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Streptomyces: Sources of Novel Discoveries in Antibiotic Research to Combat Antimicrobial Resistance

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Abstract

Antimicrobial resistance (AMR) is one of the most serious challenges to global public health this century. The first World Health Organization (WHO) Global report on AMR surveillance, published in April 2014, collected data for the first time from national and international surveillance networks, demonstrating the extent of this phenomenon in many parts of the world as well as the presence of significant gaps in existing surveillance. Given the rising reporting of multi-resistant bacteria and the shortage of newly licensed treatments, researchers have started looking into severe and uncommon conditions as a new supply of antibiotics. Streptomyces, a genus of gram-positive, filamentous bacteria, represents a cornerstone of natural product discovery in antibiotic research. Streptomyces species are well-known for their ability to create a wide range of bioactive secondary metabolites, including more than two-thirds of therapeutically useful antibiotics. This paper explores the biological and genomic characteristics of Streptomyces, their role in natural product biosynthesis, and recent advancements in leveraging these organisms for novel antibiotic discovery. We also discuss the challenges in addressing antibiotic resistance and strategies for maximizing the potential of Streptomyces through modern biotechnology. Antimicrobial resistance (AMR) has emerged as one of the most serious public health issues of the twenty-first century, threatening the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi that are no longer susceptible to the common antibiotics used to combat them.

Keywords: Streptomyces; Novel Antimicrobials; Antimicrobial Resistance; Antibiotic Discoveries; Novel Drugs; AMR

Abbreviations

PKS: Polyketide Synthase Pathways; RiPPs: Ribosomally Synthesized and Post-Translationally Modified Peptides; NRPS: Non-Ribosomal Peptide Synthetase Pathways; BGCs: Biosynthetic Gene Clusters; WHO: World Health Organization; LPSN: List of Prokaryotic Names; DNA: Deoxyribonucleic Acid.

Introduction

Research is primarily focused on the resistance of many pathogenic bacteria and fungi to bioactive secondary metabolites in common use, and novel antifungal and antibacterial compounds are required to combat these pathogens [1-3]. The rise of antibiotic resistance has created an urgent need for novel antimicrobial agents. *Streptomyces*, first described in 1943 with the discovery of streptomycin, have been central to antibiotic innovation. These soil-dwelling actinobacteria are characterized by their complex life cycle, production of aerial mycelia, and capacity for synthesizing structurally diverse secondary metabolites [4]. The genus is a prolific source of antibiotics, antifungals, immunosuppressants, and anticancer agents, making it a focal point for pharmaceutical research. The World Health Organization (WHO) has classified antimicrobial resistance (AMR) as one of the top 10 hazards to human health, declaring it a global health emergency [5]. Antibiotic-resistant bacteria

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were directly responsible for 1.27 million fatalities in 2019 and were linked to 4.95 million deaths. Addressing the situation requires creating new medicines and expanding access to both new and old treatments. However, despite increased financing and focus on AMR, the global response is not on track [5,6].

Biological and Genomic Characteristics of *Streptomyces*

The genomes of *Streptomyces* are unusually large for bacteria, typically ranging from 8 to 10 Mbp, and harbor a high GC content. These vast genomes encode an abundance of biosynthetic gene clusters (BGCs) responsible for secondary metabolite synthesis [7]. Advanced sequencing technologies have revealed that many of these BGCs are "cryptic," meaning their products remain unknown under standard laboratory conditions, suggesting a vast untapped reservoir of bioactive compounds. *Streptomyces* are filamentous, Gram-positive bacteria that are members of the Actinobacteria phylum [8]. According to Kampfer, multicellular life cycles involve the transformation of a vegetative mycelium into the reproductive spores required for dispersion [9]. Furthermore, with 685 species with valid published names (827 species including synonyms, LPSN data), it is the largest genus of prokaryotes [8,9].

According to Flardh and Buttner and van Dissel, et al. *Streptomyces* species begin their life cycle with spore germination, which is followed by the formation of vegetative mycelia, which includes tip extension and the commencement of new branches [10]. Then, morphological differentiation and secondary metabolite production are triggered by cues such as nutrition deprivation [10-12]. *Streptomyces* included a large number of genes implicated in this intricate developmental process, including bld genes connected to aerial mycelium deficit [13], whi genes connected to spore formation [14], ram genes linked to hydrophobic protein synthesis [14,15], and ssg genes associated with sporulation-specific cell division [15].

Secondary Metabolite Production

Historical Contributions

Streptomyces species have contributed to the discovery of iconic antibiotics, such as streptomycin, tetracycline, erythromycin, and vancomycin. These compounds target diverse bacterial pathways, including protein synthesis, cell wall biosynthesis, and DNA replication, underpinning their therapeutic importance [16,17]. Medicine, agriculture, and biotechnology are just a few of the disciplines that have historically benefited greatly from the research and application of secondary metabolite synthesis [18]. Different from primary metabolites, secondary metabolites are organic substances that are not straight engaged in an organism's steady development, growth, or reproduction but often have ecological purposes including competition, signaling, or defense [19,20]. Alexander Fleming's discovery of penicillin in 1928 was a significant step in secondary metabolite research [20]. Penicillin, a secondary metabolite produced by the fungus *Penicillium notatum*, ushered in the antibiotic era, saving countless lives by treating bacterial infections [21]. Streptomycin, discovered in 1944 by Selman Waksman from *Streptomyces griseus*, was the first effective treatment for tuberculosis and expanded the known applications of secondary metabolites [22]. Secondary metabolites like paclitaxel (Taxol), derived from the Pacific yew tree (*Taxus brevifolia*), and doxorubicin, an anthracycline antibiotic from *Streptomyces* species, have become essential in cancer therapy. The discovery of cyclosporine, a secondary metabolite from the fungus *Tolypocladium inflatum*, revolutionized organ transplantation by preventing graft rejection [22,23] (Figure 1).

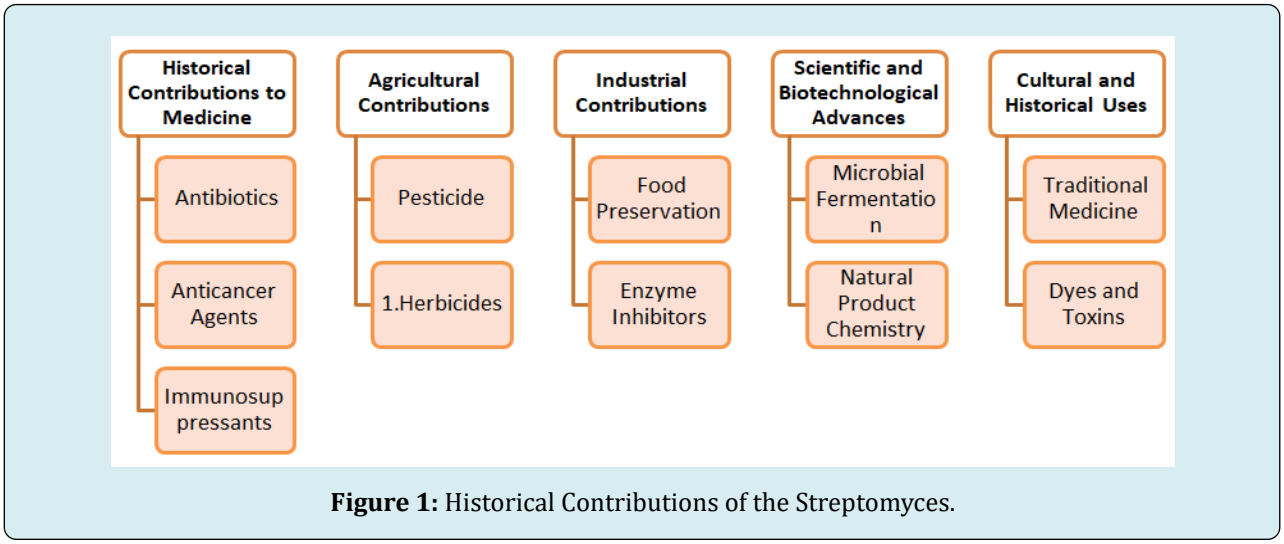

Figure 1: Historical Contributions of the Streptomyces.

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Ongoing advancements in genomics and artificial environmental science have prolonged our capacity to engineer secondary metabolite production [24]. This historical foundation has positioned secondary metabolites as a cornerstone in developing new therapeutics, sustainable agriculture, and industrial bioprocesses [24,25].

Their role underscores the intersection of natural product discovery and innovation in addressing global challenges.

Mechanisms of Biosynthesis of Antimicrobial Compounds by *Streptomyces*

Streptomyces is renowned for producing a wide array of antimicrobial compounds through complex biosynthetic pathways [25,26]. These secondary metabolites, including antibiotics like streptomycin, erythromycin, and tetracycline, are synthesized via tightly regulated enzymatic mechanisms encoded in biosynthetic gene clusters (BGCs). Biosynthesis of antimicrobial compounds by *Streptomyces* includes following major pathways:

Polyketide Synthase (PKS) Pathways: Polyketides, such as erythromycin, are synthesized by modular or iterative PKS enzymes. These enzymes catalyze the stepwise condensation of acyl-CoA precursors, leading to the assembly of diverse carbon skeletons [27]. Post-assembly tailoring steps, such as glycosylation and oxidation, enhance the bioactivity and specificity of the compound.

NRPS (Non-Ribosomal Peptide Synthetase Pathways): NRPs like vancomycin and actinomycin are assembled by NRPS enzymes [28]. These large, multifunctional proteins incorporate amino acid building blocks through an assembly line process involving activation, condensation, and modification [28].

Hybrid PKS-NRPS Pathways: Some antimicrobial compounds, such as rifamycin, are synthesized through a combination of PKS and NRPS systems, leveraging the diversity of both pathways for structural complexity [27-29].

Ribosomal Synthesized and Post-Translationally Modified Peptides (RiPPs): *Streptomyces* also produces RiPPs like lantibiotics [30]. These compounds are initially synthesized as precursor peptides by ribosomes and then enzymatically modified to form mature bioactive structures.

Regulation and Resistance: Biosynthesis is tightly regulated by transcriptional regulators and environmental cues [31]. Self-resistance mechanisms, such as target modification or efflux pumps, ensure the producing strain is not harmed by its own antibiotics.

By leveraging these sophisticated biosynthetic pathways, *Streptomyces* generates structurally and functionally diverse antimicrobials, contributing significantly to medicine and biotechnology [32,33]. Advances in genomics and metabolic engineering continue to uncover and enhance the antimicrobial potential of *Streptomyces* [34] (Figure 2).

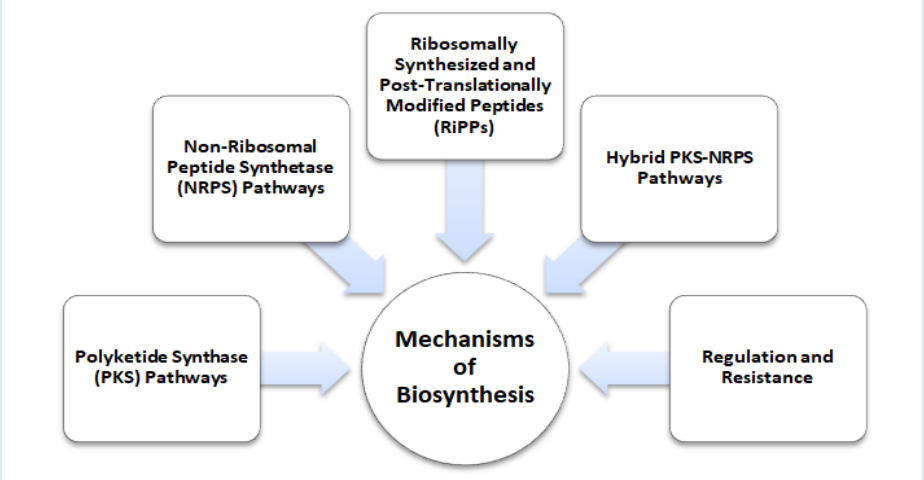

Figure 2: Biosynthesis of Antimicrobial Compounds by Streptomyces.

Strategies for Novel Antibiotic Discovery

Streptomyces is a prolific antibiotic producer, accounting for more than two-thirds of all therapeutically relevant natural antibiotics [35]. However, discovering novel antibiotics requires innovative strategies due to the challenges of rediscovery and resistance. The following approaches are commonly employed:

Genome Mining: Unexplored Biosynthetic Gene Clusters (BGCs); Advances in sequencing technologies have revealed

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that *Streptomyces* genomes harbor numerous "cryptic" or "silent" BGCs that are not expressed under standard laboratory conditions [36]. Platforms like AntiSMASH and PRISM predict potential secondary metabolites from genomic data, guiding targeted discovery efforts. Cloning and expressing silent BGCs in heterologous hosts or through CRISPR/Cas-based activation can lead to the production of novel antibiotics [37].

Environmental and Niche Exploration: Isolating *Streptomyces* from unique environments (e.g., deep-sea sediments, arid soils) increases the likelihood of finding novel compounds [38]. Culturing under stress, co-culture with competing microbes, or nutrient-limited environments can activate dormant BGCs, leading to the discovery of new metabolites.

High-Throughput Screening (HTS): Screening vast *Streptomyces* libraries for bioactivity against drug-resistant pathogens using automated HTS platforms enables rapid identification of promising candidates [39].

Metabolomics: Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR) techniques detect and characterize novel metabolites directly from cultures [40]. Comparing metabolic profiles under different conditions can uncover unique bioactive compounds.

Resistance-Guided Discovery: Leveraging *Streptomyces*' inherent resistance mechanisms helps identify novel antibiotics designed to evade known resistance pathways [41]. Identifying compounds that inhibit unexplored bacterial targets increases the novelty of the discovered antibiotics [42].

Machine Learning and Artificial Intelligence: AI models analyze large datasets, including genomic, metabolomic, and environmental data, to predict potential new antibiotics and guide experimental efforts [43].

Collaborative and Open-Source Approaches: Collaborative platforms like crowdsourced antibiotic discovery programs pool resources and knowledge to accelerate the discovery of new compounds [44]. By combining these strategies, researchers aim to unlock the untapped potential of *Streptomyces*, addressing the urgent need for novel antibiotics to combat rising antimicrobial resistance [45,46] (Table 1).

S.N.	*Streptomyces* sp.	Name of Antibiotic
1.	*S. orchidaccus*	Cycloserin n
2.	*S. orientalis*	Vancomycin
3.	*S. fradiae*	Neomycin, Actinomycin, Fosfomycin, Dekamycin
4.	*S. nodosus*	Amphotricin B
5.	*S. noursei*	Nystatin
6.	*S. mediterranei*	Rifampin
7.	*S. griseus*	Streptomycin
8.	*S. knanamyceticus*	Kanamycin
9.	*S. tenebrarius*	Tobramycin
10.	*S. spectabilis*	Streptomycin
11.	*S. viridifaciens*	Tetracyclin
12.	*S. lincolensis*	Lincomycine, clindamycin
13.	*S. rimosus*	Oxytetracyclin
14.	*S. erythraeus*	Erythomycin
15.	*S. vensuella*	Chloramphenicol
16.	*S. aureofaciens*	Chlotetracycline, dimethychlor
17.	*S. ambofaciens*	Spiramycin
18.	*S. avermitilis*	Avermicin
19.	*S. elboniger*	Puromycin

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20.	*S. niveus*	Novobicin
21.	*S. platenisi*	Platenmycin
22.	*S. roseosporus*	Daptomycin
23.	*S. ribosidificus*	Ribostamycin
24.	*S. garyphalus*	Cycloserine
25.	*S. vinaceus*	Viomycin
26.	*S. davuligerus*	Cephalosporin

Table 1: A compilation of antimicrobial compounds that produced by Streptomyces species.

Challenges in Antibiotic Discovery

In the process of developing an antibiotic, discovery and exploratory research are crucial since they allow for the identification of novel chemical classes and biological targets [47]. The vast majority of antimicrobial compounds discovered have insufficient biological activity, toxicity issues, or unfavorable pharmacokinetics for development into a drug, making discovery and exploratory research highly challenging. More "push" funding for early-stage research has been called for (mostly by small teams in the public, corporate, and not-for-profit sectors) [48]. Many national and international public and philanthropic funding organizations give financing for this field. However, the entire attrition rate and the first difficulties in completing effective early-stage research have been anticipated to necessitate an additional global expenditure of $250 million to $400 million per year. It's possible that policymakers are misjudging who could be best positioned to succeed as well as why current attempts to research and develop new antibiotics have failed [49]. One frequently given explanation for the dearth of new antibiotics is that big Pharma and other institutions are not very interested in conducting antimicrobial discovery research and development because the potential profits from these drugs do not provide a high enough return on investment to warrant the risk and expenditure. Thus, several businesses have stopped researching and developing antibiotics [50,51].

Because of this lack of business interest, politicians are concentrating on financial and regulatory tools to stop big pharmaceutical companies from leaving, particularly through "pull" incentives [52,53]. However, pull incentives do not address the barriers to early-stage research and the high attrition rates that follow from them. They aim to replicate the predicted earnings that firms typically obtain for new medications under patent.

Overcoming Challenges in Antibiotic Discovery

Despite their promise, several challenges hinder the exploitation of *Streptomyces*. The rediscovery of known compounds, limited scalability of some natural products, and regulatory hurdles complicate the pipeline from discovery to clinical use. Addressing these challenges requires integrated efforts across genomics, chemistry, and pharmaceutical development.

Conclusion

Streptomyces is still an important source of antibiotics and other bioactive chemicals, providing hope in the fight against antibiotic-resistant infections. The integration of traditional microbiological techniques with cutting-edge genomic and synthetic biology approaches promises to unlock the full potential of these organisms. Continued investment in Streptomyces research will not only yield novel antibiotics but also advance our understanding of microbial ecology and natural product biosynthesis.

CRediT Authorship Contribution Statement

NS, NS contributed to data collection; conceptualization; NS, AS, DD concept designing; review; drafting; conceptualization, writing manuscript.

Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this review. All data discussed are cited from published sources available in the referenced literature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

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