Short Review

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Exploring Novel Compounds from Soil *Streptomyces*: An Intervention for The Challenge of Drug Resistance and A Potential Avenue for New Drug Discovery

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ABSTRACT

The increasing development of antimicrobial resistance among pathogenic microorganisms and the challenges it poses to the health sector requires an urgent need for investigation of natural products for novel bioactive compounds. New drugs are needed to alleviate the menace of antimicrobial resistance which is a global concern coupled with emerging strains of disease-causing organisms. Due to this resistance, clinicians and medical practitioners have shifted their focus to older antimicrobial agents such as tetracyclines and aminoglycosides isolated from *Streptomyces* spp. as a result of chemical modification to the existing antibiotic scaffold. The World Health Organisation recently updated the list of multidrug-resistant bacteria to which there is an urgent need for new antibiotics. *Streptomyces* produces large numbers of clinically important antibiotics and is readily available in natural sources such as soil and plants. This review explores old and effectively used antibiotics produced from *Streptomyces* and the potential of newly discovered antimicrobial agents from this source.

Keywords: *Streptomyces*; Antimicrobial Resistance; Antimicrobial Agents; Soil; Bioactive Compounds

Introduction

Streptomyces are spore-forming bacteria mostly found in soil. They belong to the genus Actinobacteria which forms the largest genus of over 500 described species [1]. They are characterized by their filamentous, leathery, tough, and pigmented colonies. These organisms were first thought to be fungi when they were first discovered but their prokaryotic origin was established because they do not have nuclear membrane and also characterised by the presence of peptidoglycan. Like other Actinobacteria, they are Gram-positive and posses genomes with high content of guanine and cytosine [2]. They are known for a distinct "earthy" smell which is from the volatile metabolite they procuced. This metabolite is known as geosmin [1]. *Streptomyces* have a complex secondary metabolism and are known to produce over two-thirds of antibiotics of clinical importance derived from natural origin like

chloramphenicol and neomycin [3]. They have a notable degradative ability due to their capability to derive carbon and energy from the breakdown of complex organic materials in the soil. This also makes them useful in agriculture as they produce fertile soil. Streptomycetes are less pathogenic, though there are some human infections, such as mycetoma, can be caused by *S. sudanensis* and in plants can be caused by *S. scabies* and *S. caviscabies* (Madigan and Martinko, 2006). *Streptomyces* grow best at temperature of 25°C and pH 8 to 9. Their degradative ability makes them very important in the production of fertile soil for agriculture.

Bioactive Metabolites from Soil *Streptomyces*

Bioactive metabolites are organic compounds produced by microorganisms. These metabolites are not directly responsible for the normal growth or reproduction of the organism but serve as a competition mechanism for the producing organisms as well as regulators of cellular differentiation processes [4]. Glycopeptides, b-lactams, polyenes, aminoglycosides, peptides, tetracyclines, actinomycins, and various compounds of microbial importance have been isolated and characterized from different species of *Streptomyces*. These metabolites, most of which are extracellularly produced are secreted in culture media and have been used as an antibacterial, antifungal, herbicides, immunoregulators, anticancer and antiparasitic agents [5]. For instance, the culture supernatant of *Streptomyces* sp. No. 87 isolated from agricultural soil in Sakon Nakhon Province, Thailand, was partially purified and characterized charoensopharat et al. Its antimicrobial activity against various plant pathogens showed that the active substance from *Streptomyces* sp. No. 87 inhibited the growth of the plant pathogens including Gram-negative bacteria [6]. *Streptomyces* albus isolated from soil samples in Ondo state Nigeria was reported to show a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. The Infrared spectra also showed that the compound extracted from the fermentatuion of this organism contain the carbonyl and hydroxyl group which can be contribute to the antibacterial property [7]. Crude extract prepared from the strain of *Streptomyces* spp. from the Puducherry coast in India was screened for antifungal activities by Thenmozhi and Kannabiran. Eight strains of *Streptomyces* isolated from the marine sediment were screened for antifungal activity. The metabolite was extracted using ethyl acetate and tested against *Aspergillus* fumigatus, *A. niger* and *A. flavus*. The strain named as VITSTK7 was isolated and reported for antifungal properties [8].

Historically Important Antibacterial Compounds Made by *Streptomyces*

Tetracyclines

Tetracycline is a broad-spectrum polypeptide antibiotic produced by *Streptomyces* rimosus and *Streptomyces* aureofaciens. It has proven effectiveness in the treatment of different bacterial infections. It inhibits the synthesis of protein and is used commonly for the treatment of acne [9]. Tetracycline is distributed under the brand names like Tetracyn, Sumycin, and Panmycin. They have a four-ring system commonly characterized by octahydronapthacenes skeleton [10].

Mechanism of Action

Tetracyclines act by binding to the 30s subunit of a microbial ribosomes. They inhibit synthesis of protein through the blockage of the attachment of charged aminoacyl-tRNA to the ribosomal 'A' site. They thus stop the introduction of new amino acids to the nascent peptide chain [11]. The action is reversed upon withdrawal of the drug. The development of resistance to tetracycline occurs through changes in the permeability of the microbial cell membrane. The antibiotic is concentrated in the cell of susceptible bacteria and does not leave the cells readily. It is different in resistant cells; the antibiotic leaves the cell rapidly because they are not actively transported [12]. Mammalian cells do not contain 30S ribosomal subunit and are therefore not susceptible to the effect of tetracyclines [13].

Spectrum Of Bacterial Susceptibility and Resistance

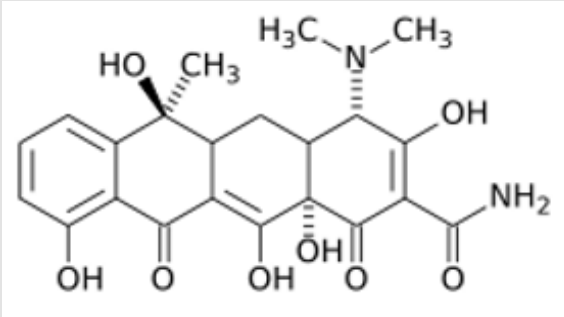

Figure 1: Chemical structure of tetracycline.

Tetracyclines are broad spectrum antibiotic, effective against Gram-positive and Gram-negative. Originally, they possessed some degree of bacteriostatic effect against many medically important Gram-positive and Gram-negative aerobic and anaerobic bacterial with the exception of some bacteria like Pseudomonas aeruginosa and Proteus spp. which have intrinsic resistance [12]. However, acquired resistance developed by many pathogenic bacteria has diminished the versatility of this group of antibiotics. Resistance to tetracycline is prevalent among *Neisseria gonorrhoeae*, anaerobes, species of *Staphylococcus* and *Streptococcus*, members of the Enterobacteriaceae and several other previously sensitive organisms [14]. Tetracyclines are also important in the treatment of infections caused by spirochetes, such as syphilis, Lyme disease and leptospirosis. Some infections, including anthrax, brucellosis

and plague have also shown susceptibility to tetracyclines. Activity of tetracycline against certain eukaryotic parasites such as those causing malaria and balantidiasis have also been reported [14] Figure 1.

Chloramphenicol

Chloramphenicol is a bacteriostatic broad-spectrum antimicrobial produced by *Streptomyces venezuelae*. It was first produced in 1949. It is easily produced and cost effective; this makes it a frequent antibiotic of choice in developing countries [15]. Like tetracycline, chloramphenicol is used for the treatment of infection caused by Gram-positive and Gram-negative bacteria, including many anaerobic organisms. Because of the developement of resistance and the concern of the safety of this antibiotic, it is no longer considered a first line agent for any infection in developed countries, although it is sometimes applied as topical medicine for eye infections. However, the global challenge of increasing bacterial resistance to newer drugs has resulted into renewed interest in its use, especially in response to the global challenge of the continuing problem of multi-drug resistance in pathogenic microorganisms [15]. Low-income countries still widely use chloramphenicol because it is cost effective and readily available. Bone marrow toxicity is the most serious and generally fatal adverse effect associated with chloramphenicol treatment [16].

Spectrum of Activity

Broad spectrum of activity against Gram negative and Gram-positive bacteria has been reported in chloramphenicol. It also inhibits bacterial protein synthesis, [17]. It was previously used to treat infections caused by *Burkholderia pseudomallei* but it has been replaced with ceftazidime and meropenem [18].

Mechanism of Action

Chloramphenicol is known to be a bacteriostatic drug and it stops the growth of bacteria through the inhibition of protein synthesis. It prevents the elongation of protein chain by inhibiting the peptidyl transferase activity of the bacterial ribosome. It binds to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit thus, preventing the formation of peptide bond [17]. Chloramphenicol and its derivative, florfenicol are inhibitors of protein synthesis. Resistance to chloramphenicol can develop in several ways such as efflux pump, modification of targets or resistance mediated by some genetic genes [19]. Apart from inhibiting formation of peptide bond, chloramphenicol can also cause a disturbance in ribosomal functions, such as biogenesis of 50S ribosomal subunits, translational accuracy and termination of ribosomal function [17] Figure 2.

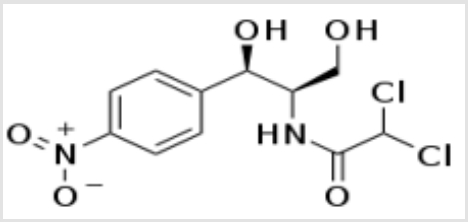

Figure 2: Chemical structure of chloramphenicol.

Streptomycin

Streptomycin is the first of a class of drugs called aminoglycosides to be discovered, and it was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium *Streptomyces griseus*. Streptomycin was first isolated on October 19, 1943, by Albert Schatz, a graduate student, in the laboratory of Selman Abraham Waksman at Rutgers University [20,21]. The urgent need to find an antibiotic that could replace penicillin which was ineffective for the treatment of tuberculosis and some Gram-negative pathogenic bacteria during World War II led to the discovery of Streptomycin from *Streptomyces griseus* isolated from manured compost soil [21]. In 1946-1947, the first attempt to check the activity of streptomycin against pulmonary tuberculosis was carried out by the MRC Tuberculosis Research Unit under the chairmanship of Sir Geoffrey Marshall (1887–1982). The randomised double-blind and placebo-controlled study showed efficacy against TB with minor toxicity and acquired bacterial resistance [22]. Streptomycin is used in the treatment of diseases caused by enterococcus in the case of resistance to gentamicin. In veterinary medicine, it was considered the first-line antibiotic for the treatment of Gram-negative bacterial diseases in animals.

Mechanism of Action

Streptomycin binds to the small 16S rRNA of the 30S subunit of the bacterial ribosome and interferes with the binding of formyl-methionyl-tRNA to the 30S subunit [23]. Codon is misread and eventually results in inhibition of protein synthesis and then death of microbial cells. The conjecture on this mechanism shows that there is an interference from the binding of the molecule to the 30S subunit and the 50S subunit association with the mRNA strand. This causes an unstable ribosomal-mRNA complex, resulting into a frameshift mutation and defective protein synthesis and eventually cell death [24]. Humans' ribosomes are structurally different from those of bacteria, thereby allowing the selectivity of this antibiotic for bacteria. Streptomycin only inhibits the growth of the bacteria at low concentration by inducing prokaryotic ribosomes to misread mRNA [25]. Streptomycin inhibits both Gram-positive and Gram-

negative bacteria and is therefore considered a useful broad-spectrum antibiotic [24] Figure 3.

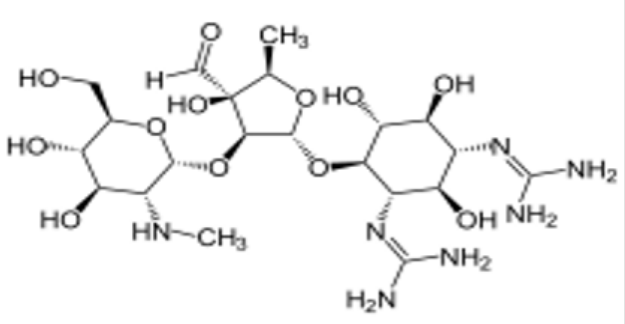

Figure 3: Chemical structure of Streptomycin.

Neomycin

Neomycin is another aminoglycoside, bactericidal antibiotic which is found in many topical medications like creams, eyedrops and ointments. It was discovered in 1949 in the laboratory of Selman Waksman in 1951. It is produced naturally by the bacterium *Streptomyces fradiae* [26]. This drug belongs to aminoglycoside in the classification of antibiotics containing two or more aminosugars connected by glycosidic bonds. Other group of aminoglycosides produduced from *Streptomyces* are Neamine, paromomycin, ribostamycin, and lividomycin. They have been reported to show great potentials in treatment of bacterial infections. Neomycin is applied topically and can be administered orally in combination with other antibiotics. It has been used to prevent hepatic encephalopathy and hypercholesterolemia.

Spectrum of Activity

Neomycin like other aminoglycosides has a broad spectrum of activity. It has excellent activity against Gram-negative bacteria, and partial activity against Gram-positive bacteria like Staphylococci, Meningococci, Pneumococci and Gonococci. It is used for the treatment of different gastrointestinal diseases including enteritis caused by antibiotic-resistant microbes. The topical application of neomycin is preferred for infected wounds, skin diseases, conjunctivitis and keratitis [27].

Daptomycin

Daptomycin is a narrow spectrum lipopeptide antibiotic used for treating certain infections caused by Gram-positive organisms [28]. It is a naturally occurring compound found in the soil saprotroph, produced by *Streptomyces roseosporus*. It is considered a last resort antibiotic because of its strong potency against methicillin-resistant *Staphylococcus aureus* [29]. It is also considered the first-line antibiotic for the treatment of infections caused by vancomycin-resistant Enterococcus faecium and methicillin-resistant *Staphylococcus aureus* [30]. Its distinct mechanism of action makes it useful in treating infections caused by multi-resistant bacteria [28]. It is also recommended for the treatment of soft tissue and complicated skin infections as well as infective endocarditis [31]. Daptomycin has been reported to be effective in the treatment of Gram-positive bacteria, especially those associated with high morbidity and mortality. A good safety profile has also been shown in clinical trials with minimal side effects [31] Figure 4.

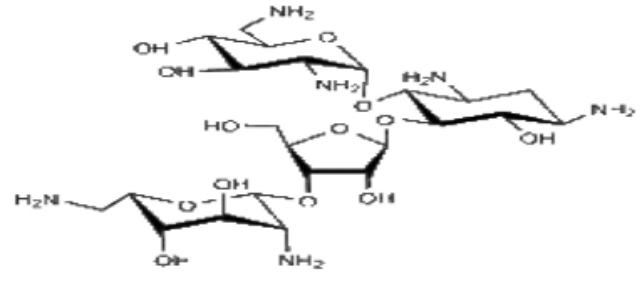

Figure 4: Chemical structure of Neomycin.

Mechanism of Action

Daptomycin acts by binding to bacterial cell membrane thereby disrupting its function [32]. It appears to bind to the membrane of Gram-positive bacteria and cause a quick depolarization, leading to loss of membrane potential, protein, DNA and RNA synthesis is inhibted, which causes bacterial cell death [5].

Spectrum of Activity

Daptomycin is active against Gram-positive bacteria only. It's in vitro activity against, Streptococci, Corynebacteria, enterococci [including glycopeptide-resistant Enterococci (GRE)] and staphylococci (as well as methicillin-resistant *Staphylococcus aureus* has been proven [33]. Reported that the Nuclear Magnetic Resonance data of daptomycin suggested complexes with calcium to form small daptomycin micelles which may enhance antimicrobial delivery to the bacterial membrane [32].

Fosfomycin

Fosfomycin, an ancient phosphoenolpyruvate analogue antibiotic agent was discovered in the year 1969. It is produced by species of *Streptomyces* including *Streptomyces wedmorensis, S. fradiae* and *S. viridochromogenes* [15]. It was initially administered as an oral treatment for mild urinary tract infections. This antibiotic is considered to be a useful option for treating patients with infections caused by resistant bacteria due to its reported activity against resistant pathogens [34]. The use of fosfomycin combined with tobramycin for treatment of lung infections in patients having cystic fibrosis was also explored [35]. Recently, there has been renewed interest in the use of this antibiotic as a result of the global problem of increasing antimicrobial resistance [34] Figure 5.

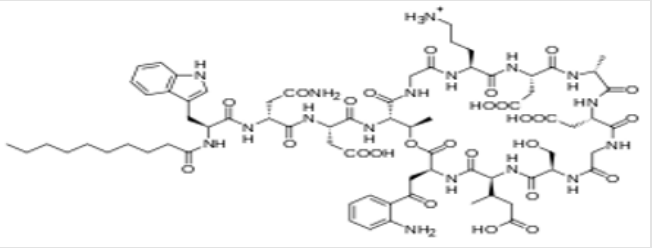

Figure 5: Chemical structure of Daptomycin.

Mechanism of Action

Fosfomycin is a bactericidal antibiotic which acts by inhibiting biogenesis of bacterial cell wall through inactivation of UDP-N-acetylglucosamine-3-enolpyruvyl-transferase, also known as MurA. This enzyme catalyzes the step involed in peptidoglycan biosynthesis including the ligation of phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-N-acetylglucosamine. This pyruvate moiety provides the linker that bridges the glycan and peptide portion of peptidoglycan [36]. Fosfomycin is a phosphoenol pyruvate analogue that inhibits MurA by alkylating an active site cysteine residue (Cys 115 in the *Escherichia coli* enzyme) [34]. Fosfomycin enters the bacterial cell through the glycerophosphate transporter. This antibiotic binds to position 115 in *E. coli* numbering (target Cys115) in the active site of MurA and thereby inactivating it [37]. In addition, fosfomycin causes suppression of platelet activator receptors in respiratory epithelial cells, thereby resulting in the reduction of adhesion of *Haemophilus influenzae* and *Streptococcus pneumoniae* [38].

Antibacterial Spectrum and Susceptibility

Fosfomycin is reported to exhibit a broad antibacterial activity against both Gram-positive and Gram-negative pathogens, with useful activity against species of Enterococcus (which include *Enterococcus faecium* and *E. faecalis*), *Staphylococcus epidermidis* and *S. aureus*. Also, it is active against Gram-negative bacteria like *Citrobacter* spp, *Salmonella* spp, *Shigella* spp, *E. coli*, and *Proteus mirabilis* [34] Figure 6.

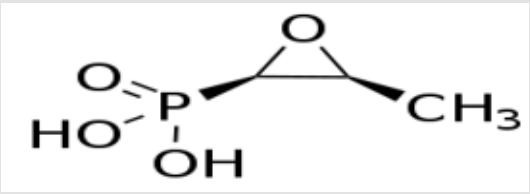

Figure 6: Chemical structure of Fosfomycin.

Historically Important Antifungal Compounds Produced by *Streptomyces*

Nystatin

Nystatin is a polyene antifungal medication to which many moulds and yeast infections are sensitive and has been used over the years for the treatment of superficial candidiasis including vulvovaginal candidiasis [39]. Nystatin like other antifungals and antibiotics was isolated from *Strptomyces noursei* in 1950 by Elizabeth Lee Hazen and Rachel Fuller Brown, from the New York State Department of Health, Laboratories and Research division. The promising micro-organism was isolated from the soil of a dairy farm. Hazen named it *Streptomyces noursei*, after William Nourse, the owner of the farm from which the bacteria was isolated [40]. Hazen and Brown also named nystatin after the New York State Health Department Laboratory (now known as the Wadsworth Center) in 1954. Nystatin is often used as prophylaxis in patients that are at risk for fungal infections, acquired immunodeficiency syndrome patients with a low CD4+ count and patients receiving chemotherapy. Nystatin is not absorbed from the gut, and therefore considered safe for oral use and does not have drug interactions problem. It is also used in cellular biology as the lipid raft-caveolae endocytosis pathway inhibitor on mammalian cells, at concentrations of about 3 µg/mL [39] Figure 7.

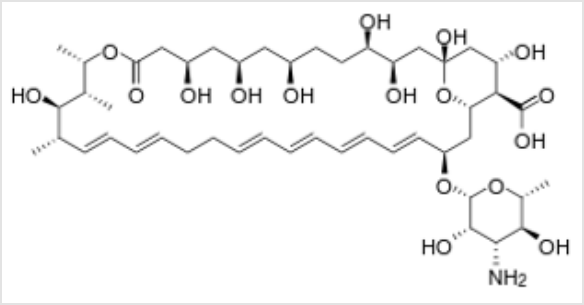

Figure 7: Chemical structure of Nystatin.

Mechanism of Action: Nystatin binds to ergosterol, which is a major component of fungal cell membrane. It forms pore at sufficient concentrations in fungal cell membrane this leads to leakage of positively charged potassium ion and eventual death of the fungus [41]. Additionally, nystatin causes the withdrawal of cholesterol located on the plasma membrane of eukaryotic cells and cause an alteration in lipid rafts microstructure which plays an important role in the regulation of adaptive and innate immune response through activation of lymphocyte, signalling of cytokine and pathogen recognition (Varshney et al. [42]).

Amphotericin B: Amphotericin B, a polyene antifungal drug, is mostly used as an intravenous drug for systemic fungal infections. It was produced in 1955 from *Streptomyces nodosus*, a filamentous bacterium, at the Squibb Institute for Medical Research from cultures of streptomycete isolated from the soil collected in the Orinoco River region of Venezuela. Its name originates from the chemical's amphoteric properties [43]. Two amphotericins namely amphotericin A and B are known, but only Amphotericin B is used clinically because it has a significant activity in vivo while Amphotericin A has little antifungal activity but almost similar to amphotericin B (having a double C=C bond between the 27th and 28th carbons) [44]. Oral preparations of amphotericin B are used for the treatment of thrush and different systemic fungal infections particularly critically ill patients, and those with comorbid infection or immunocompromised patients, including cryptococcal meningitis. In addition, it is commonly used in tissue culture to prevent fungi from contaminating cell cultures. It is usually sold in a concentrated solution, either on its own or in combination with the antibiotic's penicillin and streptomycin [45]. Amphotericin B is also used as a drug of last resort in resistant parasitic protozoan infections such as primary amoebic meningoencephalitis and visceral leishmaniasis [46].

Mechanism of Action: Amphotericin B acts by binding with ergosterol which is a component of fungal cell membranes. It forms a transmembrane channel that leads to the leakage of monovalent ion (K+, Na+, H+ and Cl−), this leakage therefore leads to fungal cell death. Researchers have recently found evidence that pore formation is not necessarily linked to cell death. The actual mechanism of action may be more complex and multifaceted [47] Figure 8.

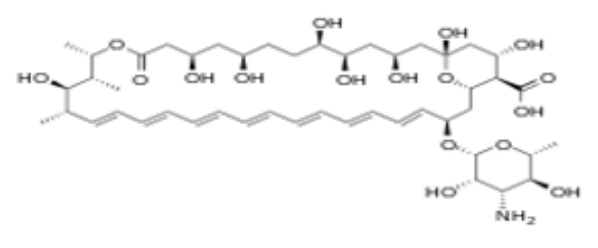

Figure 8: Chemical structure of Amphotricin B.

Natamycin: Natamycin is a naturally occurring antimicrobial agent produced during fermentation by the bacterium *Streptomyces natalensis*, commonly found in soil. It is considered a safe ingredient for food applications and is used as a preservative in food products like sausages, yoghurt, and wines [48]. Natamycin is classified as a macrolide polyene antifungal used to treat fungal keratitis. It is especially effective against *Aspergillus* and *Fusarium* corneal infections [49]. Natamycin has been used for decades in the food industry as a hurdle to fungal outgrowth in dairy products, meats, and other foods. Potential advantages for the usage of natamycin include the replacement of traditional chemical preservatives, a neutral flavour impact, and less dependence on pH for efficacy, as is common with chemical preservatives [50]. Natamycin is also approved for use in various dairy applications in the United States. It has been found commonly used in products such as cottage cheese, sour cream, yoghurt and packaged salad mixes [51]. Natamycin is used for the treatment of fungal infections, including Cephalosporium, *Candida*, *Aspergillus*, and *penicillium*. It is also applied as a cream, in eye drops, or lozenge for oral infections [51] Figure 9.

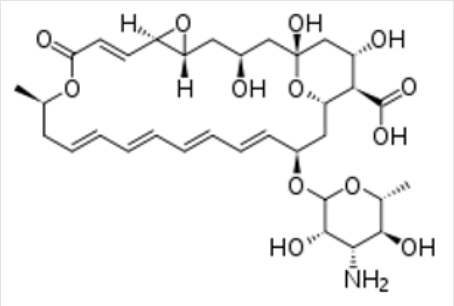

Figure 9: Chemical structure of Natamycin.

Conclusion

The challenge of emerging worldwide antimicrobial resistance can be attributed to the unavailability of newer drugs. This has led to renewed interest in old drugs that are long been discontinued in clinical practice. Effort is therefore needed to study resistant microorganisms and optimize the use of these old antibiotics. *Streptomyces* has been a great contribution to human health through the production of antimicrobial compounds. Re-evaluating older antibiotics and exploring potential antimicrobial agents produced by this organism can help to replenish the expended reservoir of antibiotics to address the problem of resistance and create the diversity needed for new novel antibiotics. Finally, to ensure continuous availability, the habitats where these *Streptomyces* spp. are isolated must be preserved.

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