J Current Pharma Sci. Res., 2024; 1(1):18-22.
https://jcpsr.com

Review Article

Unraveling the Molecular Mechanisms of Antimicrobial Resistance: A Comprehensive Exploration

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ABSTRACT

Background: The worldwide health community faces a serious threat of Antimicrobial Resistance (AMR), which occurs when bacteria develop resistance to drugs, thereby reducing the effectiveness of therapy. **Aim:** Unraveling the Molecular Mechanisms of Antimicrobial Resistance: A Comprehensive Exploration. **Materials and Methods:** Conducting a comprehensive literature search using various databases (PubMed, Google scholar, Research gate etc.,) to identify relevant studies on antimicrobial resistance mechanisms. Selected articles were critically evaluated, synthesized and organized to present a cohesive overview of the topic. **Results:** The key mechanisms underlying AMR include efflux pumps, target site changes, gene mutations, biofilm formation, quorum sensing and enzyme inactivation. A multimodal strategy involving cautious antimicrobial usage, strong infection control protocols, research on novel medicines and international collaboration is required to tackle this epidemic. **Conclusion:** The threat of AMR is jeopardizing global healthcare systems and calling for immediate action to protect public health and maintain the efficacy of antibiotic treatment.

Keywords: AMR, Superbugs, Efflux pump, Gene mutation, Biofilm.

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Received: 01-02-2024;
Revised: 06-03-2024;
Accepted: 25-03-2024.

INTRODUCTION

AMR occurs when bacteria, viruses, fungi and parasites evolve, rendering medications ineffective. This phenomenon makes infections more challenging to treat and increases the likelihood of diseases. AMR jeopardizes the efficacy of treatment for a variety of infections caused by these microorganisms.[1] Antimicrobials encompass a broad category of medications, including antibiotics, antivirals and antifungals, all designed to combat infections. These powerful drugs play a crucial role in preventing and treating a wide range of microbial infections, from bacterial to viral and fungal diseases. By targeting and inhibiting the growth or spread of microorganisms, antimicrobials play a vital role in safeguarding public health and promoting well-being. Their use is pivotal in both clinical settings and broader public health initiatives aimed at controlling the spread of infectious diseases.[2]

Superbugs

Superbugs, colloquial terms for microorganisms that have developed resistance to antimicrobial treatments, pose a significant threat to public health. Several factors contribute to the emergence and spread of Antimicrobial Resistance (AMR). One critical mechanism is the active efflux of drugs, where microorganisms expel antimicrobial agents from their cells, thereby reducing their effectiveness.[3] Additionally, microorganisms can modify their target sites, making them less susceptible to antimicrobial drugs. Gene mutations play a pivotal role in AMR by altering the genetic makeup of microorganisms and allowing them to withstand the effects of medications (Figure 1). Biofilm formation and quorum sensing enable microorganisms to thrive in protected environments and coordinate their resistance mechanisms.[4] Physicochemical factors, such as variations in pH and temperature, can influence the efficacy of antimicrobial treatments. Furthermore, microorganisms may employ enzyme inactivation strategies to neutralize antimicrobial agents. Understanding these multifaceted factors is crucial for developing effective strategies to combat the increasing threat of antimicrobial resistance.[5]

Mechanism of antibacterial resistance by efflux pump

In eukaryotic cells, efflux pumps have been known since the discovery of P-glycoprotein in 1976 by Julian and Ling. Efflux, as a mechanism of antibiotic resistance, was first described in 1980. Genetic elements encoding efflux pumps may be encoded on chromosomes and/or plasmids, thus contributing to both intrinsic and acquired resistance. Efflux pumps are transport channels that transport antibiotics from the intracellular to the external environment. The expression of several efflux pumps

DOI: 10.5530/jcpsr.2024.1.1.4

may lead to broad-spectrum resistance. Primary efflux pumps obtain energy from ATP hydrolysis, whereas secondary efflux pumps obtain energy from the chemical gradient mechanism of the protons (Figure 2).

- MATE: Aminoglycosides, Cationic drugs, etc.,
- RND: Multiple drugs.
- MFS: Chlorhexidine, cetrimide etc.,
- SMR: Benzalkonium.
- ABC: Multiple drugs.

Target site modification

The enzyme or protein essential for microorganism survival undergoes genetic modification that renders the antimicrobials ineffective.

Alterations in target protein structure.

Preventing antimicrobial agents from binding effectively.

Modifying enzymatic activity to bypass the inhibitory effect of antimicrobial agents.

This alteration renders the antimicrobial agent ineffective at inhibiting or killing microorganisms. In bacteria, this often involves mutations in genes encoding target proteins, such as enzymes or cell membrane receptors, which are usually essential for microorganism survival. mutations can lead to changes in the structure and shape of proteins (Figure 3).[6]

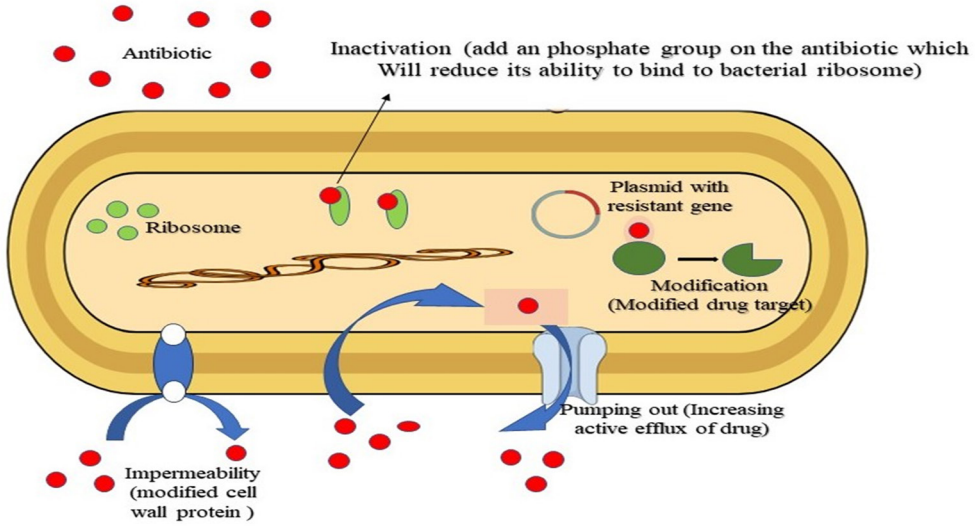

Figure 1: Mechanism of antibacterial resistance.

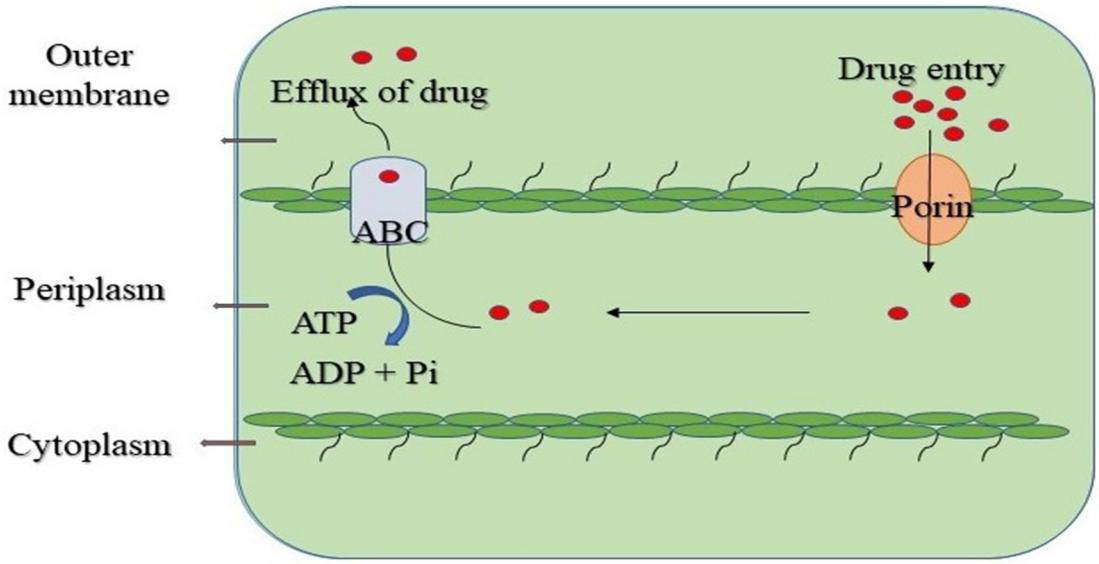

Figure 2: Antibacterial resistance mechanism by efflux pump.

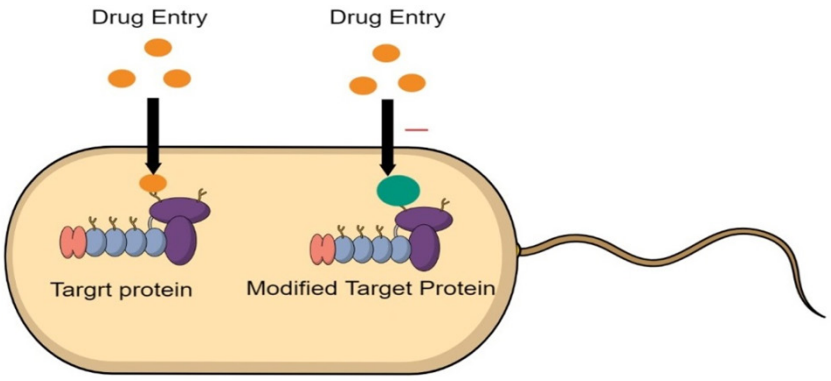

Figure 3: Antibacterial resistance by receptor target site alteration.

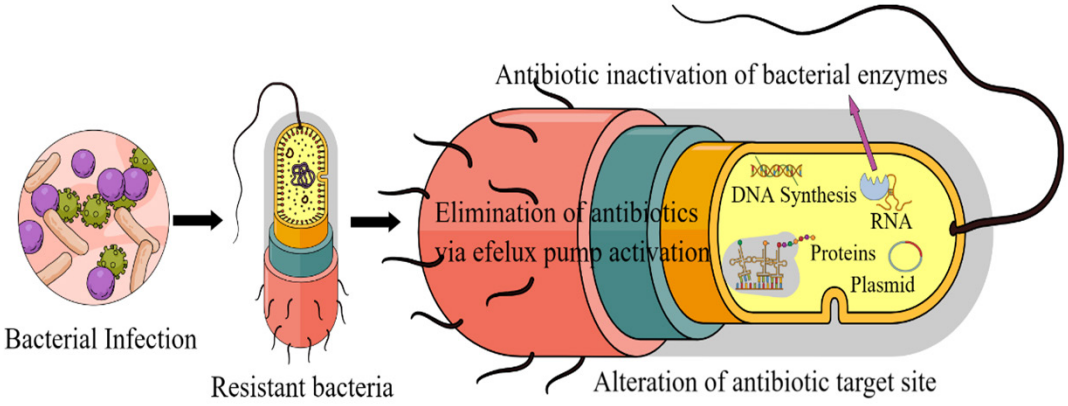

Figure 4: Antibacterial resistance mechanism target changes by gene mutation.

Gene mutation

Gene mutations are an important mechanism by which microorganisms develop antimicrobial resistance. This works through spontaneous mutation: Bacteria have a natural tendency to acquire genetic mutations during replication and occur randomly in bacterial DNA, leading to changes in the genetic code. Conjugation: This is a process whereby a donor bacterium conjugates or makes physical contact with a recipient bacterium through a sex pilus and transfers genetic elements to it. Resistance Transfer Factor (RTF)-This plasmid is of great importance as it leads to the spread of multiple drug resistance among bacteria. Selection pressure: Exposure to antimicrobial agents creates selective pressure that favors the survival of bacteria with mutations that confer resistance (Figure 4). Target modification: Mutations occur in genes encoding target sites, such as enzymes or cell wall components. Efflux pumps: Mutations that increase efflux pump activity can reduce intracellular antibiotic concentrations and promote resistance. Enzyme production: Mutation can also lead to overproduction or modification of enzymes involved in antibiotic inactivation and degradation. Horizontal gene transfer Mutations can occur in genes involved in horizontal gene transfer mechanisms, such as plasmids or transposons, which enhance the transfer of resistance genes between bacteria and accelerate the spread of resistance within the bacterial population. Gene mutations are dynamic processes that enhance the evolution of antimicrobial resistance.[7,8]

Biofilm formation and quorum sensing

Biofilms are a complex community of bacteria that adhere to surfaces and are encased within a self-produced extracellular polymeric substance, which serves as a physical barrier that protects bacteria from antimicrobial agents. Bacteria within biofilms can enter a dormant or slow-growing state, known as persister cells. Bacteria hide exopolymeric substances in biofilms and provide stability to inhabiting cells. Quorum Sensing (QS) plays an important role in biofilm formation-once the quorum is reached, bacteria initiate the expression of genes involved in biofilm formation, leading to the secretion of extracellular matrix components and assembly of structured community of bacteria (Figure 5).[9]

Enzyme inactivation

The most common mechanism of resistance in pathogenic bacteria to aminoglycosides, beta-lactams (penicillin and cephalosporin) and chloramphenicol involves the enzymatic

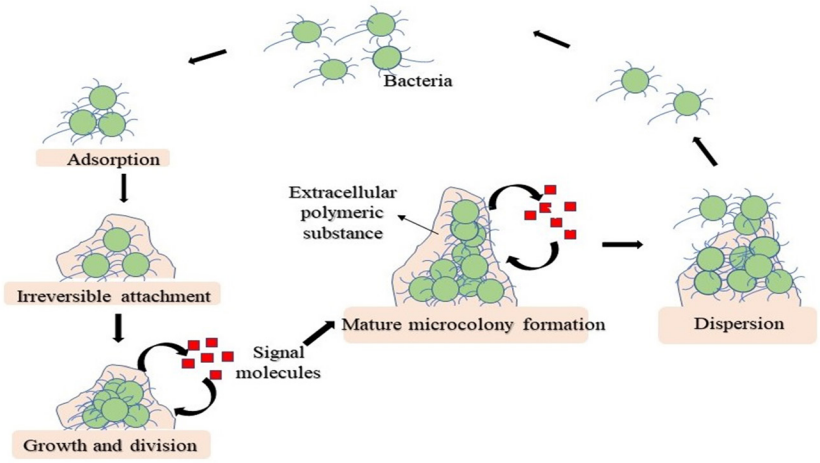

Figure 5: Antibiotic resistance by biofilm formation.

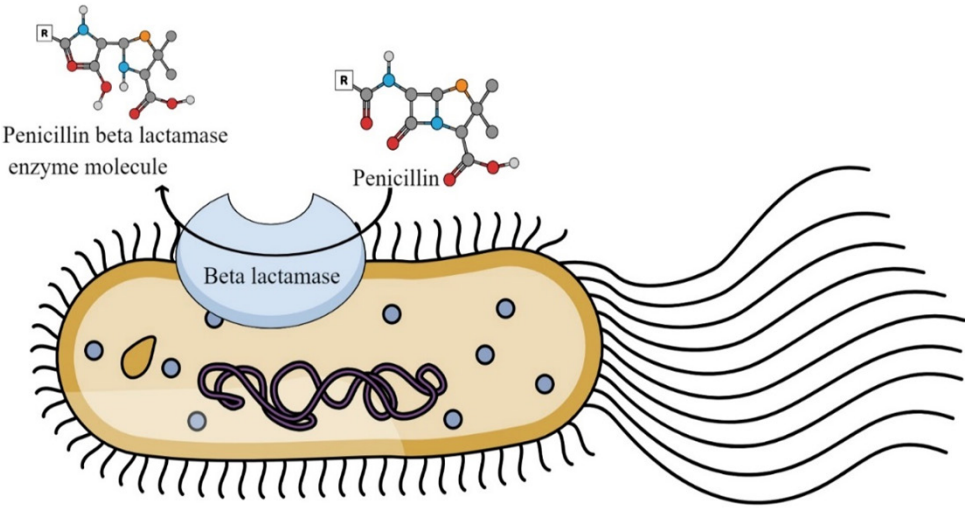

Figure 6: Antibiotic resistance by enzyme inactivation.

inactivation of antibiotics by hydrolysis or formation of inactive derivatives (Figure 6).[10]

CONCLUSION

AMR poses a serious and complex threat to public health. The efficacy of medicinal interventions against infections is threatened by the evolution of bacteria that resist antimicrobial therapies through a variety of methods. Comprehensive and cooperative efforts, including stakeholders from the healthcare, research, policy and international sectors, are needed to tackle Antimicrobial Resistance (AMR). Coordinated efforts are needed to address Antimicrobial Resistance (AMR) by promoting the responsible use of antibiotics, improving infection prevention and control methods, advancing research into novel treatment alternatives and fostering worldwide cooperation. Inaction against AMR compromises global public health systems and puts current medical procedures at risk of failure. Prioritising and maintaining efforts to lessen the effects of AMR and guarantee the ongoing effectiveness of antimicrobial medicines for future generations is essential.

ACKNOWLEDGEMENT

The authors express their gratitude to Jamia Salafiya Pharmacy College for providing the necessary facilities to undertake this brief review.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimicrobial resistance; **ATP:** Adenosine triphosphate; **MATE:** Multidrug and toxic extrusion; **RND:** Resistance-nodulation-division; **MFS:** Major facilitator superfamily; **SMR:** Small multidrug resistance; **ABC:** ATP-binding

cassette; **ADP:** Adenosine diphosphate; **Pi:** Phosphate group; **RTF:** Resistance transfer factor; **DNA:** Deoxyribonucleic acid; **RNA:** Ribonucleic acid; **QS:** Quorum sensing.

REFERENCES

1. Gil-Gil T, Laborda P, Sanz-García F, Hernando-Amado S, Blanco P, Martínez JL. Antimicrobial resistance: A multifaceted problem with multipronged solutions.*Microbiologyopen*. 2019;8(11):e945.
2. Prasad S, VP S, Abbas HS, Kotakonda M. Mechanisms of Antimicrobial Resistance: Highlights on Current Advance Methods for Detection of Drug Resistance and Current Pipeline Antitubercular Agents. Current Pharmaceutical Biotechnology. 2022:23(15):1824-36.
3. Christaki E, Marcou M, Tofarides A. Antimicrobial Resistance in Bacteria: Mechanisms, Evolution and Persistence.*J Mol Evol*. 2020;88(1):26-40.
4. Aslam B, Khurshid M, Arshad MI, *et al.* Antibiotic Resistance: One Health One World Outlook.*Front Cell Infect Microbiol*. 2021;11:771510.
5. Parmanik A, Das S, Kar B, Bose A, Dwivedi GR, Pandey MM. Current Treatment Strategies Against Multidrug-Resistant Bacteria: A Review.*Curr Microbiol*. 2022;79(12):388. Published 2022 Nov 3. doi:10.1007/s00284-022-03061-7.
6. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: A guide for clinicians.*J Anaesthesiol Clin Pharmacol*. 2017;33(3):300-305.
7. Urban-Chmiel R, Marek A, Stępień-Pyśniak D, *et al.* Antibiotic Resistance in Bacteria-A Review.*Antibiotics (Basel)*. 2022;11(8):1079.
8. Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial Antibiotic Resistance: The Most Critical Pathogens.*Pathogens*. 2021;10(10):1310.
9. Rather MA, Gupta K, Mandal M. Microbial biofilm: formation, architecture, antibiotic resistance and control strategies.*Braz J Microbiol*. 2021;52(4):1701-18.
10. Egorov AM, Ulyashova MM, Rubtsova MY. Bacterial Enzymes and Antibiotic Resistance.*Acta Naturae*. 2018;10(4):33-48.