compounds from marine actinomycetes isolated from Lagos Lagoon sediment. *J. Pharm. Anal.* 2019; 9: 201–208.
92. Lin, Y, Chen, Y, Ukaji, T, Okada, S, Umezawa, K. Isolation of ketomycin from actinomycetes as an inhibitor of 2D and 3D cancer cell invasion. *J. Antibiot.* 2018; 72: 148–154.
93. Gupte, M, Kulkarni, P, Ganguli, B.N. Antifungal antibiotics. *Appl. Microbiol. Biotechnol.* 2002; 58: 46–57.
94. El Sayed, K.A. Natural Products as Antiviral Agents. *Stud. Nat. Prod. Chem.* 2000; 24:473–572.
95. Lee JG, Yoo ID, Kim WG. Differential antiviral activity of benzastatin C and its dechlorinated derivative from *Streptomyces nitrosporeus*. *Biological and Pharmaceutical Bulletin.* 2007; 30(4): 795-797.
96. Raveh A, Delekta P, Dobry C, Peng W, Schultz P, et al. Discovery of potent broad-spectrum antivirals derived from marine actinobacteria. *PloS one.* 2013; 8(12): e82318



97. Kim SH, Ha TKQ, Oh W, Shin J, Oh DC . Antiviral indolosesquiterpenoid xiamycins C–E from a halophilic actinomycete. *Journal of natural products*. 2016; 79(1): 51-58.
98. Barreiro, C, Prieto, C, Sola-Landa, A, Solera, E, Martínez-Castro, M, Pérez-Redondo, R, García-Estrada, C, Aparicio, J.F, Fernández-Martínez, L.T, Santos-Aberturas, J et al. Draft genome of *Streptomyces tsukubaensis* NRRL 18488, the producer of the clinically important immunosuppressant tacrolimus (FK506). *J. Bacteriol*. 2012; 194: 3756–3757.
99. Takehana, Y, Umekita, M, Hatano, M, Kato, C.; Sawa, R, Igarashi, M. Fradiamine A, a new siderophore from the deep-sea actinomycete *Streptomyces fradiae* MM456M-mF7. *J. Antibiot*. 2017; 70: 611–615.
100. Chen, Z, Ou, P, Liu, L, Jin, X. Anti-MRSA Activity of Actinomycin X2 and Collismycin A Produced by *Streptomyces globisporus* WA5-2-37 From the Intestinal Tract of American Cockroach (*Periplaneta americana*). *Front. Microbiol*. 2020; 11: 555.
101. Bierer, B.E, Mattila, P.S, Standaert, R.F, Herzenberg, L.A, Burakoff, S.J, Crabtree, G, Schreiber, S.L. Two distinct signal transmission pathways in T lymphocytes are inhibited by complexes formed between an immunophilin and either FK506 or rapamycin. *Proc. Nat. Acad. Sci. USA* 1990; 87: 9231–9235.
102. Dixit VS, Pant A. Hydrocarbon degradation and protease production by *Nocardopsis* sp. NCIM 5124. *Letters in applied microbiology*. 2000;30(1): 67-69.
103. Kumar CG, Takagi H. Microbial alkaline proteases: from a bioindustrial viewpoint. *Biotechnology advances*. 1999; 17(7): 561-594.
104. Vigal T, Gil L, Daza A, García-González M, Martín J. Cloning, characterization and expression of an α -amylase gene from *Streptomyces griseus* IMRU3570. *Molecular and General Genetics* MGG. 1991; 225(2): 278-288.
105. Pisano MA, Sommer MJ, Taras L. Bioactivity of chitinolytic actinomycetes of marine origin. *Applied microbiology and biotechnology*.1992; 36(4): 553-555.
106. Kunz C, Ludwig A, Bertheau Y, Boller T. Evaluation of the antifungal activity of the purified chitinase 1 from the filamentous fungus *Aphanocladium album*. *FEMS microbiology letters*. 1992; 90(2): 105-109
107. Bode W, Huber R. Natural protein proteinase inhibitors and their interaction with proteinases. *EJB Reviews*. 1993; pp: 43-61
108. Oldfield C, Wood N, Gilbert S, Murray F, Faure F. Desulphurisation of benzothioephene and dibenzothioephene by actinomycete organisms belonging to the genus *Rhodococcus*, and related taxa. *Antonie Van Leeuwenhoek*. 1998; 74(1): 119-132
109. Hough DW, Danson MJ. Extremozymes. *Current opinion in chemical biology*. 1999; 3(1): 39-46.
110. Ochiai T, Nakajima K, Nagata M, Suzuki T, Asano T et al. Effect of a new immunosuppressive agent FK 506 on heterotopic cardiac allotransplantation in the rat In *Transplantation Proceedings*. Elsevier USA. 1987; 19 (1): 1284- 1286.
111. Zeevi A, Duquesnoy R, Eiras G, Todo S, Makowka L et al. In vitro immunosuppressive effects of FR 900506 on human T lymphocyte alloactivation, *Surg Res Commun*. 1987; 1315.
112. Ohta, Y, Ikeda, M. Deodorization of pig feces by actinomycetes. *Appl. Environ. Microbiol*. 1978; 36: 487–491.
113. Tanaka, Y, Murata, A, Shinsaku, H. Accelerated composting of cereal shochu-distillery wastes by actinomycetes. *J. Ferment. Bioeng*. 1995; 80: 421.
114. Mansour, F.A.; Mohamedin, A.H. Enzymes of *Candida albicans* cell-wall lytic system produced by *Streptomyces thermodiastaticus*. *Acta Microbiol. Immunol. Hung*. 2001; 48: 53–65.
115. Alvarez, A, Saez, J.M, Davila Costa, J.S, Colin, V.L, Fuentes, M.S, Cuozzo, S.A, Benimeli, C.S, Polti, M.A, Amoroso, M.J. Actinobacteria: Current research and perspectives for bioremediation of pesticides and heavy metals. *Chemosphere*. 2017; 166: 41–62.
116. Fuentes, M, Benimeli, C, Cuozzo, S, Amoroso, M. Isolation of pesticide-degrading actinomycetes from a contaminated site: Bacterial growth, removal and dechlorination of organochlorine pesticides. *Int. Biodeterior. Biodegrad*. 2010; 64: 434–441.
117. Roy, S, Das, I, Munjal, M, Karthik, L, Kumar, G, Kumar, S, Rao, K.V.B. Isolation and characterization of tyrosinase produced by marine actinobacteria and its application in the removal of phenol from aqueous environment. *Front. Biol*. 2014; 9: 306–316.
118. Myronovskiy, M, Rosenkränzer, B, Stierhof, M, Petzke, L, Seiser, T, Luzhetskyy, A. Identification and heterologous expression of the albucidin gene cluster from the marine strain *Streptomyces albus* subsp. *chlorinus* NRRL B-24108. *Microorganisms*. 2020; 8: 237.
119. Fang, H, Cai, L, Yang, Y, Ju, F, Li, X, Yu, Y, Zhang, T. Metagenomic analysis reveals potential biodegradation pathways of persistent pesticides in freshwater and marine sediments. *Sci. Total Environ*. 2014; 470–471: 983–992.
120. Arasu, M.V, Al-Dhabi, N.A, Saritha, V, Duraipandiyam, V, Muthukumar, C, Kim, S.J. Antifeedant, larvicidal and growth inhibitory bioactivities of novel polyketide metabolite isolated from *Streptomyces* sp. AP-123 against *Helicoverpa armigera* and *Spodoptera litura*. *BMC Microbiol*. 2013; 13: 105.
121. Xiong, L, Li, J, Wang, H. *Streptomyces avermitilis* from marine. *J. Environ. Sci*. 2005; 17: 123–125.
122. Amoroso, M.J, Castro, G.R, Carlino, F.J, Romero, N.C, Hill, R.T.T, Oliver, G. Screening of heavy metal-tolerant actinomycetes isolated from the Salí River. *J. Gen. Appl. Microbiol*. 1998; 44: 129–132.
123. El Baz, S, Baz, M, Barakate, M, Hassani, L, El Gharmali, A, Imzilin, B. Resistance to and accumulation of heavy metals by actinobacteria isolated from abandoned mining. *Sci. World J*. 2015; 14: 761834.
124. Li, X, Ding, C, Liao, J, Du, L, Sun, Q, Yang, J, Yang, Y, Zhang, D, Tang, J, Liu, N. Bioaccumulation characterization of uranium by a novel *Streptomyces sporoverrucosus* dwc-3. *J. Environ. Sci*. 2016; 41: 162–171.

For any questions related to this article, please reach us at: globalresearchonline@rediffmail.com

New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com

