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Production of secondary metabolites in Streptomyces and their impact in biotechnology: A Systematic Review Protocol

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Abstract

Actinobacteria are recognized for their ability to produce diverse secondary metabolites with significant pharmaceutical and industrial value. Streptomyces is traditionally viewed as the most prolific genus, yet recent genomic studies suggest that other Actinobacteria may possess important but underexplored biosynthetic capacities. This systematic review aims to compare the production, diversity, and applications of secondary metabolites from Streptomyces and other Actinobacteria.

The review will search PubMed and Scopus for experimental, observational, and computational studies published within the last ten years. Selected articles will be screened by two independent reviewers, and relevant data (such as metabolite types, biosynthetic gene clusters, yields, biological activities, and biotechnological applications) will be extracted into a standardized table. The methodological quality of each study will also be evaluated.

The collected data will be synthesized qualitatively, and quantitative comparisons will be considered when sufficient comparable information is available. The results will provide an updated overview of the biosynthetic potential of Actinobacteria and help identify genera with promising value for future biotechnological development.

Objectives

1 Primary Objective: To determine, based on available scientific evidence, whether the genus Streptomyces produces a greater number and diversity of high-potential secondary metabolites than other Actinobacteria.

2 Secondary Objectives:

2.1 To identify and characterize the main classes of secondary metabolites produced by Streptomyces and other Actinobacteria (antibiotics, antifungals, antitumor agents, immunosuppressants, industrial enzymes, etc.).

2.2 To compare the diversity, yield, and bioactivity of metabolites derived from Streptomyces with those produced by other genera of Actinobacteria.

2.3 To evaluate the biotechnological applications of Streptomyces-derived metabolites in medical, pharmaceutical, agricultural, environmental, and industrial sectors.

2.4 To analyze the technological approaches and tools used to enhance secondary metabolite production in Streptomyces (metabolic engineering, activation of silent gene clusters, genome mining), and compare them with those applied to other Actinobacteria.

2.5 To identify limitations, methodological challenges, and opportunities for improvement in the biotechnological exploitation of Actinobacteria for novel secondary metabolite discovery.

2.6 To provide an up-to-date synthesis of knowledge to guide future research and industrial strategies aimed at maximizing the production and diversity of metabolites of biotechnological interest.

Research Question (PICO)

3 Does the exploitation of Streptomyces yield more high-potential metabolites than other Actinobacteria?

Eligibility Criteria

4 In order to obtain scientific articles dealing exclusively with our subject, we have determined eligibility criteria for the parameters presented below:

	Inclusion criteria	Exclusion criteria
Population	Bacteria in the actinobacteria familia	-
Intervention	The study investigates the production, regulation, optimization, identification, or valorization of secondary metabolites produced by *Streptomyces*.	Studies addressing general bacterial physiology without any connection to biosynthetic pathways, metabolite regulation, or specialized metabolites.

Information Sources

5 For the collection of our data, we will conduct our searches on databases such as PubMed, Science Direct, Scopus and Google Scholar (in order to reduce publication bias).

Search Strategy

6 To identify relevant data, a search strategy was built from the PICO and the following keywords: “Streptomyces”, “Actinobacteria”, “secondary metabolites”, “bioactive compounds”, “antibiotics”, “biotechnology”, “industrial application”, “valorization”. The queries are adapted to each database:
PubMed
Combination of MeSH terms and free-text keywords: ("Streptomyces"[MeSH Terms] OR Streptomyces[Title/Abstract] OR "Actinobacteria"[MeSH Terms] OR Actinobacteria[Title/Abstract]) AND ("Metabolites, Secondary"[MeSH Terms] OR "secondary metabolites"[Title/Abstract] OR "Bioactive Compounds"[MeSH Terms] OR "bioactive compounds"[Title/Abstract] OR antibiotics[MeSH Terms] OR antibiotics[Title/Abstract]) AND ("Biotechnology"[MeSH Terms] OR biotechnology[Title/Abstract] OR "industrial application"[Title/Abstract] OR valorization[Title/Abstract])
Scopus/Science Direct
Keywords combined with Boolean operators: TITLE-ABS-KEY(Streptomyces OR Actinobacteria OR actinomycetes) AND ("secondary metabolites" OR "bioactive compounds" OR antibiotics OR antifungals) AND (biotechnology OR "industrial application" OR valorization OR pharmaceutical)
This approach makes it possible to find all articles dealing with the link between the production of secondary metabolites by Streptomyces and their applications in biotechnology.

Study Screening / Selection

7 After the articles are collected, a rigorous screening process is carried out. First, the titles and abstracts are analyzed to exclude irrelevant studies based on the research

question. Next, the selected articles are read in full to verify that they meet the inclusion and exclusion criteria. Finally, two independent reviewers complete these steps to minimize bias. This sorting and selection step is carried out using the Ryyan tool, which facilitates the classification, comparison and validation of the selected articles in a collaborative and transparent manner.

Data Extraction

8 All the data we retain from the selected articles, as described in the previous step, will be compiled in an Excel spreadsheet. This format seems to us to be easy to manipulate while ensuring efficient data collection. Furthermore, for each study, we will extract the specific strains of the genus Streptomyces studied, the experimental conditions used, the diversity and yield of secondary metabolites, as well as the applications found for these products. This data will be compared with that of other types of bacteria in the phylum Actinobacteria. In addition, we will include the study's specific characteristics, such as the authors' names, the year, and even the journal of publication for each study. Two people will be responsible for data collection, and a third person will be involved in case of discrepancies.

Risk of Bias

9 Given that several study designs are to be included in our systematic review, as defined earlier in the inclusion criteria, it is necessary to assess the methodological quality of each study according to its classification. The quality of observational and descriptive laboratory studies will be assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional analytical studies. The STREGA checklist will be used to assess data transparency, the validation of computational predictions, and the reproducibility of the workflows used. Based on these analyses, the studies will be ranked according to their quality and organized in a table. This step will be carried out by two systematic reviewers, and a third person will be involved to resolve any discrepancies in assessment.

Data Synthesis

10 Once the data extraction process is completed, the collected information will be analyzed and synthesized in a structured and methodical way. Given the diversity of study types included in this review (experimental, metabolomic, genomic, and computational studies), the synthesis will primarily be qualitative.
First, the extracted variables—such as the types of secondary metabolites identified, their biosynthetic pathways, yield levels, biological activities, and biotechnological applications—will be grouped into thematic categories. These categories will allow us to highlight similarities and differences between Streptomyces and other Actinobacteria.

Second, comparative tables will be constructed to organize the data and facilitate interpretation. These tables will include information on metabolite diversity, the number and types of biosynthetic gene clusters identified, the optimization strategies used, and the applications reported.
If the amount and nature of available data permit numerical comparison (for example, standardized yield measurements or activity values such as MIC or IC_{50}), a quantitative synthesis may be conducted. However, a formal meta-analysis will only be performed if sufficient homogeneity in the reported outcomes is observed.
Finally, the results will be summarized in descriptive form, supported by tables, charts, and conceptual diagrams when appropriate. This approach will enable a clear evaluation of the biosynthetic potential of Streptomyces compared to other Actinobacteria, as well as an assessment of their relative contributions to biotechnological innovation.