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Actinomycetes: Natural Biofactories for Antimicrobial and Antitumor Compounds: A Review

Omoyajowo O. S[1], Adegoke S. A.[1], Ohimai .A[1]

Department of Microbiology, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria

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***Corresponding Author:** Omoyajowo O. S

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Abstract **Review Article**

Actinomycetes are spore-forming filamentous, saprophytic bacteria that have capacity to generate a wide range of antimicrobial compounds. It has been documented that actinomycetes have generated over twenty thousand secondary metabolites, some of which are of great value in animal medicine, agrochemicals and pharmaceuticals. These bacteria are widely distributed across diverse ecosystems and can thrive in various environmental conditions. Actinomycetes have been categorized into various distinct genera based on their chemical and morphological characteristic. Given this metabolic diversity, the bioactivity and the antimicrobial potential of the secondary metabolites produced by actinomycetes present a promising solution to the global challenge of antimicrobial resistance. This review highlights the extensive diversity of secondary metabolites produced by actinomycetes strains, emphasizing their biological activities and ecological origins.

Keywords: Actinomycetes, Secondary Metabolites, Antimicrobial Compounds, Saprophytic Bacteria, Pharmaceutical Applications, Antimicrobial Resistance, Metabolic Diversity, Bioactivity, Ecological Origins, Genera Classification.

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1.0 INTRODUCTION

Actinomycetes are Gram-positive bacteria characterized by a filamentous, fungus-like morphology with high guanine-cytosine (GC) content in their DNA. They are renowned for producing a diverse array of secondary metabolites with significant antimicrobial activities. Gram-positive bacteria are typically divided into two major phylogenetic groups based on their GC content: "low-GC" and "high-GC." GC content refers to the proportion of guanine and cytosine base pairs in an organism's genome. Bacteria with low GC content have a higher proportion of adenine-thymine (AT) pairs. While GC content is a relatively basic metric, it remains a useful tool for distinguishing broad phylogenetic groups of microorganisms. Actinomycetes also display a wide variety of life cycles, many of which are uniquely complex among prokaryotes (Naghavi *et al*., 2024; Zahr *et al*., 2022; Helmi, 2025)

Actinomycetes are known for their ability to produce the therapeutic substances capable of killing or inhibiting microorganism, such substances includes: antifungal, antiviral, antibacterial, anti-parasitic, immune-suppressant and anticancer. (Jagannathan *et al*., 2021, Sui *et al.*, 2025). These organisms have capacity to produce industrial enzymes, used in textile, pharmaceutical, wastewater management and agriculture (Berdy, 2005). Many of these metabolites exhibit potent antibacterial activity, making *Streptomyces* species are cornerstone of antibiotic production in the pharmaceutical industry (Helmi, 2025). Beyond antibiotics, members of this genus also produce a range of clinically valuable antitumor agents, including anthracyclines (e.g., aclarubicin, daunomycin, and doxorubicin), peptides (e.g., bleomycin and actinomycin D), aureolic acids (e.g., mithramycin), enediynes (e.g., neocarzinostatin), antimetabolites (e.g., pentostatin), and other compounds such as carzinophilin and mitomycins (Newman and Cragg, 2012). Despite the availability of hundreds of antibiotics today, the ongoing emergence of resistant pathogens highlights the continued need for novel antimicrobial agents. The prevalence of antimicrobial resistance is stark: more than seventy percent (70%) of the

pathogenic organisms are now resistance to one or more antibiotics, presenting a serious and escalating global health threat. ESKAPE—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. are known for multidrug resistance and have contributed to nosocomial infections (Mancuso *et al*., 2021; Garay, 2019; Davies-Bolorunduro *et al*., 2021; Alenazi *et al.*, 2023).

The World Health Organization and numerous public health agencies have identified these organisms as critical targets for new drug development. It has been projected that by 2050, multidrug-resistant (MDR) infections may become the foremost global cause of mortality, potentially exceeding cancer-related deaths. This growing crisis has intensified the search for novel antibiotics and alternative therapeutic strategies, with particular attention on previously untapped or underexplored microbial sources (Tenebro *et al*., 2021; Alenazi *et al.*, 2023).

2.0 DISTRIBUTION OF ACTINOMYCETES

Actinomycetes thrive in many habitats and spread across several natural ecosystems (Meenakshi *et al* 2024). Actinomycetes can be classified into several distinct general base on their morphological and chemical characteristics. *Streptomyces* species remains the most isolated genus among Actinomycetales, This is due to their pivotal contributions across medicine, research, ecology, and biotechnology (Olanrewaju and Babalola, 2019). These bacteria inhabit diverse habitats such as soil, freshwater, marine environments, plant tissues, insect guts, and deserts (Meenakshi *et al.*, 2024), as detailed in Table 1.

Table 1: Distribution of the Actinobacteria

Habitat	Description	Bacterial strain	References
Actinmycorrhizal Plants	There are actinomycetes found in the root nodule of plant helping in nitrogen fixation	*Frankia* sp	Selim *et al.,* 2021)
Soil	Actinomycetes are known to most prevalent microbial inhabitants of the soil	*Streptomyces sp. Nocardiopsis sp. Nocardia sp.,. Actinomadura sp., Streptoverticillium sp Amycolatopsis sp.*	Goel *et al.,* (2021)
Limestone	These reside within sedimentary rock containing aragonite and calcite minerals.	*Streptomyces sp. MBRL 10*	(Selim *et al.,* 2021)
Endophhytes	Endophytes are microorganisms that reside within plant tissues for all or part of their life cycle.	*Nocardia globerula, Streptomycetes s*p.	(Selim *et al.,* 2021)
Actinmycorrhizal Plants	There are actinomycetes found in the root nodule of plant helping in nitrogen fixation	*Frankia* sp	Selim *et al.,* 2021)
Freshwater	Freshwater serve as a source of actinomycetes. It has been established, and most found in stream sediments	*Micromonospora sp. Rhodococcus sp.Actinoplanes sp., Streptomyce sp*	Goel *et al.* (2021) Selim *et al.(*2021)
Marine	The marine actinomycetes has ability to lives in both biofilm and planktonic a habitats, and most of these actinomycetes strains have been identified in the sediments	*Mycobacterium sp, Pseudonocardia sp., Agrococcus sp. Gordonia sp. Dietzia sp Arthrobacter sp.,*	Goel *et al.* (2021) Selim *et al.(*2021)
Volcanic cave-hot spot	Research on volcanic cave microbiology in Canada suggests this unique habitat has extraordinary potential for isolating novel bioactive secondary metabolites**.**	*Beutenbergia cavernae*, *Agromy*	Selim *et al.(*2021)

Air	Studies on ir samples shows the presence of actinomycetes spores, indicates their airborne nature.	*Nocardia* sp.	Selim *et al.(*2021)
Insect gut	The digestive tracts of insects harbor communities of both symbiotic and transient microorganisms, which serve as a source of novel bioactive microbial products.	*Nocardiopsis alba*	Selim *et al.(*2021)
Hypersaline soil	Some actinomycetes live in environments that have an extremely high concentration of salt, significantly exceeding the salinity of typical seawater.	*Streptomyces diasticus, Streptomyces* albus, and, *Streptomyces exfoliates*	(Selim *et al.,* 2021)

3.0 ANTIMICROBIAL AGENT

An antimicrobial is a substance that inhibits or kills growth of microorganisms like bacteria, fungi, viruses, and parasites. These substances can either be broad spectrum or narrow spectrum. These substances are used to treat and prevent infections in humans, animals, and plants. Antimicrobials include a variety of agents, such as antibiotics, antivirals, antifungals, and antiparasitics (Di Martino, 2022).

3.1 Antibacterial

Currently, most antibiotic used in pharmaceutical are from actinobacteria, majorly the *Streptomyces* species accounting for approximately fifty percent (50%) of them. The phylum actinomycetes have capacity to produce several bioactive compounds, actinomycetes strains can produce between 10 and 20 different types of secondary metabolites. Example of such secondary metabolites are tetracyclines, kanamycin, cephamycin, vancomycin, neomycin, streptomycin, erythromycin, and tylosin. (Mast and Stegmann, 2019).

Tetracycline, synthesized by *Streptomyces aureofaciens*, inhibits bacterial ribosomes. Rifampicin and cycloserine targets *Mycobacterium tuberculosis*, while erythromycin from *Saccharopolyspora erythraea* inhibits Legionnaires' disease. Daptomycin, from *Streptomyces roseosporus* combats against Methicillin-resistant *Staphylococcus aureus*. Chloramphenicol, synthesized by *Streptomyces venezuelae*, fight against several *Pseudomonas*, *Staphylococcus*, and *Streptococcus* strains. Gentamicin from *Micromonospora purpurea*, inhibits both Gram-positive and Gram-negative bacteria. *Streptomyces cinnamonensis* synthesized by monensin, has profound solution to multidrug-resistant Gram-positive bacteria (Fatahi-Bafghi, 2019; Schneider, 2021; Ngamcharungchit *et al*., 2023). The continuous exploration of actinomycetes remains major source for novel antimicrobial agents. (Bergeijk *et al*., 2020). Figure 1 shows some of antibacterial drugs derived from actinomycetes and their site of inhibition.

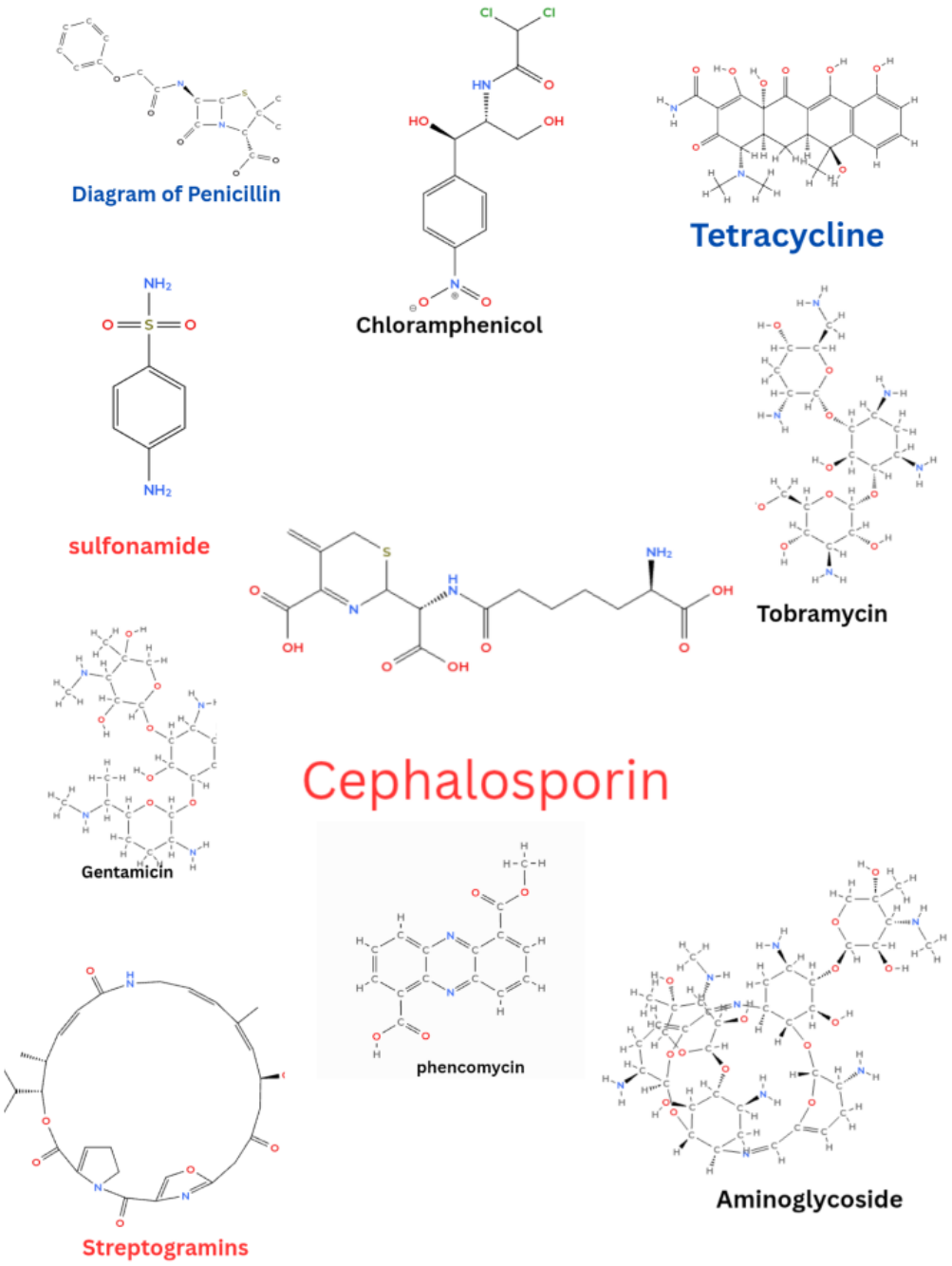

Figure 1: Structure of Antibacteria compounds Derived from Actinomycetes

Table 2. Antibacterial compounds isolated from different actinomycetes strains and their spectrum of activity.

Actinomycetes strain	Bioactive compound	Spectrum of activity	References
Streptomyces lavendulae	Penicillin	Penicillin inhibit the synthesis of essential structural components of bacterial cell wall i.e. peptidoglycan which are absent in mammalian cells.	Chaudhary *et al*. (2013)
Streptomyces ansochromogenes.	Macrolide	The groups macrolide obstruct the growth of bacteria by inhibiting protein synthesis through interruption of ribosome function.	Chaudhary *et al*. (2013)
S*treptomyces* sp and *Micromonospora* sp	Aminoglycosides	Aminoglycosides act by inhibiting synthesis of proteins. They specifically bind to the A-site on 16S rRNA of the small ribosomal subunit	Zahr *et al*. (2022)
Streptomyces clavuligerus	Cephalosporins	It cephalosporins have a β-lactam ring structure that interferes with synthesis of the bacterial cell wall and so are bactericidal	Chaudhary *et al*. (2013)
S. rimosus, S. aureofaciens, and S. viridofaciens.	Tetracycline	Tetracyclines exhibit their bactericidal activity by preventing formation of proteins. This occurs by not allowing the binding of aminoacyl-tRNA to its acceptor site (A-site) on the ribosome	Zahr *et al.* (2022)
Streptomyces virginiae	Streptogramins	Streptogramins inhibit the bacteria protein synthesis by binding to 50s ribosomal subunits	Zahr *et al.* (2022)
	Chloramphenicol	It inhibits protein synthesis by compete with aminoacyl tRNA.	Zahr *et al.* (2022)
Streptomyces lincolnensis	Lincomycin and Clindamycin	they inhibit protein synthesis	Chaudhary *et al*. (2013
Streptomyces sp.	Phencomycin	Enzyme inhibitor	Chaudhary *et al*. (2013
Streptomyces sp.	*Peptides*	Prevent the synthesis of cell wall	Zahr *et al.* (2022)
Streptomyces sp.	*Sulphonamides*	Affect the folates synthesis and inhibit nucleic acid sythesis	Zahr *et al.* (2022)

3.2 Antitumor Agents

Actinomycetes, especially species within the genus *Streptomyces*, represent a rich source of bioactive secondary metabolites with ability to destroy cancer cells. Marine-derived actinomycetes have gained more researchers attention for producing cytotoxic compounds with improved therapeutic ratio, such as salinosporamide A, a potent proteasome inhibitor exhibiting selective anticancer activity with reduced systemic toxicity. Adriamycin (doxorubicin), isolated from *Streptomyces peucetius*, acts by intercalating DNA and inhibiting topoisomerase II, thereby disrupting DNA replication and transcription. Examples of other clinically important chemotherapeutics syntesized by actinomycetes include mitomycin C, actinomycin D, bleomycin, anthracyclines like daunorubicin, and mitosanes, synthesized by *S. verticillus*, *S. peucetius*, and *S. caespitosus* through complex biosynthetic pathways (Ngamcharungchit *et al*., 2023; Lee *et al.*, 2020). These antitumor agents acting through mechanisms such as DNA damage induction, inhibition of proteasomal degradation, or disruption of cell cycle progression (Zou and Kwok, 2021). Figure (2) below showed the chemical structure of some of antitumor drugs derived from actinomycetes.

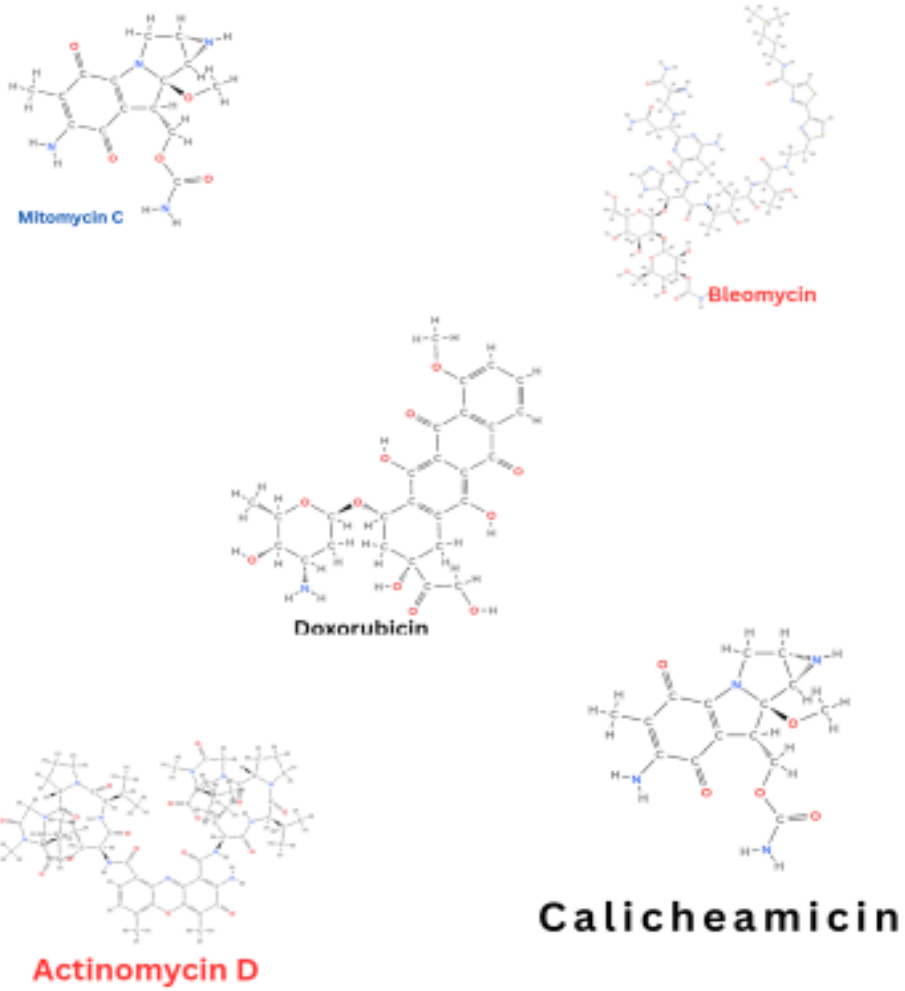

Figure: 2 Structure of Antitumor Compounds Derived from Actinomycetes

Table 3 Antitumor compounds isolated from different actinomycetes strains and their spectrum of activity.

Compounds	**Sources**	**Spectrum of activity**	**References**
Actinomycin D	S. *antibioticus*	Binds to the transcription initiation complex, thereby inhibiting the elongation of RNA by RNA-polymerase	Solecka *et al*. (2012)
Doxorubicin	*Streptomyces peucetius*	It prevents the proliferation of cancer cells by intercalating to DNA and prevent topoisomerase II from functioning.	Zahr *et al.* (2022)
Bleomycin	*Streptomyces verticillus*	Bleomycin's antitumor activity is represented by its ability to degrade DNA. It prevents thymidine	Zahr *et al.* (2022)

		from incorporating into the DNA.	
Mitomycin C	*Streptomyces caespitosus*s	It is potent against different solid tumors, including bladder, breast, lung, and gastrointestinal tumors (upper gastrointestinal, anal)	Alenazi *et al. (*2023)
Calicheamicin	*Micromonospora echinospora*	it is used to treat acute myeloid leukemia	Zahr *et al.* (2022)

3.3 Antiviral agent

The investigation on *Streptomyces* species, offers a promising approach to tackle viral infections. *Streptomyces* species produce a diverse range of bioactive secondary metabolites, some of which possess antiviral properties (Alam *et al*., 2022). These microbial metabolites represent a valuable resource for the development of new antiviral therapeutics targeting a variety of viral pathogens. These compounds have demonstrated potential in inhibiting viral infections by interfering with different stages of viral replication or by disrupting virus-host cell interactions (Lacey and Rutledge, 2022**;** Kumar *et al.,* 2024; Abdel-Razek *et al*., 2020; Kumar *et al*. 2024). Notably, these compounds have shown efficacy against a range of viruses, including influenza viruses, herpesviruses, and HIV, by targeting viral replication processes or disrupting interactions between viruses and host cells.

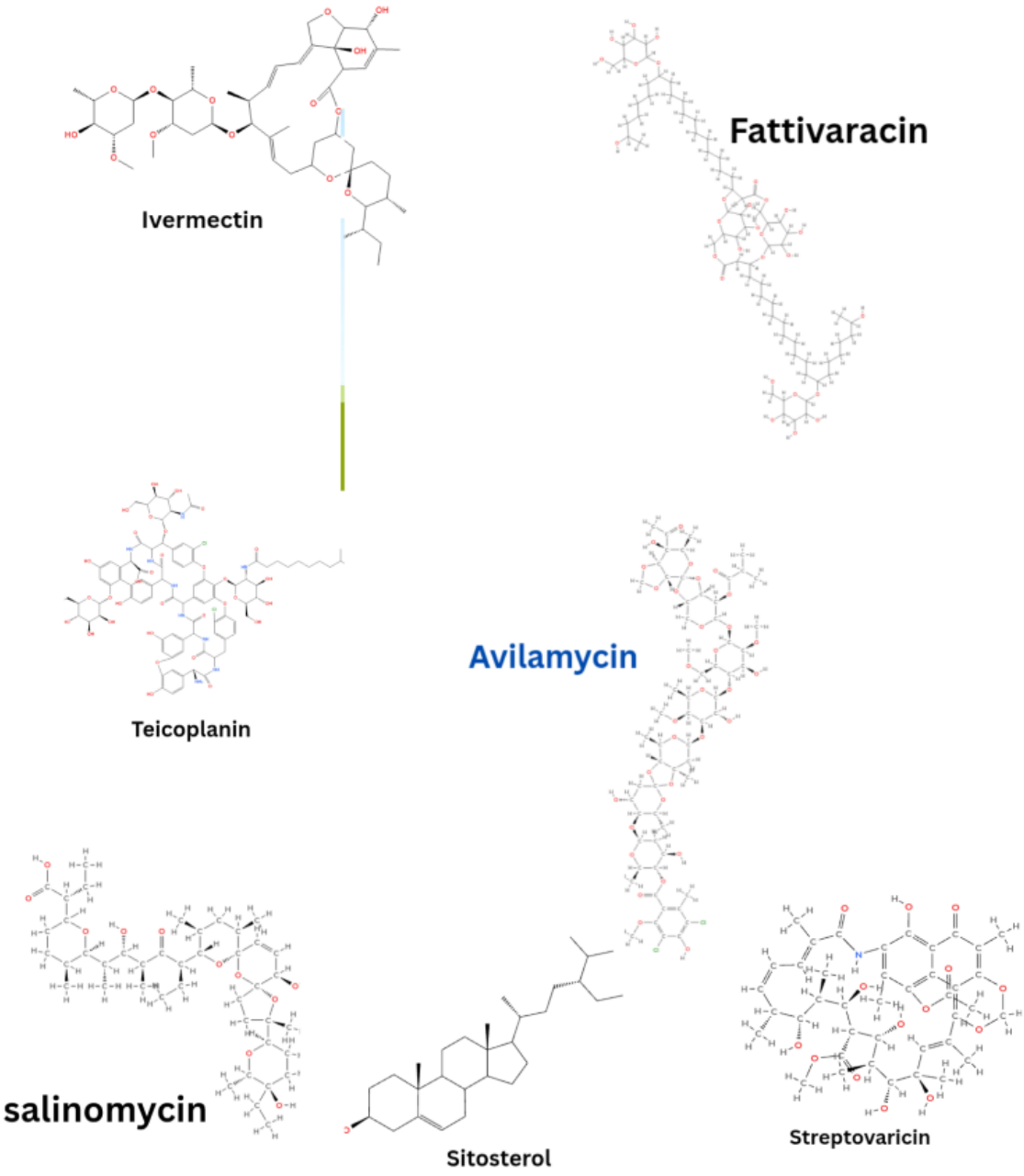

Figure 3: Structure of Antiviral Compounds Derived from Actinomycetes

Table 4: Antiviral compounds isolated from different actinomycetes strains and their spectrum of activity.

Compounds	Organism	Mode of action	References
Teicoplanin	*Actinoplanes teichomyceticus*	It inhibits L-cathepsin, an enzyme crucial for the glycoprotein proteolysis required for membrane fusion during the entry of SARS-CoV, MERS-CoV, and Ebola viruses.	Manikkam *et al. (*2023)
Fattiviracins	*Streptomyces microflavus*	Fattiviracins are potent against enveloped DNA viruses like the herpes family (including HSV-1 and VZV), as well as enveloped RNA viruses such as influenza A and B	Chaudhary *et al*. (2013)
Salinomycin	*Streptomyces albus*	Restrict the growth of RNA viruses, including Zika virus and influenza A virus	Kumar *et al.(*2024)
Streptovaricins	*Streptomyces griscus*	Exhibit antiviral activity against vaccinia virus and herpes simplex virus (HSV) by disrupting viral membrane integrity	Kumar *et al.(*2024)
Azalomycin	*Streptomyces hygroscopicus*	It exhibit antiviral agent Herpes simplex virus (HSV) -1 and -2	Gomes *et al*. (2023)
Ivermectin	*Streptomyces avermectinius*	It exhibits antiviral activity against a broad spectrum of human DNA and RNA viruses, including COVID-19.	Manikkam *et al. (*2023).
Avilamycin	*Streptomyces viridochromogenes*	Avilamycin obstruct the transcription in HIV-1 and other retroviruses	Parra1 *et al*. (2023)
α-sitosterol and β-sitosterol	*S. misakiensis*	Target the surface of the spike glycoprotein on the viral particle against SARS-CoV-2,	Alenazi *et al*., (2023)

3.4 Antifungal agents

Antifungal peptides (AFPs) produced by actinomycetes demonstrate broad-spectrum antifungal activity through multiple mechanisms. One major mode of action involves the obstructing of cell wall synthesis by targeting enzymes such as chitin synthase (CHS) and (1-3)-β-D-glucan synthase. This compromises the normal morphology and integrity of the fungal cell wall, impairing the cell's ability to regulate osmotic pressure. Additionally, these peptides exert effects on fungal cell membranes and various intracellular components, including proteins, nucleic acids (DNA and RNA) and mitochondrial membranes, further contributing to their antifungal efficacy (Zahr *et al*., 2020; Thevissen *et al*., 2020)

Kribellosides A-D

Kribellosides A–D were isolated from a novel actinomycete strain, *Kribella* MI481-42. These alkyl glyceryl ether metabolites demonstrated potent in vitro inhibition of the RNA 5'-triphosphatase enzyme from *Saccharomyces cerevisiae*, with IC_{50} values ranging from 5 μM to 8 μM. They also exhibited antifungal activity against *S. cerevisiae* with minimum inhibitory concentrations (MICs) between 3.12 μg/ml and 100 μg/ml (Igarashi *et al*., 2017; Zahr *et al*., 2020).

Nikkomycins and polyoxins are two major groups of antifungal nucleotides that competitively inhibit essential enzymes involved in fungal cell wall biosynthesis and chitin synthase. Polyoxins, was first isolated in the 1960s from *Streptomyces cacaoi* subspecies *asoensis*, it inhibits several plant pathogenic fungi, including *Alternaria kikuchiana and Pyricularia oryzae*. But Nikkomycins such as nikkomycin Z, shows stronger antifungal effect against disease-causing organism in human such as *Candida albicans*. Nikkomycins was discovered in the 1970s from *Streptomyces tendae*, nikkomycins inhibit diverse range of fungi, such as *Botrytis cinerea* and *Rhizopus carcinans*. Nikkomycin X and Z, members of the peptidyl nucleoside antibiotic class produced by *Streptomyces ansochromogenes*, share highly similar structures; however, nikkomycin Z demonstrates superior antifungal potency compared to nikkomycin X. Building on this, Liao *et al*. (2020) successfully manipulated the biosynthetic pathways of *Streptomyces* to selectively enhance the production of nikkomycin Z, thereby maximizing its therapeutic potential (Solecka *et al*., 2013; Zahr *et al.,* 2020).

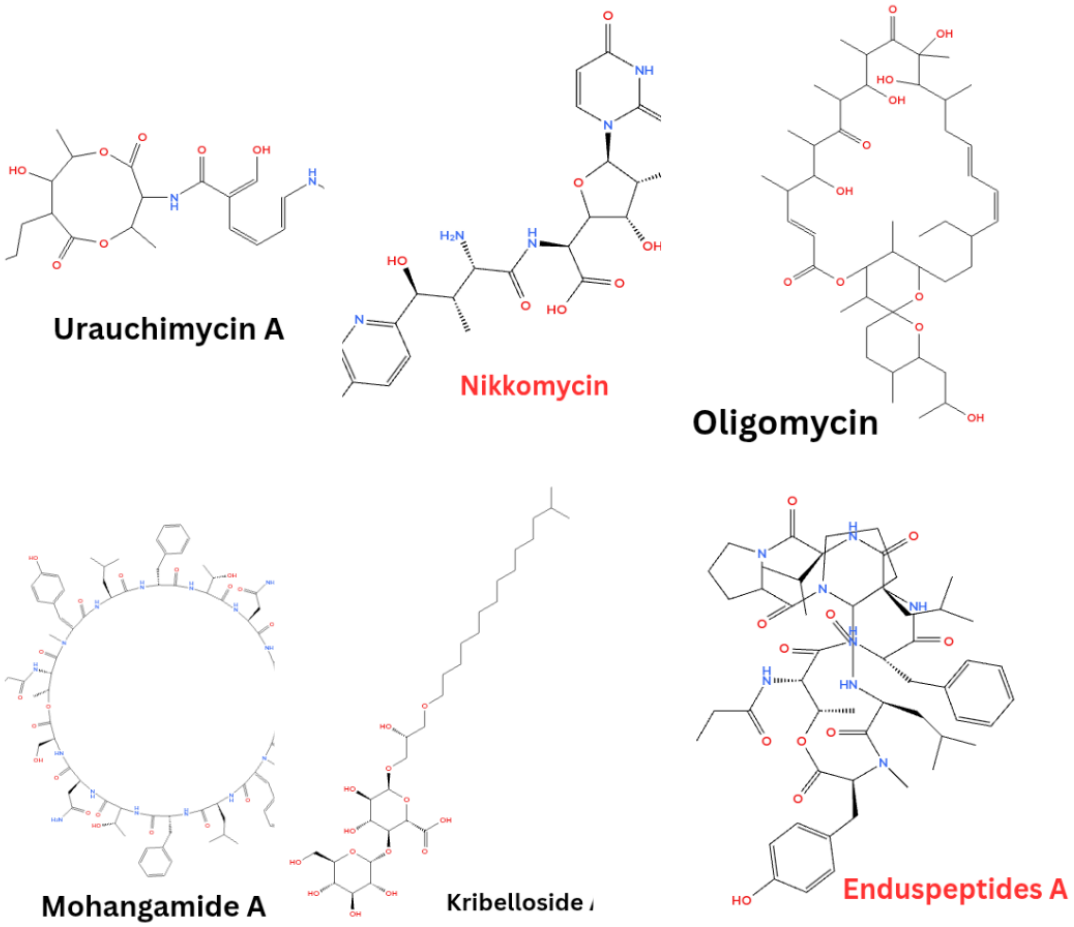

Figure 4: Structure of Antifungal compounds Derived from Actinomycetes

Table 5: Antifungal compounds isolated from different actinomycetes strains and their spectrum of activity

Actinomycetes strain	Bioactive compound	Spectrum of activity	References
Kribella MI481-42F6	Kribellosides A-D	It is effective against *S. Cerevisiae*	Zahr *et al*. (2022)
Streptomyces sp	Enduspeptides A-F	It is active against *C. glabrata*	Zahr *et al*. (2022)
Streptomyces species SNM55	Mohangamides A and B	t is potent against C. *albicans*	Zahr *et al*. (2022)
Streptomyces ansochromogenes	Nikkomycins	It is effective against *C. albicans*	Zahr *et al*. (2022)

S. diastatochromogenes	Oligomycins	antifungal activity against *Aspergillus niger and Alternaria alternate*	Chaudhary *et al.* (2013)
Stre*ptomyces sp*	**U**rauchimycins A-D	inhibitory action against C. albicans, and *Mucor miehei,*	Gomes *et al*. (2018)

3.5 Antiparasitic from Actinomycetes

Anti-parasitic are drugs or agents that are used to cure or prevent infections caused by parasites. There are different types of anti-parasitic drugs isolated as secondary metabolites from actinomycetes and fungi. These bioactive compounds interfere with essential parasitic cellular functions such as energy and lipid metabolism, protein biosynthesis, neurotransmission, and membrane integrity, exhibiting selective toxicity towards susceptible parasitic species. Although relatively few of these antibiotics have been translated into clinical therapeutics, several remain commercially available and are extensively employed as molecular probes in parasitological and biochemical research (Pérez and Santos, 2021). Figure (5) shows anti-parasitic drugs derived from actinomycetes.

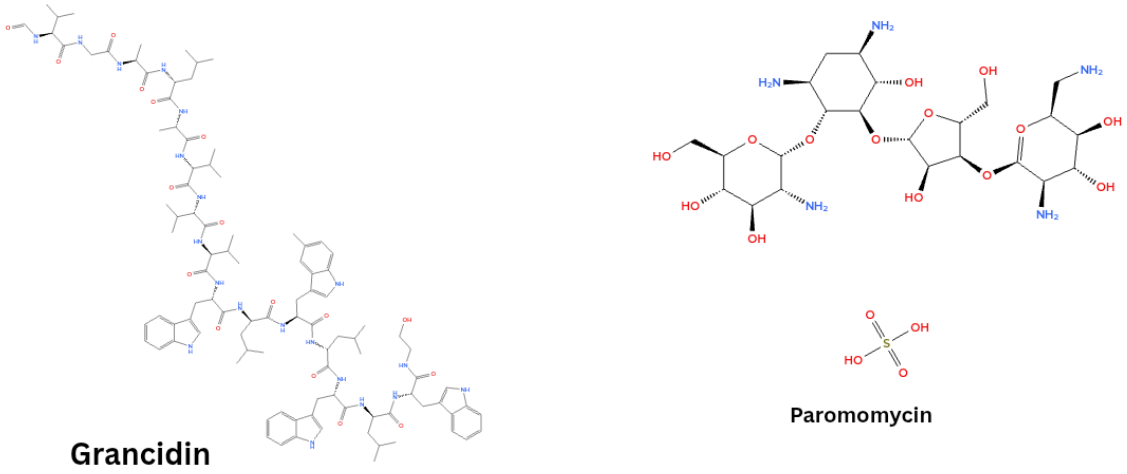

Figure 5: Structure of Anti-parasitic compounds derived from actinomycetes

Table 6 Antiparasitic derived from Actinomycetes

Actinomycetes strain	**Bioactive compound**	**Spectrum of activity**	**References**
Streptomyces rimosus	Paromomycin	Effective against leishmaniasis	Awada *et al*. (2022)
Streptomyces sp	*Streptomyces sp.* HAS1	It inhibits the replication of the intracellular amastigotes of an *L. tropia*	Awada *et al*. (2022
Monstera sp.	Coronamycin	*It inhibits the Plasmodium falciparum*	Alenazi *et al*. (2023)
Streptomyces sp	Gancidin-W	Effective against *Plasmodium berghei* NK 65	Alenazi *et al*. (2023)

4.0 FUTURE PROSPECTS OF ACTINOMYCETES

The high rate of antimicrobial resistance has resulted in increased rates of illness and death, especially among vulnerable groups like children, the elderly, and those with weakened immune systems. It has been estimated by World Health organization (WHO) that by 2050, antimicrobial resistance could lead to 10 million deaths annually, emphasizing the urgent need for novel antimicrobial agents (Alanis, 2005; Mancuso *et al*., 2021; Naghavi *et al*., 2024). The bioactivity or antimicrobial potential of secondary metabolites, produced by actinomycetes, presents a promising solution to the global challenge of Antimicrobial Resistance (AMR). As drug-resistant pathogens continue to emerge, these secondary metabolites offer a crucial alternative in the fight against AMR. Actinomycetes, dwelling within diverse environments have been observed to produce an impressive array of bioactive secondary metabolites, showcasing remarkable antimicrobial activity against various pathogenic microorganisms, a more holistic approach is needed in exploring and discover of new actinomycetes that have medicinal value.

5.0 CONCLUSION

This review emphasized on roles of actinomycetes on fighting against diseases, there has been a growing emphasis on the exploration of natural bioactive compounds as alternative strategies. Natural sources of these bioactive molecules include plants, animals, and microorganisms. Among these, actinomycetes have emerged as the most prolific and preferred producers, owing to their distinctive biological and physiological attributes. Actinomycetes exhibit considerable advantages over other natural sources, such as a vast genetic diversity encompassing numerous well-characterized strains, rapid growth kinetics, the capacity to achieve high cell densities, robust production of secondary metabolites, efficient secretion mechanisms, ease of cultivation under laboratory conditions, and genetic tractability. Collectively, these features render actinomycetes valuable reservoirs for the discovery and biotechnological exploitation of novel therapeutic agents. It is necessary to conduct further research on multispecies combinations of *actinomycetes* and other bacterial species to fully exploit their therapeutic potential against infectious diseases.

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