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Diversity and Versatility of Actinomycetes and its Role in Antibiotic Production

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ABSTRACT

This review summarizes about the actinomycetes and their capability to produce bioactive secondary metabolites, many of which have been successfully isolated and turned into useful drugs and other organic chemicals. Microbial pathogens are becoming increasingly resistant to available treatments so new antibiotics are needed, but the channel of compounds under development is scarce. There is frantic need of new microbial agents to fight against the antibiotic resistant strains of pathogenic microorganisms, which are rapidly increasing gradually. Therefore, actinomycetes hold a prominent position due to their diversity and proven ability to produce new bioactive compounds predominantly used in antibiotic production. A critical element in a drug discovery based on microbial extracts is the isolation of unexploited groups of microorganisms that are at the same time good producers of secondary metabolites. Few of the antibiotics produced by actinomycetes are included in this review along with their activities to prove the versatility of this powerful microbial organism. Many ecological niches still remain unexplored yet which needs to be studied for a greater diversity of novel actinomycetes. Different strains of actinomycetes generally produce different compounds. For this reason intensive efforts can be increased for isolation and screening of new strains to discover new compounds.

INTRODUCTION

Actinomycetes are aerobic, spore forming gram-positive bacteria, belonging to the order Actinomycetales characterized with substrate and aerial mycelium growth (Lechevalier and Lechevalier, 1981). It has a high (G+C) ratio of the DNA (>55mol %), which are phylogenetically related from the evidence of 16S ribosomal cataloguing and DNA:rRNA pairing studies (Goodfellow and Williams, 1983; Korn-Wendisch and Kutzner, 1992). It represents one of the largest taxonomic units among the 18 major lineages currently recognized within the domain bacteria (Ventura *et al.,* 2007). The name "Actinomycetes" was derived from Greek "atkis" (a ray) and "mykes" (fungus), having characteristics of both Bacteria and fungi (Das *et al.,* 2008) but yet possess sufficient distinctive features to delimit them into 'Kingdom bacteria'. The actinomycetes are potential producers of antibiotics and of other therapeutically useful compounds. The bioactive secondary metabolites produced by actinomycetes include antibiotics, antitumor agents, immunosuppressive agents and enzymes. These metabolites are known to possess antibacterial, antifungal, antioxidant, neuritogenic, anti-cancer, anti- algal, anti-helmintic, anti-malarial and anti-inflammatory (Kekuda *et al.,* 2010; Ravikumar *et al.,* 2011). They exhibit a range of life cycles which are unique among the prokaryotes and appear to play a major role in the cycling of organic matter in the soil ecosystem (Veiga *et al.,* 1983). Actinomycetes have proved their ability to produce a variety of bioactive secondary metabolites and for this reason, the discovery of novel antibiotic and non-antibiotic lead molecules through microbial secondary metabolite screening is becoming increasingly important.

NATURE AND HABITAT

Actinomycetes are the most abundant organisms that form thread-like filaments in the soil. They grow as hyphae like fungi responsible for the characteristically "earthy" smell of freshly turned healthy soil (Sprusansky *et al.,* 2005)The actinomycetes exist in various habits in nature (George *et al.,* 2012)and represent a ubiquitous group of microbes widely distributed in natural ecosystems around the world (Srinivasan *et al.,* 1991) They are primarily soil inhabitants (Kuster, 1968) but have been found widely distributed in a diverse range of aquatic ecosystem, including sediments obtained from deep sea (Walker and Colwell, 1975; Colquhoun *et al.,* 1998), even from greatest depth Mariana Trench (Takami *et al.,* 1997; Pathom-aree *et al.,* 2006).

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Their presence in extreme environments specially at cryophilic region (Raja *et al.*, 2010) for example soil taken from Antarctica (Moncheva *et al.*, 2002) and even from desert soil has been reported (Diraviyam et al., 2010).

It has been demonstrated in a comparative survey that actinomycete population is largest in soils of surface layer and gradually decreases with as depth increased; individual actinomycete strains are present in all soil layers (Takahashi and Omura, 2003).

STRUCTURE

Actinomycetes are characterized by the formation of normally branching threads or rods. The hyphae are generally non-septate; under certain special conditions, septa may be observed in some forms. The sporulating mycelium may be branching or non-branching, straight or spiral shaped. The spores are spherical, cylindrical or oval.

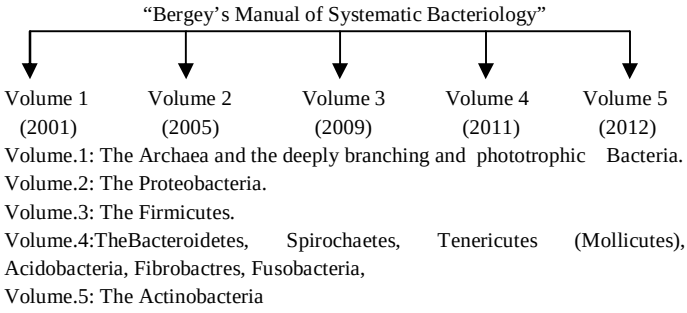
Actinomycetes produce initial micro colonies composed of branching system filaments that after 24~48 hours, fragment into diptheroids, short chain and coccobacillary forms (Waksman, 1940). The cell wall of actinomycetes is a rigid structure that maintains the shape of the cell wall of actinomycetes that maintains the shape of the cell ad prevents bursting of the cell due to high osmotic pressure (Manuselis and Mahon, 2007; Goodfellow *et al.*, 1998).

The wall consists of a large variety of complex compounds including peptidoglycan, teichoic and teichuronic acid and polysaccharides. The peptidoglycan consists of glycan (polysaccharides) chains of alternating N-acetyl-d-glucosamine (NAG) and N-acetyl-d-muramic acid (NAM) and diaminopimelic acid (DAP), which is uique in prokaryotic cell walls. Teichoic and teichuronic acid are chemically bonded to peptidoglycan (Manuselis and Mahon, 2007; Davenport *et al.*, 2000).

The chemical composition of their cell wall is similar to that of gram positive bacteria but because of their well developed morphological (hyphae) and cultural characteristics, actinomycetes have been considered as a group, well separated from other common bacteria (Das *et al.*, 2008; Cummins and Harris, 1954).

Taxonomic Outline of Phylum Actinobacteria

Actinomycetes are traditionally classified as part of the bacteria. In the Bergey's Manual of Determinative Bacteriology, Actinomycetes are included in several sections of volume four. All Actinomycetes are included under the order Actinomycetales. The order Actinomycetales is divided in to four families- Streptomycetaceae, Actinomycetaceae, Actinoplanaceae, and Mycobacteriaceae (Williams *et al.*, 1989). The "Bergey's Manual of Systematic Bacteriology-2nd edition" for actinomycetes classification has five volumes, that contain internationally recognised names and descriptions of bacteria species. Classification of actinomycetes has been rearrange d as follows:



In volume 5, the phylum actinobacteria is divided into 6 classes namely Actinobacteria, Acidimicrobiia, Coriobacteriia, Nitriliruptoria, Rubrobacteria and Thermoleophilia. The class actinobacteria is further divided into 16 orders which are Actinomycetales, Actinopolysporales, Bifidobacteriales, Catenulisporales, Corynebacteriales, Frankiales, Glycomycetales, Jiangellales, Kineosporiales, Micrococcales, Micromonosporales, Propionibacteriales, Pseudonocardiales, Streptomycetales, Streptosporangiales, Incertae sedis.

The family Actinomycetaceae (under the order Actinomycetales) and Streptomycetaceae (under the order Streptomycetales) comprise those actinomycetes, with which this treatise is primarily concerned (Goodfellow *et al.*, 2012).

Actinomycetes have also been classified into several groups based on biochemical parameters. Based on major cell wall constituent, four groups have been identified in Actinomycetes (Lechevalier and Lechevalier, 1970).

Cell wall type	Sugar Pattern	Genera
I	No characteristic sugar pattern	*Streptomyces, Streptoverticillicum* etc.
II	Araginose, Xylose (monosaccharide)	*Actinoplanes, Micromonospora* etc.
III	No Sugar	*Dermatophilus, Planomonospora* etc.
IV	Galactose,Arabinose	*Mycobacterium, Nocardia* etc.

SIGNIFICANCE OF ACTINOMYCETES

Actinomycetes are biotechnologically valuable bacteria which are well exploited for secondary metabolites (Balagurunathan and Radhakrishnan, 2010). Screening, isolation and characterization of promising strains of actinomycetes producing potential secondary metabolites has been a major area of research by many groups worldwide for many years (Hacène *et al.*, 2000; Laidi *et al.*, 2006). Among various genera of Actinomycetes; Streptomyces, Saccharopolyspora, Amycolatopsis, Micromonospora and Actinoplanes are the major producers of commercially important biomolecules (Solanki *et al.*, 2008). Actinomycetes especially Streptomyces species are widely recognized as industrially important microorganisms as they are a rich source of several useful bioactive natural products with potential applications (Korn-Wendisch and Kutzner, 1992; Williams *et al.*, 1989; Williams *et al.*, 1983; Lakshmipathy and Kannabiran, 2009) and are prolific producers of secondary

metabolites, many of which have commercial importance as antibiotics, anti-parasitics and antifungal agents, herbicides, pesticides, anticancer or immunosuppressive agents as well as industrially important enzymes (Takahashi and Omura, 2003; Curl *et al.*, 1983; Atta and Ahmad, 2009). Of all known drugs, 70% have been isolated from Actinomycetes bacteria and out of which 75% and 60% are used in medicine and agriculture respectively (Miyadoh, 1993; Tanaka and Omura, 1993). Secondary metabolites, to a large extent, are species-specific and in contrast to primary metabolites, often accumulate in substantial quantity, which is a key factor in their commercial importance (Turner, 1973; Demain, 1981; Demain, 1983). Actinomycetes are of tremendous economic importance as the secondary metabolites produced by them includes antibiotics, other medicinals, toxins, pesticides and animal and plant growth factors (Demain and Fang, 1995). The best known of the secondary metabolites produced by Actinomycetes are the antibiotics.

Antibiotics are truly referred as the 'wonder drugs' for their virtual success against pathogenic microorganisms (Demain, 1999). This remarkable group of compounds forms a heterogeneous assemblage of biologically active molecules with different structures and modes of action. They attack virtually every type of microbial activity such as DNA, RNA, and protein synthesis, membrane function, electron transport, sporulation, germination and many others (Kohanski *et al.*, 2010). As a result, they are effective treatments for bacterial infections. Prior to the discovery of antibiotics, people with simple wounds and infectious diseases could not be treated.

The first antibiotic discovered by Sir Alexander Fleming in 1928 (Fleming, 1980) facilitated the discovery of many other secondary metabolites with similar properties. The secondary metabolites produced by actinomycetes serve as the sources of life saving environments**.**These have a broad spectrum of biological activities; e.g. antibacterial (streptomycin, tetracycline, chloramphenicol), antifungal (nystatin), antiviral (tunicamycin), antiparasitic (avermectin), immunosuppressive (rapamycin), antitumor (actinomycin, mitomycinC, anthracyclines), enzyme inhibitory (clavulanic acid) and diabetogenic (bafilomycin, streptozotocin), Cancer (doxorubicins, daunorubicin, mitomycin and bleomycin), transplant rejection (cyclosporine and rapamycin) and high cholesterol (statins such as lovastatin and mevastatin (Bérdy, 2005; Farnet and Zazopoulos, 2005).

Members of Actinomycetes group,in addition are producers of clinically useful antitumor drugs such as Anthracyclines (Aclarubicin, Daunomycin and Doxorubicin), Peptides (Bleomycin and Actinomycin D), Aurelic acids (Mithramycin), Enediynes (Neocarzinstatin), Antimetabolites (Pentostatin), Carzinophilin, Mitomycins and others. Actinomycetes products are not able not only for their potent therapeutic activities but also for the fact that they frequently possess the desirable pharmacokinetic properties required for clinical development (Farnet and Zazopoulos, 2005).

The actinomycetes are important not only in the field of pharmaceutical industries and also in the agriculture. Actinomycetes have the potential to inhibit the growth of several plant pathogens e.g. *Erwinia amylovora* (bacteria that cause fireblight to apple), *Agrobacterium tumefaciens* (casual agent of Crown Gall disease) etc (Jeffrey et al., 2007; Jeffrey, 2008; Oskay et al., 2004).

Actinomycetes decompose complex mixtures of polymer in dead plant, animal and fungal material resulting in production of many extracellular enzymes which are conductive to crop production. Apart from this, Actinomycetes have major contribution in biological buffering of soils, biological control of soil environments by nitrogen fixationand degradation of high molecular weight compounds like hydrocarbons in the polluted soil (Srinivasan *et al.*, 1991; Suzuki *et al.*, 1994). Actinomycetes have the capacity to synthesize many different biologically active secondary metabolites such as cosmetics, vitamins, nutritional materials, herbicides, antibiotics, pesticides, anti-parasitic and enzymes like cellulose and xylanase used in waste treatment (Ogunmwonyi *et al.*, 2010).

Actinomycetes also synthesize and excrete dark pigments, melanin or melanoid (Zenova, 1965; Arai and Mikami, 1972; Amal *et al.*, 2011). These melanin compounds are irregular, dark brown polymers having radio protective and antioxidant properties that can effectively protect the living organisms from ultraviolet radiation (Romero-Martinez *et al.*, 2012). Melanins are frequently used in medicine, pharmacology, and cosmetics preparations (Quadri and Asgar, 2012).

Role of Actinomycetes As Potential Producer of Antibiotics

Actinomycetes are the mainstay of the antibiotics industry and hold a significant role in producing variety of drugs that are extremely important to our health and nutrition (Magarvey *et al.*, 2004). Search for new antibiotics effective against multi-drug resistant pathogenic bacteria is presently an important area of antibiotic research.

Natural products having novel structures have been observed to possess useful biological activities (Dancer, 2004). Although, considerable progress is being made within the fields of chemical synthesis and engineered biosynthesis of antibacterial compounds, nature still remains the richest and the most versatile propitious source for new antibiotics (Koehn and Carter, 2005; Baltz, 2006; Peláez, 2006; Bull and Stach, 2007). Although thousands of antibiotics have been discovered till today, only a few of them are useful to humans and animals; the reason being their toxicity. In order to get through this problem search of new antibiotics is in progress which is more effective and does not have any toxic side effects.

Another major healthcare problem is that of antibiotic resistance. The rapid emergence of drug resistance among pathogenic bacteria, especially multi drug resistant bacteria, underlines the need to look for new antibiotics (Alanis, 2005; Sharma *et al.*, 2011). One approach to solve this problem is to search for new antibiotics with new mechanism of action. Majority of antibiotics are derived from microorganisms especially from the species actinomycetes (Bérdy, 1995).

Table 1: Antibiotics and Bioactive secondary metabolites from actinomycetes.

Source	Antibiotics	Bioactive metabolites			Total bioactive metabolites
	Total	With other activity	No antibiotic activity	Antibiotics Plus other Active compounds	
Bacteria	2900	780	900	1680	3800
Actino mycetes	8700	2400	1400	3800	10100
Fungi	4900	2300	3700	6000	8600
Total	16500	5500	6000	11500	22500

Adapted from Berdy, 2005 and reproduced from Kurtböke, 2010.

Almost 80% of the world's antibiotics are known to come from actinomycetes, mostly from the genera Streptomyces and Micromonospora (Jensen *et al.,* 1991; Hassan *et al.,* 2011). Among Actinomycetes, around 7600 compounds are produced by *Streptomyces* species. Many of these secondary metabolites are potent antibiotics, which has made streptomycetes the primary antibiotic-producing organisms exploited by the pharmaceutical industry (Ramesh *et al,* 2009; Jensen *et al.,* 2007). The capacity of the members of the genus *Streptomyces* to produce commercially significant compounds, especially antibiotics, remains unsurpassed, possibly because of the extra-large DNA complement of these bacteria (Kurtböke, 2012). The last 5decades have seen the discovery of more than 12,000 antibiotics. The actinomycetes yielded about 70% of them and the remaining 30% are products of filamentous fungi and non- actinomycete bacteria (Zhu *et al.,* 2001). The antibiotics from actinomycete sort into several major structural classes such as amino glycosides (e.g., streptomycin and kanamycin) (Nanjawade et al., 2010), ansamycins (e.g., rifampin) (Floss and Yu, 1999), anthracyclines (e.g., doxorubicin) (Kremer and Van Dalen, 2001), β-lactam (cephalosporins) (Kollef, 2009) , macrolides (e.g., erythromycin) and tetracycline (Harvery and Champe, 2009). Streptomyces strains have produced many of the antibiotics known to humans as a result of their competition against other soil microorganisms. It appears that these organisms produce antibiotics to kill off potential competitors (Laskaris *et al.,* 2010). One of the first antibiotics used is streptomycin produced by *Streptomyces griseus* (Schatz *et al.,* 2005). Indeed, different *Streptomyces* species produce about 75% of commercially and medically useful antibiotics. They have provided more than half of the naturally occurring antibiotics discovered to date and continue to be screened for useful compounds (Miyadoh, 1993). In the course of screening for new antibiotics, several studies are oriented towards isolation of Streptomycetes from different habitats. The ability of *Streptomyces* cultures to form antibiotics is not a fixed property but can be greatly increased or completely lost under different conditions of nutrition and culturing, (Waksman, 1962) and hence the medium constitution together with the metabolic capacity of the producing organism greatly affect antibiotic biosynthesis. Antagonistic actinomycetes produce a variety of antibiotics that vary in chemical nature, in antimicrobial action, in toxicity to animals, and in their chemotherapeutic potentialities. The antibiotics that have been isolated so far from Actinomycetes, vary in the degree of purification. Some are crude preparations, whereas others have been crystallized, and considerable information has been gained concerning their chemical nature. They include: actinomyces lysozyme, actinomycin, micromonosporin, streptothricin, streptomycin, and mycetin. Some actinomycetes produce more than one antibiotic substance (eg. *Streptomyces griseus*) as well as the same antibiotic may be produced by different species of actinomycetes (eg: Actinomycin, streptothricin). A given antibiotic may, therefore, be identical, even when produced by different actinomycetes, as shown by its chemical composition and antibiotic spectrum (Waksman et al., 2010).

AVAILABLE ANTIBIOTICS OF ACTINOMYCETES

Penicillin

Structurally the penicillins comprise a ß-lactam ring fused with a thiazolidine ring; this structure is termed 6-aminopenicillanic acid. Connected to this common backbone structure are characteristically different amide-bonded side chains in every member of this class of compounds, influencing their properties including spectrum of activity (Batchelor et al., 1965). Penicillin inhibit the synthesis of essential structural components of bacterial cell wall i.e. peptidoglycan which are absent in mammalian cells. Thus host cell metabolism remains unaffected and penicillins are regarded as one of the safest and most efficacious class of antibiotics being used for bacterial infections. It has a wide spectrum of activity against gram-positive organisms but shows poor activity against aerobic gram-negative rods. It is widely recommended for treatment of infections caused by streptococci, susceptible staphylococci, *Pasteurella multocida, Neisseria, Clostridia* (Park and Strominger, 1957). Penicillin V acylase is reported to be produced in high levels by *Streptomyces lavendulae* (Torres *et al.,* 1999).

Cephalosporins

Cephalosporins are the most frequently prescribed class of antibiotics, structurally and pharmacologically related to the penicillins. Like the penicillins, cephalosporins have a β-lactam ring structure that interferes with synthesis of the bacterial cell wall and so are bactericidal (which means that they kill bacteria). Cephalosporins are β-lactam antibiotics that differ from the penicillins in that the β ring is a 6-membered dihydrothiazine ring. Cephalosporins are used for the treatment of infections caused by most gram-positive and gram-negative bacteria, especially *Escherichia coli, Proteus mirabilis and klebsiella sp.* Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity**.** *Streptomyces clavuligerus* is reported for ceplalosporin production (Rius and Demain, 1997; Xiao *et al.,* 1991; DePestel *et al.,* 2008).

Tetracyclines

Tetracycline molecules comprise a linear fused tetracyclic nucleus to which a variety of functional groups are attached. They are so named for their four

(tetra) hydrocarbon rings (cycle) derivation. These inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. Tetracyclines are broad-spectrum agents, exhibiting activity against a wide range of gram-positive and gram-negative bacteria, atypical organisms such as *chlamydiae*, *mycoplasmas*, and *rickettsiae*, and protozoan parasites. They are also widely used as growth additives in animal feed. The first tetracycline, aureomycin, was discovered by Benjamin Duggar in 1945 produced by *Streptomyces aureofaciens*. Because of the widespread use of tetracyclines, resistance developed in many pathogens, which limited their utility. Two new classes of tetracycline, the glycylcyclines and aminomethylcyclines, represented by tigecycline and PTK-0796, respectively, have been discovered. Besides natural tetracyclines isolated from various strains of streptomyces, many derivatives (e.g. doxycycline, minocycline) have been prepared by their chemical conversion (Darken *et al.,* 1960; Blackwood *et al.,* 1963; Chopra and Roberts, 2001).

Quinolone

Quinolones are heterocycles with a bicyclic core structure, known for their ability to inhibit bacterial topoisomerases (Hardman *et al.,* 1996). Quinolones are bactericidal and exhibit concentration-dependent killing. The targets of quinolone activity are the bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and transcription. Early quinolones, such as nalidixic acid, had poor systemic distribution and limited activity and were used primarily for Gram-negative urinary tract infections. The next generation of quinolone agents, the fluoroquinolones (i.e., ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, and enoxacin), were more readily absorbed and displayed increased activity against Gram-negative bacteria. Newer fluoroquinolones (i.e., levofloxacin, sparfloxacin, trovafloxacin, and grepafloxacin) are broad-spectrum agents with enhanced activity against many Gram-negative and gram-positive organisms. The quinolones appear to be specific and very potent against H. pylori. Quinolones have been isolated from the actinomycete *Pseudonocardia sp* (Dekker *et al.,* 1998; Smith, 1986; Siegmund *et al.,* 2005).

Aminoglycosides

In an aminoglyside molecule, one or several aminated sugars are joined in glycosidic linkages to a dibasic cyclitol (Mingeot-Leclercq *et al.,* 1999). Aminoglycosides are the best characterized class of antibiotics that bind directly to ribosomal RNA. Aminoglycosides cause decreases in translational accuracy and inhibit translocation of the ribosome (Davies *et al.,* 1965; Davies and Davis, 1968). They are valuable in the treatment of serious infections caused by gram-negative bacteria. They inhibit the protein synthesis of microorganism resulting in a rapid concentration dependent bactericidal action (Bryan *et al.,* 1977). *Streptomyces sp (Streptomyces kanamyceticus, Streptomyces spectabilis, Streptomyces tenjimariensis)*and *micromonospora sp.*have specific role in production of aminoglycosides. Aminoglycosides that are derived from bacteria of the Streptomyces genus are named with the suffix -mycin, whereas those that are derived from Micromonospora are named with the suffix –micin (Benveniste and Davies, 1973).

Fattiviracins

Fattiviracins have macrocyclic diesters consisting of four D-glucose units and two (C24 and C33) hydroxy fatty acids. Fattiviracins have a potent activity against enveloped DNA viruses such as the herpes family, HSV-1 and VZV and enveloped RNA viruses such as influenza A and B viruses, and three strains of HIV-1, in the order of a few µg/ml of EC50.The producing organism of Fattiviracins is *Streptomyces microflavus* (Uyeda, 2003). Fattiviracins act on HIV-1 particles directly without lysis of the particles, and it affords the inhibition of viral entry into the host cells (Habib *et al.,* 2001).

Cephamycins

Cephamycins are beta-lactam antibiotics with a cephem structure produced by actinomycetes. Ten enzymatic steps are involved in the formation of cephamycin C (Liras and Demain, 2009). Unlike most cephalosporins, cephamycins are a very efficacious antibiotic against anaerobic microbes. The ornithine carbamoyltransferases (OTCases) from the β-lactam-producing actinomycetes *Streptomyces clauligerus* and *Nocardia lactamdurans* showed a reverse activity on citrulline and used lysine and putrescine as substrates (Miller *et al.,* 1972; Fuente *et al.,* 1996). These antibiotics exhibit antibacterial activity against a broad spectrum of bacteria which includes many that are resistant to the cephalosporins and penicillins (Stapley *et al.,* 1972).

Macrolides

Macrolides are characterized by a large lactone ring containing from 12 to 16 atoms to which are attached, via glycosidic bonds, one or more sugars (Mazzei *et al.,* 1993). These agents are generally used to treat infection in the respiratory tract, skin and soft tissues and genital tract caused by gram-positive organisms, mycoplasma species and certain susceptible gram-negative and anaerobic bacteria. Most of them are derived from various strains of streptomyces and serve as an alternative for patients exhibiting penicillin sensitivity. They inhibit growth of bacteria by inhibiting protein synthesis on ribosomes (Brisson-Noël *et al.,* 1988). Macrolides include the following antibiotics: Erythromycin and its related substances, azithromycin, clarithromycin, dirithromycin, roxithromycin, flurithromycin, josamycin, rokitamycin, kitasamycin, mycinamycin, mirosamycin,oleandomycin, rosaramicin, spiramycin and tylosin (Alvarez-Elcoro and Enzler, 1999). Macrolides are reported to be produced by *Streptomyces Venezuela* (Xue *et al.,* 1998).

Sulphonamides

Sulfonamide is an organic sulfur compounds containing the radical $-SO_2NH_2$ (the amides of sulfonic acids). Its molecular structure is similar to p-Aminobenzoic acid (PABA) which is

needed in bacteria organisms as a substrate of the enzyme dihydropteroate synthetase for the synthesis of tetrahydrofolic acid (THF). Sulfonamides, derived from chiefly sulfanilamide, are capable of interfering with the metabolic processes in bacteria that require PABA. They act as antimicrobial agents by inhibiting bacterial growth and activity and called sulfa drugs (Henry, 1943). These are the first drugs effective against bacterial septicemias, but also effective in tissue infections due to streptococci and fungus related *nocardia*. They are used in the prevention and treatment of bacterial infections, diabetes mellitus, edema, hypertension, and gout. Nowadays they are widely used in farm animal feedstuff and fish cultures as veterinary drugs for prophylactic and therapeutic purposes. Sulfonamides inhibit growth of bacteria in-vivo. In the third world countries where problems of storage and lack of medical personnel make appropriate use of antibiotics difficult, they are of great value (Weinstein *et al.,* 1960). Sulphonamide antibiotics are reported to be produced by *Streptomyces sp* (Fukuda *et al.,* 2009).

Fluostatins

Fluostatins are named by their characteristic fluorenone chromophore, the fluorenone bearing two phenolic hydroxyl groups. Two positions are available for the attachment of an additional aliphatic ring. Fluostatins A and B are potent inhibitors of Dipeptidyl Peptidase III, which is proposed to play a role in the regulation of hormonal peptides. Fluostatin C shows moderate activity against selected human tumor cell lines. These are produced by *Streptomyces sp* (Akiyama *et al.,* 1998; Baur *et al.,* 2006; Schneider *et al.,* 2006).

MISCELLANEOUS

Rifampin

Rifampin is a bactericidal antibiotic from the rifamycin group which acts on both intracellular and extracellular organisms. It is a semi-synthetic compound derived from *Amycolatopsis rifamycinica* (formerly known as *Amycolatopsis mediterranei* and *Streptomyces mediterranei)*. It has a broad antibacterial spectrum, including activity against several forms of Mycobacterium. In susceptible organisms it inhibits DNA-dependent RNA polymerase activity by forming a stable complex with the enzyme. It thus suppresses the initiation of RNA synthesis (Atlas and Turck, 1968; Kunin *et al.,* 1969; Farr, 2000).

Chloramphenicol

Chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$ is a protein synthesis inhibitor that has a broad spectrum of activity but it exerts a bacteriostatic effect. Chloramphenicol was first employed in the late 1940s to treat a typhus epidemic in Bolivia. Chloramphenicol inhibits the bacterial enzyme peptidyl transferase, thereby preventing the growth of the polypeptide chain during protein synthesis but to a lesser extent in eukaryotic cells. It has an antimicrobial spectrum similar to that of tetracycline. Nowadays it is mainly applied in veterinary medicine because of its adverse reaction in humans (Ehrlich *et al.,* 1948) Chloramphenicol production is reported in Streptomyces venezuelae (Ahmed and Vining, 1983; He et al., 2001).

Lincomycin and clindamycin

Lincomycin is a lincosamide antibiotic that comes from the actinomyces Streptomyces lincolnensis. It has been structurally modified by thionyl chloride to its more commonly known 7-chloro-7-deoxy derivative, clindamycin. Lincomycin and its clinically more useful analogue, clindamycin are active against many gram-positive bacteria but are inactive against gram-negative species as they inhibit protein synthesis of former. Lincomycin is used as ahydrochloride & clindamycin is used as a phosphate ester (dihydrogenphosphate of clindamycin) (Verdier et al., 2000; Michalik et al., 1975; Spízek and Rezanka, 2004)

Phencomycin

Phencomycin chemically known as 1, 6-Phenazinedicarboxylicacid, 1-methyl esters is a phenazine derivative which is active in vitro against a number of Gram-positive bacteria. Accordingly, it may be used as a therapeutic drug in human and veterinary medicine. It has an antibiotic action, an action as enzyme inhibitor and an influence on the kallikrein-kinin system.Phencomycin is reported to be isolated from Streptomyces sp (Chatterjee et al., 1995; Pusecker et al., 1997).

Oligomycin

Oligomycin are a family of macrolide antibiotics that inhibits ATP synthase by blocking its proton channel (Fo subunit), which is necessary for oxidative phosphorylation of ADP to ATP (energy production). The inhibition of ATP synthesis would also stop electron transport chain. Because the high proton concentration build up is not dissipated, the free energy released by biological oxidation of substrates is not enough to pump any more protons against the steep gradient (Laatsch et al., 1993; Nakata et al., 1995). Various streptomyces sp have been reported in Oligomycin production eg. Streptomyces avermitilis (Lin et al., 2009), Streptomyces griseolus (Grammatikova et al., 2003).

Sparsomyin

Sparsomycin is a cytotoxic drug exhibiting a broad spectrum of in vitro activity against murine tumors and many tumor cell lines (Zylicz et al., 1987). This antitumor antibiotic is a universal translation inhibitor that blocks protein synthesis in prokaryotic and eukaryotic cell (Lazaro et al., 1991). The drug binds and causes important conformational changes in the peptidyl transferase active center. Thus, it was found that sparsomycin can block the binding of substrates at the A-site (24) but it enhances binding to the P-site (Ravel et al., 1970). Recently, this antibiotic was found to interact with nucleotide A2602 in the peptidyl transferase center of the bacterial ribosome (Porse et al., 1999) . The drug was initially developed as a potential antitumor agent, although toxicity soon limited its clinical application (McFarlane etal.,1966). Sparsomyin is produced by Streptomyces sparsogenes, which is obviously resistant to the drug (Cundliffe, 1989).

Table 2: Some clinically important antibiotics from actinomycetes.

Antibiotic	Produced by	Activity	Reference
Sagamicin	*Micromonospora sagamiensis*	Antibacterial	(Okachi *et al*., 1974)
Amiclenomycin	*Streptomyces lavendulae*	Antibacterial	(Okami *et al.*, 1974)
Methylenomycin	*Streptomyces violaceoruber*	Antibacterial	(Haneishi *et al*., 1974)
Roseoflavin	*Streptomyces davawensis*	Antibacterial	(Matsui *et al*., 1979; Grill *et al.*, 2008)
Minosaminomycin	*Streptomyces sp.*	Antibacterial	(Hamada *et al.*, 1974)
Libramycin	*Streptomyces sp.*	Antifungal	(Yahagi *et al.*,1974)
Candihexin	*Streptomyces viridoflavus*	Antifungal	(Martin and McDaniel, 1974)
Nanaomycin	*Streptomyces rosa*	Antifungal	(Omura *et al*., 1974)
Purpuromycin	*Actinoplanes ianthinogenes*	Antifungal	(Coronelli *et al.*, 1974)
Zorbonomycin	*Streptomyces bikiniensis*	Antifungal	(Argoudelis *et al.*, 1971)
Validamycin	*Streptomyces hygroscopicus* 5008	Antifugal	(Wu *et al.*, 2012)
Rosamicin	*Micromonospora rosaria*	Antibacterial	(Anzai *et al*., 2009)
Rifamycin	*Micromonospora rifamycinica*	Antibacterial	(Huang *et al*., 2008; Huang *et al.*, 2009)
Platenomycin	*Streptomyces platensis*	Antibacterial	(Furumai *et al*., 1973)
Lincomycin	*Streptomyces lincolnensis*	Antibacterial	(Michalik *et al.*, 1975)
Azalomycin	*Streptomyces hygroscopicus*	Antifungal	(Arai and Hamano, 1970)
Azalomycin	*Streptomyces malaysiensis*	Antifungal	(Cheng *et al*., 2010)
Streptimidone	*Streptomyces sp*.	Agricultural	(Chatterjee *et al*., 1995)
Kinamycin	*Streptomyces murayamaensis*	Antibacterial	(Gould *et al.*, 1998)
Kuwaitimycin	*Streptomyces kuwaitinensis*	Antibacterial	(Shimi *et al*., 1973)
Sarkomycin	*Streptomyces sp*.	Antitumor	(Umezawa *et al.*, 1954)
Salinomycin	*Streptomyces albus*	Antiparasite	(Naidenova *et al.*, 2001)
Antimycin	*Streptomyces antibioticus*	Antifungal	(Xu *et al.*, 2011)
Antimycin	*Streptomyces lucitanusus*	Antifungal	(Han et al., 2012)
Tomaymycin	*Streptomyces achromogenes*	Antiviral	(Arima *et al.*, 1972)
Erythromycin	*Actinopolyspora sp.*	Antibacterial	(Huang *et al*., 2009)
Rapamycin	*Streptomyces Hygroscopicus*	Anti-proliferative immunosuppressant	(Garrity *et al.*, 1993)
Myomycin	*Nocardia sp*	Antibacterial	(French *et al*.,1973)
Lomofungin	*Streptomyces lomondensis*	Antifungal	(Bergy, 1969; Das *et al.*, 2012)
Sclerothricin	*Streptomyces scleogranulatus*	Antifungal	(Kono *et al.*, 1969)
Spoxamicin	*Streptosporangium oxazolinicum*	Antitrypanosomal	(Inahashi *et al*., 2011)
Avermectin	*S. avermitilis*	Antiparasitic	(Kitani *et al*., 2011)

Future Prospects of Actinomycetes

The discovery of Actinomycetes secondary metabolites is unrivaled and unmatched in medical significance. Actinomycetes are the main source of clinically important antibiotics, most of which are too complex to be synthesized by combinatorial chemistry (Baltz, 2007; Kekuda *et al.*, 2010). Structurally and functionally diverse bioactive compounds have been isolated from Actinomycetes as antibiotics with antibacterial, antifungal, anti-parasitic, anti-viral and anti-tumor activity. Majority of the actinomycetes that are potential drug sources remain uncultivable, and therefore inaccessible for novel antibiotic discovery. Less than one part in 10^{12} of the earths' soil has been screened for Actinomycetes (Baltz, 2007). Only 1-3% of Streptomycete antibiotics have been discovered and to find the remaining 97-99% will require modern technologies for screening, selection and enrichment of Actinomycetes (Clardy *et al.*, 2006; Goodfellow, 2010).

Public health officials consider the current state of available antibiotics to be perilous, as some organisms are close to having complete resistance to all commercially available antibiotics. Fortunately, new antibiotics are constantly being discovered from *Streptomyces*. Also, older drugs that were not deemed suitable for use are being re-examined. In some cases, they are being chemically modified. This can cause them to have new abilities to inhibit other microorganisms (Donadio *et al.*, 2010). No doubt, Actinomycetes represent the biggest possibility to obtain further medically, agriculturally and industrially useful compounds which may serve as direct drugs or indirectly as lead compounds for structural modifications and templates for the rational drug design and other derivatives. Chemical diversity of bioactive compounds, particularly from rare and "yet to be discovered" actinomycetes is promising, however, detection of bioactive actinomycete taxa requires in-depth understanding of their true diversity and eco-physiology through which target-directed isolation strategies can be implemented (Kurtböke, 2012 ;Bull *et al.*, 2007).

As long as the major challenges in biotechnology and biomedicine remain (e.g. emerging diseases, established diseases, antibiotic resistance, environmental pollution and need for renewable energy) microbial resources will be of interest to mankind providing sustainable and environmentally friendly solutions. Actinomycetes and their bioactive compounds show antibacterial and antimicrobial activity against various pathogens and multi drug resistant pathogens e.g vancomycin resistant enterococci, methicillin resistant *Staphylococcus aureus, Shigella dysenteriae, Klebsiella sp., Escherichia coli, Pseudomonas aeruginosa* etc (Saadoun *et al.*, 1999; Selvameenal *et al.*, 2009; Servin *et al.*, 2008; Singh *et al.*, 2012). With the efforts of mankind, this natural treasure can become a gainful source of utilization. The best is yet to come as microbes move into the environmental and energy sectors. As stated many years ago by Jackson W. Foster "Never underestimate the power of the microbe," and by David Perlman "If you take care of your microbial friends, they will take care of your future".

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Production of antibiotics is a naturally occurring event, that thanks to advances in science can now be replicated and improved upon in laboratory settings. Due to the discovery of penicillin by Alexander Fleming, and the efforts of Florey and Chain in 1938, large-scale, pharmaceutical production of antibiotics has been made possible. As with the initial discovery of penicillin, most antibiotics have been discovered as a result of happenstance. Antibiotic production can be grouped into three methods