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Role of Efflux Pump Genes in the Antibiotic Resistance of *Klebsiella Pneumoniae* Bacteria Isolated from Clinical Cases: A Review Paper

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Abstract

Klebsiella pneumoniae causes opportunistic infection, generally influencing debilitated immune systems and immune-compromised and it is a reason for nosocomial diseases. This pathogen is commonly acquired in hospitals causing acute respiratory diseases such as pneumonia. Urinary tract diseases, wound infections abscesses, sepsis, inflammation, and diarrhea. *Klebsiella pneumoniae* possess an array of virulence factors to invade and multiply within the host cell. These include primarily surface antigens, particularly capsular polysaccharide (CPS) (K antigen); Iron-restricting proteins generated by the host bind ferric iron through siderophores; as well as adherence variations accountable for restricting to host cell surfaces, for example, type 3 and 1 fimbriae, and non-fimbrian adherence proteins. Antibiotic resistance leads to more effects of these infections. Antibiotic resistance of *K. pneumoniae* to carbapenems is mediated by a numeral of mechanisms, counting the production of potent carbapenems, as well as beta-lactamases with weak carbapenemase activity in association with membrane permeabilization. Colistin is widely considered the last line of defense against KPC-producing *K. pneumoniae*. However, there are continuous reports of colistin-resistant *Klebsiella* isolates. The effectiveness

of antibiotics in killing bacterial cells largely depends on their ability to inhibit specific cellular functions through interactions with drug targets. The main targets of antibiotics include the cell wall, cell membrane, DNA, RNA, as well as folate and proteins.

Keywords: *Klebsiella pneumoniae,* Antibiotic, Resistance, Efflux pumps.

Introduction

Klebsiella spp. is a Gram-negative bacteria belonging to the Enterobacteriaceae family [1]. Enterobacteriaceae are the most common group of pathogens and groups of non-pathogenic Gram-negative bacilli [2]. This bacterium was isolated by Karl Friedlander from the lungs of an infected patient with pneumonia [3], called Bacillus Friedlander, which is a severe and fatal pneumonia factor [4]. It is generally rod-shaped and may appear as diplococci, it is usually encapsulated bacteria; its diameter is (0.3-1) micrometers and its length is (0.6-6) micrometers [5]. It produces large, soft, raised, very mucous colonies when grown on a solid medium such as MacConkey's medium and is pink in color due to lactose fermentation [6]. It is a non-mobile substance that is widely distributed in the environment.

Pathogenicity of *Klebsiella pneumoniae*

Klebsiella pneumoniae is an unscreened microorganism, representing a continuous healthiness interest for immunocompromised patients, especially the elderlies older, and children. Records of *K. pneumoniae* isolation from different sources, a large number of which express multidrug resistance (MDR) phenotypes, are expanding [7]. Pathogenesis of *Klebsiella* spp. depends on the type of infection and the mode of infection that adheres to and attacks epithelial cells, enterocytes, endothelial cells or urothelial cells of the upper respiratory tract followed by colonization of the mucous membranes [8]. The typical *K. pneumoniae* infection is caused by a cunning pathogen that generally targets weakened immune systems and tends to lead to nosocomial infections [9]. Formerly healthy people may get ill from a subset of extremely virulent *K. pneumoniae* serotypes with high capsular polysaccharide production, which poses a serious risk to the community obtained illnesses including, pyogenic liver abscess, meningitis, necrotising fasciitis, endophthalmitis, and severe pneumonia. *K. pneumoniae* uses a variability

of virulence factors, particularly capsular polysaccharides, lipopolysaccharides, fimbriae, outer membrane proteins and causes of iron acquisition and nitrogen source utilization, for survival and immune circumvention during infection [10, 11]. It causes mainly opportunistic infections for healthy people and nosocomial infections commonly acquired in hospitals, and it lead to acute respiratory diseases such as pneumonia. [12]. Further infections produced by this organism these including urinary tract infections, wound infections Abscesses, sepsis, inflammation, diarrhea [13] and tract infection after *Escherichia coli*, however, the pathogenesis higher than it counterpart [14]. Due to the position of the reproductive organs and susceptibility to infections, women are eight times more likely to develop a urinary tract infection by remaining asymptomatic for a long time [15].

Virulence factors of *Klebsiella pneumoniae*

Klebsiella pneumoniae employs a variety of virulence factors to invade and replicate in the host cell. Bacteria have at least one surface antigen, particularly capsular polysaccharide (CPS) (K antigen); (b) Siderophores responsible for the required ferric iron that is hidden by host iron-binding proteins; and (c) adherence variations responsible for the required adhesion to host cell surfaces, such as type 1 and 3 fimbriae and non-fimbrian adherence proteins [16].

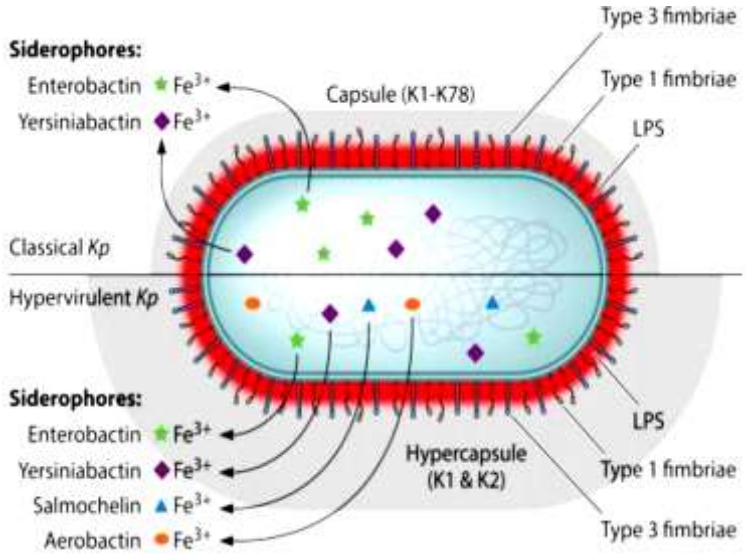

Figure 1: Well-characterized virulence factors in classical and hyper virulent *K. pneumoniae* [13].

***Klebsiella pneumoniae*'s antimicrobial resistance**

The significant emergence of antimicrobial resistance and the absence of development of new antimicrobial drugs have progressively reduced treatment decisions for bacterial infections [17]. Multidrug-resistant organisms reason serious community-acquired and nosocomial diseases, limiting the therapeutic options using available antibiotics. *K. pneumoniae* isolates are in some reports resistant to cephalosporins, carbapenems, trimethoprim, sulfamethoxazole, fluoroquinolones, and aminoglycosides [18]. Infections caused by *K. pneumoniae* are associated with common healthcare and community-acquired infections including pneumonia, urinary tract, wound, and blood infections [19]. However, resistance leads to more serious effects of this infection [20]. Resistance of *K. pneumoniae* to carbapenems is mediated by a numeral of mechanisms, including the production of potent carbapenems, as well as beta-lactamases with weak carbapenemase activity in association with membrane permeabilization [21]. Colistin is widely viewed as the last line of defense against KPC-producing *K. pneumoniae*, nevertheless, reports of colistin-resistant *Klebsiella* isolates are continuously increasing [22]. One of the most important features. The case of biofilms is antimicrobial-resistant biofilms. They are up to 1,000 times more resistant to antibiotics Planktonic cells [23].

Mechanisms of antibiotic action

Antibiotics work in contradiction to bacteria in two diverse methods, either as a bactericidal agent or as a bactericidal factor. The denotation of its presence as a bacteriostatic or bactericidal factor seems identically vibrant to microbiologists. Factor, that inhibits the growth of bacteria, that is to say, saves the bacteria in a constant growth phase, identified by way of bactericidal inhibitors, destroys the bacteria mentioned like bactericidal [20]. The response of antibiotics to kill cells of bacteria is mostly dependent on the inhibition of certain cellular functions concluding a drug-target interaction. The main targets of antibiotics are the cell wall, cell membrane, DNA, RNA, folate, and protein synthesis [24].

1. **Antibiotics targeting cell wall**

Bacterial cells are enclosed by a cell wall that protects them from harsh environmental changes. Therefore the bacteria are classified into Gram stain positive and Gram stain negative [25].

Gram negative bacteria's cellular walls are made up of a fine peptidoglycan layer, which is surrounded by an outer membrane. Nonetheless, Gram-positive bacteria lack outer membranes and have a single thicker peptidoglycan layer, as opposed to Gram-negative bacteria [26]. Peptidoglycan is an elongated glycopolymer that provides crosslinking among glycan bands and peptide chains protruding from sugars that produce crosslink from one peptide to another [27]. β-lactams and glycopeptides inhibit the production of cell walls. The main target of β-lactams, like cephalosporins, penicillins, monobactams, and carbapenems, is PBP. Meanwhile the beta-lactam ring has a similar construction to the D-alanyl D-alanine moiety of peptides, it contains certainly linked to PBP, and similar PBP cannot be obtained on behalf of new peptidoglycan combination. Therefore, disruption of the peptidoglycan layer reasons bacterial lysis [28]. Furthermore beta-lactams, glycopeptides (vancomycin, bacitracin, and other) likewise inhibit cell wall combination [29]. Glycopeptides are known to attach with the D-alanyl D-alanine moiety of the peptide cross chain of the peptidoglycan subunit. Consequently, the major antibiotic agent vancomycin prevents the formation of a bond between the PBP subunit and D-alanyl, and thus cell wall synthesis is too inhibited [30].

2. Antibiotics targeting cellular membrane

Polymyxins interrupt the construction of the outer or inner cellular of bacteria through interaction by lipopolysaccharide or phospholipids, correspondingly. When polymyxins attach with lipopolysaccharide or phospholipids, they adjust the cellular membrane construction, therefore this membrane becomes further leaky. Consequently, osmotic balance is disturbed, cellular molecules leak out, inhibiting respiration, and water absorption increases, leading to cell death [31].

3. Antibiotics targeting nucleic acid

Throughout procedures called transcription or transcription, DNA cleavage is important, wherein DNA gyrase of bacteria plays an essential function. This enzyme is identified to inhibit by fluoroquinolones [32]. Rifampicin, unique of the rifamycins, arrests the initiation of the synthesis of RNA via obstructive RNA polymerase of bacteria. Due to the inhibition of DNA gyrase enzyme and RNA polymerase enzyme, DNA synthesis is obstructed [33].

4. **Antibiotics targeting protein**

Ribosomes play an essential function in processes of protein synthesis. The 70S ribosome of bacteria consists of 30S and 50S subunits [34]. Antimicrobials, targeting the subunits of 30S or 50S, arrest protein biosynthesis [35]. Tetracyclines antibiotic and aminoglycosides antibiotic are identified to target the 30S, with the antibiotics macrolides, clindamycin, linezolid, chloramphenicol while streptogramin targeting the 50S subunit. Consequently, antibiotics targeting the subunits (30S or 50S) arrest protein combination [35].

5. **Antibiotics targeting the folic acid metabolism**

Sulfonamides and trimethoprim inhibit various stages in process of folic acid metabolism [35].

Efflux pumps system

Efflux pumps are recognized as carriage proteins that are active pumping systems, which are essential in the unloading of toxic elements since cells into the extracellular milieu. The efflux pumps are found not alone in Gram negative and Gram positive bacteria, nevertheless also in cells of eukaryotic [36]. It is accepted that overexpression in these pumps is associated with drug resistance [37]. Efflux pumps reduce the medication concentration deprived of modifying the antibiotic itself. Decreased outer membrane permeability results in a reduction in the efflux of antimicrobial substances. So, this reasons resistance in many imperative medical microorganisms. Stuart Levy *et al.* discovered the first efflux pump system, which belongs to *Escherichia coli* and is known tetracycline efflux pump [38]. The membrane proton ascent initiates this pump, which is a secondary active transporter [39]. The resistance is limited by plasmids or chromosomes. Consequently, efflux pumps are thought to be defense mechanisms against certain antibiotics of different classes that are employed by a wide variety of bacterial species [40]. Tetracyclines, beta-lactams, sulfonamides, cationic peptides, phencols, oxazolidinones, quinolones, rifamycins, lincosamides, aminoglycosides, and streptogramins are a few examples of these antibiotics. Though the structure and operation of the outer membrane was previously thought to be responsible for the bacterial resistance to a range of antimicrobial agents, particularly in Gram-negative bacteria [41]. Efflux pumps have a fundamental role in antibiotic resistance in the microbes. These pumps are recognized to specialize in the resistance

of lone one complex or principal to an extensive range of chemicals, such as cancer chemotherapy agents, biocides, detergents, antimicrobial peptides, and antibiotics, colorants, and heavy metals that released from the bacterial cell, which might prompt to multidrug resistance (MDR). As for mechanisms of efflux pumps, these pumps are activated by regulatory gene mutations or signals of the environment and both need energy [42]. Resisting cells utilize ATP-driven transporters and/ or proton-driven counter transporters to conjugate the toxic combinations that allow common movement inside the cell by passive diffusion method. For the explanations these reasons, resisting of bacteria is the little concentration of antibiotics inside the cell, which might make the chance of resisting mutations. There are two chief kinds of mechanisms cause a decrease in the concentration of antibiotics in the cell, because of efflux pumps and alterations in cell surfaces such as reducing the numeral of entry channels, such as porins, which are adaptive and mutational kinds of resistance. These two mentioned factors are of abundant significance in accelerating antimicrobial resistance in pathogenic microorganisms. The both of influx and efflux of endogenous or exogenous complexes are controlled via membrane transport proteins [43]. About 5-10% ratio of all genes of bacteria are associated with transport and the most of mentioned genes encoding efflux pumps.

Classification of the efflux pump systems

The efflux proteins have been characterized into five distinct super families': small multidrug resistance (SMR), resistance nodule division (RND), ATP binding cassette (ABC), major facilitator (MF), and multidrug and toxic complex extrusion (MATE) [44].

1 Major facilitator (mf) super family

The major facilitator superfamily (MFS) is considering one of the two biggest of membrane transport proteins families [45]. MF transmitters comprise around five hundred amino acids [46]. MFS permeases typically contain 12 or 14 transmembrane α-helices [45] by a large cytoplasmic loop amid helices VI and VII. The MFS and ATP-binding cassette (ABC) [47] are two superfamilies, universally initiated in whole organisms. They control uniport, symport and antiport processes [48]. MFS transport sugar [49], drugs, and Krebs cycle metabolites [50]. This

efflux pump transfers aminoglycosides, tetracycline, rifampin, fluoroquinolone, macrolides, chloramphenicol, lincosamide, and pristinamycin out of the organism's cell [51].

2 Multidrug and toxic compound extrusion (mate) super family

MATE transporters require a similar quantity to MFS transporters, which are composed of approximately 450 amino acids and 12 α-helical segments [46]. First, they were identified like a drug transporter family of bacteria, but now they are identified to be present in almost all eukaryotes and prokaryotes organisms [52]. The MATE family causes multidrug resistance via transport broad-spectrum therapeutic combinations transversely the cellular membrane [53].

3 Resistance nodulation division (rnd) super family

Compared to MFS transporters, which require 12 α-helical segments and almost a thousand amino acids, resistance node division (RND) transporters require a larger size [46]. RND pumps are main sources of multidrug resistance, particularly in Gram negative bacteria [42]. The outset inhibitor detected was phenylalanine-arginine β-naphthylamide (PAβN) that blocks RND-type efflux pumps [54]. This kind of efflux pumps carriage beta-lactams, fusidic acid, and sulfonamides out of the organism cell [51].

4 Small multidrug resistance (smr) super family

The family of SMR protein consists of the proteins that are multidrug transporters bacteria. As showed by their name, they are considered minor proteins containing approximately 100 to 140 amino acids and require four Tran's membrane α-helical segments. The finest identified SMR pump is EmrE that is found in *Escherichia coli* and donates to resistance in opposition to each of Ethidium bromide (EtBr) with methyl violet [55]. This type of efflux pump removes erythromycin, sulfadiazine, and tetracycline from the bacterial cell [51].

5 ATP binding cassette (ABC) superfamily

The efflux pumps of ABC-type consist of proteins that use substratum, like numerous drugs, xenobiotics (containing toxins and drugs of food) besides endogenous complexes to carriage them across membranes [56]. Whereas ABC superfamilies of membrane transporters pump their substratum across the cellular membrane, meanwhile they are considered essential active transporters, and provide the energy needed for transport since ATP hydrolysis [57]. This is the

situation for microorganisms as well, ABC efflux transporters that assist the transport of together endogenous and exogenous complexes across membranes are normally displayed in the cellular membranes of many tissues of the human body, for example, the testis, lungs, heart, brain, gut, kidney, liver, and the mammary gland, uterus, and placenta [58]. Particular essential memberships of the ABC superfamily, like breast cancer resistance protein (BCRP), multidrug resistance-associated proteins (MRPs), and P-glycoprotein (P-gp), require a significant role in the drug detoxification and pharmacokinetics and metabolites of drugs that promote drug excretion such as in urine at the kidneys and secretion of the intestine in bile at the liver [59]. ABC proteins can be found in both normal and malignant cells. Drugs are carried across membranes by ABC-type efflux pumps, which support the presence of malignant cells and the progression of malignancy [60]. The conveyed complexes are either antibiotics or malignancy drugs, and resistance that develops toward numerous medications is identified as multidrug resistance (MDR) [60]. This kind of efflux pump transports the antibiotics aminoglycosides, tetracyclines, rifampicin, fluoroquinolones, macrolides, chloramphenicol, and lincosamides into the extracellular milieu [57].

The structure of efflux pumps

Membrane-spanning efflux pumps are found in bacteria, and they are used to release hazardous complexes ranging from organic compounds to heavy metal ions and antibiotic medications. These efflux pumps' overall structure is largely intact: by an exterior membrane channel subunit that permits the release of hazardous substances into the environment, connected to an inner membrane energy transport subunit through an adapter protein [61]. ATP hydrolysis energy is used to generate drug efflux pumps, which are the primary active transporters and can be classified based on substrate specificity, evolutionary relationship, and energy source. They are members of the ABC superfamily. Drug pumps known as secondary active transporters use the sodium motive force (SMF) or the proton motive force (PMF) to unload the medicines. For H+/drug or Na+/drug, this system functions as an antagonist. MF, SMR, RND, and MATE superfamilies are among the many families whose secondary active transporters are connected [62]. Changes are observed in the structures of the flow systems as a result of the type of cellular

wall of bacteria. A single pump protein can speed up efflux in Gram-negative bacteria, whereas a pump system made up of three protein components can speed up efflux in Gram-positive bacteria [63]. Along with a channel protein that serves as an outer membrane factor (OMF) or outer membrane channel (OMC) and a membrane fusion protein (MFP) that maintains continuous communication between these two proteins, this three-part system includes the cell membrane-located transporter efflux pump protein [64].

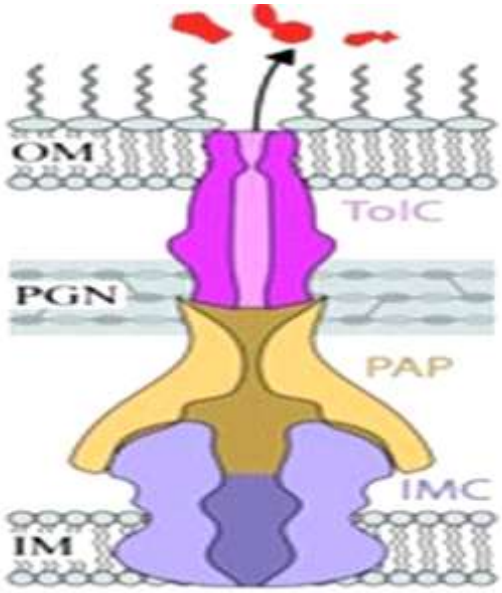

Figure 2: Tripartite efflux pumps [61].

Efflux pump system

acrAB :- One efflux system included for this resistance phenotype is the multidrug efflux system AcrAB which is encoded in *K. pneumoniae* through the acrRAB operon. In this operon, acrR encodes an AcrAB repressor, whereas acrA and acrB encode a 40-kDa peripheral lipoprotein committed to the inner membrane, which links the outer and inner membranes and a 113.5-kDa integral membrane protein with 12 membrane-spanning α-β.-Helices, located in the cytoplasmic membrane, respectively [65].

OqxAB:- goes to the resistance nodulation division (RND) Family [66]. OqxB is an RND (resistance partition) efflux pump, which has developed as a contributing factor to antibiotic

resistance in *Klebsiella pneumoniae*. The spread of multidrug resistance is a result of OqxB being transferred horizontally and being present in other Gram-negative bacterial pathogens, such as *Escherichia coli*, *Enterobacter cloacae*, and *Salmonella* [67].

Efflux pump genes and their role in antibiotic resistance

Antimicrobial resistance is a global issue that affects all countries and people, regardless of wealth or social status. This problem is expected to kill an estimated 50 million people and cost the global economy $100 trillion by 2050 [69, 70]. Therefore, the need for new drugs, delivery technologies, and bacterial diagnostics is critical. In the era of antibiotic resistance, *Klebsiella pneumoniae* is one of the most concerning infections. Liver abscesses, UTIs (urinary tract infections), and pulmonary infections are all caused by *K. pneumoniae* [71]. Antibiotics have been widely used to treat infectious diseases for more than 70 years, leading to antibiotic resistance. The significant increase in the prevalence of infection is due to XDR (extensively drug-resistant) and MDR (multi-drug-resistant) bacteria [72, 73]. It has recently been recognized that overexpression of the efflux pump, one of several resistance mechanisms exhibited by *K. pneumoniae*, produces low-level cross-resistance to antibiotics. Regarding antibiotic resistance, the efflux pumps AcrAB and OqxAB have been extensively investigated in *K. pneumoniae* and other members of the Enterobacteriaceae [74]. MDR strains represent a difficult treatment challenge, especially for the elderly, immunocompromised patients, and children with immature physiology. There are many reasons that can contribute to the emergence, growth, and spread of antibiotic resistance, including the use of medical devices, limited diagnostic facilities, and the acquisition of new resistance genes. The AcrAB and OqxAB efflux regulons have received the most attention in the Enterobacteriaceae family, especially in *K. pneumoniae*, and have been linked to antibiotic resistance [75]. Gabr *et al.* [76] found that the function of efflux pumps (OqxAB) conferred resistance to fluoroquinolones, tetracyclines, trimethoprim, and chloramphenicol in clinical isolates of *K. pneumoniae*. Several genes associated with antibiotic resistance, including those genes acrAB and oqxAB and the transcriptional activators ramA and soxS, have been found to be overexpressed in eravacycline-nonsusceptible *K. pneumoniae* isolates [77]. AlMatar *et al*. [70] showed that acrA and acrB

were overexpressed in 29 (63%) and 24 (52%) *K. pneumoniae* isolates. Most MDR- *K. pneumoniae* isolates were found (65%) had upregulation and/or increased expression of acrB and/or oqxB, which is consistent with our findings Park *et al.* [78] who reported that *acrB* and *marA* expression levels were significantly greater in the tigecycline-resistant group than in the tigecycline-susceptible group. Elgendy *et al.* [79] documented that 13% of *K. pneumoniae* strains overexpressed acrAB and oqxAB, both of which are associated with tigecycline resistance [80]. Overexpression of *oqx-AB* genes appears to reduce exposure to a number of antibiotics such as quinoxaline compounds, chloramphenicol, quinolones and fluoroquinolones, and trimethoprim by more than four-fold. Furthermore, the OqxAB multidrug efflux pump system facilitated reduced exposure to detergents and disinfectants such as benzalkonium chloride and triclosan [81]. AcrB chaperone increased the MICs of piperacillin/ tazobactam (TZP), ceftolozane/ tazobactam (C/T), tigecycline, and ciprofloxacin, suggesting that acrB plays a role in reducing allergies [82]. Furthermore, the OqxAB multi-drug efflux pump facilitated reduced exposure to detergents and disinfectants such as benzalkonium chloride, and triclosan [81]. MDR isolates of *K. pneumoniae* were attributed to overexpression of *oqxAB* genes, as demonstrated by gene expression analyses. Transfer of *oqxAB* genes from the chromosome to the plasmid resulted in an increase in *oqxAB* efflux pump expression that was 80-fold higher, resulting in MDR phenotypes. Over the past few decades, there has been an increase in the number of studies reporting the extent to which the OqxAB efflux pump contributes to reducing exposure to different classes of drugs, as well as the prevalence of the *oqxAB* gene complex in bacteria derived from human and animal sources [83]. The OqxAB efflux pump has also been linked to heterologous tigecycline resistance in Salmonella, which was attributed to overexpression of the AcrAB-TolC and OqxAB efflux pumps, as PAβN restored tigecycline sensitivity in heterologous resistant isolates and reduced tigecycline accumulation in cells [84]. Jomehzadeh *et al*. [84] documented that 21.7% of *K. pneumoniae* isolates were not susceptible to ciprofloxacin due to the presence of *oqxA* and *oqxB* genes. In addition, the expression of both *oqxA* and *oqxB* was low during initial exposure [85]. However, increasing the dose of ciprofloxacin increased *oqxB* expression by 22.8-fold. Veleba *et al.*[86] confirmed the

importance of *ramA* and *rarA* in the overexpression of *acrAB* and *oqxAB*, as well as their contribution to tigecycline resistance in *K. pneumonia*, *E. cloacae* and *E. aerogenes*. The transcriptional activators *marA*, *ramA* and *soxS* may play a role in *acrAB* regulation. Therefore, the increase in *acrAB* expression appears to be related to the overexpression of *marA* in MDR-isolates *K. pneumoniae*. The regulatory mechanisms governing the OqxAB efflux pump in *K. pneumoniae* have been extensively investigated. Interestingly, among ciprofloxacin-resistant *K. pneumoniae* isolates, upregulation of OqxAB efflux pump encoding genes was detected. The transcription factors ramA and rarA stimulate the OqxAB efflux pump. The observed overexpression of *oqxA* and *oqxB* in this study may be a result of increased expression of *rarA* rather than other transcriptional regulators. Overexpression of RarA enhances the expression of the downstream efflux pump processes, *oqxAB* and *acrAB* [86]. The *RarA* gene has been detected in the genomes of a variety of enterobacteria, including Enterobacteriaceae, *Serratia proteimaculans*, and *Coppa pneumoniae*. In the absence of *soxS*, *marA*, or *rob*, plasmid-mediated overexpression of *rarA* can give rise to MDR phenotypes in *K. pneumoniae* or *E. coli*, however, it requires the assistance of a functional AcrAB efflux pump. A transcriptomic and phenotypic microarray study revealed that *rarA* in *K. pneumoniae* is associated with cell envelope biogenesis, post-translational modification, and transport proteins, thereby improving growth under the stress of several classes of antibiotics, including beta-lactams, minocycline, fluoroquinolones (FQs), foraltadone. , polymyxin B, and sanguinarine. Jiménez-Castellanos *et al*. [87] showed that *rarA* and *ramA* regulate the OqxAB efflux pump, however, *ramA* and *soxS* regulate the AcrAB efflux pump, and all of these regulators regulate TolC in *K. pneumoniae*. The most important transcriptional regulators in *K. pneumoniae* that control antibiotic sensitivity are *ramA*, *marA*, *soxS*, and *rarA*. One *GntR* regulator, *oqxR*, was discovered close to *oqxA* and *oxqB* was able to reduce the expression of *oqxAB* genes [86]. The OqxAB efflux pump is regulated by *ramA* and *rarA* (Ara C-type transcriptional activators) and *oqxR* (GntR-type transcriptional repressor) [75]. Furthermore, *rarA* and *oqxB* transcript levels were shown to be greater in tigecycline-resistant *K. pneumoniae* isolates compared to tigecycline-susceptible strains [88].

Conclusion

The concentration of drugs is decreased by efflux pumps without altering the antibiotic itself. The efflux of antimicrobial agents is decreased due to decreased outer membrane permeability. Consequently, this results in resistance in several essential clinical microorganisms that are organized through plasmids or chromosomes. Many bacteria use efflux pumps as a method of resistance against different antibiotics, which include tetracyclines, beta-lactams, macrolides, aminoglycosides, streptogramins, lincosamides, phencols, oxazolidinones, pyrimidines, quinolones, rifampicins, sulfonamides, and cationic peptides. The mechanisms of antibiotic resistance of *K. pneumoniae* are omplicated and various. Therefore, we should give insights into suitable strategies to conflict this important pathogen. How to avoid and to treat infection has developed a crucial problem to be resolved. It is important to control the main antibiotic resistance genotypes for the balanced use of antibiotics.

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