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Efflux Pumps Role in the Emergence of MDR Bacteria

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ABSTRACT

The emergence multidrug tolerance is the most threatening obstacle for the population health. During the last years, transporting pumps are implicated in the emergence of antibiotic resistance. More trans-membrane proteins have been observed in prokaryotes, archae-bacteria, fungi, and eukaryotic cells, involved in transferring various types of toxic substances out of cells. The upgrowth of resistance to various antibiotics is attributed to the spread of genes encoding different efflux pump proteins through horizontal transfer mechanisms. Antibacterial tolerance is obtained as a result of the encoding of efflux pump proteins, which increases the efficiency of pumps in eliminating the toxic substance by altering the types of amino acid involved in the efflux pump structure. There are five families belonged to efflux pumps protein. The transport proteins found in the cytoplasmic membrane have been involved in the evolution and spread the phenotype of antibiotic tolerance among bacterial strains. So, Perception the physiological function of MDR transport pumps still requires more research due to the sustained capacity of bacterial cells to manipulate and degrade antibiotics.

Key words:
Efflux pumps; Antibiotic resistance; MATE;RND; Inhibition mechanisms.

INTRODUCTION

During the last years, more trans-membrane proteins have been observed in prokaryotes, archaebacteria, fungi, and eukaryotic cells, involved in transferring various types of toxic substances out of cells [1]. Current studies have demonstrated the presence of five classes of efflux pumps in microorganisms and cancer cells that involve Moncarboxylate transporter (MCT),Multidrug resistance proteins (MDR,P-glycoprotien), Multidrug resistance -associated proteins (MDPs) ,Peptide transporters (PEPT) ,and Na+ phosphate transporters (NPTs)[2]. Based on the required energy sources, the transport system in bacteria and archaea can be grouped into (i) the channels which permit the passage of solutes without restrictions and consuming energy, (ii) the primary transport system that depends on electrochemical gradients derived from the light ,and the energy of redox and chemical required to transport solutes like ATB-binding cassette (ABC)transports,(iii) the secondary transport system that is employing the proton motive force (PMF) or sodium motive force (SMF) to pump and uptake solutes ,includes unioport channels, symport channels and antiport channels,(iv) protein secretion system that needs ATP and proton gradient or sodium gradient to translocate proteins through the plasma

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membranes,(v) Phosphoenol-pyruvate phosphotransferase systems (PTS) that requires phosphoenol pyruvate to phosphorylate and transfer sugars[3]. Many individuals related to the SMR, the ABC, RND, and MFS were recorded among the transporters distributed in bacterial genome and members of the ABC superfamily were abundant among prokaryotic species due to the existence of transport pumps. Furthermore, RND is the only one of five transport system super families identified in Gram-negative bacteria. Individuals related to SMR, ABC, RND, and MFS were determined among the many transporters distributed in bacterial genomes, and the ABC superfamily members are the most common in prokaryotic organisms. Furthermore, RND is only one of five transport system families identified in Gram-negative bacteria [4]. The surface of bacterial cell contains active transport proteins called efflux pump that reduce the concentration of antimicrobial agents by expelling them outside the cell [5]. Some of genes responsible for encoding efflux pumps found on bacterial chromosome such as Teta and CmlA that conferred bacteria inheritance resistance towards defined antibiotics. In addition, there several of efflux pump genes are carried on transposons (MefA and MefE),plasmids(OqxAB, qax, qepA, and tet), or integrons(OqxAB, qax, qepA, and tet)[6] The genes encoding transport proteins are determined in both bacteria that either susceptible or resistant to antibiotics . Antibacterial tolerance is caused from the high levels of the encoding of efflux pump proteins ,which increases the efficiency of pumps in eliminating the toxic substance by altering the types of amino acid involved in the efflux pump structure [7]. Several articles have revealed that transporting pumps are implicated in the emergence of antibiotic resistance. In 1980, tetracycline resistance was observed in Enterobacteriaceae associated with efflux pumps [8].

MDR efflux pumps types

The plasma membrane, which is maintains the integrity of the cytoplasm, limits the transduction of the substances of a hydrophilic or hydrophobic nature a cross the membrane. The proton motive force obtained from the difference in pH gradient and electrical potential across membrane, organizes the transduction of solutes [3]. The transport proteins found in the cytoplasmic membrane is involved in the evolution and spread the phenotype of antibiotic tolerance among bacterial strains. As exhibited in figure(1)Proteins composed of efflux pumps that act as transporter can be divided to five families including the ATP-binding cassette (ABC), The major facilitator super families (MFS), the resistance nodulation division (RND),the multidrug and toxic compound extrusion(MATE) ,and the small multidrug resistance (SMR) families [9].

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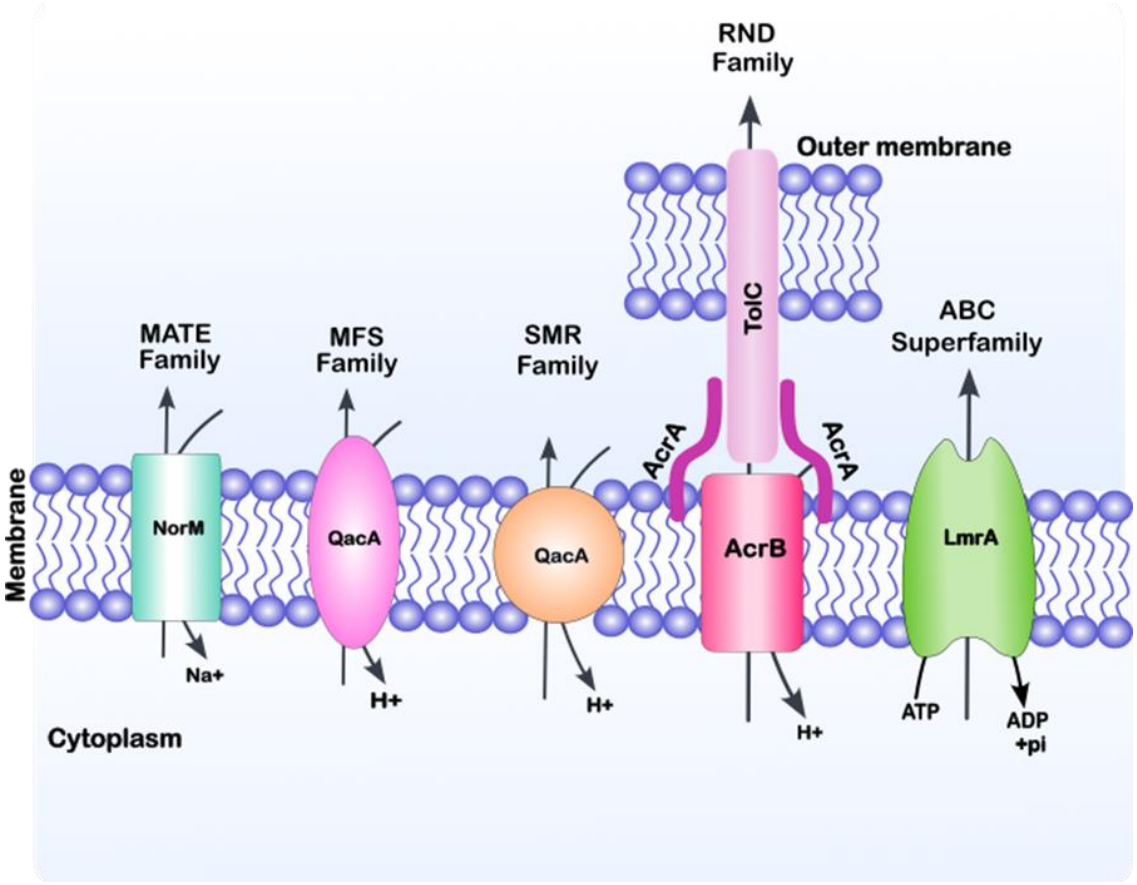

Figure(1): The efflux pumps structure (in the current review)

Multidrug and toxic compound extrusion (MATE)

This family is considered the major protein transporters distributed among livening organisms such as bacteria, mammalians, as well as plants. Depending on the results of Phylogenetic analysis of the known sequences, the MATE superfamily have been grouped into (i) bacterial MATE efflux pumps including NorM and DinF ,(ii) eukaryotic MATEs which classified into yeast - fungi MATEs, plant MATEs, protozoan MATEs; and animal MATEs,(iii) bacterial and archae bacterial MATEs[10].The related members of this family were assumed to be cation transporters that remove metabolic organic cations or xenobiotic organic cations out of the cell [11]. Among transporter substances, fluroquinolones ,aminroglycosides ,and cationic dyes (especially acriflavine and ethidium bromide) can be identified and pumped out the bacterial cells using numerous MATE transporter. It is obvious that many of MATE transporters utilize Na ions rather than H ions to pump out antimicrobial agents especially where the concentration of H ions is reduced[12]. Depending on the similarity and the order of the amino acid sequences, MATE transportes in bacteria can be categorized as follows: DinF and NorM superfamilies, which involve two types of transporters whose mechanisms to transport various substances depends on the circulation of H+ ions and Na+ ions through membrane. A variety of Na+dependent DniF transporters were identified in V.cholera like VcmB,VcmD and VcmH are able to extrude Ethedium bromide (EtBr),which are responsible for drug resistance to

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norfloxacin,ciprofloxacin,ofloxacin [11] .Whereas the multidrug resistance to these antibiotics is due to the presence VcmN related to the DniF transports based on H+ driven mechanism[13]. The common construction of NorM and DinF efflux pumps composed of two domains which extend across the membrane. Each domain consists of six tran-smemrane helix (TMH) called the N domain which is assembled from TMH1,TMH2,TMH3,TMH4,TMH5,TMH6 , involves the site responsible for binding with Na+ ion , and the C domain consist of TMH7,TMH8,TMH9,TMH10,TMH11,TMH12. The interface between the amino-terminal domain and the carboxyl-terminal domain forms a central V- shaped cavity capable of binding to substrates [14]. Many studies demonstrated that NorM efflux pumps are utilized from the movement of Na+ through the plasma membrane to assist transporting various substances including sucrose and amino acids [12].

Major facilitator superfamily (MFS)

It is defined as single polypeptide derivative carrier transport a wide range of solutes through bio-membranes depending on electrochemical gradient force. Many studies have demonstrated the electrochemical gradient forces of MFS members are related to (i) the passive transport involving transferring the substances from high concentration to low concentration through plasma membrane until equilibrated ,and(ii) the active transport systems involving transferring substances from low concentration to high concentration consuming energy that acquired from the ATP hydrolysis or the various in an ionic concentration via the plasma membrane[15]. The members related to the superfamily can groubed into 17 families including Sugar porter family (SP),Drug:antiporter 14 spinnner family (DHA14), Drug:antiporter 12 spinnner family (DHA12),Organophosphate :inorganic phosphate antiporter (OPA)family,Oligosaccharide:H1symporter(OHS)family,Metabolite:H1symporter(MHS)family, Fucose-galactose-glucose:H1symporter(FGHS)family, Nitrate-nitrite porter(NNP) family, Phosphate:H1symporter(NHS)family, Nucleoside:H1symporter(NHS)family, Oxalate:formate antiporter (OFA)family, Sialate:H1symporter(SHS)family, Monocarboxylate porter (MCP)family, Anion:cation symporter(ACS)family,Aromatic acid:H1symporter(AAHS) family, Unknown major facilitator (UMF)family, Cyanate permase(CP)family.The suger porter (SP)family is considered the largest family responsible for the removal various substrates such as organic cations, quinate, inositols, hexoses, pentoses, and disaccharides[16] . MFS transporters are divided into 3 major categories : uniporters which expel a single substance without requiring external enrgy; symporters which are transported a substrate combined with an coupling ion, and antiporters which are pumped out a substrate and a co-substrate in two different directions with utilizing the energy supplied from the difference gradient of their linked ion or co-substrate concentration inside bacterial plasma membrane compared to the outside [17].The carrier belonged to Sugar porter family (SP), Oligosaccharide: H1symporter (OHS)family, and Fucose-galactose-glucose:H1symporter(FGHS)family are specific to pump out various types of sugers and the transporters related to Drug:antiporter 14 spinnner (DHA14) family, and Drug:antiporter 12 spinnner (DHA12) family are able to expel drugs and deleterious substances. The different anionic compounds are removed out the cell via the transporters associated to Organophosphate :inorganic phosphate antiporter (OPA)family, Metabolite:H1symporter(MHS)family, Nitrate-nitrite porter(NNP) family,

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Phosphate:H1symporter(PHS)family, Oxalate:formate antiporter (OFA)family, Anion:cation symporter(ACS)family, Cyanate permase(CP)family [15]. All members related to MFS superfamily transporters are characterized by sharing the same structural framework. The structural nucleus of MFS transporters found in tow identical domain .The first part called N-domain composed of six transmebrane helicases (TM1-TM6) and the other portion called C-domain composed of six transmebrane helicases (TM7-TM12). Furthermore, each domain consists of two inverted repeats containing three helicase. At the center of MFS transporters is the binding site which contains remnant associated with the N domain and C domain [18]. MFS transporters can take three different conformational situation either open to inside, open to outside or locked [17]. The protein of the MFS transporters engaged a various motifs composed of very conserved amino acid pattern . Motif A, observed in all members of the MFS , exists in the loop surrounded by the second and third helix domains [15].

Small multidrug resistance (SMR) protein family

In general, it is recognized as small bacterial protein consisting of 100 to 140 amino acid in length integrated in the inner membrane that gives bacterial cells tolerance to a variety of quaternary ammonium substrates (QAC) such as cetyltrimethylammonium bromide (CTAB),and intercalating cationic dyes such as ethedium bromide (Et),crystal violet(CV),and safranin O (SO)[19]. Horizontal gene transfer through plasmid and various types of transposable agents possess a crucial part in transferring the genes encoding to SMR proteins and emergence multidrug resistance among pathogenic isolates. The obtained data from the GEBA institution have been demonstrated that nearly tow third of bacterial genome owing at least one gene count on of the encoding SMR proteins and one third of bacterial genome are encoding more than one SMR proteins. Gdx and Qac genes are most prevalent SMRs genes found in bacterial genome including Actinobacteria, Proteobacteria and Bacteroides, and Firmicutes [20]. The bacterial multidrug transporter family is made up of five to fourteen transmembrane strands and contributes in circulating a various types of substance like peptides, complex carbohydrates, metals in various ionic state utilizing electrochemical proton gradient or ATP-dependent mechanisms. The SMR proteins contrast with other efflux pump proteins in thier capacity to extrude lipophilic compounds, especially quaternary ammonium compounds(QAC) and different antibiotics [19]. The members of SMR family are identified into three subgroups: (i) the small multidrug pumps (SMP), (ii) suppressor of groEL mutation proteins (SUG), and (iii) paired small multidrug resistance proteins (PSMR)[21].

Resistance nodulation division (RND) family

It's an extended family of transporters determined in bacteria. It expels various substrates including metabolites, antibiotics, toxins, or metal ions. Some types of RND are associated in transferring of the quorum sensing molecules and siderophores. According to the nature of the export substrate, members of RND family can be categorized to heavy metal efflux (HME), and hydrophobic and amphilic efflux (HAE) pump [22]. The structure of RND include three major components as follows: an outer membrane protein (OMP) , an inner membrane protein(IMP),and a preplasmic membrane fusion protein that connects the inner and outer

components. Many studies have been demonstrated the AcrAB-TolC pump found in *E.coli* and Mex pumps in *P. aeruginosa* are responsible for multidrug resistance to extensive range of classical antibiotics[23].Destruction of at least one of the main components of efflux pump disrupt its function. The component of efflux pumps are distributed in different positions of bacterial cell wall [24].

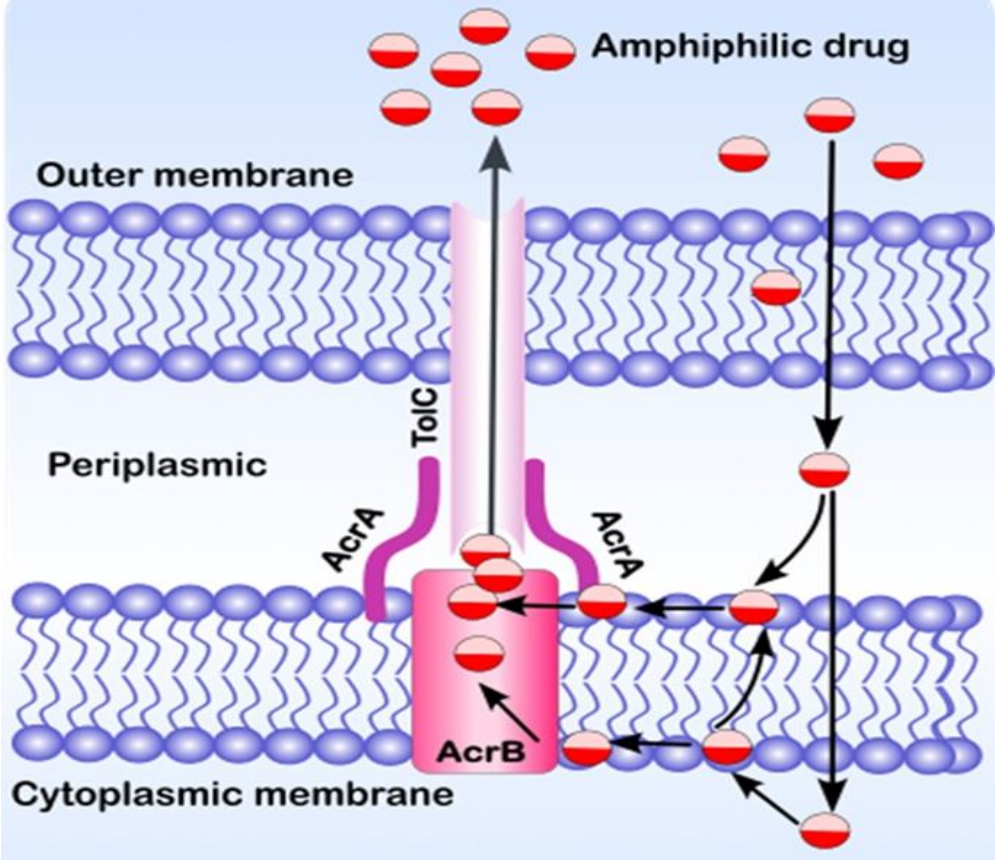

Figure (2): the structure of RND Efflux pump (in the current review)

AcrAB efflux pump, encoded primarily in *E. coli* , is charge of inheritance tolerance for many substances, involving dyes, detergents, and nearly all hydrophobic antibiotics. As exhibited in figure (2) , it is made up of an AcrB protein inserted inside the cytoplasmic membrane and an AcrA secondary protein observed in periplasmic region. The outer membrane protein called TolC cooperates with AcrB, AcrA to transport drug molecules through periplasmic region and extrude them out of the outer membrane [25]. Numerous studies have exhibited that the existence of four types of multidrug efflux pumps in *P. aeruginosa* including MexAB-Oprm,MexXY-Oprm ,MexEF-OprJ,and MexEF reduces the antibacterial impact of antibiotics by expelling the antibiotics outside the bacteria . These efflux pumps identified as drug/proton antiporters contain three complex proteins: that expel specific substrates from the periplasm region to the outer membrane. The first subunit of this efflux pump from inside out bacterial cell are a periplasmic adaptor protein termed as a periplasmic membrane fusion protein (PMFP)

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including MexA, MexX, MexC, or MexE. The second components of these efflux pumps are a resistance-nodulation-cell division transporter (RNDt) including: MexB, MexY, MexD, or MexF. The third components of these efflux pumps are known as a channel-forming outer membrane factor (OMF) including OprM, OprJ, or OprN. P.aeruginosa that withstand many antibiotics belonged to quinolones, tetracyclines,macrolidase,lincomycin,chloramphenicol, novobiocin and beta –lactams, has overexpressed MexAB-OprM gene. In addition, MexGH-OpmD and MexJK-OpmD found in p.aeruginosa are other efflux pumps that involved in the modulation of quorum sensing and the communication among cells [26].

ABC (ATP Binding Cassette) family

It is one of the extensive membrane proteins in eukaryotes, bacteria and archaea that use the energy obtained from ATP to translocate various substances through phospholipid of the plasma membranes. According to functional type , efflux pump of ABC family can be classified into (1) importers which are involved in absorbance of nutrients ; (2) exporters is attributed in secretion of substance outside the cell ; and (3) those which have crucial role in cellular process including mRNA translation , and reform DNA [27]. In many bacteria, a common basic structure of all ABC transporters composed of four domains include: two transmembrane domains (TMDs) (each one of them consist of six transmembrane helix), and two nucleotide-binding domains (NBDs) formed L-shape. The NBDs are working as the motor domains in the ABC transporters. The histidine transporter HisP is the first subunit of NBD creating a dimer in which hydrophobic interactions between each monomer generated the interface of dimer. As exhibited in figure (3) , All architecture ABC-NBDs composed of a RecA-like catalytic domain and a smaller helical domain [27]. ATP Binding Cassette transporters in eukaryotic are consist of a single polypeptide comprising four functional units with several additional members composed of homodimeric or heterodimeric halves. In addition to the four major domains found bacteria, there are accessory subunits consist of proteins observed in bacteria with gram negative and lipoproteins in bacteria with gram positive that contribute to the transfer and delivery of solutes to the biding site in the TMDs [28].

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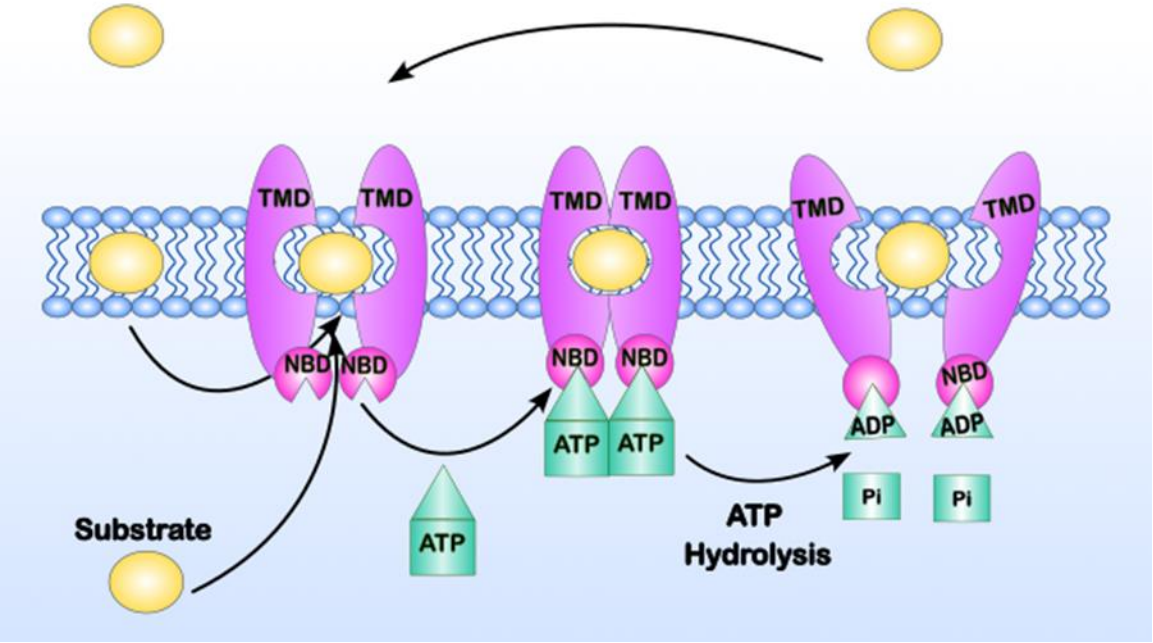

Figure(3): The structures of ABC efflux pump (in the current review)

Transferring efflux pump genes by plasmids

The emergence multidrug tolerance is the most threatening obstacle for the population health. The upgrowth of resistance to various antibiotics is attributed to the spread of genes encoding different efflux pump proteins through horizontal transfer mechanisms. During the conjugation process, involving the transfer of conjugative plasmids (plasmid F) carrying the genes expressing the TetA efflux pump protiens, *E. coli* acquires the capacity to overcome the antibacterial effect of Tetracycline (Tc) by expelling the drug from *E.coli* [29]. Several plasmids conferring bacteria the ability to tolerance a broad spectrum of antibiotics have been found to contain different genes responsible for encoding efflux pump proteins. For example , the qepA and qepA2 genes that are critical in the development of fluoroquinolones resistance, have been identified on specific plasmids encoding the MFS efflux pump proteins [30]. Many studies demonstrated the existence of a relationship between the increase in drug tolerance and the bacterial genes transmission of efflux pump. Plasmids and other transposable elements assist in the transfer of genes encoding the SMR family transport pumps, which confer bacterial strains the ability to tolerate many antibiotics, including beta-lactams, cephalosporins, dihydrofolate inhibitors, and aminoglycosides [7].

Inhibition efflux pump

Immerging resistance in bacterial cells against broad range of antibiotics forms growing threat due to the presence of pumps are capable of transferring drugs outside the cell. Some bacterial efflux pumps are limited to excrete one type of antibiotics, compared to other pumps which expel various types of antibiotics. Adoption a new strategy such as efflux inhibitors is considered as promising therapeutic agents to enhance the antimicrobial impacts of conventional antibiotics[31]. Many studies have demonstrated that many effective compounds including chalcones, piperine-like substance, and the minor compound of citral amide are worked as transferring pump repressors influenced on NorA in *S. aureus*[31]. Therefore, blocking of the outflow pumps rise the intracellular drug concentration, strengthens the antibacterial impact of drugs upon the resistant bacterial cells, and reduce the spread of resistant cell among bacterial community .The combination the inhibitors of efflux pump (EPIs) with antibiotics can reduce the invasion of *P. aeruginosa* ,as well as its role in lessen the value of the minimum inhibitory concentration (MIC). For instance, adding inhibitory compounds to ciprofloxacin lead to an increase in the susceptibility of *P. aeruginosa* toward this antibiotic. There are various mechanisms responsible of destruction the function of efflux pumps as exhibited in figure (4) (1) decrease the expression of efflux by interfering with the regulatory stages required to express the efflux pump, (2) Modification in the chemical building of antibiotics to lower their sensitivity towards connecting sites of the efflux pumps transporter, (3) Destruction of the buildup of the component parts of transport pumps, (4) reduction of the number of antibiotic connecting sites by linking with competitive or non-competitive compounds, (5) Preventing the entrance of antibiotic by obstructing the outer most pores of the efflux pumps, (6) Interfering with the energy needed for the pump function[32].

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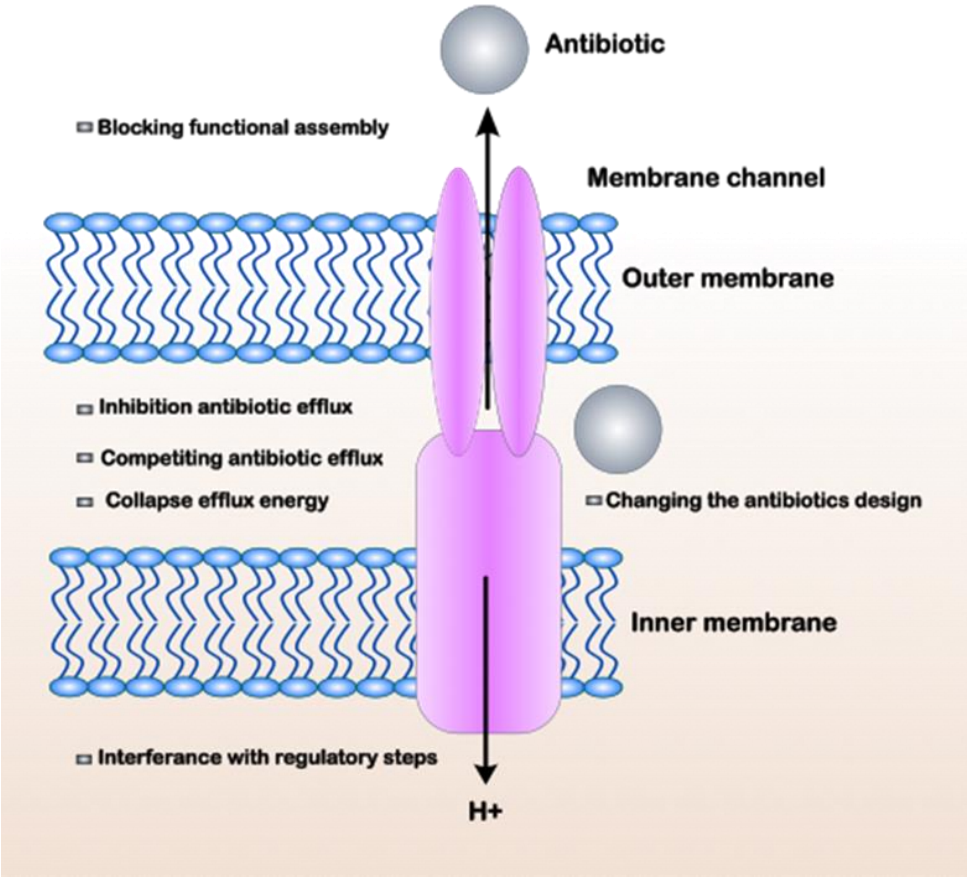

Figure (4): The inhibition mechanisms of efflux pumps (in the current review)

CONCLUSION:

In bacterial community the existence of MDR efflux pumps has a crucial function in drug resistance arising. The increase encoding of efflux pump is one of the mechanisms of multidrug resistance that bacteria developed to overcome on the anti-bacterial effect of antibiotics. The current issue represented by tolerance to many classes antibiotics, can reduce the efficiency of the pharmaceutical therapy. So it would be necessary, to improve the efficiency of antibacterial therapy, to repress the function of efflux pumps. The advent of transferring proteins has contributed to the emergence of more mechanisms for drug resistance Such as disabling the drug or changing the purpose of the drug. Therefore, familiarity with the physiological function of MDR transport pumps still requires more research due to the mechanism of these pumps is related to the sustained capacity of bacterial cells to manipulate and destruct antibiotics.

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Conflict of interests.

Non conflict of interest

References

[1] F. Van Bambeke, E. Balzi, P.M. Tulkens, Antibiotic efflux pumps Commentary, Biochem. Pharmacol. 60 (2000) 1–24.

[2] F. Van Bambeke, J.M. Michot, P.M. Tulkens, Antibiotic efflux pumps in eukaryotic cells: Occurence and impact on antibiotic cellular pharmacokinetics, pharmacodynamics and toxicodynamics, J. Antimicrob. Chemother. 51 (2003) 1067–1077. https://doi.org/10.1093/jac/dkg225.

[3] W.N. Konings, Microbial transport: Adaptations to natural environments, Antonie van Leeuwenhoek, Int. J. Gen. Mol. Microbiol. 90 (2006) 325–342. https://doi.org/10.1007/s10482-006-9089-3.

[4] D. Brown, M. Demeter, R.J. Turner, Prevalence of Multidrug Resistance Efflux Pumps (MDREPs) in Environmental Communities, Elsevier Inc., 2019. https://doi.org/10.1016/B978-0-12-814849-5.00031-9.

[5] E. Altınöz, E.M. Altuner, Antibiotic Resistance and Efflux Pumps, Int. J. Innov. Res. Rev. 3 (2019) 1–9. http://www.injirr.com/article/view/35.

[6] K.M. Zack, T. Sorenson, S.G. Joshi, Types and Mechanisms of Efflux Pump Systems and the Potential of Efflux Pump Inhibitors in the Restoration of Antimicrobial Susceptibility, with a Special Reference to Acinetobacter baumannii, Pathogens. 13 (2024). https://doi.org/10.3390/pathogens13030197.

[7] L.J.V. Piddock, Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria, Clin. Microbiol. Rev. 19 (2006) 382–402. https://doi.org/10.1128/CMR.19.2.382-402.2006.

[8] O. Lomovskaya, K.A. Bostian, Practical applications and feasibility of efflux pump inhibitors in the clinic - A vision for applied use, Biochem. Pharmacol. 71 (2006) 910–918. https://doi.org/10.1016/j.bcp.2005.12.008.

[9] C.A. Elkins, H. Nikaido, Substrate specificity of the RND-type multidrug efflux pumps AcrB and AcrD of Escherichia coli is determined predominately by two large periplasmic loops, J. Bacteriol. 184 (2002) 6490–6498. https://doi.org/10.1128/JB.184.23.6490-6499.2002.

[10] Y. Moriyama, M. Hiasa, T. Matsumoto, H. Omote, Multidrug and toxic compound extrusion (MATE)-type proteins as anchor transporters for the excretion of metabolic waste products and xenobiotics, Xenobiotica. 38 (2008) 1107–1118. https://doi.org/10.1080/00498250701883753.

[11] H. Omote, M. Hiasa, T. Matsumoto, M. Otsuka, Y. Moriyama, The MATE proteins as fundamental transporters of metabolic and xenobiotic organic cations, Trends Pharmacol. Sci. 27 (2006) 587–593. https://doi.org/10.1016/j.tips.2006.09.001.

[12] T. Kuroda, T. Tsuchiya, Multidrug efflux transporters in the MATE family, Biochim. Biophys. Acta - Proteins Proteomics. 1794 (2009) 763–768. https://doi.org/10.1016/j.bbapap.2008.11.012.

[13] T. Kusakizako, D.P. Claxton, Y. Tanaka, A.D. Maturana, T. Kuroda, R. Ishitani, H.S. Mchaourab, O. Nureki, Structural Basis of H + -Dependent Conformational Change in a Bacterial MATE Transporter, Structure. 27 (2019) 293-301.e3. https://doi.org/10.1016/j.str.2018.10.004.

[14] M. Lu, M. Radchenko, J. Symersky, R. Nie, Y. Guo, Structural insights into H +-coupled multidrug extrusion by a MATE transporter, Nat. Struct. Mol. Biol. 20 (2013) 1310–1317. https://doi.org/10.1038/nsmb.2687.

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[15] J. Stephen, F. Salam, M. Lekshmi, S.H. Kumar, M.F. Varela, The Major Facilitator Superfamily and Antimicrobial Resistance Efflux Pumps of the ESKAPEE Pathogen Staphylococcus aureus, Antibiotics. 12 (2023). https://doi.org/10.3390/antibiotics12020343.

[16] M.H. Saier, J.T. Beatty, A. Goffeau, K.T. Harley, W.H.M. Heijne, S.C. Huang, D.L. Jack, P.S. Jähn, K. Lew, J. Liu, S.S. Pao, I.T. Paulsen, T.T. Tseng, P.S. Virk, The major facilitator superfamily, J. Mol. Microbiol. Biotechnol. 1 (1999) 257–279.

[17] E.M. Quistgaard, C. Löw, F. Guettou, P. Nordlund, Understanding transport by the major facilitator superfamily (MFS): Structures pave the way, Nat. Rev. Mol. Cell Biol. 17 (2016) 123–132. https://doi.org/10.1038/nrm.2015.25.

[18] N. Yan, Structural advances for the major facilitator superfamily (MFS) transporters, Trends Biochem. Sci. 38 (2013) 151–159. https://doi.org/10.1016/j.tibs.2013.01.003.

[19] D.C. Bay, K.L. Rommens, R.J. Turner, Small multidrug resistance proteins: A multidrug transporter family that continues to grow, Biochim. Biophys. Acta - Biomembr. 1778 (2008) 1814–1838. https://doi.org/10.1016/j.bbamem.2007.08.015.

[20] O.E. Burata, T.J. Yeh, C.B. Macdonald, R.B. Stockbridge, Still rocking in the structural era: A molecular overview of the small multidrug resistance (SMR) transporter family, J. Biol. Chem. 298 (2022) 102482. https://doi.org/10.1016/j.jbc.2022.102482.

[21] D.C. Bay, R.J. Turner, Diversity and evolution of the small multidrug resistance protein family, BMC Evol. Biol. 9 (2009). https://doi.org/10.1186/1471-2148-9-140.

[22] K. Górecki, M.M. McEvoy, Phylogenetic analysis reveals an ancient gene duplication as the origin of the MdtABC efflux pump, PLoS One. 15 (2020) 1–10. https://doi.org/10.1371/journal.pone.0228877.

[23] Y. Zhao, J. Liu, T. Jiang, R. Hou, G. Xu, H. Xu, F. Liu, Resistance-Nodulation-Division Efflux Pump, LexABC, Contributes to Self-Resistance of the Phenazine Di-N-Oxide Natural Product Myxin in Lysobacter antibioticus, Front. Microbiol. 12 (2021) 1–12. https://doi.org/10.3389/fmicb.2021.618513.

[24] H. Nikaido, Y. Takatsuka, Mechanisms of RND multidrug efflux pumps, Biochim. Biophys. Acta - Proteins Proteomics. 1794 (2009) 769–781. https://doi.org/10.1016/j.bbapap.2008.10.004.

[25] H. Nikaido, H.I. Zgurskaya, AcrAB and related multidrug efflux pumps of Escherichia coli, J. Mol. Microbiol. Biotechnol. 3 (2001) 215–218.

[26] A.B. Lorusso, J.A. Carrara, C.D.N. Barroso, F.F. Tuon, H. Faoro, Role of Efflux Pumps on Antimicrobial Resistance in Pseudomonas aeruginosa, Int. J. Mol. Sci. 23 (2022). https://doi.org/10.3390/ijms232415779.

[27] V. Kos, R.C. Ford, The ATP-binding cassette family: A structural perspective, Cell. Mol. Life Sci. 66 (2009) 3111–3126. https://doi.org/10.1007/s00018-009-0064-9.

[28] S. Wilkens, Structure and mechanism of ABC transporters, F1000Prime Rep. 7 (2015) 1–9. https://doi.org/10.12703/P7-14.

[29] S. Nolivos, J. Cayron, A. Dedieu, A. Page, F. Delolme, C. Lesterlin, Role of AcrAB-TolC multidrug efflux pump in drug-resistance acquisition by plasmid transfer, Science. 364 (2019) 778–782. https://doi.org/10.1126/science.aav6390.

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[30] X.Z. Li, P. Plésiat, H. Nikaido, The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria, Clin. Microbiol. Rev. 28 (2015) 337–418. https://doi.org/10.1128/CMR.00117-14.

[31] J. Handzlik, A. Matys, K. Kieć-Kononowicz, Recent advances in Multi-Drug Resistance (MDR) efflux pump inhibitors of Gram-positive bacteria S. aureus, Antibiotics. 2 (2013) 28–45. https://doi.org/10.3390/antibiotics2010028.

[32] M. Askoura, W. Mottawea, T. Abujamel, I. Taher, Efflux pump inhibitors (EPIs) as new antimicrobial agents against Pseudomonas aeruginosa, Libyan J. Med. 6 (2011) 1–8. https://doi.org/10.3402/ljm.v6i0.5870.

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