https://doi.org/10.51483/AFJPS.4.1.2024.1-12 ISSN: 2789-5092

SvedbergOpen
DISSEMINATION OF KNOWLEDGE

African Journal of Pharmaceutical Sciences

Publisher's Home Page: https://www.svedbergopen.com/

Review Article Open Access

Mechanisms of Antibiotic Resistance in Bacteria: A Review

Raji M. I. O.[1*] and Bello S. A.[2]

[1]Department of Pharmaceutical Microbiology and Biotechnology, Usmanu Danfodiyo University Sokoto-Nigeria. E-mail: raji.mudasiru@udusok.edu.ng

[2]Department of Biological Sciences, Al-Hikmah University, Ilorin-Nigeria. E-mail: sharafabello78@gmail.com

Article Info

Volume 4, Issue 1, March 2024
Received : 09 October 2023
Accepted : 11 February 2024
Published : 05 March 2024
doi: 10.51483/AFJPS.4.1.2024.1-12

Abstract

Antibiotic resistance occurs when bacteria change so that antibiotics already killing them can no longer kill or in inhibit their growth. As a result, bacterial infections have become more difficult to treat. Antibiotic resistance limits treatment options, increase morbidity and mortality rates and therefore a treat to the worldwide health system. This study reviews four different mechanisms adopted by bacteria in bringing about resistance. The mechanisms are: (1) Modifications (chemical modification of the drug and drug target alteration); (2) Drug inactivation (enzymatic inactivation of antibiotics); (3) Drug uptake limitation (reduction of the inner and outer membrane permeability); and (4) Drug efflux (active pumps system). It is only when these bacterial resistance mechanisms are well understood that the issue of antibiotic resistance could be properly handled and its menace eradicated, or at least minimized.

Keywords: *Antibiotic, Mechanisms of resistance, Bacteria, Review*

1. Introduction

One of the most important classes of medications and a major medical innovation of the 20th century is the antibiotic. Unquestionably, antibiotics have helped humanity combat microorganisms and save millions of lives (da Cunha *et al.*, 2019). However, the threat of incurable illnesses has been there since the start of the twenty-first century, and the frequency of diseases brought on by multidrug-resistant (MDR) bacteria is rising globally (Gajdács and Albericio, 2019). Antimicrobial resistance (AMR) is a major challenge to all healthcare systems worldwide, even though antibiotics have enabled the development of several fields of medical practice, including the successful outcomes of several surgical procedures and immunosuppressive therapies that rely on antibiotic prophylaxis, as well as the potential to manage infectious complications (Dodds, 2017; and Uddin *et al.*, 2021).

* *Corresponding author: Raji M. I. O., Department of Pharmaceutical Microbiology and Biotechnology, Usmanu Danfodiyo University Sokoto-Nigeria. E-mail: raji.mudasiru@udusok.edu.ng*

The ability of bacterial cells to thwart the bacteriostatic or bactericidal effects of antibiotics is known as bacterial resistance (Munita and Arias, 2016; and Hasan and Al-Harmoosh, 2020). Antibiotic overuse and unintentional use are factors in the development of bacterial resistance (Kraemer *et al*., 2019). Due to the widespread use of antibiotics, bacteria have evolved a resistance throughout time, and issues have emerged when trying to treat certain infections caused by these resistant pathogens (Hayder and Aljanaby, 2019a). These days, resistance is a crucial factor in the development of new drugs, and antibiotic resistance is a global public health concern (Hayder and Aljanaby, 2019b).

The fields of medicine and microbial ecology are facing a major challenge due to the worldwide rise in antibiotic resistance. Growing numbers of clinical events pose a risk to the health of people and animals as well as to environmental preservation. Antibiotic resistance is increasing these days. According to Moutafchieva and Mladenov (2020), there is a significant risk to the health of humans and animals due to its rising prevalence. Its development must be stopped by identifying and removing its causes. First and foremost, it's best to avoid using antibiotics carelessly. This entails understanding and adhering to the rational therapy tenets. Strong oversight of antibiotic use is required to stop the development of resistance (Moutafchieva and Mladenov, 2020).

Antimicrobial resistance (AMR) is a major global issue in both human and veterinary medicine. It poses a worldwide risk to human and animal health as well as environmental preservation. Unfortunately, AMP is increasing these days along with the common and mostly unjustified use of antibiotics. Resistance genes have been chosen and dispersed as a result (Moutafchieva and Mladenov, 2020). One of the biggest concerns for global health today is the emergence, spread, and durability of antimicrobial resistance (AMR). According to several studies (Checcucci *et al*., 2020; Khan *et al*., 2020; Moutafchieva and Mladenov, 2020; Pereira *et al*., 2020; and Vega-Manriquez *et al*., 2020), intensive farming may raise the risks of AMR in domestic animals, wildlife, and humans. It's not always foreseeable when it will happen. This is not shocking. According to Moutafchieva and Mladenov (2020), bacteria use their genetic makeup to adapt to environmental changes. Treatment options for numerous bacterial illnesses may be severely limited by antimicrobial resistance.

Antimicrobial resistance is an inevitable evolutionary outcome as all species evolve genetic alterations to evade deadly selection pressure. As long as antibacterial drugs are employed against them, pathogens will inevitably evolve and employ resistance mechanisms (i.e., selection pressure is present in their environment). AMR is thought to have contributed to 700,000 deaths worldwide in 2019, and by 2050, that number is expected to reach 20 million, at a cost of more than $2.9 trillion, according to a 2019 World Health Organization (WHO) assessment (Watkins and Bonomo, 2016).

Consequently, it has grown into a significant issue that endangers both our economy and way of life. The rapid evolution of antimicrobial resistance (AMR) has led to reduced investment returns for the pharmaceutical R&D industry, in addition to the high cost of antibiotic research and growth. Numerous pharmaceutical companies have already given up on developing new antibiotics and researching antibiotics (Mohr, 2016; and Uddin *et al*., 2021).

2. Mechanisms of Resistance

Antibiotic resistance can be classified into two basic categories: acquired and natural. Natural resistance can be mediated (meaning that genes that are regularly present in the bacteria are only activated to resistant levels after antibiotic treatment) or innate, meaning that it is frequently expressed in the organisms (Reygaert, 2018). Conversely, the bacterial acquisition of genetic material through conjugation (Moutafchieva and Mladenov, 2020), transduction (Schwengers *et al*., 2020), transformation (Rang and Dale, 2020), transposition (Lerminiaux and Cameron, 2019), or mutations in its own chromosomal DNA could theoretically lead to acquired resistance.

Four major categories can be used to classify antimicrobial resistance (AMR) mechanisms: (1) Modifications (chemical modification of the drug and drug target alteration); (2) drug inactivation (enzymatic inactivation of antibiotics); (3) drug uptake limitation (reduction of the inner and outer membrane permeability); and (4) drug efflux (active pumps system). Others include the use of alternative metabolic pathway (Garima *et al*., 2018; Hasan and Al-Harmoosh, 2020; and Uddin *et al*., 2021).

Gram-negative bacteria are able to use all four mechanisms due to structural differences and other factors, whereas Gram-positive bacteria are less likely to use drug efflux and limiting drug uptake mechanisms because they lack lipopolysaccharide in their outer membrane (Hoffman, 2001; and Uddin *et al*., 2021). Certain bacterial strains such as Staphylococci have been documented to be resistant to numerous antibiotics on multiple occasions (Rang and Dale, 2020).

2.1. The Modifications

The target regions of the relationship with antibiotics and the modifications that occur in the drug-related receptor are different; these target regions can include ribosomes and complex enzymes (Prashanth *et al*., 2012; and Hasan and Al-Harmoosh, 2020). The majority of resistance to macrolide antibiotics has been shown to be consistent with changes in the ribosomal target (Shaikh *et al*., 2007). The most well-known instances of this are the emergence of penicillin resistance in strains of *Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitides,* and *Enterococcus faecium* as a result of mutations in beta-lactamase enzymes, which are penicillin-binding proteins (Southon *et al*., 2020).

2.1.1. Chemical Modification of the Drug

Enzymes produced by bacteria have the ability to attach different chemical groups to pharmaceuticals. As a result, the antibiotic is unable to attach to the bacterial cell's target. Antibiotics inhibit gene enzyme detection by adding an active functional group (WHO, 2013). The most efficient way to inactivate a medication through chemical group transfer is to add phosphoryl, acetyl, and adenyl groups to the substance (Lin *et al*., 2015; Uddin *et al*., 2021). The most frequently used mechanism is acetylation, which is thought to be used by aminoglycosides, fluoroquinolones, streptogramins, and chloramphenicol.

It is thought that phosphorylation and adenylation target the aminoglycosides. When aminoglycoside modifying enzymes (AMEs) are involved, the aminoglycoside molecule's hydroxyl or amino groups are covalently changed, rendering it inert. The high level of gentamicin resistance in enterococci is caused by modified enzymes (Gil-Gil *et al*., 2020).

Enzymatic inactivation is the primary mechanism by which aerobic Gram-negative bacteria develop resistance to aminoglycosides. According to Naha *et al.* (2020), resistance to aminoglycosides is largely caused by enzyme modification. These enzymes, which include phosphotransferase and acetyltransferase, are frequently plasmid or transposon derived (Gonzalez *et al*., 2019). The -OH and CO-NH groups of *Campylobacter coli* (*C. coli*), a microaerophilic Gram-negative bacterium, are phosphorylated, nucleotidylated, and transferased by phosphotransferases, nucleotidyltransferases, and acetyl transferases, which results in resistance to aminoglycosides (WHO, 2013; and Bharadwaj *et al*., 2022). It is among the best illustrations of drug modification-induced resistance (Munita and Arias, 2016).

Resistance in bacteria mediated by this enzyme results from the inactivation of the chloramphenicol acetyl transferase (CAT) by enzymes that acetylate the antibiotic (Siibak *et al*., 2011). Inactivation through medication change was the most recent mechanism of quinolone resistance to be discovered (Ghai and Ghai, 2017). A plasmid-encoded variation of the AAC enzyme is responsible for acetylation; it can also acetylate some quinolone compounds, aminoglycosides, and unsubstituted secondary amines like norfloxacin and ciprofloxacin (Ruiz *et al*., 2012; and Hasan and Al-Harmoosh, 2020).

2.1.2. Drug Target Modification

One common way that bacteria develop resistance to antibiotics is through altering the antibiotic's target (Reygaert, 2018). The mechanism of ribosomal target modification is most common in Gram-positive bacteria; in the 50S ribosomal subunit. Methylation of an adenine molecule results in a structural change and reduces the drug's binding to ribosomal RNA. The resistance is of a structural or inducible type (Linkevicius *et al*., 2016; and Zhanel *et al*., 2020).

Antibiotics can have their binding affinity decreased by rearranging the targets. It has been discovered that *Staphylococcus aureus* and *Klebsiella pneumonia* are resistant to linezolid due to a mutation in the allele that codes for the 23s rRNA ribosomal subunit (Bharadwaj *et al*., 2022).

Modifications in the configuration and/or quantity of PBPs are among the resistance mechanisms to β-lactam medications. Variations in the PBP count have an impact on the quantity of antibiotics that can attach to the target (Bush and Bradford, 2016; Uddin *et al.*, 2021). The most prevalent proteins in Gram-positive bacteria are penicillin-binding proteins (PBPs), which are involved in peptidoglycan synthesis and are responsible for the antibiotic target of beta-lactam, carboxypeptidase PBPs, and the enzymes of trans peptidase PBP. Changes in PBPs can lead to resistance (Kong *et al.*, 2010; Hasan and Al-Harmoosh, 2020).

According to Akata *et al.* (2019), in methicillin-resistant *S. aureus* (MRSA) is willing to bear the blame for methicillin resistance in strains is due to the mecA gene, which results in PBP-2a production and enhances beta lactam antibiotic resistance. Drug binding will be lessened or eliminated entirely by a structural change, such as the emergence of the mecA gene in *S. aureus* (Foster, 2017; Bharadwaj *et al.*, 2022). Penicillin and cephalosporin resistance in *S. pneumoniae* in PBP 2b is caused by changes in the bacterium (Fisher and Mobashery, 2016).

Another illustration is the family of genes known as erythromycin ribosomal methylation (erm) genes, which methylates 16S rRNA and modifies the drug-binding site to prevent the binding of macrolides, streptogramins, and lincosamines (Peterson and Kaur, 2018). Mutations in DNA gyrase or topoisomerase IV mediate resistance to antibiotics that block nucleic acid synthesis, such as fluoroquinolones. These alterations change the structure of topoisomerase and gyrase, which decreases or eliminates the drug's capacity to bind to these components (Nainu *et al.*, 2021).

With the aid of the enzyme chloramphenicol florfenicol resistance methyltransferase, resistance to a number of other drug classes, including penicillin, pleuromutilins, lincosamides, and oxazolidons, can be attained by incorporating CH_3 to A2503 in the 23s rRNA (Sekatawa *et al.*, 2022; Bharadwaj *et al.*, 2022).

The most common mechanism of acquired quinolone resistance is modifications in the target enzymes topoisomerases, which are primarily caused by mutations that decrease the affinity of quinolones without impairing the enzyme's function. These modifications have already been reported in several bacterial species (Munita and Arias, 2016; Roberts and Schwarz, 2017). According to Santajit and Indrawattana (2016), resistance-related mutations are grouped in distinct areas of the enzyme subunits known as regions determining quinolone resistance (QRDRs). A family of tiny pentapeptide-repeat proteins known as Qnr proteins, which attach to topoisomerase targets and shield them from quinolone interaction, provides target protection in quinolone resistance (Bansal *et al.*, 2017). Similar defenses have evolved in bacteria to guard against pentapeptide-repeat family proteins called microcin, which some bacteria produce as a means of biological competition and which can kill susceptible bacteria by blocking their topoisomerases (Makarewicz *et al.*, 2017).

Tetracycline resistance is caused by a second important mechanism (Sivagami *et al.*, 2020). By altering a cytoplasmic ribosome that binds to the tetracycline, the tetM, tetO, tetQ, and tetS genes prevent drug activity (Kapoor *et al.*, 2017). Numerous taxa, including *Campylobacter*, *Mycoplasma*, *Ureaplasma*, and *Bacteroides*, are known to contain these genes. Their chromosomal and plasmid origins are well known and documented (Poole, 2007; Hasan and Al-Harmoosh, 2020).

Ribosomal target modifications are crucial in streptomycin resistance; the target of streptomycin is not connected to the ribosomal 30S subunit due to mutations in the ribosomal 30S. In enterococci, this type of resistance to streptomycin is essential (Breijyeh *et al.*, 2020).

3. Drug Inactivation (Enzymatic Inactivation of Antibiotics)

Antibiotics can be rendered inactive by bacteria in two different ways: either by destroying the drug or by changing its chemical composition (Blair *et al.*, 2015). The majority of bacteria produce enzymes that break down antibiotics, and one of the most significant methods of resistance to antibiotics is enzymatic inactivation (Pérez-Llarena and Bou, 2016). The most well-known examples in this category are erythromycin-modifying enzymes, aminoglycosidase and beta-lactamases (Sharkey and O'Neill, 2019).

Staphylococci are the pathogens that generate β-lactamases. Plasmids contain the resistance-coding genes. Transduction is the method used to transfer them (Rang and Dale, 2020; Schwengers *et al.*, 2020). β-lactamases

are also produced by Gram-negative bacteria. According to Rang and Dale (2020), they play a major role in resistance to broad range β-lactam antibiotics that are semisynthetic. The enzymes of these species can be found either in plasmid or chromosomal genes. Transposons encode a large number of these β-lactamases, which may also be resistant to other antibiotics (Rang and Dale, 2020). The primary mechanism of β-lactam resistance is the destruction of the β-lactam loop by the activity of β-lactamases. Penicillin-binding proteins (PBP) are inhibited from binding to β-lactams due to the hydrolysis of β-lactam ring formation by β-lactamases (Bush and Bradford, 2016).

The most often used antibacterial agents are β-lactam antibiotics, like cephalosporins and penicillin (Page, 2012; Uddin *et al*., 2021). Penicillins, cephalosporins, monobactams, and carbapenems are among the many antibiotics in the broad class (Fernández-Villa *et al*., 2019). All members of this pharmacological class share a four-sided β-lactam loop, which forms its core structure. β-lactamases are the enzymes that render β-lactam antibiotics inactive. The most prevalent resistance mechanism in this group is the synthesis of beta-lactamase enzymes (Zango *et al*., 2019). Penicillins and cephalosporins both have their β-lactam rings broken by them, but the resistance between the two classes is not entirely eliminated since some lactamases prefer penicillins while others prefer cephalosporins (Kitagawa *et al*., 2020). Chromosome detection and plasmid-mediated encoding genetic enzymes that degrade antibiotics—such as β-lactamase; penicillinase only degrade penicillins, cephalosporinases which inactivate cephalosporins and aminopenicillins and expanded beta-lactamases, which are crucial for breaking down all β-lactams. However, the entire β-lactamase is rendered inactive by carbapenemase and carbapenem (Davies and Davies, 2010; Bharadwaj *et al*., 2022).

There are four categories of beta-lactamase enzymes at the molecular level: A, B, C, and D (Heinz *et al*., 2019). The B-class requires zinc ions as metalloenzyme which is in contrast to the beta-lactamases A, C, and D (Walkty *et al*., 2020; Hasan and Al-Harmoosh, 2020). Both Gram-positive and Gram-negative bacteria can develop beta-lactamases Class A resistance, which are primarily caused by plasmids or transposons. They possess the ability to be induced (Walkty *et al*., 2020). The Gram-negative bacteria TEM, SHV, and ESBL are members of this category. According to Lomovskaya *et al.* (2020), *Escherichia coli* and *Klebsiella pneumoniae* are the main hosts of ESBL. *Bacteroides fragilis*, a species of *Aeromonas* and *Legionella*, produces enzymes in Beta-lactamases Class B that hydrolyze cephalosporins, penicillins, and carbapenems (De Oliveira *et al*., 2020).

According to Jacobs *et al.* (2019), beta-lactamases Class C are typically found in Gram-negative bacteria and are chromosomally localized (Group I, AmpC, etc.). Because this resistance mechanism has an inducible quality and is not inhibited by clavulanic acid, it is created in large quantities when beta-lactam antibiotics are present (Meini *et al*., 2015). They have been identified in *Enterobacter cloacae, Citrobacter freundii, Serratia marcescens,* and *P. aeruginosa*. These bacteria are commonly referred to as Inducible Beta-Lactamases (IBL) (Philippon *et al*., 2002; Hasan and Al-Harmoosh, 2020). Whereas *Staphylococcus aureus* and other Gram-positive bacteria create beta-lactamases Class D enzymes in response to beta-lactam antibiotics, which break down oxacillin (Hasan and Al-Harmoosh, 2020).

4. Drug Uptake Limitation (Reduction of the Inner and Outer Membrane Permeability)

According to Santajit and Indrawattana (2016), this mechanism is caused by variations in the permeability of the internal and exterior membranes, which lead to reduced drug uptake into the cell or quick ejection from the pump systems.

Because of the lipopolysaccharide (LPS) layer that forms a permeability shield on their outer membrane, Gram-negative bacteria are inherently less susceptible to some antibiotics than Gram-positive bacteria. An excellent example of how efficient this natural barrier is the fact that glycopeptide antibiotics, such as vancomycin, are ineffective against Gram-negative bacteria due to their inability to get through the outer membrane (Uddin *et al*., 2021).

The alterations in the permeability of the outer membrane have a significant impact on hydrophilic compounds, such as β-lactams, tetracyclines, and certain fluoroquinolones (Blair *et al*., 2015; Uddin *et al*., 2021). Enterococci's porin channel down regulation or even replacement with non-selective channels results

in polar molecules having trouble penetrating the cell wall. This provides an innate resistance to aminoglycosides.

Due to differences in their outer membrane proteins, Gram-negative bacteria have increased resistance to quinolones, which causes them to consume fewer drugs (Theuretzbacher *et al.*, 2020). Chloramphenicol resistance may also result through reduced drug uptake in some bacteria, particularly Gram-negative ones (Petrov *et al.*, 2004; Hasan and Al-Harmoosh, 2020). Decrease in membrane permeability brought on by chromosome alterations that occur spontaneously in bacteria result in the development of resistance and stop the absorption of tetracyclines (Das *et al.*, 2020).

Gram-negative bacteria may develop carbapenem resistance due to changes in their porin channels. One such bacterium is *P. aeruginosa*, which has a dedicated channel protein registered in OprD (Sauvage and Terrak, 2016). A mutation in the particular porin (OprD) can generate resistance to carbapenem in a strain of *Pseudomonas aeruginosa*. Porin mutations can also cause a decrease in membrane permeability in proteins of resistant strains (Nikaido and Pagès, 2012). Quinolone and aminoglycoside resistance may be significantly impacted by reductions in outer membrane permeability (Li *et al.*, 2012).

Mutations in the gene that specifically codes for the outer membrane porin protein allow antibiotics to diffuse throughout the cell. This leads to a shift in the OMPK36 variant porin, which in *Klebsiella pneumoniae* exhibits reduced permeability for the antibiotics (Ruggerone *et al.*, 2013). In some bacteria, including *Escherichia coli* and *Acinetobacter*, the permeability of the membrane for antibiotics is reduced due to the down regulation of the major porin protein or refilling the cell membrane with another chosen protein channel (Billal *et al.*, 2011; Bharadwaj *et al.*, 2022).

Furthermore, new research indicates that among members of the *Enterobacterales* order, *Acinetobacter* spp. and *Pseudomonas* spp. decreases in porin expression significantly contribute to drug resistance, including carbapenems. For instance, in *Enterobacterales*, resistance to carbapenems will develop if there are mutations that reduce porin production or if mutant porin alleles are present, or if there are enzymes of carbapenemase activity absent (Iredell *et al.*, 2016). Another mechanism that aids in bacterial colonization is the production of biofilms (Pang *et al.*, 2019). Polysaccharides, proteins, and DNA make up the biofilm matrix, which provides resistance by preventing antimicrobial drugs from easily penetrating the bacteria (Hall and Mah, 2017).

5. Drug Efflux (Active Pumps System)

It is possible to stop antibiotics from building up in the cell by using active pump systems. As such, resistance may result from the class of drugs that includes quinolones, tetracyclines and beta-lactams (Harkins *et al.*, 2017; Hasan and Al-Harmoosh, 2020). Others include; chloramphenicol and 14-membered macrolides, all can be successfully resisted by active pumping systems (Guo *et al.*, 2020).

The intrinsic resistance of Gram-negative bacteria is mostly due to the active export of several antibiotics from the cell through bacterial efflux pumps. Most bacteria have a variety of efflux pump configurations. According to Reygaert (2018), there are five main families of efflux pumps: ATP-binding cassette (ABC) family, small multidrug resistance (SMR) family, multidrug and toxic compound extrusion (MATE) family, resistance-nodulation-cell division (RND) family, and large facilitator superfamily (MFS). These families are classified based on their energy supply and structure. All other efflux pump families are singular pumps that transfer substrates across the cytoplasmic membrane, with the exception of the RND family, which consists of several parts pumps that efflux substrate across the cell envelope (Munita and Arias, 2016; Uddin *et al.*, 2021).

The most prevalent way that resistance arises in antibiotics is through the active pump systems of the tetracycline group (Breidenstein *et al.*, 2011). Tetracyclines are excreted from the cell and unable to concentrate inside it due to an energy-dependent active pumping system (Li *et al.*, 2019). This resistance mechanism is based on chromosomal and plasmid control.

Tetracycline resistance is an efflux-mediated resistance, whereby Tet efflux pumps (of the MFS family) expel tetracyclines by using proton exchange as an energy source. Tetracyclines can be extruded by a number of MDR efflux pumps as part of their contribution to MDR, including MexAB-OprM in *P. aeruginosa* and

AcrAB-TolC in *Enterobacterales* (of the RND family) (Grossman, 2016). Accordingly, the organisms may become resistant to tetracyclines if they have active pump systems (Böhm *et al*., 2020).

Another clinically significant trait that is caused by the efflux pathway is resistance to macrolides. The most extensively studied efflux pumps, such as erythromycin, are encoded by the mef genes, which expel the macrolide class of antibiotics. According to Munita and Arias (2016) and Uddin *et al*. (2021) MacB, a member of the ABC family, functions as a tripartite pump (MacAB-TolC) for extruding macrolide antibiotics.

6. Using an Alternative Metabolic Pathway

Unlike some of the target alterations in bacteria, the latest drug-susceptible pathway eliminates the need for objective development (Fatahi-Bafghi, 2019). Bacteria can prepare folic acid from the environment, rather than synthesizing folic acid so that it becomes resistant among sulfonamide and trimethoprim (Tan *et al.*, 2020).

7. Conclusion

Bacteria bring about resistance majorly through four different mechanisms namely: (1) Modifications (chemical modification of the drug and drug target alteration); (2) Drug inactivation (enzymatic inactivation of antibiotics); (3) Drug uptake limitation (reduction of the inner and outer membrane permeability); and (4) Drug efflux (active pumps system). There is need for better understanding of these resistance mechanisms for the issue of antibiotic resistance to be properly handled and its menace eradicated, or at least minimized.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Akata, K., Muratani, T., Yatera, K., Naito, K. and Noguchi. (2019). Induction of Plasmid-Lactamase DHA Lactams in *Enterobacteriaceae*. *PLOS ONE*, 14(7), e0218589. https://doi.org/10.1371/journal.pone.0218589.

Bansal, S., Bajaj, P., Pandey, S. and Tandon, V. (2017). Topoisomerases: Resistance versus Sensitivity, How Far We Can Go. *Medicinal Research Reviews*, 37(2), 404-438.

Bharadwaj, A., Rastogi, A., Pandey, S., Gupta, S. and Sohal, J.S. (2022). Multidrug-Resistant Bacteria: Their Mechanism of Action and Prophylaxis. *BioMed Research International*, 2022(5419874), 1-17. doi: https://doi.org/10.1155/2022/5419874

Billal, D.S., Feng, J., Leprohon, P., Legare, D. and Ouellette, M. (2011). Whole Genome Analysis of Linezolid Resistance in *Streptococcus pneumoniae* Reveals Resistance and Compensatory Mutations. *BMC Genomics*, 12(1), 512.

Blair, J.M.A., Webber, M.A., Baylay, A.J., Ogbolu, D.O. and Piddock, L.J.V. (2015). Molecular Mechanisms of Antibiotic Resistance. *Nature Review Microbiology*, 13, 42-51. http://dx.doi.org/10.1038/nrmicro3380.

Böhm, M.E., Razavi, M., Marathe, N.P., Flach, C.F. and Larsson, D.J. (2020). Discovery of a Novel Integron-Borne Aminoglycoside Resistance Gene Present in Clinical Pathogens by Screening Environmental Bacterial Communities. *Microbiome*, 8(1), 1-11.

Breidenstein, E.B., de la Fuente-Núñez, C. and Hancock, R.E. (2011). *Pseudomonas aeruginosa*: All Roads Lead to Resistance. *Trends in Microbiology*, 19(8), 419-426.

Breijyeh, Z., Jubeh, B. and Karaman, R. (2020). Resistance of Gram-Negative Bacteria to Current Antibacterial Agents and Approaches to Resolve It. *Molecules*, 25(6), 1340.

Bush, K. and Bradford, P.A. (2016). β-lactams and β-lactamase Inhibitors: An Overview. *Cold Spring Harb Perspect Med.*, 2016(6), a025247. doi: http://dx.doi.org/10.1101/cshperspect.a025247.

Checcucci, A., Trevisi, P., Luise, D., Modesto, M., Blasioli, S., Braschi I. and Mattarelli, P. (2020). Exploring the Animal Waste Resistome: The Spread of Antimicrobial Resistance Genes Through the Use of Livestock Manure. *Frontiers in Microbiology*, 11(1416), 1-9.

da Cunha, B.R., Fonseca, L.P. and Calado, C.R.C. (2019). Antibiotic Discovery: Where have We Come from, Where Do We Go?. *Antibiotics,* 8(45), 1-21. http://dx.doi.org/10.3390/antibiotics8020045

Das, B., Verma, J., Kumar, P., Ghosh, A. and Ramamurthy, T. (2020). Antibiotic Resistance in *Vibrio cholerae*: Understanding the Ecology of Resistance Genes and Mechanisms. *Vaccine*, 38(1), A83-A92.

Davies, J. and Davies, D. (2010). Origins and Evolution of Antibiotic Resistance. *Microbiology and Molecular Biology Reviews*, 74(3), 417-433.

De Oliveira, D.M., Forde, B.M., Kidd, T.J., Harris, P.N., Schembri, M.A., Beatson, S.A. and Walker, M.J. (2020). Antimicrobial Resistance in ESKAPE Pathogens. *Clinical Microbiology Reviews*, 33(3), e00181-19.

Dodds, D.R. (2017). Antibiotic Resistance: A Current Epilogue. *Biochemistry Pharmacology*, 134, 139-46. http://dx.doi.org/10.1016/j.bcp.2016.12.005.

Fatahi-Bafghi, M. (2019). Antibiotic Resistance Genes in the *Actinobacteria* Phylum. *European Journal of Clinical Microbiology and Infectious Diseases*, 38(2019), 1599-1624.

Fernández-Villa, D., Aguilar, M.R. and Rojo, L. (2019). Folic Acid Antagonists: Antimicrobial and Immunomodulating Mechanisms and Applications. *International Journal of Molecular Sciences*, 20(20), 4996.

Fisher, J.F. and Mobashery. (2016). *β*-Lactam Resistance Mechanisms: Gram-Positive Bacteria and *Mycobacterium tuberculosis*. *Cold Spring Harbor Perspectives in Medicine*, 2016(a025221), 1-19. https://doi.org/10.1101/cshperspect.a025221.

Foster, T.J. (2017). Antibiotic Resistance in *Staphylococcus aureus*. Current Status and Future Prospects. *FEMS Microbiology Review,* fux 007, 1-20. http://dx.doi.org/10.1093/femsre/fux007.

Garima, K., Saurabh, S. and Ashok, E. (2018). Action and Resistance Mechanisms of Antibiotics: A Guide for Clinicians. *J Anaesthesiol Clin Pharmacol,* 34, 46-50.

Ghai, I. and Ghai, S. (2017). Exploring Bacterial Outer Membrane Barrier to Combat Bad Bugs. *Infection and Drug Resistance*, 10, 261-273.

Gil-Gil, T., Martínez, J.L. and Blanco, P. (2020). Mechanisms of Antimicrobial Resistance in *Stenotrophomonas maltophilia*: A Review of Current Knowledge. *Expert Review of Anti-Infective Therapy,* 18(4), 335-347.

Gonzalez, M.R., Ducret, V., Leoni, S. and Perron, K. (2019). *Pseudomonas aeruginosa* Zinc Homeostasis: Key Issues for an Opportunistic Pathogen. *Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms*, 1862(7), 722-733.

Grossman, T.H. (2016). Tetracycline Antibiotics and Resistance. *Cold Spring Harbour Perspective Medicine*, 6. http://dx.doi.org/10.1101/cshperspect.a025387.

Guo, R., Li, K., Qin, J., Niu, S. and Hong, W. (2020). Development of Polycationic Micelles as an Efficient Delivery System of Antibiotics Overcoming Biological Barriers to Reverse Multidrug Resistance in *Escherichia coli*. *Nanoscale,* 12(2020), 11251-11266. https://doi.org/10.1039/DONRO1366H

Hall, C.W. and Mah, T.F. (2017). Molecular Mechanisms of Biofilm-Based Antibioticresistance and Tolerance in Pathogenic Bacteria. *FEMS Microbiol Rev*, fux 010, 1-26. http://dx.doi.org/10.1093/femsre/fux010.

Harkins, C.P., Pichon, B., Doumith, M., Parkhill, J., Westh, H., Tomasz, A., de Lencastre, H., Bentley, S.D., Kearns, A.M. and Holden, M. (2017). Methicillin Resistant *Staphylococcus aureus* Emerged Long Before the Introduction of Methicillin into Clinical Practice. *Genome Biology*, 18(1), 130. https://doi.org/10.1186/s13059-017-1252-9.

Hasan, T.H. and Al-Harmoosh, R.A. (2020). Mechanisms of Antibiotics Resistance in Bacteria. *Systematic Review Pharmacy*, 11(6), 817-823. E-ISSN 0976-2779. P-ISSN 0975-8453.

Hayder, T. and Aljanaby, A.A.J. (2019a). Antibiotics Susceptibility Patterns of *Citrobacter freundii* Isolated from Patients with Urinary Tract Infection in Al-Najaf Governorate Iraq. *International Journal of Research in Pharmaceutical Sciences*, 10(2), 1481-1488. https://doi.org/10.26452/ijrps.v10i2.722.

Hayder, T. and Aljanaby, A.A.J. (2019b). Genotypic Characterization of Antimicrobial Resistance-Associated Genes in *Citrobacter freundii* Isolated from Patients with Urinary Tract Infection in Al-Najaf Governorate-Iraq. *Journal of Biological Sciences*, 19(2), 132-145. https://doi.org/10.3844/ojbsci.2019.132.145.

Heinz, E., Ejaz, H., Scott, J.B., Wang, N., Gujaran, S., Pickard, D. and Strugnell, R.A. (2019). Resistance Mechanisms and Population Structure of Highly Drug Resistant *Klebsiella* in Pakistan During the Introduction of the Carbapenemase NDM-1. *Scientific Reports*, 9(2392), 1-7.

Hoffman, S.B. (2001). Mechanisms of Antibiotic Resistance. *Compendium,* 23(5), 464-473. http://dx.doi.org/10.1128/microbiolspec.vmbf-0016-2015.

Iredell, J., Brown, J. and Tagg, K. (2016). Antibiotic Resistance in *Enterobacteriaceae*: Mechanisms and Clinical Implications. *BMJ*, 351(h6420), 1-19. http://dx.doi.org/10.1136/bmj.h6420.

Jacobs, M.R., Abdelhamed, A.M., Good, C.E., Rhoads, D.D., Hujer, K.M., Hujer, A.M. and Kreiswirth, B.N. (2019). ARGONAUT-I: Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, against Gram-Negative Bacteria, Including Carbapenem-Resistant Nonfermenters and *Enterobacteriaceae* with Defined Extended-Spectrum-Lactamases and Carbapenemases. *Antimicrobial Agents and Chemotherapy*, 63(1), e01801-18.

Kapoor, G., Saigal, S. and Elongavan, A. (2017). Action and Resistance Mechanisms of Antibiotics: A Guide for Clinicians. *Journal of Anaesthesiology and Clinical Pharmacology*, 33(3), 300.

Khan, S.A., Imtiaz, M.A., Sayeed, M.A., Shaikat, A.H. and Hassan, M.M. (2020). Antimicrobial Resistance Pattern in Domestic Animal – Wildlife – Environmental Niche via the Food Chain to Humans with a Bangladesh Perspective: A Systematic Review. *BMC Veterinary Research,* 16(302), 1-13.

Kitagawa, K., Shigemura, K., Nomi, M., Takami, N., Yamada, N. and Fujisawa, M. (2020). Use of Oral Third Generation Cephalosporins and Quinolones and Occurrence of Antibiotic Resistant Strains in the Neurogenic Bladder (NB) Outpatient Setting: A Retrospective Chart Audit. *Spinal Cord*, 58, 705-710.

Kong, K.F., Schneper, L. and Mathee, K. (2010). Betalactam Antibiotics: From Antibiosis to Resistance and Bacteriology. *APMIS: Acta Pathologica, Microbiologica, et immunologica Scandinavica*. 118(1), 136. https://doi.org/10.1111/j.1600-0463.2009.02563.x.

Kraemer, S.A., Ramachandran, A. and Perron, G.G. (2019). Antibiotic Pollution in the Environment: From Microbial Ecology to Public Policy. *Microorganisms,* 7(6), 180. https://doi.org/10.3390/microorganisms7060180.

Lerminiaux, N.A. and Cameron, A.D.S. (2019). Horizontal Transfer of Antibiotic Resistance Genes in Clinical Environments. *Canadian Journal of Microbiology*, 65, 34-44. http://dx.doi.org/10.1139/cjm-2018-0275.

Li, H., Luo, Y.F., Williams, B.J., Blackwell, T.S. and Xie, C.M. (2012). Structure and Function of OprD Protein in *Pseudomonas aeruginosa*: From Antibiotic Resistance to Novel Therapies. *International Journal of Medical Microbiology*, 302(2), 63-68.

Li, T., Liu, C., Lu, J., Gaurav, G.K. and Chen, W. (2019). Determination of How Tetracycline Influences Nitrogen Removal Performance, Community Structure, and Functional Genes of Biofilm Systems. *Journal of the Taiwan Institute of Chemical Engineers*, 7(5), 1-11. https://doi.org/10.1016/j.jtice.2019.10.004

Lin, J., Nishino, K., Roberts, M.C., Tolmasky, M., Aminov, R.I. and Zhang, L. (2015). Mechanisms of Antibiotic Resistance. *Front Microbiol*., 6(34), 1-3. http://dx.doi.org/10.3389/fmicb.2015.00034.

Linkevicius, M., Sandegren, L. and Andersson, D.I. (2016). Potential of Tetracycline Resistance Proteins to Evolve Tigecycline Resistance. *Antimicrobial Agents and Chemotherapy*, 60(2), 789-796.

Lomovskaya, O., Nelson, K., Rubio-Aparicio, D., Tsivkovski, R., Sun, D. and Dudley, M.N. (2020). Impact of Intrinsic Resistance Mechanisms on Potency of QPX7728, a New Ultrabroad-Spectrum Beta-Lactamase Inhibitor of Serine and Metallo-Beta-Lactamases in *Enterobacteriaceae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*. *Antimicrobial Agents and Chemotherapy*, 64(6), e00552-20.

Makarewicz, O., Klinger-Strobel, M., Ehricht, R., Kresken, M. and Pletz, M.W. (2017). Antibiotic Resistance in Pulmonary Infections: Mechanisms and Epidemiology. In: Aliberti, S., Chalmers, J.D. and Pletz, M.W. (Eds.). Anti-Infectives and the Lung, Chapter 2, European Respiratory Society (ERS Monograph), Sheffield.

Meini, M.R., Llarrull, L.I. and Vila, A.J. (2015). Overcoming Differences: The Catalytic Mechanism of Metallo-Lactamases. *FEBS Letters,* 589(22), 3419-3432.

Mohr, K.I. (2016). History of Antibiotics Research. *Current Topics in Microbiology Immunology*, 398(2016), 237-272.

Moutafchieva, R. and Mladenov, D. (2020). Antimicrobial Resistance: Review. *Trakia Journal of Sciences*, 18(4), 401-404. ISSN 1313-3551 (online) doi:10.15547/tjs.2020.04.015. http://www.uni-sz.bg.

Munita, J.M. and Arias, C.A. (2016). Mechanisms of Antibiotic Resistance. In: Virulence Mechanisms of Bacterial Pathogens. *Wiley,* 481-511. http://dx.doi.org/10.1128/9781555819286.ch17.

Naha, A., Miryala, S.K., Debroy, R., Ramaiah, S. and Anbarasu, A. (2020). Elucidating the Multi-Drug Resistance Mechanism of *Enterococcus faecalis* V583: A Gene Interaction Network Analysis. *Gene*, 144704.

Nainu, F., Masyita, A., Bahar, M.A., Raihan, M., Prova, S.R., Mitra, S., Bin Emran, T. and Simal-Gandara, J. (2021). Pharmaceutical Prospects of Bee Products: Special Focus on Anticancer, Antibacterial, Antiviral, and Antiparasitic Properties. *Antibiotics,* 10(822), 1-37. http://dx.doi.org/10.3390/antibiotics10070822

Nikaido, H. and Pagès, J.M. (2012). Broad-Specificity Efflux Pumps and their Role in Multidrug Resistance of Gram-Negative Bacteria. *FEMS Microbiology Reviews*, 36(2), 340-363. https://doi.org/10.1111/j.1574-6976.2011.00290.x

Page, M.G.P. (2012). *β*-Lactam Antibiotics. In: Dougherty, T.J. and Pucci, M.J. (Eds.). *Antibiotic Discovery and Development,* Springer, New York. 79-117.

Pang, Z., Raudonis, R., Glick, B.R., Lin, T.J. and Cheng, Z. (2019). Antibiotic Resistance in *Pseudomonas aeruginosa*: Mechanisms and Alternative Therapeutic Strategies. *Biotechnology Advances,* 37, 177-92. http://dx.doi.org/10.1016/j.biotechadv.2018.11.013.

Pereira, R.V., Altier, C., Siler, J.D., Mann, D., Jordan, D. and Warnick, L.D., (2020). Longitudinal Effects of Enrofloxacin or Tulathromycin Use in Preweaned Calves at High Risk of Bovine Respiratory Disease on the Shedding of Antimicrobial-Resistant Fecal *Escherichia coli. Journal of Dairy Science*, 103(11), 10547-10559.

Pérez-Llarena, F.J. and Bou, G. (2016). Proteomics as a Tool for Studying Bacterial Virulence and Antimicrobial Resistance. *Frontiers in Microbiology*, 7(410), 1-21.

Peterson, E. and Kaur, P. (2018). Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. *Frontiers in Microbiology,* 9(2928), 1-21. http://dx.doi.org/10.3389/fmicb.2018.02928.1764

Petrov, A., Meskauskas, A. and Dinman, J.D. (2004). Ribosomal Protein L3: Influence on Ribosome Structure and Function. *RNA Biology*, 1(1), 58-64.

Philippon, A., Arlet, G. and Jacoby, G.A. (2002). Plasmid-Determined AmpC-Type Betalactamases. *Antimicrobial Agents and Chemotherapy*, 46(1), 1 11. https://doi.org/10.1128/aac.46.1.1-11.2002.

Poole, K. (2007). Efflux Pumps as Antimicrobial Resistance Mechanisms. *Annals of Medicine*, 39(3), 162-176.

Prashanth, K., Vasanth, T., Saranathan, R., Makki, A.R. and Pagal, S. (2012). Antibiotic Resistance, Biofilms and Quorum Sensing in *Acinetobacter* Species. In: Pana, M. (Ed.). *Antibiotic Resistant Bacteria – A Continuous Challenge in the New Millennium*, InTech, China. 179-212.

Rang, H.P. and Dale. M.M. (2020). *Pharmacology*, 9th Edition, Elsevier Ltd. ISBN: 978-0-7020-7448-6.

Reygaert, W.C. (2018). An Overview of the Antimicrobial Resistance Mechanisms of Bacteria. *AIMS Microbiology*, 4(3), 482-501. http://dx.doi.org/10.3934/microbiol.2018.3.482.

Roberts, M.C. and Schwarz, S. (2017). Tetracycline and Chloramphenicol Resistance Mechanisms. In: Mayers, D.L. (Ed.), *Antimicrobial Drug Resistance*, Springer, New York. 183-193.

Ruggerone, P. Murakami, S., Pos, K.M. and Vargiu, A.V. (2013). RND Efflux Pumps: Structural Information Translated into Function and Inhibition Mechanisms. *Current Topics in Medicinal Chemistry*, 13(24), 3079-3100.

Ruiz, J., Pons, M.J. and Gomes, C. (2012). Transferable Mechanisms of Quinolone Resistance. *International Journal of Antimicrobial Agents*, 40(3), 196-203.

Santajit, S. and Indrawattana, N. (2016). Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *BioMed Research International*, 2016(2475067), 1-8. http://dx.doi.org/10.1155/2016/2475067

Sauvage, E. and Terrak, M. (2016). Glycosyltransferases and Transpeptidases/Penicillin-Binding Proteins: Valuable Targets for New Antibacterials. *Antibiotics*, 5(1), 12. https://doi.org/10.3390/antibiotics5010012.

Schwengers, O., Bart, P., Falgenbauuer, L., Hain, T., Chakraborty, T. and Goesmann, A. (2020). Platon: Indentification and Characterization of Bacterial Plasmid Contigs in Short-Read Draft Assemblies Exploting Protein Sequence-Based Replicon Distribution Scores. *Microbial Genomics*, 6(2020), 1-12. http://dx.doi.org/10.1099/mgen.0.000398

Shaikh, S.A., Jain, T., Sandhu, G., Latha, N. and Jayaram, B. (2007). From Drug Target to Leads-Sketching a Physicochemical Pathway for Lead Molecule Design in Silico. *Current Pharmaceutical Design*, 13(34), 3454-3470.

Sharkey, L.K., and O'Neill, A.J. (2019). Molecular Mechanisms of Antibiotic Resistance Part II. In: Bonev, B.B. and Brown, N.M. (Eds.), *Bacterial Resistance to Antibiotics: From Molecules to Man,* Wiley-Blackwell, Hoboken, New Jersey. 27-50.

Siibak, T., Peil, L., Donhofer, A., Tats, A., Remm, M., Wilson, D.N., Tenson, T. and Remme, J. (2011). Antibiotic-Induced Ribosomal Assembly Defects Result from Changes in Synthesis of Ribosomal Proteins. *Mol Microbiol*, 80(1), 54-67.

Sivagami, K., Vignesh, V.J., Srinivasan, R., Divyapriya, G. and Nambi, I.M. (2020). Antibiotic Usage, Residues and Resistance Genes from Food Animals to Human and Environment: An Indian Scenario. *Journal of Environmental Chemical Engineering*, 8(1), 102221.

Southon, S.B., Beres, S.B., Kachroo, P., Saavedra, M.O., Erlendsdottir, H., Haraldsson, G. and Kristinsson, K.G. (2020). Population Genomic Molecular Epidemiological Study of Macrolide Resistant Streptococcus pyogenes in Iceland, 1995-2016: Identification of a Large Clonal Population with a pbp2x Mutation Conferring Reduced in vitro ?-lactam Susceptibility. *Journal of Clinical Microbiology*, 58(9), 1-13. https://doi.org/10.1128/JCM.00638-20

Tan, J., Tay, J., Hedrick, J. and Yang, Y.Y. (2020). Synthetic Macromolecules as Therapeutics that Overcome Resistance in Cancer and Microbial Infection. *Biomaterials*, 250(2020), 120078.

Theuretzbacher, U., Bush, K., Harbarth, S., Paul, M., Rex, J.H., Tacconelli, E. and Thwaites, G.E. (2020). Critical Analysis of Antibacterial Agents in Clinical Development. *Nature Reviews Microbiology*, 18(2020), 286-298. https://doi.org/10.1038/s41579-020-0340-0

Uddin, T.M. Chakrabortya, A.J., Khusrob, A., Zidana, R.M., Mitraa, S., Emranc, T.B., Dhamad, K., Ripone, K.H., Gajdácsf, M., Sahibzadag, M.U.K., Hossainh, J. and Koiralai, N. (2021). Antibiotic Resistance in Microbes: History, Mechanisms, Therapeutic Strategies and Future Prospects. *Journal of Infection and Public Health,* 14(2021), 1750-1766. http://www.elsevier.com/locate/jiph

Vega-Manriquez, X.D., Ubiarco-López, A., Verduco-Rodríguez, A., Hernández-Chiñas, U., Navarro-Ocaña, A., Ahumada-Cota, R.E., Ramíres-Badillo, D., Hernández-Díaz de Leon, N. and Eslava, C.A. (2020). Pet Dogs Potential Transmitters of Pathogenic *Escherichia coli* with Resistance to Antimicrobials. *Archives of Microbiology,* 202(5): 1173-1179.

Walkty, A., Karlowsky, J.A., Baxter, M.R., Adam, H.J., Alexander, D., Bay, D.C. *et al.* (2020). Fosfomycin Resistance Mediated by Fos Genes Remains Rare among Extended-Spectrum Betalactamase-Producing *Escherichia coli* Clinical Isolates Recovered from the Urine of Patients Evaluated at Canadian Hospitals (CANWARD, 2007-2017). *Diagnostic Microbiology and Infectious Disease*, 96(3), 114962.

Watkins, R.R. and Bonomo, R.A. (2016). Overview: Global and Local Impact of Antibiotic Resistance. *Infectious Disease Clinics of North America*, 30(2016), 313-22. http://dx.doi.org/10.1016/j.idc.2016.02.001.

WHO. (2013). Department of Communicable Disease Surveillance and Response WHO Global Strategy for Containment of Antimicrobial Resistance. December 2013. http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf.

Zango, U.U., Ibrahim, M. and Shawai, S.A.A. (2019). *β*-lactam Antibiotic Drug Resistance. *MOJ Drug Des Develop Ther.*, 3(2), 52-58.

Zhanel, G.G., Esquivel, J., Zelenitsky, S., Lawrence, C.K., Adam, H.J., Golden, A. and Bay, D. (2020). Omadacycline: A Novel Oral and Intravenous Aminomethylcycline *Antibiotic Agent. Drugs*, 80(2020), 285-313.

Cite this article as: Raji M. I. O. and Bello S. A. (2024). Mechanisms of Antibiotic Resistance in Bacteria: A Review. *African Journal of Pharmaceutical Sciences,* 4(1), 1-12. doi: 10.51483/AFJPS.4.1.2024.1-12.