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Antibacterial agents from Actinomycetes - A Review

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1. ABSTRACT

The discovery of Penicillin in 1928 and that of Streptomycin in 1943, has been pivotal to the exploration of nature as a source of new lead molecules. Globally, the microbiologist today is acknowledged as a crucial player in the drug discovery program. The microbial products, especially those from actinomycetes have been a phenomenal success for the past seven decades. Bioprospecting for new leads are often compounded by the recurrence of known antibiotics in newer microbial isolates. Despite all these deterrents, actinomycetes have proved to be a sustained mine of novel antibiotics, which selectively destroys the pathogens without affecting the host tissues. Each of these antibiotics is unique in their mode of action. Their versatility and immense economic value is something, which is extremely noteworthy. The anti-infective turn-over of over 79 billion US dollars in 2009, includes about 166 antibiotics and derivatives such as the Beta-lactam peptide antibiotics, the macrolide polyketide erythromycin, tetracyclines, aminoglycosides, daptomycin, tigecycline, most of which are produced by actinomycetes (1). Actinomycetes continue to play a highly significant role in drug discovery and development. Among the bioactive compounds that have been obtained so far from microbes, 45% are produced by actinomycetes, 38% by fungi and 17% by unicellular eubacteria (2). Further many chemically synthesized drugs owe their origin to natural sources. In this review article, we highlight the recent antibiotics from actinomycetes with emphasis on their source, structures, activity, mechanism of action and current status.

2. INTRODUCTION

Infectious diseases today are a leading cause of deaths world-wide, accounting for 25% of all deaths (around 13.3 million), (2). According to the Infectious Disease Society two million drug-resistant infections are reported each year, causing great suffering and costing the health system up to 34 billion U.S. dollars a year. Only two percent of Staphylococcus infections in the U.S. were drug-resistant in 1974. The percentage soared to 63% by 2004. According to the U.S. Centers for Disease Control and Prevention (CDCP), staphylococcus infections now kill more people in the U.S. than AIDS, (3). Some factors that contribute to this huge number include the increasing number of microbial infections, excessive use of antibiotics caused by either over-prescription or patient demands or drug resistant strains.

Among these, antibiotic resistance by pathogens is a matter of serious concern for the healthcare practitioner, as it has the potential to render hitherto curable diseases incurable. The drive to provide a panacea for the ills of the uncomprehending patient and the baffled physician has provided an impetus in either discovering or formulating a versatile drug to combat the super-bugs (4).

Disease management has undergone a sea change since the discovery of antibiotics. From the symptomatic

style of treatment of our forefathers, to the serendipitous discovery of Penicillin, drug discovery has become a highly specialized domain in any pharmaceutical company today. Time and again, the beleaguered scientist has taken recourse to natural habitats as a source of new drugs.

Early scientific observations on the antagonism among the soil flora led scientists to speculate on the existence of some microbial metabolite, which held the key to its survival. The soil, despite teeming with billions of microbes allows only some of them to survive the competition. Further investigations and observations gave way to the concept of the term "antibiosis" (against life). The renowned Nobel Laureate, Selman Abraham Waksman, coined the word "antibiotic". His pioneering work on actinomycetes spawned interest among many researchers during that period (4).

Actinomycetes, a distinct group of microbes, are a class of their own. Early interest in Actinomycetes centered mainly on their ability to form antibiotics, along with certain vitamins and enzymes (5). Beginning with the discovery of Actinomycin in 1940, the interest in the antibiotics produced by actinomycetes has been wondrous (5). Streptothricin, streptomycin, chloramphenicol, the tetracyclines, the erythromycins, neomycin, novobiocin, oleandomycin, nystatin, the chain of discoveries has been endless. The trend continues even in the twenty first century with the addition of new antibiotics such as daptomycin, epirubicin, carbapenem analogues, theinamycin (6).

In this context, tapping the natural ecosystems, where zillions of microbes engage themselves in the battle for "survival of the fittest", seems a logical choice as sources of new antimicrobial agents. A central factor in the drug discovery process from microbial extracts is the isolation of new species of microbe, which also produce secondary metabolites (7). The exploration of diverse ecosystems and habitats and the subsequent isolation of diverse genera of actinomycetes from the same are central to the procurement of new antibiotics. A total of 22,500 bioactive secondary metabolites have been reported from natural sources, out of which 16,500 compounds show antibiotic activities. Out of these total 22,500 bioactive secondary metabolites, 10,100 (45%) are reported to be produced by actinomycetes in which 7630 are from streptomycetes and 2470 from rare-actinomycetes (2). Rare- actinomycetes are those actinomycetes, which belong to groups other than the streptomycetes. Actinomycetes emerge as an extremely promising class of prokaryotes, owing to their consistency in producing new antibiotics. They are unique as they elaborate numerous antibiotics, which are also used for treating a variety of indications.

This article aims to take the reader through a journey spanning almost seven decades since the discovery of the first antibiotic from actinomycetes. In the current review we have focused essentially on those antibacterial antibiotics from actinomycetes, which are reported, and being used as antibiotic without further chemical modifications.

3. ACTINOMYCETES

Actinomycetes were originally thought of as bacteria in the guise of fungi or vice versa. It was indeed a challenge to classify them. Some scientists considered them as Eubacteriales or higher bacteria, while some thought them to belong to Hypomycetes or lower fungi. Selman Waksman opined that these microorganisms could be grouped separately.

Actinomycetes, like true bacteria (Eubacteria) are prokaryotes. Their growth (prothallus) is characterized by the formation of normally branching threads and rods, frequently giving rise to a typical mycelium, which is unicellular, especially during the early stages of growth (8). Generally non-septate, the hyphae may turn septate under special conditions (8). The mycelium is prostrate, i.e. vegetative, and growing in the substrate, or aerial, when a special mycelium is produced above the vegetative growth. Strains of streptomyces are characterized by the presence of an aerial mycelium under laboratory conditions. On the other hand, the aerial mycelium of nocardia, often invisible to the naked eye, may be altogether absent. Occasionally it may consist of few short filaments, which sometimes look like mere granules (8). Actinomycetes reproduce through special sporulating bodies or from parts of the vegetative mycelium (8).

After much speculation and the amassing of copious volumes of data, currently, Actinomycetes are classified as Actinobacteria. The taxon currently accommodates Gram-positive bacteria that have a DNA with a high guanine-plus-cytosine content (69 to 73 mol %) and that form extensive branching substrates and aerial mycelia (9-11). Actinomycetes can be isolated and identified from various natural habitats such as soils from various ecological units, marine water, insects, pollen grain, sand, alkaline lake waters etc. by the methods described elsewhere (12-16). The complete taxonomy of actinomycetes and details of each genus can be observed elsewhere, refer Figure 1, (17).

4. ANTIBIOTIC DISCOVERY- THE ODYSSEY BEGINS

Several scientific observations since late nineteenth century fuelled speculation on the antagonistic nature of certain microbial metabolites on the growth of other bacteria. The first knowledge of some probable antibiotic product from the actinomycetes dates back to 1875. Ferdinand Cohn named an organism he found in the tear duct of the human eye as *Streptothrix foersteri* (18).

The French bacteriologist, Duchesne wrote on the antagonism between fungi and bacteria in a thesis published in 1897 (19). In 1928, Alexander Fleming discovered that the mould *Penicillium* inhibited bacterial growth (19). Although Fleming discovered Penicillin, the name was given to the antibiotic from the producer, *Penicillium,* it was Florey and Chain, who successfully managed to purify Penicillin in 1940 (13), which paved the way for its commercial use. Yet, the decisive era when

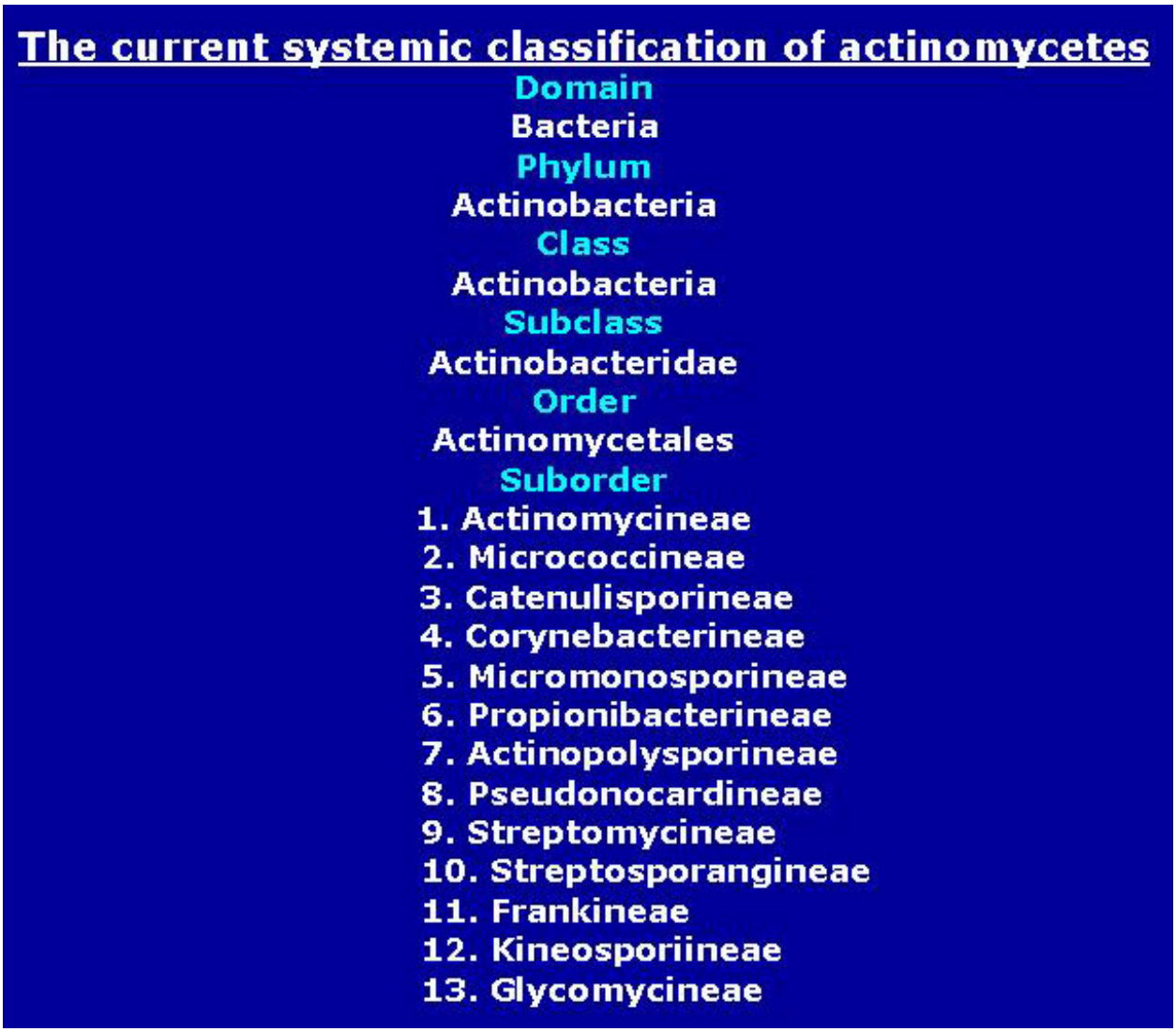

Figure 1. The current systemic classification of actinomycetes

innumerable antibacterials would be unveiled was still waiting in the wings.

In 1914, as a senior in college, studying soil bacteriology, Selman Abraham Waksman assisted Professor Jacob Lipman in making comparative monthly studies of the bacterial population of certain soil types. While Waksman isolated numerous microbes, he was in particular, struck by the appearance of fairly large number of colonies. They did not seem like the typical bacterial colonies. These colonies were compact, leathery in nature, pyramidal in structure, penetrating deep into the agar medium, frequently covered with surface fuzz that was distinct from the surface growth (Figure 2 and Figure 3). Examination of these colonies even with a low power microscope revealed the presence of aerial, branching mycelium (Figure 4, Figure 5, Figure 6), which was typical of fungus colonies. The puzzled Waksman took the plates to show them to and seek his professor's counsel. His Professor, cognizant of the existence of such bacteria, and their being grouped under a separate class as Actinomycetes, directed him to go and meet a botanist. Professor Cook, the botanist, was indeed familiar with this group of microbes, but merely to the extent that they were causative agents of potato scab. Moreover, he considered them as fungi, and not bacteria. Waksman, caught between and betwixt, fungi and bacteria, delved deeper in understanding these microbes. He felt that these organisms could be differentiated from both bacteria and fungi. These observations fuelled the quest in Waksman and these organisms were to become a major part of his future scientific life (20). After Waksman was awarded the Doctorate of Philosophy in 1918, he moved over to Rutgers University from University of California, Berkeley. It was at Rutgers that Waksman and his team discovered several antibiotics.

The actinomycetes were so far studied only from the ecological point of view. The number of

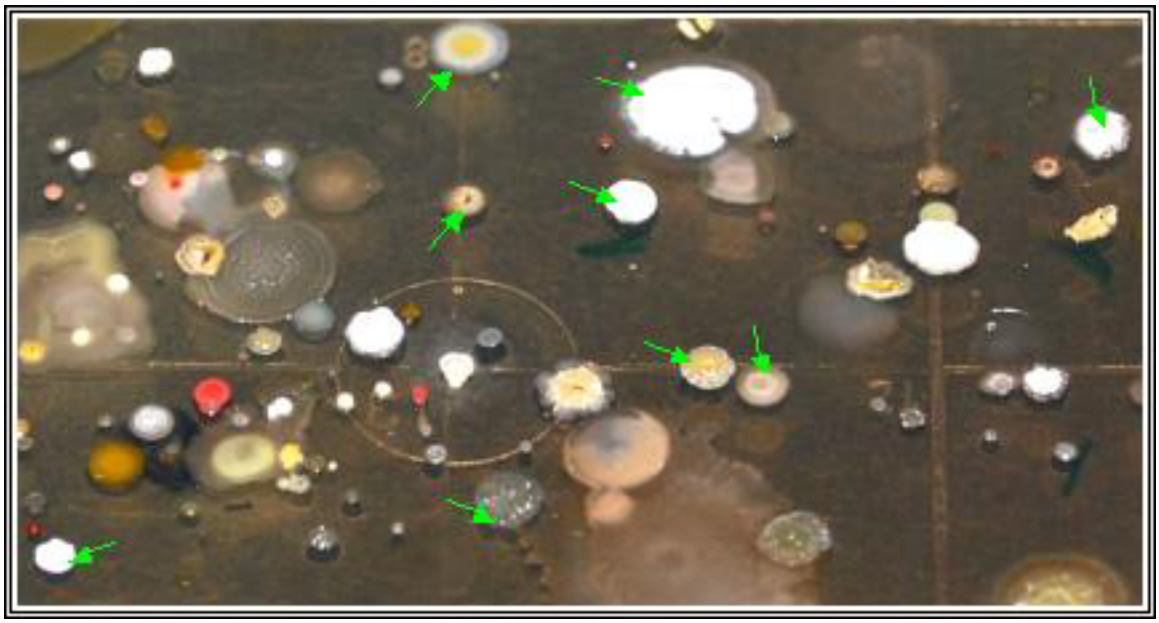

Figure 2. Colonies of various actinomycetes from alkaline soil grown on agarified nutrient medium after 7days incubation at 30°C (The image depicted in Figure 2 is captured in the Anti-infective screening and Prokaryote isolation laboratory, Department of Natural Products of Piramal Life Sciences Ltd.).

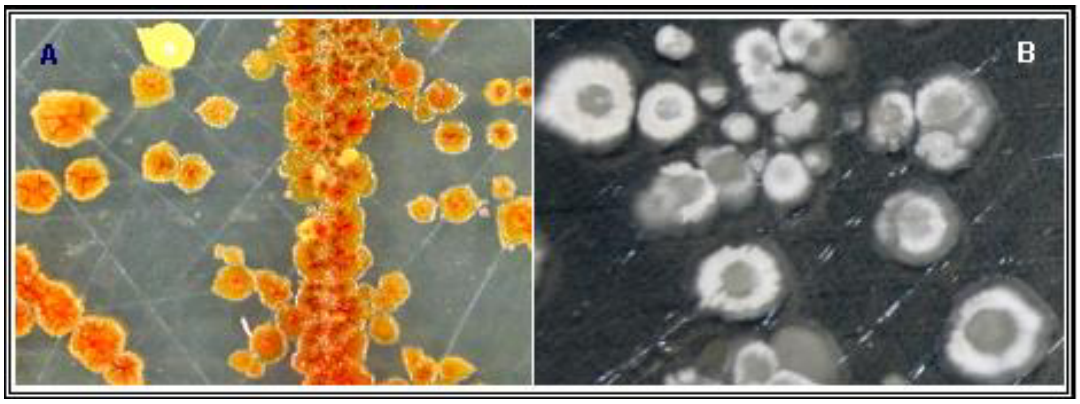

Figure 3. Colonies of rare-actinomycetes (A) and Streptomycetes (B) on agarified nutrient medium (The image depicted in Figure 3 is captured in the Anti-infective screening and Prokaryote isolation laboratory, Department of Natural Products of Piramal Life Sciences Ltd.).

laboratories studying actinomycetes for their elaboration of valuable secondary metabolites had increased. The Waksman group isolated streptomycin from the actinomycete, *Streptomyces griseus* in 1943.

One earlier observation thought of as worth pursuing by Waksman was the fact that *Mycobacterium tuberculosis*, the causative agent of Tuberculosis, did not survive in soil. It was clear that there were some factors or compounds in soil that prevented their survival. The effect of streptomycin was tested against these bacteria at several clinical centers, including the Mayo Clinic (21). The rest is history. Streptomycin went on to become the first curative agent for Tuberculosis. The US patent office granted a process patent, U.S. patent 2,449, 866 titled "Streptomycin and process of preparation" to Schatz and Waksman on September 21, 1948. Rutgers, the university where the discovery was made licensed Streptomycin to Merck. The magnanimous George.W.Merck, by giving up the exclusive right for streptomycin development, rendered Streptomycin as an affordable treatment option, (21). For this significant discovery, Selman Waksman was awarded the Nobel Prize in 1952 (22).

5. THE EARLY YEARS

The years between 1919 and 1940 has been referred to by Selman Waksman as the 'Biological period'. Intensive studies were pursued to comprehend the cultural properties of actinomycetes, their physiology, biochemical activities and most important, their antagonistic effects

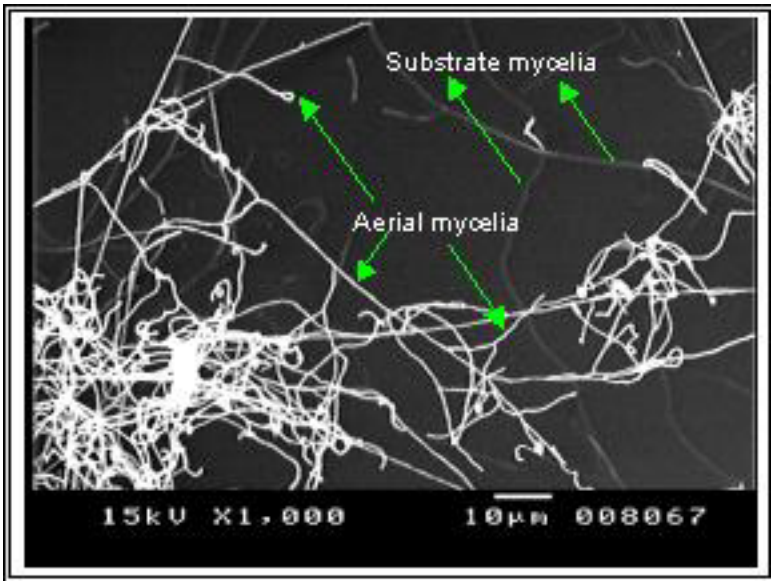

Figure 4. SEM of aerial and substrate mycelia of streptomycetes (The image depicted in Figure 4 is captured in the Anti-infective screening and Prokaryote isolation laboratory, Department of Natural Products of Piramal Life Sciences Ltd.).

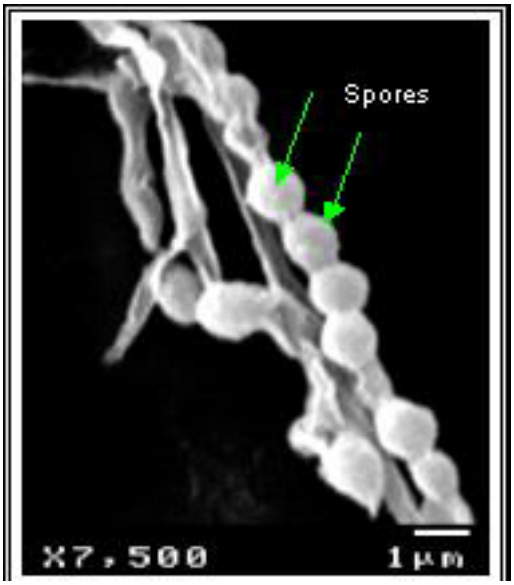

Figure 5. SEM of mature sporangiophore with linear spores arrangement in a streptomycetes (The image depicted in Figure 5 is captured in the Anti-infective screening and Prokaryote isolation laboratory, Department of Natural Products of Piramal Life Sciences Ltd.).

upon bacteria and fungi. The work of notable researchers, independently conducting studies at different laboratories like Waksman in the US, Lieske in Germany, Gratia and Dath in Belgium, Krassilnikov, Koreniako and Kriss in Russia, Rosenthal in France, led to broaden the understanding of actinomycetes. All the attention put into understand these prokaryotes were amply rewarded. The years 1939-1940 proved to be a milepost for the exposition of actinomycete antibiotics. The discovery of Actinomycin in 1940 from *Actinomyces antibioticus* generated much excitement among the scientific fraternity, but it was a practical failure on account of its extreme toxicity to experimental animals (21). The potential of Actinomycin as an anti-tumor agent was realized when Stock (1950) and Hackmann (1952) substantiated it with their investigations (1).

6. THE GOLDEN PERIOD OF ANTIBIOTICS

The preceding two decades of tenacious research bore fruit in this era. The ability of these prokaryotes, morphologically intermediate between eubacteria and fungi, in synthesizing antibiotics was established. Scientists were compelled to know more about these prokaryotes. The

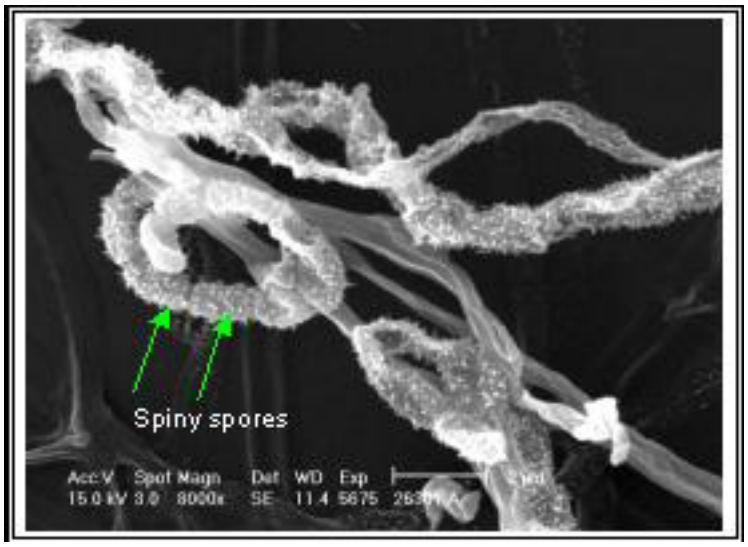

Figure 6. SEM of mature curved sporangiophore with spiny spores in a streptomycetes (The image depicted in Figure 6 is captured in the Anti-infective screening and Prokaryote isolation laboratory, Department of Natural Products of Piramal Life Sciences Ltd.)

19th day of October, 1943 (23), heralded the dawn of a new era in the discovery of antibiotics. The Waksman group, comprising of Selman Waksman, Albert Schatz and Elizabeth Bugie isolated streptomycin from the actinomycete, *Streptomyces griseus*. Subsequently they discovered many antibiotics at Rutgers. The success at Rutgers' motivated fresh screening programs all over the world.

There have been many differences among historians as to which decade or decades comprise the golden period. Some consider it to be from 1940 to 1960, while some others aver that it should be between 1940 to 1986. Nevertheless, this whole period could in the authors' opinion be concluded as the "golden period' for the discovery of antibiotics. Most of the antibiotics, which were unearthed, then, are still in use, either in the same form or in a modified form. Streptomycin continues to be prescribed in the DOTS program in the treatment of tuberculosis. Azithromycin, one of the best selling drugs, is derived from Erythromycin, which was discovered in 1949. Clarithromycin, Dirithromycin, Fluorithromycin, Roxithromycin and Telithromycin are all derived from Erythromycin. Dalfopristin, marketed, as Synercid® is a combination of two Streptogramins discovered fifty years ago. With increase in the knowledge of these antibiotics, they have been used and modified to tackle many challenges.

7. SIGNIFICANT ACTINOMYCETE ANTIBIOTICS-PAST TO PRESENT

In Table 1. we have enlisted representatives of antibacterials from actinomycetes, which represent various modes of actions and diversity of actinomycetes genera. In Table 2. we have enlisted genera of those actinomycetes, which are industrially important, and have given economically significant antibacterial drugs.

7.1. Streptomycin

This aminoglycoside antibiotic discovered in 1943 by Waksman *et al* has been hailed as a major discovery. It has a very strong and rapid bactericidal effect on bacteria. It was discovered at a time when tuberculosis was rampant. This proved to be an effective treatment against *Mycobacterium tuberculosis* infections. It is secreted by the actinomycetes *Streptomyces griseus*.

Streptomycin was used for years in monotherapy regimens in the treatment of tuberculosis leading to the emergence of resistant strains. Considering the resistance rates with the current drugs in the treatment of tuberculosis, Streptomycin is again a part of the combined drug regimen in the treatment of tuberculosis.

Streptomycin is water-soluble and consists of three components, linked glycosidically. They are N-methyl-L-glycosamine , Streptose and Streptidyne. Like all aminoglycoside antibiotics, Streptomycin inhibits protein synthesis. It combines irreversibly with the 30S subunit of the 70S ribosomes found in bacteria. It also binds to the S12 protein involved in the initiation of protein synthesis. Thus it prevents the initiation of protein synthesis by blocking the binding of initiator N-formylmethionine of the tRNA to the ribosome.

Moreover it prevents the normal dissociation of the 70S ribosomes into their 50S and 30S subunits. Thus the formation of polysomes are inhibited. The overall role of Streptomycin involves distortion of the ribosome, such that the transition from initiation to elongation is blocked. The sequence of translation is affected and thus growth is inhibited due to the lack of synthesis of vital proteins.

Table 1. Array of antibacterial compounds from actinomycetes

Antibiotic	Actinomycetes source	Chemical class	Mechanism of Action
Abyssomicins[24]	Verrucosispora AB-18-032	Natural polycyclic polyketide	PABA pathway inhibitor
Bekanamycin[25]	Streptomyces kanamyceticus	Aminoglycoside.	Inhibiting protein synthesis and increasing translation errors
Bonactin[26]	Streptomyces sp. BD21-2	Ester	-
Carbomycin[27]	Streptomyces halstedii	Macrolide	Inhibits bacterial protein synthesis
Chloramphenicol[28]	Streptomyces venezuelae	Acetamide	Inhibits protein biosynthesis by impairing translation on the 50S ribosomal subunit at the peptidyl transferase step
Chlortetracycline[29]	Streptomyces aureofaciens	Tetracyclines	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl -tRNA to the 30S subunit
Clindamycin[30]	Streptomyces sp	Galactooctopyranoside	Inhibits bacterial protein synthesis
Daptomycin[31]	Streptomyces roseosporus	Lipopeptide	Bactericidal activity by disrupting plasma membrane function without penetrating into the cytoplasm
Erythromycin[32]	Saccharopolyspora erythrea (Streptomyces erythreus)	Macrolide	Inhibits elongation at transpeptidation step of protein biosynthesis
Framycetin[33]	Streptomyces fradiae	Aminoglycoside	Inhibition of bacterial protein synthesis via binding to ribosomal subunits.
Gentamicin[34]	Micromonospora purpurea	Aminoglycoside	Inhibits protein synthesis by binding to L6 protein of 50S ribosomal subunit
Grisein[35] (albomycin)	Streptomyces griseus	Cyclic hexapeptide (Sideromycin group)	Inhibits seryl-t-RNA synthetase and impairs protein biosynthesis
Kanamycin[36]	Streptomyces kanamyceticus	Aminoglycoside	Inhibiting protein synthesis and increasing translation errors;
Lincomycin[37]	Streptomyces lincolnensis	Galactooctopyranoside	Inhibits bacterial protein synthesis
Micromonosporin[38]	Micromonospora sp	Polyene lactam macrolide antibiotic	Inhibits bacterial protein synthesis
Neomycin[39]	Streptomyces fradiae	Aminoglycoside	It binds 30S and in some cases the 50S subunit causing miscoding; inhibits initiation and elongation during protein synthesis
Novobiocin[40]	Streptomyces niveus/ S. spheroides	Aminocoumarin	Inhibits DNA synthesis by inhibiting the DNA polymerization
Oleandomycin[41]	Streptomyces antibioticus	Macrolide	Inhibits bacterial protein synthesis
Oxy tetracycline[42]	Streptomyces rimosus	Tetracycline	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl-tRNA to the 30S subunit
Pyridomycin[43]	Streptomyces pyridomyceticus	Peptide	Inhibits bacterial protein synthesis
PM181104[44]	Kocuria sp.	Peptide	Inhibits bacterial protein synthesis
Ramoplanin[45] (INN)	Actinoplanes sp ATCC 33706	Glycolipodepsipeptide	Inhibits transglycosylation in peptodoglycan synthesis
Rifamycin[46]	Amycolatopsis rifamycinica	Naphthalene containing subclass of ansamycins	Inhibits bacterial DNA-dependent RNA-polymerase
Spectinomycin[47]	Streptomyces spectabilis	Aminocyclitol	Disrupts bacterial protein synthesis
Spiramycin[48]	Streptomyces ambofaciens	Macrolide	Inhibits protein biosynthesis by rapid breakdown of polyribosomes by binding 50S unit
Streptocin[49]	Streptomyces griseus	Aminoglycoside	Inhibits bacterial protein synthesis
Streptogramin A[50]	Streptomyces virginiae	Polyketide-Streptogramin	Inhibits protein biosynthesis by binding to 50S ribosome unit
Streptomycin[21]	Streptomyces griseus	Aminoglycoside	Inhibits prokaryote protein synthesis by binding to S12 protein of 30S ribosomal subunit, causing miscoding or inhibiting initiation.
Streptothricin[51]	Streptomyces lavendulae, Streptomyces noursei	Imidazo pyridine-4-one	Inhibits polypeptide synthesis via interaction with the ribosome.
Teicoplanin[52]	Actinoplanin teichomyceticus	Glycopeptide	Binds to the D-ALA-D-ALA terminal end of peptidoglycan precursors and inhibits cell-wall synthesis
Thiolactomycin[53]	Nocardia sp	Thiolactone	Inhibition of fatty acid synthesis
Thiostrepton[54]	Streptomyces azureus and Streptomyces laurentii	Cyclic oligopeptide	Impairment of the coupling of the 30-S initiation complex to the 50-S ribosomal subunit
Vancomycin[55]	Amycolatopsis orientalis	Glycopeptide	Inhibits cell wall synthesis

Note: Superscripts against antibiotic names indicate corresponding reference number

Streptomycin is also known to disrupt the cell membrane of susceptible bacteria (56).

Streptomycin has low oral bioavailability as it is not absorbed from the gastrointestinal tract but intramuscularly bioavailability is 70-80 %. It is marketed as the sulfate salt of Streptomycin. Streptomycin sulfate has been shown to be active even against *Pasteurella pestis*, Brucella, *Klebsiella pneumoniae*, Proteus sp, *Aerobacter aerogenes*, *Enterococcus faecalis*, *Haemophilus influenza*, *Haemophilus ducrey*i, and *S. viridians*, both *in vitro* and in clinical infection.

A very important feature of streptomycin is synergism with the cell-wall affecting antibiotics (Beta-lactams, glycopeptides). This synergism is expressed against some gram-positive (Streptococci, Enterococci) as well as gram-negative *(E.coli*, Pseudomonas) bacteria.

Currently available brands of Streptomycin include ABBISTRYN-S® vial, CIPSTRYN-S® vial, ISOS® vial (57), Strepto-Fatol®, Estreptomycina®.

7.2. Tetracyclines

They were the first among broad-spectrum antibiotics to be discovered in 1945. Chlortetracycline secreted by *Streptomyces aureofaciens,* was the first in this group of antibiotics. This was followed by Oxytetracycline elaborated by *Streptomyces rimosus*. Demeclocycline, another naturally occurring tetracycline is used in the

Table 2. Representation of industrially important actinomycetes producing antibiotics

Sr no	Industrially important genera of Actinomycetes	Representatives of antibacterial compounds
1	Actinomadura	Actinotiocin, Spirocardin A
2	Actinoplanes	Lipiarmycin, Gardimycin, Friulimicin A
3	Actinosporangium	Pyrrolomycin C
4	Amycolatopsis	Resorcinomycin A, Azicemicin A, Balhimycin
5	Chromobacterium	Fujianmycin A
6	Dactylosporangium	Dactimicin
7	Faenia	Norerythromycin A
8	Kibdelosporangium	Benzanthrin A
9	Micromonospora	Microcin A, Megalomicin, Rosamicin, Sagamicin, Mutamicins, Gentamicin, Teicoplanin
10	Nocardia	Nocardorubin, Vancomycin, Nocardicin , Chloroquinocin
11	Planomonospora	Sporangiomycin
12	Pseudonocardia	Azureomycin A, Nothramicin, Tetrazomine
13	Ptilocaulis	Himalomycin A
14	Saccharopolyspora	Sporaricin, Saccharocin, Sporeamicin, Rubradirin
15	Saccharothrix	Saccharocarcin A
16	Sebekia	Glycothiohexides
17	Streptomyces	Streptothricin B, Albomycetin, Isomaltose, Grisamine, Tertiomycin, Thiomycin, Tertiomycin B, Streptogramin, Rifamycin, Lincomycin, Clindamycin, Platenomycin, Glycinothricin, Thienamycin, Siomycin, Neomycin, Carbomycin , Streptomycin, Azinothricin, Thioxamycin, Streptothricin, Tetrodecamycin, Lactonamycin, Nocathiacin
18	Streptoverticillium	Erythronolide B

Table 3. Classification of Tetracyclines based on their $T_{1/2}$ values

Short acting ($T_{1/2}$: 6-8hrs)	Intermediate acting ($T_{1/2}$: ~12 hours)	Long acting ($T_{1/2}$: 16 hours or more)
Tetracycline[1]	Demeclocycline [2]	Doxycycline [2]
Chlortetracycline[1]	Methacycline [2]	Minocycline [2]
Oxytetracycline[1]		Tigecycline [2]

[1]Naturally occuring, [2]semi-synthetic

treatment of Hyponatremia. Teracyclines are antibiotics, which exhibit Time –dependent concentration enhanced killing.

Tetracyclines are a sub-class of polyketides having an octahydrotetracene-2-carboxamide skeleton, derivatives of polycyclic naphthacene carboxamide.

Tetracycline acts on bacteria by reversibly binding to the 16S part of the 30S ribosomal subunit, thus preventing the amino-acyl tRNA from binding to the 'A' site of the ribosomes. Tetracyclines inhibit protein synthesis, but do not directly kill bacterial cells; hence they are classified as bacteriostatic agents.

They possess a broad antimicrobial spectrum, which includes gram-positive and gram-negative bacteria, and anaerobes. At present, tetracyclines are preferentially used in treatment of various infections caused by non-pyogenic bacteria. Tetracyclines are orally available as they are well absorbed from the gastrointestinal tract. They penetrate remarkably into various cells and tissues. Based on their duration of action tetracyclines may be categorized as in following Table 3.

Tigecycline is a glycylcycline antibiotic, marketed by Wyeth under the brand name TYGACIL®. It was given a U.S. Food and Drug Administration (FDA) fast-track approval and was approved on June 17, 2005. This antibiotic is the first clinically available drug in a new class of antibiotics called the glycylcycline. It is structurally similar to the tetracyclines in that it contains a central four-ring carbocyclic skeleton and is actually a derivative of minocycline. Such a similarity has rendered Tigecycline includible in this group of antibiotics, (Table 3).

7.3. Chloramphenicol

Originally produced by *Streptomyces venezuelae* in 1949, and marketed as CHLOROMYCETIN®, Chloramphenicol is now, almost entirely manufactured synthetically. It was the first actinomycetes antibiotic to be synthetically manufactured on a large scale. The antibiotic displays bacteriostatic or bactericidal activity against a variety of microbes including gram-positive and gram-negative bacteria, anaerobes, spirochetes, and obligatory intracellular pathogens (chlamydiae, rickettsiae, mycoplasmata). It turned out to be the drug of choice in the treatment of typhoid. The emergence of drug –resistant *Salmonella typhi* strains set limitations to its use. It is occasionally recommended even in brain abscess and purulent meningitis, because of its excellent penetration.

Chloramphenicol inhibits protein synthesis by binding to the 50S ribosomal subunit. Chloramphenicol palmitate ester, the form in which it is marketed is an inactive form, is rapidly hydrolysed in the gastro-intestinal tract and absorbed as free chloramphenicol. Chloramphenicol is reported to inhibit protein synthesis in mammalian cells, which may be the possible cause of irreversible bone marrow depression, manifested by anemia, leucocytopenia, thrombocytopenia, or any combination thereof (58). This coupled with the many side effects observed in patients restricted its use in regular clinical practice. The structure of Chloramphenicol was also not amenable to any modification. This proved to be a deterrent in the development of modified versions, which would probably have improved its activity and decreased

its side effects. The antibiotic is marketed under the trade name Paraxin®, Titomycine®, Chemicetina®, Chloromycetin® for treating Gram-positive and Gram-negative pathogens, rickettsiae, and some anaerobes.

7.4. Neomycin

It is an aminoglycoside antibiotic elaborated by *Streptomyces fradiae* and reported first in 1949. It is bactericidal against gram-negative bacteria and partially against gram-positive bacteria. The unique feature of Neomycin lies in its ability to be administered by different routes-dermal, oral, and ocular. Hence, Neomycin is found in dusting powders as well as eye ointments. It is also used as a post-operative bactericide, along with other antibiotics. It binds to the A-form of DNA, one of the three biologically active forms of DNA. It also induces the formation of triplex formation (Triple DNA or hybrid forms –widely believed to have a regulatory role in transcription). Neomycin trisulfate salt hydrate is being used as a selection agent used to establish a stable mammalian cell. It is relatively toxic to humans, and many people have allergic reactions to it.

Neomycin-B is the first example of an important aminoglycoside produced by a Streptomyces species and a Micromonospora species.

Currently trials are ongoing for the evaluation of nasal clearance of *Staphylococcus aureus*, a potential hazard for healthcare workers (59).

7.5. Erythromycin

It is a macrolide antibiotic reported first from *Streptomyces erythreus* in 1952. Erythromycin denotes a group of compounds rather than a single entity. Erythromycin like all macrolides inhibits protein synthesis by binding to the 50S ribosome. As with all macrolides, the volume of distribution is very large (60). Therefore, Erythromycin is very rapidly absorbed and diffuses into most tissues and phagocytes. This ensures their easy passage to the site of infection, where erythromycins are released.

Erythromycin exhibits time-dependent concentration enhanced killing with a post-antibiotic effect (PAE). Erythromycin is sensitive to gastric juice. Hence it is administered in the form of enteric-coated tablets for enhanced bioavailability. It is used in the treatment of a variety of bacterial infections, including those caused by atypical bacteria. It possesses a complex structure, which poses a challenge for synthetic production. The development of novel erythromycin-based antibiotics has been a much-researched area since the seventies. The outcome of such persistent efforts has resulted in beneficial drugs like clarithromycin, azithromycin, dirithromycin, roxithromycin, fluorithromycin, and telithromycin (61). The macrolide antibiotics erythromycin, clarithromycin, and roxithromycin have proven to be effective as long-term treatment for the idiopathic, Asian-prevalent lung disease diffuse panbronchiolitis (DPB), (62). The successful results of macrolides in DPB stems from controlling symptoms through immunomodulation (adjusting the immune response), with the added benefit of low-dose requirements. Erythromycin derivatives have been reported to inhibit HIV replication in macrophages. Some brands in use include ERY -C®, Ery-Tab®, PCE®, Dispertab®, E-Mycin®.

7.6. Vancomycin

This glycopeptide antibiotic was discovered in 1953 as a metabolite of *Amycolatopsis orientalis*. Usually it is adopted as a last line of treatment against gram-positive infections, when the penicillins and cephalosporins fail. Its discovery came at a time when the staphylococcal menace of drug resistance to the existing therapies was looming large. Early laboratory studies with the experimental compound failed to confer drug resistance in staphylococci upon serial passage in culture media with the drug. This could be one of the reasons; probably why the FDA "fast-tracked" the approval of this drug.

Vancomycin owes its bactericidal activity in gram-positive bacteria by preventing cell wall synthesis. The incorporation of N-acetyl glucosamine and N-acetylmuramic acid in the peptidoglycan of the bacterial cell wall is prevented.

Vancomycin is reported to follow concentration dependent killing up to 1.0 microgram/ml. Optimal bactericidal effects are found at concentrations 3-5 times the organism's MIC. Because the average vancomycin MIC for *Staphylococcus aureus* and *Staphylococcus epidermidis* are 1-2 microgram/ml, minimum predose and trough-steady concentrations of 5-10 microgram/ml are usually adequate to resolve infections with susceptible organisms.

It has been used very effectively against MRSA. In recent times its use is limited by the emergence of Vancomycin Resistant Enterococci strains (VREs), the leading cause of endocarditis in hospital settings. Further very recently there are reports of emergence of Vancomycin Resistant *Staphylococcus aureus* (VRSA).

These limitations have led to the explorations of derivatives or modified versions of the antibiotic. Lipidated vancomycin derivatives appear to have good potency and antibacterial activity against many gram-positive pathogens, including VRE. Introducing a disulfide bond into the lipid moiety reportedly improves the ADME profile along with retaining the potency (63).

In September 2008, FDA has approved Telavancin (VIBATIVTM), a synthetic derivative of vancomycin for complicated scalded skin and soft tissue infections (cSSSIs), (64). Dalbavancin and oritavancin are in clinical phase III of development.

7.7. Kanamycin

Kanamycin is a water-soluble, broad-spectrum antibiotic, first reported from the soil actinomycete *Streptomyces kanamyceticus* in 1957. Kanamycin is a mixture of atleast 3 components, A, B, and C with A predominating over the others. This aminoglycoside antibiotic inhibits protein synthesis in susceptible bacteria by interacting with the 30S ribosome and which reflects in

translocation inhibition during protein synthesis. The very low degree of oral bioavailability indicated the use of Kanamycin parenterally (65).

In the mid-sixties, with the gradual appearance of kanamycin-resistant strains, much knowledge about the mechanism of resistance in bacteria on account of R-factors was studied. Intensive studies on the mechanism of inactivation of Kanamycin by the bacteria prompted the development of newer Kanamycin derivatives, effective against resistant bacteria. Dibekacin, derived from Kanamycin B was the first regular commercialization of an aminoglycoside derivative (66). Amikacin is a semi-synthetic kanamycin derivative with a butyric acid moiety at the R3 position of kanamycin. It is used in the treatment of *Mycobacterium avium* infections. Kanamycin is available under the brand name Kantrex in both the intravenous and oral forms.

7.8. Rifamycin

They are a group of compounds (A, B, C, D, E, S, and SV) biosynthesized by *Amycolatopsis meditteraanei* and discovered in the late fifties. Rifamycin is a subclass of the larger benzoquinone family, Ansamycin. Ansamysins are a class of antibiotics in which an aliphatic chain (the ansa bridge) is connected to two non-adjacent positions of an aromatic nucleus. Rifamycins possess a high affinity for prokaryotic RNA polymerase. Rifamycins act by inhibition of DNA-dependent RNA synthesis. As per various reports, for inhibition to occur, it is imperative that it binds with the polymerase prior to the commencement of the chain elongation process. This point is indicative of the role of rifamycin in physically blocking the chain elongation. Rifamycin is also said to inhibit the activity of the enzyme reverse transcriptase, which could be applied in the management of HIV infections. Owing to the low potency, success seems to have evaded Rifamycin. Currently, Rifampin, a rifamycin derivative is reported to have exceptional potential in the treatment of chlamydial infections.

7.9. Gentamicin

Amongst the many antibiotics elaborated by Micromonospora, gentamicin has by far, received the maximum attention. Gentamicin, an aminoglycoside complex of various components, has been reported to be secreted by *Micromonospora purpurea* and *Micromonospora echinospora.*

Gentamicin acquired widespread acclaim on account of its unusually wide spectrum of activity, not only against gram-positive and gram-negative bacteria, encompassing Proteus and Pseudomonas species and those strains of bacteria resistant to other antibiotics. It proved to be superior in spectrum and safe to all other prevailing standards of treatment (67). Due to its low oral bioavailability, it is used by intra-venous (IV), intra-muscular (IM) and topical routes. Injections lead to peak serum concentrations in 30-60 minutes. Topical gentamicin is readily absorbed from large, burned, denuded, or granulating areas but not through intact skin. Gentamicin is unable to penetrate eukaryotic cells. This property is made use of in gentamicin protection assay, a tool used to detect the internalization of bacteria by eukaryotic cells. Gentamicin remains one of the few antibiotics to be produced by a fermentation procedure, discovered by a Chinese microbiologist.

Gentamicin is one of the few heat-stable antibiotics that remain active even after autoclaving, which makes it particularly useful in the preparation of certain microbiological growth media in which we need to incorporate antibacterial compounds. Its ophthalmic preparations are marketed under the brand name Garamycin®, GENTAK®, GENOPTIC®, and Gentasol®. Some other brands of this antibiotic are Refobacin®, Genticin®.

7.10. Daptomycin

The journey of daptomycin from the mountains in Turkey to its approval as Cubicin® makes interesting representation of antibiotic development from actinomycetes. Daptomycin, the new lipopeptide antibiotic, is a natural product derived from *Streptomyces roseosporus*. It is rapidly bactericidal for a variety of gram-positive organisms, especially those like MRSA, VRSA, and VRE.

Its structure consists of a 13-member amino acid peptide linked to 10-carbon lipophilic tail. This structure is the secret behind Daptomycin's unique mechanism of action, i.e. it involves calcium-dependent binding to the bacterial plasma membrane and disruption of membrane function. This causes a depolarization of cellular membrane affecting macromolecular synthesis, and disruption of the cell membrane (68). It is unable to permeate the outer membrane of gram-negative bacteria, hence its use is limited to the management of infections caused by gram-positive bacteria. It exhibits concentration-dependent killing (68). A significant post antibiotic effect and almost negligible cross-resistance with any other drug class are factors in Daptomycin's favour (68). Daptomycin was approved by the United States Food and Drug Administration (FDA) in 2003 at the dose of 4 mg/kg of body weight/day for treatment of complicated skin and soft tissue infections caused by susceptible bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). It is now being explored for other indications like complicated urinary tract infections and right-sided infective endocarditis.

Daptomycin's success also could be attributed to newer techniques in assessing resistance prior to its launch. At present daptomycin is marketed by Cubist pharmaceuticals as CUBICIN®. Net worldwide revenues for the year 2009 are reported to be 538 thousand dollars (69).

8. RECENT ADVANCES

Steady progress in medical research has led to the discovery of innumerable antibiotics. In fact, nearly 1300 antibiotics registered in the Japanese database over the last 60 years are antibacterials. There has been a steady flow of

antibiotics in the discovery front. Yet, not all of them see the light of the day as commercial successes. This could be due to their low potency, pharmacological properties, safety issues and also the rapid emergence of resistant pathogens. To compensate the diminished flow in the discovery pipeline, efforts are consistently being made to improve upon the older compounds from natural sources. Semi-synthetic compounds tend to improve the performance of an existing molecule while reducing its side effects. They strive to expand the antibacterial spectrum and also try to bypass the menace of drug resistance in susceptible bacteria. Nevertheless a tenacious pursuit of novel scaffolds will definitely address issues of drug resistance. Exploring natural systems to fortify the antimicrobial storehouse will be a definite exercise in the years to come (70).

A few of the latest, novel actinobacterial antibiotics, which deserve attention, are enlisted below.

8.1. Platensimycin

The search for a new class of antibiotics with a new mode of action to fight these multiple-drug-resistant strains, or "superbugs", led a team of scientists at Merck to discover novel antibiotic, platensimycin using advanced screening strategies, as inhibitors of bacterial fatty acid biosynthesis, which is essential for the survival of bacteria. Platensimycin, a metabolite of *Streptomyces platensis*, which is an excellent example of a unique structural class of natural antibiotics, has been demonstrated to be a breakthrough in recent antibiotic researches due to its unique functional pattern and significant antibacterial activity. The producing actinomycete was isolated from an African soil. Platensimycin blocks enzymes involved in the condensation steps in fatty acid biosynthesis. It works by inhibiting beta-ketoacyl synthases I/II (FabF/B) which are key enzymes in the production of fatty acids required for bacterial cell membranes (71).

Biosynthetic studies reveal the utilization of a non-mevalonate terpenoid pathway in the biosynthesis of platensimycin. A major breakthrough in antibiotic research, platensimycin has fuelled optimism in the discovery of newer molecules with different modes of action in the future.

8.2. PM181104

In pursuit of virgin molecules from actinomycetes, and to address the menace of drug resistant pathogens, scientists at Piramal Life Sciences Limited undertook an extensive screening of marine resources and marine invertebrates. This steered to the discovery of a novel and potent anti-gram-positive antibacterial lead PM181104. It has been isolated from an actinobacterium of Kocuria genus obtained from marine sponge (44). PM181104 is under pre-IND development. This discovery highlights that there are many more compounds with a new scaffold yet to be revealed from newer strains of actinobacterium from unexplored natural sources.

9. PERSPECTIVES

The discovery of antibiotics is one of the most important discoveries of the 20th century. It is a significant discovery, which has altered the life expectancy of man. The increase in life expectancy, albeit, has had its own pros and cons. To delve deeper, infectious diseases were the major cause of suffering in man in the early stages of the 20th century. The discovery of antibiotics has helped in alleviating the ravages of the diseased. In earlier times, the chemist figured prominently as a major player in drug discovery. As the scientists mined into nature, they were gifted with many new antibiotics. The management of infectious diseases was thought to be accomplished. It was widely believed that there are no more infectious diseases to tackle with, only lifestyle diseases. The major indications on which discovery focused were cancer, endocrinal disorders, and pain management. These areas are believed to be the prospective areas of research for pharmaceutical companies in the coming decade.

Just as the focus was plummeting in the discovery of anti-infectives, there has been a fresh insurgence in this area, this time in the form of drug-resistant strains of pathogenic bacteria.

Antibiotic resistance in bacteria may be acquired or intrinsic. Man has also encouraged resistance, by the use, misuse and abuse of drugs. In the long run, this is bound to prove detrimental to the patient or the individual. The use of antimicrobials for any infection, real or feared; in any dose over a period of time; forces microbes either to adapt or die. More often it is the surviving bacteria, which carry drug resistance genes. The need of the hour is antibiotics with a wide spectrum, new scaffold, safe therapeutic window, and good potency. There may be a host of other challenges waiting to be overcome. A concerted proactive drug discovery hunt is required to address potential/future challenges. Development of newer screening techniques facilitating exploration efforts is desirable. However, an interdisciplinary approach synergizing new knowledge, newer technologies and a commitment to use novel resources can help meet the continuing and ever-changing threat from infectious diseases. In all the last seven decades actinomycetes have remained as consistent sources for new antimicrobial agents overcoming new limitations and challenges. It appears to be an invaluable resource of antibacterials in the coming years.

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