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Biodiversity of Actinomycetes and Their Secondary Metabolites: A Comprehensive Review

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Abstract

Background: Among prokaryotes, Actinomycetes are one of the most explored microorganism due to their capability of novel bioactive secondary metabolites production. Actinomycetes secondary metabolites are known for their role in different cellular, physiological and biological processes.

Main body: Actinomycetes are most widely distributed in natural ecosystem habitats such as soil, hypersaline soil, rhizosphere soil, freshwater, limestone, volcanic cave, marine sediments, sponges, and desert. Actinomycetes bioactive secondary metabolites most important features are that they have specific microbial producers, diverse bioactivities and unique chemical structures. Some important antibiotics produced by actinomycetes are actinomycetin, mycetin, micromonosporin and from actinomyces are lysozyme, actinomycin, streptothricin, proactinomycin and streptomycin. These antibiotics differ greatly in their structure, antimicrobial and toxicity properties. Actinomycetes secondary metabolites include spirotetronate, quinones, lactams, aminoglycosides, β-lactams, diketones, aromatic ketones, ansamycin, glycopeptides, lactones, Tetracenediones, anthracyclines, macrolides, fattiviracins, polyenes and tetracyclines, natural polycyclic polyketide.

Conclusion: This review study summarized that Actinomycetes are naturally distributed species found in diverse environments. It is assumed that actinomycetes species found in extreme conditions have the capability to produce novel bioactive secondary metabolites that remain unexplored yet.

Keywords

Actinomycetes, Antibiotics, Biodiversity of Actinomycetes, Secondary Metabolites

1. Introduction

Actinomycetes are Gram-positive filamentous bacteria and their genome contains high GC (guanine and cytosine) content. Actinomycetes are ubiquitously found in both aquatic and terrestrial ecosystems [1]. Many actinomycetes have mycelial lifestyle and undergo complex morphological differentiation. Actinomycetes produce about two-thirds of all antibiotics available in the market. Bio-active secondary metabolites produced by actinomycetes are used as antibiotics, antifungal, anticholesterol, antiprotozoal, antiviral, anticancer, antihelminth immunosuppressant and as a single cell protein [2]. Actinomycetes are commonly found in natural environment and have an important role in biodegradation of organic matter [3]. Actinomycetes have prominent value in their diversity, their secondary metabolites have the capability of bioactive molecules which act as antibiotics, enzymes and immunosuppressive and antitumor agents and produced half of the available antibiotics on the market. For the past fifty years, due to huge antibiotic-producing sources, efforts have been focused on actinomycetes for the production of novel antibiotics [2,4].

Professor Alexander Fleming in 1928, most fortunate discovered antibiotics by chance in London, *Staphylococci* strain inoculated on agar left on his workbench, after a while, he noticed that a mold colony had contaminated the plate but around mold colonies there was no bacterial growth observed [5]. After observation, the suppressing bacterial growth was found and named as penicillin. After successful discovery, an extensive search started among other microbes for the production of such bio-active chemical compounds. During the last two decades, the most important groups of antibiotics that were discovered are tetracycline and macrolides [6].

Actinomycetes produce various bio-active compounds such as antibiotics, enzyme inhibitors and hydrolytic enzymes which are resistant to nutrient stress and desiccation by producing spores [7]. Actinobacteria play diverse roles in their associations with various higher organisms. Some Actinobacteria species and insects develop a naturally symbiotic relationship, where bacteria are formed in anatomical compartments while attine ants have symbiotic relation with fungi *Leucoagaricus gongylophorus* and these ants acquire Actinobacteria for useful antibiotics for controlling fungal counterparts. A similar relationship was found

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between *Streptomyces* and termite where sceliphrolactam was produced by *Streptomyces* strain that inhibits the growth rate of amphotericin B resistant *C. albicans* [8,9].

Biodiversity of Actinomycetes

Actinomycetes are most widely distributed in nature, free-living, saprophytic, and most commonly found in soil, water and plants. They are source of many biological important bioactive compounds and are continued for screening of novel bioactive compounds. Actinomycetes produce two-thirds of naturally occurring antibiotics [10]. Researchers are actively involved in the isolation and screening of actinomycetes from new habitats for novel antibiotics production. Many soil actinomycetes remain uncultivable and become an obstacle to the discovery of novel antibiotics [11].

Soil and Niche

Soil contains one major group of actinomycetes population which varies with types of soil. According to literature review on the isolation of actinomycetes, only 10% were isolated from nature. For discovery of novel antibiotics, it is necessary to explore new habitats of Actinobacteria, it is assumed that new species or strains will get having the capability to produce antibiotics and antibiotic-resistant drugs [12]. According to basic knowledge of habitat, the physiology and productivity of biomolecules of actinomycetes increased and the ecological properties of actinomycetes assumed significance which will way for screening sources to spread into uncommon environments. Manipur part of Indo-Myanmar hotspot has promise for novel species of actinomycetes such as *Actinoplanes, Micromonospora, Actinomadura, Nonomuria, Streptosporangium* and *Nocardia* most abundantly found [13, 14].

Hyper-saline and Rhizosphere soil

Hyper-saline habitats include salterns, saline lakes, hypersaline soils and saline soil which are extreme environments [15]. Hypersaline soils consist of 9-23 % salts. Actinomycetes genera found in saline soils are *Streptoverticillium, Streptomyces, Micromonospora, Microbispora, Nocardia, Actinoplanes, Kitasatosporia, Planomonosphora, Streptomyces albidoflavus, Streptomyces alboflavus, Streptomyces griseoflavus* and *Streptomyces rimosus* have anti-fungal activity against *Fusarium solani, Aspergillus niger, Candida albicans, Streptomyces rameus, Cryptococcus, Streptomyces albus, Streptomyces fragilis, Streptomyces exfoliates, Streptomyces violaceus, Streptomyces olivaceiseleroticus, Streptomyces albidoflavus, Streptomyces graminifaciens, Streptomyces diasticus* and *Streptomyces antibioticus*. There are many dominant groups, stable in rhizosphere and bulk soil both in winter and spring seasons. Actinomycetes are inhabitants of important rhizospheres of many plants where they act as plant growth enhancement and protect plants from phytopathogens [13, 16].

Limestone

It is a sedimentary rock composed of minerals and various crystal forms of calcium carbonate such as calcite and aragonite. Limestone quarries are assumed to be good niche for detection, as isolation and screening of isolates and novel bioactive compounds [17]. Actinobacteria produce various bio-active secondary metabolites which include antibiotics, pesticides, herbicides, anti-parasitic and various enzymes, these compounds have therapeutic and commercial applications [18].

Marine sediments and sponges

Actinomycetes in the sea are mostly unexplored, difficult to catch marine actinomycetes from indigenous oceans due to lack of effort to explore marine actinomycetes. While there is no deviation for the cultivation of marine actinomycetes. Actinomycetes are found in a unique environment in the sea such as deep-sea hydrate reservoirs, and marine organic aggregates which have high antagonistic activity within the microorganism community [19]. Bonafide actinomycetes are distributed in various ecosystems in the sea. Marine actinomycetes are secondary metabolites used in the pharmaceutical industry. It is assumed that marine actinomycetes species could provide the drugs necessary for the battle against drug-resistant infectious diseases [18, 20]. Marine microbes produce diverse antibiotics with different chemical structures. Marine sponges harbor a huge number of microbes especially bacteria in their tissue which accounts for 40 % of their biomass. New and novel actinomyces species and strains have been found in *Rhopaloeides odorabile*, *Candidaspongia flabellate* and *Psedoceratina clavata*, Mediterranean sponges, Great Barrier Reef sponges, *Theonella swinhoei* and *Aplysina aerophoba* [21].

Freshwater and Desert

Freshwater habitat valuable source of actinomycetes that have important bio-active secondary metabolites, river water contains genus *Streptomyces* while river sediments obtain genus *Micromonospora*. Actinomycetes found in freshwater habitats have antifungal activity [18]. Desert habitat is uniquely regarded as unexplored new antibacterial diversity, a large number of novel species of bacteria found from samples derived from Atacama Desert. Because of high levels of oxidation, the soil of the hyper-arid region is exhausted from organic material that contains a low number of bacteria for cultivation. Actinomycetes isolated from desert soil have antimicrobial activity and it is assumed that desert soil may contain large population of alkaliphilic and halophilic actinomycetes [22, 23].

Volcanic cave- hot spot

From Canada, volcanic cave microbiology suggests that this habitat contains diverse novel bioactive secondary metabolites producing microbes. From volcanic cave of Spain, Beutenbergia, cavernae, Agromyces subbeticus, L-lysine containing actinomycetes are isolated while in Canada the isolated actinomycetes have antimicrobial activity against multidrug-resistant pathogens [24, 25].

Endophytic actinomycetes

Endophytic microbes live for the whole life inside plant tissue, many actinomycetes secondary metabolites utilize as bio-control agents such as Nocardia globerula compounds used to control pathogens like *Helminthosporium solani*, causing silver scarf potato disease, Ansacarbamitocins and Ansamitocin isolate from actinomycetes strains used against antitumor agents [26].

Secondary Metabolites of Actinomycetes

Nowadays, antibiotic resistance of microorganisms is one of the biggest challenges to global health. Scientists are searching for novel bioactive secondary metabolites from actinomycetes to tackle the resistance of pathogenic microbes [27]. This review summaries bio-active secondary metabolites produced by actinomycetes (Table 1)

Spirotetronate compounds

Maklamicin is a spirotetronate class of polyketide, a novel polycyclic extracted from endophytic *Micromonospora* sp.GMKU326, reported since 2011. Maklamicin has antimicrobial activity against Gram-positive bacteria such as *Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, Micrococcus luteus* and *Enterococcus faecalis* also have moderate cancer cell cytotoxicity [54]. Lobophorin F, extracted from *Streptomyces* sp. SCSIO 01127 has antitumor and antibacterial activity against *S. aureus, E. faecalis* and *Bacillus thuringiensis*. It was reported that *Streptomyces* sp. strain MS1 00061 produce lobophorin family such as lobophorin A, B and G with anti-inflammatory activity and active against - *Mycobacterium bovis* [55, 56]. Nomimicin is another polyketide compound extracted from *Actinomadura* sp. TP-A0878, shows antimicrobial activity against *C. albicans*, *M. luteus* and *Kluyveromyces fragilis* and weak cytotoxicity activity against cancer [57, 58].

Quinones and Lactams

The heterologous expression of gene clusters in *Streptomyces albus*, enables the production of novel arenimycins C, D and polyketides producing potential antibacterial activity. *Pseudonocardia* sp. SCSIO 01299 collected from South China sea produces novel diazaanthraquinone analogs and pseudonocardians A-C having antibacterial and antitumor activity [59]. *Streptomyces zhaozhouensis* CA-185989 strains collected from marine sediments near Guineaproduced an important biological active secondary metabolites belonging to class isoikarugamycin, macrolactams, 28-N-methlikarugamycin and poly tetramic acid. These compounds have potential antifungal and antibacterial activity against *A. fumigatus, C. albicans*, and *S. aureus* [60, 61].

Aminoglycosides and β-lactams

Aminoglycosides metabolites were extracted from *Streptomyces, Frankia, Streptoalloteichus, Dactylosporangium, Streptoalloteichus, Micromonospora, Saccharopolyspora* and *Streptosporangium* [61]. Aminoglycosides are classified into two groups, streptamine and 2-deoxystretamine [53]. Antibiotics include aminoglycosides are astromicin, hygromycin, verdamicin, lividomycin, spectinomycin, sisomicin, netilmicin, istamycin, apramycin, gentamicin, ribostamycin, nebramycin, kanamycin, tobramycin, neomycin, amikacin, streptomycin and paromomycin [62].

β-lactams are one of the most important classes of antibiotics in clinical use. This class includes clavulanic acid, monobactams, carbapenems, cephamycins, cephalosporins and penicillins. β-lactams are bacteriocidal in nature and indicated broader spectrum of antibiotic activities against Gram-positive and Gram-negative bacteria. β-lactams was mainly produced by *S. limanii, S. jumonjinenesis, S. wadayamensis, S. viridochromogenes, S. panayaensis, S. chartreusis, Streptomyces clavuligerus, Norcardia lactamdurans*. These compounds have antibiotic activity against Gram-positive and Gram-negative bacteria [63].

β-diketones, aromatic ketones and Ansamycin compounds

From extreme hyper arid Atacama Desert soil, three novel β-diketones bioactive metabolites belong to family of polyketides, β-dike-tone were discovered from *S. asenjonii* KNN 42.f, three new asenjonamides (A–C) compounds in addition to the known N-(2-(1*H*-indol-3-yl)-2-oxoethyl) acetamide, a series of bioactive acylated 4-aminoheptosyl-β-N-glycosides, spicamycins (A–E) [64]. All of these compounds have highest antibacterial activity against methicillin-sensitive *S. aureus, E. coli, E. faecium, B. subtilis, S. aureus, C. albicans* and *E. coli* [65]. From Atacama Desert soil ansamycin-type polyketides were isolated from *Streptomyces* sp. strain C34. Chaxamycin D showed strongest antibacterial activity against *Escherichia coli* ATCC 25922, methicillin-resistant *S. aureus* [66].

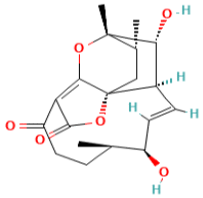
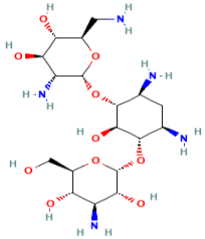
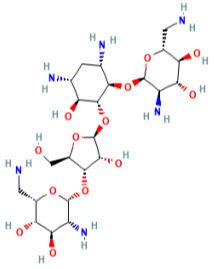
Glycopeptides and Lactones

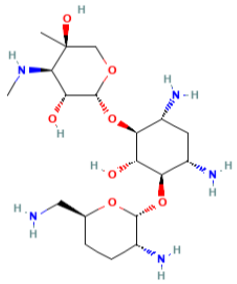
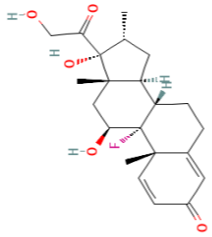
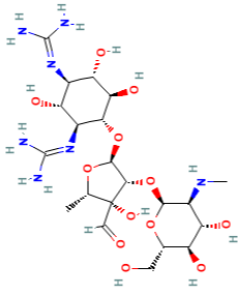
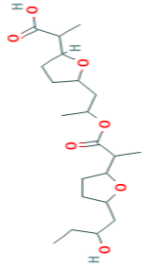
Glycopeptides are class of antibiotics composed of glycosylated cycle or polycyclic non-ribosomal peptides that contain unique long aliphatic chain attached to a sugar moiety. This class of antimicrobials contain teicoplanin, vancomycin, telavancin, actinoidin, avoparcin, chloroeremomycin decaplanin, balhimycin, ramoplanin and bleomycin. This class of antibiotics are produced by *Amy. balhimycina, Amycolatopsis orientalis, S. toyocaensis, S. candidus, S. orientalis, Actinoplanes teichomyceticus* and *N. actinoides.* Glycopeptides antimicrobials have potential to combat resistant Gram positive pathogens such as methicillin resistant *Staphylococcus aureus* [63]. Lactones are cyclic carboxylic esters, containing 1-oxacycloakan-2-one structure (-C(=O)-O-) or analogues having unsaturation or heteroatoms replacing one or more carbon atoms of the ring [64]. Rateb et al isolated *Streptomyces* sp. strain C34 from the Chilean hyper-arid Atacama Desert soil. This stain have capability to produce new compounds named as chaxalactins A–C (5″-dihydrohygromycin A, deferroxamine E and hygromycin A) that belongs to class of macrolactone polyketides. These compounds have strong antimicrobial activity against *B. subtilis, L. monocytogenes* and *S. aureus* [66] Anthracimycin extracted from *Streptomyces* sp. strain CNH365 have strong antibacterial activity against *Moraxella catarrhalis, H. influenza, S. pneumoniae, E. faecalis,* MRSA, MSSA and vancomycin-resistant *S. aureus* [67]. *S. formicae* KY5 strain isolated from kenyn ants *Tetraponera penzigi*, new polyketides formicamycins (A-L) secondary metabolites were extracted, that have strong antimicrobial activity against vancomycin resistant pathogens such as *Enterococcus faecium* [69].

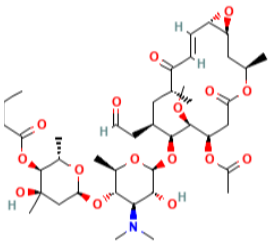
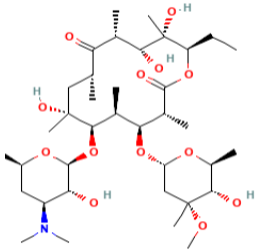
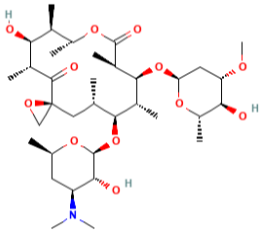
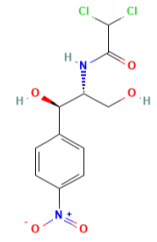
Anthracyclines and Macrolides

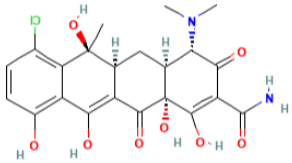
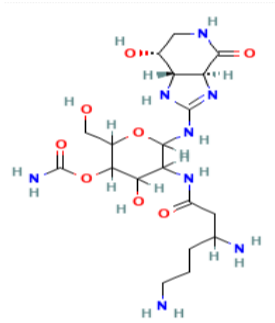
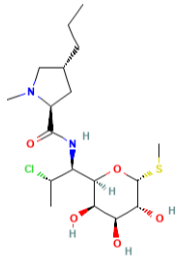
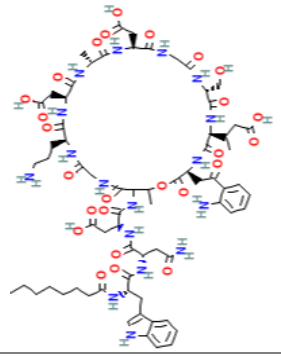
Anthracyclines are produced by *Streptomyces* sp., *S. galilaeus, S. peuceticus, S. purpurascens, S. nogalater* and *Micromonospora lupine* [62]. This class includes doxorubicin, daunorubicin, epirubicin, idarubicin, nogalamycin, rhodomycin, pirarubicin, amrubicin, aclacinomycin and valrubicin antibiotics which have potential to treat various type of cancer such as lymphomas, myeloid leukaemia, solid tumors and breast cancer [69]. Macrolides composed of macrocyclic lactone ring with one or more deoxy sugars produced by *S. venezuelae, Saccharopolyspora erythraea* and *S. hydroscopicus* [64]. This class contains erythromycin, azithromycin, clarithromycin,

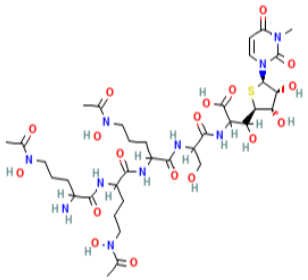
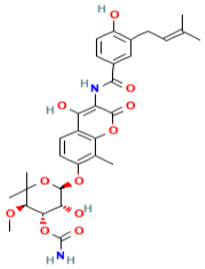
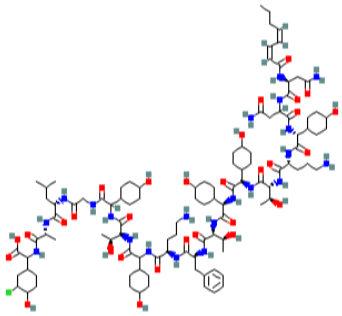
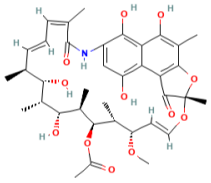
Table 1. List of antibacterial compounds from actinomycetes. Chemical structures are retrieved from PubChem, National Library of Medicine, National Center for Biotechnology Information (NCBI).

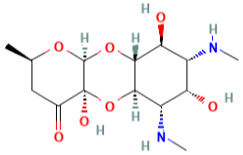
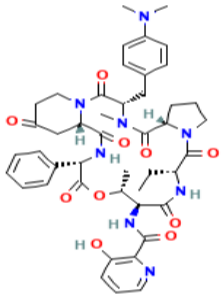
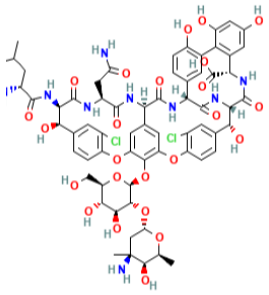
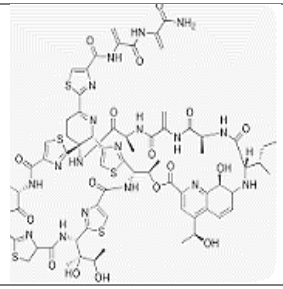
Chemical class	Antibiotic	Chemical structure	Actinomycetes source	Mechanism of Action	Pathogens	Reference
Natural polycyclic polyketide	Abyssomicins		*Verrucosispora* AB-18-032	Para-aminobenzoic acid) pathway inhibitor	*Staphylococcus aureus, Mycobacterium tuberculosis*	[28]
Aminoglycoside	Bekanamycin		*Streptomyces kanamyceticus*	Inhibiting protein synthesis and increasing translation errors	*E. Coli, Bacillus subtilis, Staphylococcus aureus*	[29]
	Framycetin		*Streptomyces fradiae*	Inhibition of bacterial protein synthesis via binding to ribosomal subunits.	*B. subtilis, Proteus vulgaris, Pseudomonas solanacarum*	[30]

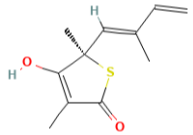
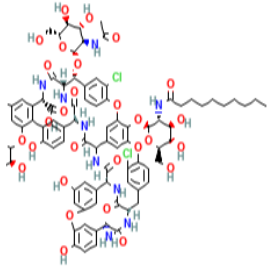
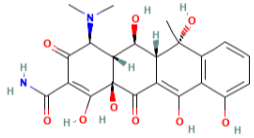
	Gentamicin		*Micromonospora purpurea*	Inhibits protein synthesis by binding to L6 protein of 50S ribosomal subunit	Pseudomonas, Staphylococcus, Streptococcus	[31]
	Neomycin		*Streptomyces fradiae*	It binds 30S and in some cases the 50S subunit causing miscoding; inhibits initiation and elongation during protein synthesis	*Pseudomonas aeruginosa*, Staphylococci	[32]
	Streptomycin		*Streptomyces griseus*	Inhibits bacterial protein synthesis	*Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*	[33]
Ester	Bonactin		*Streptomyces* sp. BD21-2	Inhibiting protein synthesis and increasing translation errors	*Bacillus megaterium*, *Micrococcus luteus*, *Kleibsiella pneumoniea*, *Staphylococcus aureas*, *Alicagenes faecalis*	[34]

	Carbomycin		*Streptomyces halstedii*	Inhibits bacterial protein synthesis	Staphylococcus, Mycoplasma	[35]
Macrolide	Erythromycin		*Saccharopolyspora erythrea*	Inhibits elongation at transpeptidation step of protein biosynthesis	*Staphylococcus aureus, Pseudomonas aeruginosa, Mycobacterium tuberculosis*	[36]
	Oleandomycin		*Streptomyces antibioticus*	Inhibits bacterial protein synthesis	*Klebsiella pneumonia, S. aureus, Bacillus subtilis*	[37]
	Chloramphenicol		*Streptomyces venezuelae*	Inhibits protein biosynthesis by impairing translation on the 50S ribosomal subunit at the peptidyl transferase step	Streptococci, Enterococci, Staphylococci Haemophilus influenzae, Neisseria species	[38]

Tetracyclines	Chlortetracycline		*Streptomyces aureofaciens*	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl -tRNA to the 30S subunit	Streptococci, Enterococci, Chlamydiae, Mycoplasmas, Rickettsiae, Protozoan parasites	[39]
Imidazo pyridine-4-one	Streptothricin		*Streptomyces lavendulae, Streptomyces noursei*	Inhibits polypeptide synthesis via interaction with the ribosome.	*E. coli*, *Salmonella*, *Pseudomonas*, and *Mycobacterium*	[40]
Galactooctopyranoside	Clindamycin		*Streptomyces* sp.	Inhibits bacterial protein synthesis	*Chlamydia trachomatis, Streptococcus pneumonia, Staphylococcus aureus*	[41]
Lipopeptide	Daptomycin		*Streptomyces roseosporus*	Bactericidal activity by disrupting plasma membrane function without penetrating into the cytoplasm	*Staphylococcus aureus*, vancomycin-resistant Enterococci.	[42]

Cyclic hexapeptide (Sideromycin group)	Grisein (albomycin)		*Streptomyces griseus*	Inhibits seryl-t-RNA synthetase and impairs protein biosynthesis	*E. coli* and *S. typhimurium*, *P. aeruginosa*	[43]
Aminocoumarin	Novobiocin		*Streptomyces niveus/ S. spheroides*	Inhibits DNA synthesis by inhibiting the DNA polymerization	*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*	[44]
Glycolipodepsip eptide	Ramopl (INN		*Actinoplanes* sp ATCC 33706	Inhibits transglycosylation in peptodoglycan synthesis	*Clostridium clostridioforme*, *Peptostreptococcus prevotii*, *Propionibacterium acnes*	[45]
Naphthalene	Rifamycin		*Amycolatopsis rifamycinica*	Inhibits bacterial DNA-dependent RNA-polymerase	*M. tuberculosis*, *Mycobacterium avium*, *M. leprae*, *M. kansasii*	[46]

Aminocyclitol	Spectinomycin		*Streptomyces spectabilis*	Disrupts bacterial protein synthesis	*Streptococcus pyogenes, Streptococcus Pneumoniae, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae*	[47]
Polyketide-Streptogramin	Streptogramin A		*Streptomyces virginiae*	Inhibits protein biosynthesis by binding to 50S ribosome unit	*Staphylococcus aureus, Enterococcus faecium,* enterococci	[48]
Glycopeptide	Vancomycin		*Amycolatopsis orientalis*	Inhibits cell wall synthesis	*Clostridium difficile, Listeria monocytogenes, Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus viridans*	[49]
Cyclic oligopeptide	Thiostrepton		*Streptomyces azureus* and *Streptomyces laurentii*	Impairment of the coupling of the 30-S initiation complex to the 50-S ribosomal subunit	*Mycobacterium abscessus*	[50]

Thiolactone	Thiolactomycin		*Nocardia* sp	Inhibition of fatty acid synthesis	*S. marcescens*, *K. pneumonia*, Salmonella	[51]
Glycopeptide	Teicoplanin		*Actinoplanin teichomyceticus*	Binds to the D-ALA-D-ALA terminal end of peptide - glycan precursors and inhibits cell-wall synthesis	*Staphylococcus aureus*, Staphylococci	[52]
Acetamide	Oxytetracycline		*Streptomyces rimosus*	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl-tRNA to the 30S subunit	*Plasmodium falciparum*,	[53]

roxithromycin, dirithromycin, josamycin, rokitamycin, spiramycin, telithromycin, flurithromycin, miocamycin, pikromycin, midecamycin and rapamycin antibiotics which act as immunosuppressant, prokinetics and antifungal [69].

Fattiviracins and Tetracyclines

Fattiviracins are produced by strain of *Streptomyces microflavus.* The strain produced thirteen derivatives of fattiviracins (FV-1to FV-13) that have potent antibiotic activity against enveloped DNA viruses such as herpes family, VZV and HSV-1, also actively against enveloped RNA viruses (influenza A and B viruses). Fattiviracins are found in white amorphous powder form, readily soluble in water, pyridine, DMSO, methanol and molecular weight range between 1400 to 1500 [68]. Tetracyclines are derivatives of polycyclic naphthacene carboxamide, produced by *S. rimosus*, *aureofaciens*, and *S. viridofaciens.* Antibiotics in this class contain tetracycline, methacycline, demeclocycline, oxytetracycline, minocycline, lymecycline, rolitetracycline and chlortetracycline exhibited a wide range of activity against Gram-positive and Gram-negative bacteria, mycoplasmas, chlamydiae, protozoan parasites and rickettsiae [61]

Conclusion

It is summarized that actinomycetes play a vital role in production of various bio-active secondary metabolites used for pharmaceutical purposes for the treatment of various diseases. The antagonistic actinomycetes evidence that the ecosystem such as soil, hypersaline soil, rhizosphere soil, freshwater, limestone, volcanic cave, marine sediments, sponges, and desert is an important source of bio-active secondary metabolites production. It is assumed that actinomycetes species found in extreme conditions have the capability to produce novel bio-secondary metabolites that remain unexplored yet.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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