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Production of secondary metabolites by *Actinomycetes* and their biological applications: A review

Yiglet Mebrat

Abstract

Bioactive metabolites are a substance that has a biological activity and should include all microbial compounds obtained either from microbes or from any other living thing. Around 23,000 bioactive metabolites produced from microorganisms, out of which 10,000 (45%) are produced by Actinobacteria alone. Actinomycetes are known to produce an extensive range of bioactive metabolites as well as variety of enzymes with multiple biotechnological applications and important for pharmaceutical, food, agricultural, and environmental applications. Bioactive metabolites are widely used and studied for obtaining antibiotics, antifungals, antivirals, immunosuppressants, compounds with anticancer and antioxidant activity, enzymes, bioinsecticides, biostimulants, biosurfactants and other applications. Bioactive metabolites derived from Actinomycetes are more attractive than bioactive metabolites from other sources because of their high stability and unusual activity specificity. The main applications of Actinomycetes, studies have focused on antimicrobial potential, enzymes production, agricultural uses, bioremediation, and others related to their secondary metabolites production. The review aimed to summarize information about the potentials of Actinomycetes novel bioactive metabolites with their applications in different prospects.

Keywords: *microorganisms, Actinomycetes, Streptomyces, secondary metabolite, antibiotics*

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About the author:
Ethiopian Biodiversity Institute, Addis Ababa, Ethiopia.

1. Introduction

Bioactive metabolites are substances that has a biological activity and should include all microbial compounds exhibiting antimicrobial and/or antitumor and/or antiviral activities obtained either from microbes or from any other living thing (Richa, 2015; Abdelghani *et al.*, 2021; Conrado *et al.*, 2022; Abdelaziz *et al.*, 2023; Hashem *et al.*, 2023; Raihan *et al.*, 2021; Amaning *et al.*, 2022; Abdel-Aziz *et al.*, 2017). Secondary metabolites are metabolic products that are not essential for vegetative growth and reproduction of the producing organisms but they are considered differentiation compounds conferring adaptive roles, for example, by functioning as defense compounds or signaling molecules in ecological interactions (Vaishnav & Demain, 2010; Marinelli & Marcone, 2011; Vijayakumar & Raja, 2018; Al-Khayri *et al.*, 2023; Divekar *et al.*, 2022; Chaturvedi & Gupta, 2021; Chen *et al.*, 2022; Ncube *et al.*, 2016). These bioactive metabolites are produced naturally from different species of fungi and bacteria, but the most attractive class of microorganisms that are able to produce these bioactive metabolites are Actinobacteria, in particular, *Actinomycetes* (Richa, 2015; De Simeis & Serra, 2021).

The total number of bioactive metabolites produced by microorganisms is around 23,000, out of which 10,000 (45% of all bioactive metabolites) are produced by Actinobacteria alone (Ouchari *et al.*, 2019; Berdy, 2012 as cited in Ouchari *et al.*, 2019; Salwan & Sharma, 2020; Golinska *et al.*, 2015; Maithani *et al.*, 2022). The metabolic diversity of the Actinobacteria class is due to their extremely large genome, which has hundreds of transcription factors that control gene expression, allowing them to respond to specific needs (Ouchari *et al.*, 2019). The bioactive metabolites are of high commercial value, and hence *Actinomycetes* are regularly screened for the production of novel bioactive compounds (Prakash *et al.*, 2013; Janardhan *et al.*, 2014; De Simeis & Serra, 2021; Subramani & Aalbersberg, 2012; Matsumoto & Takahashi, 2017; Lewis *et al.*, 2021; Olano & Rodríguez, 2024; Meenakshi *et al.*, 2024; Singh *et al.*, 2016). *Actinomycetes* are one of the ubiquitous dominant groups of gram positive bacteria and have been commercially exploited for the production of pharmaceuticals, neutraceuticals, enzymes, antitumor agents, enzyme inhibitors, and so forth (Prakash *et al.*, 2013). Current research suggests that *Actinomycetes* are also a prime resource in the finding of new natural products, due to their unique enzymatic sets that permit generating compounds that are potentially useful for diverse purposes (De Simeis & Serra, 2021; Jagannathan *et al.*, 2021; Silva *et al.*, 2022; Ryu *et al.*, 2023; Najm *et al.,* 2023; Sharma *et al.,* 2021). *Actinomycetes* hold a significant role in producing variety of drugs that are extremely important to our health and nutrition (Neha *et al.,* 2017). The search for bioactive metabolites including novel antibiotic compounds from microbial sources for potential use in agricultural, pharmaceutical, and industrial applications has become more important due to the development of drug and other bioactive metabolites. So, this review summarized recent research works about the commercial potentials of *Actinomycetes* in knowledge on novel bioactive metabolites of *Actinomycetes* and their applications in different prospects.

2. Methodology

This paper used literature review method. According to Snyder (2019), this method summarise, synthesise and evaluate existing knowledge. The data were gathered from different collective research articles and reviews related to actinomycetes bioactive metabolite production and application in various aspects. Articles were selected based on: (1) relevance to the research objective; (2) recency of publication; (3) advancement in using recent technology; (4) laboratory techniques regarding actinomycetes nature; and (5) extraction with evaluation techniques of actinomycetes bioactive metabolites and specific application. From the largest available database, Google Scholar, the author searched for articles based on keywords. Based on the inclusion criteria, the open access articles were downloaded and grouped according to application aspects (agricultural, environmental, medical etc.). The gathered data were arranged according to the two themes, nature and application of actinomycetes bioactive metabolite.

3. Findings and Discussion

3.1. The nature of Actinomycetes

Actinomycetes are spore-forming and gram-positive bacteria belonging to the phylum Actinobacteria, which can be found in soils, aquatic environments, air, and even in extreme environments, such as deserts, deep-sea sediments, and Antarctica (Nazari *et al*., 2022). *Actinomycetes* are known to produce an extensive range of bioactive compounds as well as variety of enzymes having multiple biotechnological applications (Limaye *et al*., 2017) and are the foremost abundant life style saprophytes that form thread-like filaments within the soil and grow as hyphae like fungi liable for the characteristically "earthy" smell of freshly turned healthy soil (Sutaria *et al*., 2021). In their DNA, *Actinomycetes* contain a high G+C ratio (guanine+cytosine) between 57 and 75% and have fungal characteristics, as they form hyphae and spores like fungi, but due to their prokaryote cell are classified as bacteria (class Actinobacteria) in the kingdom Monera (De Simeis & Serra, 2021; Rajivgandhi *et al*., 2022). The class Actinobacteria comprises five subclasses, 10 orders, 56 families and 286 genera (Ait Barka *et al*., 2016). They are widely distributed in soils, especially in dry, slightly acidic soils rich in organic matter and represent a high proportion of the soil microbial biomass (Saadoun *et al*., 2015; Barka *et al*., 2016). Most of the *Actinomycetes* are aerobic, chemoheterotrophic, and mesophilic and it is estimated that soils have 10^4 to 10^8 *Actinomycetes*/g soil, mainly in alkaline soils with a high concentration of organic matter (Nazari *et al*., 2022). The best growing conditions for most *Actinomycetes* are temperature between 25 and 30 °C, neutral pH (6 to 8) and low moisture content (Nazari *et al*., 2022).

The *Actinomycete* genes involved in the biosynthesis of active biomolecules belonging to the secondary metabolism, are located in the genome of the *Actinomycetes* and clustered in very long operons (Nodwell, 2017), whose general assembling is schematized in Figure 1. It is possible to identify codifying sequences (genes) and regulatory sequences (P and O) that are able to promote or inhibit the gene expression responding to specific environmental changings. These genes encode enzymes involved in the assembling and editing of the bioactive compound, in protecting the cell from its toxicity, and facilitating its extrusion in the environment (De Simeis and Serra, 2021).

Figure 1

Schematic view of an operon: promoter (P); operator (O); operon gene and terminator (T)

Source: Adapted from De Simeis and Serra (2021).

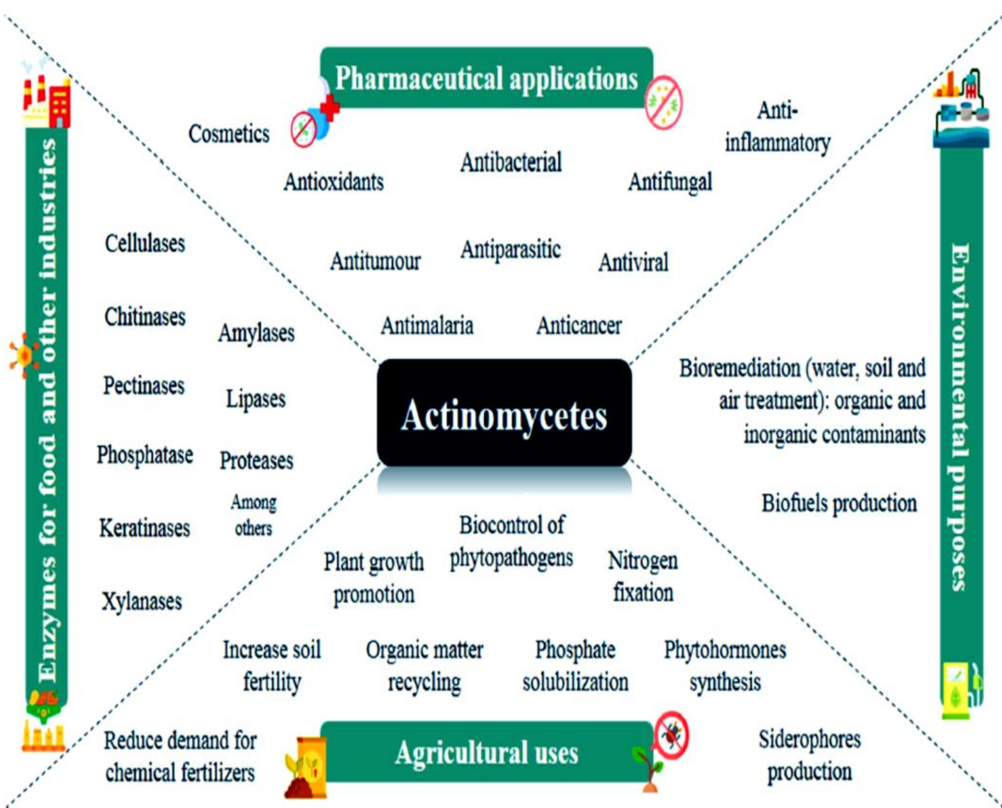
The production of secondary metabolites in *Actinomycetes* is at the end of the exponential growth phase and their syntheses greatly depend on the growth conditions, which is limited by the exhaustion of one key nutrient such as carbon or nitrogen or un-optimal environmental condition (Vaishnav & Demain, 2010). In addition, the production of secondary metabolites in *Actinomycetes* is strictly dependent on cell morphological and physiological differentiation and the factors that influence its behavior are variations, such as nutrient concentration and accessibility, competitor occurrence in the environment, metabolites, and cellular density, could influence the gene expression, and the enzymatic set inside the cell as a consequence (Thomashow *et al*., 2008).

3.2. Application of Actinomycetes

In soil, *Actinomycetes* collaborate with several processes, such as nitrogen fixation, phosphate solubilization, production of phytohormones and enzymes, organic matter decomposition, biocontrol of phytopathogens, bioremediation, among others (Nazari *et al*., 2022). *Actinomycetes* are known for producing several important secondary metabolites for medicine, food industry, and agriculture and are widely used and studied for obtaining antibiotics, antifungals, antivirals, immunosuppressants, compounds with anticancer and antioxidant activity, enzymes, bioinsecticides, biostimulants, biosurfactants, among other applications (Osama *et al.*, 2022; Rajivgandhi *et al*. 2022).

Figure 2

Potential uses of soil Actinomycetes for pharmaceutical, food, agricultural, and environmental applications



Source: Adapted from Nazari *et al*. (2022)

Antibiotic production. *Actinomycetes* are the most prolific producers of antibiotics that are best recognized and most valuable which accounts about 80% of the known antibiotics (Abdel-Aziz *et al*., 2019). *Actinomycetes* are best known for their ability to produce antibiotics and the discovery of antimicrobial agents from *Actinomycetes* led to a breakthrough in the world of medicine, due to their tremendous contribution in saving human from infectious diseases (Neha *et al*., 2017). Over 10,000 bioactive secondary metabolites are produced by *Actinomycetes,* representing 45% of all bioactive microbial metabolites discovered and these bioactive compounds were isolated and characterized and have been developed into drugs for treatment of wide range of diseases in human, animals and the agriculture sectors (Abdel-Aziz *et al*., 2019).

Table 1

Clinically important antibiotics produced by Actinomycetes

Antibiotic	Produced by	Activity
Sagamicin	*Micromonosporasaga miensis*	Antibacterial
Amiclenomycin	*Streptomyces lavendulae*	Antibacterial
Methylenomycin	*Streptomyces violaceoruber*	Antibacterial
Roseoflavin	*Streptomyces davawensis*	Antibacterial
Minosaminomycin	*Streptomyces sp.*	Antibacterial
Libramycin	*Streptomyces sp.*	Antifungal
Candihexin	*Streptomyces viridoflavus*	Antifungal
Nanaomycin	*Streptomyces rosa*	Antifungal
Purpuromycin	*Actinoplanesianthino genes*	Antifungal
Zorbonomycin	*Streptomyces bikiniensis*	Antifungal
Validamycin	*Streptomyces hygroscopicus*5008	Antifugal
Rosamicin	*Micromonospora Rosaria*	Antibacterial
Rifamycin	*Micromonosporarifa mycinica*	Antibacterial
Platenomycin	*Streptomyces platensis*	Antibacterial
Lincomycin	*Streptomyces lincolnensis*	Antibacterial
Azalomycin	*Streptomyces hygroscopicus*	Antifungal
Azalomycin	*Streptomyces malaysiensis*	Antifungal
Streptimidone.	*Streptomyces sp*	Agricultural
Kinamycin	*Streptomyces murayamaensis*	Antibacterial
Kuwaitimycin	*Streptomyces kuwaitinensis*	Antibacterial
Sarkomycin	*Streptomyces sp.*	Antitumor
Salinomycin	*Streptomyces albus*	Antiparasite
Antimycin	*Streptomyces antibioticus*	Antifungal
Antimycin	*Streptomyces lucitanusus*	Antifungal
Tomaymycin	*Streptomyces achromogenes*	Antiviral
Erythromycin.	*Actinopolyspora sp*	Antibacterial
Rapamycin	*Streptomyces Hygroscopicus*	Anti-proliferative immunosuppressant
Myomycin	*Nocardia sp*	Antibacterial
Lomofungin	*Streptomyces lomondensis*	Antifungal
Sclerothricin	*Streptomyces scleogranulatus*	Antifungal
Spoxamicin	*Streptosporangiumox azolinicum*	Antitrypanosomal

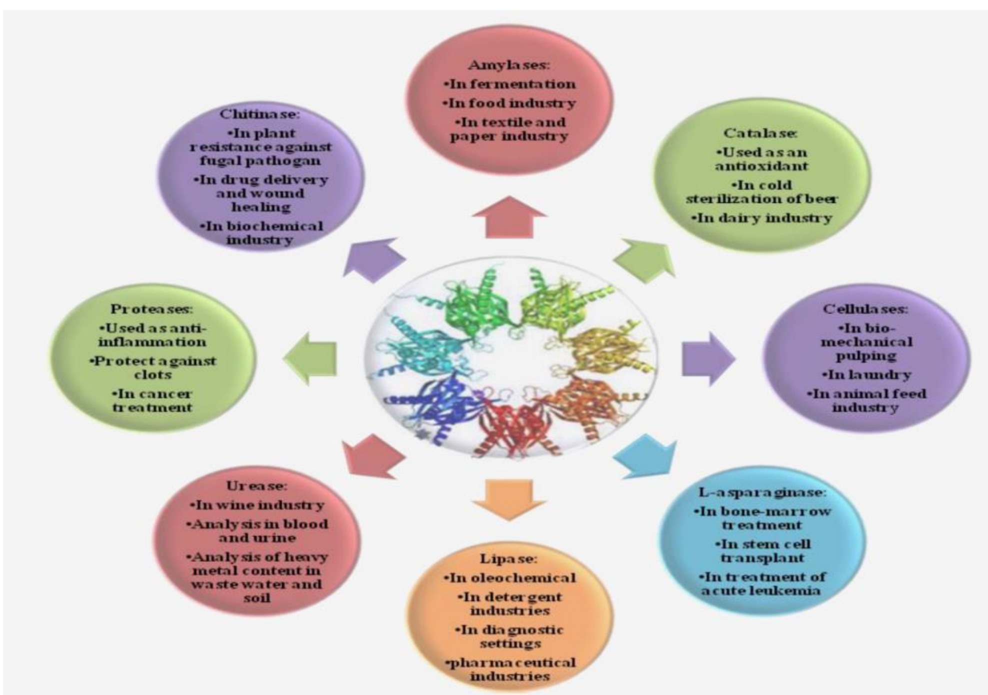
Avermectin	*S. avermitilis*	Antiparasitic

In natural soil habitat, *Streptomyces* are usually a major proportion of the total *Actinomycetes* population and recognized as prolific producers of useful bioactive compounds (Singh *et al*., 2016). Novel secondary metabolites with a wide range of biological activities may ultimately find applications as anti-infective, anticancer, antibacterial, antifungal, antiviral, anti-parasitic, immunosuppressive, enzyme inhibitory and diabetogenic (Kekuda *et al*., 2010). These antibiotics include amphotericin, nystatin, chloramphenicol, gentamycin, erythromycin, vancomycin, tetracycline, novobiocin, neomycin, among others (Sharma *et al.,* 2014).

Industrial Application of Actinomycetes (enzyme source). A wide array of enzymes and their products applied in biotechnological industries and biomedical fields has been reported from various genera of *Actinomycetes*. Enzymes derived from *Actinomycetes* are more attractive than enzymes from other sources because of their high stability and unusual substrate specificity (Prakash *et al*., 2013). Actinobacteria are known as biofactories of enzymes, with applications in the textile, bio-refineries, food, pulp and paper, agriculture, detergent and pharmaceutical industries (Ouchari *et al*., 2019). Thus, novel enzymes can be obtained from the *Actinomycetes* that are found in extreme habitats which carry huge commercial potential.

Figure 3

Applications of enzymes produced from *Actinomycetes*



Source: Adapted from Sharma *et al. (*2014)

Since there is vital information available due to the advent of genome and protein sequencing data, *Actinomycetes* have been continuously employed of the production of proteases, cellulases, chitinases, amylases, xylanases, and others (Neha *et al*., 2017). Actinomycetes are important for the production of enzymes, like chitinase (eg. *Streptomyces viridificans*), cellulases (eg. *Thermonospora* spp.), peptidases, proteases (*Nocardia* spp.), Xylanases *(Microbispora* spp.), ligninases (*Nocardia autotrophica*), amylases (*Thermomonospora curvata*), sugar isomerases (*Actinoplanes missouriensis*), pectinase, hemicellulase and keratinase (Sharma *et al.*, 2014).

Table 2

Commercially relevant enzymes produced by Actinomycetes.

Enzyme	Use	Industry of application
Protease	Detergents	Detergent
	Cheese making	Food
	Clarification- low calorie beer	Brewing
	Dehiding	Leather
	Treatment of blood clot	Medicine
Cellulase	Removal of stains	Detergent
	Denim finishing, softening of cotton	Textile
	Deinking, modification of fibers	Paper and pulp
Lipase	Removal of stains	Detergent
	Stability of dough and conditioning	Baking
	Cheese flavoring	Dairy
	Deinking, cleaning Textile	Textile
Xylanase	Conditioning of dough	Baking
	Digestibility	Animal feed
	Bleach boosting Paper and pulp	Paper and pulp
Pectinase	Clarification, mashing	Beverage
	Scouring Textile	Textile
Amylase	Removal of stains	Detergent
	Softness of bread softness and volume	Baking
	Deinking, drainage improvement	Paper and pulp
	Production of glucose and fructose syrups	Starch industry
	Removal of starch from woven fabrics	Textile
Glucose oxidase	Strengthening of dough	Baking
Lipoxygenase	Bread whitening	Baking
Phytase	Phytate digestibility	Animal feed
Peroxidase	Removal of excess dye	Textile

***Actinomycetes* as a source of biosurfactants.** Bio-surfactants are defined as surface-active molecules produced by living cells and mainly produced by those microorganisms having some influence on interfaces (Neha *et al*., 2017). Compounds with a lower molecular weight known as biosurfactants include glycolipids such as rhamnolipids, sophorolipids, mannosylerythritol lipids, and trehalose lipids, as well as lipopeptides like surfactant and fengycin (Hamed *et al*., 2021). Biosurfactants are structurally diverse group of surface active molecules synthesized by microorganisms (Atuanya *et al*., 2016). Surfactants, active metabolites that reduce surface tension, are thought to be formed by the majority of microorganisms, including *Actinomycetes* (Hamed *et al*., 2021). *Actinomycetes* play major role in production of bioemulsifiers and Trehalosedimycolates produced by *Rhodococcus erythropolis* has been extensively studied (Neha *et al*., 2017). A list of important biosurfactants produced from *Actinomycetes* is given in table 3.

Table 3

Types of Biosurfactants produced from Actinomycetes

Biosurfactant	Microorganism
Glycolipids:	
Glycolipids	Rhodococcusaurantiacus
Glycolipids	Rhodococcus sp. 5AT7
Pentasaccharide lipids	Nocardiacorynebacteroids
Trehalosetetraester	Rhodococcuserythropolis
Trehalosedicorynomycolate	Rhodococcuserythropolis
Lipopeptides/ Aminolipids:	
Lipopeptide	Streptomyces canus
Peptidolipids „Na"	Nocardia asteroids
Fatty acids/ Neutral lipids:	
Fatty acids + Neutral lipids	Nocardiaerythropolis
Others:	
Biosurfactant types I and II	Nocardia sp.L-417
Phosphatidylethanolamines	Rhodococcuserythropolis

Applications of Actinomycetes in agriculture. Overuse of agrochemicals has led to significant deterioration in soil fertility and threatens to deprive a major population of essential food sources. Due to their extraordinary properties compared to other microbes, *Actinomycetes* are beneficial for improving the soil quality, enhancing plant growth, and thereby contributing toward the "Green Revolution" (Saloni *et al*., 2022). *Actinomycetes* are involved in all processes that contribute to soil fertility such as nutrient cycling, decomposition of various compounds, formation of beneficial soil humus and in the biological control of plant pathogens, insects and weeds (Neha *et al*., 2017). *Actinomycetes* applied as plant growth-promoting Rhizobacteria (PGPR), as biofertilizer (nitrogen fixation, phosphate solubilization and potassium solubilization), in the production of phytohormones, role as biocontrol agents (BCAs) (production of antibiotics, production of siderophores, production of hydrogen cyanide (HCN), production of lytic enzymes and production of volatile organic compounds (VOCs)) (Sathya *et al*., 2017; Saloni *et al*., 2022). The spores of most *Actinomycetes* endure desiccation and show slightly higher resistance to dry or wet heat than vegetative cells (Neha *et al*., 2017).

Figure 4

PGPR activity of Atinomycetes through direct and indirect methods

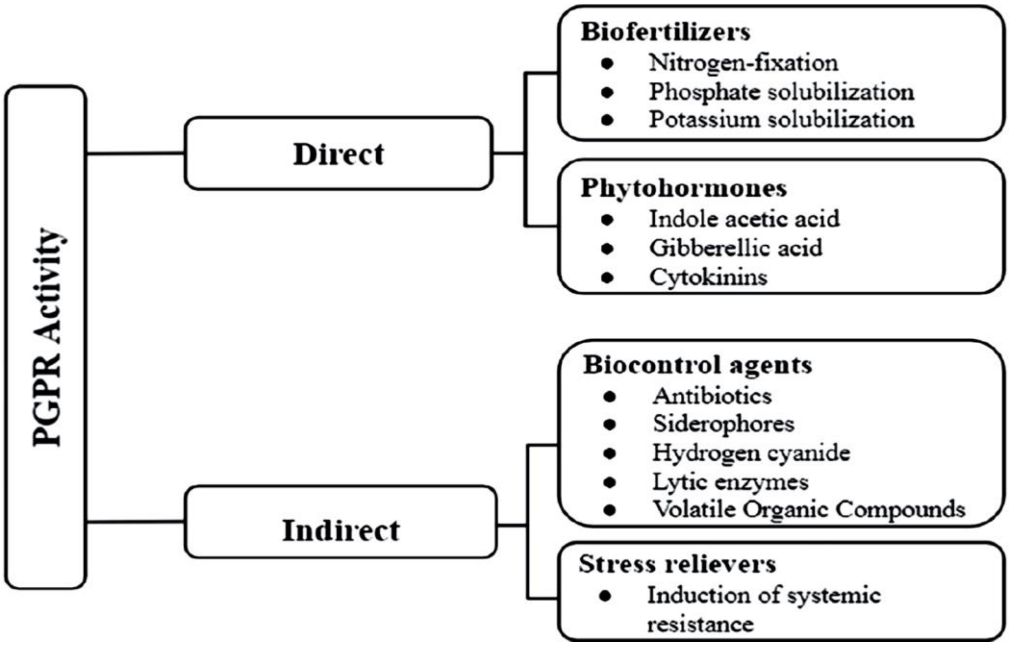
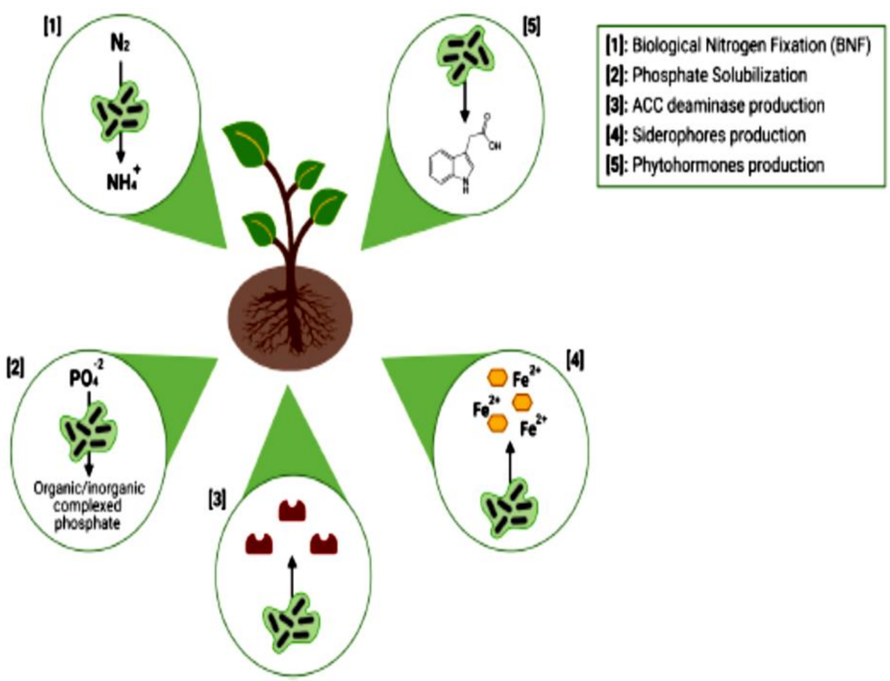


Figure 5

Roles of *Actinomycetes* as Plant growth promoters (PGP)



Source: Adapted from Silva *et al*. (2022)

Agriculture is constantly affected by the presence of pests, which are undesirable organisms that colonize crops and cause a disbalance in plant health and productivity (Silva *et al*., 2022). Several varieties of microorganisms including fungi and nematodes have been reported as strategies to biologically control insect pests, but, *Actinomycetes* especially, play an important role in the biological control of insects through the production of a large variety of insecticidally active compounds against different order of insects (Gomes *et al*., 2018). The effective action of *Actinomycetes* (**displayed in figure 6**) against insects is not only attributed to the production of bioactive compounds, but especially attributed to their capacity to produce chitinase enzyme, which degrades the insect chitin surface, allowing penetration of bioactive toxic lethal compound in the insect body (Brzezinska *et al*., 2014). *Actinomycetes* have been shown to be a vast source of novel agents having considerable potential for the biocontrol of insect pests and many of the secondary metabolites actinomycetes show insecticidal activity (Gomes *et al*., 2018).

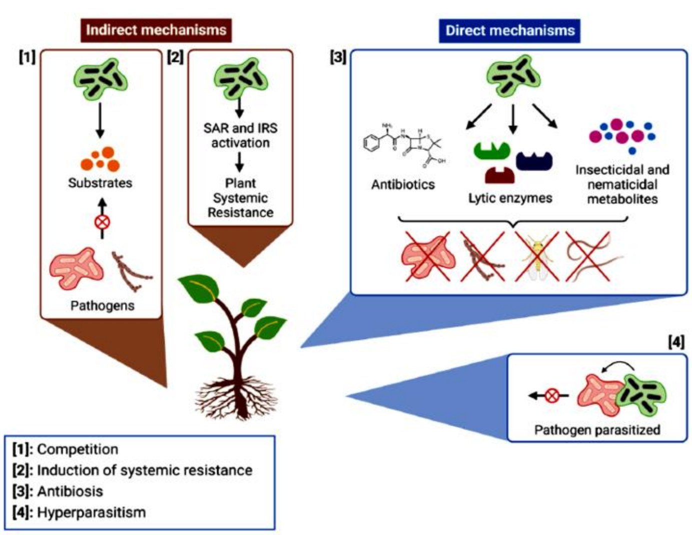
Table 4

Some bioactive compounds produced by actinomycetes and their related biological activities

Bioactive compound	Actinomycete	Activity
Lomofungin	*Streptomyces lomondensis*	Antifungal
Sclerothricin	*Streptomyces scleogranulatus*	Antifungal
Spoxamicin	*Streptosporangium oxazolinicum*	Antitrypanosomal
Avermectin	*S. avermitilis*	Antiparasitic
Antimycin	*Streptomyces lucitanusus*	Antifungal
Rosamicin	*Micromonospora rosaria*	Antibacterial
Validamycin	*Streptomyces hygroscopicus*	Antifugal
Azalomycin	*Streptomyces malaysiensis*	Antifungal
Roseoflavin	*Streptomyces davawensis*	Antibacterial
Rifamycin	*Micromonospora rifamycinica*	Antibacterial

Figure 6

Mechanisms of Actinomycetes as Biocontrol agents

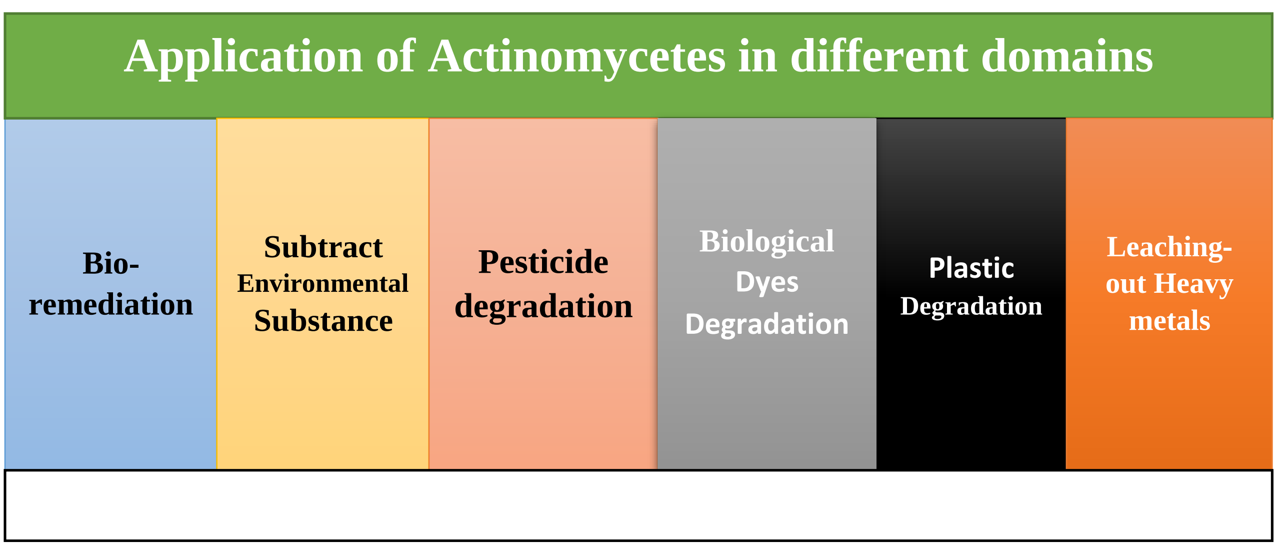


Source: Adapted from Silva *et al*. (2022)

Environmental application. Petroleum hydrocarbons are widely used in our daily life as chemical compounds and fuel. Greater use of result, petroleum has become one of the most common contaminants of large soil surfaces and eventually is considered as a major environmental problem (Sanscartier *et al*. 2009). Since *Actinomycetes* species have the capability to live in an oily environment, they possess many properties that make them good candidates for application in bioremediation of soils contaminated with organic pollutants and plays an important role in the recycling of organic carbon and are able to degrade complex polymers (Sharma *et al.,* 2014). In addition, *Actinomycetes* help in degrading a wide range of hydrocarbons, pesticides, aliphatic and aromatic compounds and they play an important role on organic compounds transformations (Neha *et al*., 2017). Furthermore, the application of chemical insecticides on crops for controlling deleterious insects has become hazardous to environment and human health, many efforts have been oriented in order to amend their use for a more ecofriendly and safe alternative control methods (Gomes *et al*., 2018). *Actinomycetes* are abundant in soil, and are responsible for much of the digestion of resistant carbohydrates (chitin and cellulose) and liable for the pleasant odor of freshly turned soil (Sharma *et al.,* 2014). Several *Actinomycetes* and other actinobacteria are renowned as degraders of toxic materials and are used in bioremediation and significantly well adapted to survival in harsh environments (Sharma *et al.*, 2014).

Figure 7

Environmental Applications of Actinomycetes in different domains



4. Conclusion

Actinomycetes bioactive metabolite production and applications are highly divers based on their habitats and are the best known for their ability to produce antibiotics and several pharmaceutical companies used their bioactive metabolite as one of the major source of novel drugs. Thus, the discovery of antimicrobial agents from *Actinomycetes* led to a breakthrough in the world of medicine, due to their tremendous contribution in saving human from infectious diseases. Due to these, *Actinomycetes* are recognized as the most prolific and most valuable producers of antibiotics which accounts about 80% of the known antibiotics. *Actinomycetes* bioactive metabolites also plays a vital role in agriculture, environment and industries. They are also renowned as degraders of toxic materials and are used in bioremediation and significantly well adapted to survival in harsh environments. The application of chemical insecticides on crops for controlling deleterious insects has become hazardous to environment and human health. Thus, *Actinomycetes* are open to newer approaches to minimize the hazardous effects of such chemicals and they will be the safe alternative control methods for the environment. The attractiveness of *Actinomycete* derived enzyme is due to their unusual substrate specificity and stability. More research is needed to be conducted for the deeper understanding of *Actinomycetes* therapeutic potential by using metabolomics, metagenomics and proteomics approach. Apart from this, the role of *Actinomycetes* in several industries with their potential and utilization of their product in plant biotechnology, environmental mitigation and waste management with some other applications in developing country yet to be done.

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ORCID
Yiglet Mebrat – https://orcid.org/0000-0001-9056-7032

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