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Research Progress in Identifying PqsR Antagonists for Treating Pseudomonas Aeruginosa Infection

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Abstract: ***Pseudomonas aeruginosa (PA), a gram-negative bacterium, is a major pathogen responsible for serioussevere infections in immunocompromised individuals and patients with cystic fibrosis. It causes nosocomial (medically related) healthcare-associated) infections and is known for its resistance to antibiotics resistance. PA utilizes complex quorum sensing networks to regulate the production of virulence factors and the development of biofilm, thus contributing to its multidrug resistance. The bacterium uses employs three interconnected quorum sensing systems: the las and rhl systems, which use N-acyl homoserine lactones, and the pqs system, which is based relies on alkyl quinols. A major focus of current research is on the transcriptional regulator PqsR (also known as the multiple virulence factor regulator or MvfR), a key protein in the quorum sensing system. This review examines recent advances in combating PA infections by disrupting these quorum sensing networks. We describe the potential of targeting these networks to reduce virulence and resistance, with a specific focus on PqsR antagonists. These antagonists disrupt the cell-cell communication that the bacteria rely on to produce virulence factors, thereby limiting and potentially eliminating multidrug-resistant infections. We evaluate both natural and synthetic PqsR inhibitors, providing a detailed description of their mechanisms and efficacy. In addition, the review discusses drug repurposing, highlighting various approved compounds that may modulate the quorum sensing system of PA. Through molecular docking studies and in vitro assays, several compounds were identified as potential candidates for further development. In conclusion, the review provides directions for future research to identify novel, safe, and effective natural products to inhibit infections caused by this pathogen.***

Keywords: Pseudomonas aeruginosa, Drug resistance, PQSR, Quorum sensing, Antagonists**.**

1. Introduction

Pseudomonas aeruginosa (PA), a gram-negative bacterium also known as pyocyanic bacteria, is commonly found in soil, water, and air. It can cause serious infections in damaged skin tissue or in immunocompromised individuals and is a leading cause of death among patients with cystic fibrosis [1]. In China, PA accounts for approximately 17.27% of nosocomial infections, second only to the 10%–31.5% prevalence observed in other countries [2]. PA is an important pathogen characterized by a predominant clonal population structure, categorized into specific sequence types (STs), that are closely associated with widespread transmission and carbapenemase production [3]. For example, ST235, ST111, and ST175 are referred to as high-risk clones due to their ability to acquire and/or maintain antibiotic resistance genes. Long-term use and misuse of antibiotics have led to resistance in PA against first-line treatmenst such as carbapenems, penicillins, and cephalosporins. Although next-generation antibiotics such as doripenem, cefepime, and cephalexin show promise, additional clinical testing is required before these drugs can be used on a large scale.

Multidrug-resistant bacteria represent a major challenge in antibiotic therapy and require the development of new therapeutic approaches. Therefore, it is crucial to identify novel antimicrobials with unique mechanisms of action. Bacteria use a communication mechanism termed quorum sensing, which regulates gene expression in response to cell-population density [4] and is closely related to the onset and development of bacterial infectious diseases. Quorum sensing signaling molecules (QSSMs) induce specific genes that depend on cell density, causing bacteria to exhibit new community level behaviors such as the regulation of virulence factor secretion, budding spore formation or biofilm formation, cell differentiation, motility, and extracellular polysaccharide formation [5]. Targeting quorum sensing regulators represents a novel strategy for treating microorganism-related diseases by reducing virulence, biofilm production, and antimicrobial resistance [6,7]. Compounds that disrupt the quorum sensing network without affecting bacterial growth or viability may provide advantages over traditional antibiotics, potentially reducing the development of drug resistance and minimizing side effects. To date, various quorum sensing and biofilm inhibitors have been used, including curcumin [8], m-bromothiothioester [9], halofuranone [10], ellagic acid [11], triazole-containing 2-phenylporphyrin esters, salicylic acid, 6-gingerol [12], trans-anisole [13], patchouliene [14], cinnamic acid, 7-fluoroindole [15], ibuprofenacin [16], and flavonoids [17].

PA uses quorum sensing networks to regulate the production of virulence profiles, including but not limited to byproducts such as pyocyanin, hydrocyanic acid, elastase, lectin, pyrrolidine, drug efflux pumps, and factors required for immune evasion. PA uses three highly interconnected quorum sensing systems: the las and rhl systems, which depend on N-Acyl homoserine lactone (AHL), and the pseudomonas quinolone signal (pqs) system, which relies on alkyl quinolones (AQ)-derived self-inducers [18]. The pqs system involves signaling molecules such as AQs 2-Heptyl-4-quinolone (HHQ) and 2-heptyl-3-hydroxy-4(1H)-quinolone (PQS) (Figure 1). HHQ is synthesized by the enzymes encoded by the pqsABCDE-phnAB operon and is converted to PQS by PqsH monooxygenase. Both HHQ and PQS can bind to and activate the transcription regulator PqsR (also known as multiple virulence factor regulator or MvfR). This gene binds to the PpqsA promoter region in its active form to promote the transcription of genes involved in quorum sensing and virulence. Therefore, HHQ and PQS

accelerate their own synthesis as self-inducers. The main function of HHQ is to drive this positive feedback loop dependent on PqsR, with signaling factors such as PQS and PqsE (the latter is encoded by the fifth gene of the pqsABCDE-phnAB operon) serving as the main effectors of the pqs QS system. In addition to its role in activating PqsR, PQS is an essential factor for the growth of ectodermal vesicles as an iron chelator and promotes the expression of virulence genes via PqsR-independent pathways. PqsE is a multifunctional protein that participates in the synthesis of HHQ and positively regulates the expression of multiple alkyl quinolone virulence factors. It may activate the transcriptional regulator RhlR, possibly through signaling molecules within the pqs and rhl quorum sensing systems. Therefore, activation of PqsR by HHQ/PQS may influence the stimulation of their own biosynthesis, leading to an exponential increase in signal factor concentration. PqsR binds to and directly controls the expression of the PA gene groups, including main regulators such as LasR and RhlR, as well as genes involved in protein translation secretion, and the oxidative stress response.

PqsR plays a critical role in the virulence of PA. Mutant strains (knockout) lacking PqsR exhibit significantly reduced virulence. HHQ and PQS levels are considered diagnostic biomarkers for infectious diseases, with their concentrations displaying a positive correlation with the severity of cystic fibrosis in patients and the degree of burn injuries. Additionally, HHQ and PQS are also associated with the quantitative bioburden of PA in the early stages of pulmonary exacerbations. Therefore, in vitro and animal models of infectious disease have validated PQS inhibitors as effective in decreasing the virulence of PA. This quorum sensing transcriptional regulator constitutes an ideal target for identifying new antivirulence drugs via molecular docking simulations. Pharmacological interventions in this pathway using small molecules structurally similar to PQS/HHQ can reduce the pathogenicity and antibiotic resistance of this pathogen. This review describes the mechanism by which PqsR antagonists disrupt cell-cell communication essential for producing virulence factors. These compounds limit and remove multidrug-resistant infections, thereby demonstrating their potential in contributing to a new research strategy for developing effective clinical therapeutic methods.

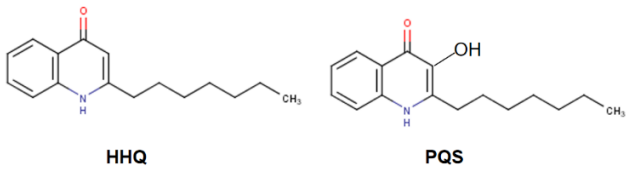

Figure 1: 2D schematic diagram of HHQ and PQS

2. Search for Natural Compounds Effective Against PA

The development of new Western medicines in China is becoming increasingly difficult due to long lead times, high costs, and serious side effects. Traditional Chinese medicines (TCM) are widely used in China for treating infectious diseases. TCM is valued for its ability to regulate immunity, improve blood circulation, and address secondary pathological reactions and other antibacterial aspects. It offers multi-targeted action, a broad antibacterial spectrum, and a low tendency to induce drug resistance, making it a promising new direction for treating bacterial infections and reducing drug resistance. Researchers are actively developing new antibiotics for treating bacterial infections caused by PA. However, the research and development of new antibiotics is time-consuming and expensive. Recent studies have focused on understanding the mechanisms of action of TCM in combating drug-resistant bacteria. The findings indicate that individual TCM components, single-flavored TCM, and TCM compounds can target drug-resistant PA through multiple mechanisms. Furthermore, TCM and antibiotics can work synergistically to enhance treatment effectiveness.

Molecular docking in virtual screening (VS) identifies small compounds from a library of natural compounds that bind to the binding pockets of PqsR protein crystal structure. These compounds are then validated by in vitro antimicrobial tests. Research indicates that many single components of TCM, including single-flavored TCM, TCM compounds, and patented Chinese medicine, possess growth-inhibiting or antimicrobial effects on pathogenic bacteria. For example, San Huang Di Yu San effectively inhibits the growth of multidrug-resistant (MDR) PA and significantly downregulates serum leukocyte levels and in vivo inflammatory factor levels in rats [19]. Berberine alkaloids enhance the susceptibility of clinically isolated multidrug-resistant PA to antibiotics such as cefepime and levofloxacin. Berberine has synergistic antimicrobial effects in combination with imipenem and meropenem, thereby partially reversing Carbapenem-resistant Pseudomonas Aeruginosa (CRPA) drug resistance [20].

Yang et al. [21] found that the minimum inhibitory concentrations (MIC) of 12 TCM drugs against PA andthat Houttuynia cordata shows different antimicrobial effects against PA. Among these, Coptis chinensis, Prunella vulgaris, Honeysuckle, and Andrographis paniculata demonstrated the strongest antimicrobial effects against PA.

Chu et al. [22] screened the MIC of 113 TCM drugs using solid serial dilution to identify the most effective antimicrobials against PA. They reported that Chinese peony, Chinese nutgall, pomegranate rind, Senecio scandens, Prunella vulgaris, Phyllanthus emblica, Sargentodoxa cuneata, and Chinese skullcap exhibited strong antimicrobial effects. Additionally, Indian gooseberry, Chinese nutgall, pomegranate rind, Senecio scandens, Sargentodoxa cuneata, and Chinese skullcap showed bactericidal effects against PA. These results provide valuable insights for developing new antimicrobial drugs.

Hayashi et al. [23] used the AutoDock Vina program to carry out a methodological study of the three co-crystals of the PA LasR signaling receptor proteins (2UV0, 3IX3, and 6MVM). They applied Lipinski's rule to do a primary screening of the Topscience TCM Database and conducted virtual screening using molecular screening. Compounds satisfying Lipinski's criteria and with binding energies below a certain threshold were then tested in vitro. Among these, baicalein-7-methylether exhibited significant antimicrobial activity with an MIC of 500 μg/mL.

3. Search for Synthetic Compounds Effective Against PA

Adequate solubility is a crucial factor in ensuring optimal pharmacokinetics, as poor solubility often leads to failures in pharmaceutical research and development.

Lu et al. [24] designed and synthesized four classes of quinolones based on the first PqsR antagonist and systemically researched their structure-activity relationship (SAR) and structure-property relationship (SPR). They identified a highly efficacious compound named Compound-16, with an IC50 of 72 nM. This compound demonstrated improved water solubility and enhanced inhibition of virulence factor. Their research demonstrated that the substituent at the 3-position plays a key role in the function of the ligand, whereas the carbon at the 4-position is important for ligand-protein interactions.

Cenbin Lu [18] further edited the 3D electronic structure of HHQ by adjusting the length of alkyl side chains and introducing electron-donating and electron-withdrawing groups into the benzene ring of the quinolone structure. Biological tests conducted on Escherichia coli using the β-galactosidase reporter gene showed that Compound-19 had an IC50 of 54 ± 23 nM. This antagonist was effective in vivo at a concentration of 3 mM and reduced the production of the virulence factor pyocyanin in the PA strain (PA14) by 74% and also decreased chlorpyrifos production.

Soukarieh et al. [25] optimized the structure of candidate compounds for novel PqsR inhibitors, enhancing their potency against PA strains PAO1-L and PA14. Their optimized compound, Compound 40, significantly decreased chlorpyrifos expression and interfered with AQ signaling biosynthesis at sub-micromolar concentrations, leading to significantly reduced production of these two PA strains. Their IC50 values were 0.25 ± 0.12 µM (PAO1-L) and 0.34 ± 0.03 µM (PA14), respectively.

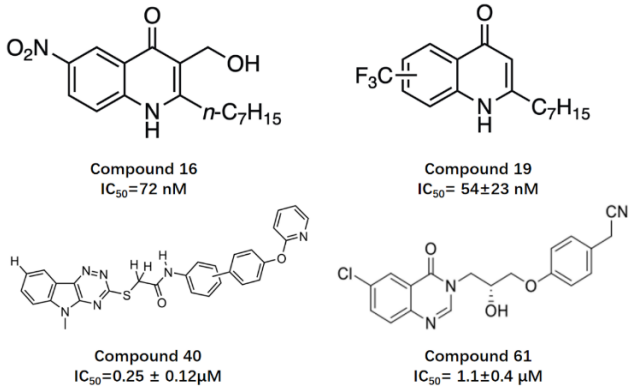

Figure 2: Chemical structures of the four crystallographic ligands.

Soukarieh et al. [26] also found that Compound 61 significantly reduced the levels of pyocyanin, PQS, and HHQ in PAO1-L and PA14 laboratory strains and PAK6085 clinical isolate with an IC50 value of 1.1 ± 0.4 µM. Another important phenotype of PA is the ability to form antimicrobial resistant biofilms. Compound 61 is more effective in the initial treatment phase of PA infections. The Compound 61 monotherapy showed limited effects when treated with either Compound 61 alone (monotherapy) or co-treated with ciprofloxacin, but enhanced ciprofloxacin treatment after 5 h, improving its efficacy in the early stages of biofilm treatment and in PA infections of Galleria mellonella. These data show that Compound 61 exhibits potential as a PqsR inhibitor and warrants further investigation for preclinical development.

4. Repurposing Existing Drugs to Combat PA Infection

Developing new antibiotics is a lengthy and expensive process, often hindered by the lack of in vitro activity in live bacterial cells. Repurposing existing drugs offer a promising alternative. This approach aims to discover new clinical uses for existing drugs that might have antimicrobial effects, or to produce enhanced effects when combined with other antibiotics. Anti-pqs drugs show potential for the treatment of PA infections; however, their progression to clinical trials has been limied by insufficient pharmacological profiling and the lack of ADME-TOX studies. However, drug repurposing methods have already identified potentially promising candidates. For example, the anthelmintic clonidine [27] and the antibiotic chlorojotol [28] have shown effectiveness against gram-positive bacteria. Further, this quorum sensing inhibitor is also safe to use and targets AHL and AQ. Clonidine, in particular, targets the las quorum sensing system, leading to reduced las-controlled expression of bacterial virulence factors and providing protection for G. mellonella larvae against PA infection.

Virtual screening provides a quick and cost-effective way to select target ligands from large molecular libraries. It significantly reduces the manual screening needed for activity experiments, thus speeding up the process of locating anti-PA natural compounds. Mellini et al. [29] identified a new quorum sensing inhibitor for the PA pqs QA system by combining virtual screening with drug repurposing. They virtually screened 1, 467 FDA-approved drug information databases using molecular docking and identified 5 hits that had the highest binding affinity to pqs quorum sensing acceptor PqsR. Phenotypic analyses validated the effects of the most promising hit, the antipsychotic drug pimozide, which blocked pqsr-controlled virulence traits, including the production of PqsR-controlled virulence traits, such as the production of the virulence factors, swarm motility, and biofilm formation.

In another study, Tatiana et al. [30] found five FDA-approved compounds—venetoclax, indocyanine green, nilotinib, cabozantinib, and montelukast—that inhibited quorum sensing abilities of PA. The study highlighted key PqsR activity pockets involved in the quorum sensing system, including Ile149, Ala168, 170, 186, 189, 207, 208, 221, 236, Tyr258, Asp264, and Thr265 (Figure 3). The pqs QS system controlled the expression of multiple virulence factors and the formation of biofilm, thus PA mutants defective in the pqs quorum sensing system exhibited reduced pathogenicity in animal and plant infection models. Changes in the positions of two key residues, Ile186 and Tyr258, affecting the MvfR activation mechanism were observed. The interactions between π–π and Tyr258 suggested an important role in protein-ligand affinity. This characteristic should be focused on by researchers in future design and optimization of new

antibiofilm molecules.

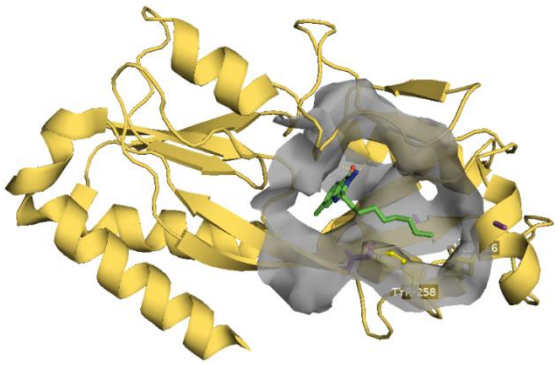

Figure 3: Three-dimensional schematic diagram of PQSR structure. (PDB: 4JVI) Gray: PQSR active pocket

D'Angelo et al. [28] found new inhibitors of the pqs quorum sensing system by screening a library of 1600 FDA-approved drugs, identifying the antifungal drugs clotrimazole and miconazole, along with an antibacterial compound clofoctol as inhibiting the pqs system, probably by targeting the transcriptional regulator PqsR. Clotrimazole and miconazole are usually applied as creams or ointments, limiting their use as partial treatment of chronic wound infections caused by PA. To treat lung infections, these drugs would need to be reformulated into an inhalable nanosuspension. This method has recently been used as a treatment for PA infections using anthelmintic clonidine. Clofoctol specifically inhibited the pqs-controlled virulence traits in PA, such as pyocyanin production, swarming motility, biofilm formation, and expression of genes involved in siderophore production. Additionally, clofoctol demonstrated protection against PA infections in G. mellonella larvae and exhibited inhibitory effects on the pqs OS system in isolates obtained from patients with cystic fibrosis.

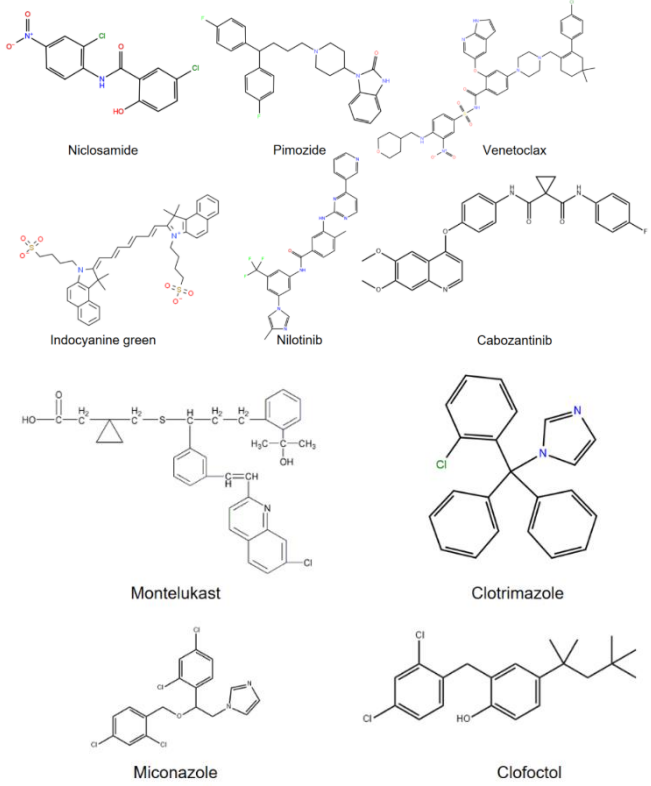

Figure 4: Chemical structures of the Clinical agents for inhibiting Pseudomonas aeruginosa

5. Discussion

Prolonged use of antibiotics has greatly accelerated the emergence of multidrug-resistant and even pan-drug-resistant bacterial pathogens worldwide. This surge in resistance has led to a dramatic increase in infections, particularly with ESKAPE pathogens (Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae spp.). These bacteria have shown resistance to almost all available antibiotics. Therefore, the development of new antibiotics is becoming increasingly attractive for many companies, although the de novo synthesis of a drug is a lengthy and expensive process. The redevelopment of existing antibiotics also requires significant cost and may be uneconomical due to the rapid emergence of antibiotic resistance and the drugs short commercial lifespan.

PA is a major opportunistic pathogen that causes severe infections and is a leading cause of death in patients with cystic fibrosis. Because its outer membrane barrier is rich in lipopolysaccharides, it forms microcolonies encapsulated by extracellular polysaccharides. This covering protects the bacteria from unfavorable conditions, circumvents the human immune response, and markedly reduces antibiotic susceptibility. Few alternative therapies developed in vitro and in vivo to counteract drug-resistant PA have progressed to the clinical trial stage due to issues such as cytotoxicity or unfavorable pharmacological properties. The ability to cause acute and chronic infections at different sites in the body is largely dependent on the pathogen's ability to adapt to the host by fine-tuning the expression of various virulence factors, many of which are controlled by quorum sensing. The transcriptional regulator pqsR is a key target in this context.

6. Conclusion

This article provides a comprehensive overview of the research and development of pqsR antagonists based on the quorum sensing system in drug-resistant PA. We believe that drug repurposing can provide a new approach to identifying new antimicrobial agents. Several FDA-approved drugs have shown in preclinical studies that they can reduce the the pathogenicity of PA in vivo and may be useful for further research. In conclusion, the search for novel, safe, and effective natural products that inhibit PA activity remains a critical area of research. Continued research into new antimicrobial agents and strategies is critical to address the increasing threat of drug-resistant pathogens.

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