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Comprehensive Review on Mechanism Responsible for Creating Antibiotic Resistance Bacteria

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Abstract

Antibiotic resistance [AR] is a global health concern, as multidrug-resistant bacteria emerge in hospitals and communities. Antibiotic resistance genes can be found outside of hospitals. Antibiotic resistance is primarily caused by bacterial responses under selective forces. Bacteria use numerous defenses mechanisms to survive, such as chemical modification of an antimicrobial agent, breakdown mediated by enzymes, modified permeability, efflux pump, target site alteration, and biofilm development. Bacteria can develop resistance to commonly used antibiotics. Different pathways can rise in the spread of AR in microbes, making previously vulnerable microorganisms resistant to antibiotics. The overuse of antibiotics by humans is one of several causes that exacerbate the antibiotic resistance dilemma.

Keywords – Antibiotic, Antibiotic resistant bacteria, resistance mechanism, Biofilms, Efflux pump.

INTRODUCTION

A drug called an antibiotic is used to treat infections brought on by bacteria along with other microorganisms. The discovery of antibiotics in 1928 and their widespread application beginning in the 1940s revolutionized daily living and society by enabling us to successfully fight infectious diseases. Thanks to this development, health and safety have significantly improved, making formerly fatal conditions much more treatable. [1] Antibiotics are commonly used to treat infections in both people and animals, including pets, cattle, wildlife, and aquatic animals. AR is a naturally occurring process which is increased by exposure to antibiotics. [2] ARBs, commonly present in fruits, vegetables, and animal products like meat, milk, and eggs. [3] AR is the capability of microorganisms to withstand effects of antimicrobial agents, i.e. the germs are not killed or their development is not slowed. Some examples of antimicrobial plant are turmeric, aloe vera, Tulsi, Peppermint. [4,5,6] Resistance bacteria can develop in the body after being exposed to antibiotics, possibly causing more damage and spreading to other animals or humans.

Antibiotic resistance develops accidentally through processes that could be the result of microbial competition that occurs naturally. Since the processes, genes, and pathways involved in the development and resistance to antibiotics aid in the competition of microbes for natural niches, they constitute essential elements of microbial life and typical evolutionary events. Unfortunately, the use of antibiotics—whether justified or not—amplifies these abnormalities. Antibiotic resistance can develop accidentally, but it can spread more slowly.

Contaminated food can transmit ARB, which can lead to a number of diseases and infections, including bronchitis, pneumonia, cellulitis, abscesses, the GI tract infections, UTI, and, in severe cases, bloodstream infections, also known as bacteremia or septi-cemia.[7]

Basis for Antibiotic Resistance

Bacteria's evolutionary response to the challenges presented by medicinal antibiotics is known as antibiotic resistance. Whenever an antimicrobial is first administered, all of the bacteria it targets are still vulnerable towards this from a clinical standpoint; but, over time, bacteria become resistant to the antibiotic. [8] Bacteria with antibiotic resistance may have genes via inherent, obtained, or adaptable sources.

The term "intrinsic resistance" describes a bacterium innate ability for exhibit opposition towards specific antibiotic categories because those antibiotics are present in their chromosomal genes without causing mutations or gene gain. "Intrinsic resistance implies that if specific antibiotics are used to treat the diseases caused by these bacteria, they will inevitably develop resistance to them. [9,10]"

Acquired resistance occurs when a previously sensitive bacterium acquires resistance through chromosomal gene mutation via transverse transfer of genetic material. It involves 3main processes: transformation, substitution, conjugation. [11]

Adaptable resistance is a trait that reacts to changes in the environment and might be temporary or permanent, depending on selective strain. People and animals can become adaptively resistant to microorganisms when exposed to subinhibitory antibiotic doses, as well as environmental cues such pH, stress, diet, and growth hormones, and ion concentration. [12]

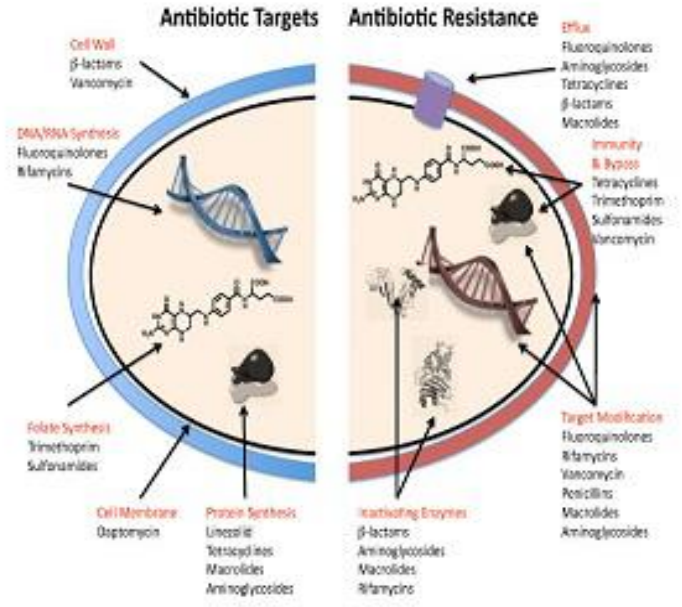

***Figure 1*:** *Antibiotic Targets and Antibiotic Resistance*

Mechanism of Anti-Microbial Resistance [AMR]

Bacteria and antimicrobials share a biological home, and microbes acquire resistance to antibiotics. Antibiotics have four key targets in bacterial cells: creation of nucleic acids, proteins, cell walls, and cell membranes. Antimicrobial resistance can occur through reducing medication uptake, changing drug targets, inactivating drugs, or increasing active efflux.

While the primary causes of intrinsic resistance are drug uptake limitation, drug inactivation, and drug efflux, bacteria often use drug target alteration, drug inhibition, and drug efflux mechanisms for acquired resistance. Gram-positive and gram-negative bacteria differ in their drug-resistance mechanisms due to structural variations.

Gram-positive bacteria have a limited ability proposing a mechanism of efflux to specific drug groups and absence of the outer membrane of lipopolysaccharide [LPS], which makes them less likely to apply the strategy of limiting drug absorption. It has been demonstrated that gram-negative bacteria employ each among the four primary drug resistance mechanisms. [13,14]

Restricting Drug Consumption

The outer membrane of gram-negative bacteria is mainly made up of lipopolysaccharides [LPS], which operate as an essential defense against a variety of chemicals, including antibiotics. Many antimicrobial medicines find it difficult to efficiently pass through the membrane because to this special structure, which adds to their intrinsic resistance. Porin proteins, which allow hydrophilic antibiotics like fluoroquinolones and β-lactams to flow through, affect its ability to penetrate of the outer membrane. Porin expression or function variations can result in acquired resistance, especially when paired with other mechanisms that resist as efflux pumps or drug enzymatic degradation [15,16].

Treatment of gram-negative bacterial infections is significantly complicated by biofilm formation in addition to porin changes. Colonies of bacteria that stick to surfaces and are covered in an exopolysaccharide matrix make up biofilms. In addition to increasing bacterial survival, this structure prevents antibiotics from diffusing, decreasing the effectiveness of therapies and encouraging the development of persistent infections. E. Coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa are notable gram-negative bacteria that create biofilms and demonstrate increased resistance through these processes. Developing ways to address antimicrobial resistance in these diseases requires an understanding of these mechanisms [17,18].

Bacteria change antibiotic target molecules

Since antimicrobial agents which made to specifically sim for certain particles including the smallest change may stop the antibiotics from binding, which can result in the establishment of antibiotic resistance.

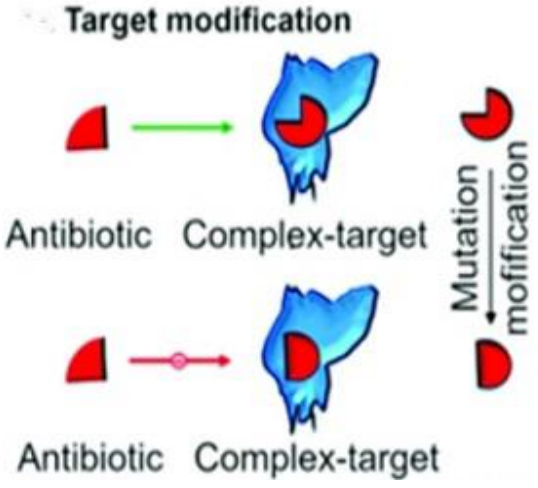

Figure 2*: *Target Modification

Alterations to the 30s or 50s ribosomal subunits

"It is known that antibiotics that disrupt protein synthesis, such as aminoglycosides, tetracycline, macrolides, chloramphenicol, lincosamides, and streptogramin, can generate resistance in bacteria by changing their ribosomal 30S or 50S subunits [19,20]".

Penicillin-binding protein [PBP] modifications

Proteins that bind penicillin [PBPs] are categorized as transpeptidases and They're necessary for the formation of micro cell walls because those cross-link peptidoglycan precursors. Since β-lactam antibiotics primarily target these enzymes, alterations within their arrangement or purpose may result in bacteria becoming resistant to these medications.

Alterations to the enzyme's topoisomerase and DNA gyrase

"The enzymes topoisomerase and DNA gyrase are involved in replication. Changes in their structure can result in bacterial resistance to quinolone antibiotics since these two enzymes are especially targeted by quinolone antibiotics [21]".

Modifications in D-alanyl-D-alanine

The D-alanyl-D-alanine is a dipeptide residue found in peptidoglycan precursors that is essential for the development of cell walls. Bacterial resistance to drugs that target this D-alanyl-D-Alanine residue may result from changes to it [22]

Protection of ribosome

It is well known that tetracycline antibiotics target the 30S component of the ribosome, although ribosomes contain defensive strategies that prevent them from doing their damage. [23]

RNA polymerase enzyme modification causing rifampicin antibiotic resistance

An antibiotic called rifampicin is frequently used to treat bacterial infections. It functions by attaching to the DNA-dependent RNA polymerase enzyme's beta-subunit, which inhibits the RNA production process in bacteria. Because of that interaction, the enzyme is unable to properly convert DNA to RNA, which inhibits bacterial development and event results in death of cell. However, changes to the RNA polymerase enzyme can cause bacteria to become resistant to rifampicin. Resistance to rifampicin may result from alterations in the rpoB gene, which produces the RNA polymerase beta-subunit. These changes may lessen antibiotic's capacity to suppress RNA production by altering the Rifampicin's ability to bind to the RNA polymerase enzyme. Rifampicin resistance can arise via changes in the RNA polymerase enzyme, which can have a number of effects. The concentrations of precursors of peptidoglycan, which are crucial elements of the cell wall of bacteria, are altered as one of the impacts. Variations in these precursors' concentrations may have an effect on the stability and integrity of the cell wall, which may change how susceptible bacteria are to other antibiotics like beta-lactams. It's crucial to remember that changes in the RNA polymerase enzyme are only one of the many ways that rifampicin resistance might develop. "Other ways include the increased efflux pump activity, which are able to actively remove rifampicin from the bacterial cell, and the acquisition of resistance genes by horizontal gene transfer [24]".

Inactivation of Drug

The process of antibiotic inactivation involves three primary enzymes. These are some of the enzymes:

Beta-lactamases enzymes

Bacterial enzymes possess the capability to degrade any B-lactam antibiotic that is attached to an ester or an amide. In turn, bacteria that are able to producing beta-lactamase enzymes become resistant to beta-lactam antibiotics.

Aminoglycoside modifying enzymes [AGES]

It is well recognized that enzymes are essential to antibiotic resistance. It has been discovered that some enzymes, including AMEs [aminoglycoside-modifying enzymes], stop aminoglycoside antibiotics from attaching to their ribosomal target [25]. Numerous bacterial strains, such as S. pneumoniae, S. aureus, and E. faecalis have these enzymes. These enzymes not only help to avoid antibiotic attachment, but they also support in the formation of resistance toward aminoglycosides, fluoroquinolones. Consequently, the existence of AMEs in bacterial Strains are a major problem in the world of antibiotic resistance because they pose a significant challenge to the efficacy of antibiotics in treating bacterial infections.

CAT enzymes

CAT are a type of enzyme that changes the CM by acetylating its OH group. As a result, the antibiotic changes and becomes unable to bind to its ribosome target.

Therefore, chloramphenicol antibiotics are ineffective against bacteria that harbor the enzyme chloramphenicol-acetyltransferase because they are resistant to them [26].

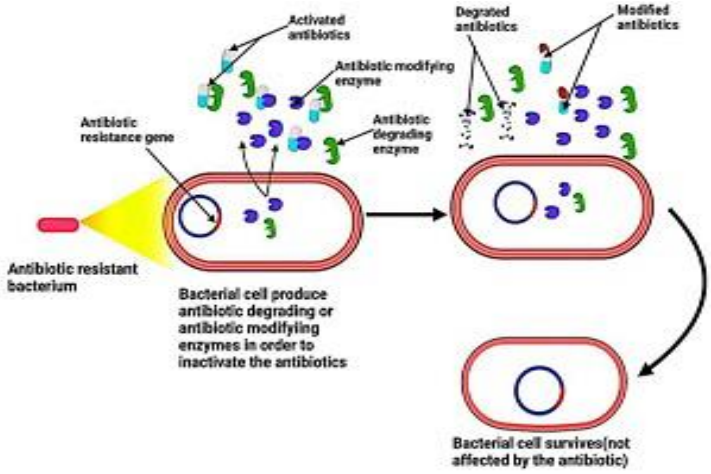

Figure 3: *Inactivation of Drug*

Efflux pump

One important cause of antibiotic resistance in bacteria is the ability of efflux pumps to remove antimicrobial drugs from their cells, which lowers the drug's effective concentration inside the bacterium. The effectiveness of several different antibiotics, including as beta-lactams, tetracyclines, and fluoroquinolones, can be considerably reduced by this process.

Mechanism of Action

Structure and Function

Membrane proteins called efflux pumps move a range of substances, including antibiotics, out of cells. According to their structure and energy source, they are usually divided into a number of families, including the resistance-nodulation-division [RND] family, the major facilitator superfamily [MFS], and the ATP-binding cassette [ABC] transporters.

Energy Sources

A variety of energy sources can be used by these pumps. For instance, RND pumps typically use the proton motive force, whereas ABC transporters use ATP hydrolysis.

Broad-Spectrum Resistance

Bacteria can simultaneously expel several kinds of antibiotics due to the wide substrate range of many efflux pumps. Treatment choices may become more complicated due to this multi-drug resistance.

Examples of Efflux Pumps

-AcrAB-TolC: *Escherichia coli* has a well-researched RND efflux mechanism that provides resistance to a range of antibiotics, such as tetracycline and chloramphenicol. -NorA: *Staphylococcus aureus* has an efflux pump that helps the bacteria withstand fluoroquinolones. [27,28]

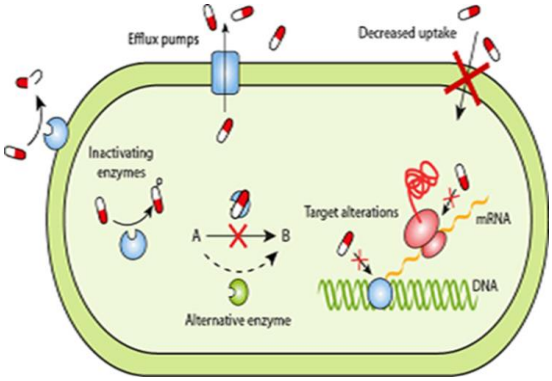

Figure 3*: *Efflux of Antibiotic

Reduced permeability

Most antibiotics are designed to target certain intracellular microorganisms. For antibiotics to work, they must be able to cross the cytoplasmic membrane. But certain microbes can block antibiotics from reaching their target areas by reducing their absorption [29]. There is an outer membrane on gram-negative bacteria which saves them while maintaining necessary material exchange for survival. Gram-negative bacteria's outer membrane acts as a barrier, making them less vulnerable to antibiotics than Gram-positive bacteria [30].

Porins are proteins that make up Gram-negative bacteria's outer membrane. Numerous porin types have been identified; they can be categorized in accordance with the regulation of expression, structure [monomeric versus trimeric], and selectivity. Among the best-characterized porins are OprD, also known as protein D2, from Pseudomonas aeruginosa and OmpC, OmpF, and PhoE, the three main proteins from E. coli [31]. Additionally, these two bacteria demonstrate how porin-mediated antibiotic resistance is used by Gram-negative bacteria.

Since porins are used by antibiotics with hydrophilic qualities, such tetracyclines, certain fluoroquinolones, and β-lactam, to pass through barriers, they are most impacted by changes in the permeability of outer membranes. There are three main processes that cause permeability changes:

Altering the level of porin expression;

Changing the kind of porins expressed;

Impairing porin functions.

Changes in the expression level of porin are among the common mechanisms of Porin-mediated resistance to antibiotics. Research indicates that decreased porin expression plays a significant part in the emergence of resistance to newer antibiotics like cephalosporin's and carbapenems in the Enterobacteriaceae family, Acinetobacter species, and Pseudomonas species, where resistance is typically mediated by enzyme degradation. For example, it has been noted in the Enterobacteriaceae family that resistance to carbapenem can still be attained in the absence of carbapenems production because of the reduction in porin production [caused by gene mutation].

The modification in the kind of porin expressed is another process at work. The external membrane's decreased permeability may be attained by substituting certain kind of porin with one that forms more selective channels, hence reducing the entry of antibiotics into bacterial cells [32]. Numerous drug-resistant K. pneumoniae strains provide an illustration of the alteration in the expression of porin. OmpK35 causes porin expression to shift to OmpK36, which has a shorter channel size, making K. pneumoniae strains less sensitive to β-lactams like carbapenem and cephalosporins. A reduction of four to eight times was observed in sensitivity to certain β-lactam antibiotics when OmpK36 porin was present.

Formation of Biofilms

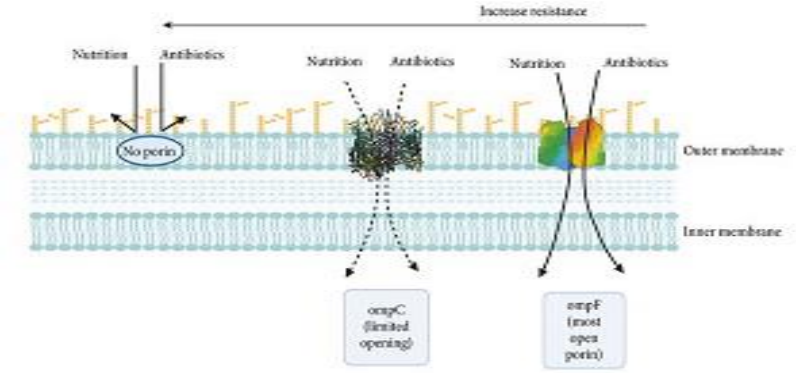

Figure 4*: *Reduction of Permeability of Antibiotic

Biofilms are intricate structures made up of several cell kinds, such as algae, fungus, and bacteria. These cells are surrounded by a heterogeneous extracellular matrix that contains different amounts of lipids, proteins, polysaccharides, and other substances [33]. Biofilms are ubiquitous in both natural and artificial environments, and they are widely acknowledged as a primary cause of antibiotic resistance. Antibiotic resistance can result from biofilm formation in a number of ways:

Physical barrier

The presence of biofilms between bacteria and antibiotics creates a barrier that hinders the antibiotics' ability to enter and get to the cells of the bacteria.

Slow rate of growth

Biofilms are less susceptible to antibiotics than planktonic bacteria because they develop and digest more slowly [34], as drugs usually target fast expanding bacterial cells.

Quorum sensing

Bacteria in biofilms are able to coordinate their activities and react to external stimuli by communicating with one another through the use of signaling molecules [35]. This may cause genes that offer antibiotic resistance to become active.

Phenotypic resistance

In reaction to their surroundings, bacteria in biofilms may display phenotypic resistance, which is characterized by changes in their metabolic activity and gene expression [36]. This may lessen their sensitivity to antibiotics. Persistent infections can result from bacteria that are resistant to antibiotics due to biofilm formation, which makes them harder to eradicate.

Some Examples

Biofilm Formation Inhibition: Research has examined turmeric's potential to stop microbial biofilms from forming. Microorganisms that stick to surfaces and may be resistant to standard antimicrobial treatments are known as biofilms. [37,38]

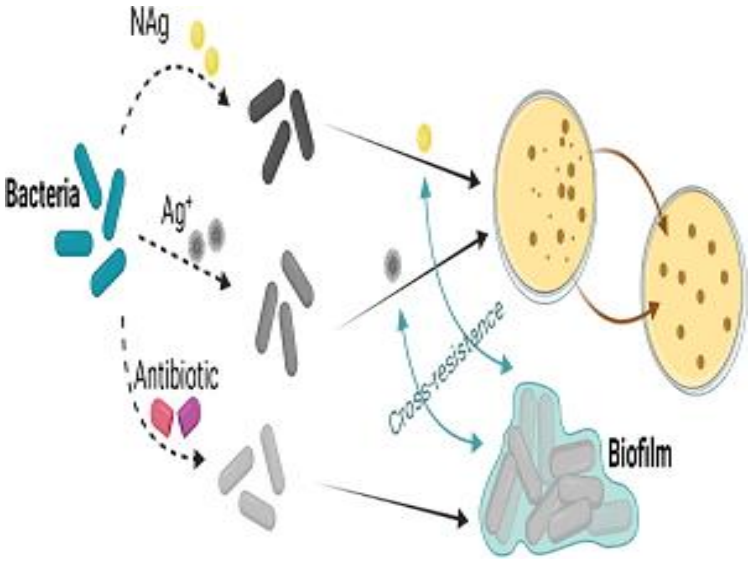

Figure 5*: *Biofilm Formation

Metabolic changes or auxotrophy

While it has been shown that metabolism actively contributes to antibiotic lethality, metabolic dysregulation is not an often-reported mechanism of antibiotic resistance, and mutations that cause antibiotic resistance are only found in metabolic genes. Numerous essential genes linked to metabolic processes, including the sucA gene [2-oxoglutarate dehydrogenase enzyme], who promote the tricarboxylic acid cycle, are found in the genome of clinically pathogenic E. Coli. In 2021, James et al. discovered for the 1st time that alterations in these genes can induce antibiotic resistance.

This mutation lowers basal respiration by preventing metabolic toxicity, reducing the effectiveness of antibiotics, and ultimately causing antibiotic resistance [39]. It also inhibits the actions of the TCA cycle, which is evoked by antibiotics.

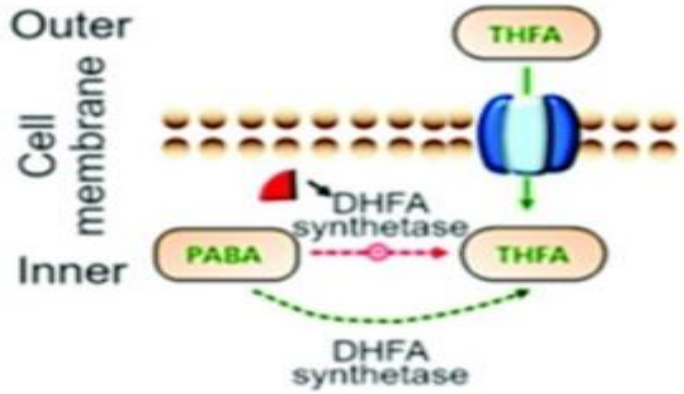

Figure 6*: *Metabolic Change or Auxotrophy

Self-Repair System Initiation

In order to increase antibiotic resistance, enteric bacteria's multiple antibiotic resistance operon modifies the integrity of the outer membrane and DNA repair. Research has indicated that one of the main causes of bacteria's multidrug resistance is the active efflux system controlled by the worldwide operon.

Multiple antibiotic resistance protein family, also known as the Mar family, is a transcriptional regulatory protein that is involved in several physiological processes, drug resistance, and the manufacture of hazardous substances. The E. Coli MarR protein, the progenitor of a family of numerous antibiotic resistance proteins, functions negatively to regulate the MarRAB operon and prevents the expression of genes linked to drug resistance downstream [40].

Through gene regulation of related gene expression, the beginning of self-repair processes decreases the pace at which antibiotics penetrate cells and their impact on cell structure and metabolism. Although this approach cannot totally remove the bacteriostatic effect of antibiotics, it can increase the bacteria's resistance to them.

Figure 7*: *Self Repair System Initiation

Modifications in Cell Morphology

Antibiotics work by modifying the mechanical feedback between morphology and cell development, which modifies relative body area and changes absorption efficiency.

In order to reduce the amount of antibiotics that pass through its surface, twisting and broadening both help to decrease the surface volume ratio, the increase in cell volume helps dilute the antibiotics that enter the bacteria.

Bypass of Antibiotic Inhibition

Bacteria create a substitute target, typically an enzyme, one of the enzymes that prevent antibiotic suppression [MRSA, considering instance, generates a substitute PBP]. Additionally, bacteria create a local target that being susceptible for medications the same time. By taking on the characteristics of a native protein, an alternate target enables bacterial survival. Resistance to trimethoprim and sulphonamides is caused by altered enzymes such as dihydropteroate reductase [DHFR] and dihydropteroatesynthetase [DHPS], which exhibit reduced sensitivity and binding to these drugs [41]

Bacteria inhibit antibiotic buildup in their cells

There are two pathways for inhibiting antibiotic buildup in bacterial cell as follows

Limiting the entry of medicines into bacterium cells

Porin channels are found in gram-negative bacteria's outer membrane as gatekeepers, these channels only let specific into the bacterial cell. Thus, the decreased quantity of bacterial porins may prevent these antibiotics, including B-lactams and quinolones, from entering the cell, increasing the drug's resistance [42].

Speeding up how quickly antibiotic leave microorganisms

Bacterium, cytoplasmic membranes contain multi drug resistance pump, which are essential for preserving the solute balance inside of bacterial cells. Nevertheless, by removing drugs from microbial cell earlier than they reach their intended site of action, AR is additionally facilitated by these pumps. Notably, it was discovered that efflux systems provide resistance to every kind of antibiotic, along the exception regarding polymyxin, to all antibiotic classes [43]. Gaining further insight into the workings of efflux systems could lead to the development of fresh approaches to the fight against antibiotic resistance.

Genetic Mutations

In essence, mutational resistance is a two-step procedure. A mutated genome first causes a change in the course of biological activities, which in turn causes the bacterium to grow in culture—albeit more slowly—when exposed to a usually effective concentration of the antibiotic. In actively growing bacterial cultures, spontaneous mutations happen infrequently—typically one in 109 cells. A common risk factor in clinical treatment is a low-complete-factor resistance mutation rate, which is made worse by the use of broad-spectrum medicines since more targets are subject to selective pressure when using antimicrobials with a wider range.

Bacteria can develop AMR through several hereditary mechanisms such as random mutations and horizontal gene transfer-induced acquisition of resistance genes. Either selection or the direct production of adaptive responses in bacteria can lead to antibiotic resistance. Antibiotic exposure induces genomic alterations, and treatment with antibiotics may select for a subpopulation of cells, enriching already-existing mutants that are either totally or partially resistant to the medication [44] .On the other hand, extended exposure to antibiotics can raise the probability that a spontaneous mutation in the genome will take place in one or more genes related to the regulation of gene expression, transport, modification, or enzymatic degradation of a specific antibiotic or related antibiotics. If the mutation confers a growth advantage under these circumstances, it may ultimately result in antimicrobial agent resistance.

Horizontal transmission of genes

Other HGT pathways, such as transformation and transduction, can also propagate drug resistance. [45]" While transduction is the result of viral [bacteriophage] transfer, transformation is the reception of naked double-stranded DNA from the environment.

Certain species have been shown to release genetic material that can be subsequently absorbed by another prokaryotic cell when gene transfer agent is used, that enable third, vesicle-mediated mode of HGT. HGT includes the transfer of genetic components that are mobile via one cell another, such as plasmids, chromosomally. transposable elements [such as composite transposons and integrons], and episomes [elements that can exist as plasmids or integrated in a chromosome]. Particularly in situations when antibiotic medications or other forms of enhanced selection are present, horizontally transferable genetic elements like plasmids containing resistance genes aid in the obtaining of resistance traits in bacteria that pass through.

Selective pressure

Environmental variables including the presence of subinhibitory antibiotic concentrations in food products may have a substantial impact on the establishment and spread of antimicrobial resistance [AR] [46] .A major factor in the development and persistence of AR in bacterial populations is selection pressure. When exposed to subinhibitory antibiotic dosages, bacteria with particular resistance mechanisms acquire a selection advantage over prone microbes in the environment.

Different adaptive responses in bacteria can be induced by subinhibitory concentrations of drugs. They have the ability to trigger stress response pathways or promote the development of resistance genes, which aid bacteria in surviving and adapting to antibiotic exposure. Bacteria are more likely to survive and proliferate at subinhibitory antibiotic doses if they already have resistance mechanisms or can develop them through HGT [47]. Antibiotic-resistant bacteria may become more prevalent in a population as a result of this selective pressure.

CONCLUSION

The worldwide pandemic of antibiotic resistance affects the ability to cure all infectious diseases. Resistance is currently essentially uncontrollable. Because of how big the problem is, it is nearly hard to think of a single solution or set of related remedies that will make a meaningful difference in the world. Resistance was established and propagated for a variety of complicated, mostly multifaceted, and largely unknown reasons. Research connecting the fields of medicine, chemistry, and the environment is urgently needed. Antibiotics are used in many different fields, however because of resistance problems, their usage is still questionable. There are four main ways that antibiotics work to either remove or stop the growth of bacteria. Nevertheless, Bacteria have evolved ways to resist antibiotics which reduces the efficacy of these medications. Although creating novel antibiotics is difficult, resistance to them may be prevented by the use of adjuvants, phage therapy, botanicals, and nano antibiotics.

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