Review Article

JHSMR Journal of Health Science and Medical Research

Comprehensive Review of a Particularly Intriguing Bacterial Genus, *Streptomyces*: Traits and Antimicrobial Potential

Mohammed Abu Sayeed, M. Pharm Thesis, Ph.D. candidate[1,2],
Mohammad Arman, M. Pharm thesis[1], Israt Jahan, M. Pharm thesis[1],
Md. Abdul Mojid Mondol, Ph.D., Postdoc[3]

[1]Department of Pharmacy, Faculty of Science and Engineering, International Islamic University Chittagong, Kumira, Chattogram 4318, Bangladesh.

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Dhaka, Dhaka 1000, Bangladesh.

[3]School of Science and Technology, Bangladesh Open University, Board Bazar, Gazipur 1705, Bangladesh.

Received 28 March 2025 ● Revised 11 May 2025 ● Accepted 17 June 2025 ● Published online 17 November 2025

Abstract:

This review aimed to thoroughly investigate the changing traits, ecological roles, and current studies pertaining to the soil-dwelling bacteria of the genus *Streptomyces,* which morphologically resemble fungi. These gram-positive bacteria exhibit a filamentous structure and are found in diverse environments, including various types of soil, compost, water, and plant matter. A defining feature of *Streptomyces* is their capacity to synthesize secondary metabolites, particularly antibiotics. They are responsible for producing more than two-thirds of the clinically relevant antimicrobials derived from natural sources, such as chloramphenicol, neomycin, etc. *Streptomyces* are noted for their broad substrate with branches and aerial mycelium. Factors such as carbon and nitrogen sources, oxygen levels, acidity or alkalinity, temperature, ions, and certain precursors can influence antibiotic production. This review also explored different approaches for evaluating the antimicrobial characteristics of *Streptomyces* species. The increasing problem of microbial resistance to traditional antibiotics, along with the difficulties in controlling infectious diseases, has prompted continuous global initiatives to identify new antibiotics.

Keywords: antibiotics, antimicrobial activity, nutritional media, pH, soil, *Streptomyces*

Contact: Mohammed Abu Sayeed, M. Pharm Thesis, Ph.D. candidate
Department of Pharmacy, Faculty of Science and Engineering,
International Islamic University Chittagong, Kumira, Chattogram 4318, Bangladesh.
E-mail: sayeed@iiuc.ac.bd

J Health Sci Med Res 2026;44(3):e20251281
doi: 10.31584/jhsmr.20251281
www.jhsmr.org

Introduction

The major producers of natural bioactive compounds in the world are soil-dwelling bacteria grouped as *Streptomyces*, which are members of the bacterial order *Actenomycete*. They arise as branching filaments of cells which become a network of strands called a *mycelium,* like to some fungi. The introduction of the genus *Streptomyces* can be attributed to the work of Waksman and Henrici in the year 1943[1]. The genus *Streptomyces* is classified within the family Streptomycetaceae[2]. The Streptomycetaceae family is defined by distinct biological and morphological traits, cell wall composition, peptidoglycan type, phospholipid nature, fatty acid structure, GC content, DNA-DNA hybridization, and 16S rRNA analyses[3]. This family is classified under the phylum Actinobacteria and the order Actinomycetales, and contained by the class Actinobacteria, with the genus *Streptomyces* being the only representative[4]. *Streptomyces* is recognized as one of the most extensive taxonomic groups within the Actinomycetes, both in terms of the number and diversity of species identified[5]. These organisms are characterized as aerobic, Gram-positive, non-acid-fast bacteria with a guanine-cytosine (G-C) content exceeding seventy percent (70%)[6]. *Streptomyces* species exhibit the ability to thrive in a variety of environmental conditions[7]. They are known for producing aerial hyphae that form spore chains. To date, over 550 *Streptomyces* species have been identified, with nearly two-thirds of naturally occurring antibiotics derived from them[8].

Methods

An extensive literature search was conducted to gather articles, editorials, and reviews on the characteristics, sources, habitats, and medicinal value of the soil bacterium *Streptomyces*. Seven electronic databases—PubMed, Medline, Scopus, Google Scholar, ResearchGate, ScienceDirect, and Springer Link—were searched for relevant studies, primarily published between January 2005 and December 2024. Search terms included 'antibiotics,' 'antimicrobial activity,' 'nutritional media,' 'pH,' 'soil organisms,' '*Streptomyces* sp.,' 'actinomycete,' 'secondary metabolites,' and 'metabolites.' These terms were used in titles, abstracts, and MeSH keywords, employing Boolean operators to refine the search.

Characteristics of *Streptomyces*

Streptomyces is the largest genus within the phylum Actinobacteria and the representative genus of the Streptomycetaceae family[9]. Over 1,147 *Streptomyces* species (plus 73 subspecies) of *Streptomyces* bacteria have been identified and documented[10]. These Gram-positive, filamentous, chemoorganotrophic bacteria are non-acid-fast and distinct from fungi, despite sharing similar habitats[11]. Their genomes have a high GC content (69–78%)[12] *Streptomyces* filaments and spores are extremely small (≤1 µm)[13], and spore chains can be spiral, undulating, or linear[14]. Colonies grow slowly and emit a characteristic earthy odor due to geosmin[15]. Initially smooth, colonies develop aerial mycelia with floccose, granular, powdery, or velvety textures and produce diverse pigments[16,17]. Figure 1 shows pigment variation of *Streptomyces* colonies grown on different media (SCA, PDA, GAA, NA), displaying typical spherical, wrinkled morphology and a color range including pink, red, white, grey, yellow, and cream. Images were taken after two weeks of incubation at 28 °C[18].

Streptomyces species are nonmotile, catalase-positive, and reduce nitrates to nitrites. They degrade compounds like L-tyrosine, adenine, esculin, casein, gelatin, hypoxanthine, and starch[19]. Their cell walls are rich in L-diaminopimelic acid (L-DAP) and lack mycolic acids[20]. They contain saturated, iso-, and anteiso-fatty acids, with menaquinones composed of nine isoprene units in hexa- or octahydrogenated forms. Their complex polar lipid profiles include mannosides of phosphatidylinositol, phosphatidylethanolamine, and diphosphatidylglycerol[21].

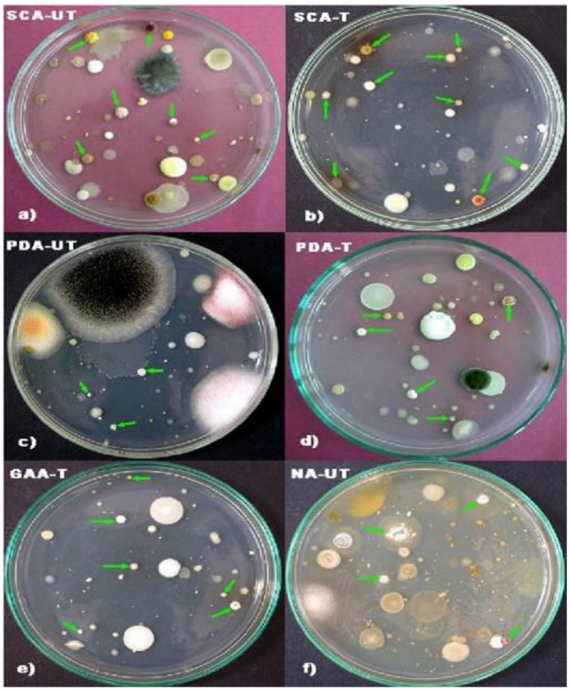

Figure 1 Distinguished *Streptomyces* colonies on four different media

Taxonomic classification and phylogenetic positioning of *streptomyces*

Selman Waksman and Arthur Henrici reclassified the Actinomyces genus into more specific genera in 1943, but they were unable to discover a valid generic name for the aerobic sporulating species; consequently, a new name was devised[22]. *Streptomyces* is the type genus for the Streptomycetaceae family[23], which currently has over 700 species, with the number increasing year after year[24,25]. Estimates indicate that the total number of *Streptomyces* species may approach 1600[26]. Strains previously classified as acidophilic and acid-tolerant within this genus were reassigned to Kitasatospora in 1997 and Streptacidiphilus in 2003[27,28]. Species are typically named after the color of their hyphae and spores. *Saccharopolyspora erythraea* was previously classified in this genus as *S. erythraeus*. The individual taxa of *Streptomyces* are summarized as[25]:

Domain: Bacteria

Phylum: Actinomycetota (formerly Actinobacteria)

Class: Actinomycetia

Order: Streptomycetales

Family: Streptomycetaceae

Genus: *Streptomyces*

To determine the phylogenetic position of a *Streptomyces* species, its 16S rRNA gene sequence is obtained via PCR (e.g., using primers 27F and 1492R) or from databases like NCBI, EzBioCloud, or SILVA. Homologous sequences from related species are aligned using tools like Clustal Omega, MUSCLE, or MAFFT, and a phylogenetic tree is constructed using MEGA X, RAxML, IQ-TREE, or Phylogeny.fr[29].

Selecting the right tree-building method—Neighbor-Joining for simplicity or Maximum Likelihood/Bayesian Inference for accuracy—is essential, along with applying the best-fit substitution model. After tree construction, analyze topology and branch support (e.g., bootstrap values) to assess relationships with known *Streptomyces* species. Tools like iTOL and FigTree aid in visualization, while sequence quality checks and alignment trimming enhance analysis reliability[30,31].

Here is an example of a phylogenetic tree representing various *Streptomyces* species:

This tree was constructed using a concatenated alignment of 646 orthologous genes conserved across 16 *Streptomyces* strains, along with the closely related outgroup *Kitasatospora setae*. The analysis was performed using the maximum-likelihood method, and bootstrap support values are provided at each node to indicate the reliability of the branching (Figure 2).[32]

Life cycle of *Streptomyces*

Streptomyces resemble fungi in both cell structure and life cycle. During vegetative growth, DNA replicates without cell division, forming filamentous structures. They later produce spores (conidia) on aerial filaments called sporophores. This fungal-like life cycle makes *Streptomyces* a useful model for studying developmental processes in complex organisms. (Figure 3).

The *Streptomyces* life cycle begins when a spore lands on a nutrient-rich substrate, germinates, and forms elongating germ tubes without binary fission. These develop into a branching filamentous network called the substrate mycelium[17]. As the colony matures, the central mycelium differentiates into spiraling aerial hyphae, which halt growth at a certain point and synchronously divide into monoploid compartments, each forming a spore[33]. Using nuclear staining (Robinow HC1-Giemsa), the *Streptomyces* life cycle is divided into nuclear division, primary mycelium formation, secondary mycelium development (including aerial structures), and spore formation. Primary mycelium branches and forms swollen multinucleate cells, while secondary mycelium rises to produce aerial structures that develop into spore chains[34].

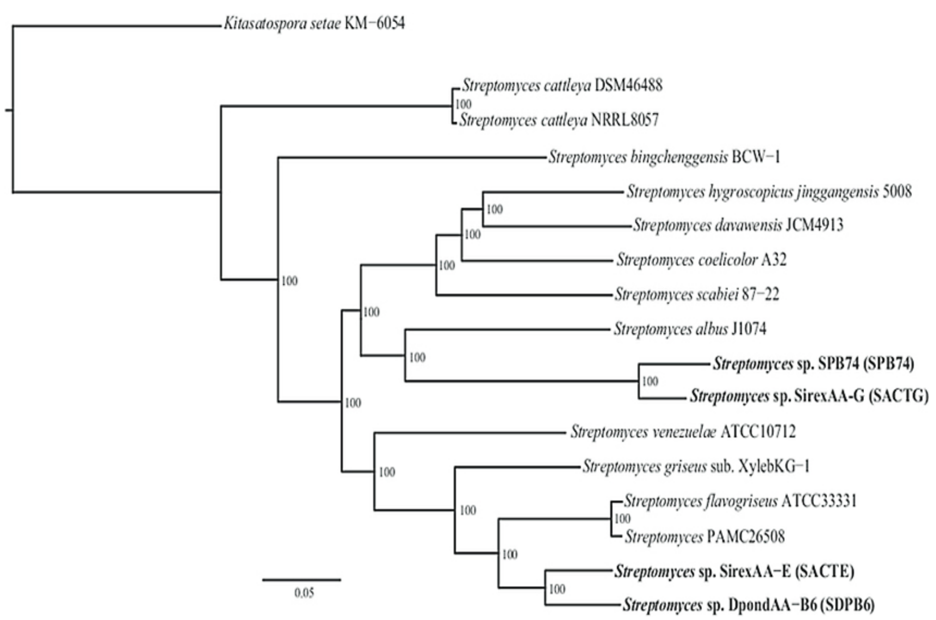

Figure 2 A typical phylogenetic tree representing different *Streptomyces* species

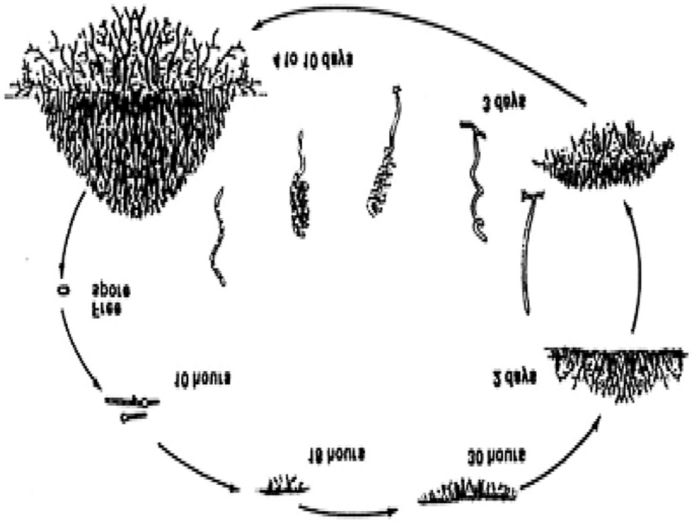

Figure 3 Life cycle of *Streptomyces*

Habitats of *Streptomyces*

Numerous ecological conditions are found in *Streptomyces*, including marine ecosystems such as water bodies, coral reefs, seawater, and mangrove forests, as well as terrestrial ecosystems that include soil, plants, and insects.[35]

Streptomyces are widely distributed in natural environments like soil and water[36,37], making up about 40% of soil bacteria[40]. Their population is shaped by various physical, chemical, and biological factors[38]. Identifying new ecological systems is critical for the discovery of new *Streptomyces* species[39]. These filamentous bacteria, especially abundant in dry, alkaline soils, help improve soil texture and prevent erosion by wind and rain[41]. Their abundance tends to increase with soil depth, and they can be isolated from different soil layers[42]. Factors such as nutrient availability, temperature, pH, moisture, salinity, soil type, and climate affect their distribution in both aquatic and terrestrial habitats, with soil being their primary environment (Figure 4)[43]. *Streptomyces* is known to inhabit soil as its primary habitat[44], although these organisms can also be found in other environments:

Grass and different organic substances: Thermophilic and mesophilic *Streptomyces* strains can degrade various natural materials like plastics, textiles, paper, and rubber[45]. Originally, soil microbes played a key role in biogeochemical cycles by breaking down cellulose, lignocellulose, chitin, and other organics[46,47].

Habitats in freshwater and the ocean: Apart from systems of drinking water designed to drain following heavy downpours, there are also *Streptomyces* accessible[48]. *Streptomyces* have been found in drainage and marine environments, including marine invertebrates like sponges[49]. Over the past two decades, research has highlighted their potential as sources of novel antibiotics and anticancer agents[50,51].

Plants: While specific strains of *Streptomyces*, including *S. tumescans, S. aureofaciens, S. turgidiscabies, S. acidiscabies,* and *S. ipomoea,* have been linked to a variety of plant diseases, some *Streptomyces* strains cause

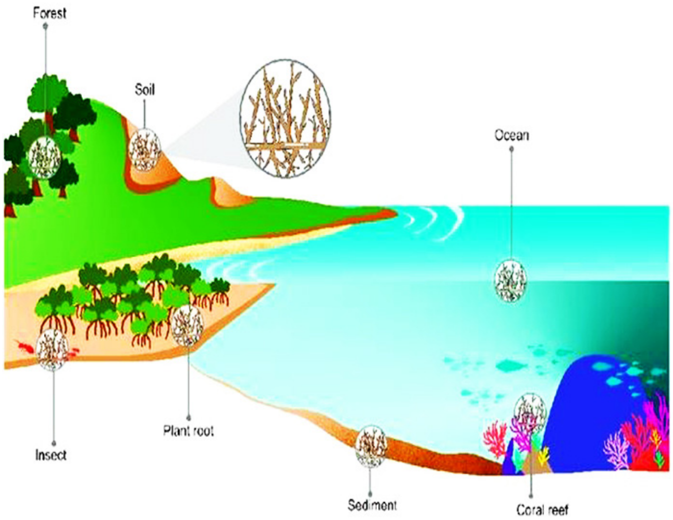

Figure 4 Diversity of *Streptomyces* habitats

plant diseases like root gall and potato scab, but their role as pathogens is minor[52]. A few *Streptomyces* species function as biological control agents[53]. Conversely, certain species serve as effective biological control agents against plant diseases such as sunflower stem rot and potato scab[54-56].

Animals and humans: Though clinical *Streptomyces* isolates are rare, they can cause human infections[3] like mycetoma, which are mainly linked to S*. sudanensis* and *S. somaliensis*, highlighting their role as occasional pathogens[57].

Biotechnological aspects of *Streptomyces*

Streptomyces are well-known for producing diverse secondary metabolites, including the most clinically used antibiotics, antifungals, immunosuppressants, and antitumor agents. Their complex biosynthetic gene clusters make them ideal for genetic engineering. They also play key roles in bioremediation, agriculture, and nutrient cycling, and are used in biotechnology for heterologous protein expression[58-60]. However, expressing eukaryotic proteins in E. coli is challenging due to issues like protein misfolding, insolubility, inclusion body formation, and reduced bioactivity. While E. coli has secretion pathways, they are often inefficient, limiting protein export to the periplasm[56]. *Streptomyces*, as Gram-positive bacteria, efficiently secrete proteins into the medium, simplifying purification and boosting yields. This makes them strong alternatives to *E. coli* and *B. subtilis*[61] for protein production. Their genomic instability also allows for genome reduction to create synthetic strains for industrial use[26].

Scale-up aspects of antibiotic production from *Streptomyces*

Enhancing antibiotic production in *Streptomyces* involves optimizing fermentation conditions, genetic modifications, and efficient downstream processing. Key strategies include adjusting pH, temperature, and nutrients, exploring solid-state fermentation, and using fed-batch or CSTR systems to boost yield[62,63]. Genetic and metabolic engineering, like overexpressing regulatory genes and modifying precursor pathways, greatly enhance antibiotic production. High-throughput screening helps identify high-yield strains, while careful bioreactor design enables industrial scale-up. Efficient downstream processing ensures pure antibiotics for clinical use, supporting scalable *Streptomyces*-based production[64].

The use of cell factories for sustainable fermentation-based production has gained great interest, but success depends not only on efficient strains but also on optimal extracellular conditions, suitable media, and proper scaling (Figure 5)[65].

The ecological role of *Streptomyces* in soil microbiomes or microbial interactions

Streptomyces play a vital role in soil ecology by breaking down complex organic materials like cellulose, chitin, and lignin. Their enzyme secretion aids nutrient cycling and releases key elements, enhancing soil fertility[66,67].

Streptomyces bacteria support plants as growth-promoting rhizobacteria by solubilizing phosphate, producing indole-3-acetic acid (IAA), and suppressing pathogens. They act as keystone species in microbial communities through chemical signaling and antagonism. Their genetic adaptability facilitates horizontal gene transfer, aiding the environmental response and trait spread. Additionally, their ability to degrade contaminants highlights their role in bioremediation and soil health[68,69].

Nutritional and physical requirements for growth of *Streptomyces*

Streptomyces are aerobic, chemoorganotrophic bacteria that require an organic carbon source, inorganic nitrogen sources, and mineral salts for their growth; they do not necessitate vitamins or growth factors[70]. The requirements of *Streptomyces* have been investigated by Kutzner[71]. Since most *Streptomyces* sp. are mesophiles, they can grow in temperatures between 10 and 37 °C, while three species, namely S. *thermovulgaris, S. thermonitrificans,* and *S. thermoflavus,* are thermophiles and grow in temperatures between 45 and 55 °C, and they

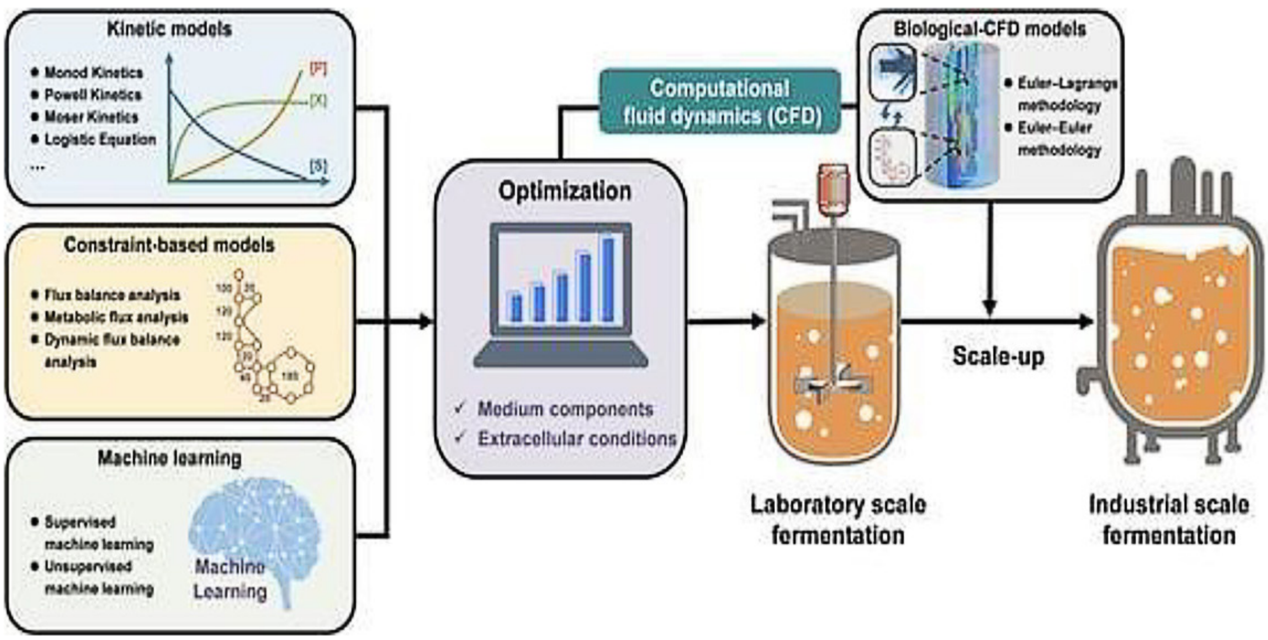

Figure 5 optimization and scale-up of fermentation processes for antibiotic production from *Streptomyces*

can grow in pH 6.5–8[72–74]. Compared to other bacterial species, *Streptomyces* is more drought resistant and has the capacity to form arthrospores, all the while requiring less moisture. They do, however, exhibit a noticeable sensitivity to wet conditions[45]. According to certain reports, sandy loam and calcareous drained soils have a greater amount of *Streptomyces* than heavy clay soils[75].

Metabolites of *Streptomyces*

Primary metabolites are essential for an organism's growth, development, and reproduction, performing vital physiological functions; they are found broadly across organisms[76]. In contrast, secondary metabolites do not directly support these basic processes[77]. They differ from primary metabolites in that: a) they are not critical for growth; b) their production depends on growth conditions; c) they are often produced as related compound clusters; and d) their production can be enhanced beyond normal levels[78]. *Streptomyces* is notable for producing secondary metabolites with antibacterial, antifungal, antiviral, and antitumor activities. For example, *S. coelicolor* and *S. griseus* industrially produce antibiotics like dihydrogranticin and streptomycin. Additionally, *Streptomyces* synthesizes secondary metabolites, such as doxorubicin, an anticancer agent, and rapamycin, an immunomodulatory drug[79,80]. The earthy smell is caused by sidrophore and Geosmin, another *Streptomyces* metabolite[81]. The distinct smell of *Streptomyces* may come from the volatile compounds they produce. For example, *S. bangladeshiensis* was found to produce bis (2-ethylhexyl) phthalate, an antimicrobial phthalic acid derivative[82–84]. Additionally, the ethyl acetate fraction of *S. maritimus* showed strong antimicrobial activity[85].

Streptomyces and medicinal substances

The ability of *Streptomyces* to produce secondary metabolites is high, such as antibiotics[86], anthelminthic enzymes, herbicides, anticancer drugs, growth elements like vitamin B_{12} (cobalamin), and immunomodulators[87–90]. One of the 19th-century forerunners in the development of modern antibiotic knowledge was Louis Pasteur[91]. He discovered that some microbes were capable of eradicating other microbes. While studying *Penicillium notatum* in 1929, Alexander Fleming made the crucial discovery of penicillin as the first antibiotic[92]. The discovery of streptothricin marked the beginning of the history of antibiotics derived from *Streptomyces* spp. With the discovery of Streptomycin in 1943, scientists concentrated on looking for additional antibiotics in the same genus. Between 1945 and 1960, antibiotic discovery was at its most productive[81,93,94]. In 1949, Rachel Brown isolated nystatin—the first antifungal antibiotic-from *S. noursei*[95]. Today, *Streptomyces* species produce about 80% of the clinically useful natural antibiotics, including neomycin and chloramphenicol. This genus, part of the phylum Actinomycetota, is the most prolific bacterial producer of bioactive secondary metabolites. These filamentous, Gram-positive soil bacteria have complex life cycles and large genomes (over 8 Mb) with numerous biosynthetic gene clusters that generate diverse and potent compounds[96,97].

Over half of the clinically effective antibiotics are derived from *Streptomyces*[98]. About 450 million years ago, branched filamentous organisms that were adapted to the breakdown of plant matter gave rise to *Streptomyces*.[97] Some antimicrobials and other drugs are noted in Tables 1 to 4. Despite antibiotic success, microbial diseases remain a leading cause of death[99] due to resistance arising from genetic mutations, horizontal gene transfer, and biofilm formation[100]. Conversely, persistent infections often show antibiotic resistance, prompting efforts to develop improved or novel antimicrobials[101,102]. Granaticin, produced by *S. thermoviolaceus*, is a temperature-sensitive antibiotic optimally synthesized at 45 °C via a thermotolerant pathway. Although biomass peaks at 37 °C, granaticin yield is higher at 45 °C, indicating an inverse relationship between cell growth and antibiotic production within 30–50 °C[103,104].

Antifungal drugs

It has been reported that several soil actinomycetes, primarily those belonging to the *Streptomyces* genus, are antifungal agents that can prevent or reduce the growth of phytopathogenic fungi[105–107]. Several antifungal substances isolated from *Streptomyces* are shown in Table 1. Nystatin and amphotericin B share structural features, including 38-membered macrolactone rings and seven conjugated double bonds. Natamycin has a smaller ring and fewer double bonds, binding ergosterol without forming membrane pores. Amphotericin B is preferred for systemic use due to better pharmacokinetics but carries nephrotoxicity risks, while natamycin is mainly used in food preservation and topical treatments. All three are produced by the *Streptomyces* species via aerobic submerged fermentation with optimized media and pH[108,109].

Antibacterial drugs

Streptomyces species produce diverse, clinically important antibiotics, including aminoglycosides, macrolides, polyketides, and glycopeptides. *S. griseus* produces streptomycin, an aminoglycoside effective against Gram-negative bacteria and the first antibiotic for tuberculosis. *S. aureofaciens* produces tetracycline, a broad-spectrum polyketide that inhibits protein synthesis. *S. venezuelae* produces chloramphenicol, effective against anaerobic bacteria and rickettsiae[96,110].

Macrolides like erythromycin from *S. erythraea* target Gram-positive bacteria and atypical pathogens. Rifamycin from *S. rifamycinica* is key against *Mycobacterium tuberculosis*. Actinomycin D, from *S. antibioticus*, acts as an antitumor agent by intercalating DNA and inhibiting transcription. Vancomycin, produced by *Amycolatopsis orientalis* (formerly *S. orientalis*), is a glycopeptide effective against Gram-positive bacteria, including MRSA.[111] These antibiotics are produced via submerged aerobic fermentation with conditions tailored to each compound. Streptomycin requires a glucose-rich, neutral pH medium; erythromycin thrives with corn steep liquor at pH ~6.8. Tetracycline is often made by fed-batch fermentation, while rifamycin yields best in oil-based media. Nutrients, pH, temperature, and fermentation methods are optimized for large-scale production, showcasing *Streptomyces*' vital role in natural product research and pharmaceutical development.[94] Many antibacterial pharmaceutical agents are derived from members of the genus *Streptomyces*; the most significant of them are compiled in Table 2[20].

S. clavuligerus produces clavulanic acid, used with antibiotics like amoxicillin to inhibit beta-lactamase and reduce resistance. Guadinomine, from *Streptomyces* sp. K01-0509, is an anti-infective in development that blocks the Type III secretion system (T3SS) of Gram-negative bacteria. By targeting virulence rather than killing bacteria, it offers a non-bactericidal approach that limits resistance and preserves the host microbiota, making it a promising strategy against drug-resistant pathogens[112].

Table 1 Some medicinally important antifungals from *Streptomyces* and their close relatives

Sl	Drug	Source	Purposes/activity spectrum
1	Nystatin	*S. noursei*	to treat fungal infections that affect the lining of the stomach, intestines, and inside of the mouth
2	Amphotericin B	*S. nodosus*	for managing fungus infections that worsen over time and may even be fatal
3	Natamycin	*S. natalensis*	to treat fungal eye infections

Table 2 Some medicinally important antibiotics from *Streptomyces* and their close relatives

Sl	Drug	Source	Purposes/activity spectrum
1	Chloramphenicol	*S. venezuelae*	to cure fungus-related infections of the oral cavity, stomach lining, and intestines, to treat typhoid
2	Daptomycin	*S. roseosporus*	to treat gram-positive bacterial infections of different kinds, such as vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA)
3	Fosfomycin	*S. fradiae*	to treat women's cystitis, or bladder infections, and urinary tract infections
4	*Lincomycin,* Clindamycin	*S. lincolnensis*	to treat specific kinds of bacterial infections, such as those affecting the blood, female reproductive system, lungs, skin, and internal organs
5	Neomycin, Actinomycin, Fosfomycin, Dekamycin	*S. fradiae*	to provide perioperative prophylaxis and treat hepatic coma
6	Nourseothricin	*S. variants*	To treat against broad spectrum of pro- and eukaryotic organisms (i.e., Gram-positive and Gram-negative bacteria, yeast, filamentous fungi, protozoa, microalgae, plants and many more)
7	Puromycin	*S. alboniger*	as a discriminating agent in cultured cells in the lab
8	Streptomycin	*S. griseus*	to address specific bacterial infections
9	Tetracycline	*S. rimosus and S. aureofaciens*	to treat infections of pneumonia and other respiratory tract infections, certain infections of skin, eye, lymphatic, intestinal, genital and urinary systems
10	Oleandomycin	*S. antibioticus*	to treat the upper respiratory tract
11	Tunicamycin	*S. torulosus, S. clavuligerus, S. lysosuperficus*	to inhibit tumor cell growth and aggressiveness
12	*Mycangimycin*	*S. antibioticus*	prevents the beetles' antagonistic fungus *Ophiostoma minus* and has potent inhibitory activity against malaria
13	Boromycin	*S. antibioticus*	to cure and shield susceptible poultry from coccidiosis
14	Bambermycin	*S. bambergiensis* and *S. ghanaensis*	to treat abscesses, dental infections and infected wounds, particularly those caused by Gram positive organisms. Use in animal nutrition
15	Vulgamycin	*S. candidus*	used for controlling foodborne pathogens
16	Clavulanic acid	*S. clavuligerus*	to treat bacterial infections capable of producing beta-lactamase, pathogens with transmissible penicillin resistance
17	Cycloserin	*S. orchidaccus*	to treat tuberculosis (TB)
18	Vancomycin	*Amycolatopsis (formerly Streptomyces) orientalis*	to treat antibiotic induced colitis (inflammation of the intestine caused by certain bacteria) and methicillin-resistant *Staphylococcus aureus* (MRSA).
19	Rifampin	*S. mediterranei*	to treat and prevent bacterial infections such as tuberculosis.
20	Kanamycin	*S. knanamyceticus*	to treat severe bacterial infections across various body regions.
21	Tobramycin	*S. tenebrarius*	in the therapy of different ocular and systemic infections.
22	Spectinomycin	*S. spectabilis*	to treat gonorrhea infections.
23	Tetracycline	*S. viridifaciens*	to treat infections of skin, eye, lymphatic, intestinal, genital and urinary systems, pneumonia and other respiratory tract infections etc.
24	Oxytetracyclin	*S. rimosus*	to treat infections of respiratory system (pneumonia), the skin, soft tissues, urinary tract etc
25	Erythromycin	*S. erythraeus*	in infections of the respiratory tract pertussis diphtheria.
26	Chlortetracycline	*S. aureofaciens*	in the treatment of bacterial infection in poultry and is used as a growth promoter for meat-type broilers and turkeys.
27	Dimethylchlor, Methoxychlor, Tetracycline	*S. aureofaciens*	as an insecticide to kill a wide range of insects, including cockroaches, mosquitoes, chiggers, and flies.
28	Spiramycin	*S. ambofaciens*	to treat many kinds of infections, toxoplasmosis in pregnant women.
29	Novobicin	*S. niveus*	alternative to penicillins against penicillin-resistant Staphylococcus spp.
30	Platenmycin	*S. platensis*	antibacterial activity against enterococci and staphylococci, two types of Gram-positive bacteria that are resistant to drugs.
31	Ribostamycin	*S. ribosidificus*	to treat sepsis, superficial skin infection, deep skin infection, lymphangitis/lymphadenitis etc
32	Cycloserine	*S. garyphalus*	to treat tuberculosis
33	Viomycin	*S. vinaceus*	to treat tuberculosis

Table 2 (continued)

Sl	Drug	Source	Purposes/activity spectrum
34	Cephalosporin	*S. clavuligerus*	used in various infections caused by both Gram positive and Gram-negative bacteria
35	*Rifampicin*	*Amycolatopsis* (formerly *Streptomyces*) *mediterranei*	used in TB and leprosy
36	Rapamycin	*S. hygroscopicus*	as an immunomodulatory agent

Antiparasitic drugs

Many important antiparasitic drugs come from *Streptomyces*, especially macrocyclic lactones. Ivermectin, from *S. avermitilis*, is effective against nematodes and arthropods and is widely used in human and veterinary medicine. Similarly, milbemycin, produced by *S. hygroscopicus* subsp. *aureolacrimosus*, shares structural similarity with ivermectin and treats parasitic diseases in animals, especially when other treatments fail[113]. These drugs are produced by aerobic submerged fermentation, with conditions tailored to each compound. Optimal media are rich in carbohydrates and proteins (e.g., glucose, starch, soybean meal), with pH 6.0–7.5 and proper aeration. Sometimes, oil-based media or fed-batch methods boost yields. Such fermentation processes enable scalable, cost-effective production of *Streptomyces*-derived antiparasitics. Recently, *S. avermitilis* MICNEMA2022 was identified as a new strain producing abamectin for nematode management[114].

Avermectin and its derivative ivermectin are widely used antiparasitic drugs that paralyze parasites by activating glutamate-gated chloride channels in their nervous systems. *Streptomyces* species produce diverse bioactive compounds, including macrolides, glycopeptides, polyketides, and alkaloids. Notable examples are migrastatin (anti-metastatic), bleomycin (antitumor via DNA breaks), boromycin (antibacterial and antimalarial), staurosporine (kinase inhibitor), bialaphos (herbicide and antibacterial), and daunomycin (chemotherapy agent). These compounds are produced through aerobic submerged fermentation with specific media and conditions tailored for each drug, underscoring *Streptomyces*' industrial importance in pharmaceutical production[96,119,120]. *Streptomyces* also produces a variety of other bioactive substances, including immunosuppressants, antivirals, anticancer agents, herbicides, antimigraines, etc., along with antimicrobial medications. These are noted down in Table 3[115-118,121,122].

Current limitations or bottlenecks in antibiotic discovery from *Streptomyces*

Streptomyces, once a key antibiotic source, now faces hurdles in finding new compounds due to repeated activation of known pathways. Many potential antibiotic genes remain silent in lab conditions, requiring advanced methods like co-culturing or genetic manipulation to activate them[123,124].

Challenges in fermentation and production of *Streptomyces*-derived compounds remain, as optimizing growth and scaling up require careful control of conditions like media, pH, and aeration. Many identified compounds often resemble existing drugs, limiting their effectiveness against resistant pathogens. Additionally, high costs, long approval processes, and low financial incentives have reduced pharmaceutical investment, collectively hindering the development of new *Streptomyces*-based antibiotics[125,126].

Table 3 Some medicinally important antiparasitic and miscellaneous drugs from *Streptomyces* and their close relatives

Sl	Drug	Source	Purposes/activity spectrum
1	Avermectin B1	*S. avermitilis*	To treat river blindness and as a pesticide to eradicate parasitic worms and pests
2	Valinomycin	*Streptomyces sp. S8*	as antiparasitic and antifungal
3	Staurosporine	*S. staurosporeus*	Used as polypharmacological nature with significant anti-cancer activities and as a potent ATP-competitive kinase inhibitor, although lacking selectivity
4	Butenolide	*S. albus*	used as inflammation produced by fungal infections.
5	Milbemycin	*S. hygroscopicus*	as antiparasitic and antifungal
6	Migrastatin –	*S. platensis*	migraine treatment
7	Bleomycin	*S. verticillus*	cancer treatment
8	Boromycin	*S. antibioticus*	antiviral activity against the HIV-1 strain of HIV
9	Staurosporine	*S. staurosporeus*	antifungal to antineoplastic
10	Bialaphos	*S. hygroscopicus* and *S.viridochromogenes*	natural herbicide
11	Daunomycin	*S. coeruleorubidus*	cancer treatment

ATP=Adenosine Triphosphate, HIV=human immunodeficiency virus

Nutritional requirements for antibiotic production

Streptomyces is adept at growth on various nutritional media, including Trypticase soy agar, Muller Hinton agar, Nutrient agar supplemented with calcium chloride salt, etc[127]. The synthesis of antibiotics can be influenced by numerous factors, such as the availability of carbon and nitrogen sources, oxygen levels, pH, temperature, trace elements, and specific precursors[128].

Carbon: According to some researchers, glucose may prevent the synthesis of antibiotics by inhibiting the enzymes essential to the biosynthesis of antibiotics. This may also be connected to the impact of the growth rate on this process[129]. Conversely, because they encourage a slower growth rate that is favorable to the production of antibiotics, glycerol and polysaccharides like starch are frequently regarded as the top sources of carbon[130]. Utilizing new carbon can result in optimal microbial growth and antibiotic production, as demonstrated by Slavica Ilić et al. The culture media containing lactose and glucose showed the highest production of certain antibiotics, whereas the medium containing ribose showed the lowest production of antibiotics[130,131].

Nitrogen: Numerous investigations have demonstrated a relationship between the kind and amount of nitrogen sources found in culture media and the synthesis of antibiotics[84]. Inorganic nitrogen sources usually reduce antibiotic production[132]. The medium's slow breakdown of some of the compounds makes complex sources of nitrogen like corn steep liquor, soybean meal, and yeast extract usable, which could boost the antibiotic manufacture. Antibiotic yield increased when soybeans were replaced with Isatin-Schiff bases, namely isatin-3-thiosemicarbazone (ITC), isatin-3-semicarbazone (ISC), and isatin-3-phenylhydrazone (IPH), according to research by Slavica Ilić and colleagues[131].

Rate of growth: Antibiotic production can be increased by bacterial proliferation during the logarithmic phase, which is marked by its peak growth rate[132]. One characteristic that sets microorganisms apart is their ability to synthesize antibiotics, which is influenced by the environment in which they are grown[133]. These microbes grow on a variety of substrates, but many of these substrates can negatively impact the synthesis of secondary metabolites. Secondary metabolite production will be greater in the presence of multiple nutrient limitations than in the absence of nutrient limitations[132].

Trace Elements and Minerals: Antibiotic production is elevated by trace amounts of minerals like phosphorus, potassium, iron, zinc, and manganese. Antibiotic biosynthesis is typically stimulated by divalent ions like Mn^{2+}, Cu^{2+}, and Fe^{2+}[134,135]. The production of numerous secondary metabolites is contingent upon phosphate being a borderline nutrient. Synthesis of antibiotics begins when the phosphate source decreases[134].

Oxygen: *Streptomyces* are Aerobic bacteria. Therefore, the right percentage of oxygen greatly affects their development and the production of antibiotics[39].

Acidity/Alkalinity: Most antibiotics are best produced at a pH of about 7.0[136]. Some *Streptomyces* separated from the Rift Valley in Ethiopia could grow better at pH levels ranging from 4.0 to 11.0, with pH 7.5 being the optimum[137].

Precursors: Precursors, including amino acids and short-chain fatty acids, serve as foundational components for certain antibiotics and are incorporated into media during industrial processes[138].

Antibacterial activity of *Streptomyces*

Sampling

Numerous studies indicate that soil sampling should be conducted from different areas at a depth ranging from 5 to 10 centimeters[8]. Because of their stringent aerobic metabolic requirements, *Streptomyces* can be found in a variety of soil types, but they are more prevalent in the upper soil layers. River and riverbed sediments, compost, and alkaline soils are the areas where their populations are most common[87]. Different physical attributes of soil, such as organic substances, pH levels, humidity, reactions of soils, and surface, affect the presence of these organisms[122]. Because *Streptomyces* can withstand high salinities so well, many species are found in salty soils, marine foam, and similar environments[50].

Protocols used in the antimicrobial activity test

There are several approaches available for analyzing the antimicrobial properties of isolated *Streptomyces* species.

Cross streak method

A single streak is used to prepare and inoculate agar plates with *Streptomyces* isolates in the center of the petri dishes. Then the petri dishes are incubated for seven days at 30 °C. Following a single streak inoculation at a 90° angle to the *Streptomyces* isolates, the petri dishes were incubated at 37 °C for 24 hours with the test bacteria, and the zone of inhibition (ZOI) was used to measure antibacterial activity[139].

Agar overlay method

To facilitate the streak inoculation of a medium containing *Streptomyces* isolates, this methodology maintains a temperature of 30 °C for 7 days. One ml of chloroform is added during incubation to prevent the inoculated isolates from growing. The isolates were then covered with seven milliliters of semisolid nutrient agar (0.7%) after being inoculated with one milliliter of an overnight culture of the bacteria being studied and left for 40 minutes. After a 24-hour incubation at 37°C, the resulting zones of inhibition on the agar plates are then measured in millimeters[140].

Disc Diffusion assay

Each 500 ml Erlenmeyer flask contains 100 ml of *Streptomyces* broth medium inoculated with isolates and incubated for five days at 30°C and 200 rpm in a shaking incubator. After incubation, cultures are centrifuged at 1500 rpm for 15 minutes. The broth filtrates are then extracted with an equal volume of ethyl acetate by shaking for 20 minutes. The organic layer is collected and evaporated at 40°C using a rotary evaporator to yield a crude dry extract. This extract is reconstituted in ethyl acetate at 1 mg/ml for antibacterial testing. Sterile blank discs (6 mm) are soaked in 50 µl of the extract, dried, and placed on agar plates inoculated with target bacteria. Plates are incubated at optimal bacterial growth temperature for 24 hours, then inhibition zone diameters are measured to assess antibacterial activity[141,142].

Agar well diffusion assay

After aseptically inoculating 250 ml Erlenmeyer flasks containing 150 ml sterile starch casein nitrate broth with *Streptomyces* spore suspension, they are aerobically incubated at 30°C for 10 days. Post-incubation, the culture is filtered through Whatman No. 1 paper and centrifuged. The supernatant is extracted four times with an equal volume of ethyl acetate, shaking for 30 minutes each time. The combined ethyl acetate layers are evaporated at 40°C using a rotary evaporator. Bacterial isolates are cultured on nutrient agar plates at 1.5×10^8 CFU/ml (0.5 McFarland standard) using sterile swabs. Wells of 6 mm diameter are made in the agar and filled with 5 mg/ml ethyl acetate extracts prepared in 25% DMSO. Plates are then incubated at the optimal temperature for 24 hours before analysis[105].

Conclusion

The study suggests that marine *Streptomyces* spp. produce valuable secondary metabolites influenced by culture conditions. Advanced techniques like GC-MS can isolate these compounds. Overcoming antibiotic discovery challenges requires sophisticated screening, activating silent gene clusters, and optimizing fermentation. Prioritizing antibiotics with novel actions, using synthetic biology, and fostering interdisciplinary collaboration will accelerate development. Clinically, strategic use, antibiotic stewardship, and targeted trials are vital to combat resistance. A comprehensive approach combining research and clinical methods is essential to sustain *Streptomyces*' role against infectious diseases.

Acknowledgement

The authors are grateful and thankful to the Center for Research and Publication (CRP) and Department of Pharmacy, International Islamic University Chittagong, Chattogram 4318, Bangladesh, for supporting this research work.

Authors' contributions

Sayeed MA: conceptualization, writing – original draft, data extraction, figure drawing, and data analysis; Arman M: writing – original draft; writing – original draft; Jahan I: writing – original draft, data extraction; Mojid MA: conceptualization, supervision, and manuscript revision.

Conflict of interest

The authors declare that they have no competing interests.

Funding sources

This research was supported by the IIUC research grants 2018, Center for Research and Publication (CRP), International Islamic University Chittagong (Grant No. IRG 180109), Chittagong, Bangladesh.

References

1. Williams ST, Goodfellow M, Alderson G, Wellington EM, Sneath PH, Sackin MJ. Numerical classification of Streptomyces and related genera. Microbiol 1983;129:1743-813. doi: 10.1099/00221287-129-6-1743.
2. Arai T. What are Actinomycetes? Atlas of actinomycetes', the society for actinomycetes Japan (SAJ). Tokyo: Asakura Publishing Co., Ltd.; 1997:p.176-91.
3. Korn-Wendisch F, Kutzner HJ. The family Streptomycetaceae. The Prokaryotes, Vol. II, 2nd ed. (Balows A, Trüper HG, Dworkin

M, Hardeer W & Schleifer KH, eds). New York: Springer-Verlag; 1992;p.923-95.
4. Anderson AS, Wellington EM. The taxonomy of Streptomyces and related genera. Int J Syst Evol Microbiol 2001;51:797-814. doi: 10.1099/00207713-51-3-797.
5. Bhattacharyya BK, Pal SC, Sen SK. Antibiotic production by Streptomyces hygroscopicus D1. 5: Cultural effect. Revista de microbiologia 1998;29:167-9. doi: 10.1590/S0001-37141998000300003
6. Reza Dehnad A, Yeganeh LP, Bakhshi R, Mokhtarzadeh A, Soofiani S, Monadi AR, Gasanova S, Abusov R. Investigation of antibacterial activity of Streptomycetes isolates from soil samples, west of Iran. Afr J Microbiol Res 2010;4:1685-93.
7. Maleki H, Dehnad A, Hanifian S, Khani S. Isolation and molecular identification of Streptomyces spp. with antibacterial activity from northwest of Iran. BioImpacts: BI 2013;3:129-34. doi: 10.5681/bi.2013.017.
8. Mohanraj G, Sekar T. Isolation and screening of actinomycetes from marine sediments for their potential to produce antimicrobials. Int J Life Sci Pharma Res 2013;2:115-26.
9. Hong K, Gao AH, Xie QY, Gao H, Zhuang L, Lin HP, et al. Actinomycetes for marine drug discovery isolated from mangrove soils and plants in China. Mar drugs 2009;7:24-44. doi: 10.3390/md7010024.
10. Butt UD, Khan S, Liu X, Sharma A, Zhang X, Wu B. Present status, limitations, and prospects of using Streptomyces bacteria as a potential probiotic agent in aquaculture. Probiotics Antimicrob. Proteins 2024;16:426-42. doi: 10.1007/s12602-023-10053-x.
11. Ikeda H, Ishikawa J, Hanamoto A, Shinose M, Kikuchi H, Shiba T, et al. Complete genome sequence and comparative analysis of the industrial microorganism Streptomyces avermitilis. Nat Biotechnol 2003;21:526-31. doi: 10.1038/nbt820.
12. Kavitha A, Vijayalakshmi M, Sudhakar P, Narasimha G. Screening of Actinomycete strains for the production of antifungal metabolites. Afr J Microbiol Res 2010;4:027-32.
13. Willemse J, Borst JW, de Waal E, Bisseling T, van Wezel GP. Positive control of cell division: FtsZ is recruited by SsgB during sporulation of Streptomyces. Genes Deve 2011;25:89-99. doi: 10.1101/gad.600211.
14. Chater KF. Genetics of differentiation in Streptomyces. Annu Rev Microbiol 1993;47:685-714. doi: 10.1146/annurev.mi.47.100193.003345.
15. Jüttner F, Watson SB. Biochemical and ecological control of geosmin and 2-methylisoborneol in source waters. Appl Environl Microbiol 2007;73:4395-406. doi: 10.1128/AEM.02250-06.
16. Ambarwati A, Sembiring L, Soegihardjo C. Antibiotic produced by streptomycetes associated with rhizosphere of purple nut sedge (Cyperus rotundus L.) in Surakarta, Indonesia. Afr J Microbiol Res 2012;6:52-7. doi: 10.5897/AJMR11.832.
17. Flärdh K, Buttner MJ. Streptomyces morphogenetics: dissecting differentiation in a filamentous bacterium. Nat Rev Microbiol 2009;7:36-49. doi: 10.1038/nrmicro1968.
18. Oskay M. Comparison of Streptomyces diversity between agricultural and non-agricultural soils by using various culture media Sci Res Essays 2009;4:997-1005.
19. Smaoui S, Mathieu F, Fguira LF, Merlina G, Mellouli L. Taxonomy and antimicrobial activities of a new Streptomyces sp. TN17 isolated in the soil from an oasis in Tunis. Arch Biol Sci 2011;63:1047-56. doi: 10.2298/ABS1104047S.
20. Hasani A, Kariminik A, Issazadeh K. Streptomycetes: characteristics and their antimicrobial activities. Int J Adv Biol Biom Res 2014;2:63-75.
21. Cummins CS, Harris H. Studies on the cell-wall composition and taxonomy of Actinomycetales and related groups. Microbiol 1958;18:173-89. doi: 10.1099/00221287-18-1-173.
22. Waksman SA, Henrici AT. The nomenclature and classification of the actinomycetes. J Bacteriol 1943;46:337-41. doi: 10.1128/jb.46.4.337-341.1943
23. Anderson AS, Wellington EM. The taxonomy of Streptomyces and related generaInt. J Syst Evol Microbiol 2001;51:797-814. doi: 10.1099/00207713-51-3-797.
24. Labeda DP. Multilocus sequence analysis of phytopathogenic species of the genus Streptomyces. Int J Syst Evol Microbiol 2011;61:2525-31. doi: 10.1099/ijs.0.028514-0.
25. Parte AC. LPSN–List of Prokaryotic names with Standing in Nomenclature (bacterio. net), 20 years on. Int J Syst Evol Microbiol 2018;68:1825-9. doi: 10.1099/ijsem.0.002786.
26. Nikolaidis M, Hesketh A, Frangou N, Mossialos D, Van de Peer Y, Oliver SG, Amoutzias GD. A panoramic view of the genomic landscape of the genus Streptomyces. Microb Genom 2023;9:001028. doi: 10.1099/mgen.0.001028.
27. Zhang Z, Wang Y, Ruan J. A proposal to revive the genus Kitasatospora (Omura, Takahashi, Iwai, and Tanaka 1982). Int J Syst Evol Microbiol 1997;47:1048-54. doi: 10.1099/00207713-47-4-1048.

28. Kim SB, Lonsdale J, Seong CN, Goodfellow M. Streptacidiphilus gen. nov., acidophilic actinomycetes with wall chemotype I and emendation of the family Streptomycetaceae (Waksman and Henrici (1943) AL) emend. Rainey et al. 1997. Antonie van Leeuwenhoek 2003;83:107-16.
29. Kim M, Oh HS, Park SC, Chun J. Towards a taxonomic coherence between average nucleotide identity and 16S rRNA gene sequence similarity for species demarcation of prokaryotes. Int J Syst Evol Microbiol 2014;64:346-51. doi: 10.1099/ijs.0.059774-0
30. Guo Y, Zheng W, Rong X, Huang Y. A multilocus phylogeny of the Streptomyces griseus 16S rRNA gene clade: use of multilocus sequence analysis for streptomycete systematics. Int J Syst Evol Microbiol 2008;58:149-59. doi: 10.1099/ijs.0.6522.
31. Book AJ, Lewin GR, McDonald BR, Takasuka TE, Doering DT, Adams AS, et al. Cellulolytic Streptomyces strains associated with herbivorous insects share a phylogenetically linked capacity to degrade lignocellulose. Appl Environ Microbiol 2014;80:4692-701. doi: 10.1128/AEM.01133-14.
32. Kiepas AB, Hoskisson PA, Pritchard L. 16S rRNA phylogeny and clustering is not a reliable proxy for genome-based taxonomy in Streptomyces. BioRxiv 2023;15:2023-08. doi: 10.1101/2023.08.15.553377
33. Kieser T, Bibb MJ, Chater KF, Hopwood D. General introduction to Actinomycete Biology. Practical Streptomyces Genetics, The John Innes Foundation, Crowes, Norwich, England 2000;2000:2-42.
34. Mc Gregor, J. Nuclear division and the life cycle in a Streptomyces sp. J gen Microbiol 1954;11:52-6.
35. Ngamcharungchit C, Chaimusik N, Panbangred W, Euanorasetr J, Intra B. Bioactive metabolites from terrestrial and marine actinomycetes. Molecules 2023;28:5915. doi: 10.3390/molecules28155915.
36. Seong CN, Park JH, Baik KS. An improved selective isolation of rare actinomycetes from forest soil. J Microbiol 2001;39:17-23.
37. Singh LS, Baruah I, Bora TC. Actinomycetes of Loktak habitat: isolation and screening for antimicrobial activities. Biotechnol 2006;5:217-21. doi: 10.3923/biotech.2006.217.221.
38. Kharat K, Kharat A, Hardikar, B. Antimicrobial and cytotoxic activity of Streptomyces sp. from Lonar lake. Afr J Biotechnol 2009;8:6645-8.
39. Wang Y, Zhang ZS, Ruan JS, Wang YM, Ali SM. Investigation of actinomycete diversity in the tropical rainforests of Singapore. J Ind Microbiol Biotechnol 1999;23:178-87. doi: 10.1038/sj.jim.2900723.
40. Boone R, Castenholtz R, Garrity G. Bergey's manual of systematic bacteriology'. Springer- Verlag. New York, Berlin Heidelber 2001;1:163-164. doi: 10.1371/journal.pbio.1001184.
41. Vetsigian K, Jajoo R, Kishony R. Structure and evolution of Streptomyces interaction networks in soil and in silico. PLoS Biology 2011;9:e1001184. doi: 10.1371/journal.pbio.1001184.
42. Kim SB, Seong CN, Jeon SJ, Bae KS, Goodfellow M. Taxonomic study of neutrotolerant acidophilic actinomycetes isolated from soil and description of Streptomyces yeochonensis sp. nov. Int. J Syst Evol Microbiol 2004;54:211-14. doi: 10.1099/ijs.0.02519-0.
43. Locci R. Streptomycetes and related genera. Bergey's manual of systematic bacteriology 1989;4:2451-508.
44. Mokrane S, Bouras N, Sabaou N, Mathieu F. Actinomycetes from saline and non-saline soils of Saharan palm groves: Taxonomy, ecology and antagonistic properties. Afr J Microbiol Res 1989;7:2167-78. doi: 10.5897/AJMR2013.5656.
45. Subbarao NS. Soil Microbiology 4th edition. Science publishers, inc. USA; 1999:p.279-283.
46. Rahmansyah M, Agustiyani D, Julistiono H, Dewi TK. Growth and adaptation of four Streptomyces isolates in the media containing propoxur. Research center for Biology, Indonesian Institute of Sciences Cibinong Science Center, Jalan Raya Jakarta Bogor, Cibinong, Indonesia. ARPN J Agri Biol Sc 2012;7:773-81.
47. Horn SJ, Vaaje-Kolstad G, Westereng B, Eijsink V. Novel enzymes for the degradation of cellulose. Biotechnol Biofuel 2012;5:1-3. doi: 10.1186/1754-6834-5-45.
48. Rowbotham TJ, Cross T. Ecology of Rhodococcus coprophilus and associated actinomycetes in fresh water and agricultural habitats. Microbiol 1977;100:231-40. doi: 10.1099/00221287-100-2-231.
49. Remya M, Vijayakumar R. Isolation and characterization of marine antagonistic actinomycetes from west coast of India. Med Biol 2008;15:13-9.
50. Selvakumar D, Arun K, Suguna S, Kumar D, Dhevendaran K. Bioactive potential of Streptomyces against fish and shellfish pathogens. Iran J Microbiol 2010;2:157.

51. Baskaran R, Vijayakumar R, Mohan PM. Enrichment method for the isolation of bioactive actinomycetes from mangrove sediments of Andaman Islands, India. Malays J Microbiol 2011;7:26-32. doi: 10.21161/mjm.24410.
52. Fatope M, Al-kindi M, Abdulnour O. Research trends: Natural products as pest, microbial disease and tumor control agents Sci Technol 2000;2000:55-71. doi: 10.24200/squjs.vol5iss0pp55-71.
53. Rugthaworn P, Dilokkunanant U, Sangchote S, Piadang N, Kitpreechavanich V. A search and improvement of actinomycete strains for biological control of plant pathogens. Agric Nat Resour 2007;41:248-54.
54. Baniasadi F, Bonjar GS, Baghizadeh A, Nik AK, Jorjandi M, Aghighi S, Farokhi PR. Biological control of Sclerotinia sclerotiorum, causal agent of sunflower head and stem rot disease, by use of soil borne actinomycetes isolates. Am J Agric Biol Sci 2009;4:146-51. doi: 10.3844/ajabssp.2009.146.151.
55. Aghighi S, Bonjar GS, Saadoun I. First report of antifungal properties of a new strain of Streptomyces plicatus (strain101) against four Iranian phytopathogenic isolates of Verticillium dahliae, a new horizon in biocontrol agents. Biotechnol 2004;3:90-7. doi: 10.3923/biotech.2004.90.97.
56. Kalantarzadeh M. Antagonistic potential of two native Streptomyces strains in biocontrol of the major causals of common scab of potato in Iran. Asian J of Plant Sciences 2006;5:5-8. doi: 10.3923/ajps.2006.5.8.
57. Quintana ET, Wierzbicka K, Mackiewicz P, Osman A, Fahal AH, Hamid ME, et al. Streptomyces sudanensis sp. nov., a new pathogen isolated from patients with actinomycetoma. Antonie Van Leeuwenhoek 2008;93:305-13. doi: 10.1007/s10482-007-9205-z.
58. Barka EA, Vatsa P, Sanchez L, Gaveau-Vaillant N, Jacquard C, Klenk HP, et al. Taxonomy, physiology, and natural products of Actinobacteria. Microbiol Mol Biol Rev 2016;80:1-43. doi: 10.1128/mmbr.00019-15.
59. Brawner M, Poste G, Rosenberg M, Westpheling J. Streptomyces: a host for heterologous gene expression. Curr Opin Biotechnol 1991;2:674-81. doi: 10.1016/0958-1669(91)90033-2.
60. Payne GF, DelaCruz N, Coppella SJ. Improved production of heterologous protein from Streptomyces lividans. Appl Microbiol Biotechnol 1990;33:395-400. doi: 10.1007/BF00176653.
61. Binnie C, Cossar JD, Stewart DI. Heterologous biopharmaceutical protein expression in Streptomyces. Trends Biotechnol 1997;15:315-20. doi: 10.1016/S0167-7799(97)01062-7.
62. Al Farraj DA, Varghese R, Vágvölgyi C, Elshikh MS, Alokda AM, Mahmoud AH. Antibiotics production in optimized culture condition using low cost substrates from Streptomyces sp. AS4 isolated from mangrove soil sediment. J King Saud Univ Sci 2020;32:1528-35. doi: 10.1016/j.jksus.2019.12.008.
63. Bérdy J. Thoughts and facts about antibiotics: where we are now and where we are heading. J Antibiot 2012;65:385-95. doi: 10.1038/ja.2012.27.
64. Ochi, K. Metabolic engineering of Streptomyces for enhanced antibiotic production. Biotechnol Adv 2017;35:237–48. doi: 10.1016/j.biotechadv.2016.12.002.
65. Du YH, Wang MY, Yang LH, Tong LL, Guo DS, Ji XJ. Optimization and scale-up of fermentation processes driven by models. Bioengineering 2022;9:473. https://doi.org 10.3390/bioengineering9090473.
66. Muok AR, Claessen D, Briegel A. Microbial hitchhiking: how Streptomyces spores are transported by motile soil bacteria. ISME J 2021;15:2591-600. doi: 10.1038/s41396-021-00952-8.
67. Olanrewaju OS, Babalola OO. Streptomyces: implications and interactions in plant growth promotion. Appl Microbiol Biotechnol 2019;103:1179-88. doi: 10.1007/s00253-018-09577-y.
68. Abbasi S, Spor A, Sadeghi A, Safaie N. Streptomyces strains modulate dynamics of soil bacterial communities and their efficacy in disease suppression caused by Phytophthora capsici. Sci Rep 2021;11:9317. doi: 10.1038/s41598-021-88495-y.
69. Zappelini C, Alvarez-Lopez V, Capelli N, Guyeux C, Chalot M. Streptomyces dominate the soil under betula trees that have naturally colonized a red gypsum landfill. Front Microbiol 2018;9:1772. doi: 10.3389/fmicb.2018.01772.
70. Lee M, Demain A. Effects of nitrogen source on production of antibiotics. J Microbiol 1977;1977;412-22.
71. Küster E, Williams ST. Selection of media for isolation of streptomycetes. Nature 1964;202:928-9.
72. Deeble V, Fazeli M, Cove J, Baumberg S. Effects of temperature on production of antibiotics in Streptomyces griseus. J Antibiot 2005;2005:171-8. doi: 10.1038/202928a0.
73. Srivibool R, Kurakami K, Sukchotiratanac M, Tokuyamab S. Coastal soil actinomycetes: Thermotolerant strains producing N-Acylamino acid racemase. ScienceAsia 2004;30:123-6. doi: 10.2306/scienceasia1513-1874.2004.30.123.

74. Basilio A, Gonzalez I, Vicente MF, Gorrochategui J, Cabello A, Gonzalez A, et al. Patterns of antimicrobial activities from soil actinomycetes isolated under different conditions of pH and salinity. J Appl Microbiol 2003;95:814-23. doi: 10.1046/j.1365-2672.2003.02049.x.
75. Sujatha P, Raju B, Ramana T. Actinomycetes of Loktak habitat: isolation and screening for antimicrobial activities. Microbiol Res 2005;160:119-126. doi: 10.1016/j.micres.2004.10.006.
76. Demain AL. Microbial production of primary metabolites. Sci Nat 1980;67:582-7. doi: 10.1007/BF00396537.
77. Shomura T, Yoshida J, Amano S, Kojima M, Inouye S, Niida T. Studies on actinomycetales producing antibiotics only on agar culture i. screening, taxonomy and morphology-productivity relationship of Streptomyces halstedii, strain SF-1993. J. Antibiot 1979;32:427-35. doi: 10.7164/antibiotics.32.427.
78. Drew SW, Demain AL. Effect of primary metabolites on secondary metabolism. Annu Rev Microbiol 1977;31:343-56. doi: 10.1146/annurev.mi.31.100177.002015.
79. Mukhtar H, Ijaz S, Ul-Haq I. Production of antitumor antibiotic by Streptomyces capoamus Pak J Bot 2012;44:445-52.
80. Ying Y, Marta M. Effects of L-lysine on production of rapamycin. J Drugs 2001;102-5.
81. Sanglier JJ, Wellington EM, Behal V, Fiedler HP, Ghorbel RE, Finance C, et al. Novel bioactive compounds from actinomycetes. Microbiol Res 1993;144:661-63. doi: 10.1016/0923-2508(93)90071-9.
82. Bais YG, Nimbekar TP, Wanjari BE, Timande SP. Isolation of antibacterial compound from marine soil Actinomycetes. Int J Biomed Adv Res 2012;3:193-6.
83. Al-Bari MA, Sayeed MA, Rahman MS, Islam MAU. Toxicological studies of an antimicrobial compound and ethyl acetate extract from Streptomyces bangladeshiensis sp. nov., on long Evan's rats. Int J Pharmacol 2006;2:66-9. doi: 10.3923/ijp.2006.66.69.
84. AL BARI MA, Sayeed MA, Rahman MS, Mossadik MA. Characterization and antimicrobial activities of a phenolic acid derivative produced by Streptomyces bangladeshiensis a novel species collected in Bangladesh. Res J Med Sci 2006;1:77-81.
85. Al-Bari MA, Sayeed MA, Alam Khan AK, Islam MR, Proma Khondokar PK, Rahman MM, Islam MAU. In vitro antimicrobial activities and cytotoxicity of ethyl acetate extract from Streptomyces maritimus. Biotechnol 2007;6:81-85. doi: 10.3923/biotech.2007.81.85.
86. MCIntyre J. Antibiotic drugs. J Antibiot 2002;34:356-70.
87. Kariminik A, Baniasadi F. Pageantagonistic activity of Actinomycetes on some Gram negative and Gram positive bacteria. World Appl Sci J 2010;8:828-32.
88. Berdy J. Bioactive microbial metabolites. J Antibiot 2005;58:1-26. doi: 10.1038/ja.2005.1.
89. Bibb MJ. Regulation of secondary metabolism in streptomycetes. Curr Opin Microbiol 2005;8:208-15. doi: 10.1016/j.mib.2005.02.016
90. Mann J. Natural products as immunosuppressive agents. Nat Prod Rep 2001;18:417-30. doi: 10.1039/b001720p.
91. Gray W, Jacobs F. Penicillin: the first miracle drug. J Drug 2001;390-396.
92. Silva MG, Dose A. The best penicillin for resistant bacteria. J Antibiot 2004;48:562-9.
93. Schatz A, Bugle E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. Proc Soc Exp Biol Med 1944;55:66-9. doi: 10.3181/00379727-55-14461.
94. Watve MG, Tickoo R, Jog MM, Bhole BD. How many antibiotics are produced by the genus Streptomyces? Arch Microbiol 2001;176:386-90. doi: 10.1007/s002030100345.
95. Orna M. Women chemists in the national inventors hall of fame: Their remarkable lives and their awaer-winning research. Bull Hist Chem 2001;34:50-60.
96. Bérdy J. Bioactive microbial metabolites. J Antibiot 2005;58:1–26. doi: 10.1038/ja.2005.1
97. Chater KF. Streptomyces inside-out: a new perspective on the bacteria that provide us with antibiotics. Philos Trans R Soc Lond B Biol Sci 2006;361:761-68. doi: 10.1098/rstb.2005.1758.
98. Kieser T, Bibb MJ, Buttner MJ, Chater KF, Hopwood DA. Practical Streptomyces genetics: John innes foundation. Norwich Research Park, Colney 2000;2000:44-61.
99. Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem 2009;78:119-46. doi: 10.1146/annurev.biochem.78.082907.145923.
100. Wright GD. Antibiotic resistance in the environment: a link to the clinic?. Curr Opin Microbiol 2010;13:589-94. doi: 10.1016/j.mib.2010.08.005.
101. Hassan A, Usman J, Kaleem F, Omair M, Khalid A, Iqbal M. Evaluation of different detection methods of biofilm formation in the clinical isolates. Braz J Infect Dis 2011;15:305-11. doi: 10.1590/S1413-86702011000400002.

102. Garza-Ramos U, Silva-Sánchez J, Martínez-Romero E. Genetics and genomics for the study of bacterial resistance. Salud publica de Mexico 2009;51:s439-46.
103. James PD, Edwards C. The effects of temperature on growth and production of the antibiotic granaticin by a thermotolerant streptomycete. Microbiol 1989;135:1997-2003. doi: 10.1099/00221287-135-7-1997.
104. Procópio RE, Silva IR, Martins MK, Azevedo JL, Araújo JM. Antibiotics produced by Streptomyces. Braz J Infect Dis 2012;16:466-71. doi: 10.1016/j.bjid.2012.08.014.
105. Pallavi S, Manasa M, Yashoda Kambar YK, Asha MM, Chaithra M, Vivek MN, et al. Anti-Staphylococcus aureus and anti-yeast activity of Streptomyces species isolated from rhizosphere soil of Sahyadri Science College, Shivamogga, Karnataka. Asian J. Biomed Pharm Sci 2013;3:7-11.
106. Palla MS, Guntuku GS, Muthyala MKK, Pingali S, Sahu PK. Isolation and molecular characterization of antifungal metabolite producing actinomycete from mangrove soil. Beni-Suef Univ J Basic Appl Sci 2018;7:250–6. doi: 10.1016/j.bjbas.2018.02.006.
107. Shi L, Nwet TT, Ge B, Zhao W, Liu B, Cui H, et al. Antifungal and plant growth-promoting activities of Streptomyces roseoflavus strain NKZ-259. Biol Control 2018;125: 57–64. doi: 10.1016/j.biocontrol.2018.06.012.
108. Hamilton-Miller JM. Chemistry and biology of the polyene macrolide antibiotics. Bacteriol. Rev 1973;37:166-96. doi: 10.1128/br.37.2.166-196.1973.
109. Georgopapadakou NH, Walsh TJ. Antifungal agents: chemotherapeutic targets and immunologic strategies. ntimicrob. Agents Chemother 1996;40:279-91. doi: 10.1128/AAC.40.2.279.
110. Demain AL, Sanchez S. Microbial drug discovery: 80 years of progress. J Antibiot 2009;62:5-16. doi: 10.1038/ja.2008.16.
111. Katz L, Baltz RH. Natural product discovery: past, present, and future. J Ind Microbiol Biotechnol 2016;43:155-76. doi: 10.1007/s10295-015-1723-5.
112. Holmes TC, May AE, Zaleta-Rivera K, Ruby JG, Skewes-Cox P, Fischbach MA, et al. Molecular insights into the biosynthesis of guadinomine: a type III secretion system inhibitor. J Am Chem Soc 2012;134:17797-806. doi: 10.1021/ja308622d.
113. Crump A, Omura S. Ivermectin,'wonder drug'from Japan: the human use perspective. Proc Jpn Acad Series B 2011;87:13-28. doi: 10.2183/pjab.87.13.
114. Radwan WH, Abdelhafez AA, Mahgoub AE, Zayed MS. Streptomyces avermitilis MICNEMA2022: a new biorational strain for producing abamectin as an integrated nematode management agent. BMC Microbiol 2024;24:329. doi: 10.1186/s12866-024-03466-3.
115. Martín JF, Rodríguez-García A, Liras P. The master regulator PhoP coordinates phosphate and nitrogen metabolism, respiration, cell differentiation and antibiotic biosynthesis: comparison in Streptomyces coelicolor and Streptomyces avermitilis. J Antibiot 2017;70:534-41. doi: 10.1038/ja.2017.19.
116. Pimentel-Elardo SM, Kozytska S, Bugni TS, Ireland CM, Moll H, Hentschel U. Anti-parasitic compounds from Streptomyces sp. strains isolated from Mediterranean sponges. Mar Drugs 2010;23;8:373-80. doi: 10.3390/md8020373.
117. Jeon CW, Kim DR, Kwak YS. Valinomycin, produced by Streptomyces sp. S8, a key antifungal metabolite in large patch disease suppressiveness. World J Microbiol Biotechnol 2019;35:1-10. doi: 10.1007/s11274-019-2704-z.
118. Gao M, Lee SB, Lee JE, Kim GJ, Moon J, Nam JW, et al. Anti-inflammatory butenolides from a marine-derived Streptomyces sp. 13G036. Appl Sci 2022;29;12:4510. doi: 10.3390/app12094510.
119. Nakae K, Yoshimoto Y, Sawa T, Homma Y, Hamada M, takeuch T, et al. Migrastatin, a new inhibitor of tumor cell migration from Streptomyces sp. MK929-43F1 taxonomy, fermentation, isolation and biological activities. J Antibiot 2000;53:1130-6. doi: 10.7164/antibiotics.48.1217.
120. Umezawa H. New antibiotics, bleomycin A and B. J Antibiotics 1966;19:200-9. doi: 10.7164/antibiotics.19.200.
121. Bonjar GHS. Screening for antibacterial properties of some Iranian plants against two strains of Escherichia coli. Asian J Plant Sci 2004;3:310-4. doi: 10.3923/ajps.2004.310.314.
122. Nonoh JO, Lwande W, Masiga D, Presnail KJ, Schepers E, Okech MA, et al. Isolation and characterization of Streptomyces species with antifungal activity from selected national parks in Kenya. Afr J Microbiol Res 2010;4:856-64. doi: 10.5897/AJMR.9000455.
123. Chater KF, Biró, S. New and better antibiotics from Streptomyces. Nat Rev Microbiol 2016;14:14–19. doi: 10.1038/nrmicro.2015.5.
124. Baltz RH. Streptomyces griseus and the origins of clinical antibiotic discovery. Biotechnol Adv 2008;26:107–117. doi: 10.1016/j.biotechadv.2007.12.003

125. Crispino M, Miele, A. Activation of cryptic biosynthetic pathways in Streptomyces species: New challenges and strategies. Front Microbiol 2014;5:598.
126. Hodgson DA, Nallapareddy SR. Overcoming bottlenecks in antibiotic discovery from Streptomyces and other actinobacteria. Microb Biotechnol 2012;5:629–635. doi: 10.1111/j.1751-7915.2012.00342.x.
127. Busti E, Yushi O. Media conditions for growthing Actinomycetes. Microbial Res 2006;2006:424-7.
128. Rafieenia R. Effect of nutrients and culture conditions on antibiotic synthesis in Streptomycetes. Asian J Pharm Health Sc 2013;3:810-15.
129. Lounes A, Lebrihi A, Benslimane C, Lefebvre G, Germain P. Regulation of spiramycin synthesis in Streptomyces ambofaciens: effects of glucose and inorganic phosphate. Appl Microbiol Biotechnol 1996;45:204-11. doi: 10.1007/s002530050671.
130. Jonsbu E, McIntyre M, Nielsen J. The influence of carbon sources and morphology on nystatin production by Streptomyces noursei. J Biotechnol 2002;95:133-44. doi: 10.1016/S0168-1656(02)00003-2.
131. Ilić S, Konstantinović S, Veljković V, Savić D, Gojgić-Cvijović G. The impact of different carbon and nitrogen sources on antibiotic production by Streptomyces hygroscopicus CH-7. Current research, Technology and Education. Appl Microbiol Biotechnol 2010;2:1337-42.
132. Sejiny M. Growth phases of some antibiotics producing Streptomyces and their identification. J King Abdulaziz Univ 1991;3:21-9. doi: 10.4197/Sci.3-1.2.
133. Young MD, Kempe LL, Bader FG. Effects of phosphate, glucose, and ammonium on cell growth and lincomycin production by Streptomyces lincolnensis in chemically defined media. Biotechnol. Bioeng 1985;27:327-33. doi: 10.1002/bit.260270318.
134. Martín JF. Phosphate control of the biosynthesis of antibiotics and other secondary metabolites is mediated by the PhoR-PhoP system: an unfinished story. J Bacteriol 2004;186:5197-201. doi: 10.1128/JB.186.16.5197-5201.2004
135. Gesheva V, Ivanova V, Gesheva R; Effects of nutrients on the production of AK-111-81 macrolide antibiotic by Streptomyces hygroscopicus. Microbiol Res 2005;160:243-8. doi: 10.1016/j.micres.2004.06.005.
136. Saadoun I, Al-Momani F, Malkawi HI, Mohammad MJ. Isolation, identification and analysis of antibacterial activity of soil streptomycetes isolates from north Jordan. Microbios 1999;100:41-6.
137. Elias F, Muddada S, Muleta D, Tefera B. Antimicrobial potential of Streptomyces spp. isolated from the rift valley regions of Ethiopia. Adv Pharmacol Pharm Sci 2022;2022:1724906. doi: 10.1155/2022/1724906.
138. Tang L, Zhang YX, Hutchinson CR. Amino acid catabolism and antibiotic synthesis: valine is a source of precursors for macrolide biosynthesis in Streptomyces ambofaciens and Streptomyces fradiae. J Bacteriol 1994;176:6107-19. doi: 10.1128/jb.176.19.6107-6119.1994.
139. Kumar PS, Raj JP, Duraipandiyan V, Ignacimuthu S. Antibacterial activity of some actinomycetes from Tamil Nadu, India. Asian Pac J Trop Biomed 2012;2:936-43. doi: 10.1016/S2221-1691(13)60003-9.
140. Şahin N, Uğur A. Investigation of the antimicrobial activity of some Streptomyces isolates. Turk J BioL 2003;27:79-84.
141. Gebreyohannes G, Moges F, Sahile S, Raja N. Isolation and characterization of potential antibiotic producing actinomycetes from water and sediments of Lake Tana, Ethiopia. Asian Pac J Trop Biomed 2013;3:426-35. doi: 10.1016/S2221-1691(13)60092-1
142. Manivasagan P, Gnanam S, Sivakumar K, Thangaradjou T, Vijayalakshmi S, Balasubramanian T. Antimicrobial and cytotoxic activities of an actinobacteria (Streptomyces sp. PM-32) isolated from an offshore sediment of the Bay of Bengal in Tamilnadu. Adv Biol Res 2009;3:231-6.