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Efflux Pumps in Bacterial Antibiotic Resistance: Mechanisms, Clinical Implications, and Future Directions

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مضخات التدفق في مقاومة البكتيريا للمضادات الحيوية: الاليات الانعكاسات السريرية، والتوجهات المستقبلية

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ABSTRACT

Due to the discovery of new resistance mechanisms and the decline in effective and high-quality treatments for common pathogenic illnesses, the increased spread of antibiotic resistance across many infectious pathogens has become an increasingly pressing global public health concern. This has resulted in microbial responses to traditional medication that have not been successful, which may increase the risk of death, extend disease, and increase health care costs.

. Multiple drugs Protein complexes called efflux pumps are found in the cell envelope and allow bacteria to expel a variety of chemicals important for infection in addition to drugs. They thus have a significant role in the pathogenesis of microbes. Efflux pumps have the ability to expel external substances, such as antibacterial chemicals produced by the host. Pathogens can withstand antibiotics and get past the host's defenses by means of this extrusion. Nevertheless, endogenous substances including metabolites, virulence factors, and signaling molecules for bacterial communication are also extruded via efflux pumps. Consequently, efflux pumps have a role in regulating bacterial pathogenicity and behavior additionally to preserving bacterial homeostasis in response to various host-derived stimuli. Thus, the purpose of this work is to inform the public about the threat posed by the global rise in multiple medication resistance and the need for prompt action to treat microbial diseases. The purpose of this review was to give a general overview of efflux pumps' use in One Health settings.

Keywords: Efflux pump; Antibiotic resistance; Gram positive bacteria; Gram negative bacteria; Multidrug resistance.

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INTRODUCTION

- **Overview of Antibiotic Resistance:**

Throughout history, infectious diseases have caused pandemics and outbreaks that have claimed countless lives. The Peloponnesian War (430 BC) Plague in Athens, which killed around one-third of the population [1]. Consequently, antimicrobial drugs are created to reduce infection-related death. For example, plant, animal, and microbial sources yield potent antimicrobial substances such as santonin, cathelicidins, and aminoglycosides [2].

Antibiotic contamination happens when antibiotics are misused or overused. When an antibiotic is consumed, its active component is released by the body's enzymes, which inhibit the growth of the germs and cure the infection. Then, as sewage systems discharge antibiotic residues or un-metabolized antibiotics into the environment as feces or urine, there are more antibiotics in nature. When antibiotics are used excessively, bacteria undergo a selection process in the environment that leads to pathogen mutation and the emergence of antibiotic resistance [3]. It is commonly known that toxic substances are released from cells into the extracellular environment by efflux pumps, which are active pump systems known as transport proteins. Gram-positive and gram-negative bacteria, as well as eukaryotic cells, have these pumps .It is acknowledged that overexpression of these pumps is associated with medication resistance [4].

- Importance of Efflux Pumps in Resistance Mechanisms:

In Gram-negative bacteria, drug efflux is a major mechanism of resistance. Solutes are driven out of the cell by these methods. Efflux pumps help microorganisms control their internal environment by eliminating toxic substances such as metabolites, antibacterial drugs, and quorum sensing signal molecules [5].

Bacterial cytoplasmic membranes contain transport proteins called efflux pumps, which actively shuttle chemicals across the membrane. Through the extrusion of toxic compounds, Efflux pumps, biofilm formation molecules, quorum sensing molecules, and virulence factors of the bacteria all have an impact on the management of the internal environment [6]. Efflux pumps are a promising target for the creation of new inhibitors that could bring long-used antibiotics back to life because they are essential to the functioning of various stress scenarios in which bacteria find themselves. Nevertheless, the usefulness of efflux pump blockers in therapeutic settings is still debatable because of the substrate heterogeneity of efflux pumps. The development of innovative wide-spectrum efflux pump inhibitors can address this problem.

Types of Efflux Pumps

As shown in figure .1 [7] , there are six families of efflux pumps

ATP-binding cassette (ABC) superfamily

Lipids, sterols, and medications are among the many solutes that are translocated across membranes by the ABC superfamily, a chief efflux pump family. The process of actively

hydrolyzing ATP provides it with energy. The basic architecture common by all ABC families consists of two membrane-integral component domains (six transmembrane domains [TMDs]) and two nucleotide binding domains (NBDs). The NBD binds and hydrolyzes ATP to power the transport cycle, whereas the TMDs are engaged in substrate binding [8]. ABC transporters are present in human pathogenic bacteria, and they have a role in virulence, pathogenicity, and multidrug resistance through a number of mechanisms. ABC transporters can work as importers or exporters, giving them dual functionality. By obtaining vital nutrients such vitamins, amino acids, transitional metals, peptides, and osmoprotectants, ABC transporters contribute to pathogenicity. By exporting xenobiotics and necessary materials needed for the formation of glucose conjugates, such as lipopolysaccharides and capsular polysaccharides, ABC transporters enhance pathogenicity [9]

Resistance nodulation cell division (RND) superfamily

The core of the RND superfamily is composed of twelve transmembrane rings that are divided into asymmetric trimers by two large loops. Although the transmembrane domain primarily serves as a pathway for protons to use energy for substrate translocation, the outer loops contain binding sites for export ligands [10]. The pump, which consists of an outer membrane factor (OMF), an inner membrane RND-transporter, and periplasmic adapter protein (PAP) pumps for efflux, is sometimes referred to as tripartite resistance-nodulation-division (RND) [11]. It is known that RND super families contribute to pathogenicity and resistance. The bacteria must be able to stick to surfaces and infiltrate host cells in order to effectively colonize and infect them [12].

Major facilitator superfamily (MFS)

Extensively widespread across bacteria, archaea, and eukaryotes, the MFS family is the biggest identified superfamily of secondary active carriers. People with solute uniport (solute movement without the presence of ions), solute/cation symport (solute and ion movement in the similar direction), solute/cation antiport (ion and solute movement in conflicting directions), and/or solute/solute antiport with polarity directed either interiorly or externally are included in this group of people [13]. MFS transporters are necessary for adherence, an invasion, intracellular their existence, and the creation of biofilms between the host and the pathogen. Blocking the action of multidrug resistance (MDR) transporter is a useful tactic to lessen disease pathogenicity and fight drug resistance. In a Caenorhabditis elegans model, for example, it has been shown that inhibiting the Acinetobacter baumannii MFS efflux pump, AbaF, decreases bacterial pathogenicity [14].

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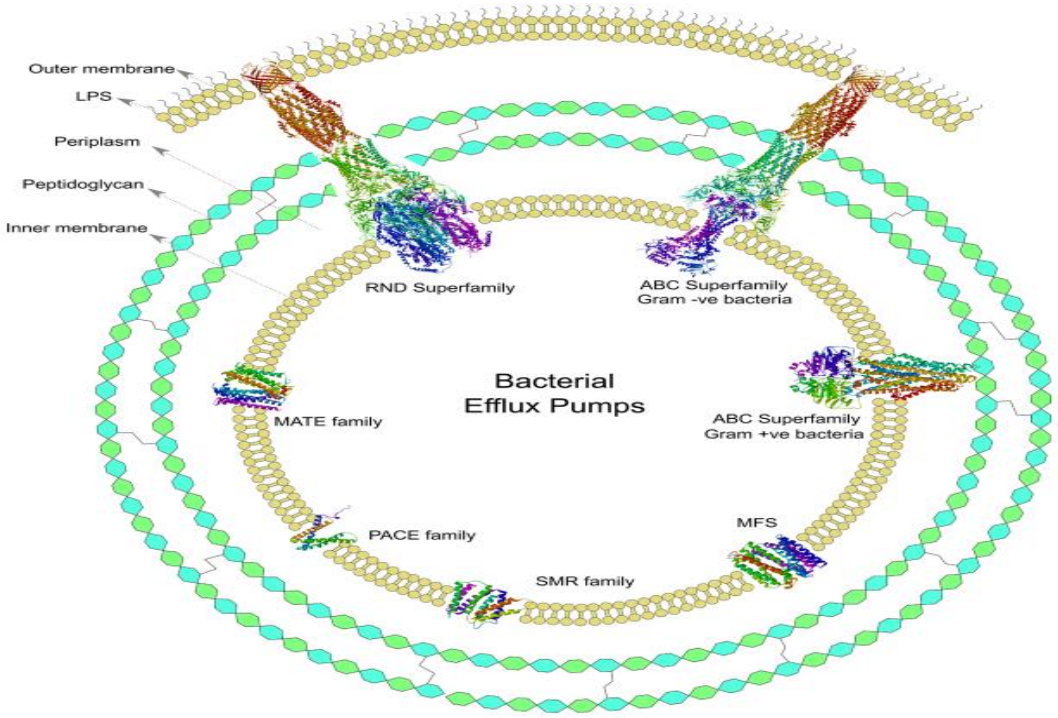

Figure 1. Schematic representation of bacterial efflux pumps. All bacterial efflux pumps are located on the inner membrane. Gram-negative bacteria have three components in their cell envelope, i.e. outer membrane,peptidoglycan layer, and inner membrane. Gram-positive bacteria have only two components in their cell envelope, i.e. peptidoglycan layer and inner membrane. Representative structures from each family (superfamily) have been presented here. Currently, six types of efflux pump families have been identified in bacteria, i.e. ATP-binding cassette (ABC) superfamily, major facilitator superfamily (MFS), small multidrug resistance (SMR) family, proteobacterial antimicrobial compound efflux (PACE) family, multidrug and toxin extrusion (MATE) family, and resistance-nodulation-cell division (RND) superfamily. [7]

Multidrug and toxic compound extrusion (MATE) family

Using a rocker-switch alternating access mechanism, the MATE superfamily flips between conformations that are substrate-bound and outward-facing and ion-bound and inward-facing to transport cationic materials throughout the membrane in the function of a secondary antiporter (influx of H+ or Na+) [15]. MATE transporters extrude cationic compounds such tetraphenylphosphonium, acriflavine, berberine, and norfloxacin, which lessen the susceptibility of bacteria to these medications. Staphylococcus aureus infections resistant to vancomycin and methicillin may become resistant to tigecycline when MepA overexpression occurs in the bacteria. Furthermore, changes in the expression level of the MATE superfamily can cause bacteria to become resistant [16].

Small multidrug resistance (SMR) family

The SMR family, despite its small size, can function as either homodimers or heterodimers. The basic mode of transport for the SMR family is a give-and-take between the substrate and an antiport (a proton) [17]. Many SMR proteins have been found in bacterial pathogens, and resistance to a

number of clinically utilized antibiotics, such as aminoglycosides, β-lactams, dihydrofolate inhibitors, and antiseptics, has been found [18].

Proteobacterial antimicrobial compound efflux (PACE) family

Recent findings indicate that the PACE family of bacterial pharmaceutical transportation proteins, among which AceI from A. baumannii is the prototypes, may be important since they are expressed by genes found in the bacterial core genome as opposed to mobile genetic elements [19]. Furthermore, AceI has broad resistance to a variety of structurally varied antimicrobial compounds as well as biosynthetic biocides (such as chlorhexidine, benzalkonium, diqualinium, acriflavin, and proflavin) [20].

Substrate and specificity of Efflux Pumps

Numerous ABC efflux pumps, such as MacAB-TolC in Escherichia coli, LmrA in L. lactis, EfrAB in E. faecalis, and PATA/B in S. pneumoniae, have been discovered as multidrug transporters. Chloramphenicol, aminoglycosides, lincosamides, macrolides, hydrophilic fluoroquinolones, and disinfectants can all pass through membranes with the help of these efflux pumps [21].

With more than 10,000 sequenced members, the MFS efflux pumps represent the largest family of secondary transporters. Sugar is the primary payload of these efflux pumps, despite the fact that some MFS carriers additionally contribute to chemical efflux, which increases antibiotic resistance [22].

The three primary classes of MATE transporters are NorM, DNA damage-inducible protein F (DinF), and eukaryotic subfamilies [23]. DinF may efficiently reverse the susceptibility to ciprofloxacin, moxifloxacin, and levofloxacin [24], while NorM may neutralize the damaging effects of oxidative stress on cells by exporting intracellular reactive oxygen [25]. Inner membrane transporters, periplasmic connector proteins, and outer membrane protein channels make up the RND efflux pumps [26]. SMR transporters, the smallest MDR efflux pumps, can be broadly classified into two physiological subtypes: (i) an example subtype of quaternary ammonium substances that is responsible for the extrusion of toxic compounds, and (ii) a guanidinium exporters that plays a role in the allocation of bacterial metabolites [21]. The Acinetobacter chlorhexidine efflux protein I (AceI) of the bacteria A. baumannii is one recently identified PACE family transport protein [27].

Role of Efflux Pumps in Antibiotic Resistance

- Efflux Pumps in Gram-positive Bacteria:

Gram-positive bacteria have the capacity to cause dangerous illnesses in people. Among the bacteria that are especially important to human medicine are Streptococcus pneumoniae, Clostridium difficile, Enterococcus faecalis and Enterococcus faecium, coagulase-negative staphylococci such Staphylococcus epidermidis and Staphylococcus haemolyticus, and Staphylococcus aureus. Membrane-based efflux proteins, or "pumps," are partially responsible for

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the resistance of first-line antimicrobial drugs to these bacteria, which makes treating infections caused by them more challenging. All bacteria use non-drug-resistant transport mechanisms including efflux to establish the correct charge and pH level gradient over the cytoplasmic membrane, absorb nutrients, and eliminate metabolic waste [28]. These natural processes are essential to bacteria's survival in the face of the many environmental obstacles they may encounter. If the pump has minimal substrate selectivity, or if an antibacterial agent or environment biocide fits its natural substrate or substrates, the proteins enabling these actions may be linked to drug resistance. Drug-specific efflux pumps, such as TetK from S. aureus, are typically found on plasmids and are thus readily transmissible, but efflux pumps that confer multidrug resistance (MDR) are typically encoded on chromosomes and are more challenging to transfer to another organism. This general norm does, however, include several exceptions. The plasmid-encoded MDR transporters QacA and QacC, which are present in S. aureus and coagulase-negative staphylococci, are important examples. They belong to two distinct families of proteins [29]. Transport proteins can be divided into five groups according to their structural traits, mode(s) of action, and source of energy for substrate translocation. Figure 2 [30] illustrates this, while secondary active transporters link the movement of a substrate with the transport of an ion (often H+ but also perhaps Na+) along an electrochemical concentration gradient, primary active transporters use ATP energy to move substrates. Secondary active transporters rely on both the proton gradient and the electrical potential across the membrane, which are the main sources of the proton motive force (pmf). The pump protein families are: resistance-nodulation-division RND, the small multidrug resistance (SMR) families; ATP binding cassette (ABC); multidrug and toxin extrusion (MATE); and major facilitator superfamily (MFS). Gram-positive organisms have been reported to include MDR pumps from all of these families.

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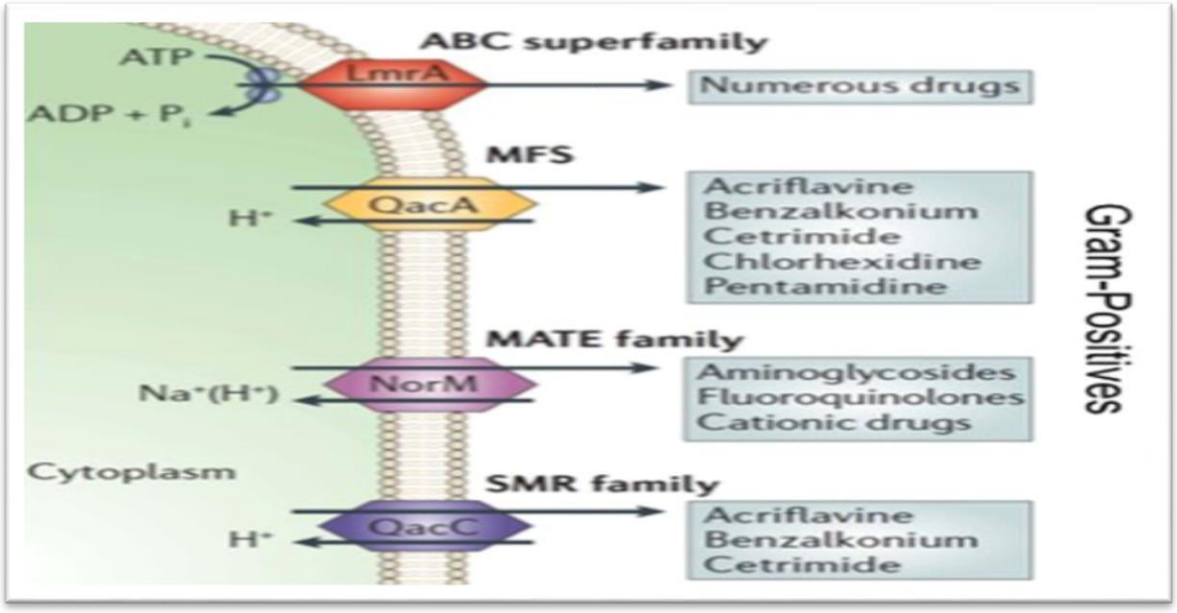

Figure 2. Different types of efflux pumps that are represented in both Gram-positive. There is a diagrammatic comparison of all the families illustrating how they get their energy, along with illustrations of medications and substances that act as substrates. [30]

- Efflux Pumps in Gram-negative Bacteria:

Most illnesses caused by highly or extremely drug-resistant bacteria are caused by gram-negative (GN) bacteria. There are currently few pharmacological treatment options available for the most critically resistant infections, hence new or enhanced antibacterial are desperately needed [31].

Key proteins that are crucial for drug permeability are found in the cytoplasmic membrane (CM) and outer membrane (OM) of the cell envelope (Fig. 3). It is believed that porin proteins, whose pores have particular geometries and are strongly polar with a strong transversal electrostatic field, are the main mechanism by which inward drug penetration across the OM occurs [32]. Specifically, most medications are effectively recognized and eliminated from the bacterial periplasm before they can reach their therapeutic targets by GN bacterial tripartite efflux pumps,

which span the CM, OM, and periplasm (Fig. 3) [33].

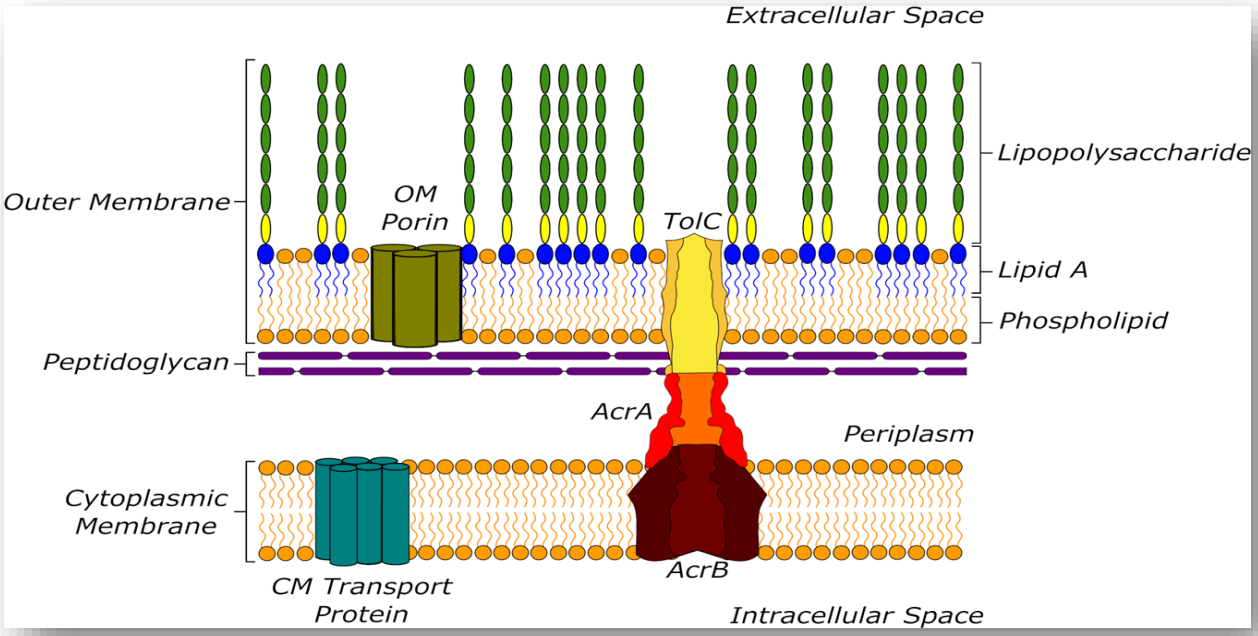

Figure 3. The periplasm and its underlying peptidoglycan layer are surrounded by the outer and inner membranes. Porins give polar molecules access points into the periplasm. Tripartite efflux pumps, such as the AcrAB-TolC complex found in E. coli, effectively remove medications from the periplasm by spanning both the inner and outer membranes [33].

Electrochemical gradients across the CM or ATP hydrolysis in the cytoplasm are the two sources of drive for tripartite efflux pumps [34].

- Efflux Pumps and Multidrug Resistance

Gram-negative bacterial infections that are resistant to multiple drugs (MDR) pose a significant worldwide risk to human health. Clinical use of last-resort antibiotics like colistin and carbapenems is driven by MDR infections, which further amplifies the development of resistance and the emergence of panresistant pathogens [35]. One promiscuous mechanism covering a range of antibiotic classes is the expression of termed resistance-nodulation-division (RND) superfamily exporters, thereby which mediate the active drainage of tiny molecules, involving numerous antibiotics, from the periplasm and the inner membrane to the extracellular environment. The phenomena of resistance are multifaceted [36].

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Genetic Regulation of Efflux Pumps

A variety of regulators and regulation cascades, some of which are key actors and others which act as substitutes or other pathways, interact to govern the expression of the diverse efflux systems. The internal concentration of harmful substances that are involved in the trigger of the cascade-inducing efflux expression appears to be linked to the regulation signal [37]. The genetic control of pumps in Gram-negative bacteria is primarily controlled by two important mechanisms:

Pathway 1: the fixation on the promoters of genes to induce protein-modulating gene expression. Regulatory genetic proteins can function as either activators or repressors and have α-helix-turn-α-helix (HTH) DNA-binding motifs [38].

Pathway 2: When environmental stressors necessitate bacterial adaptation, a two-component system (TCS) is activated, interfering with gene expression [39].

1. The HTH Line of Regulators :

Positive regulation is carried out by the AraC-XylS family, which has been thoroughly investigated in Enterobacteriaceae (MarA, RamA, SoxS, Rob, RarA) and H-NS proteins (histone-like structuring nucleoid protein) (SdiA, FIS, CsrA). Representative repressors in this group are TetR/AcrR/RamR/MexR and the OqxR family, which they are repressors of the genetic cascade control or operons of the pumps genes [37].

2 TCS Systems :

When bacteria sense changes in their surroundings, such as dangers to their essential physiological processes, their TCS systems help them adapt and defend themselves. TCS systems (CpxAR, Rcs, BaeSR, PhoPQ, and EnvZ/OmpR) (RocS2-RocA2, ParR-ParS, AmgR-AmgS, CzcR-CzcS, and CopR-CopS) can sense a range of external medium modifications, including pH, osmotic strength, oxidative stress, nutritional deficit, and hazardous chemicals [39].

Clinical Implications of Efflux Pumps:

The main efflux mechanism in bacterial cells is largely the original mechanism with membrane impenetrability when it relates to clinical isolates and antibiotics [40]. Although the basal activity in a wild strain cannot be clinically detected, it can be quickly triggered to start overexpressing and synthesizing. Despite not being well acknowledged, the efflux allows the most radical resistance mechanisms to emerge [41]. Sub-inhibitory antibiotic concentrations within cells then promote the development or acquisition of more specialized resistance mechanisms, like enzymatic reactions or target mutations [42]. For example, it has been shown that certain mutations in the gyrA and parC genes, which code for the gyrase target, are associated with efflux, raising the MIC. Although the MIC is significantly reduced, the lowering of efflux mechanisms identified in the lab for these kinds of strains never completely eliminates resistance to the antibiotic. Numerous studies have looked at this, especially with Pseudomonas aeruginosa, despite the fact that efflux is typically not investigated in epidemiological studies involving data from clinical strains due to the lack of automated techniques to measure efflux activity [43].

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Future Directions

Most of the structural makeup of Gram-positive bacteria's major facilitation superfamily (MFS) multidrug efflux pump systems is still unknown. The characteristics of the MFS fold structure arrangement of MFS proteins thought to contain transmembrane sections (14-TMSs) were unknown until recently [42]. The similarity between the known structures of MdfA, YajR, LmrP, NorA, and EmrD and the protein structures of antimicrobial transporters that have been extensively studied, such as QacA from S. aureus infections, is not entirely evident. Therefore, it is necessary to gain a better understanding of how closely bacterial pathogens resemble the protein structures and transport mechanisms of MFS antibiotic efflux pumps across their membranes. The majority of the structural components of the major facilitator superfamily (MFS) multidrug efflux pump systems found in Gram-positive bacteria remain unknown.

Consequently, a deeper comprehension of the degree to which bacterial pathogens mimic the protein structures and membrane-transporting mechanisms of MFS antibiotic efflux pumps is required. It is necessary to take into account the molecular properties of each antimicrobial pump in the MFS that dictate its substrate selection profiles. Therefore, there is still much to learn about how to determine each transporter's multidrug specificity while preventing ion or water leakage. The links between specific efflux pump blockers and possible boosts in antimicrobial activity when used with clinical antimicrobial medications to achieve synergy during clinical therapy represent one unexplored field of research. It was recently demonstrated that 1,8-naphthyridine sulfonamides and norfloxacin worked together to combat S. aureus, possibly offering a non-toxic means of treating infection [44]. These kinds of studies provide a useful paradigm for further research. While various efflux pump blockers for the bacterial multidrug efflux pumps of the MFS have been identified, only a small number of these modulators have been successfully developed into medications for diseases caused by bacterial pathogens [45]. Why there seems to be a discrepancy is yet unknown. To translate these discoveries into a medication that successfully treats illnesses caused by harmful bacterial pathogens, more investigation is needed.

CONCLUSION

There are several methods that can be used to block the efflux activity: decreasing the efflux system's resemblance for the antibiotic; increasing the level at which the antibiotic enters the body; overflowing the efflux system's capacity due to opponents that resemble the substrate; depleting the energy source of the expel; hindering the drainage channel; and (vi) blocking or weakening the efflux system.

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Conflict of interests.

There are non-conflicts of interest

References

[1] D. Huremović, "Brief history of pandemics (pandemics throughout history)," *Psychiatry pandemics a Ment. Heal. response to Infect. outbreak*, pp. 7–35, 2019. doi: 10.1007/978-3-030-15346-5_2.

[2] E. De Barros, R. M. Gonçalves, M. H. Cardoso, N. C. Santos, O. L. Franco, and E. S. Cândido, "Snake venom cathelicidins as natural antimicrobial peptides," Front. Pharmacol., vol. 10, p. 1415, 2019. doi: 10.3389/fphar.2019.01415.

[3] M. H. Kollef *et al.*, "The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship," *Intensive Care Med.*, vol. 43, pp. 1187–1197, 2017. doi: 10.1007/s00134-017-4682-7.

[4] J. Sun, Z. Deng, and A. Yan, "Bacterial multidrug efflux pumps: mechanisms, physiology and pharmacological exploitations," *Biochem. Biophys. Res. Commun.*, vol. 453, no. 2, pp. 254–267, 2014.

[5] J. P. Pearson, C. Van Delden, and B. H. Iglewski, "Active efflux and diffusion are involved in transport of Pseudomonas aeruginosa cell-to-cell signals," J. Bacteriol., vol. 181, no. 4, pp. 1203–1210, 1999.

[6] L. J. V Piddock, "Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria," *Clin. Microbiol. Rev.*, vol. 19, no. 2, pp. 382–402, 2006.

[7] Gaurav A., Bakht P., Saini M., Pandey S., and Pathania R., "Role of bacterial efflux pumps in antibiotic resistance, virulence, and strategies to discover novel efflux pump inhibitors," *Microbiology (Reading)*, vol. 169, no. 5, p. 001333, 2023.

[8] C. Thomas and R. Tampé, "Structural and mechanistic principles of ABC transporters," *Annu. Rev. Biochem.*, vol. 89, no. 1, pp. 605–636, 2020. doi: 10.1146/annurev-biochem-011520-105201.

[9] A. A. Akhtar and D. P. J. Turner, "The role of bacterial ATP-binding cassette (ABC) transporters in pathogenesis and virulence: Therapeutic and vaccine potential," *Microb. Pathog.*, vol. 171, p. 105734, 2022. doi: 10.1016/j.micpath.2022.105734.

[10] H. Nikaido, "RND transporters in the living world," *Res. Microbiol.*, vol. 169, no. 7–8, pp. 363–371, 2018. doi: 10.1016/j.resmic.2018.03.001.

[11] I. Alav *et al.*, "Structure, assembly, and function of tripartite efflux and type 1 secretion systems in gram-negative bacteria," *Chem. Rev.*, vol. 121, no. 9, pp. 5479–5596, 2021. doi: 10.1021/acs.chemrev.1c00055.

[12] V. Spaniol, S. Bernhard, and C. Aebi, "Moraxella catarrhalis AcrAB-OprM efflux pump contributes to antimicrobial resistance and is enhanced during cold shock response," *Antimicrob. Agents Chemother.*, vol. 59, no. 4, pp. 1886–1894, 2015. doi: 10.1128/AAC.03727-14.

[13] N. Yan, "Structural advances for the major facilitator superfamily (MFS) transporters," *Trends Biochem. Sci.*, vol. 38, no. 3, pp. 151–159, 2013. doi: 10.1016/j.tibs.2013.01.003.

[14] M. Pasqua *et al.*, "Host-bacterial pathogen communication: the wily role of the multidrug efflux pumps of the MFS family," *Front. Mol. Biosci.*, vol. 8, p. 723274, 2021. doi: 10.3389/fmolb.2021.723274.

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[15] Y. Morita *et al.*, "NorM, a putative multidrug efflux protein, of Vibrio parahaemolyticus and its homolog in Escherichia coli," *Antimicrob. Agents Chemother.*, vol. 42, no. 7, pp. 1778–1782, 1998. doi: 10.1128/AAC.42.7.1778.

[16] J. Kim, R. J. Cater, B. C. Choy, and F. Mancia, "Structural insights into transporter-mediated drug resistance in infectious diseases," *J. Mol. Biol.*, vol. 433, no. 16, p. 167005, 2021. doi: 10.1016/j.jmb.2021.167005.

[17] F. Van Bambeke, E. Balzi, and P. M. Tulkens, "Antibiotic efflux pumps," *Biochem. Pharmacol.*, vol. 60, no. 4, pp. 457–470, 2000. doi: 10.1016/s0006-2952(00)00291-4.103.034546.

[18] D. C. Bay, K. L. Rommens, and R. J. Turner, "Small multidrug resistance proteins: a multidrug transporter family that continues to grow," *Biochim. Biophys. Acta (BBA)-Biomembranes*, vol. 1778, no. 9, pp. 1814–1838, 2008. doi: 10.1016/j.bbamem.2007.08.015.

[19] K. A. Hassan, Q. Liu, P. J. F. Henderson, and I. T. Paulsen, "Homologs of the Acinetobacter baumannii AceI transporter represent a new family of bacterial multidrug efflux systems," *MBio*, vol. 6, no. 1, pp. 10–1128, 2015. doi: 10.1128/mBio.01982-14.

[20] K. A. Hassan *et al.*, "Pacing across the membrane: the novel PACE family of efflux pumps is widespread in Gram-negative pathogens," *Res. Microbiol.*, vol. 169, no. 7–8, pp. 450–454, 2018. doi: 10.1016/j.resmic.2018.01.001.

[21] S. Chetri, "The culmination of multidrug-resistant efflux pumps vs. meager antibiotic arsenal era: Urgent need for an improved new generation of EPIs," *Front. Microbiol.*, vol. 14, p. 1149418, 2023. doi: 10.3389/fmicb.2023.1149418.

[22] M. Pasqua *et al.*, "The varied role of efflux pumps of the MFS family in the interplay of bacteria with animal and plant cells," *Microorganisms*, vol. 7, no. 9, p. 285, 2019. doi: 10.3390/microorganisms7030285.

[23] Y. Guo *et al.*, "Luteolin increases susceptibility to macrolides by inhibiting MsrA efflux pump in Trueperella pyogenes," *Vet. Res.*, vol. 53, pp. 1–11, 2022. doi: 10.1186/s13567-022-00997-6.

[24] N. Tocci, F. Iannelli, A. Bidossi, M. L. Ciusa, F. Decorosi, C. Viti, G. Pozzi, S. Ricci, and M. R. Oggioni, "Functional analysis of pneumococcal drug efflux pumps associates the MATE DinF transporter with quinolone susceptibility," Antimicrob. Agents Chemother., vol. 57, pp. 248–253, 2013. doi: 10.1128/AAC.01601-12

[25] J. R. Guelfo, A. Rodríguez-Rojas, I. Matic, and J. Blázquez, "A MATE-family efflux pump rescues the Escherichia coli 8-oxoguanine-repair-deficient mutator phenotype and protects against H2O2 killing," *PLoS Genet.*, vol. 6, no. 5, p. e1000931, 2010. doi: 10.1371/journal.pgen.1000931.

[26] H. Nikaido and Y. Takatsuka, "Mechanisms of RND multidrug efflux pumps," *Biochim. Biophys. Acta (BBA)-Proteins Proteomics*, vol. 1794, no. 5, pp. 769–781, 2009.

[27] G. Spengler, A. Kincses, M. Gajdács, and L. Amaral, "New roads leading to old destinations: efflux pumps as targets to reverse multidrug resistance in bacteria," *Molecules*, vol. 22, no. 3, p. 468, 2017.

[28] J. S. Lolkema, B. Poolman, and W. N. Konings, "Bacterial solute uptake and efflux systems," *Curr. Opin. Microbiol.*, vol. 1, no. 2, pp. 248–253, 1998. doi: 10.1016/S1369-5274(98)80018-0.

[29] M. H. Brown and R. A. Skurray, "Staphylococcal multidrug efflux protein QacA," *J. Mol. Microbiol. Biotechnol.*, vol. 3, no. 2, pp. 163–170, 2001.

ISSN: 2312-8135 | Print ISSN: 1992-0652
info@journalofbabylon.com | jub@itnet.uobabylon.edu.iq | www.journalofbabylon.com

[30] L. J. V Piddock, "Multidrug-resistance efflux pumps? not just for resistance," *Nat. Rev. Microbiol.*, vol. 4, no. 8, pp. 629–636, 2006. doi: 10.1038/nrmicro1484

[31] S. R. Shrivastava, P. S. Shrivastava, and J. Ramasamy, "World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics," *J. Med. Soc.*, vol. 32, no. 1, pp. 76–77, 2018.

[32] S. Acosta-Gutiérrez et al., "Getting drugs into gram-negative bacteria: rational rules for permeation through general porins," ACS Infect. Dis., vol. 4, pp. 1487–1498, 2018.

[33] V. V. Rybenkov et al. "The whole is bigger than the sum of its parts: drug transport in the context of two membranes with active efflux," 2021.

[34] D. Du et al., "Multidrug efflux pumps: structure, function and regulation," Nat. Rev. Microbiol., vol. 16, pp. 523–539, 2018.

[35] B. Spellberg and D. Shlaes, "Prioritized current unmet needs for antibacterial therapies," Clin. Pharmacol. Ther., vol. 96, pp. 151–153, 2014. doi: 10.1038/clpt.2014.106.

[36] J. Dreier and P. Ruggerone, "Interaction of antibacterial compounds with RND efflux pumps in Pseudomonas aeruginosa," Front. Microbiol., vol. 6, p. 660, 2015. doi: 10.3389/fmicb.2015.00660.

[37] E. Dumont, J. Vergalli, L. Conraux, C. Taillier, A. Vassort, J. Pajovic, M. Réfrégiers, M. Mourez, and J. M. Pagès, "Antibiotics and efflux: Combined spectrofluorimetry and mass spectrometry to evaluate the involvement of concentration and efflux activity in antibiotic intracellular accumulation," J. Antimicrob. Chemother., vol. 74, pp. 58–65, 2019. doi: 10.1093/jac/dkz420 .

[38] E. R. Holden and M. A. Webber, "MarA, RamA, and SoxS as Mediators of the Stress Response: Survival at a Cost," Front. Microbiol., vol. 11, p. 828, 2020. doi:10.3389/fmicb.2020.00828.

[39] M. Masi, M. Réfregiers, and K. M. Pos, "Mechanisms of envelope permeability and antibiotic influx and efflux in Gram-negative bacteria," *Nat. Microbiol.*, vol. 2, no. 3, pp. 1–7, 2017.

[40] A. M. Langevin, I. El Meouche, and M. J. Dunlop, "Mapping the role of AcrAB-TolC efflux pumps in the evolution of antibiotic resistance reveals near-MIC treatments facilitate resistance acquisition," *Msphere*, vol. 5, no. 6, pp. 10–1128, 2020.

[41] J. Vergalli *et al.*, "The challenge of intracellular antibiotic accumulation, a function of fluoroquinolone influx versus bacterial efflux," *Commun. Biol.*, vol. 3, no. 1, p. 198, 2020. doi: 10.1038/s42003-020-01053-w .

[42] A. E. Ebbensgaard, A. Løbner-Olesen, and J. Frimodt-Møller, "The Role of Efflux Pumps in the Transition from Low-Level to Clinical Antibiotic Resistance," Antibiotics (Basel), vol. 9, no. 11, p. 855, 2020. doi: 10.3390/antibiotics9110855.

[43] L. J. V. Piddock, "The 2019 Garrod Lecture: MDR efflux in Gram-negative bacteria-how understanding resistance led to a new tool for drug discovery," J. Antimicrob. Chemother., vol. 74, pp. 3128–3134, 2019. doi: 10.1093/jac/dkz482 .

[44] C. D. de M. Oliveira-Tintino, D. F. Muniz, C. R. dos S. Barbosa, R. L. S. Pereira, I. M. Begnini, et al., "The 1,8-naphthyridines sulfonamides are NorA efflux pump inhibitors," J. Glob. Antimicrob. Resist., vol. 24, pp. 233–240, 2021. doi: 10.1016/j.jgar.

[45] M. F. Varela, J. Stephen, D. Bharti, M. Lekshmi, and S. Kumar, "Inhibition of multidrug efflux pumps belonging to the major facilitator superfamily in bacterial pathogens," *Biomedicines*, vol. 11, no. 5, p. 1448, 2023.

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الخلاصة

أصبح الانتشار المتزايد لمقاومة المضادات الحيوية عبر العديد من مسببات الأمراض المعدية مصدر قلق متزايد للصحة العامة العالمية وذلك بسبب اكتشاف آليات مقاومة جديدة وتراجع علاجات فعالة وعالية الجودة للأمراض الشائعة. أدى هذا إلى استجابات جرثومية غير ناجحة للأدوية التقليدية، مما قد يزيد من خطر الوفاة ويطيل مدة المرض ويزيد من تكاليف الرعاية الصحية.

توجد معقدات بروتينية تسمى مضخات التدفق في غلاف الخلية وتسمح للبكتيريا بضخ مجموعة متنوعة من المواد الكيميائية المهمة للعدوى بالإضافة إلى الأدوية. وبالتالي، تلعب هذه المضخات دورًا مهمًا في تسبب الميكروبات للأمراض. تمتلك مضخات التدفق القدرة على طرد المواد الخارجية، مثل المواد الكيميائية المضادة للبكتيريا التي ينتجها الجسم المضيف. يمكن للمسببات المرضية مقاومة المضادات الحيوية والتغلب على دفاعات المضيف من خلال هذه العملية. ومع ذلك، يتم أيضًا طرد المواد الداخلية مثل المستقلبات وعوامل الضراوة وجزيئات الإشارات للتواصل البكتيري عن طريق مضخات التدفق. نتيجة لذلك، تلعب مضخات التدفق دورًا في تنظيم مسببات الأمراض السلوكية والبكتيرية بالإضافة إلى الحفاظ على التوازن البكتيري استجابةً لمختلف المحفزات المشتقة من المضيف. وبالتالي، فإن الغرض من هذا العمل هو نشر الوعي بالتهديد الذي يشكله الارتفاع العالمي لمقاومة الأدوية المتعددة والحاجة إلى اتخاذ إجراء فوري لعلاج الأمراض الميكروبية.

الكلمات المفتاحية: مضخات التدفق; مقاومة المضادات الحياتية; بكتريا موجبة لصبغة جرام ; بكتريا سالبة لصبغة جرام; مقاومة الادوية المتعددة

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