Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[2] January 2020 : 164-177

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

Ubiquity, Significance and the Molecular Techniques used for deciphering Actinomycetes

Vishal Mathur, Indrani Jadhav*, Roshan Vasniwal, Divya Shrivastava and Kapilesh Jadhav
School of Life Science, Jaipur National University (Rajasthan), Jaipur 302017
Email: Indranij4@rediffmail.com

ABSTRACT

Actinomycetes are widely distributed in soil, water, air and in plant remains. Actinomycetes are present in extreme type of habitats, Alkalophilic actinomycetes are present in alkaline soils, Cryobacterium psychrophilum with optimum growth temperature at 9-12°C, acidophilic actinomycetes isolated from acidic forest and Psychrophilic actinomycetes colonies were isolated from ice point region and some of the rare marine actinomycetes Salinispora require seawater for their growth. A large number of the rare genera of actinomycetes have been not explored yet with vast biotechnological and industrial potential. With the assistance of molecular approaches and ongoing advances in genomics and sequencing technologies, culture-independent molecular techniques have started another period of actinomycetes environment. The modern molecular technologies provide new source of chemical diversity with novel actinomycetes. The Streptomyces family gives us the vital class of antibiotics that we are utilizing today, The Frankia family, works in non leguminous plants as nitrogen fixing organism, some Actinomycetes are likewise utilized in plant development (help to deliver plant development hormone Indole-3-acidic). Certain enzymes from actinomycetes example, amylase, lipase, and cellulases play a vital part in textile, food, fermentation, agriculture as well as in paper industry. Actinomycetes are also responsible in degrading pesticides, degrading hydrocarbons have major source of bioremediation and are also utilized in biocorrosion.

Keywords: *Alkalophilic actinomycetes, Silinispora, cellulases, Hydrocarbons, Bioremediation.*

Received 23.07.2019 Revised 15.11.2019 Accepted 04.12.2019

INTRODUCTION

The actinomycetes are gram-positive bacteria with high G+C percentage that form branching pattern and filamentous in nature. These bacteria closely resemble fungi in overall morphology .Therefore, they are also known as ray fungi. They are characterized by a complex life cycle belonging to the phylum *Actinobacteria*. *Actinobacteria* occur in coccoid (*Micrococcus*), bar coccoid (e.g., *Arthrobacter*) to partitioning hyphal shapes morphologically (e.g., *Nocardia spp.)* or forever and exceedingly isolated spread mycelium (e.g., *Streptomyces spp*.) It has been estimated that one-third of the thousands of naturally occurring antibiotics have been produced from actinomycetes [1]. The increasingly antibiotic resistant occur in the bacteria, especially occur in the Multidrug Resistant Microbes (MDRM) and therefore need to look for new antibiotics [2].

Actinomycetes play a great role in the development of large number of bioactive compounds, which after isolation, processing and characterization have been transformed into drugs for treating different diseases in both plants and animals keeping this reality in view, actinomycetes are considered to be the effective sources for the generation of various antibiotics and other biologically active compounds. Each strain of actinomycetes has the innate capability of producing approximately around 10-20 secondary metabolites. Actinomycetes are extraordinary producers of antibiotics and among actinomycetes the major role is played by *Streptomyces,* which alone represent an outstanding 80% of the natural products produced by actinomycetes [3]. *Streptomyces* have been a source to different analytics; including anti-bacterial, anti-fungal and anti-cancer drugs [4]. *Streptomyces* accompanied by actinomycetes keep maintaining the pace as a source of novel metabolites exhibiting various biological activities such as anti-infectant and anti-cancer activity, apart from being the source of various other pharmaceutically useful compounds [5].

Many bioactive compounds are isolated from Actinomycetes are source of diverse clinical effects and have a great important applications in human medicine. The need for novel and safe antibiotics is key challenge for the pharmaceutical industry now days. The discovery of new antibiotics represents screening of more and more microbes. These microorganisms may have capability to produce some of the most important medicines ever developed .The resistance problem demands to discover new antibacterial agents effective against resistant pathogenic bacteria and fungi. So, we need to screen more and more actinomycetes from different habitats for antimicrobial activity in the hope of getting some new actinomycetes strains that produce novel antibiotics, which have not been discovered yet and are active against drug-resistant pathogens [1].

NATURE AND SOURCES OF ACTINOMYCETES

The actinomycetes have been found in different niches such as soil, air, fresh water, oceans and variety of materials like manure, compost, plant residues and food products. Actinomycetes are found in aquatic environments and consequently in drinking water system. Only a couple of examination has been carried out to understand the diversity of actinobacteria in the extreme environments, ecological role and their adaptation. In order to find novel bioactive compounds of pharmacological and industrial relevance, actinobacteria have been isolated from exotic and unexplored locations such as desert marine and wetland areas [6].

Soil actinomycetes or Terrestrial habitat

Actinomycetes constitute a major component of the microbial population in most soils. It was estimated that actinomycetes commonly obtained from soil at the ratio of almost 1 million per gram and over twenty genera have been isolated from soil. It was found that 95% of the isolates belonged to *streptomycetes*. Environmental factors influence most the type and population of actinomycetes present in the soil. Most of the isolate obtained from actinomycetes behave as neutrophiles in culture, with their growth range in between pH 5.0 to 9.0 and an optimum pH around 7.0. The pH is a major environmental factor determining the distribution, availability and activity of soil actinomycetes. Neutrophiles are present less in acidic soils whereas acidophilic and *acidoduric streptomycetes* are found numerous in acidic soils. For the most part actinomycetes found in the research facility carry on as mesophiles, with their ideal development temperature at 25 to 30^{o}C. Numerous mesophilic actinomycetes are dynamic in compost [7].

AQUATIC HABITAT

Fresh water Actinomycetes

Actinomycetes are abundant in fresh water lakes. They are also found in sewage. Various members of genera *Actinoplanes, Micromonospora, Rhodococcus, Streptomyces* and the endospore-forming *Thermoactinomycetes* have been isolated from freshwater habitats. Majority of these actinomycetes most probably are wash-in from land and accumulated in fresh water habitats. The presence of *Rhodococcus coprophilus* a coprophilic species in lakes is believed due to wash in of contaminated herbivore dung. The presence of *Streptomyces* in freshwater habitat is because of their spores being continuously washed into rivers and lakes [7].

Marine Actinomycetes

Microbial diversity constitutes an infinite pool of novel chemistry, making up a valuable source for innovative biotechnology [8]. The recent estimates suggest that the culturability of microorganisms in marine sediments (0.25). The marine environment is a source of interesting research for new species and a promising source of pharmaceutically important compounds [9]. 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 [8]. The isolation of rare actinomycetes warrants suitable isolation procedures including the use of appropriate selective media containing macromolecules like casein, chitin and humic acid for promoting growth of rare actinomycetes present in the samples and simultaneously suppressing and hindering contaminant bacterial fungal colonies . Actinomycete genera identified by cultural and molecular techniques from different marine ecological niches include *Actinomadura, Actinosynnema, Amycolatopsis, Arthrobacter, Blastococcus, Brachybacterium, Corynebacterium, Frankia, Frigoribacterium, Geodermatophilus, Gordonia, Kitasatospora, Mycobacterium, Nocardioides, Nocardiopsis, Nonomurea, Micromonospora, Micrococcus, Microbacterium, Salinispora, Solwaraspora, Streptomyces, Williamsia Streptosporangium, Tsukamurella, Dietzia, Psuedonocardia, Rhodococcus, Saccharopolyspora, Turicella, Serinicoccus* and *Verrucosispora* [10].

Actinomycetes from plant

Actinomycetes isolate from various medicinal plants part (leaves, fruits, twig) of *Catharanthus rosea, Calotropis procera, Brassica sps., Eugenia caryophyllus and Emblica officinalis* (CR1, CR2, CR3, BS1, BS2, BS3, BS4 and BS5) are 8 actinomycetes species isolated from plant parts [11]. Novel Substances, Trehangelins Found from the Metabolites of Plant-Derived Rare Actinomycete *Polymorphospora rubra* K07-0510 and after Purification of this compound eventually identified three new compounds, which were named trehangelin A, B, C [12].

Actinomycetes from extreme environments

Actinomycetes are also present in extreme type of habitats. Alkalophilic actinomycetes (*Streptomyces* and *Nocardiopsis* are the dominant genera) are present in alkaline soils (pH 10-12) surrounding mineral springs. Isolated *Saccharomonospora halophila*, a halophilic actinomycete with optimum growth at 10% NaCl from marsh soil *Modestobacter multiseptatus*, psychrophilic strains with optimum growth at temperature 11-13^{o}C was isolated from transantarctic mountain soils. An obligate psychrophilic actinomycetes, *Cryobacterium psychrophilum*, with optimum growth temperature 9-12^{o}C and did not grow at temperature higher than 18^{o}C was isolated from Antartica soil. Other than that, acidophilic actinomycetes have also been isolated from acidic forest and peat soils, mainly *Streptomyces* and *Micromonospora*. Few rare thermotolerant actinomycetes isolated from desert soils of Mojave Desert, California belonged to genera *Microbispora, Nocardia, Microtetraspora, Amycolaptosis, Actinomadura and Saccharothrix* [7].

Actinomycetes identification and characterization

Isolation and identification proof is mandatory before finding the novel characteristic features of any microbial isolates. With the advancement in genomics, the complexity of microbial world is largely understandable. In such manner, recent advancements in microbial systematics have led to a 'polyphasic taxonomic approach' which intends to produce all phenotypic, genotypic and phylogenetic information of a microbial taxon. The prevalent conventional strategies are not adequate to give a complete draft for microbial taxonomy as these conventional system describe only shape, colour, size, staining properties, motility, host-range, pathogenicity and absorption of carbon sources. However, Microorganisms present in the environment can be enumerated, isolated and characterised by various culture dependent classical techniques such as pour plate and spread plate methods followed by Gram's staining and biochemical tests to decipher their physiological characteristics. Based upon colony morphology on growth medium, microscopic observation and biochemical tests isolated bacteria can be assigned to specific genera [13].

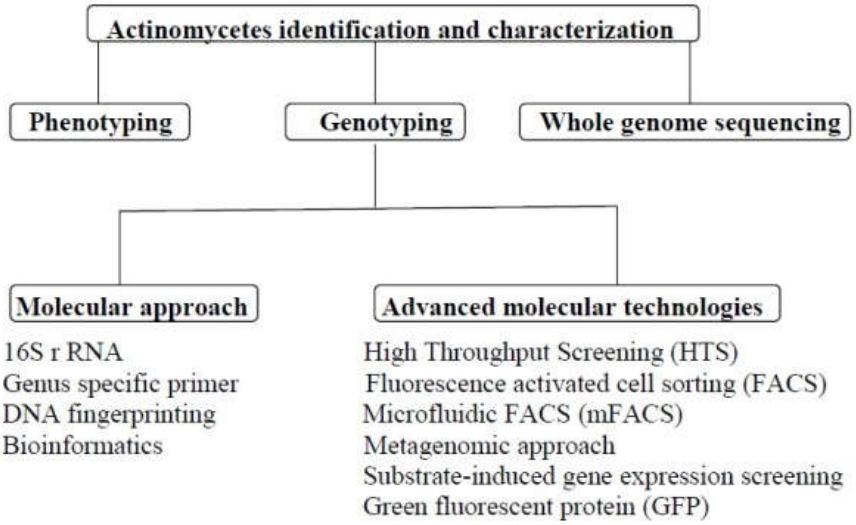

Figure 1 (Courtesy: **[14]**, **[5]** and **[15]**)

Phenotyping

Phenotypic procedures are generally not meant for discrimination among strains of different species. Determination of unique characteristics of a microorganism allows study of colonization or cross-infection and enables the establishment of phylogenetic relationships. Biochemical tests alone usually allow species identification but may also help distinguish among strains of organisms [14].

Genotyping

The identification of DNA analyses aimed that genome of every individual is unique and is basic to all organisms that reproduce sexually, differences may occur because the offspring inherits different alleles

from either parent [14]. For identification and characterization of any important biological organism (prokaryotic or eukaryotic), nucleic acid based molecular approach is required to be the most powerful methodology [5]. Actinomycetes and its identification based on bacterial sequences of 16S ribosomal DNA has been started by isolating DNA of 16S rDNA and implying the polymerase chain reaction (PCR) and [16, 17] Universal Primers was used to amplify the 16S rRNA gene of actinomycetes. For sequencing reactions, DNA sequencer is used [5]. The Amplification of polymorphic DNA through specific selection of annealing sites of primer by DNA fingerprinting and differences in the primer-binding sites and between existence sites lead to synthesis of amplified DNA fragments (amplimers) which vary in length. Terms such as amplification fragment length polymorphism, interrepeat PCR, DNA amplification fingerprinting, arbitrarily primed PCR, Restriction fragment length polymorphism (RFLP) and random amplification of polymorphic DNA (RAPD) are used [15]. Closely related homologs were recognized through using Basic Local Alignment Tool (BLAST) program and the evolutionary relationships in the sequences were depicted by constructing a phylogenetic tree for this dendrogram/ phylogram was constructed [18].

Advanced molecular technologies in identification and characterization of Actinomycetes

Different types of physical and chemical pretreatment strategies have been formulated for isolating desirable rare actinomycetes genera. The utilization of these genus oriented strategies in modern screening programs has given a significant revelation of new bioactive compounds. These methods valuable to circumvent the problem of recharacterization of known bioactive molecules and to help in screening of novel compounds and use of the advanced molecular strategies should make feasible the discovery of novel pharmaceutical and modern industrial important product [5].

HIGH THROUGHPUT SCREENING (HTS)

The Screening of multiple samples against highly characterized targets unlike the largely cell-based systems of the past, where efforts were less tailored on the molecular aspects conversely, concluded that screening compounds using a cell-based biological approach could save three years and more than $300 million of the cost of developing a novel drug [19]. The most noticeable and promising technique for enzymatic characterization of any microbial population is High Throughput Screening (HTS) strategy however this strategy is expanded very little for actinomycetes. The HTS strategy is essentially utilized in drug discovery related field of science mainly chemistry and in biology and some portion of the important applications of HTS strategy in microbial innovation are all well adopted HTS based strategy; proteomics approach is starting at now reporting its well acknowledgment in the method for finding the microbial worlds. High-throughput screening involves screening large libraries of small metabolites against a particular target [5].

An effective HTS screening system should start with a vigorous assay for the targets. In a study, has estimated that 100,000 results per system per day are likely to be dwarfed in the future because of the evolving capabilities of high-throughput screening. This technology is, simultaneously, cross-fertilized by advances in both automation and bioinformatics [20].

Fluorescence activated cell sorting (FACS)

The requirement of sensitive, high-throughput technologies for the directed evolution of new enzymes has spurred the development of a new generation of library screening formats. Fluorescence activated cell sorting (FACS) is a technology that can rapidly separate the cells from suspension dependent on size and the color of their fluorescence [21]. It is essentially represented with some fluorescent substrates that are quite certain for a particular enzyme is utilized in the experiment. The positive fluorescence assigns a definite biocatalytic activity of the clone and the technology is effectively drawn in for desired clones arranging from a genomic DNA library [5].

Microfluidic FACS (mFACS)

A successful utilization of microfluidic FACS (mFACS) chips in prokaryotic system was published in a reputed journal on 1999. *Escherichia coli* cells expressing green fluorescent protein recognized and separated from a background of nonfluorescent *E. coli* cells which encouraged a considerable enhancement of micron-sized fluorescent bead populations with various colors. This detachment was also confirmed the viability of the bacteria after extraction from the sorting device. This device can be adopted useful for Actinomycetes cell isolation from a complex microbial population where the device will be functioned as remain solitary device of an integrated microanalytical chip. Enzyme-fluorescence technology is Gel MicroDrop technology which is essentially based on identification of positive clones specific to particular enzymes by catching the fluorescence produced because of catalytic breakdown of biotinylated substrate by the clone [5].

Metagenomic approach

Metagenomic approach is another old yet fascinating methodology principally manages the preparation of a clonal library from the metagenome acquired from extreme habitats (ocean beds, arid regions, stratosphere, hot stream areas and other) taking into consideration of inability of developing of actual microbes under laboratory conditions. Despite the fact that this procedure additionally ensured the quick screening approach by exploring the bioactive potential for unculturable microbes however it limits the opportunity of regular advantage mainly exhibiting the very low or no expression of desired gene [22].

Substrate-induced gene expression screening (SIGEX)

Most encouraging and pioneering methoodology can be investigated for Actinomycetes characterization are metagenomic DNA rearranging, Coupling classical functional screens of metagenomic libraries with innovative approaches are substrate-induced gene expression screening (SIGEX) and pre-amplification inverse-PCR (PAIPCR) that present learning of useful metagenomics for a specific microflora [5]. With SIGEX, qualities perhaps engaged with benzoate and catechol degradation have been found in a groundwater metagenomic library. Despite the limitations of SIGEX, which can only recognized genes that are effectively induced in a heterologous host, the strategy is extremely high throughput since vast number of clones can be screened in moderately short timescales [23].

Green fluorescent protein (GFP)

HTS strategy additionally ensures the advancement of technology with the space of rate, parallel execution and financial to the screening protocol. It comprises of drop based microfluid stage carries a complex system governing a small foot print chip with a variety of insoluble substrates specific for the enzyme of interest. Reporter gene technology is another part of the advancement of screening technique which deals with simplicity and sensitivity of reporter enzyme i.e., Green fluorescent protein (GFP) have made easier detection of genes in host systems [5].

WHOLE GENOME SEQUENCING APPROACH IN IDENTIFICATION AND CHARACTERIZATION OF ACTINOMYCETES

Although molecular and advanced technologies have incredible role to blossom up the knowledge by exploring the Actinomycetes, yet there are few ambiguities still remain related to genomics controlling the entire mechanics of microbe's activity. In such cases whole genome sequencing (WGS) approach out from single cells has made a scientific achievement, which open the whole molecular and biochemical potential of uncultured microbe from a complex environment. The nucleotide sequence is determined with an automated sequencing instrument [5]. Instruments of DNA sequencing depends on the modification of dideoxynucleotide chain terminator chemistry in which the sequencing primer is labeled at 5' end with anyone of the four fluorescent dyes. Each fluorescent dye represents one of the four nucleotides and thus four different annealing and extension reactions are performed. At last, the four sets of arrangements are combined, concentrated and loaded in a single well on a polyacrylamide gel. During electrophoresis the fluorescently labeled products are excited and the relating signal is automatically detected. In this way, the subsequent information is processed into a final sequence with the aid of computer software. Despite the fact that the ultimate technique for identification, DNA sequencing is highly expensive and requires a high degree of specialized competency. In this manner, the future sequencing technique should be simplified and automated further for their appropriateness. At present the genomes of approximately 200 microbes have been sequenced completely [15].

SIGNIFICANCE OF ACTINOMYCETES

Antibiotics

Actinomycetes have been known as the greatest producer of antibiotics. Almost two third of the total antibiotics are obtained from actinomycetes [24]. There are almost 45% of 23,000 bioactive microbial metabolites produced by actinomycetes and the most frequent producers, the *Streptomyces* species produce 7,600 compounds. The products from rare actinomycetes in 1970 were only 5%. In that gathering Streptoverticillium, Micromonospora, Nocardia, Streptosporangium, Saccharopolyspora, Actinoplanes, and Actinomadura, species are the most successive makers; every one create a few several antibiotics. Antifungal agent chitinase is produced by actinomycetes that suppress plant pathogenic fungi and mosquitoes and they may also used in production of single-cell protein, estimation of fungal biomass, morphogenesis, medical application and degradation of fish wastes, etc. Natural strategies utilized on huge scale in finding new anti-microbials from actinomycetes. The importance of actinomycetes in antibiotic production has stimulated many aspects of basic research on these microorganisms. A range of useful actinomycete antibiotics were reported [25].

Table.1 Actinomycetes antibiotics and their biological property

Antibiotic	Producer	Biological Property
Aburamycin	*Streptomyces aburaviensis*	Active on gram positive and gram negative bacteria
Actinomycetin	*Streptomyces albus* and *Streptomyces* sp.	Active on gram positive bacteria
Actinomycin	*Streptomycetaecae*	Older chemotherapy drug
Actinorubin	*Streptomyces* sp.	Active on gram positive, negative bacteria and mycobacteria
Actinoxanthine	*Streptomyces globisporus*	Active on gram positive bacteria
Alkavin	*Streptomyces* sp.	Active on variety of bacteriophages
Alboverticillin	*Streptomyces* sp.	Active on fungi and yeast
Amphotericin-A	*Streptomyces* sp.	Active against fungi
Amphotericin-B	*Streptomyces nodosus*	Active against fungi
Antibiotic of Chandrasekhar	*Streptomyces* sp.	Active on gram positive and negative bacteria
Carcinomycin	*S. carcinomycicus, Streptomyces* sp. and *Streptomyces gannmycicus*	Active on gram positive bacteria and Fungi
Chloramphenicol	*Streptomyces venezuelae, Streptomyces phaeochromogenes var. chloromyceticus* and *Streptomyces omiyaensis*	Active on gram positive and negative Bacteria
Cyclohexamide	*Streptomyces griseus, Streptomyces sp.* and *Streptomyces noursei*	Active on variety of plant pathogens
Enteromycin	*Streptomyces albireticuli*	Active on gram negative bacteria
Erythromycin	*Saccharopolyspora erythraea, Streptomyces erythreus*	Antibacterial and Active on gram positive bacteria, mycobacteria and Corynebacterium
Framycetin	*Streptomyces lavendulae*	Active on gram positive and negative bacteria
Geomycin	*Streptomyces xanthophacus*	Active on gram positive and negative bacteria
Gentamycin	*Micromonospora* sp.	Antibacterial against gram-negativemicroscopic organisms
Hygromycein	*Streptomyces hygroscopicus* and *S. noboritoensis*	Active on gram positive, negative bacteria and mycobacteria
Hygromycein- B	*Streptomyces hygroscopicus*	Active against gram positive and gram negative bacteria and Mycobacteria
Kanamycin-A	*Streptomyces kanamyceticus*	Active on gram positive, negative bacteria and mycobacteria
Kanamycin-B	*Streptomyces kanamyceticus*	Active on gram positive, negative bacteria and mycobacteria
Lavendulin	*Streptomyces lavendulae*	Active on gram positive, negative bacteria and mycobacteria
Litmocidin	*Nocardia cyanca*	Active on gram positive, negative bacteria and mycobacteria
Levomycin	*Streptomyces* sp.	Moderate activity against gram positive and gram negative bacteria and Mycobacteria
Matamycin	*Streptomyces matensis*	Active on gram positive bacteria
Melanosporin	*Streptomyces melanosporus*	Active on gram positive bacteria and Fungi
Miamycin	*Streptomyces* sp.	Active on gram positive bacteria

Miramycin	*Streptomyces mirabilis*	Active on gram positive and gram negative bacteria
Moldin	*Streptomyces phaeochromogenes*	Active on gram positive bacteria
Neomycin	*Streptomyces fradiae, S. albogriscolus and Streptomyces* sp.	Active on gram positive and gram negative bacteria
Nocardicin A	*Nocardia uniformis*	Antibacterial
Novomycin	*Streptomyces roscochromogenes*	Active on gram positive and negative bacteria
Nucleocidin	*Streptomyces calvus*	Active on gram positive and negative bacteria and mycobacteria
Nystatin	*Streptomyces noursei*	Antifungal against organisms partcularly fungi especially *Candida* sp.
Oligomycins	*Streptomyces* sp.	Active on filamentous fungi
Paromomycin	*Streptomyces rimosus*	Active on gram positive and negative bacteria and mycobacteria
Perimycin	*Streptomyces coelicolor*	Active on yeasts and filamentous fungi
Picromycin	*Streptomyces fellas* and *Streptomyces* sp.	Active on gram positive bacteria
Puromycin	*Streptomyces alboniger*	Active on gram positive bacteria
Pyridomycin	*Streptomyces pyridomyceticus*	Active against mycobacteria
Rhodomycetin	*Streptomyces griseus*	Active on gram positive bacteria
Rifamycin	*Amycolatopsis mediterranei*	Antibacterial against *M. tuberculosis*
Ristocetin	*Amycolatopsis lurida*	Antibacterial against *Streptococcus* sp.
Rubromycin	*Streptomyces collinus*	Active on gram positive bacteria
Ruticin	*Streptomyces* sp. And *S. rutgerscnsis*	Active on gram positive and negative bacteria
Sistomycosin	*Streptomyces viridosporus*	Active on yeasts and filamentous fungi
Spinosyns	*Saccharopolyspora spinosa*	Insecticidal
streptomycin	*Streptomyces griseus, S. bikiniensis* and *S. olivaceus*	Antibacterial against gram- positive and gram-negative bacteria
Streptothricin	*Streptomyces lavendulae*	Active on gram positive and negative bacteria
Streptozotocin	*Streptomyces achromogenes*	Active on gram positive and negative bacteria
Teicoplanin	*Actinoplanes teichomyceticus*	Antibacterial against gram- positive bacteria
Telomycin	*Streptomyces* sp.	Active on gram positive bacteria
Tetracycline	*Streptomyces aureofaciens*	Antibacterial activity
Tetrin	*Streptomyces* sp.	Active on filamentous fungi and yeast
Vancomycin	*Amycolatopsis orientalis*	Antibacterial against *Streptococcus* sp., mycobacteria and some spirochetes
Xanthomycins	*Streptomyces* sp. And *S. rutgerscnsis*	Very active on gram positive and negative bacteria
Xanthothricin	*S. albus* and *Streptomyces* sp	Moderate activity against gram positive and gram negative bacteria and Mycobacteria
Zaomycin	*Streptomyces zaomyceticus*	Active against gram positive bacteria

[Source: 26, 27 and 1]

Actinomycetes in plants

In disease control

For the most part actinomycetes in soil have a place with the family Streptomyces and just about 60% of organically dynamic aggravates that have been created that are utilized as a part of the farming are started from them **[28]**. Mycostop a commercial item, in light of S. griseoviridis K16 and *S. lydicus* WYEC108 can control root rots and wilt diseased caused by *Pythium* spp. *Fusarium* spp., *Rhizoctonia* spp. and *Phytophthora* spp. **[29]**.

Production of plant growth hormone (indole-3-acetic acid)

Actinomycetes mostly used in the analysis of bioactive compounds. A few animal groups shape secondary metabolites, hostile to helminthic compounds, against tumor specialists and anti-infection agents [30]. Free-living species of actinomycetes have additionally been concerned in the improvement of plant growth by production of plant growth-producing substances like auxins and gibberellin-like compounds. Indole-3-acetic acid (IAA), which regulates many basic cellular processes including cell division, elongation and differentiation, is the principal form of auxin [31].

Biogenic synthesis of metal nanoparticles from actinomycetes

The biosynthesis of metal nanoparticles occurs intracellularly or extracellularly. According to in actinomycetes, intracellular reduction of metal ions occurs on the surface of mycelia along with cytoplasmic membrane leading to the formation of nanoparticles. Different metal nanoparticles such as silver, gold, zinc, and copper synthesized by using actinomycetes showed antimicrobial activity against a wide range of microbes including multidrug-resistant bacteria and fungi [32].

The mechanism of action of metal nanoparticles involves three mechanisms. Firstly, metal nanoparticles bind with cell membrane and disturb its power functions, such as permeability and respiration. Silver nanoparticles may cause depletion of intracellular ATP by rupture of plasma membrane or by blocking respiration in association with oxygen and sulfhydryl groups on the cell wall to form RS- S-R bonds leading to cell death. Secondly, silver nanoparticles are able to penetrate into the bacterial cell membrane, interact with sulfur-containing and phosphorus-containing compounds, such as DNA, and cause damages inside it [33]. Thirdly, the silver nanoparticles release silver ions, which may contribute to the bactericidal activity of metal nanoparticles. It is believed that DNA loses its replication ability, and cellular proteins become inactivated after interaction with silver nanoparticles. The higher concentration of silver nanoparticles has shown to interact with cytoplasmic components and nucleic acids [34].

Secondary Metabolites secreted by Actinomycetes

Soil habitats and marine environments samples have been used to isolate novel actinomycetes [25]. The secondary metabolites produced by actinomycetes serve as the sources of life saving environments and have a broad spectrum of biological activities; e.g. antibacterial (streptomycin, tetracycline, chloramphenicol), antifungal (nystatin), antiviral (tunicamycin), antiparasitic (avermectin), immunosuppressive (rapamycin), antitumor (actinomycin, mitomycinC, anthracyclines), Cancer (doxorubicins, daunorubicin, mitomycin and bleomycin), enzyme inhibitory (clavulanic acid) and diabetogenic (bafilomycin, streptozotocin), transplant rejection (cyclosporine and rapamycin) and high cholesterol (statins such as lovastatin and mevastatin [35].

Actinomycetes not only play a great role in the biological activities in addition to this Actinomycetes species, are makers of clinically valuable antitumor medications, for example, Anthracyclines (Aclarubicin, Daunomycin and Doxorubicin), Aurelic acids (Mithramycin), Peptides (Bleomycin and Actinomycin D), Enediynes (Neocarzinstatin), Antimetabolites (Pentostatin), Carzinophilin, Mitomycins and others. Actinomycetes are not capable for their powerful remedial exercises or essential organic exercises yet additionally for the use of pharmacokinetic properties required for clinical advancement [35].

In the start of the anti-toxin time the contagious (penicillin, griseofulvin) and bacterial(Gramicidin) species were in intrigue, yet after the revelation of streptomyces species the more consideration swings to *streptomyces* species, the antibiotics discovered from streptomyces were streptomycin and later chloramphenicol, tetracyclines and macrolides. In Fifties and sixties Majority of antibiotics almost 70% were reported from *streptomyces* and 45% of the presently known metabolites almost about 10000 compounds were still isolated from the various actinomycetales species, 34% of them were from *streptomyces* and 11% of them from rare actinomycetes species produce 7600 compounds (74% of all actinomycetales), although the typical Actinomycetes represent 26%, altogether 2500 compounds [36]. The representation of rare actinomycetes products in 1970 was only 5%. In the gathering *Nocardia, Streptoverticillium, Micromonospora, Streptosporangium, Actinoplanes, Saccharopolyspora and Actinomadura*, species are the most continuous makers; every deliver a few many antibiotics [37].

Table.2 Number of actinomycetales species producing bioactive microbial metabolites.

Actinomycetales species	No.	Actinomycetales species	No.
Streptomycetaceae:		**Thermomonosporaceae:**	
Streptomyces	8000	Actinomadura	345
Streptoverlicillium	258	Saccharothrix	68
Kitasatosporia	37	Microbispora	54
Chainia	30	Actinosynnema	51
Microellobosporia	11	Nocardiopsis	41
Nocardioides	9	Microtetraspora/Nonomuria	26/21
Micromonosporaceae: (Actinoplanetes)		Thermomonospora	19
Micromonospora	740	Micropolyspora/Faenia	13/3
Actinoplanes	248	Thermoactinomyces	14
Dactylosporangium	58	Thermopolyspora	1
Ampullariella	9	Thermoactinopolyspora	1
Glycomyces	2	**Mycobacteriaceae: (Actinobacteria)**	
Catenuloplanes	3	Nocardia	357
Catellatospora	1	Mycobacterium	57
Pseudonocardiaceae:		Arthrobacter	25
Saccharopolyspora	131	Brevibacterium	17
Amycalotopsis/Nocardia	120/357	Proactinomyces	14
Kibdellosporangium	34	Rhodococcus	13
Pseudonocardia	27	**Other (unclassified) species:**	
Amycolata	12	Actinosporangium	30
Saccharomonospora	2	Microellobosporia	11
Actinopolyspora	1	Frankia	7
Streptosporangiaceae: (Maduromycetes)		Westerdykella	6
Streptosporangium	79	Kitasatoa	5
Streptoalloteichus	48	Synnenomyces	4
Spirillospora	11	Sebekia	3
Planobispora	10	Elaktomyces	3
Kutzneria	4	Excelsospora	3
Planomonospora	2	Waksmania	3
		Alkalomyces	1
		Catellatospora	1
		Erythrosporangium	1
		Streptoplanospora	1
		Microechinospora	1
		Salinospora	1

[Source: **36, 37**]

Actinomycetes as source of Agroactive compounds

Kasugamycin is a bactericidal and fungicidal metabolite discovered from *Streptomyces kasugaensis* **[26].** The inhibitor of protein biosynthesis in microorganism's occure due to this antibiotic, and its toxicological properties are excellent. Hokko Chemical Industries build up a production process to advertise the systemically active kasugamycin for control of rice blast *Pyricularia oryzae* Cavara and bacterial *Pseudomonas* diseases in several crops.

The isolated Polyoxin B and D were metabolites of *Streptomyces cacaoi*var. *Asoensis* and in 1965 by classified it as a new class of natural fungicides. They play role in the fungal cell wall synthesis by specifically inhibiting chitin syntheses. Polyoxin B has application against a number of fungal pathogens in fruits, vegetables and ornamentals. Polyoxin D is marketed by several industries to control rice sheath blight caused by *Rhizoctonia solani* Kùhn [26].

Antifungal metabolite mildiomycin isolated from a culture of *Streptoverticillium rimofaciens* Niida was reported in 1978, also by Takeda scientists [38]. Mildiomycin antibiotics is strongly active against several

powdery mildews on various crops, Furthermore compounds mentioned are agroactive compounds isolated from actinomycetes and microbial screening and chemistry techniques have been until recently the main tools to discover new agroactive compounds [39].

Actinomycetes as Biopesticide Agents

Microorganisms including bacteria, fungi, nematodes and viruses that are antagonistic to insects are accounted as strategies to biologically control them. Actinomycetes play a great role in the biological control of insects through the production of insecticidally active compounds against the house fly *Musca domestica* [40]. The mortality rates were measured very high almost reaching up to 90% after actinomycetes treatments at larval and pupal stages and Chitinase enzyme is extremely necessary within the biological control of insects and the largest chitinase activity among bacteria has been determined in species of *Streptomyces, Serratia, Vibrio* and *Bacillus* [41].

Enzyme production from Actinomycetes

Physiological, Biochemical and Molecular characteristics in actinomycetes followed by metabolic pathway yield a variety of biologically active enzymes. The varieties of enzymes secreted by actinomycetes are chitinase (eg. *Streptomyces viridificans*), cellulases(eg. *Thermonospora* spp.), proteases (*Nocardia* spp.), peptidases, Xylanases *(Microbispora* spp.), ligninases (*Nocardia autotrophica*), amylases (*Thermomonospora curvata*), sugar isomerases (*Actinoplanes missouriensis*), hemicellulase, pectinase and keratinase [42].

Table.3 Applications of enzymes produced from actinomycetes.

Enzymes	Application	References
1. Amylase	I. In fermentation II. Food industry III. In textile and paper industry	[43]
2. Catalase	I. Used as an Antioxidant II. In Dairy industry III. In cold Sterilization of beer	[26]
3. Cellulases	I. In animal feed industry II. In biomechanical pulping III. In laundry	[44,26]
4. L- asparaginase	I. In Bone marrow treatment II. In stem cell transplant III. In treatment of acute leukemia	[45,46,47 and 48]
5. Lipase	I. In oleochemical II. In detergent industry III. Pharmaceutical industries IV. In diagnostic setting	[49,50]
6. Urease	I. In wine industry II. Analysis in blood and urine III. Analysis of heavy metal content in waste water and soil	[26]
7. Proteases	I. In cancer treatment II. Protect against clots III. Used as Anti-inflammation	[51]
8. Chitinase	I In plant resistance against fungal pathogen II In biochemical industry III In drug delivery and wound healing	[52,53]

[Source: **7, 26]**

Actinomycetes in bioremediation/biodegradation

The pesticides degradation are responsible because of actinomycetes with various different chemical structures, including organochlorines, s-triazines, triazinones, carbamates, organophosphates, organophosphonates, acetanilides, and sulfonylureas [7]. Petroleum hydrocarbons are widely used as chemical compounds and fuel in our daily life. Greater use results, petroleum now one of the most serious contaminants of large soil surfaces and finally are considered as a major environmental problem [54].

Several ways in which hydrocarbons degraded in the environment and one such mechanism through which they can be removed from the environment is bioremediation. Bioremediation is the use microbes to degrade harmful pollutants to harmless substances. Some reports on *Streptomyces* flora indicated that they could play a very important role in degradation of hydrocarbons. Actinomycetes have numerous such properties that make them utilized for application in bioremediation of soils contaminations. They play role in the recycling of organic carbon and are being able to degrade complex polymers. In some reports in a few reports Actinomycetes are having more preference among the degraders Actinomycetes species are having the capacity to live in oil domain. So we can apply these microorganisms in Bioremediation to deduct oil contaminations. Numerous strains may be able to solubilise lignin and debase lignin-related compound by creating cellulose-and hemicellulose-degrading proteins and extracellular Peroxidase [26].

Actinomycetes in Biocorrosion

Corrosion is a main reason of pipe failure and of high costs in gas pipelines [55]. Biocorrosion is characterized as a sarcastic harm started by the immediate or aberrant exercises of microorganisms Antimicrobial substance (AMS) delivered by a *Streptomycetes* strain having its action against a vigorous bacterium *B. pumilus* LF-4, and sulfate-diminishing bacterium D. alaskensis NCIMB 13491 known to be engaged with biofilm arrangement and biocorrosion [26]. One of Strain 235 was identified that belong to *S. lunalinharesii* species was initially isolated from a Brazilian soil. This strain was beforehand known as maker of bioactive mixes against microscopic organisms and parasites [56]. The antimicrobial activity was seen at different pH, chemicals and temperature but not seen with Proteinase K and trypsin. The antimicrobial substance are of proteic nature, has advertised for use in oil making plants, demonstrated its strength within the sight of a few synthetic chemicals, solvents, and at various temperature and pH values [57].

Nitrogen-fixing actinobacteria Frankia

Frankia is a species of actinomycetes in the family Frankiaceae that fix nitrogen, both are advantageous and free-living oxygen consuming, while most rhizobia don't [58]. The filamentous gram-positive Frankia *sp.* recommends the significant gatherings of nitrogen-fixing symbionts have obtained mechanism for nitrogen fixation from various transformative starting points [59]. The very first successful isolation of *Frankia* was reported recently from *Comptonia peregrina* root nodules. Till now, we have 200 strains of *Frankia* have been isolated from many, despite the fact that not all, actinorhizal plant species. Phylogenetic examinations uncovered that *Frankiae* shape an intelligent clade inside actinobacteria. The *Frankia* family of actinobacteria and their host plants is form symbiotic relationships with various species and fixed 15% of the world's nitrogen **[60].**

Volatile Organic Compounds (VOCs)

Actinomycetes, especially the genus *Streptomyces*, are well characterized for their capability of producing a variety of secondary metabolites such as antibiotics **[61]**. Despite this, there has been little systematic investigation of the production of volatile organic compounds by these organisms, geosmin and much attention has been paid to the production of off-odor, musty, aroma compounds produced by these organisms, mainly geosmin (*trans*-1, 10-dimethyl-*trans*-9-decalol) and 2-methylisoborneol, due to the detrimental effects of these compounds on the quality of fresh water sources and aquaculture-raised fish (wood *et al*., 1983). *Streptomycetes* are characterized by a complex secondary metabolism. They make more than 66% of the clinically valuable anti-microbials of normal source (e.g. neomycin, chloramphenicol) **[62]**. The odor of freshly turned soil is that the results of geosmin, a volatile organic compound obtained from actinomycetes. Geosmin is additionally made by some cyanobacteria and produces an earthy taste in drinking water [**26]**.

CONCLUSION

Indirect 23,000 bioactive secondary metabolites delivered by microorganisms have been accounted for and more than 10,000 of these compounds are created by actinomycetes. A few pharmaceutical organizations utilized microbial natural items as one of the significant source of novel medications. Analysts have been going ahead to find more novel metabolites with potential remedial application particularly from actinomycetes. Further, just little data is accessible on the actinomycetes. Ongoing discoveries from culture-dependent and culture free techniques have exhibited that indigenous actinomycetes exist in the seas and are broadly conveyed in various marine biological systems. These marine actinomycetes deliver diverse kinds of new secondary metabolites. Diversity and novelty tremendously among in actinomycetes present in marine environments and several new methods have been used to detach novel actinomycetes from various conditions and natural surroundings include Different molecular approaches such as genetic fingerprinting, metagenomics, metaproteomics, 16S r

RNA, genus specific primers, RAPD, RFLP, Proteomics and bioinformatics tools are vital for discovering and characterizing the vast actinomycetes diversity. For novel medication conveyance, researchers still adventure the synthetic and biological variety from different actinomycetes for successful disclosure of novel strain in cost effective manner and these techniques useful to circumvent the problem of recharacterization of known bioactive molecules and to help in screening of novel compounds. Use of the above mentioned strategies should make feasible the discovery of novel pharmaceutical and industrial important product from actinomycetes.

CONFLICT OF INTEREST

The authors have no conflicts of interest

ACKNOWLEDGEMENT

The authors are grateful to acknowledge all the colleagues and Jaipur National University, Jaipur, Rajasthan, India for carried out work in the School of Life Science, Main Campus by providing necessary facilities in the laboratory for this study.

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CITATION OF THIS ARTICLE

V Mathur, I Jadhav, R Vasniwal, D Shrivastava and K Jadhav. Ubiquity, Significance and the Molecular Techniques used for deciphering Actinomycetes. Bull. Env. Pharmacol. Life Sci., Vol 9[2] January 2020 : 164-177