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MINI REVIEW

Challenges to Explore Genus *Streptomyces* in Ethiopia-A Mini Review

Endeshaw Abatneh*

Department of Biotechnology, College of Biological and Chemical Engineering, Addis Ababa Science and Technology University, P.O Box 16417, Addis Ababa, Ethiopia

ABSTRACT

Genus *Streptomyces* is gram-positive bacteria that grow in various environments. It has plentiful biotechnological attributes on the area of agricultural, bioremediation, biofuel, clinical, food, industrial, medical, pharmaceutical, and veterinary. The aim of the review is to frontward challenges to explore potent *Streptomyces* species in the case of Ethiopia. There is lack of the extent and quality of the genetic research regarding to genome sequence, bioactive compound discovery, and genetic manipulation. Their functional and structural diversity is not full studied. To find a new *Streptomyces* species: Culture media formulation and optimization as wells culture-independent method like Next Generation Sequencing approach should incorporate at national level.

***Corresponding author**

Endeshaw Abatneh, Department of Biotechnology, College of Chemical and Biological Engineering, Addis Ababa Science and Technology University, Addis Ababa, Ethiopia

E-mail: endeshewab@gmail.com

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INTRODUCTION

Genus *Streptomyces* is gram-positive bacteria that grow in various environmental conditions. They're ecologically diverse in nature. It found inside plant tissue as endophytic form of life [1] and soil samples [2]. *Streptomyces* represents the largest taxonomic group within the bacteria domain which is ubiquitously distributed in both aquatic and terrestrial ecosystems [3]. The genus Streptomyces is the most prominent family Streptomycetaceae (order Actinomycetales), which comprises more than 700 species. They are Gram-positive, neutrophilic, facultative aerobic, mesophilic filamentous bacteria, with a growth temperature between 25 and 35°C, whose DNA has a G + C content higher than 70% [4].

Species of the genus Streptomyces, which constitute the vast majority of taxa within the family Streptomycetaceae, are a predominant component of the microbial population in soils throughout the world and have been the subject of extensive isolation and screening efforts over the years because they are a major source of commercially and medically important secondary metabolites. Some of species are *Streptomyces galbus, Streptomyces longwoodensis, Streptomyces canaries, Streptomyces chibaensis, Streptomyces corchorusii, Streptomyces olivaceoviridis, Streptomyces caeruleatus, Streptomyces lincolnensis, Streptomyces antibioticus, Streptomyces griseoruber, Streptomyces acidiscabies, Streptomyces alanosinicus, Streptomyces bambergiensis, Streptomyces cyanoalbus, Streptomyces emeiensis, Streptomyces hirsutus, Streptomyces prasinopilosus, Streptomyces prasinus, Streptomyces griseorubiginosus, Streptomyces phaeopurpureus, Streptomyces canus, Streptomyces ciscaucasicus, Streptomyces lucensis, Streptomyces niveoruber, Streptomyces durhamensis, Streptomyces filipinensis, Streptomyces puniciscabiei, Streptomyces lanatus, Streptomyces psammoticus, Streptomyces recifensis, and Streptomyces ederensis* [5].

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Genus *Streptomyces* produce aerial hyphae that divide, producing spores that can resist unfavourable conditions and are easily dispersed to new environments or sources of nutrients. During this growth phase *Streptomyces* produce secondary metabolites: compounds that are not strictly necessary for growth or reproduction, but can give the organism a competitive advantage [6].

Streptomyces has made a massive contribution to the field of medicine, not only through antibacterial antibiotics, but also through antifungal, antiparasitic and anticancer compounds. The new source of *Streptomyces* can also help to replenish of emergency antibiotics to combat multi-resistant pathogens. Genus Streptomyces isolated from the terrestrial or aquatic environments are responsible for the highest share (in terms of novelty and frequency) of antimicrobial substance production [7].

Novel screening techniques and investigating new sample sources from underexplored habitats has remarkable advantage to explore potential *Streptomyces* strains. Exploring new habitats around the globe is increasingly becoming the focus for discovering new Streptomyces's [8].

The situation of *Streptomyces* exploration is little done. Three antibiotic producing Actinomycetes isolates were obtained from potential soil samples of Gondar town, Ethiopia. That crude extracts have been shown antagonistic activity against *Klebsiella pneumonia* ATCC7000603, *Escherichia coli* ATCC25922, Methicillin Resistant *Staphylococcus Aureus* Strains 2 (MRSA2) and MRSA4 [9]. In Ethiopian context, Activity profiles of the crude extracts from selected *Streptomyces viridochromogenes* DSM 40736, *Streptomyces* sp. XY006, *Streptomyces chartreusis* NRRL 12338, Streptomyces vitaminophilus DSM 41686, Streptomyces africanus DSM 41829 against *C. albicans, C. neoformans, S. aureus, B. subtilis, E. coli, S. typhimurium, S. boydi* were verified [10].

On this planet, Ethiopia is a mega diversified country and center of origin [11,12]. But, Streptomyces diversity is not well-studied when compare with European. There is scientific information asymmetry. This mini-review intends to consider challenges and to fill gaps. The aim of this short-review is to insight application of genus *Streptomyces* in many sectors and to forward challenges to explore novel *Streptomyces* species in Ethiopia.

SOME BIOTECHNOLOGICAL BENEFITS OF GENUS *STREPTOMYCES*

Streptomyces as antibiotic producer

The production of most antibiotics is species specific, and these secondary metabolites are important for *Streptomyces* species in order to compete with other microorganisms cause for deaths. The world's demand for antibiotics is steadily growing because they are "miracle drugs" [13].

Streptomyces currently provides many of the world's clinical antibiotics, the contribution of *Streptomyces* to antibiotics and the potential of newly discovered species in traditional medicine. Clinically and economically important bioactive molecules from *Streptomyces* species have role on Broad-spectrum antibiotic against urinary tract infections, antibacterial, antifungal, antiparasitic, antitumor and immunosuppressive [14,15]. The most interesting characteristics of *Streptomyces* is the ability to produce bioactive secondary metabolites such as antifungal, antiviral, antitumor, antihypertensive, antibiotics and immune-suppressive [16].

Streptomycin is product of *Streptomyces griseus* originating from heavily manured compost soil and another from a chicken gizzard [17]. As Quinn, et al. [18] reviewed *Streptomyces* are sources of new innovations in antibiotic discovery. *Streptomyces hygroscopicus* (Herbicide), *Streptomyces verticillus*'(Anticancer), *Streptomyces venezuelae*(Antibiotic), *Streptomyces cinerochromogenes* (Inhibits adipocyte differentiation of 3T3-L1 cells via Kruppel-like factors 2 and 3) *Streptomyces clavuligerus*, (β-lactamase inhibitor), *Streptomyces roseosporus* (Lipopeptide antibiotic), *and Streptomyces noursei* (Antifungal) from several regions of the world.

Streptomyces are better known as prolific producers of commercially, important clinical antibiotics [9]. They are the source of most clinically used antibiotics, as well as of several widely used drugs against common diseases. The production of novel pharmaceuticals: Gentamycin [19] and Thiostrepton [20] from Streptomyces species. One of these compounds is Platensimycin, a new class of antibiotic from *Streptomyces platensis* that selectively inhibits cellular lipid biosynthesis. This was discovered by the Merck group [21].

This is believed to be a new strain of *Streptomyces sioyaensis* that has strong antimicrobial activities against both human and plant pathogens, including an antibiotic-resistant pathogen, *Staphylococcus haemolyticus* MR-CoNS [22]. Tuberculosis is one of the leading causes of mortality produced by an infectious agent. *Streptomyces coelicolor* suggested *as* a live vector immunization to induce a protective response against mycobacterial *tuberculosis* H37Rv and *Mycobacterium bovis* AF2122/97 [23].

Streptomyces as plant growth-promoting bacteria

Streptomyces have a role as plant growth-promoting bacteria. Bio-inoculation of Streptomyces on plants has a positive result on plant heights, leaf volume, roots volume, and stem weights [24]. Plant Growth Promoting Rhizobacteria affects the plants fitness and growth in two different manners, which are directly or indirectly. While PGPR are able to trigger plant growth by mobilizing nutrients in soils or producing numerous growth regulators, they protect plants from plant pathogens either by controlling invaders or by triggering plant defense mechanisms. Colonization of plant roots by PGPR can induce a systemic resistance in plants [25].

Streptomyces sampsonii KP096298, *Streptomyces cavourensis* NR_112345.1, *Streptomyces olivochromogenes* KF317983, *Streptomyces pseudovenezuelae* NR_114832.1, *Streptomyces spectabilis* NR_112398.1, *Streptomyces albidoflavus* NR_041095.1, *Streptomyces misionensis* NR_044138.1, *Streptomyces rishiriensis* NR_112392.1, and *Streptomyces peucetius* NR_112574.1 strains were positive for IAA production, siderophore production, and HCN production. There is a significant enhancement was observed with the length of the root and shoot as well as weight of the fresh plant when compared to the control. The integrated application Plant Growth Promoting Streptomyces from the rhizosphere of oilseed rape is a promising strategy to improve the growth of oilseed rape [26].

Streptomyces corchorusii strain UCR3-16 was exhibited significant bio-control potential against important rice fungal pathogens showing highest inhibition against *Rhizoctonia solani* [27]. The strain able to enhance the growth of rice plants even under pathogen challenged conditions. The strain could be a promising agent for development as bio-fertilizers [28].

Streptomyces species are effective biocontrol agents toward many plant pathogens. These microorganisms are well known for producing secondary metabolites, promoting plant growth and inducing plant defense mechanisms. *Streptomyces globisporous* (Krasil'nikov) strain F8 and *Streptomyces praecox* (Millard and Burr) strain R7 were able to enhance the expression of lipoxygenase and phenylalanine ammonia lyase in tomato plants. It revealed an induced defense status in Tomatoes against *Rhizoctonia solani* [29].

Biocontrol activities of *Streptomyces kasugaensis* (Provoked effects on *Fusarium* spp.), *Streptomyces sanglieri* (Elicited *Ganoderma boninense*) *Streptomyces felleus* YJ1 (Triggered effects on *Sclerotinia sclerotiorum*). Plant growth-promoting activities of *Streptomyces anulatus* S37 (Elicited effects on Grapevine), *Streptomyces mutabilis* (Caused effects on Wheat), *Streptomyces fumanus* gn-2 (Stimulated effects on Soybean) were reported through intensive empirical literature reviewed [30].

Streptomyces as a source of industrial enzymes

Microbial enzymes play a key role as metabolic catalysts, leading to their diverse applications and use in various industries such as detergent, paper and pulp, textile, pharmaceutical, leather, food, beverage, and pharmaceutical. *Streptomycetes* were identified from the extreme environments are known to be producers of novel enzymes with great industrial potential. Wide ranges of enzymes were produced by *Streptomycetes species.* Some of enzymes applied in different industries are cellulases, proteases, amylases, lipases, xylanases, chitinases, cutinases and pectinases [31].

Streptomyces lividans is a frequently used platform for industrial enzyme (Xylanase and Amylase) production and a rational strain-development approach delivered significant improvement of protein production by this host. Xylanase from *Streptomyces halstedii*, A-amylase from *Streptomyces griseus*, and Laccase from *Streptomyces coelicolor* were extracted [32].

Streptomyces as a biosynthesis of secondary metabolites

The genus Streptomyces alone accounts for approximately 75% of all bioactive compounds, including antibiotics. The ability of this genus to produce antibiotics and other secondary metabolites has been an evolutionary advantage, facilitating its adaptation to different and variable stress situations. In addition, the diversity of their metabolism has given them the ability to colonize different habitats and use varied carbon and nitrogen sources [33].

It is known that actinobacterial sources are estimated as about 45% of all microbial bioactive metabolites with 7,600 of these compounds (80%) being produced by the Streptomyces species [34]. Hence, actinobacteria are a rich and tremendous source for screening of novel metabolites with potential pharmaceutical applications [35].

Streptomyces strains have a broad spectrum of antibiotics, Volatile Organic Compounds (VOC), which act against pathogens, disrupting bacterial cell-cell communication (quorum sensing), and a variety of enzymes that degrade the cell wall of fungi [36].

The biological roles of Volatile Organic Compounds (VOCs) are only now beginning to be analyzed, and initial studies show that they can have wide ranging effects on both their producing organisms and their neighbors. VOCs can alter the antibiotic resistance profiles of bacteria, act as antifungal or antibiotic compounds, promote group behaviors such as motility and biofilm formation, and induce widespread changes in the gene expression of nearby microbes. VOCs can act as signaling molecules that influence gene expression, metabolism, and group behavior of responding microorganisms. Natural products are still referred to promising biotechnological and pharmaceutical agents for development of and potential new drugs [37].

Actinomycete bacteria have a widely recognized potential for the production of bioactive secondary metabolites and valuable enzymes [38]. Streptomycetes usually possess 20–50 gene clusters dedicated to the biosynthesis of secondary metabolites in their genomes, underscoring their potential for the discovery of new bioactive compounds [39]. Most of such clusters remain "silent" in laboratory conditions, but tools are being developed for activation of these genes, thus prompting production of previously undetected compounds [40]. In search for Actinomycetes capable of producing novel bioactive metabolites, it appears especially beneficial to look into extreme habitats and unique environmental niches [41].

In Ethiopian context, Activity profiles of the crude extracts from selected *Streptomyces viridochromogenes* DSM 40736, Streptomyces sp. XY006, *Streptomyces chartreusis* NRRL 12338, *Streptomyces chartreusis* NRRL 12338, *Streptomyces vitaminophilus* DSM 41686, *Streptomyces africanus* DSM 41829 against *C. albicans, C. neoformans, S. aureus, B. subtilis, E. coli, S. typhimurium, S. boydi* [10]. They provided many important bioactive compounds of high commercial value and continue to be routinely screened for new bioactive compounds [42].

Streptomyces as Antimicrobial Resistance(AMR)

Antimicrobial Resistant (AMR) bacteria are a pressing global health concern with dangerous consequences. In recent years, clinically relevant bacteria with Multiple Drug Resistant (MDR) strains with increasing alarming rate of dissemination being reported globally. Apart from the economic cost due to pro-longed hospital stays and the high cost of drugs, MDR bacteria are responsible for clinical failure resulting in high mortality and morbidity rates worldwide. Indiscriminate use and prescription of antibiotics has been reported as factors responsible for the development of resistance in bacterial populations. Bacterial resistance to their unique ability to adapt to changes in their environment and to develop drug resistance mechanisms, such as mutations that protect them against toxic compounds. Bacteria of the genus *Streptomyces* are well known for their prolific abilities to produce antibiotics [43].

Antibiotic resistance is a worldwide problem that can cross international boundaries and spread between continents with ease. Antibiotic resistance results in reduced efficacy of antibacterial agents make the treatment of patients difficult, costly, or even impossible. The impact on susceptible patients is most obvious, resulting in prolonged illness and even mortality. The magnitude of the problem and the impact of Antimicrobial Resistance (AMR) on human health including on costs for the health-care due to AMR still largely need further investigation [44]. Rapid and ongoing spread of antimicrobial-resistant organisms threatens the ability to successfully treat a growing number of infectious diseases [45].

This resistance may be due to genetic changes such as mutation or acquisition of resistance genes through horizontal transfer. Mutations can cause changes at the site of drug action, hindering the action of the antibiotic. The increasing resistance of pathogenic organisms, leading to severe forms of infection that are difficult to treat, has further complicated the situation, as in the case of carbapenem-resistant *Klebsiella pneumonia* [46].

Antimicrobial resistance is a global health crisis and few novel antimicrobials have been discovered in recent decades. Natural products, particularly from Streptomyces, are the source of most antimicrobials, distinct evolutionary lineages of Streptomyces from insect microbiomes as a source of new antimicrobials through large-scale isolations, bioactivity assays, genomics, metabolomics, and in vivo infection models. Insect-associated Streptomyces inhibit antimicrobial-resistant pathogens more than soil Streptomyces. Genomics and metabolomics reveal their diverse biosynthetic capabilities. Further, Cyphomycin is a new molecule active against multidrug resistant fungal pathogens including *Aspergillus fumigatus 11628, Candida glabrata 4720, and Candida auris B11211)* [47].

Streptomyces ceolicolor strain AOBKF977550 their antimicrobial activity against included Methicillin-resistant *Staphylococcus aureus* (Labora-tory strain 144m), *Klebsiella pneumoniae* ATCC 8308, *Gardnerella vaginalis* ATCC 14019, and clinical *Escherichia coli* isolates were observed [48]. *Streptomyces parvulus* strains were exhibited antibacterial activities against multidrug-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* resulted in outcompeting other bacteria through differential antibiotic production [49].

Antibiotic resistance is a global challenge in the public health sector and also a major challenge in Ethiopia. It is truly difficult to report bacterial antibiotic resistance pattern in Ethiopia due to the absence of multi drug resistant clinical Streptomyces species database. The resistance of *M. tuberculosis* for antituberculosis drugs ranges from 0% up to 32.6%. The percentage of resistance increases among previously treated tuberculosis cases. *Neisseria gonorrhea,* S. typhimurium, S. Virchow, Group a Streptococci (GAS), and Group B Streptococci were highly susceptible for most of the tested antibiotics. Methicillin-Resistant *Staphylococcus aureus* was highly resistant to most of the antibiotics with a slightly increased susceptibility to gentamycin [50].

Almost a remarkable resistance was observed here to most of the antibiotics mainly, penicillin G and cotrimoxazole for S. aureus. The Klebsiella spp also show high resistance to ampicillin, tetracycline and cotrimoxazole [51]. Moreover, K. pneumoniae isolates showed a high rate of resistance was observed to cefotaxime, ceftriaxone, trimethoprim-sulfamethoxazole, and cefepime [52]. *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis*,Coagulase-negative *Staphylococcus* species, *Escherichia coli, Klebsiella oxytoca* Bacterial species were most frequently proposed as multi-drug resistant. Drug-resistance of strepomycetes species in the Ethiopian patient population clinical database is still scarce [53].

SOME CHALLENGES TO EXPLORE GENUS *STREPTOMYCES* IN ETHIOPIA

Exploration of new habitats with unusual environment and poorly explored areas of the world has become important and useful for the discovery of novel compounds produced by actinobacteria [54].

In Ethiopia context, there is no well-known evidence finding of from the natural habitat widely. There is scarcity of new antibiotics development. Ethiopian government expenditure high cost to import synthetic drugs from foreign countries annually. It may be the economic impact of Streptomyces genetic research is underestimated.

The potential of streptomycetes to control postharvest bacterial and fungal diseases of cereal crops, pulses, oilseeds, fruits and vegetables is unexplored. It may be the dependency of imported synthetic agro-chemicals used as pesticides

Antibiotic activity, agricultural role, industrial application, phylogeny, biodiversity, abundance, and distribution of Streptomyces were undermined. It may be Streptomyces species responsible for production of new antibiotics against multi-resistance bacteria no related study has been conducted.

There is lack of the extent and quality of the genetic research regarding to genome sequence, bioactive compound discovery, and genetic manipulation. It might be anticipates to loses of antibiotic production genes and many "sleeping" gene clusters for the production of secondary metabolites.

Research on *Streptomyces* genetics has contributed, and continues to contribute to marked improvements in antibiotic productivity, providing significant cost reductions to pharmaceutical companies. But, there is unusual about potential animal health drug discoveries; Development of genome mining; Understanding antibiotic biosynthesis and its regulation; Understanding fundamental aspects of *Streptomyces* physiology; and Commercialization of Streptomyces.

Exploration of *Streptomyces* for agricultural, bioremediation, biofuel, clinical, food, industrial, medical, pharmaceutical, and veterinary is until now intermittent. It may Streptomyces genetic database related to their source, morphology, taxonomy, and physiology is not scientifically documented for further uses. The discovery of novel Streptomyces from different agro-ecological areas is uncommon. It may be drug research and development is expensive, risky, and time-consuming.

Currently, Culture media preparation was incorporated to characterize bacterial at colony level. An extra advanced omics technology is until now confronted universally. It may be create gap with developed nation in terms of studying microorganisms and producing bioactive compounds.

The structural and functional diversity of Streptomyces study is needed for a new generation of novel antibiotics, and extraction of appropriate bioactive compounds. The status and distribution of *Streptomyces species* is not clearly distinguishable. It may be due to lack of specialized team; advanced laboratory equipment; financial source, and good governance strive for microbial studies.

SOME APPROACHES TO EXPLORE A NOVEL STREPTOMYCES SPECIES IN ETHIOPIA

To suggest powerful ways to study genus Streptomyces entirely using different approaches are mandatory. Recent innovations have seen researchers incorporate some native (isolation) material in their media to cultivate antibiotic-producing organisms and to increase their antimicrobial production [55]. They also focus on optimization of medium [56]. Culture media combination were implemented to screen potential antimicrobial agents (includes Streptomyces fulvissimus, Streptomyces cyaneus, Streptomyces antibiaticus, Streptomyces griseoruber, and Streptomyces lovendulae) from Rhizosphere soil sample in Saudi Arabia [57].

Culture media formulation helps to stimulate some strains of *Streptomyces* to increase their antimicrobial production by 12-fold [58]. Alternatively, other researchers have dispensed with intricate media formulations and tried to cultivate antibiotic-producing organisms *in situ* [59].

In developed countries, complete genome sequences of Streptomyces species almost fully understood and preserved in gen-bank [60,61]. The diversity analysis of *Streptomyces sudanensis* was properly investigated in Sudan [8]. *Streptomyces griseus* ATCC 10137 (Y15501), *Streptomyces albidoflavus* DSM 40455T (Z76676), and *Streptomyces coelicolor* A3(2) (Y00411) were identified from water-damaged building, Finland using 16S rDNA [62].

As a result of 16S rRNA gene sequencing *Streptomyces* werraensis, *Streptomyces althioticus*, *Streptomyces griseomycini*, *Streptomyces albogriseolus*, *Streptomyces longispororuber*, *Streptomyces djakartensis*, *Streptomyces rochei*, *Streptomyces fragilis, Streptomyces chromofuscus, Streptomyces leeuwenhoekii*, *Streptomyces carpinensis*, *Streptomyces misionensis*, and *Streptomyces prasinosporus* were confirmed [63].

When come to Ethiopia (Menagesha Suba and Ataye protected forest soil), a few studies on Genome Sequencing and Analyses of Streptomyces was conducted using TruSeq PCR-free sequencing library that was sequenced applying protocol on an Illumina MiSeq system [10], but it is not fully describe the whole nation.

The first systems for applying genome editing to Streptomyces's will soon accelerate the construction of diverse kinds of mutant while the discovery of a CRISPR-Cas system in *Streptomyces avermitilis* may open up new approaches. Along with new strategies for the cloning and deletion of very large segments of *Streptomyces* DNA, sufficient to encompass almost all antibiotic biosynthetic gene clusters [64].

Exploring a novel antibiotics, bio-fertilizer, bio-control agent, and industrial enzymes is not impossible, but it is a complex and challenging area of research. In our nation, a few research papers were conducted on the screening, identifying, and characterizing of Streptomyces conventionally. To analyze *Streptomyces* community, to find novel species, and to scale up the nation economy the following options should conveyed: Using Culture Dependent by optimization and formulation of culture media; Using Next Generation Sequencing; and Metabolic Engineering of *Streptomyces* (i.e improvement of cellular activities through the manipulation of enzymatic, transport and regulatory functions of the cell via recombinant-DNA technology).

CONCLUSION

Ethiopia has a plentiful microbial genetic resource. Isolation, identification and characterization of microorganisms using culture dependent techniques are not enough to generalize genetic make-up, metabolic profiles and bioactivity of *Streptomyces* spp. Over all, to utilize genus *Streptomyces* for new antibiotics fabrication against multiple drug-resistant pathogen's and production of useful bioactive compounds more attention is needed to explore at a taxonomic unit level using modern approaches rather than conventional methods.

RECOMMENDATIONS

I would like to suggest more attention to genomics, proteomics, metabolomics, and transcriptomics types of modern skills has allowed for more efficient to study and exploit its benefits exhaustively. Ex-situ conservation and preservation practices should implement. Finally, Insinuation of genus Streptomyces on the area of probiotics and climate change mitigation should investigate.

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