Conventional Antibiotics from Actinomycetes: A mini review

Krishna Kumar Das¹, Smaranika Pattnaik², Santosh Kumar Behera²

¹Laboratory of Medical Microbiology, Dept. of Biotechnology and Bioinformatics, Sambalpur University, Jyoti Vihar, Burla-768019
²National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India

ABSTRACT

Actinomycetes are considered as a natural sink for production of antibiotics. Since many decades, the actinomycetes have drawn attention to mankind because of synthesis of bioactive metabolites. Among these antibiotics are considered to be the most potent biomolecules effective against infectious agents including bacteria, viruses and more of fungal strains. This mini review emphasized upon the antibacterial agents, synthesized in the power house of actinomycetes. The antibiotics belonging to class of aminoglycosides, macrolides, tetracyclines, penicillins and moreover, Rifampicin’s are of utmost importance in clinical set up. The antibiotics have taken the throne to regulate the degree of infection cause by candidate bacteria including both Gram positive and Gram negatives. The tubercle bacteria are also inhibited by the antibiotic namely Rifampicin, which is a potential product of Streptomyces. The mechanism of action of each of antibiotic molecules is target oriented. The antibiotics are able to interact with Bacterial cell wall cross linkage enzymes, Ribosomes, RNA polymerases, protein synthesis events, thus killing the bacteria. Therefore, it may be concluded that this literature survey had inferred about the specific drug categories, synthesized from Actinomycetes and respective target oriented mechanism of action. It was also found that Actinomycetes are never ending source of bioactive compounds. Therefore, studies are mandate to reveal the Pandora’s Box containing the bioactive antibiotics from the actinomycetal strains.

Key words: Actinomycetes, Antibiotics, Mechanism of action, Rifampicin, bioactive metabolites.

1. INTRODUCTION

Actinomycetes are high GC content, bearing transient characteristics, of both bacteria and fungiare Gram-positive (Adegboye MF et al, 2012). This is important to mention that actinomycetes are the prolific source of antibiotics and other bioactive metabolites since six decades. The antibiotics are produced as secondary metabolites in response to stress, to evade the action of predators and also to inhibit the growth of neighborhood organisms. Therefore, the name antibiotic was given appropriately; molecule(s) are produced from a living organism and able to inhibit the growth of other organism (Chandramohan, D., 1992). Since its discovery, the prescription page is always filled with the antibiotics of Actinomycetes origin. Of late, due to advent of combinatorial approach as well as development of hybrid chemotherapeutics, the mankind has taken a deep breath in the context of relieved from grasp of infectious agents (Pandey B et al, 2004, S. Dharmaraj, 2010). There is fusion of chemically synthesized antibiotic moiety and annotation of functional groups of actinomycetes derived antibiotics or vice versa (T. W. Hodges et al., 2012, H. W. G. Kuilderd, 2008). Finally there are success stories of classes of the antibiotics of actinomycetes origin namely, aminoglycosides, β-lactam, Macrolides, Chloramphenicol, Tetracyclines, Ivermectins and more over Rifamycins (Cross, T. (1981), Ramesh S et al. (2009), Jensen PR et al. (2007)). In addition to these molecules, this cluster also produced a plethora of industrially important enzymes, like amylase, lipase, deoxyribonuclease and protease (Cross, T. (1981), Ramesh S et al. (2009), Jensen PR et al. (2007)). Therefore, this communication reports about past literature on the subject of bioactive compounds and also industrially important enzymes.

1.1. Antibiotics from Actinomycetes

From the literature survey, it was acknowledged that the Streptomyces spp. in particular, could produce around 7600 compounds. Table.1 is showing the names of antibiotics of Actinomycetes origin and specific bioactivity (Dejong PJ (1972), Narayana KJ et al. (2008), Madigan M T et al (2012)).

<table>
<thead>
<tr>
<th>Antibiotic compound</th>
<th>Class of Antibiotics</th>
<th>Actinobacteria</th>
<th>Contributory Author’s name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8-Dihydroxy-2-ethyl-3-methylnorlanthraquinone</td>
<td>Polyketide</td>
<td>Streptomyces sp.</td>
<td>Huang YF et. al. (2006)</td>
</tr>
<tr>
<td>1-Hydroxy-1-norresistomycin</td>
<td>Polyketide</td>
<td>Schisandra chinensis</td>
<td>Gorajana A et. al. (2005)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>anthracyclinone</td>
<td>S. galileus</td>
<td>Anthracyclines, Nicholas R. Bachur, in Encyclopedia of Cancer (Second Edition), 2002</td>
</tr>
<tr>
<td>Arenicolides A–C</td>
<td>polyketides</td>
<td>Salinispora arenicola</td>
<td>Carlos Olano et al. 2009</td>
</tr>
</tbody>
</table>

Table.1: Showing list of antibiotics produced from Actinomycetes
<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arenimycin</td>
<td>benzo[α]naphthacene quinone</td>
<td>S. arenicola</td>
<td>Ratnakar N Asolkar et al. (2009)</td>
</tr>
<tr>
<td>Avermectin</td>
<td>lactone endectocides</td>
<td>Streptomyces avermitilis</td>
<td>G.M. Fent, 2014</td>
</tr>
<tr>
<td>Bafilomycin</td>
<td>macroide</td>
<td>S. griseus, Streptomyces halstedii</td>
<td>E J Bowman et al. 1988</td>
</tr>
<tr>
<td>Butenolides</td>
<td>tetracycline</td>
<td>Streptoverticillium luteoverticillatum</td>
<td>Qi Yin et al. 2019</td>
</tr>
<tr>
<td>Chinikomycins</td>
<td>macroide</td>
<td>Streptomyces sp.</td>
<td>Fuchao Li et al. 2005</td>
</tr>
<tr>
<td>Glaciapyrroles</td>
<td>heterocyclic</td>
<td>Streptomyces sp.</td>
<td>Shamsuzzaman et al. 2015</td>
</tr>
<tr>
<td>Hygromycin</td>
<td>aminoglycoside</td>
<td>Streptomyces hygrosopicus</td>
<td>Maria A. Borovinskaya et al. 2008</td>
</tr>
<tr>
<td>Pacificanones A &amp; B</td>
<td>polyketides</td>
<td>S. pacifica</td>
<td>Dong-Chan Oh et al. 2010</td>
</tr>
<tr>
<td>Piericidins</td>
<td>α-pyridone</td>
<td>Streptomyces sp.</td>
<td>Xuefeng Zhou et al. 2016</td>
</tr>
<tr>
<td>Proximicins</td>
<td>aminofuran</td>
<td>Verrucosispora sp.</td>
<td>Hans-Peter Fiedler et al. 2008</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>macrocyclic lactone</td>
<td>S. hygrosopicus</td>
<td>C Vézina et al. 1975</td>
</tr>
<tr>
<td>Resistoflavins methyl ether</td>
<td>methyl ether</td>
<td>Streptomyces sp.</td>
<td>Ines Kock et al. 2005</td>
</tr>
<tr>
<td>Salinispyrone</td>
<td>rifamycin</td>
<td>S. pacifica</td>
<td>Ratnakar N Asolkar et al. 2010</td>
</tr>
<tr>
<td>Streptomyces</td>
<td>aminoglycoside</td>
<td>S. griseus</td>
<td>Mitchell Waters&amp; Prasanna Tadi, 2021</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>methyl</td>
<td>S. achromogenes</td>
<td>M. Abdollahi and A. Hosseini et al., 2014</td>
</tr>
</tbody>
</table>

### 1.2. Aminoglycoside (AGls) producing actinomycetes

Aminoglycosides with formula, C38H64N8O14 are highly potent, broad-spectrum antibiotics that kill bacteria by binding to the ribosomal decoding site and reducing the fidelity of protein synthesis, against Gram-negative bacteria. The AGls are prescribed in severe infections of the abdomen and urinary tract, complicated skin, bone, or soft tissue infection, severe pelvic inflammatory disease, bacteremia (bacteria in the blood), ocular infections (topical), inflammation of ear (topical), neonatal sepsis, and endocarditis. Gentamicin, tobramycin, and amikacin are used as first line of prescribed antibiotics, even against Mycobacterium tuberculosis. Specifically, Tobramycin is used against Pseudomonas aeruginosa and Enterobacter spp., which are notorious multi drug resistant and opportunistic bacteria. **Figure.1** is demonstrating the skeletal structure of typical aminoglycoside with IUPAC name, 6,14,20,28-tetraamin-5,19-bis[[3,5-dihydroxy-5-methyl-4-(methylamino)oxan-2-yl]oxy]-2,16,29,30-tetraoxa-9,23-iazapentacyclo[23.3.1.111,15.03,8.017,22]triaconta-9,11,23,25-tetraene-4,18-diol.
The amino glycoside class of antibiotics consists of many different agents. In the United States, gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, and paromomycin are approved by the US Food and Drug Administration (FDA) and are available for clinical use. Micromonospora spp. is reported to be potential source of Aminoglycosides. The aminoglycoside group includes gentamicin, sisomicin, mutamicin, sagamicin, verdamicin, fortimicin, antlermicins, tetrocarcin, and calicheamicins (Talukdar et al., 2016). Paromomycin, a 2 deoxystreptamine aminocyclitol aminoglycoside antibiotic, (2DOS-ACAGA) from *Streptomyces (S.) rimosus*, was reported by Ibrahim et al., (2019).

### 1.3. β-lactams producing actinomycetes

Although penicillins are produced from filamentose fungi, cephamycin-type antibiotics have been identified from a range of *Streptomyces* spp. (Tahlan and Jenssen, 2013). The β-lactamase inhibitor clavulanic acid (C8H9NO5), IUPAC name, (2R, 3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid was originally identified in cultures of *Streptomyces clavuligerus* (Bennett et al., 2020). The 2 dimensional structure of Clavulanic acid is given in **Figure.2**.

![Figure.1: A typical skeletal structure of amino glycoside (www.pubchem.ncbi.nlm.nih.gov)](image1)

**Figure.1:** A typical skeletal structure of amino glycoside (www.pubchem.ncbi.nlm.nih.gov)

### 1.4. Macrolides from Actinomyces

Polyene macrolides are a large family of natural products typically produced by soil actinomycetes. Polyene macrolides(C35H61NO12) are usually biosynthesized by modular and large type I polyketide synthases (PKSs), followed by several steps of sequential post-PKS modifications such as region-specific oxidations and glycosylations.ammocidins,
bafilomycins, neomaclafungins, rosaramicins, spinosyns, and tiacumicins. Most macrolides are from the genus, Micromonospora, with smaller contributions from genera such as Saccharothrix, Amycolatopsis, Nocardiopsis and Catenulispora. These macrolides display unique cytotoxic, antibacterial, antifungal, antimicrobial, insecticidal, anti-trypanosomal, antimalarial, antiprotozoal, antinococcal and anti-herpetic activity (Al-Fadli, et al., 2022). The original macrolide complex, erythromycin A, was isolated in 1952 as a natural product of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*). Macrolides structurally contain three characteristic parts in every molecule, that is, a macrocyclic lactone ring, multiple ketone & hydroxyl group, and two deoxy sugars attached by glycosidic bond. According to the carbon number of lactone ring, macrolides are classified into several types. That is, 12-membered ring, 13-membered ring, 14-membered ring, 15-membered ring, 16-membered rings, etc. The antibiotic drugs comprised of 14-membered and 16-membered lactone rings. The IUPAC name is 

\[

*Figure.3* The macrolide chemical structure (www.pubchem.ncbi.nlm.nih.gov).

The macrolide-bound ribosome is unable to polymerize specific amino acid sequences in the nascent protein. They bind at the nascent peptide exit tunnel and partially occlude it. Thus, macrolides have been viewed as ‘tunnel plugs’ that stop the synthesis of every protein. The putative mechanisms of action of macrolides are given in *Figure.4*.

*Figure.4* The mechanism of action of macrolides on growing poly peptide chain. The clockwise directed arrowmark is indicating the target of Macrolides in ribosome cleft (Reproduced from www.lecturio.com/concepts/macrolides-and-ketolides.

1.5. Tetracyclinoproducing actinomycetes

Tetracyclines (molecular formula,C22H24N2O8), IUPAC name,(4S,4aS,5aS,6S,12aR)-4-(dimethylamino)-1,6,10,11,12α-pentahydroxy-6-methyl-3,12-dioxo-4,4a,5,5α-tetrahydro-tetracene-2-carboxamide are a class of antibiotic compounds discovered in the second half of 20th century. Chemically, they possess a naphthacene carboxamide nucleus generally substituted on carbon
C2, C4, C6, and C7 of the naphthacene core. *Streptomyces aureofaciens* is a Gram-positive actinomycete that produces the antibiotics tetracycline and chlortetracycline (Gradnigo et al., 2016). Figure 5 is showing the structure of Tetracycline. Tetracycline molecules comprise a linear fused tetracyclic nucleus (rings designated A, B, C, and D to which a variety of functional groups are attached. The prime mechanism of action of tetracyclines that the molecules inhibit bacterial protein synthesis by preventing the association of aminoacyl-tRNA with the bacterial ribosome (Chopra and Roberts, 2001).

![Figure 5](image-url)

**Figure 5**: The structure of Tetracycline as retrieved from (www.pubchem.ncbi.nlm.nih.gov).

![Figure 6](image-url)

**Figure 6**: The mechanism of action of Tetracycline. There is blocking of attachment of tRNA to 30 s subunit resided mRNA codons (Reproduced from https://thealevelbiologist.co.uk/penicillin-and-tetracycline).

### 1.6. Rifampicin producing actinomycetes

Rifampicin is a member of the class of rifamycins that is a semisynthetic antibiotic derived from Amycolatopsis rifamycinica (previously known as Amycolatopsis mediterranei and Streptomyces mediterranei). It is an RNA polymerase inhibitor, a DNA synthesis inhibitor, and more over a protein synthesis inhibitor. Rifampin (also referred to as rifampicin) is a macrocyclic antibiotic (Figure 7).
Rifampin specifically inhibits bacterial RNA polymerase, the enzyme responsible for DNA transcription, by forming a stable drug-enzyme complex (Wehrli, 1983). And more so this antibiotic got its reputation for antitubercular activity, by binding with β sub unit of RNA polymerase of *Mycobacterium tuberculosis*.

**Figure 7:** The skeletal structure of Rifampicin (Structure retrieved from [www.pubchem.ncbi.nlm.nih.gov](http://www.pubchem.ncbi.nlm.nih.gov)).

**Figure 8:** Mechanism of action of Rifampicin to bind RNA polymerase and distorts the functionality of Polymerase.
2. CONCLUSION

From this mini review, it may be concluded that the actinomycetal strains are the natural sink containing thousands of antibiotics. And more so the antibiotics have already panelized by mankind by considering the high therapeutic index of each of antibiotics so far been discovered. But this is also seen that the discovery of bioactive compounds from potent actinomycetes strains is never ending process. Hence, efforts should be more rigorous to screen for novel and/or previously characterized antibiotic derivatives.

Acknowledgement:
This mini review report is part of Thesis work registered under Sambalpur University.

REFERENCES


30. Mitchell Waters; Prasanna Tadi (2021), Streptomycin.


41. Yong-Fu Huang, Li Tian, Hong-Wei Fu & Hui-Ming Hua (2006), One new anthraquinone from marine Streptomyces sp FX-58, Natural Product Research 20(13): 1207-10, DOI:10.1080/1748610600899142.


