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REVIEW ON A POTENTIAL OF ANTIBIOTICS

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Abstract - Since the beginning of time, man and microbes have coexisted. While certain microbes were capable of living successfully with humans, acting as resident germs that protect and balance the body, harmful bacteria enter and develop in man's tissues, producing infections and physical harm that can occasionally result in death. In the 1940s, antibiotics were discovered and put to use as a result of man's effort for a treatment for her and her numerous bacterial enemies. Antimicrobial are reported to have negative impacts on the beneficial and healthy bacteria of the animal living process while combating disease-causing microorganisms. Antimicrobial use hence depends on the total expected effect while taking into account any adverse side effects. Therefore, it is essential to accurately identify and know the mechanism of action of antimicrobial in order to protect person's health care system. Knowing how medicines fight bacteria has tremendously benefited from modern molecular biology techniques. The classifications of antibiotics are therefore addressed in this work.

Key Words: Antimicrobial, Bacteria, Beta-lactums, Macrolides, Tetracyclines

INTRODUCTION

Drugs are substances that help people stay healthy by preventing sickness or recovering their health. They are a necessary part of new medicine. Medicinal chemistry is the branch of research responsible for the development of these medications, whether by discovery or design. Classical medications were mostly discovered in the last century by altering natural chemicals or wholly through chemical synthesis. An increased understanding of disease biology has led to novel options for purposeful design, synthesis, and evaluation of potential therapeutic molecules in recent years. With the race to discover novel drug molecules, the drug discovery programed has become a multidisciplinary approach. Thus, the activity of medicinal chemist essentially encompasses biological (understanding of the enzymology and pharmacology) and physicochemical aspects (understanding of thermodynamic, quantum mechanics, spectroscopy, crystallography etc.). These aspects have acquired increasingly mechanistic underpinnings with the development and quantitation of the enzyme/ receptor concept and the availability of receptor-based assays. Lead discovery and lead optimization are the two important concepts of drug design in medicinal chemistry and the process of lead structure identification and refinement, now manifest further sophistication in accordance with developments in structural and molecular biology and with combinatorial chemical synthesis and automated screening techniques. [1]

The genomics revolution has changed the face of drug development, with DNA and protein sequences revealing a slew of new therapeutic targets as well as a mountain of data. To filter through and make sense of the massive amounts of public and proprietary data, the application of computational tools has become a necessity. Only 10% of therapeutic compounds discovered in research make it to the development stage. This means that a lot of prospective medications never make it to market, and a lot of money and time is spent on compounds that will never produce money. By increasing the efficiency of drug development, decreasing costs, and boosting margins, molecular modeling, simulations, and information can greatly improve these odds. To summarized, medicinal chemistry, which has its origins in organic chemistry, is becoming more and more intertwined with structural chemistry, computational chemistry, and molecular biology at the discovery edge, toxicology and pharmacology at the development edge, and medicine at the clinical edge. As a result, medicinal chemistry has played a significant role in the development of new medicines.

1. The brief history of Antibiotics:

Antibiotic-producing bacteria have been utilized to prevent disease for millennia, with traditional dressings of moldy bread being utilized to treat serious injuries in ancient Greece, Serbia, China, and Egypt have been around for almost 2000 years ago. A list of cures includes medicinal soil given in Eber's papyrus. [2] A 1000-year-old Anglo-Saxon method was also newly discovered to killed MRSA (methicillin-resistant Staphylococcus aureus). [3] Anti-infective drugs, on the other hand, are still being developed. The basic idea of chemotherapy is generally licensed to Paul Ehrlich, who

fostered the synthetic arsenic-based supportive of medications salvarsan (salvation arsenic) and neo-salvarsan around 100 years prior to treat Syphilis is caused by the bacterium Treponema pallidum. [4]

Salvarsan was eventually replaced by Prontosil, a sulfonamide drug found by Gerhard Domagk [5], a Bayer bacteriologist who used it to save his daughter's hand from amputation. Domagk and colleagues were successfully continuing Paul Ehrlich's work because these medicines were used for many specific bacterial cells.

Sulfonamides were the first effective, antibiotic in medical practice, which is still used as medicine. Alexander Fleming's discovered penicillin in 1928 [6], on a contaminated Petri plate. Norman Heatley, Howard Florey, Ernst Chain, and colleagues at Oxford refined penicillin, as they were crucial in the development of penicillin as a medicine. [7] Antibiosis between bacteria has been reported long before penicillin was discovered, by Louis Pasteur who was found that bacteria might release something that kills other microbes. [9] By the turn of the century, the generation of soluble and heat-stable chemicals by microorganisms was being described and their efficacy in the fight against transmissible infections had been investigated. [10] Possibly the first clinical trial Antibiotic usage was first recognized in the 1890s when Emmerich and Low utilized a *Pseudomonas aeruginosa* extract (Bacillus pycyaneus) to cure many of people, this extract, known as pyocyanase, was utilized on a group of patients until the 1910s. [11]

The active mechanisms of pyocyanase were likely a mixture of pyocyanin, phenazine, and 2-alkyl-4-hydroxyquinolones. The disclosures of penicillin, tyrocidine and various reports of the creation of antimicrobial mixtures by microorganisms. Selman Waksman to start an investigation of organisms which produce antimicrobial mixtures in 1930s. Waksman described an anti-infection as ' *a compound made by a microbe to destroy other microbes*' He was found that Actinomycetales ('actinomycetes') as productive makers of antimicrobial mixtures Waksman identified a number of antibiotics produced by soil-dwelling actinomycetes, such as neomycin and streptomycin, the first tuberculosis-fighting drug. [12]

Waksman's important research discovered the *Streptomyces genus* as a productive maker of natural products, which are substances not required for an organism's healthy improvement, progression in the laboratory. Many streptomycete natural products have been created as anti-cancer and immunosuppressive medications and are active against bacteria, fungus, viruses, nematodes, and insects. [13]

From the 1940s to the 1960s was the Golden Age of antibiotic discovery due to Waksman's efforts. The majority of these antibiotics are still in clinical use, but their efficacy has been undermined by the growth of antimicrobial resistance (AMR). Indeed, the quick and relatively simple discovery of numerous classes of natural product antibiotics over a short period of time led to their overuse. Instead of new antibiotic classes, most antibiotics in clinical studies today are modifications of established classes of NP or synthetic antibiotics. Because of this, detection of new NP families was reduced and the continued rediscovery of existing compounds in regular screening using microbial fermentation extracts, primarily actinomycetes. [14]

2. Classification of antibiotics:

Antibiotics are classified in a variety of ways, but the most popular categories are based on their chemical structures, method of action, and spectrum of activity [15] Antibiotics belonging to the same structural class will have similar efficacy, toxicity, and allergic-potential side effects.

Beta-lactams, Macrolides, Tetracyclines, Quinolones, Aminoglycosides, Sulphonamides, Glycopeptides, and Oxazolidinones are some of the most important antibiotic types based on chemical or molecular structures [16,17,18]

2.1 Beta – Lactams:

Members of this class of antibiotics have a highly reactive 3-carbon and 1-nitrogen ring (Figures 1 and 2). They are inhibitor of the bacterial cell wall production. In this synthesis they are killing or inhibiting the bacteria's development. To put it another way, during the manufacture of peptidoglycan, some bacterial enzymes known as penicillin-binding protein (PBP) are responsible for cross-linking peptide units. Beta-lactam antibiotics have the ability to bind to these PBP enzymes, causing loses and cell death by interfering with peptidoglycan production. [19] Penicillins, Cephalosporins, Monobactams, and Carbapenems are the most well-known members of the beta-lactam class.

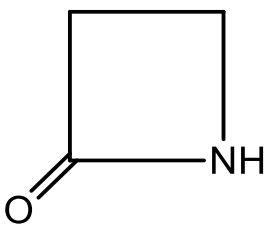

Figure 1. Chemical structure of a Beta- lactam ring

2.1.1 Penicillins:

Penicillin, the first antibiotic discovered and published by Alexander Fleming in 1929. Penicillins are found in a wide range of compounds, the majority of which end in the suffix –cillin All of these compounds are beta-lactams with a 6-animopenicillanic acid (lactam plus

thiazolidine) ring nucleus and various ring side chains. [20]

Penicillin G, Penicillin V, Oxacillin (dicloxacillin), Methicillin, Nafcillin, Ampicillin, Amoxicillin, Carbenicilin, Piperacillin, Mezlocillin, and Ticarcillin are all members of the Penicillin class. [21] Among this group of antibiotics, and indeed all antibiotics, Penicillin G was the first to be discovered. Even if Alexander Fleming exposed penicillin G in the 1920s, it took several other researchers, including Ernst Chain, Edward Abraham, Norman Heatley, and Howard Florey, until 1945 to comprehend the fungus's culture requirements and clinical usefulness. Alexander Flemming was exposed and isolate

Penicillin G from fungus named *P. notatum*, *Penicilliun chrysogenum* also used as source to isolate it. Penicillin G had narrow spectrum of activity, only Gram positive and some Gram negative bacteria are sensitive to it. [22]

Certain bacteria can respond antibiotic activity by encoding enzymes, just like any other biological interaction system in which living things seek to protect themselves from attack. As a result, antibiotics like ampicillin, carbenicillin, and amoxicillin have been created semi-synthetically with various side-chains. These side chains enable antibiotics to avoid the degradation activity of particular enzymes formed by specific bacterial strains while also helping antibiotic movement over the outer membrane of such bacterial cell walls. This double capability expands their spectrum activity against Gram-negative bacteria. Some penicillins, such as Augmentin, are manufactured in conjunction with non-antibiotic compounds that inhibit the function of the bacterial penicillinase enzyme. Augmentin is a medication that combines the antibiotic amoxicillin with the non-antibiotic clavulanic acid. Clavulanic acid extending the antibacterial efficacy of amoxicillin component present in Augmentin, even against bacteria that produce penicillinase.

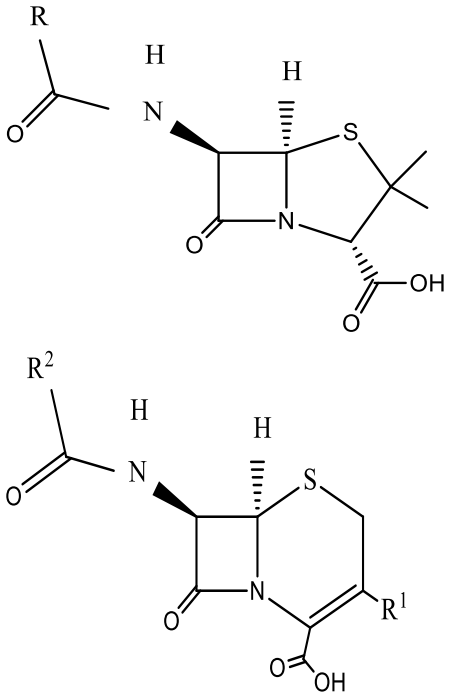

Figure 2. Chemical structure of beta-lactam structure. Core structure of penicillins (first) and cephalosporins (second). [24]

2.1.2 Cephalosporin:

The structure and mode of action of antibiotics in this class are similar to those of penicillin. They are among the most widely approved and provided antibiotics; to put it another way, they account for one-third of all antibiotics approved by the United Kingdom's National Health Service. [22] Guiseppe Brotzu identified the first member of this class of antibiotics from the fungus *Cephalosporium acremonium* in 1945, but Edward Abraham was the first to patent it after successfully extracting it. Cephalosporins have a 7-aminocephalosporanic acid nucleus and a 3,6-dihydro-2 H-1,3-thiazane ring side chain (Figure 3). Cephalosporins are antibiotics that are used to treat bacterial infections and diseases caused by Penicillinase-producing, Methicillin-susceptible Staphylococci and Streptococci, Proteus mirabilis, some Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Enterobacter aerogenes, and Neisseria meningitides. [25]

They are classified into five generations based on the organism they are target, but later versions are more efficient against Gram-negative bacteria. Cephalosporins feature a variety of side chains that allow them to connect to distinct penicillin-binding proteins (PBPs), avoid the blood-brain barrier, fight failure by penicillinase-producing bacteria, and ionize to ease entry into Gram-negative bacterial cells. [26]

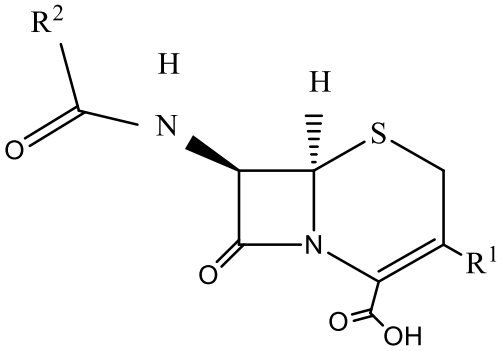

Figure 3. Structure of Cephalosporins [25]

2.1.3 Monobactams:

Skyes and colleagues were the first to report the finding of this class of antibiotics. The antibiotic derived from the *Chromobacterium violaceum* bacteria. Monobactams are beta-lactams, however unlike most other beta-lactams, their beta-lactam ring stands alone and is not bonded to another ring. (Figure 4) [27,28]

Aztreonam is the only monobactam antibiotic that is commercially available and has a restricted spectrum of activity. Aztreonam is exclusively active against Gram-negative bacteria that are aerobic in nature, such as *Neisseria* and *Pseudomonas*; it is used to treat pneumonia, septicemia, and urinary tract infections caused by these bacteria. Gram-positive bacteria and anaerobes are not affected by monobactams. They are used as inhalers and injectables. [29]

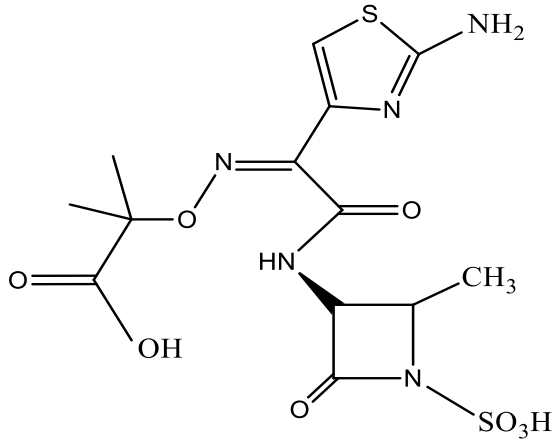

Figure 4. Structure of Monobactam [28]

2.1.4 Carbapenem:

In 1976, this class of antibiotics (shown in Figure 5) was exposed out of requirement. The usefulness of penicillin had been very susceptible in the late 1960s due to the advent of beta-lactamase in bacteria. Bacterial beta-lactamases imparted penicillin resistance to bacteria. [30] This ominous scenario prompted researchers to embark on a global quest for beta-lactamase inhibitors. In 1976, olivanic acids, which are generated by the Gram-positive bacterium *Streptomyces clavuligerus*, were discovered to inhibit beta-lactamase. [31, 32]

Unluckily, these acids were chemically unstable, and they were unable to permeate the bacterial cell easily due to which future research on olivanic acids was stopped. [33], while two improved beta-lactamase inhibitors were identified by Brown et al. (1976) which were isolated clavulanic acid from *S. clavuligerus*, and thienamycin was isolated from *Streptomyces cattleya.* [34] Thienamycin is said to be the first "carbapenem," and it serves as a benchmark for all other carbapenems.[30] There have also been a number of other carbapenems discovered.[35,36]

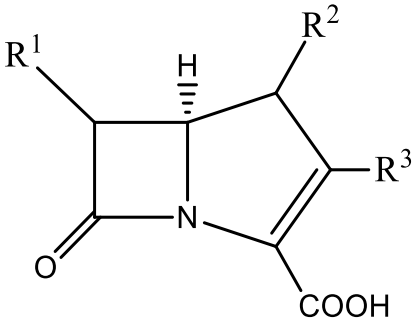

Figure 5. Structure of Carbapenem [30]

Carbapenems play a critical role in our struggle against bacterial illnesses. This is due to their resistance to the hydrolytic action of the beta-lactamase enzyme. Carbapenems have the largest breadth of activity and the best effectiveness against Gram-positive and Gram-negative bacteria among the hundreds of beta-lactams known. As a result, they are typically referred to as "antibiotics of last resort," and they are used when patients become critically ill or are suspected of carrying antibiotic-resistant germs. [37]

2.2 Macrolides :

J. M. McGuire identified and isolated the first antibiotic in this class as a metabolic product of the soil constraining fungus *Saccharopolyspora erythraea* in 1952. This fungus was previously known as *Streptomyces erythraeus*, a member of the actinomycete bacterium genus *Saccharopolyspora*.

The uncommon deoxy sugars L-cladinose and D-desosamine are linked to 14-, 15-, or 16-membered macrocyclic lactose rings in macrolides (Figure 6). They offer a broader antibacterial spectrum than penicillins and are frequently used to treat people who are allergic to penicillin. [38]

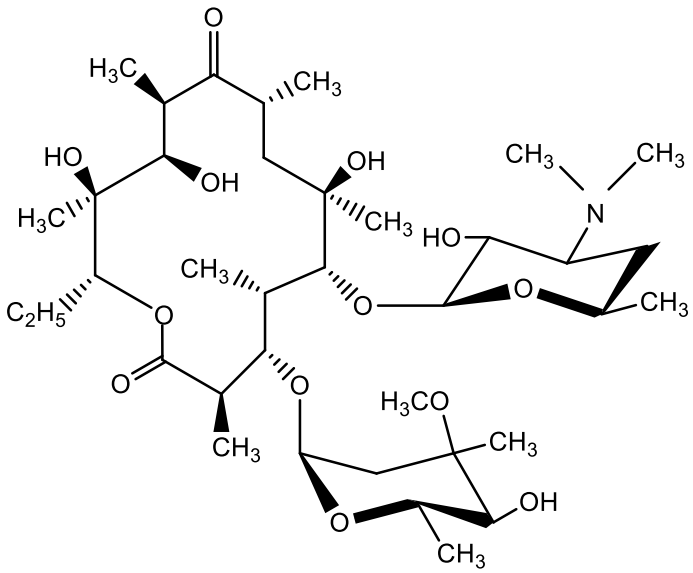

Figure 6. Structure of Macrolide[39]

The uncommon deoxy sugars L-cladinose and D-desosamine are linked to 14-, 15-, or 16-membered macrocyclic lactose rings in macrolides (Figure 6). They offer a broader antibacterial spectrum than penicillins and are frequently used to treat people who are allergic to penicillin. [38] By successfully reducing bacterial protein synthesis, macrolides either kill or inhibit microorganisms. They achieve this by adhering to the bacterial ribosome and preventing amino acid addition to polypeptide chains during protein synthesis. Because the liver can recycle macrolides into bile, they tend to build up in the body. They have the ability to produce inflammation as well.

As a result, experts typically advise using minimal doses. Despite the fact that Macrolides are generally broad spectrum antibiotics, some bacterial species, such as *Streptococcus pneumoniae,* have developed resistance to them. Erythromycin, Azithromycin, and Clarithromycin are examples of members [39]

2.3 Tetracyclines

Benjamin Duggar found tetracycline in 1945 from a soil bacterium of the genus *Streptomyces* [40] (Sanchez et al., 2004). Chlorotetracycline (Aureomycin) was the first member of this class. Members of this class feature four hydrocarbon rings (Figure 7) and are given the suffix "–cycline" in their names.

Members of this class of antibiotics have traditionally been divided into generations based on the manner of synthesis. Those produced through biosynthesis are referred to as first generation. Tetracycline, Chlortetecycline, Oxytetracycline, and Demeclocycline are all members. Those produced with semi-synthesis derivatives are referred as second generation members which include Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, and Rolitetracycline. Third generation drugs include those made via complete synthesis, such as Tigecycline. [41]

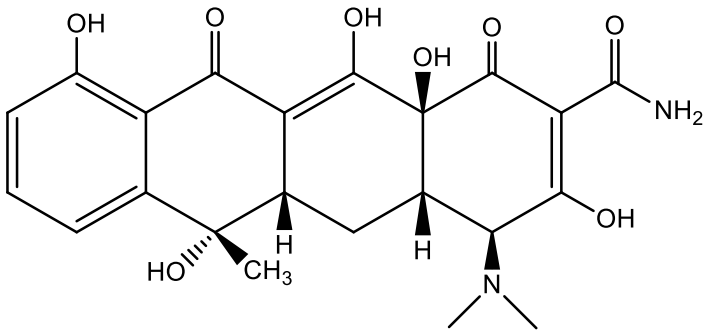

Figure 7. Structure of Tetracycline [42]

The ribosome is the target of their antibacterial activities in bacteria. In this bacterial organelle, they disturb the addition of amino acids to polypeptide chains during protein synthesis. Tetracyclines should be taken at least two hours before or after mealtimes for optimal absorption. All tetracyclines are only suggested for patients above the age of eight years old because they have been linked to tooth discoloration in children under this age. Tetracyclines are used to treat malaria, elephantiasis, amoebic parasites, and rickettisia. [40]

2.4 Quinolones :

Scientists searching for antimalarial medicines originally found this class of antibiotics called nalidixic acid. During the improvement of quinine in the early 1960s, an impurity called nalidixic acid was found. In bacteria, they have the ability to disrupt DNA repetition and translation. Quinolones and naphthyridones, which include cinoxacin, norfloxacin, ofloxacin, ciproxacin, temafloxacin, sparfloxacin, nalidixic acid, and enoxacin, have been produced from the basic molecule. Quinolones have a two-ring structure in general, but recent generations have an additional ring structure that allows them to extend their antibacterial spectrum to bacteria that were previously resistant to quinolones, especially anaerobic bacteria.

There are various changes made into its parent structure, resulting in the discovery and synthesis of a large number of derivatives with proven antibiotic efficacy. Members of this class of antibiotics are known by the suffix–oxacin, such as floxacin, ciprofloxacin, and levofloxacinQuinolones' bioavailability and range of activity and effectiveness have been found to improve as a result of changes to their basic structure, making them more effective in the treatment of disorders such as urinary, systemic, and respiratory tract infections. Despite these achievements, there are still safety anxieties about several members of this family of antibiotics, which has resulted in the withdrawal of quinolones such as grepafloxacin, sparfloxacin, temafloxacin, trovafloxacin, and others from the market. [43]

2.5 Amonoglycosides:

Streptomycin was the first antibiotic to be identified in this class in 1943.[44] Streptomycin has long been used

to treat *Mycobacterium tuberculosis*, the bacteria that cause tuberculosis in humans. Aminoglycosides are glycosidic-bonded molecules with usually three amino sugars (Figure 8). They're made from *Actimomycetes* in the soil.

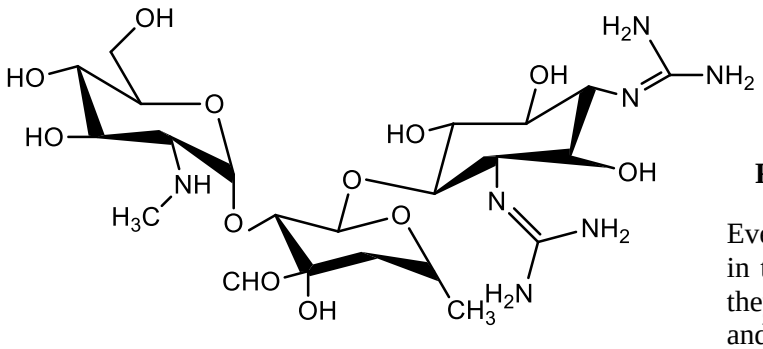

Figure 8. Structure of Aminoglycoside (Streptomycin) [45]

Aminoglycosides offer a wide range of antibacterial properties. They work against Gram-negative and some Gram-positive bacteria by attaching to one of the ribosomal subunits and inhibiting protein synthesis in bacteria. [46] Streptomycin is the oldest known aminoglycoside, and has been used to treat bubonic plague, tularemia, and tuberculosis. [22] Despite its efficiency against a wide range of illnesses, streptomycin has been discovered to be extremely hazardous. Because of this unfavorable aspect of the medicine, researchers had to look for new aminoglycosides that were still efficient against germs but less hazardous to people. Antibiotics such as Gentamicin, Neomycin, Tobramycin, and Amikacin were discovered as a result of the search. Gentamicin is a less hazardous antibiotic that is commonly used to treat Gram-negative infections (Escherichia, Pseudomonas, Shigella and Salmonella). Pseudomonas infections in cystic fibrosis patients are treated with tobramycin in particular. [47]

2.6 Sulphonamides:

Sulphonamides were said to be the first antibiotics used in therapeutic medicine, and they continue to play an essential role in medical and veterinary care. Sulphonamides are recommended for the treatment of infections such as tonsillitis, septicemia, meningococcal meningitis, bacillary dysentery, and some urinary tract infections. They inhibit both Gram-positive and Gram-negative bacteria. [48] Sulphonamides are antibacterial synthetic antimicrobial agents that include the sulphonamide group (Figure 9). [49]

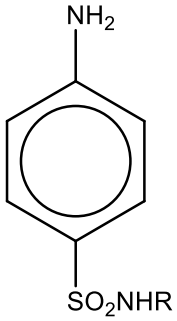

Figure 9. General structure of Sulphanoamides [49]

Even if sulphonamides have been found to be effective in the treatment of a variety of diseases and infections, they should be used with caution due to their toxicity and side effects, which include urinary tract disorders, haemolytic anaemia, porphyria, and hypersensitivity reactions. [50,51]

2.7 Glycopeptides:

Glycopeptide antibiotics (GPAs) were first discovered as natural compounds, but in the last 20 years, semi-synthetic derivatives with better activity and pharmaceutical features have developed.[52,53] Glycopeptides are naturally made up of a 7-amino-acid cyclic peptide with two sugars attached to it, so the name given glycopeptides. [54]

The creation of 5 hydrogen bonds with the peptidic backbone of the antibiotic allows it to bind to its target. During the synthesis of some drugs, such as oritavancin, an extra chlorine and sugar is added to the backbone of the molecule. Drugs having such extra connections are known to bind to the target more effectively. [55,56] A lipophilic side chain has antibacterial properties and extends the half-life of glycopeptides.

2.8 Oxazolidinones :

Oxazolidinones are a new class of synthetic antibiotics that have recently been approved for usage. Linezolid was the first member to be synthesized and was only licensed for clinical use in the year 2000. (Figure 10)

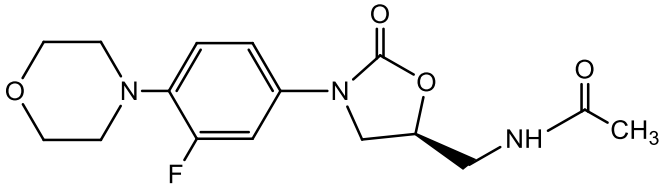

Figure 10. Structure of Linezolid

Despite the fact that the mechanism of action of oxazolidinone is unknown, it is known to interfere with protein synthesis. Oxazolidinones bind to the P site of the ribosomal 50S subunit, inhibiting protein synthesis. [57,58] Linezolid is a drug that is used to treat Gram-positive bacterial infections of the respiratory tract and skin. [59] Because they quickly enter and aggregate in

tissue such as bone, lung, haematoma, and cerebrospinal fluid, oxyazolidinones are the preferred treatment for postoperative infections. [58] Although following standard linezolid delivery procedures is normally safe, adverse effects such as myelosuppression, which results in anaemia and thrombocytopenia, are common when treatment is extended. [60]

3. CONCLUSIONS

It is clear that the continuous research, advancement, and integration of antibiotics in the health care system have significantly benefited our efforts to fight viral infections brought along to germs and so enhanced both personal and community health. It is quite concerning, however, as germs are becoming increasingly resistant to almost every existing antibiotic, and as a result, development of new and more effective antibiotics is proceeding is this. While roughly 2,000 antibiotics have been found as of now, only a small number of these are now utilized medically. This is reportedly because the majority of the identified antibiotics come with adverse effects. The protection of the human healthcare system depends on an accurate description and understanding of the mechanism of action of antibiotics.

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