Tracing the Journey of Actinomycetes: Past Insights and Current Advances

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ABSTRACT

Actinomycetes are Gram-positive, filamentous bacteria belonging to the phylum Actinomycetota (formerly Actinobacteria). They are widely distributed across various ecological niches, especially in soil, where they are commonly found. Actinomycetes are classified based on their morphology and possess diverse characteristics. Understanding their traits and mechanisms in organic waste degradation is crucial for developing sustainable waste management strategies. Methods such as conventional, chemotaxonomic, numerical taxonomic, and molecular techniques are routinely used to identify actinomycetes. These bacteria play important roles in cancer treatment, bioremediation, and the production of valuable antibiotics. Actinomycetes produce over 22,500 secondary metabolites, many of which have antibacterial and therapeutic properties. Their metabolites act as antimicrobial agents against a range of infections. Recent advances in actinobacteria research highlight the importance of rare genera (such as Micromonospora and Actinoplanes), the CRISPR-Cas system in actinomycetes, and synthetic biology approaches for drug discovery.

Keywords: Actinobacteria; Antimicrobial; Bioremediation; Enzymes; Secondary metabolites.

INTRODUCTION

The name actinomycetes comes from the old Greek words for “ray” and “fungus” (1). These bacteria have a shape like threads and make spores (2). They are Gram-positive, filamentous and have a branching pattern that place them in the phylum Actinomycetota. These bacteria are commonly found in soil and are important for breaking down organic matter, recycling nutrient ,and producing bioactive compounds such as antibiotics, plant growth- promoting substance, enzymes, and other secondary metabolites(3). Actinomycetes have a high amount of guanine and cytosine in their DNA. They grow in a filamentous way like fungi, forming branched hyphae and spores. These bacteria are generally set up in soil (5). Actinomycetes are renewned for their capability to produce bioactive secondary metabolites, including antibiotics, antifungals, and anticancer agents (Barka et al., 2016). They produce different colors on the media which are red, pale, brown and black colour (6).

This review covers current knowledge about soil actinomycetes, focusing on their variety, biotechnology applications, and roles in carbon sequestration and environmental system. Actinobacteria produces enzymes and these enzymes have multitudinous significance in different field. Actinobacteria have a establishment that involves their special structure (filamentous excrescency), environmental acclimatizations (spore conformation), and secondary metabolite product (Antibiotics).

Taxonomy and diversity of soil actinomycetes:

Actinomycetes show high phylogenetic diversity, with major groups inclung *Streptomyces*, *Micromonospora*, *Nocardia*, *Actinomyces*, and *Frankia* (Goodfellow & Williams, 1983). Among these, Streptomyces is the most studied because it produces a wide range of antibiotic (7).

Habitat and Distribution

Actinomycetes thrive in different soil surroundings, involving agricultural, timber, desert, and rhizospheric soils. Their cornucopia is told by soil pH, moisture, organic matter, and temperature (8). Acidic soils favor Streptomyces, while alkaline soils are pacified by *Nocardia* and *Micromonospora* (Goodfellow & Williams, 1983). Actinomycetes constitute 10 – 30 of the grand soil microbial population. Actinobacteria are soil-dwelling bacteria and are spread throughout the environment. The most dominant actinomycetes species set up in soil *Streptomyces*, *Norcardia*, *Microbispora*, *Micromonospora*, *Actinomyces*, *Actinoplanes* and these actinomycetes species have been also isolated from the soil. Actinomycetes are especially rich in alkaline soils and rich in organic matters and form several structurally different bioactive mixes of medicinal and agricultural significance. Actinomycetes support to reclaim nutrients by slighting vast numbers of organic matter in the soil and generally set up incompost (9).

Molecular Techniques for Diversity Assessment

Molecular ways for Diversity Assessment It's a civilization-independent ways analogous as 16S rRNA gene sequencing and metagenomics have revealed a vast common diversity of actinomycetes (10). High- outturn sequencing has linked new actinobacterial lineages in extreme terrain (11). *Streptomyces*, *Micromonospora*, *Nocardia*, *Actinoplanes*, *Saccharopolyspora*. These groups vary depending on soil type, pH, temperature, leafage, and agricultural practices (12).Genome sequencing, metagenomics, and genome mining have revealed numerous cryptic biosynthetic gene clusters. CRISPR-Cas genome editing and heterologous expression platforms have enabled activation of silent pathways and enhanced metabolite production, offering promising routes for novel drug discovery.

Cell Wall Structure:

The cell wall structure of actinomycetes differs among groups and taxonomic classification. Four major cell wall mores are in these filamentous bacteria on the base of the features of peptidoglycan composition and structure.

These features are (i) diaminopimelic acid isomer on tetrapeptide side chain position 3, (ii) sugar content of peptidoglycan, and (iii) the presence of glycine in interpeptide bridges. The characteristic of sugar patterns are present only in cell wall types II-IV of those actinomycetes with meso-diaminopimelic acid.

Comparision between Normal bacteria and Actinobacteria

Normal bacteria are true bacteria (Eubacteria) and actinobacteria are filamentous bacteria (Gram-Positive, high G+C content); Morphology of normal bacteria are Unicellular, cocci, bacilli, or spirilla and actinobacteria are filamentous, branching hyphae (resemble fungi); normal bacterial cell wall are peptidoglycan (gram positive or gram negative) and actinobacteria cell wall are thick peptidoglycan (Gram-Positive); reproduction of normal bacteria are binary fission, budding, or conjugation and in actinobacteria are fragmentation, spore, formation of conidia; Normal bacterial habitat are ubiquitous(soil, water, human body, extreme environment) and actinobacterial habitat are Predominantly soil, decaying organic matter; normal bacteria are produce some antibiotics (e.g. *Bacillus*, Pseudomonas) and actinobacteria are produce major antibiotics (e.g. Streptomyces-source of streptomycin, tetracycline).

Life cycle of Actinobacteria

The life cycle of actinobacteria takes place in two main stages in spore-forming actinomycetes. The first stage is called substratum mycelium, which is the main mycelium that produce spores. The second stage is aerial mycelium. The substratum mycelium is the primary mycelium that develops into spores. The secondary mycelium, also known as the ‘initial cell’, starts growing, and when it produces spores, it goes through certain changes during the process. The life cycle of the actinomycetesis :

a. The first mycelium

b. The origin of the initial cells

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c. The secondary mycelium

d. The formation of the spores [13].

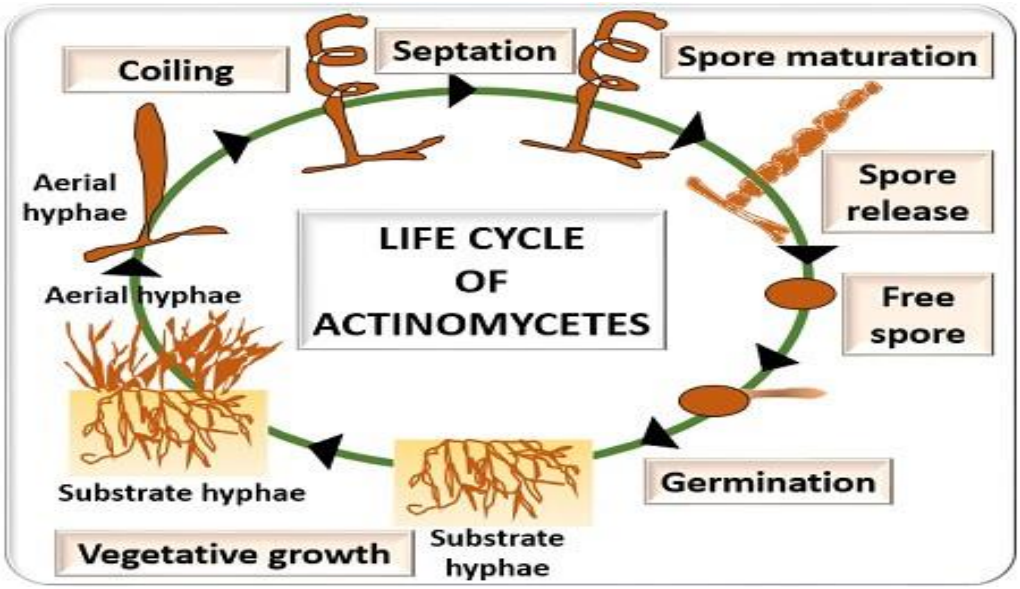

Figure: life cycle of actinomycetes

https://biologyreader.com/wp-content/uploads/2019/07/life-cycle-of-actinomycetes.jpg

Isolation Techniques

Common isolation methods:

✓ **Sequestration Techniques:**

These involve diluting and plating samples on specialized media like Starch Casein Agar, Actinomycetes Sequestration Agar, or Glycerol Asparagine Agar.

✓ **Pre-treatment of Soil Samples:**

Before isolation, soil samples can be pre-treated (e.g., air drying, heating) to minimize the growth of fast-growing bacteria and fungi, making it easier to isolate specific microorganisms. (14).

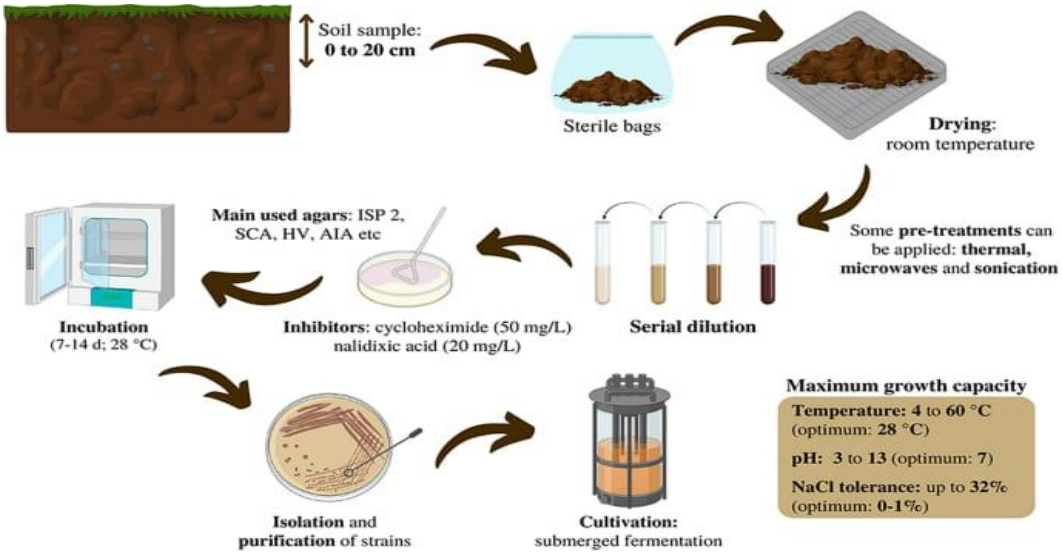

Figure: Isolation of Actinomycetes

Different sources and media for isolation of :

➢ From soil:

- Source: forest soil;

Media: starch-casein medium;

Reference: Kuster & Williams(1964)

- Source: Humus Layer of forest Soil;

Media: Humic acid; Reference: Cho et al, 1994

Starch casein nitrate agar; Reference: Hayakawa et al, 1987a

Hair hydrolysate vitamin agar (HHVA); Reference: Hayakawa et al, 1987b

Bennet's agar; Reference: Seong C.N., 1992

- Source: Corn Field, Cow Barn yard, Forest

Media: Arginine-glycerol salt (AGS) medium; Reference: Porter et al, 1960

Chitin medium; Reference: Lingappa & Lockwood, 1961

Modified Benedict's medium; Reference: Porter,Wilhelm & Tresner, 1960

Soyabean meal-giucose medium; Reference: Tsao,Leben & Keitt, 1960

Gauze's agar medium; Reference: Rehacek, 1959

Czapek's agar medium; Reference: Waksman, 1961

Egg albumen medium; Reference: Waksman, 1961

Glucose-asparagine medium; Reference: Waksman, 1961

Glycerol-asparaginate agar 2; Reference: Waksman, 1961

- Source: Lake Soil

Media: Chitin agar; Reference: S.C. HSU & J.L. Lockwood, 1975

- Source: Soil

Media: Coal-vitamin agar; Reference: Wakisaka et al, 1982

- Source: Antaric Soil

Media: Mineral Salt (MS) medium; Reference: Kosmachev (1954)

- Source: Mitidja plain (Algeria)

Media: Yeast extract-malt extract agar; Reference: Shirling & Gottlieb, 1966

- Source: Marine Soil

Media: Starch casein nitrate (SCN) agar medium; Reference: Ravel J, Amorso (1998)

➢ From Water:

- Source: Stream Sediments & Lake muds;

Media: Chitin agar media; Reference: Lingappa & Lockwood (1961,1962)

M3 agar medium; Reference: Jones, 1949

Benett's medium; Reference: Jones, 1949

- Source: Marine Sediments

Media: Starch-casein agar; Reference: A.Grein & S.P. Meyers, 1958

Aspargine agar; Reference: A.Grein & S.P. Meyers, 1958

Glycerol-giycine agar; Reference: Lindenbein, 1952

- Source: Marine Sediments (South China)

Media: AIM medium; Reference: J.L. You et al

➢ From Other Sources: Root & Stem samples of four plants

- Source: Cinnamomum zeylanicum, Zingiber spectabile, Elettariopsis curtisii, Labisia pumila

Media: Starch yeast casein agar (SYCA), Actinomycetes Isolation agar (AIA), Humic Acid vitamin gellan gum (HVG), Tap water yeast extract agar (TWYE), Coal-vitamin agar (CVA); Reference: Zin et al, 2007

- Source: Mangroove Sediments
- Media: Asparagine-glucose agar medium; Reference: Shirling & Gottlieb, 1966

Secondary metabolites and Production of secondary metabolites

Antibiotics

Antibiotics are biologically active composites with colorful structures and mechanisms of action. The different antibacterial composites insulated from colorful actinomycetes. The particularity of antibiotic exertion is caused by the interruption of the essential processes related to bacterial survival. They majorly target each kind of bacterial processes similar as conflation of protein, DNA, and RNA, biosynthesis of cell wall, transport of electrons, the function of the membrane, germination, sporulation, and other different functions. Antibiotics released by actinomycetes are divided into different chemical classes including macrolides, aminoglycosides, etc…

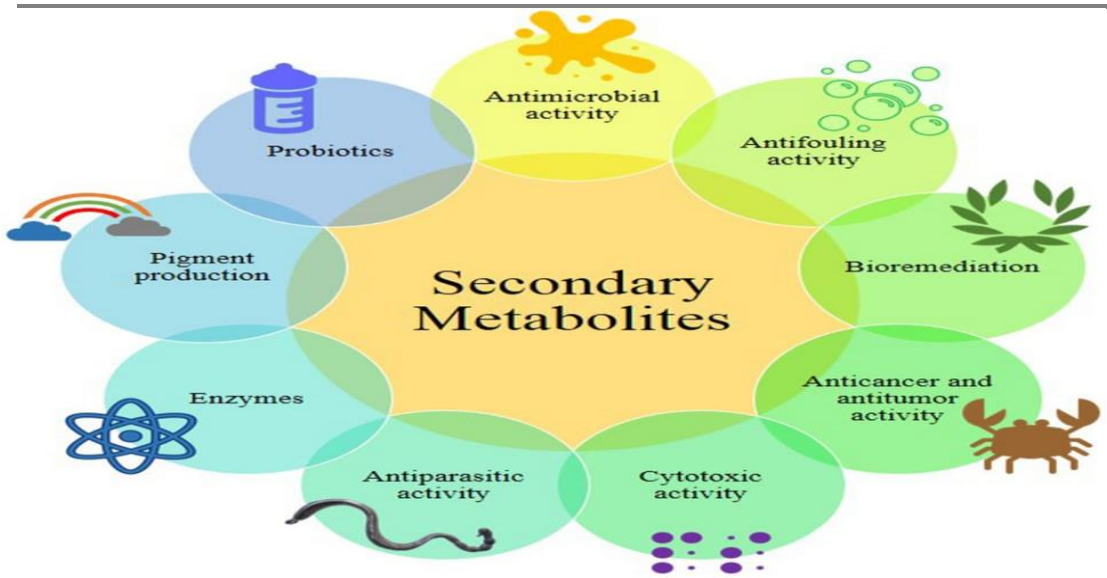

Figure: Secondary metabolites

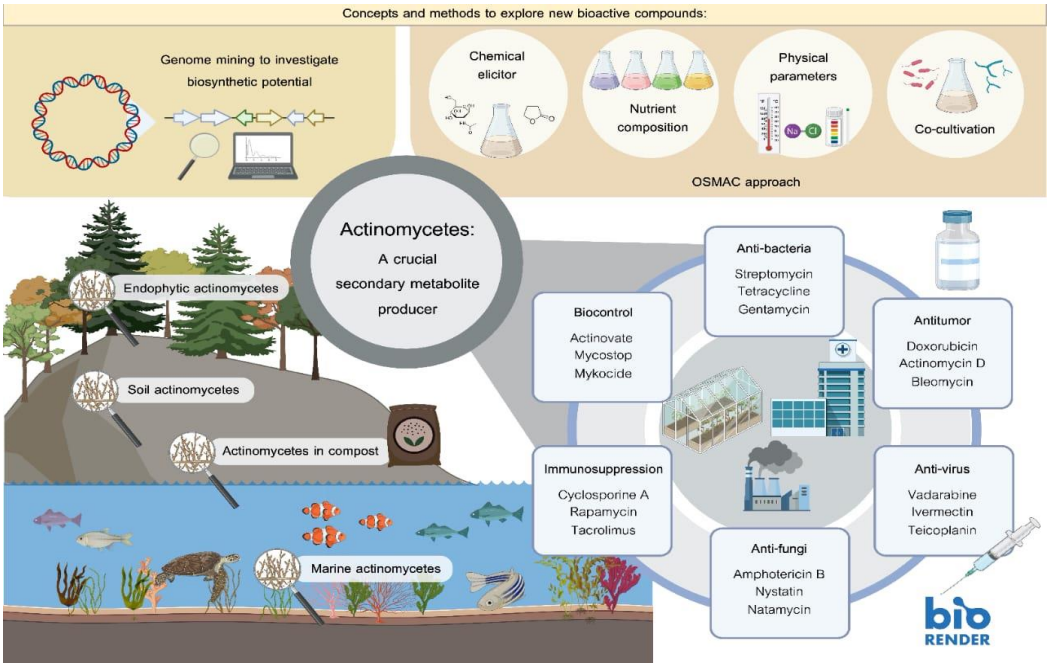

Figure: Secondary metabolites producers

Aminoglycosides

Aminoglycosides are antibiotics that contain amino sugars linked by glycosidic bonds to an aminocyclitol ring. They're a group of antibiotics with a broad- diapason exertion against different gram-positive and gram-negative bacteria. They're effective against colorful members of *Enterobacteriaceae* family, *E. coli*, *Serratia spp*, *E. aerogenes*, *Proteus spp*., *Klebsiella pneumoniae*. Aminoglycosides are potent against *Francisella tularensis* as well as *Yersinia pestis*, which beget tularemia, and pest. Aminoglycosides also work well against *S.aureus*. They bind to the A-site on 16S rRNA of the small ribosomal subunit (15).

Tetracyclines

Tetracyclines have fused tetracycline ring and have 4- dimethylamino groups to which can be attached colorful functional groups. They are broad diapason antibacterial composites active towards colorful gram-negative and gram-positive bacteria, obligate intracellular bacteria, protozoan spongers, and spirochetes. They work by preventing protein synthesis.

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Natural tetracyclines, such as demethylchlortetracycline insulated from *S. aureofaciens*, and tetracycline from *S. rimosus*, *S. aureofaciens*, and *S. viridofaciens*. The semisynthetic products were brought into the clinical field including minocycline, methacycline and doxycycline.

Chloramphenicol (C11H12C12N2O5)

Chloramphenicol was first uprooted from Streptomyces venezuelae insulated from soil in 1947. An antibacterial agent with a bacteriostatic effect illustrated by inhibiting protein conflation. This exertion targets a large number of organisms including spirochetes, gram-positive and gram-negative bacteria, and obligatory intracellular pathogens. Chloramphenicol competes with Aminoacyl tRNA in attaching to the large ribosomal subunit, specifically on peptidyl- transferase point. Despite its bacteriostatic effect, chloramphenicol exhibits a poisonous effect on mammalian cells. This may pose different health issues including depression of the bone gist, displayed by thrombocytopenia, anemia, or leukocytopenia, therefore requires farther clinical examinations (16).

Beta lactams

β- Lactam antibacterial agents, enjoying a β- lactam ring within their chemical formula, are the biggest family of antimicrobial substances, and the prominent agents are use in the clinical field. They include monobactams, penicillin, carbapenems, and cephalosporins. These antibiotics kill bacteria by stopping them from forming their cell walls. These antibiotics inhibit Penicillin- List Proteins (PBPs), needed for the transpeptidation of the peptidoglycan subcaste of the prokaryotic cell wall. The enzymes are responsible for peptidoglycan cross-links hydrolysis remain active. When these links are broken, the cell wall becomes weak and the bacteria die. The gram-positive bacteria have a thicker peptidoglycan wall and are morecross-linked than gram-negative bacteria (17).

Peptides

Out of the most classes of antibiotics, peptide antibiotics are the predominant group, substantially for inhibiting the growth of resistant bacterial strains. There's a order called Non-Ribosomal Peptides(NRPs). NRPs have anon-peptide group or anon-proteinogenic amino acid attached to a peptide chain. In 2019,730 NRPs were linked. This order possesses a broad variety at the structural and compositional position. For this reason, they display a broad diapason of principal natural goods. Lipopeptides have been discovered for further than 50 times. Glycopeptides and glycolipopeptides parade an antibacterial effect by precluding the biosynthesis of the bacterial cell wall(18). In general, microorganisms retain an enzyme, videlicet dihydropteroate synthetase that utilizes PABA to produce dihydrofolic acid. Microbes use folic acid to make purines and pyrimidines. Eukaryotic cells are n't affected by sulfonamides, because they formerly absorb folic acid, performing in a broad remedial indicator.

Antimicrobial exertion of actinomycetes:

lately studies are fastening on the response of antimicrobial exertion against microorganisms. *Streptomyces*, *Nocardia* are stylish species and which may produce different types of bioactive composites with antioxidant, anti-tumour, anti-inflammatory and antioxidant parcels. This Antioxidants play main part in microorganisms defence against human body less or high infection (19). Well known bioactive composites inhibit the growth of microorganisms. Gram positive and Gram negative microorganisms are considered as test microorganisms in the antimicrobial exertion of wireworks and extensively habituated test microorganisms were *Bacillus subtilis*, *Bacillus cereus*, *Micrococcus*, *Staphylococcus aureus*, *luteus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Saccharomyces cerevisiae* etc (20).

Antifungal exertion of actinomycetes:

Urauchimycins are a group of strong antifungal compound. Antimycins are inhibiting the electron inflow in the mitochondrial respiratory chain. Antimycins have been linked in Streptomyces insulated from the integument of attine ants (21)(22). Composites of this class may have an effective part in the attine ant- microbe association. Another antifungal compound, candicidin, is produced by Streptomyces connected to attine ants. Urauchimycins

A and B were discovered from *Streptomyces species*. In 2006, two new urauchimycins were found: urauchimycin C, is isolated from marine sediment, and urauchimycin D, isolated from soil. Urauchimycin B showed a broad range of activity against *Candida spp.* with MIC values equal to the nystatin antifungal. Antimycins were used from numerous times for the cure of mortal infections, but due to confederated side goods, its use in the treatment of mortal complaint was discontinued. Still, with the critical need for new antifungal agents that round for the inadequate products accessible in the business. Recent studies focus on the chemical makeup of bioactive compounds from actinobacteria associated attine ants. An disquisition program of insulation of bioactive motes from actinobacteria will affect in the discovery of new composites with exertion against microorganisms that are potentially pathogenic to humans.

Ecological places of Actinomycetes in Soil

Corruption and Nutrient Cycling

Actinomycetes degrade complex organic polymers like cellulose, chitin, and lignin, contributing to guck conformation (23). They also solubilize phosphates and fix nitrogen in symbiotic associations with shops (24).

Biocontrol and Plant Growth

Several actinomycetes produce antifungal and antibacterial metabolites that suppress soil- borne pathogens(Barka et al., 2016). Streptomyces spp. Enhance factory growth by producing siderophores, phytohormones, and unpredictable organic composites (VOCs)(22)(Gopalakrishnan et al., 2011).

Pharmaceutical Applications

Antibiotic	Producing Actinomycetes	Medical Use
Streptomycin	*Streptomyces griseus*	Tuberculosis treatment
Vancomycin	*Amycolatopsis orientalis*	MRSA infections
Rapamycin	*Streptomyces hygroscopicus*	Immunosuppressant
Daptomycin	*Streptomyces roseosporus*	Skin infections

Table: Clinically importance of antibiotics from actinomycetes

Biotechnological Importance

Figure: Applications of Actinomycetes

A. Antibiotic Production

Actinomycetes are the largest source of naturally being antibiotics. Example *Streptomyces griseus* produces streptomycin. Over 70 of antibiotics used in drug and husbandry are produced by actinomycetes (23). Genome mining has revealed cryptic biosynthetic gene clusters (BGCs) garbling new antimicrobial composites (24).

B. Enzyme Production

Actinomycetes Produce cellulases, xylanases and chitinases used in biodegradation and artificial processes (25). They release amylases outside their cells to help digest food. Alpha amylase, a type of amylolytic enzyme, is very useful in food, brewing, and paper (Pandey et al. 2000). They are also known to break down cellulose (Jang and Chenks 2003, Arunachalam et al. 2010). Cellulases are a collection of hydrolytic enzymes. Lipase, which break down fats, are made by actinobacteria along with some bacteria and fungi (Kulkarni and Gadre 2002).

C. Plant Growth Promotion

Some strains of actinomycetes help plants by making phosphate soluble and producing siderophores, which help plants get iron. They also help fix nitrogen. For example, *Streptomyces species* improve plant root growth and crop yield. Actinomycetes are also used as plant growth promoting agents (help to produce factory growth hormone Indole-3-acetic acid), biocontrol tools, biopesticide agents, antifungal composites. They are also useful in bio corrosion and produce agroactive composites. Actinomycetes play a significant part in the product of colorful antimicrobial agents and other industrially important substances similar as enzymes, which is important in the field of biotechnology and biomedical exploration.

D. Biocontrol Agents

Some actinomycetes inhibit factory pathogens by producing antifungal composites. Actinomycetes are important in the rhizosphere (Barakate et al. 2002, Crawford et al. 1993, Doumbou et al. 2001, Miller et al. 1990), where they may impact factory growth and defend factory roots against irruption by root pathogenic fungi (Lechevalier 1988). However, research on root microorganism has mainly focused on nitrogen fixing *Frankia species* (Sardi et al. 1992) and some *Streptomyces species* that phyto pathogens [harmful to plant](Loria et al. 1997).

E. Industrial Enzymes

Actinomycetes produce extracellular enzymes (cellulases, xylanases, proteases) used in biofuel product, food processing, and waste operation (26).

F. Bioremediation

Actinomycetes degrade adulterants similar as fungicides, petroleum hydrocarbons, and heavy essence due to their enzymatic versatility (27). Actinomycetes are responsible for fungicides declination with colorful different chemical structures, including organochlorines, s- triazines, triazinones, carbamates, organophosphates, organophosphonates, acetanilides, and sulfonylureas. Indigenous soil actinomycetes had been reported to degrade the pesticide in soil. Actinomycetes are well-suited for cleaning soil contaminated with organic pollutants. They play an important part in the recycling of organic carbon and are suitable to degrade complex polymers (Goodfellow and Williams 1983. Some reports are indicate that Streptomyces foliage could play a veritably important part in declination of hydrocarbons (Radwan et al. 1998, Barabas et al. 2001). Contribute to soil health by demeaning complex polymers (e.g., cellulose, lignin). Share in bioremediation of defiled soils by demeaning adulterants (e.g., hydrocarbons, fungicides) (28).

G. Phosphate solubilization

Microorganisms, including actinobacteria from the groups *Saccharopolyspora, Thermobifida* and *Thermonospora,* release phosphatase enzymes that break down organic phosphates. Actinobacteria from groups like *Micromonospora sp., Nocardia sp., Actinomadura sp., Rhodococcus sp., Actinoplanes sp., Microbispora sp.* and *Streptosporangium sp.* produce phosphatase enzymes.

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The Evolution of Actinobacteria Research: From Classical Antibiotic Discovery to Multi-Omics and Synthetic Biology Frontiers:

1. Past Work (Pre-2000s) – The Golden Age of Discovery

✔ "Antibiotic discovery"– (e.g., streptomycin, tetracycline, vancomycin from Streptomyces).

✔"Taxonomy & morphology"– Early classification based on spore formation and biochemical traits.

✔ "Soil & marine isolation"– Traditional culture-based methods dominated.

2. Modern Era (2000–2020) – Genomics & Bioprospecting

✔ "Genome mining"– Identification of cryptic biosynthetic gene clusters (BGCs).

✔ "CRISPR-Cas9"– Genetic engineering for enhanced metabolite production.

✔ "Extreme environments"– Isolation of rare actinomycetes from deserts, deep-sea, and mangroves.

3. Current Trends (2020–Present) – Multi-Omics & Synthetic Biology

✔ "Multi-omics integration"– (genomics, transcriptomics, metabolomics).

✔ "Heterologous expression"– (e.g., E. coli as a chassis for actinobacterial BGCs).

✔ "AI & machine learning"– Predicting novel antibiotics from genomic data.

4. Future Directions (2025 & Beyond) – Challenges & Opportunities

✔ "Unculturable actinomycetes" – Single-cell genomics & microfluidics.

✔ "Sustainable bioproduction" – Actinomycetes in circular bioeconomy (e.g., plastic degradation).

✔ "Phage therapy & microbiome engineering* – Actinophages for antibiotic-resistant pathogens.

Challenges in Actinomycetes Research

1. Cultivation Difficulties

Many soil actinomycetes can't grow under standard laboratory conditions. Innovative civilization styles, similar as prolixity chambers andco-culture ways, have bettered recovery rates (29).

2. Antimicrobial Resistance

Using too many actinomycetes for antibiotics has caused resistance, making it hard to find new drugs (30).

Emerging and Unexploited Frontiers in Actinomycetes Research:

- *Metagenomic and synthetic biology techniques * can help unlock the potential of common actinomycetes (Charlop- Powers et al., 2014).

- *CRISPR- grounded genome editing * can enhance secondary metabolite product in Streptomyces (Tong et al., 2015).

- *Microbiome engineering * may optimize actinomycetes communities for sustainable husbandry (Arif et al., 2020).

- Numerous actinomycetes are not cultivable by traditional styles (the “great plate count anomaly”).

- Metagenomic approaches are now used to discover new biosynthetic gene clusters.

- Future work may use genome mining and CRISPR- Cas editing to reactivate silent genes. Actinomycetes from extreme surroundings (e.g., comeuppance, deep- ocean(Barka, E. A., et al. 2016 (Taxonomy, physiology, and natural products of Actinobacteria, Microbiology and Molecular Biology Reviews, 80(1), 1 – 43.)

- Declining discovery rates of new antibiotics (Lewis, 2013).

- Metagenomic approaches to explore unculturable species (Handelsman, 2004).

- Synthetic biology for engineering novel metabolites (Zhang et al., 2017).

CONCLUSION

Soil actinomycetes are vital to ecosystem functioning and represent a rich and underexplored resource for applied science and biotechnology. Their ecological roles in nutrient cycling and soil health, combined with their capacity to produce a wide range of bioactive metabolites, underscore their significance in pharmaceutical development, sustainable agriculture, and environmental remediation. Advances in omics technologies, genome mining, and improved cultivation strategies have substantially enhanced the exploration of their metabolic diversity. Moreover, the application of genetic engineering and synthetic biology tools has enabled the activation of silent biosynthetic pathways, opening new avenues for novel compound discovery. Continued interdisciplinary research integrating microbiology, bioinformatics, and biotechnology will be essential to fully exploit the potential of soil actinomycetes and to develop innovative solutions to emerging challenges in health, agriculture, and environmental sustainability.

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