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Chapter 6

Streptomyces Secondary Metabolites

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Abstract

Actinobacteria are found spread widely in nature and particular attention is given to their role in the production of various bioactive secondary metabolites. Tests on soil samples show that there can be a diversity of actinomycetes depending on the climate, the area it is growing in, how dry the soil is, and the quality of the soil. However, it was agreed after tests in Yunnan, China, that the genus *Streptomyces* sp. is most important in ecological function, representing up to 90% of all soil actinomycetes, and therefore helping to show the important characteristics needed of the soil actinomycete population. Streptomycete compounds are used for other biological activities, not just for antibiotics. It has been found that metabolites can be broadly divided into four classes: (1) regulatory activities in compounds, these include consideration of growth factors, morphogenic agents and siderophores, and plants promoting rhizobia; (2) antagonistic agents, these include antiprotozoans, antibacterials, antifungals, as well as antivirals; (3) agrobiologicals, these include insecticides, pesticides, and herbicides; and (4) pharmacological agents, these include neurological agents, immunomodulators, antitumorals, and enzyme inhibitors. It is found that *Streptomyces hygroscopicus* is one of the very best examples because it secretes in excess of 180 secondary metabolites to locate simultaneous bioactivities for a given compound. Increasingly, both its agricultural and pharmacological screenings are being used in conjunction with antimicrobial tests and have revealed several unusual aerobiological and therapeutic agents, which were hitherto unknown for biological use as antibiotics. Since streptomycetes are now being used increasingly to screen for antimicrobial activity, reports show the existence of secondary metabolites with other activities that may have been missed. Currently, nearly 17% of biologically active secondary metabolites (nearly 7600 out of 43,000) are known from streptomycetes. It has been found that soil streptomycetes are the main source used by bioactive secondary metabolites. However, recently there have been many and varied types of structurally unique and biologically active secondary metabolites found and obtained from marine actinomycetes, including those from the genus *Streptomyces*. Also, compounds that are synthesized by streptomycetes exhibit extreme chemical diversity. Diverse form made from from simple amino acid

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derivatives to high molecular weight proteides, and macrolactones from simple eight membered lactones to different condensed macrolactones. Berdy (1974) introduced the first classification scheme for antibiotics referring to the chemical structure. On the basis of Berdy's scheme, (1996) recognized that both low and high molecular weight compounds from 63 different chemical classes are produced by streptomycetes.

Keywords: antibiotics, PKS, NRPS, *Streptomyces*, secondary metabolites, antibacterial

1. Introduction

Streptomyces are Gram-positive, filamentous bacteria belonging to the group actinomycetes, a group that encompasses the majority of soil bacterial species. It is estimated that a gram of soil contains 109 CFU (colony-forming units) and out of these 109 CFUs, 107 are Actinobacteria [1]. They are ubiquitous soil bacteria, which are also found in the marine environment such as sediments [2]. Some are symbionts of sponges, for example, or insects like the ant *Acromyrmex octospinosus*, which lives in symbiosis with *Streptomyces* (*Streptomyces* S4)-producing antifungals, which help protect fungi cultivated by phytopathogenic ants [3]. *Streptomyces* have a particular development cycle. This cycle begins with a spore that germinates forming vegetative hyphae very little septate that will be structured in a network, the vegetative mycelium whose role is to explore the environment in search of nutrients. The bacterium will form aerial hyphae compartmentalized during a deficiency in element nutrients; these hyphae will then differentiate into spores, which are the form of resistance and dissemination of this bacterium [4].

The production of many secondary metabolites, including antibiotics, is coupled with morphological differentiation. Indeed, we observe a greater production of secondary metabolites during the transition from vegetative growth to aerial growth [5]. During this change in growth type, partial lysis of the mycelium vegetation takes place to provide the necessary nutrients for the creation of aerial mycelium; this release of nutrients could attract competitors. This synchronization of the cycle of development and production of secondary metabolites could be a way for the bacteria to dispel the invaders to keep these nutrients, or else kill the surrounding bacteria to feed them.

The secondary metabolite-producing microorganisms synthesize these bioactive and complex molecules at the lag phase and stationary phase of their growth (**Figure 1a**). However, regarding actinomycetes and *Streptomyces* especially, secondary metabolites can be produced at exponential, stationary, and death phases [6, 7]. It appears in times of environmental issues that nutrient depletion-limiting growth conditions allow formation of secondary metabolites. These are mostly found in fungi, plants, soil, and marine environments and organisms. Its has also been found that different organisms can produce metabolites that have various biological abilities, which include metal transporting agents, sex hormones, toxins, pigments, pesticides, immunosuppressants, anticancer agents, antibacterial agents, immunomodulating agents, antagonists, and receptor antagonists. The intermediate or finished products of primary metabolic pathways are obtained from their own systematic pathways for the synthesis

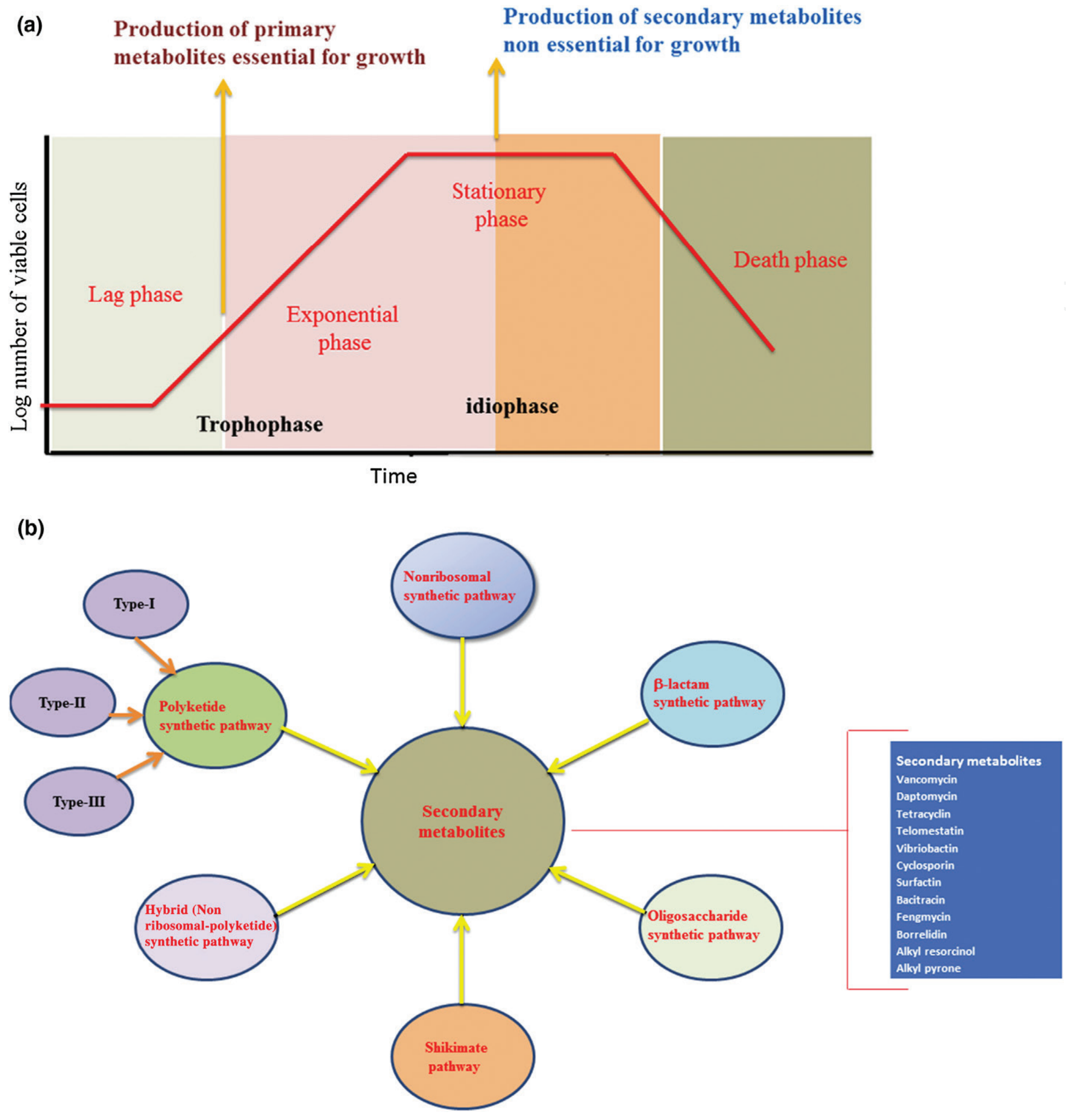

Figure 1. (a) Phases of bacterial growth and metabolite production. Overall, the major metabolites can be produced at the late interval phase and center of exponential phase, since the minor metabolites can be produced at the end of the stationary phase and during the constant phase. (b) Various pathways responsible for the assembly of secondary metabolites.

of secondary metabolites. To be able to obtain secondary metabolites, metabolic pathway reaction methods are conducted using multienzyme complexes or an individual enzyme. Genes that encode the synthetic pathway enzyme in general are within chromosomal DNA mostly arranged in cluster formation. As an example, *Streptomycetes griseus* and *Streptomyces glaucescens* chromosomal DNA contain 30 or more str/sts and blu genes that participate in streptomycin biosynthesis.

There are many varieties of known secondary metabolites synthesized by six pathways of different biosynthesis (**Figure 1b**): the peptide pathway, the polyketide synthase (PKS) pathway, the nonribosomal polypeptide synthase (NRPS) pathway, the hybrid (nonribosmial polyketide synthetic) pathway, the shikimate pathway, the β-lactam synthetic pathway, and the carbohydrate pathway. The pathway peptide concerns a part of the protein secondary metabolites: they are synthesized by simple translation of mRNAs into peptides by ribosomes. NRPSs are enzymes capable of condensing amino acids to form peptides without going through the ribosomal synthesis pathway. PKSs are enzymes capable of synthesizing a particular family of secondary metabolites: polyketides. The enzymes necessary for the synthesis of these polyketides are homologous to fatty acid synthase (FAS), which is responsible for the synthesis of fatty acid chains. Like the FASs these enzymes can couple precursors to form a chain. This chain will then undergo eight post-PKS changes before becoming active. Regarding the carbohydrate (known scientifically as oligosaccharide) route, it is based on the use of enzymes capable of coupling different sugars to form a carbohydrate precursor; this chain will then undergo modifications that will make the precursor active [8].

2. Bioactivity of *Streptomyces*

Streptomyces produce 70–80% of the natural bioactive substances known for their pharmaceutical or agrochemical applications [9, 10]. Continuously new metabolites with different biological activities are isolated from *Streptomyces* strains [11–14]. The first and most important product of *Streptomyces* is antibiotics [15]. From 1955 the genus *Streptomyces* has been the major supplier of new antibiotics [16]. They are the source of antibacterial, antifungal, antitumor, antiparasitic [17–19], antiviral, insecticide, pesticide, and herbicide substances, in addition to pharmacological substances such as immunomodulators (immunosuppressive and immunostimulatory agents), vasoactive substances, and neurological agents [20].

Enzymes are the most important products of *Streptomyces* after antibiotics [21], such as proteases, lipases, cellulases, amylases, pectinases, and xylanases [22, 23].

2.1. Production of antibiotics by *Streptomyces*

2.1.1. General

Antibiotics are produced by a wide range of fungal microorganisms and bacteria, and inhibit or kill other microorganisms at low concentrations [24]. A large number of antibiotics have been identified in natural environments, but less than 1% are medically useful. Many antibiotics have been structurally modified in the laboratory to increase their effectiveness, forming the class of semisynthetic antibiotics [25].

The history of antibiotics began with the discovery of penicillin by Fleming in the 1940s. The antimicrobial activities of antibiotics produced by microorganisms have been extensively studied, and the research undertaken has allowed completion of the antibacterial arsenal available to doctors and the general public.

Microorganisms producing chloramphenicol, neomycin, tetracycline, and terramycin were isolated in 1953. The discovery of chemotherapeutic agents and the development of new, more powerful drugs revolutionized medicine and have greatly reduced human suffering [26]. It is very well known that the genus *Streptomyces* produces the majority of antibiotics and biologically active secondary metabolites. Nearly 50% of the species *Streptomyces* isolated are recognized as producers of antibiotics [25]. Actinomycetes synthesize two-thirds of the microbial antibiotics of which about 80% are isolated from the genus *Streptomyces*. Even if other secondary metabolites are included, the actinomycetes remain the largest suppliers with about 60% (*Streptomyces* always have the biggest part with 80%). More than 60 substances with antibiotic activity produced by *Streptomyces* species are used not only in the world of veterinary and human medicine, but also in the field of agriculture and industry. The capacity of the members of the genus *Streptomyces* [27, 28] to produce commercially significant compounds, especially antibiotics, remains unsurpassed, possibly because of the extra-large DNA complement of these bacteria [17]. Antibiotics that come from Actinobacteria are grouped together so that they belong in their major structural classes. Examples of these are ansamycins (ritamycin), macrolides (erythromycin, azithromycin, and clarithromycin), aminoglycosides (streptomycin, kanamycin, tobramycin, gentamicin, and neomycin), tetracyclines, anthracyclines (doxorubicin), and β-lactam (penicillin, cephalosporin, carbapenems, and monobactams). Streptomycin and its varying species strains have been responsible for the production of most antibiotics and it appears that these organisms produce antibiotics to kill off potential competitors [29]. Streptomycin was one of the first antibiotics found. It is produced by *S. griseus* [30]. Today, various *Streptomyces* species are responsible for approximately 75% of both medical and commercial antibiotics and work very well in these areas. Due to the need for new antibiotics, studies have steered towards the isolation of streptomycetes and the careful screening of different habitats in which they are used. It has also been found through research that different conditions such as nutrients, culturing, and other factors may affect how *Streptomyces* develop to form antibiotics. With this in mind the medium constitution along with metabolic capacity of any organism production can affect antibiotic biosynthesis. Research into actinomycetes has found that they are capable of producing more one antibiotic (e.g. *S. griseus and S. hygroscopicus*) and also the same antibiotic can produce various species of Actinobacteria (e.g. streptothricin and actinomycin). Therefore, an antibiotic may be exactly the same with the same chemical composition and antibiotic spectrum as a produced Actinobacterium (**Table 1**). The table gives a list of antibiotics produced by variations of Actinobacteria and how the antimicrobial application has had a profound impact on the medical world where previously cancers, tumors, and even malaria could not be treated.

2.2. Production of enzymes

Research has reported that there are a great variety of enzymes that can be applied to biomicrobial fields and biotechnological industries from different genera of actinomycetes. Using the information available from genome and protein sequencing data, actinomycetes are constantly screened and used for producing amylases, xylanases, proteases, chitinases, cellulases, and other enzymes. Industrial applications, for example, the pronase of *S. griseus* and the kerase of *Streptomyces fradiae*, are used for the commercial production of biotechnology products such as hydrolysate proteins from different protein sources [31]. The proteases of *Streptomyces* have the advantage of easy elimination of the mycelium by filtration or simple centrifugation [32]. Similarly, Actinobacteria have been revealed to be an excellent resource for L-asparginase, which is produced by a range of Actinobacteria, mainly those from soils such as *S. griseus*, *Streptomyces karnatakensis, Streptomyces albidoflavus*, and *Nocardia* spp. [33, 34] (**Table 2**).

Antibiotic compound	*Streptomyces* species	Application
1,4-Dihydroxy-2-(3-hydroxybutyl)-9,10-anthraquinone 9,10 anthrac	*Streptomyces* sp. RAUACT-1	Antibacterial
1,8-Dihydroxy-2-ethyl-3-methylanthraquinone	*Streptomyces* sp.	Antitumor
2-Allyloxyphenol	*Streptomyces* sp.	Antimicrobial; food preservative; oral disinfectant
Anthracyclines	*S. galileus*	Antitumor
Arenimycin	*S. arenicola*	Antibacterial; anticancer
Avermectin	*S. avermitilis*	Antiparasitic
Bafilomycin	*S. griseus*, *S. halstedii*	ATPase; inhibitor of microorganisms, plant and animal cells
Bisanthraquinone	*Streptomyces* sp.	Antibacterial
Carboxamycin	*Streptomyces* sp.	Antibacterial; anticancer
Chinikomycin	*Streptomyces* sp.	Anticancer
Chloramphenicol	*S. venezuelae*	Antibacterial; inhibitor of protein biosynthesis
Chromomycin B, A2, A3	*S. coelicolor*	Antitumor
Daryamides	*Streptomyces* sp.	Antifungal; anticancer
Elaiomycins B and C	*Streptomyces* sp. BK 190	Antitumor
Frigocyclinone	*S. griseus*	Antibacterial
Glaciapyrroles	*Streptomyces* sp.	Antibacterial
Hygromycin	*S. hygroscopicus*	Antimicrobial; immunosuppressive
Lajollamycin	*S. nodosus*	Antibacterial
Lincomycin	*S. lincolnensis*	Antibacterial; inhibitor of protein biosynthesis
Mitomycin C	*S. lavendulae*	Antitumor; binds to double-stranded DNA
Pacificanones A and B	*S. pacifica*	Antibacterial
Piericidins	*Streptomyces* sp.	Antitumor
Proximicins	*Verrucosispora* sp.	Antibacterial; anticancer
Pristinamycine	*S. pristinaespiralis*	Antibacterial
Rapamycin	*S. hygroscopicus*	Immunosuppressive; antifungal
Resistoflavin methyl ether	*Streptomyces* sp.	Antibacterial; antioxidative
Saliniketal	*S. arenicola*	Cancer; chemoprevention
Salinispyrone	*S. pacifica*	Unknown
Salinispyrone A and B	*S. pacifica*	Mild cytotoxicity
Salinosporamide A	*Salinispora tropica*	Anticancer; antimalarial
Salinosporamide B and C	*S. tropica*	Cytotoxicity

Antibiotic compound	*Streptomyces* species	Application
Sesquiterpene	*Streptomyces* sp.	Unknown
Staurosporinone	*Streptomyces* sp.	Antitumor; phycotoxicity
Streptokordin	*Streptomyces* sp.	Antitumor
Streptomycin	*S. griseus*	Antimicrobial
Streptozotocin	*S. achromogenes*	Diabetogenic
Tetracyclines	*Streptomyces achromogenes*; *S. rimosus*	Antimicrobial
Tirandamycins	*Streptomyces* sp.	Antibacterial
Valinomycin	*S. griseus*	Ionophor; toxic for prokarotes, eukaryotes

Table 1. List of antibiotics produced by different Actinobacteria and their applications.

Enzyme	Industry	Use	*Streptomyces* strains
Aminoacylase	Pharmaceuticals	Production of semisynthetic penicillins and celpholosorin	*S. olivaceus*
			S. roseiscleroticus
			S. sparsogenes
Amylase	Detergent	Removal of stains	*Streptomyces* sp.
	Baking	Softening of bread; volume	*S. erumpons*
	Paper and pulp	Deinking	
		Drainage improvement	
	Starch	Production of glucose, fructose, syrups	
	Textile	Removal of starch from woven fabrics	
Cellulase	Detergent	Removal of stains	*S. thermobifida*,
	Textile	Denim finishing, softening of cotton	*halotolerans*, *S.*
	Paper and pulp	Deinking, modification of fibers	*thermomonospora*, *S. ruber*
Chitinase	Bioremediation	Utilization of chitin waste	*S. griseus*
			S. antibioctius
Glucose oxidase	Baking	Strengthening of dough	*S. coelicolor*
Keratinase			
Laccase	Bleaching	Clarification (juice), flavor (beer), cork stopper treatment	*S. brahimensis*
L-Asparaginase	Medicine	The treatment of acute lymphoblastic leukemia	*S. karnatakensis*
			S. halstedii

Enzyme	Industry	Use	*Streptomyces* strains
Lipase	Detergent	Removal of stains	*S. griseus*
	Baking	Stability of dough	
	Dairy	Cheese flavoring	
	Textile	Deinking, cleaning	
N-Acetylmuramidase	Bacteriology	Bacteriostatic enzymes	*S. globisporus*
Neuraminidase	Medical research	Cell surface and clinical studies	*Streptomyces* sp.
Pectinase	Beverage	Clarification, mashing	*S. lydicus*
	Textile	Scouring	
Penicillin amidase	Commercial significance	Production of 6-aminopenicillanic acid on an industrial scale	*Streptomyces* sp.
Peptide hydrolase	Pharmaceuticals	Industrial biosynthesis of oxytetracycline	*S. rimosus*
Phytase	Animal feed	Phytate digestibility	*S. luteogriseus* R10
Protease	Food	Cheese making	*S. pactum*, *S.*
	Brewing	Clarification; low calorie beer	*thermoviolaceus*, *Streptomyces* sp.
	Leather	Dehiding	
	Medicine	Treatment of blood clot	
Tyrosinase	Pharmacy	L-Dopa synthesis	*S. cyaneofuscatus*
Xylanase	Baking	Conditioning of dough	*Streptomyces* spp.
	Animal feed	Digestibility	
	Paper and pulp	Bleach boosting	
β-*N*-Acetyl-D-glucosaminidase	Studying their biochemical functions	Structural determination of the carbohydrate moiety of several glycoproteins	*S. griseus*

Table 2. List of enzymes produced by various Actinobacteria and their industrial application.

2.3. Bioherbicides

Secondary metabolites of Actinobacteria are used as herbicides against unwanted herbs and weeds (**Table 3**).

2.4. Probiotics

The use of *Streptomyces* sp. on the growth of tiger shrimp has been previously documented. Also, it was found that antibiotic product extracted from marine Actinobacteria and supplemented in feed was efficient in exhibiting the in vivo effect on feed and the detection of the efficient effect of in vivo white spot syndrome virus in black tiger shrimp. The murine actinomycete

Bioherbicides	Biocontrol	*Streptomyces* strains
Anisomycin	Inhibitor of growth of annual grassy weeds such as barnyardness and common crabgrass and broad-leaved weeds	*Streptomyces* sp.
Bialaphos	Control of annual and perennial grassy weeds and broad-leaved weeds	*S. viridochromogenes*
Carbocyclic coformycin and hydantocidin	Control of several weeds	*S. hygroscopicus*
Herbicidines and herbimycins	Monocotyledonous and dicotyledonous weed	*S. saganonensis*
Phthoxazolin, hydantocidin, and homoalanosin	Control of several weeds	*Streptomyces* sp.

Table 3. Exemles of herbicides produced by actinobacteria used against unwanted herbs and weeds.

activity was found to be an effective microorganism against biofilms resulting from *Vibrio* spp., suggesting therefore the potential preventive effect of Actinobacteria against *Vibrio* deseases [35]. Moreover, Latha [36] identified 18 Actinobacteria with probiotic properties isolated from chicken, and their results support the potential preventive effect of *Streptomyces* sp. JD9 as probiotic agents against deseases.

2.5. Aggregative peptide pheromones

The production of pheromone is considered to have important criteria: it is used as a defense against predators, in mate selection, and to conquer host-habitats through mass attack. Sex pheromone peptides in culture supernantrants were mainly found to support aggregation together by the same related species [37, 38]. A good example for aggregative peptide pheromones is *Streptomyces werraensis* LD22, which secretes a heat-stable, acidic pH resistant, low molecular weight peptide pheromone that promotes aggregation propensity and enhances the biofilm-forming ability of other Actinobacterial isolates.

2.6. Biosurfactants

Microbially derived compounds that share hydrophilic and hydrophobic moieties are surface active biosurfactants that are independent of mineral oil as a feedstock compared with chemically derived surfactants.

Biosurfactants are widely used in scientific research topics (nutrients, cosmetics, textiles, varnishes, pharmaceuticals, mining, and oil recovery) [39, 40]. The lipopeptide antibiotic daptomycin has received great interest as a treatment for Gram-positive bacterial infections; it is marketed as Cubicin by Cubist Pharmaceuticals. Various biosurfactant drugs or bioemulsifiers have been described as a class of Actinobacteria. The best described biosurfactants include a class of glucose-based glycolipids, most of which have a hydrophilic backbone, including glycosides associated with glucose units forming a trehalose moiety.

2.7. Vitamins

Vitamin B12 or cobalamine can be synthesized through the fermentation of Actinobacteria [41, 42], and has aroused considerable interest in the possible production of vitamins through microbial fermentation. In addition, cobalt salts in media act as a general Actinobacteria precursor in producing vitamins. Because cobalt is a rather effective bactericidal agent, this precursor must be added carefully. The fermentations producing the antibiotics streptomycin, aureomycin, grisein, and neomycin produce vitamin B12 as well if the medium is supplemented with cobalt without affecting the yields of antibiotic substances.

2.8. Pigments

Microbe-oriented pigments are of great concern. Especially, Actinobacteria are characterized by the production of various pigments on natural or synthetic media and are considered an important cultural characteristic in describing the organisms. Generally, the morphological features of colonies and production of different pigments and aerial branching filaments are known as hyphae, giving them a fuzzy appearance. These pigments are usually various shades of blue, violet, red, rose, yellow, green, brown, and black, which can be dissolved in the medium or may be retained in the mycelium. These microbes also have the ability to synthesize and excrete dark pigments, melanin or melanoid, which are considered useful criteria for taxonomical studies in the textile industry (**Table 4**).

2.9. Nanoparticle synthesis

The chemical techniques of nanoparticle preparation are less expensive when produced in high quantities; however, the nanoparticles may be contaminated by precursor chemicals, toxic solvents, and risky by-products. As a result, the development of high-yield, low-charge, nontoxic effects, and beneficial environmental procedures for metallic nanoparticle synthesis, and thus the biological method of nanoparticle synthesis, is considered important. Actinobacteria are actually effective nanoparticle producers, showing a number of biological properties, including antibacterial, antifungal, anticancer, antibiofouling, antimalarial, antiparasitic, and antioxidant activities. *Streptomyces* and *Arthrobacter* genera have proved to be "nanofactories" for developing clean and nontoxic procedures for the preparation of silver and gold nanoparticles (**Table 5**).

Pigments	*Streptomyces* strain	Class
III Undecylprodigiosin	*S. longispororuber* DSM 40599	Prodigiosin
IV Metacycloprodigiosin		
Actinomycin	*Streptomyces* sp.	Phenoxazinone
Granaticin	*S. litmocidin* DSM 40164	Naphthoquinone
Rhodomycin	*Synodontis violaceus* DSM 40704	Anthracycline glycoside

Table 4. Exemples of pigments produced by some streptomyces species and their classification.

Streptomyces strains	Nanoparticles
Streptomyces sp. GRD, *Streptomyces* sp., *S. albidoflavus*, *S. hygroscopicus*, *S. rochei*	Silver
S. aureofaciens, *S. glaucus*, *S. viridogens*, *S. hygroscopicus*	Gold
Streptomyces sp.	Zinc, copper, manganese

Table 5. Exemples of nanoparticules produced by some streptomyces species.

2.10. Bioremediation

Streptomyces have an important role in the recycling of organic carbon and are able to degrade complex polymers [43]. As reported, the wide use of petroleum hydrocarbons as chemical compounds and fuel in everyday life was considered well-known pollutants of large soil surfaces, causing serious environmental damage. Some studies proved the possible beneficial role of *Streptomyces* flora in the degradation of hydrocarbons [44, 45]. Many Actinobacterial strains are able to solubilize lignin and break down lignin-related compounds following the production of cellulose and hemicellulose-degrading enzymes and extracellular peroxidase [46]. Actinobacteria species are able to grow and live in oil-rich environments, and thus they could be in bioremediation to reduce oil contaminants.

2.11. Control of plant diseases

Results of new approaches to control plant diseases. Actinobacteria are potentially used in the agro-industry as a source of agroactive compounds of plant growth (rhizobacteria (polyglycerol polyricinoleate, PGPR) promoting) and for biocontrol [47, 48]. Approximately 60% of the new insecticides and herbicides derived from *Streptomyces* were discovered in the last 5 years. Kasugamycin, a bactericidal and fungicidal metabolite discovered *in Streptomyces kasugaensis* [49], inhibits protein biosynthesis in microorganisms but not in mammals, since its toxicological features are excellent. Inhibition of plant pathogenic *Rhizoctonia solani* under in vitro conditions was assessed with the culture supernatant of *Streptomyces* sp., which showed that the tested Actinobacteria had the ability to reduce damping-off severity in tomato plants (**Table 6**).

2.12. Nematode control

The majority of microorganisms were identified as antagonists of plant-parasitic nematodes, in particular Actinobacteria, which are effectively used in biological control because of their ability to produce antibiotics. The *Streptomyces* species-producing avermectins show that high nematicidal compounds can be produced by soil-borne organisms. *Streptomyces avermitilis* produces ivermectin, having an efficient activity against *Wucheria bancroftii* [50]. Similarly, various other antiparasitic compounds are produced from various *Streptomyces* sp.

2.13. Enhancement of plant growth

PGPR can directly or indirectly affect the growth of plants in two common ways. Indirect growth happens when PGPR decreases or prevents the harmful effects of one or more damaging

Disease	***Streptomyces* strains**	**Antibiotic produced**
Asparagus root diseases	*S. griseus*	Faeriefungin
Blotch of wheat	*S. malaysiensis*	Malayamycin
Broad range of plant diseases	*S. griseochromogenes*	Blasticidin S
Brown rust of wheat	*S. hygroscopicus*	Gopalamycin
Damping-off of cabbage	*S. padanus*	Fungichromin
Grass seedling disease	*S. violaceusniger* YCED9	Nigericin and guanidylfungin A
Phytophthora blight of pepper	*S. humidus*	Phenylacetic acid
Phytophthora blight of pepper	*S. violaceusniger*	Tubercidin
Potato scab	*S. melanosporofaciens*	Geldanamycin
	EF-76 and FP-54	
Powdery mildew	*Streptoverticillium rimofaciens*	Mildiomycin
Powdery mildew of cucumber	*Streptomyces* sp. KNF2047	Neopeptin A and B
Rice blast disease	*S. kasugaensis*	Kasugamycin
Rice sheath blight	*S. cacaoi* var. *Asoensis*	Polyoxin B and D
Root rot of pea geldanus	*S. hygroscopicus*	Geldanamycin
Sheath blight of rice	*S. hygroscopicus* var. *Limoneus* No. T-7545	Validamycin

Table 6. Antibiotics produced by the Actinobacteria that suppress various plant diseases.

microorganisms. This is mainly researched through biocontrol or the antagonism of soil plant pathogens. Particularly, the effects of pathogen invasion and establishment can be strongly prevented by colonization or the biosynthesis of antibiotics and other secondary metabolites. Direct growth promotes plant growth by PGPR when the plant is supplied with a bacterial synthesized compound, or when PGPR otherwise facilitates plant uptake of soil nutrients. Merriman [51] reported the use of *S. griseus* for seed treatment of barley, oat, wheat, and carrot to increase their growth. The isolate was originally selected for the biological control of *Rhizoctonia solani*. It has been reported that *Streptomyces pulcher*, *Streptomyces canescens*, and *Streptomyces citreofluores* were used in the control of bacterial, *Fusarium*, and *Verticillium* wilts, early blight, and bacterial canker of tomato.

Like most rhizobacteria, it seems highly probable that streptomycetes are capable of directly enhancing plant growth.

2.14. Phytohormone production

Manulis et al. [52] described plant hormone production, including indole-3-acetic acid (IAA), as well as the underlying pathways of synthesis by a variety of *Streptomyces* spp. (*Streptomyces violaceus*, *Streptomyces scabies*, *S. griseus*, *Streptomyces exfoliatus*, *Streptomyces coelicolor*, and *S. lividans*),

***Streptomyc*es strain**	**Odor type**	**Secondary metabolite**
Streptomyces sp.	Earthy	Trans-1,10-dimethyl-trans-9-decalol (geosmin)
	Musty	1,2,7,7-Tetramethyl-2-norbornanol
	Potato-like	2-Isobutyl-3-methoxypyrazine or 2-isopropyl-3-methoxypyrazine

Table 7. Odor-producing compounds from Actinobacteria.

since earlier works have studied the IAA synthesis process in *Streptomyces* spp. This was the first investigation confirming IAA production according to new analytical methods, i.e. high-performance liquid chromatography and gas chromatography–mass spectrometry. Furthermore, Manulis et al. [53] described well the biosynthetic pathways of IAA in *Streptomyces.* On the other hand, Aldesuquy et al. [54] studied the effect of streptomycetes culture filtrates on wheat growth, showing a subesquent significant increase in shoot fresh mass, dry mass, length, and diameter statistically exhibited with some bacterial strains at different sample times. *Streptomyces olivaceo-viridis* revealed a remarkable effect on yield components (spikelet number, spike length, and fresh and dry mass of the developing grain) of wheat plants. This activity may result from the increase in phytohormone bioavailability defined as PGPR produced, since all PGPR strains (*Streptomyces rimosus, Streptomyces rochei*, and *S. olivaceoviridis*) produce significant amounts of auxins (IAA), gibberellins, and cytokinins.

2.15. Biolarvicides

Dhanasekaran et al. [55] obtained that the isolates *Streptomyces* sp., *Streptosporangium* sp., and *Micropolyspora* sp. presented with great larvicidal activity against *Anopheles* mosquito larvae. Rajesh et al. [56] prepared silver nanoparticles from *Streptomyces* sp. GRD cell filtrate and found remarkable larvicidal activity against *Aedes* and *Culex* vectors, causing transmission of dengue and filariasis. In addition, studies carried out on the larvicidal effect of Actinobacterial extracts against *Culex* larvae have shown that a concentration of 1000 ppm of the isolate *Streptomyces* sp. appeared as KA13-3 with 100% mortality and KA25-A with 90% mortality. Other secondary metabolites obtained from Actinobacteria (tetranectin [56], avermectins [57], macrotetrolides [58], and flavonoids [59]) are classified as toxic to mosquitoes.

2.16. Odor and flavor compound production

The work carried out by Gaines and Collins [60] on the metabolites of *Streptomyces odorifer* led them to conclude that the earthy odor is likely due to a combination of trivial compounds (acetic acid, acetaldehyde, ethyl alcohol, isobutyl alcohol, isobutyl acetate, and ammonia). Consequently, other components contributing to the odor could also be produced. Several odor-producing compounds have been defined from Actinobacteria (**Table 7**). Earthy odors in sufficiently treated water supplies led to considerable interest from consumers, who may classify water with these odors as harmful for human drinking needs. These odors are the second most common cause of odor problems recorded by water utilities, behind chlorine.

3. Metabolic pathways in the production of secondary metabolites of bacteria

Secondary metabolic pathway reactions are formed by an individual enzyme or multienzyme complexes. Intermediate or end products of primary metabolic pathways are channeled from their systematic metabolic pathways that lead to the synthesis of secondary metabolites. There are six known pathways: the peptide pathway, the PKS pathway, the NRPS pathway, the hybrid (nonribosomal polyketide) synthetic pathway, the shikimate pathway, the β-lactam synthetic pathway, and the carbohydrate pathway. The genes encoding these synthetic pathway enzymes are generally present in chromosomal DNA and are often arranged in clusters.

3.1. Nonribosomal peptide synthesis pathways

Nonribosomal peptides are peptides that are not synthesized at the level of ribosomes. One of the peculiarities of nonribosomal peptides is their small size. These peptides are not encoded by a gene, and they are not limited to the 20 basic amino acids. Indeed, the peculiarity of the NRPS system is the ability to synthesize peptides containing proteinogenic and nonproteinogenic amino acids. In many cases, these enzymes are activated in collaboration with polyketone synthases giving hybrid products. The products of these multifunctional enzymes have a broad spectrum of biological activities, and some of them have been useful for medicine, agriculture, and biological research [61].

NRPS are organized in a modular way. Each module is responsible for the incorporation of a specific monomer. The modules are subdivided into domains, and each domain catalyzes a specific reaction in the incorporation of a monomer. The number and order of modules and the type of domain present in the modules of each NRPS determine the structural variation of synthesized peptides by dictating the number, order, and choice of amino acid to incorporate during elongation. Four main areas are needed for complete synthesis (**Figure 2**). Each domain has a specific function when incorporating the monomer. Domain A, from 500 to 600 amino acid residues, is necessary for the recognition of the amino acid and its activation.

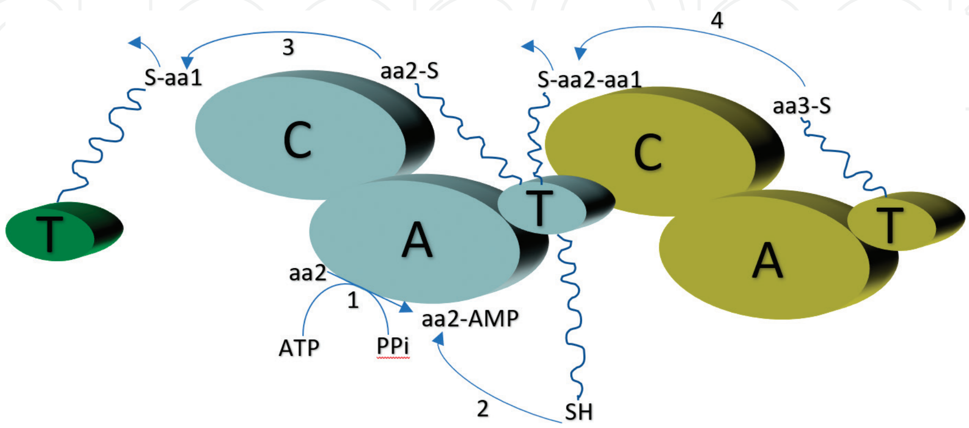

Figure 2. Minimum domains required in an NRPS [62].

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The 80–100 amino acid residues of domain T, located downstream of domain A, form a thioester bond (covalent bond) between the activated monomer and the NRPS, and this allows the peptide being synthesized to remain attached to the NRPS throughout the process of elongation. The condensation domain C (450 amino acids) is usually found after each A–T module and catalyzes the formation of peptide bonds between bound residues on two adjacent modules. In general, the number and order of modules present in an NRPS determine the length and the resulting nonribosomal peptide structure. The thioesterase domain, present only in the last module, releases the peptide from the NRPS.

3.2. Polyketide synthase pathways

Polyketides are kown as natural products, having diverse functions in medical applications, and they are assembled by PKS enzymes. PKS enzymes act exactly like fatty acid synthase to generate a diverse extent of polyketides. Also, PKS enzymes start the polyketide assembly by priming the initiator molecule to the catalytic residue, and then making an extender unit for the elongation chain. On the basis of structural architecture and variation in enzymatic mechanism, PKS enzymes have been classified into three types: (1) type I PKS, (2) type II PKS, and (3) type III PKS.

This section describes all three types of PKS enzymes (**Table 8**). Modular PKSs include active sites, called modules; they are polypeptides used to synthesize a string of carbon. The active sites of each module are used only once during assembly of the molecule and determine the choice of units of structure and the level of reduction or dehydration for the cycle of expansion. They catalyze the length of the string of carbon, and the number of cycles of reaction is determined by the number and order of the modules in the polypeptide constituting the PKS [63].

3.2.1. Type I PKS

These are multidomain proteins (containing several domain enzymes on the same polypeptide) that can be modular (**Figure 3**), for example, the modular systems responsible for the synthesis of macrolides (erythromycin, rapamycin, rifamycin B, etc.) in bacteria, which is iterative (**Figure 4**) (for example, lovastatin nonaketide).

Either modular PKS or type I	Either discrete PKS or type II	Either ketosynthase polyketide or type III
Many functional enzymes organized into modules. Each module has a specific function and use; acyl carrier protein (ACP) domain activates acyl-CoA substrates malonyl-CoA or methylmalonyl-CoA or ethylmalonyl-CoA, an extender unit	Includes a series of modular heterodimeric enzymes. Each enzyme has a special function and use; the ACP domain transfers activated acyl-CoA substrate malonyl-CoA, an extender unit	The homodimeric ketosynthase enzyme can carry out various biochemical reactions at a single active site; it acts in the absence of ACP or directly recognizes the acyl-CoA molecules malonyl-CoA or methylmalonyl-CoA, an extender unit

Table 8. Classification of polyketide synthase enzymes and the functional and mechanistic differences between them.

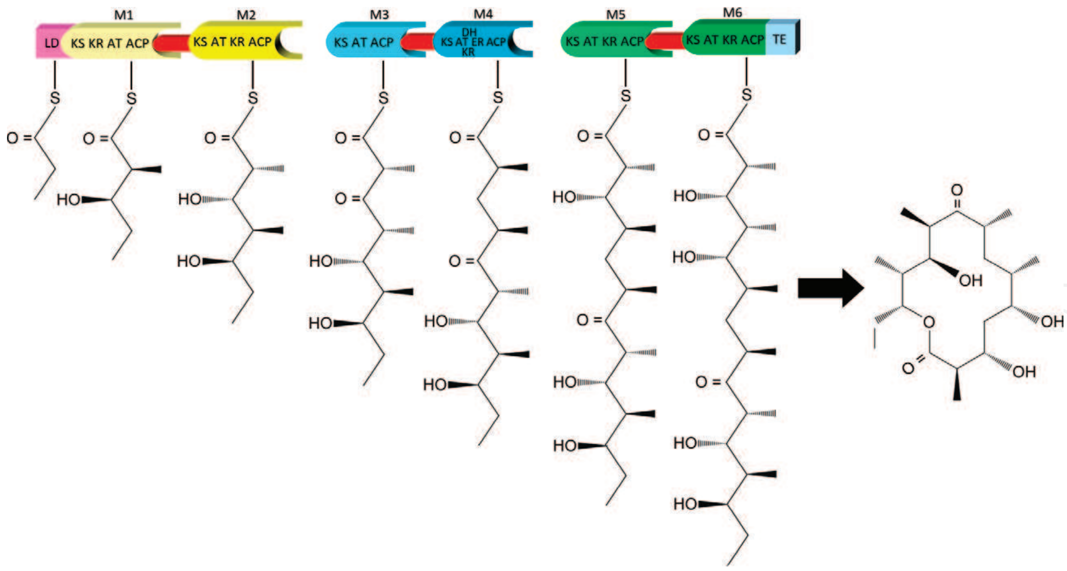

Figure 3. Structure of a modular type I PKS [64]. Note: KS, ketosynthase; AT, acyl transferase; KR, ketoreductase; ACP, acyl carrier protein; TE, Thioesterase; DH, dehydrate.

3.2.2. Type II PKS

These are monofunctional protein complexes (for example, actinorhodin from *S. coelicolor*). These PKSs catalyze the formation of compounds that require aromatization and cyclization steps but no reduction or dehydration. These PKSs are involved in the biosynthesis of aromatic bacterial products such as actinorhodin, tetracenomycin, and doxorubicin [66].

3.2.3. Type III PKS

These have a single active site to catalyze the extension of the polyketide chain and cyclization without the use of an ACP (**Figure 5**). They are responsible for the synthesis of chalcones and stilbenes in plants, as well as polyhydroxy phenols in bacteria. Chalcone synthases are small

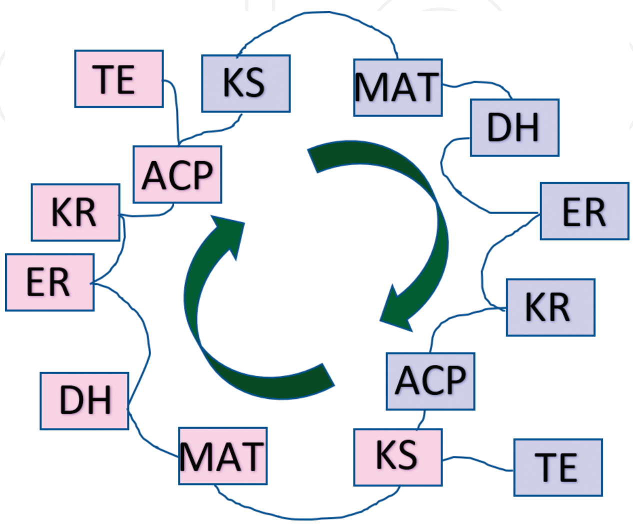

Figure 4. Structure of an iterative type I PKS [65].

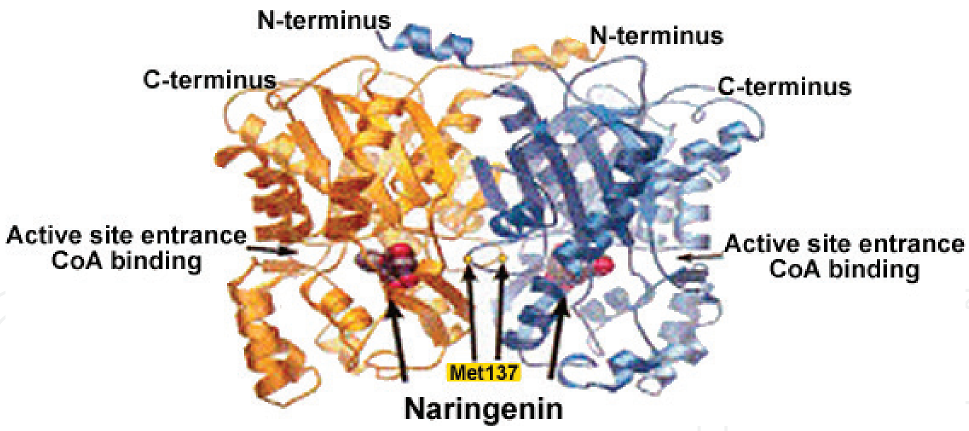

Figure 5. Type III PKS [68].

proteins with a unique polypeptide chain, and are involved in the biosynthesis of flavonoid precursors [67].

The shikimate pathway groups the essential building blocks for a large assembly of aromatic metabolites and amino acids. Metabolites of the aromatic compounds present protection against ultraviolet radiation, electron transport, and signaling molecules, and also act as antibacterial agents. The shikimate pathway enzymes use specific chemical substrates, i.e. erythrose-4-phosphate and phosphoenol pyruvate (primary metabolites), to start the synthesis of aromatic building blocks. Herein, the first seven enzymes catalyze the chemical reactions in a chronological manner to produce chorismate. Two bacterial enzymes are able to transfer a complete enolpyruvoyl moiety to a metabolic pathway. 5-Enolpyruvoyl shikimate 3-phosphate synthase is considered one of the shikimate pathways. Chorismate synthase is an enzyme involved in this pathway, and its function needs the presence of a reduced cofactor, flavin mononucleotide, for its activation [69].

The Gram-positive, filamentous *Streptomyces venezuelae* (soil bacterium) and other actinomycetes gather chloramphenicol with the help of aromatic precursors. Aromatic building blocks originated from the shikimate pathway act as precursors for the phenylpropanoid unit of chloramphenicol. First, chorismic acid branches out from the shikimate pathway to produce *p*-aminophenylalanine, which could afterwards be converted into a *p*-nitrophenylserinol component by an enzymatic reaction. 4-Amino-4-deoxychorismic acid (ADC) was found as a common precursor for both para-aminobenzoic acid and PAPA: a flexible tool for identifying pleiotropic pathways using genome-wide association study summaries pathways. The genetic map reveals that pabAB genes encode enzymes for ADC biosynthesis that are clustered in a distinct region of the *S. venezuelae* chromosome. Echinosporin isolated from *Saccharopolyspora erythraea* has antibacterial and anticancer activities. This molecule has a sole tricyclic acetal-lactone structure, and the main structure does not show its biosynthetic pathway. The shikimate pathway intermediate is guided to group the echinosporin by enzymatic reactions [70].

3.3. Lactam ring synthetic pathways

Cephalosporins belong to the family of β-lactam antibiotics, used for treating bacterial infections for more than 40 years. Interestingly, Gram-positive bacteria, Gram-negative bacteria, and fungi are the major sources of β-lactam antibiotics. The Gram-positive *Streptomyces clavuligerus* is able to produce both clavulanic acid and cephamycin, since the Gram-negative bacterium *Lysobacter lactamgenus* produces cephabacins. Two hypotheses have been put forward for β-lactam biosynthesis: (1) horizontal gene transfer (HGT) from bacteria to fungi and (2) vertical descent (originated from a common ancestor). Bioinformatics, genetic designs, and sequence identity are more beneficial in HGT.

The production of β-lactam antibiotic occurs through three different steps: prebiosynthetic steps, intermediate formation steps, and late steps (also known as decorating steps) [71–76]. The biosynthesis of building blocks for β-lactam consist of L-α-aminoadipic acid, L-cysteine, and L-valine. L-α-Aminoadipic acid is not a proteinogenic amino acid formed from L-lysine. The actinomycete lysine 6-aminotransferase converts L-lysine into L-α-aminoadipic acid.

The two starting enzyme reactions are omnipresent in fungi and cephalosporin biosynthesis. D-(L-Aminoadipyl)-L-cysteinyl-D-valine synthase is the first enzyme, using all three amino acids gathered into a tripeptide through condensation reaction. This enzyme is NRPS encoded by the acvA (pcbAB) gene. The next step is the synthesis of a bicyclic ring (a four-member β-ring is fused with a five-member thiazolidine ring) through an oxidative reaction, catalyzed by isopencillin N-synthase, and results in the formation of isopenicillin N. Cephalosporin–cephamycin biosynthesis is the development of the five-member thiazolidine ring into a six-member dihydrothiazine ring. Several enzymes consecutively contribute to this ring conversion. β--Lactam biosynthesis is synthesized by a gene, which is usually clustered in the DNA of all reproducing bacteria. Bacterial species capable of producing β--lactam antibiotics exhibit an ecological benefit. In contrast, β-lactam–producing bacteria show low sensitivity to β-lactams on their own, or they have evolved to inactivate β-lactam antibiotics by β-lactamase enzymes.

4. Conclusion

Streptomyces are able to produce a number of antibiotics and other important pharmaceutical drugs to treat infections caused by bacteria and fungi, cancer, and heart-related diseases. Bacterial species reveal a complex lifecycle with physiological and biochemical adaptability, along with the ability to synthesize a large variety of secondary metabolites, presenting complex structures following different metabolic pathways. Understanding the secondary metabolite biosynthesis and pathways would lead to progress in combinatorial biosynthesis in the pharmaceutical and biotechnology industries.

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Conflict of interest

The authors declare that no conflicting interest exists.

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