International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 719-725 www.ijprajournal.com ISSN: 2456-4494

A Pharmacological Review on Bacterial Drug Resistance Mechanisms

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Date of Submission: 20-07-2024 Date of Acceptance: 30-07-2024

ABSTRACT:-
Antibiotic resistance (AR) is a major global health issue today. The misuse of antibiotics in healthcare, veterinary care, and farming, such as prescribing them when not needed, using them too much in raising animals, and not practicing good hygiene in hospitals, all contribute to the increase in AR. Bacteria have various ways to defend against antibiotics, and understanding these defenses is crucial for tackling this problem. Lab tests can determine if bacteria are resistant to antibiotics or not. Proper use of antibiotics, vaccination, education, research on new antibiotics, and policies to monitor antibiotic use all play key roles in reducing antibiotic resistance.Bacteria develop different ways to overcome antibiotics' effects based on how the antibiotics work against them. These strategies include changing the target of the drug, producing enzymes to break down the antibiotic, and pumping the antibiotic out of their cells using special pumps. Over time, bacteria have evolved new methods to resist antibiotics, such as protecting their targets with proteins and altering their cell structures. This ability to resist multiple drugs has led to the rise of multi-drug resistant bacteria, making some antibiotics ineffective in treating infections. Scientists are researching these resistance mechanisms to develop better ways to fight bacterial infections. While traditional antibiotics are still useful against some bacteria, they are becoming less effective against multi-drug resistant strains.

Keywords:- bacterial drug resistance, Antibiotic resistance , Chemotherapy

I. INTRODUCTION:-

Antibiotics are essential for treating and preventing bacterial infections. They greatly contributed to the increased life expectancy during the latter half of the 20th century. Additionally, antibiotics revolutionized agriculture and livestock farming. Livestock industries used antibiotics to prevent diseases, treat infections, and even promote growth to improve the efficiency of food production [1].In 2019, researchers discovered that 1.27 million individuals died directly due to antibiotic resistance. This was determined from analyzing cases across 204 countries and regions worldwide. Another 4.95 million people were associated with deaths related to antibiotic resistance, with many attributed to methicillin-resistant Staphylococcus aureus (MRSA), exceeding 100,000 deaths.[2,3].Different kinds of antimicrobial drugs have been developed. Antibiotics are categorized according to how they work. These drugs either kill or stop the growth of microorganisms, allowing the body's immune system to remove them naturally. They work by preventing bacteria from multiplying and disrupting their ability to make essential components like proteins, DNA, or RNA. This can happen through damaging the bacterial membrane or other targeted actions.[4,5].Antibiotics attach to the bacterial cell wall, enter host cells, and use energy-dependent processes in ribosomes to block protein production. Besides, antibiotics and similar drugs are extensively used in veterinary medicine to treat or prevent animal illnesses, stop disease spread, prevent food contamination, and boost productivity.[6].

A Brief History-

Alexander Fleming's discovery of penicillin in 1928 laid the foundation for modern bacterial infection treatments.[7]. Antibiotics have been around for several decades and play a crucial role in stopping harmful microbes from growing. Antibiotic resistance started becoming a problem in the 1960s, when many bacteria, including some that cause intestinal and other infections, developed resistance to commonly used drugs. The development of antibiotic resistance involves three main factors: how resistance emerges, how it spreads, and the severity of infections caused. For instance, Neisseria gonorrhoeae became resistant to ampicillin, and Haemophilus bacteria developed resistance to ampicillin, tetracycline, and chloramphenicol.[8,9]. Likewise, resistance to sulfonamides emerged in the 1940s, followed closely by the challenge posed by aminoglycoside-

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resistant S. aureus for pharmaceutical companies and researchers. Subsequently, as new antibiotics like methicillin, vancomycin, and fluoroquinolones were introduced, resistance to these drugs also began to surface. Methicillin-resistant S. aureus (MRSA) strains are notable examples of bacteria that have rapidly spread despite these antibiotics.[10].

Bacterial Resistance Mechanisms:-

Understanding the various ways bacteria defend against antibiotics is crucial for addressing the crisis of antibiotic resistance. Misusing antibiotics can contribute to the development of resistant bacteria; incomplete courses of antibiotics may not fully eliminate bacterial colonies, leading to the emergence of resistance. Mechanisms of drug resistance can be broadly categorized, including through active efflux pumps, altering or deactivating drugs, modifying drug targets, reducing drug accumulation inside cells by changing cell permeability, forming biofilms, and other methods.[11,12].

1) Efflux Pumps:-

Efflux pumps are proteins that transport toxic substances out of cells and into the external environment. In bacteria, these pumps play a significant role in drug resistance by expelling a wide range of antibiotics from the organism's interior to the outside.[13].

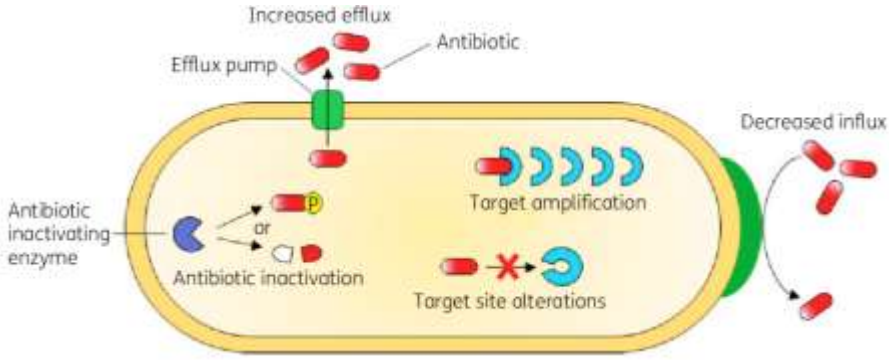

Figure 1: Bacterial efflux system

Depending on the specific antibiotic or toxin encountered, efflux can function as the quickest and most efficient resistance mechanism within the range of stress responses bacteria possess.[14].Certain efflux pumps are designed to transport either a single drug or multiple substances. There are five main families of these pumps: SMR (small multidrug regulator), MFS (Major Facilitator Superfamily), ABC (ATP binding cassette), RND (Resistance Nodulation Cell Division), and MATE (Multidrug and Toxic Efflux). The MFS, RND, MATE, and SMR families operate by using a proton motive force generated through the movement of protons in the opposite direction. Efflux pump genes can either be naturally present (intrinsic) or acquired. Intrinsic efflux mechanisms are encoded within the chromosome and are activated in response to environmental signals or mutations in regulatory genes.[15].

2) Inactivation of Antibiotics:-

Bacteria produce inactivating enzymes like antibiotic hydrolases or modifying enzymes that can alter antibiotics upon entry into the cell, rendering them ineffective before they can act at their target site. A variety of aminoglycoside-modifying enzymes are found in bacteria, including N-acetyltransferase, O-phosphotransferase, and O-adenosyltransferase. These enzymes respectively acetylate, phosphorylate, or adenylate aminoglycoside antibiotics, modifying their structure. Common inactivating enzymes produced by bacteria include β-lactamase, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferase.[16].]

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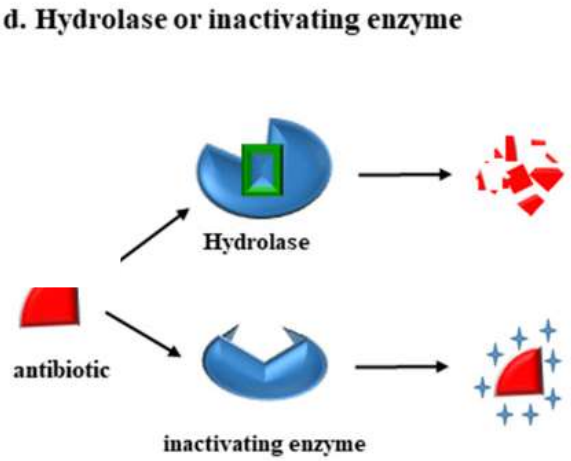

Figure 2: Inactivation of Antibiotics by Enzymes

The β-lactamase enzyme can irreversibly attach to the carbonyl group of the antibiotic, causing its cyclic structure to break down, thus initiating degradation of the β-lactam antibiotic prior to reaching its intended target. Additionally, it can effectively and quickly bind to β-lactam antibiotics through a non-hydrolytic mechanism, thereby preventing these antibiotics from developing resistance by binding to their target sites.[17].

3) Modification of Target:-

For antibiotics to exhibit their antibacterial effect, they must bind to their target site. Any mutation or alteration of this site disrupts this binding, thereby diminishing the antibiotics' effectiveness (Figure 1a). The frequency of spontaneous mutations leading to antibiotic resistance is approximately 10^(-8) to 10^(-9), indicating that one in every 10^8 to 10^9 bacteria will develop resistance through mutation.[18].

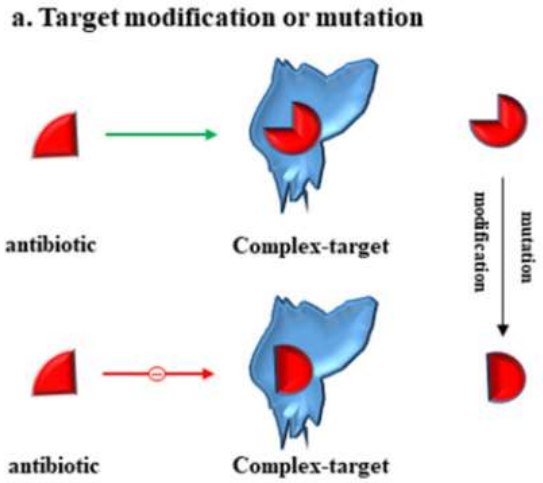

Figure 3: Modification of Target

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Modifying the sites targeted by antibiotics is a prevalent mechanism of resistance among bacterial pathogens, impacting nearly all categories of antimicrobial agents. These modifications encompass various strategies: 1) genetic mutations within the target genes, 2) enzymatic changes like methylation that affect binding, and 3) substitution or evasion of the original target. Regardless of the method employed, the ultimate outcome remains consistent: reduced affinity between the antibiotic and its target site.[19].

4) Reducing Entry of Antimicrobial Agents:-

In Gram-negative bacteria (GNB), the cell wall primarily consists of proteins and lipopolysaccharides. These hydrophilic compounds face difficulty passing through the lipid bilayer and thus require facilitation via porin channels or outer membrane porins (Omps).[20].Mostly antimicrobial compounds always require access into the bacterial cell to reach their target site. Porin channels are the passageways by which antibiotics normally cross the bacterial outer membrane. Some bacteria protect themselves by prohibiting these antimicrobial compounds from entering to their cell walls.[21].

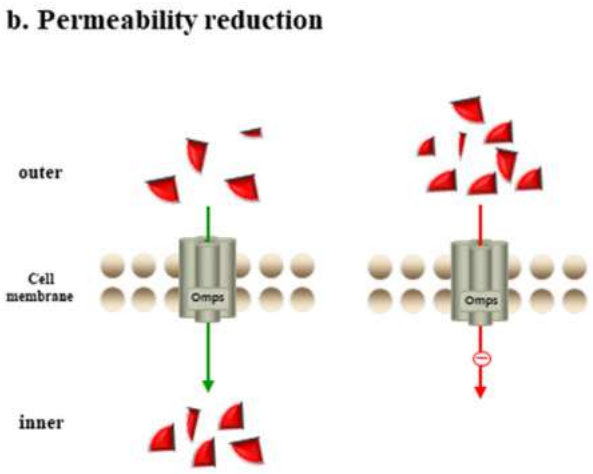

Figure 4: Permeability Reduction

5) Mutation:-

A mutation is an unplanned alteration in the DNA sequence of a gene, potentially resulting in a modification of the trait it encodes.[22].A single alteration in a base pair can cause a subsequent change in one or more amino acids it codes for, potentially altering the enzyme or cell structure. This adjustment can affect the affinity or effective activity of targeted antimicrobials. In prokaryotic genomes, mutations often result from base modifications due to external factors, errors during DNA polymerization, deletions, insertions, or duplications.[23].Penicillin-Binding Proteins (PBPs) reside on the bacterial cytoplasmic membrane and play crucial roles in peptidoglycan synthesis, serving as the target for β-lactam antibiotics. Mutations can abolish the binding affinity between β-lactam antibiotics and their target PBPs, leading to antibiotic failure in binding to the target and consequently inducing bacterial resistance. An illustrative instance of target site modification involves the structural modification of PBPs in MRSA. In this case, methicillin resistance in S. aureus arises from the acquisition of an exogenous gene, mecA, which encodes PBP2a. PBP2a exhibits diminished affinity for most β-lactams compared to typical PBPs, rendering most β-lactam antibiotics ineffective against MRSA upon acquiring mecA. Similar modifications at the target site also contribute to bacterial resistance against antibiotics such as vancomycin, macrolides, lincosamides, and streptogramins.[24].

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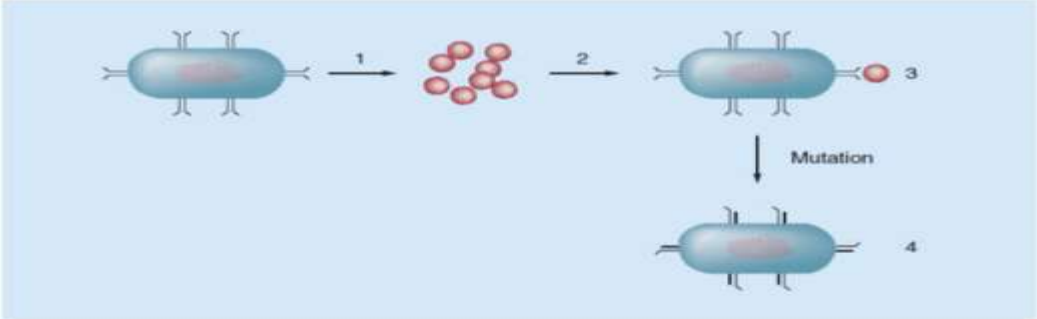

Figure 5: Mutation in Bacterias

6) Biofilm Formation:-

Bacterial biofilms represent a specialized survival structure where bacteria adhere to inert surfaces such as medical devices or mucosal surfaces, encapsulating themselves within an extracellular polymer matrix. These dense biofilms serve to shield their inhabitants, creating physical barriers that restrict antibiotic diffusion and augment protection through antibiotic inactivation. Furthermore, nutrient and oxygen gradients lead to reduced metabolic activity in the biofilm's core, promoting a tolerant cellular state that increases the proportion of persistent cells within the population. Additionally, biofilms can boost drug resistance by modifying the expression of pre-existing antibiotic resistance genes (ARGs).[25].

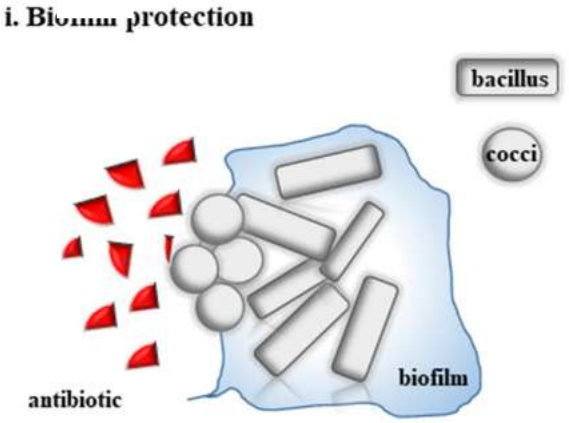

Figure 6: Formation of Biofilm

Controls of Antibiotic Resistance:-

Antibiotic-resistant bacteria spread globally through pathways similar to other bacteria, moving between people, animals, food products, and the environment. These interconnected links emphasize the necessity for a comprehensive approach to combat antibiotic resistance. It is crucial to adopt prudent antibiotic use practices across healthcare, animal health, and agricultural sectors to mitigate the emergence of resistance and prolong the effectiveness of antibiotics. The worsening treatment outcomes for bacterial infections are directly linked to antibiotic resistance and the scarcity of new drugs. It is increasingly evident that antibiotic use contributes to the rise of antibiotic-resistant bacteria, highlighting the importance of reducing unnecessary prescriptions as an effective strategy to alleviate selection pressures.[26].

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Strategies to combat antibiotic resistance encompass a range of measures. These include enhancing hygiene and sanitation practices, implementing infection control protocols to curb the transmission of resistant bacteria, developing novel antimicrobials that pathogens have not yet developed resistance to, improving efforts to preserve the effectiveness of existing antimicrobials, promoting the prudent use of antimicrobials across healthcare settings, advocating for the adoption of new and rapid diagnostic technologies to minimize unnecessary antibiotic treatments, and supporting the development and utilization of vaccines and alternative treatments.[27].

II. CONCLUSION:-

Antibiotic resistance is escalating to alarming levels worldwide. Novel resistance mechanisms continue to emerge and spread globally, posing a significant threat to our ability to effectively treat common infectious diseases. Infections caused by antibiotic-resistant pathogens often present formidable treatment challenges and can sometimes become untreatable. Hence, it is imperative to exercise cautious antibiotic use across healthcare, animal health, and agricultural sectors to mitigate the rise of resistance and preserve the efficacy of antibiotics for as long as possible.Antimicrobial resistance inevitably emerges as part of the evolutionary process, as the mechanisms enabling its persistence are not fully understood and can persist even without selective pressure from antibiotic use. Veterinary professionals, including veterinarians and paraprofessionals, play a crucial role in combatting antimicrobial resistance by overseeing and regulating antimicrobial usage, providing guidance to farmers and animal owners, and collaborating closely with the healthcare sector. A thorough comprehension of resistance mechanisms is critical for developing innovative strategies to address this challenge. It's essential to recognize that microorganisms will naturally develop resistance to both new and existing antibiotics due to evolutionary pressures. Therefore, continuous and robust efforts in antibiotic development and resistance mechanism research are essential for this ongoing battle against highly adaptable and resilient organisms.

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