

MECHANISM ACTION AND RESISTANCE STYLE OF ANTIBIOTICS

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Abstract

Antibiotics are the natural, synthetic or semi synthetic compound .For decades it used as weapon in the battle against pathogens (bacteria, fungi, parasite, etc.) that attach the life of agriculture and animal husbandry. For that, the antimicrobial agents used in therapeutic and prophylactic purpose. Unfortunately, the microbes have become resistant to different antibiotics by development of their mechanism action. The lists of infectious diseases were grown due to increase of resistance at an alarming rate and the then antibiotics are less effective. High morbidity and mortality ratio come from wrong diagnosis of pathogen that lead to wrong treated by antibiotics because appeared new strains called multidrug-resistant bacteria .The aim of this review is to explore the Mechanism action and resistance style of antibiotics

Keywords: β -lactam, Cephalosporins, Aminoglycosides, Macrolide, Quinolones

Introduction

Antibiotics

Antibiotics are the products of secondary metabolism and have anti-microbial activity. Or it can be defined as organic chemicals produced by different microorganisms and has the effect of inhibiting the growth or killing of bacteriocidal other microorganisms without affecting the host cells (Shuwaikh, 2016).

β -lactam antibiotics

The ring of beta-lactam is part of the basic buildings of multiple antibiotic classes (Penicillins, Cephalosporins, Carbapenems, Monobactam), these antibiotics prevent the synthesis of the cell wall and have bactericidal on the bacteria in spite of the presence of bacterial resistant species (Brandt et al., 2017). The beta-lactum ring is found in the synthesis of these antibodies figure(1), and it has a role in preventing the cell wall of bacteria from synthesis through binding the antibiotic to special proteins within the cell membrane named penicillin Binding Proteins (PBPs).They inhibit the enzyme Transpeptidase, which forms peptide chains that bind to the peptidoglycan forming layers figure (2)(Zervosen et al., 2012).

Penicillins

Divide the penicillins into: -

- Natural penicillins such as penicillin G (Benzyl penicillin) and penicillin V (Phenoxy methyl penicillin).

-Semi-synthetic penicillins contain broad-spectrum penicillins include carboxy penicillin such as Carbenicillin and Ticarcillin and the Ureido penicillin group and include antibiotic Azlocillin, Mezlocillin, Piperacillin (Shuwaikh, 2016).

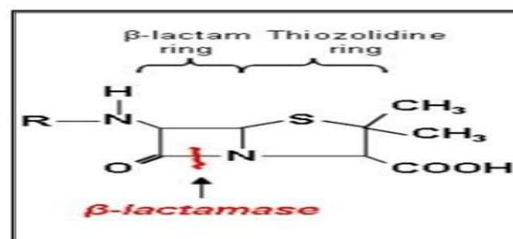


Figure (1): Core structure of penicillins

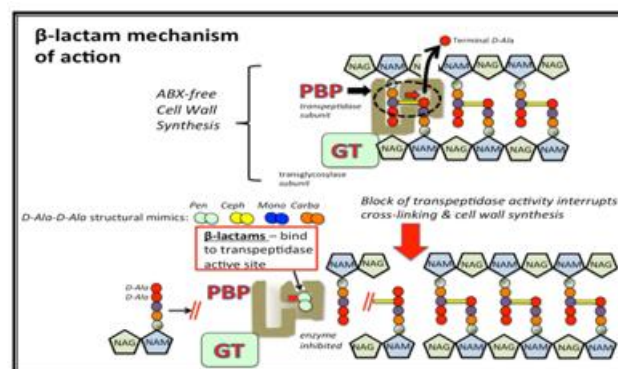


Figure (2): Mechanism of action of beta-lactam antibiotics

Cephalosporins

Semi-synthetic antibiotics, containing in their composition a beta-lactam ring linked to a dihydrothiazine ring figure (3), and they have a broad spectrum activity against Gram-positive and other bacteria and are resistant to penicillin and are used as alternatives for patients who are allergic to penicillin (Hancu et al., 2013). Depending on their chemical composition and antimicrobial activity, cephalosporins are divided into generations:

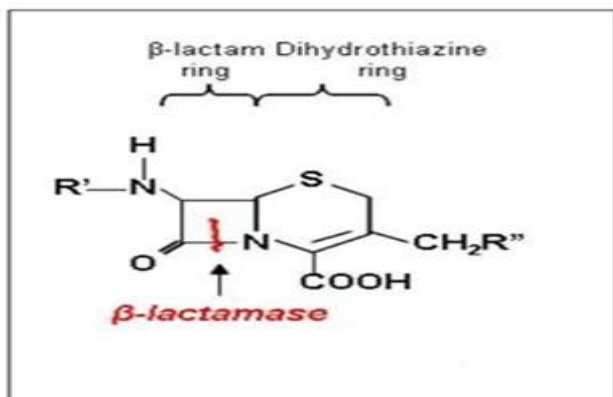


Figure (3): Core structure of Cephalosporins

First generation Cephalosporins

Includes a group of antibiotics taken by the muscle such as Cephalothin Cefazolin, Cephapirin and others taken orally (such as Cephalexin and Cephadrine) almarjanu (2011).

Second generation Cephalosporins

These compounds are stable based on the presence of beta-lactamase enzymes, increasing their activity against Gram-negative bacteria such as Cefoxitin and Cefotetan (Metha and Sharma, 2016).

Third generation Cephalosporins

Antibiotics include Ceftibuten, Ceftizoxime, Ceftriaxone, Ceftazidime, Cefotaxime (Metha and Sharma, 2016).

Fourth generation Cephalosporins

Such as Cefepime

Fifth generation Cephalosporin

They include Ceftobiprole, Ceftaroline (Bassetti and Matheo, 2013).

Carbapenems

It has a wide spectrum of activity against the positive and negative bacteria of the gram stain. It works on the binding proteins of Penicillin - Binding Proteins. This inhibits cell wall synthesis, including Imipenem and Meropenem figure (4) (Metetis, 2016).

Monobactam

Aztreonam is the first member of this group and is effective against Gram-negative bacteria and has no ability to bind to penicillin Binding Proteins (PBPs) of gram-positive bacteria and anaerobic bacteria, so its effect is weak on them (almarjanu (2011).

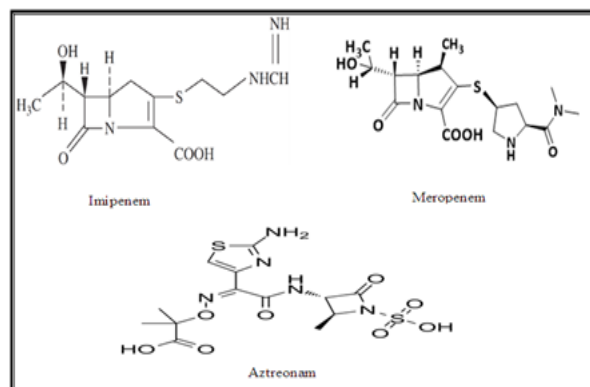


Figure (4): Chemical structure of Imipenem, Meropenem and Aztreonam

Aminoglycosides

A range of broad-spectrum antibiotics that is effective against most Gram-positive and negative bacteria such as Staphylococcus aureus, including Amikacin, Gentamicin, Tobramycin, Kanamycin, Its chemical composition is characterized by the presence of cyclic amino alcohol associated with some amino sugars. All these compounds are derived from glucose by life synthesis figure (5). These antibiotics act on protein synthesis sites in the bacterial cell figure (6). The resistance of aminoglycosides is generally due to modifying enzyme enzymes, which include Acetyltransferases, Phosphotransferases, and Nucleotidyltransferases, and this group has a Bactericidal effect against pathogenic bacteria by inhibiting bacterial protein synthesis (Lambert, 2012).

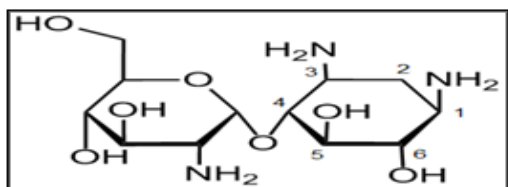


Figure (5): Structure of aminoglycoside

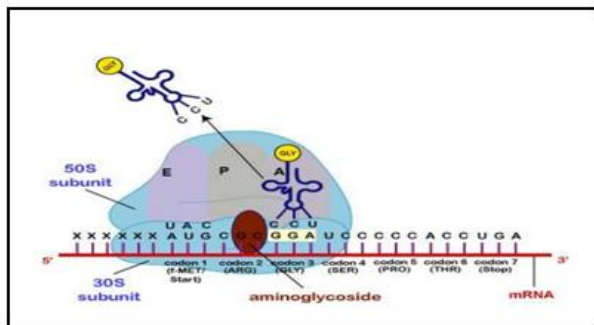


Figure (6): Mechanism action of aminoglycoside

Quinolones

Quinolins are antibiotics that are effective against bacteria and are divided according to their effectiveness in four generations. Acid quinolones fall within the first generation, which includes Nalidixic acid figure (7), and the second generation includes fluoroquinolones, which include several anti-Norfloxacin, Ciprofloxacin, and Levofloxacin and the third generation includes anti-Grepafloxacin, Gatifloxacin, Sparfloxacin. The fourth-generation antibiotics include Trorafloxacin Gemifloxacin and Moxifloxacin (Kocsis, 2012), quinoline resistance usually arises in *A. baumannii* as a result of genetic mutations in the gene encoding DNA gyrase and Topoisomerase IV (Guler and Erac, 2016). Quinolones mainly inhibit the bacterial enzymes DNA gyrase and Topoisomerase IV that have to do with altering the supercoiling of DNA synthesis and thus preventing cell division figure (8) (Correia et al., 2017).

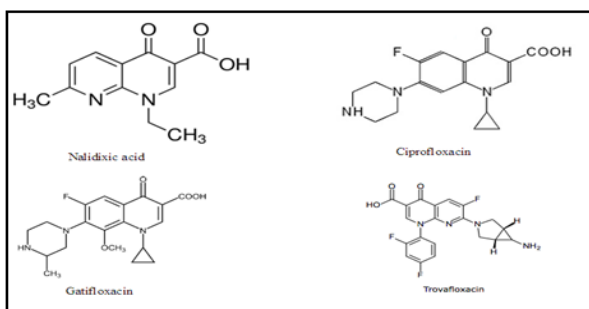


Figure (7): Structure of Quinolones

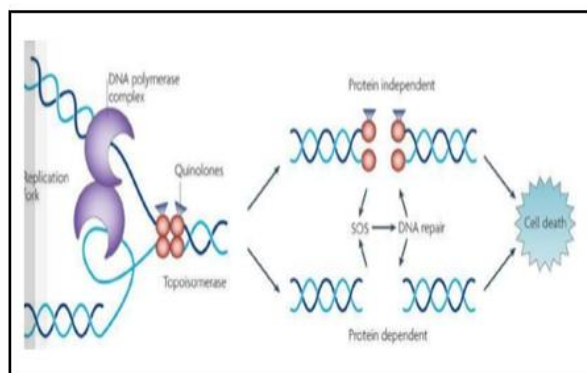


Figure (8): Mechanism action of Quinolones

Tetracycline group

These antibiotics were named because they contained four hydrocarbon rings figure (9). They are bacteriostatic inhibitors of the growth of negative and positive bacteria of the gram stain (Atlas et al, 1995), where they inhibit protein synthesis by blocking the binding of Aminoacyl tRNA to the target ribosome figure (10) (Maleki et al., 2014). One of the most common mechanisms of resistance to tetracyclines is due to flow pumps as well as modulation in the chemical molecules of the target site (Castanheria et al., 2014).

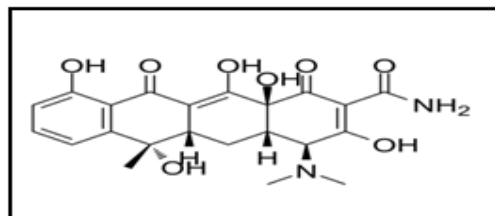


Figure (9): Structure of Tetracycline

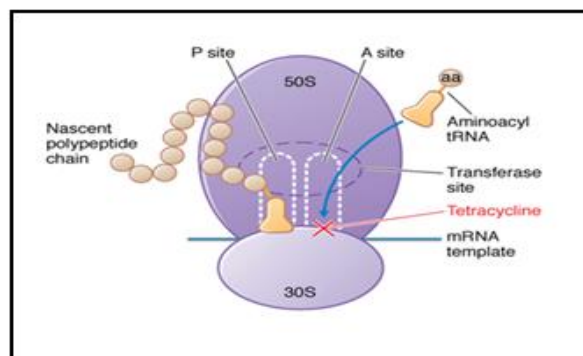


Figure (10): Mechanism action of Tetracycline

Trimethoprim/Sulfonamides

The antibiotic inhibits the enzyme Dihydrofolate reductase necessary in the manufacture of folic acid important in the manufacture of peptides and

nucleotides involved in the formation of nucleic acids in the bacteria figure (11,12)(Brook et al., 2007).

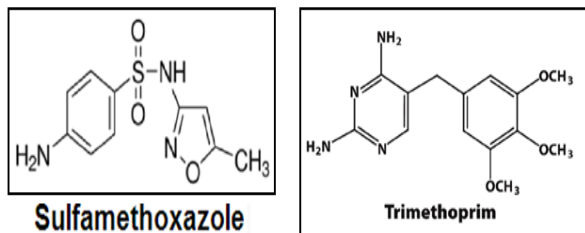


Figure (11): Structure of Trimethoprim/ Sulfonamides

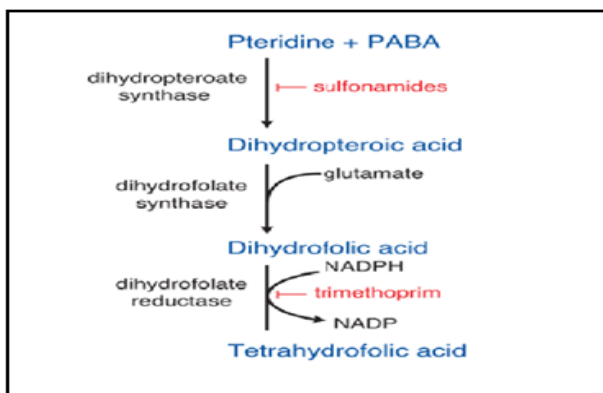


Figure (12): Mechanism action of Trimethoprim/ Sulfonamides

Colistin

This antibiotic belongs to the group Polymyxin figure (13) and is used to control many hospital-acquired infections caused by the negative bacteria of the gram stain with multiple antibiotic resistance, where it blocks the entry of substances through the outer membrane of the bacterial cell, which loses its function leading to the death of the bacterial figure(14)(Bialvaei and Samdi kafil, 2015)

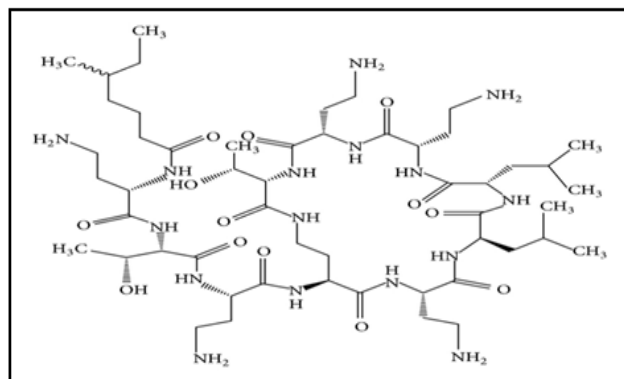


Figure (13): Structure of Colistin

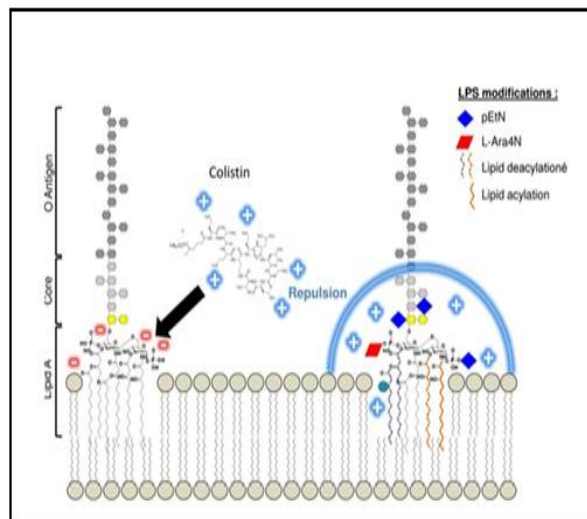


Figure (14): Mechanism action of Colistin

Mechanisms of bacterial resistance to antibiotics

1- Production of beta-lactamase enzymes

Beta-lactamase enzymes are produced by gram-negative and gram-positive bacteria, as these enzymes act to destroy beta-lactam antibiotics before they reach the target site (Almarjani and khadam, 2016). These enzymes are classified into the following:

1. Ambler classification This classification depends on the similarity in the amino acid sequence included in this enzyme, and is divided into four classes:

- **Class A serine β -lactamase:** This category includes several families of broad-spectrum beta-lactamase enzymes (EBLs), including the TEM β -lactamase family. The name came after a Greek patient named Temoniera (Brandt et al., 2017), first known in 1965. In the Enterobacteriaceae family, it has spread to other bacteria including Haemophilus spp., Neisseria spp., Vibrio spp. Likewise, the SHV I -lactamase family was first isolated from Klebsiella spp and E. coli. It was found that the TEM and SHV family enzymes have the ability to analyze the first, second and third-generation Cephalosporins and penicillins such as Ampicillin (Ghafourian et al., 2015). In addition, there is a family of CTX-M β -lactamase, which has activity against Ceftriaxone and Cefotaxime and does not affect Ceftazidime, and was divided according to the amino acid

sequence into five groups: CTX-M9, CTX-M8, CTX-M2, CTX-M1, CTX-M25 (Alyamani et al., 2015).

- Class B serine β -lactamase: it is also called Metallo- β -lactamase that differs from the classes D, C, and A because it analyzes all beta-lactam antibiotics, which includes carbapenem except Monobactam, such as the Aztreonam. This class includes family enzymes VIM, IMP, GIM, SPM, SIM, NDM-1 (Amudhan et al., 2012).

- Class C serine β -lactamase: This class contains AmpC and is called Acinetobacter-Derived Cephalosporinase (ADC) in *A. baumannii*, it is not inhibited by Clavulanic acid and can be inhibited by Cloxacillin (Liu, 2015).

- Class D serine β -lactamase: also known as Class D serine Oxacillinases. This class's enzymes have the ability to analyze Oxacillin and 50% Benzyl Penicillin, Cephalosporins and Carbapenem (Shaikh et al., 2015). This class includes enzymes OXA-58, OXA-51, OXA-24, OXA-23. These enzymes were found in *A. baumannii* bacteria. OXA-23 and OXA-24 were known in several countries including Poland, Iran, and Ireland, and OXA-enzymes were known. 58 and OXA-23 in Saudi Arabia, Croatia, and Italy. (Ibrahimagic et al., 2017).

B- Bush- Jacoby- Medeiros Classification

It depends on the (inhibitor pattern - the basic substance) and it also includes four classes or groups, namely

- First group: Chromosomally encoded cephalosporins that are poorly inhibited with Clavulanic acid.

- Second group: Penicillinase, Cephalosporinase and Carbapenem are widely specialized enzymes, whether plasma or chromosomal encoder that inhibits Clavulanic acid and other beta-lactamase inhibitors.

- Third group: Metallo- β -Lactamase are enzymes that are not affected by all beta-lactamase inhibitors.

- Group IV: includes a specific number of Penicillinase enzymes that are not prescribed and that are not inhibited with Clavulanic acid (Bush and Jacoby, 2010).

2-Possession of a permeability barrier

This mechanism of resistance is specific to bacteria Gram-negative, as changes occur in the outer membrane, as this membrane contains protein

channels called porines, which are channels that allow the passage of substances with few molecular weights from outside the cell into them (Galdiero et al., 2012). There are some types of these porines, initially known as Outer membrane protein F (Omp F) and Outer membrane protein (Omp C) (Szabó et al. 2006). Omp F in *E. coli* is the first membrane protein that has been carefully studied by the X-ray and is similar to two other proteins, Omp F and Omp E. Water-soluble antibiotics can pass through ordinary channels such as beta-lactamase while the lipid-like molecule is more difficult to diffuse through the porines channels (Bhamidimarri et al., 2019). Antibiotic resistance occurs by reducing the number of porines channels or making their diameters too narrow to prevent the antibiotic from entering the cell (Fallah, 2018). This resistance is one of the most dangerous types. When a change occurs in the protein channels, more than one type of antibiotic will be prevented from entering the bacterial cell (Blair et al., 2015).

3-Modification of the target site

• The resistance of beta-lactamase antibiotic

Another method for bacterial resistance to beta-lactam antibacterial is a site change the target of the antibiotic which is the enzymes of PBPs intended to bind to these antibiotics, so the antibiotic becomes inactive (Konaklieva, 2014). This resistance is found in positive and negative bacteria of gram stain (Bhatti et al., 2014).

• Macrolide resistance

Most of the gram-positive bacteria resist antibiotic of erythromycin by producing a methylase or N-methyl transferase enzyme acting on methyl adenine in 23S rRNA in the ribosome and thus the bacteria become resistant to the antibiotic action as they prevent its binding to the 50S subunit (Fallahpour et al., 2017).

• Quinolones resistance

The target site for these antibiotics is the enzyme DNA gyrase, so mutations can occur in the genes of *parC* and *gyr A* encoded by the enzymes above, which makes the bacteria resistant to the action of quinolones (Correia et al., 2017).

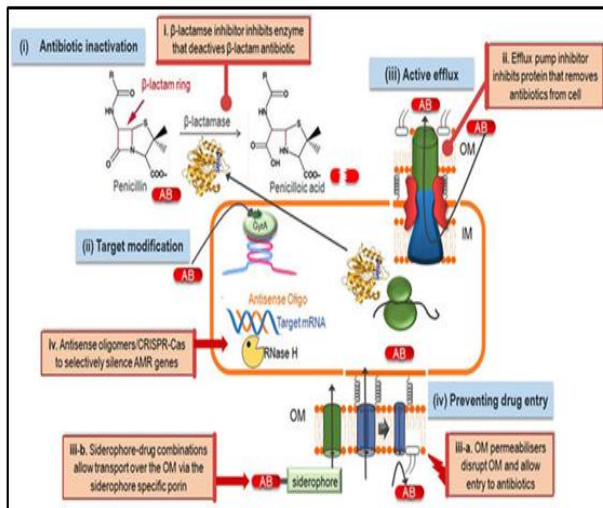


Figure (15): Mechanisms of microbial resistance to the bacteria Gram-negative. The main four methods of antibiotic resistance in Gram negative bacteria (blue boxes) are (i) antibiotic inactivation, for example, the making of β -lactamase enzymes that hydrolyse the β -lactam ring thus deactivating this class of antibiotics; (ii) target modification, for instance modifications in the GyrA protein confers resistance to fluoroquinolones; (iii) active efflux.

- Aminoglycoside resistance

Resistance to the aminoglycoside group of antibiotics is attributed to several reasons, including modification at the target site and that includes a mutation of change in the ribosomal unit (16S rRNA) (Chandra et al., 2017), enzymatic modification of the amino or hydroxyl group of aminoglycoside antibiotics by three classes of Aminoglycoside phosphotransferase (APHs) Aminoglycoside acetyltransferase (AAGs); Aminoglycoside nucleotidyltransferase (ANTs) (Garneau-Tsodikova, & Labby, 2016)

- Rifampin resistance

Mutations in the subunit B of target enzyme RNA polymerase are responsible for bacterial resistance to rifampin (Brandis et al., 2016).

- Sulphonamides resistance

Trimethoprim

There are in the gram-negative bacteria 16 genes responsible for the enzyme dihydrofolate reductase which is the location of the action of the trimethoprim. The bacteria that are resistant to the

trimethoprim produce highly modified DHFR enzymes (Wróbel et al., 2019).

Sulphonamide

Resistance to this antibiotic is obtained by mutations in the gene responsible for the enzyme dihydropteroate synthase (DHPS) (Capasso & Supuran, 2014)

4-Drug efflux pump

There are different types of flow pumps in prokaryotes and eukaryotes that have an important role in the resistance of antibiotics and toxic substances, (Spengler et al., 2017) include.

Major facilitator family (MFS)

Resistance nodulation-division family (RND)

Small multidrug resistance family (SMR)

ATP binding cassette family (ABC) (Lekshmi et al., 2018).

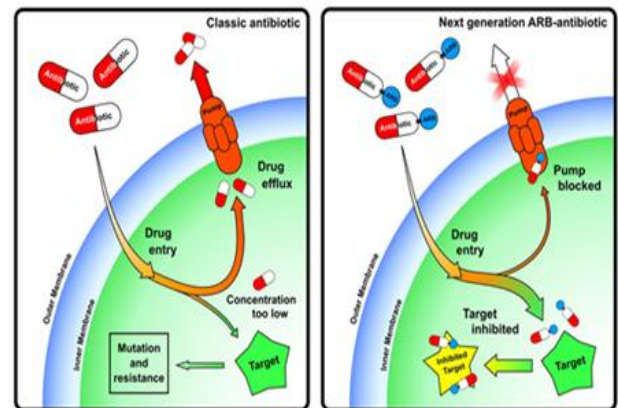


Figure (16): efflux pumps in development of bacterial resistance

5-Increased reproductive material production

Para-aminobenzoic acid is a primary compound that enters the metabolic pathway for the synthesis of folic acid and interacts with the hydroxymethyl dihydropteridine compound with the presence of dihydropterotic synthetase to the synthesis of folic acid (Gorelova, et al., 2017), which is then converted into tetrahydrofolic acid in the presence of dihydrofolate reductase (Zheng et al., 2013). It then converts into pyrimidines and purines, which enter into DNA synthesis. The antibiotic sulphonamide inhibits the action of the DHPS enzyme while the trimethoprim inhibits the DHFR enzyme. The

antibiotic binds to the bacterial enzyme at a rate of 60,000 times higher than the human enzyme binding rate (Chandrashekar Lele et al.,2016).

Bacteria resist these antibiotics by increasing the production of PABA to enter the pathway of synthetic folic acid and thereby competing with the sulphonamide and thus continue synthesis folic acid (Nguyen,2016).

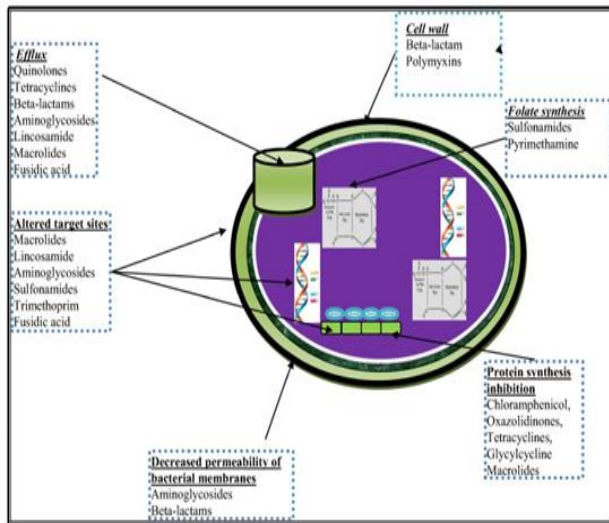


Figure (17): Antibiotic resistance vs. antimicrobial activity mechanism (Shaikh et al.,2015).

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