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Inhibition of Microbial Quorum Sensing Mediated Virulence Factors by *Pestalotiopsis sydowiana*

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Quorum sensing (QS)-mediated infections cause severe diseases in human beings. The control of infectious diseases by inhibiting QS using antipathogenic drugs is a promising approach as antibiotics are proving inefficient in treating these diseases. Marine fungal (*Pestalotiopsis sydowiana* PPR) extract was found to possess effective antipathogenic characteristics. The minimum inhibitory concentration (MIC) of the fungal extract against test pathogen *Pseudomonas aeruginosa* PAO1 was 1,000 µg/ml. Sub-MIC concentrations (250 and 500 µg/ml) of fungal extract reduced QS-regulated virulence phenotypes such as the production of pyocyanin, chitinase, protease, elastase, and staphylolytic activity in *P. aeruginosa* PAO1 by 84.15%, 73.15%, 67.37%, 62.37%, and 33.65%, respectively. Moreover, it also reduced the production of exopolysaccharides (74.99%), rhamnolipids (68.01%), and alginate (54.98%), and inhibited the biofilm formation of the bacteria by 90.54%. In silico analysis revealed that the metabolite of *P. sydowiana* PPR binds to the bacterial QS receptor proteins (LasR and RhlR) similar to their respective natural signaling molecules. Cyclo(-Leu-Pro) (CLP) and 4-Hydroxyphenylacetamide (4-HPA) were identified as potent bioactive compounds among the metabolites of *P. sydowiana* PPR using in silico approaches. The MIC values of CLP and 4-HPA against *P. aeruginosa* PAO1 were determined as 250 and 125 µg/ml, respectively. All the antivirulence assays were conducted at sub-MIC concentrations of CLP (125 µg/ml) and 4-HPA (62.5 µg/ml), which resulted in marked reduction in all the investigated virulence factors. This was further supported by gene expression studies. The findings suggest that the metabolites of *P. sydowiana* PPR can be employed as promising QS inhibitors that target pathogenic bacteria.

Keywords: *Pestalotiopsis sydowiana*, *Pseudomonas aeruginosa*, anti-biofilm, anti-quorum sensing, gene expression, in silico

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Introduction

Quorum sensing (QS) regulates the infectious diseases in bacteria [1]. It operates through the signaling molecules, that is, autoinducers. The QS system in bacteria coordinates and influences the expression of genes responsible for the secretion of various virulence factors and biofilm formation, which lead to pathogenicity. Inhibition of QS-mediated gene expression can help control bacterial infection and biofilm development without affecting their growth pattern [2, 3]. Due to this unique feature, the bacteria develop less resistance to QSIs compared to antibiotics [4]. In recent years, various QS inhibitors of chemical and biological origin have been reported [5-8].

Pseudomonas aeruginosa is an opportunistic human pathogen that causes several clinical complications including chronic lung infection in cystic fibrosis patients [9, 10]. *P. aeruginosa* infection operates via the QS-mediated expression of several virulence traits like elastase, lipopolysaccharide, rhamnolipids, pyocyanin, cyanide, and exotoxin as well as flagellar motility, biofilm maturation, antimicrobial resistance, and alginates, which lead to biofilm formation [11]. Rhamnolipids play a significant role in evading the host immune response and facilitate the bacteria in successfully establishing the infection [12]. The infection system of *P. aeruginosa* is