Review on Pharmaceutical Products from Actinomycetes

Rishabha Malviya, Assistant Professor, Department of Pharmacy, Galgotias University

ABSTRACT

The ineffectiveness of existing antibiotics inculcates the search of novel metabolites from specific ecosystems. Microbial ecosystem specially, actinomycetes a fungi like bacteria consist an extensive and diverse species with an unparalleled ability to produce diverse secondary metabolites high frequently studied by researchers. These bacteria have been studied extensively by the pharmaceutical industry and account for a disproportionately large amount of the $25.3 billion annual global sale. According to the data 2007, the contribution of biologically occurring chemicals in drug development. The actinomycetes products have a tremendous success for the past few decades. Universally Actinomycetes are acknowledged as a vital player in the drug discovery process. Actinomycetes are highly significant in drug discovery and development due to its high G+C content. Among the bioactive compounds, nearly 45 percentage produced by actinomycetes, 35 % by fungi and 20 % by unicellular eubacteria. Apart from infectious disease, Actinomycetes are also reported to produce many industrially and medically important enzymes. Acarbose is an oral alpha-glucosidase and alpha-amylase inhibitor for the oral treatment of type II diabetes mellitus is isolated from actinomycetes. Thus actinomycetes are potent secondary metabolite producer and biotechnologically interesting organism need to explore much. By this review, we explore and update our knowledge on the potential of actinomycetes and their bio-discovery potential.

Key words: Streptomyces, Micromonospora, myeloma, Natamycin, Diabetes

Introduction

Sulfa drugs are broad-spectrum and were used against many bacterial infections and dropped soon after their use because of bacterial resistance, which arises by mutations in the DHPS enzyme[1], and the discovery of penicillin and other natural product antibiotics. Nowadays they are given in combination with trimethoprim, which inhibits a later step in folate synthesis. Actinomycetes are the most widely distributed group of filamentous bacteria which primarily inhabit the soil and marine system reported as capable to synthesis versatile bioactive compounds of which are high commercial value. Search on actinomycetes metabolites has been successfully isolated two thirds of medical important naturally occurring antibiotics. world's best effective known antibiotics are came from actinomycetes like the genera *Streptomyces* and *Micromonospora*[2].The discovery, development and exploitation of antibiotics was one of the most significant advances in medicine in provided mankind with a wide range of structurally diverse and effective agents to treat microbial infections[3]. *Actinobacteria* are predominant microorganisms that produce various useful enzymes and secondary metabolites like immunomodulators, antitumor compounds and antibiotics[4]. There was a drastic increase in the prevalence of antibiotic resistance in both community and hospital settings for the past 10-15 years. Last line of antibiotics such as vancomycin might also become ineffective against super-bugs such as vancomycin

intermediate- resistant *S. aureus* isolates. There is a necessary for new classes of antibiotics with a novel mode of action (e.g. Linezolid™) to fight against the existing and emerging infectious diseases arising from multiple drug resistant agents[5]. Isolation of diverse group of actinomycetes from marine, salt pan, deep sea, mangroves, estuaries, symbionts may fulfil and overcome the drawback of Drug resistance and lead a new path on drug research. Many natural environments are still either unexplored or underexplored and thus can be considered a prolific resource for the isolation of poorly studied microorganisms including rare actinomycetes[6]. Many extremophilic bacteria are recognized to be of industrial interest as potential candidates for future biotechnological applications[7]. Recent studies have described the isolation of different species of actinomycetes of the genus *Micromonospora* one of the most extensively studied endolithic microbial associations with lichens[8]. Sponge-associated actinomycetes produce small molecules which are reported as dynamic bioactive compounds. Eg.aromatic polyketides. Actinomycete-based aromatic polyketide have exhibited a broad range of bioactivities and clinical importance[9]. A new drugs such as doxorubicin (antineoplastic) and tetracycline (antibiotic) have emerged as clinical drugs for the decades.

Actinomycetes and drug discovery

Among the number of eubacteria, the order *Actinomycetales* have proved to be a particularly rich source of secondary metabolites with extensive industrial applications. Actinomycetes are one of the most important sources of chemical diverse metabolite producer[10] . Their extremely rich metabolic pathway and extreme chemical diversity that have been suggested to play an important role in drug discovery. Members from genus streptomyces is the runner up antibiotic producer and are even predicted to be the producers of many novel yet to be discovered bioactive compounds[11].over-prescription and the improper use of antibiotics has led to the generation of antibiotic resistance in many bacterial pathogens(WHO). Infections caused by bacteria resistant to commonly used antibiotics become a serious global healthcare problem in the 21st century[12].The drug resistant strains of pathogen emerge high frequently than the frequency of drug discovery. Because of emerging drug resistance, drug industry have actively involved in screening of actinomycetes from different untouched habitats, for their production of antibiotics. More number of actinomycetes from terrestrial ecosystem are potential drug sources remain uncultivable, and therefore inaccessible for novel antibiotic discovery. Although soils have been studied by the pharmaceutical industry over 50 years, only little surface of the globe has been sampled, and only a small fraction of actinomycetes taxa has been discovered. From the late 60s', followed by the discovery of gentamycin from *Micromonospora*, the study of non-streptomycete actinomycetes received increasing attention. Commonly, it was recorded that most of the rare actinomycetes products had already existed among streptomycetes metabolites.

Streptomyces A prolific antibiotic producer

The genus *Streptomyces* is a prolific antibiotic producer among the actinobacteria, a number of which have been developed as antifungals, antibacterials, and chemotherapeutic (anticancer) drugs. Each year thousands of *Streptomyces* strains are screened by pharmaceutical companies as source of new antimicrobial compounds[13].

Streptothricin was the first antibiotic which was discovered from this genus in the year 1942. Streptomycin, the first antibiotic used for tuberculosis, isolated from an actinobacterium *Streptomyces griseus* in 1943. Chloramphenicol, a broad spectrum antibiotic was originally isolated from the soil microbe *Streptomyces venezuelae* in 1947. The tetracyclines are a large family of antibiotics produced my many species of streptomyces, which were discovered as natural products first described in 1948.After the streptomycin discovery, in the period known as the golden era of TB research (1940–70).

Streptomyces-derived antifungals tend to be macrolide polyenes[14] eg. The first actinobacteria-sourced human antifungal, made by *S. Noursei (*nystatin), amphotericin B, and natamycin. There are tonne of *Streptomyces*-derived antibiotics used specifically as antibacterial agents. These include: streptomycin (*S. griseus*), neomycin (*S. fradiae*), and kanamycin (*S. kanamyceticus*).

Other antibacterial antibiotics erythromycin (*S. erythraea*), tetracycline (by *S. rimosus*), chloramphenicol (*S. venezuelae*), vancomycin (*S. orientalis*) and thienamycin (*S. cattleya*) has been isolated from actinomycetes. A number of the antibiotics produced by *Streptomyces* have proven to be too toxic for use as antibiotics in humans, but because of their toxicity towards dividing cells they have been reinvented as chemotherapy drugs. Eg. actinomycin-D, bleomycin (glycopeptide made by *S. verticullus*), mitomycin (aziridine made by *S. lavendulae*), and plicamycin (made by *S. plicatus*). In addition to that anthracyclines daunorubicin and doxorubicin from *S. peucetius* and migrastatin by *S. Platensis* also used as chemotherapy drugs[15]. several synthetic drugs were introduced into the market. However, nature still played a crucial role in drug discovery against TB. For example, other aminoglicosides such as kanamycin from *Streptomyces capreolus*, the semisynthetic amikacin produced from kanamycin A and capreomycin from *Streptomyces kanamyceticus* as well as D-cycloserine from *Streptomyces sp*., are used nowadays in TB treatment as second-line drugs[16].

Rare Actinomycetes in drug discovery

Group of actinomycetes are prolific antibiotic producers, making three quarters of all known products and other class of biologically active secondary metabolites[17]. There has been a turn down

in the past two decades in the discovery of novel compounds from common soil-derived actinomycetes metabolites[18] . Hence, the need for increased exploration of previously unexplored habitats for new actinomycete taxa has become a major focus in the search for the next generation of pharmaceutical agents[19]especially with the increasing trend in development of antibiotic resistance in microbial pathogens. Actinomycetes from the genera *Actinoplane*, *Streptomyces*, and *Actinopolyspora* have been reported to produce over 300 broad-spectrum antibiotic substances and representatives of these genera are widely abundant in aquatic ecosystems.

Polyketide synthases and non-ribosomal peptide synthetases are the major enzymes of secondary metabolite synthesis also discoverd from actinomycetes and produced ansamycins, tetracyclines, polyenes and glycopeptides[20]. through these biosynthetic pathways the antibiotics like ansamycins, tetracyclines, polyenes and glycopeptides are produced. Many compounds characterized from actinomycetes comes under polyketides

which are structurally diverse with wide range of bio activities. More than 500 polyketide has been characterized from actinomycetes. Diverse group of antibiotics obtained from actinomycetes.eg, macrolide Erythromycin A from *Saccharopolyspora erytherea*, glycopeptides Vancomycin from *Amycolatopsis* sp, Gentamycin from *Micromonospora* sp streptomycin from *Streptomyces aureofaciens.* Novel drugs are desperately needed to combat the increasing number of antibiotic resistant strains of pathogenic microorganisms. The isolation frequency of the rare actinomycetesis much lower than that of streptomyces. Many natural ecosystems are still either unexplored or under-explored and thus, can be considered as a prolific resource for the isolation of less exploited microorganisms. Different ecological niches need to be studied as sources of a greater diversity of novel actinomycetes. The mycinamycins are a group of macrolide antibiotics produced by *Micromonospora griseotubida*. The broad spectrum antibiotic Oleandomycin is isolated from *Streptomyces antibioticus* with similar to that of erythromycin activity. A 16-membered lactone ring Rosaramicin glycosidically linked with single sugar residue desosamine produced by *Micromonospora rosaria* and *Micromonospora capillata* and has activity against both gram-positive and gram-negative bacteria[21].

Marine actinomycetes

Currently the discovery of new compounds from terrestrial actinomycetes has decreased, due tore-isolation of known compounds. Therefore it is crucial time to discover a new groups of actinomycetes from unexplored or underexploited habitats be pursued as sources of novel bioactive secondary metabolites.Table 1 shows novel secondary metabolites isolated from marine actinomycetes from 2003 to 2005.Abyssomicin C is a novel polycyclic polyketide antibiotic produced by a marine Verrucosispora strain[22]. It is a potent inhibitor of para-aminobenzoic acid biosynthesis and, therefore, inhibits the folic acid biosynthesis at an earlier stage than the well-known synthetic sulfa drugs[23].

Abyssomicin C or its analog[24] has the potential to be developed as antibacterial agent against drug-resistant pathogens. Abyssomicin C a potent activity against Gram-positive bacteria, including clinical isolates of multiple-resistant and vancomycin-resistant *Staphylococcus aureus*. Diazepinomicin is a unique farnesylated dibenzodiazepinone produced by a Micromonospora strain[25]. It possesses antibacterial, anti-inflammatory and antitumor activity. It has a broad spectrum of in vitro cytotoxicity and has demonstrated in vivo activity against glioma, breast and prostate cancer in mouse models[26]. Number of marine actinomycetes is found to be effective against many forms of cancer. Thiocoraline is a compound obtained from a marine *Micromonospora marina*, is found to be effective against colon cancer, lung cancer and melanoma. Salinamides A and B are bicyclic depsipeptides produced by a *Streptomyces sp.*, CNB-091, isolated from jelly fish Cassiopeia xamachana. These metabolites act as both antibiotic and anti-inflammatory agents. Cyclomarins A-C is cyclic peptides produced by a Streptomyces sp. that showed anti-inflammatory and antiviral activities[27] . Members of the genus Salinispora from marine system have proven to be a particularly rich source of new chemical structures, like salinosporamide A, terpenoids, amino acid–derived metabolites and polyene macrolides.

Table 1- Source of actinomycetes and drugs

Abyssomicins	***Verrucosispora sp.***	**Antibacterial**
Aureoverticillactam	*Streptomyces aureoverticillatus*	Anticancer
Bonactin	*Streptomyces sp.*	Antibacterial,
Caprolactones	*Streptomyces sp.*	Antialagl, antibacterial
Chandrananimycins	*Actinomadura sp.*	anticancer; antifungal
Chinikomycins	*Streptomyces sp.*	Anticancer
Diazepinomicin	*Micromonosproa sp.*	Antibacterial, anticancer
3,6-disubstituted indoles	Streptomyces sp	Anticancer
Frigocyclinone	*Streptomyces griseus*	Antibacterial
Glaciapyrroles	*Streptomyces sp.*	Antibacterial
Gutingimycin	*Streptomyces sp.*	Antibacterial
Helquinoline	*Janibacter limosus*	Antibacterial
Himalomycins	*Streptomyces sp.*	Antibacterial
IB-00208	*Actinomadura sp.*	Anticancer
Komodoquinone A	*Streptomyces sp.*	Neuritogenic activity
Lajollamycin	Streptomyces nodosus	Antibacterial
Marinomycins	*'Marinispora'*	Antibacterial, anticancer
Mechercharmycins	*Thermoactinomyces sp.*	Anticancer
Salinosporamide A (NPI-	*Salinispora tropica*	Anticancer
Trioxacarcins	*Streptomyces sp.*	Antibacterial, anticancer,
Lipopeptides *daptomycin*	*Streptomycin roseoporus*	Antibacterial

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