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Sesamin and sesamolin rescues *Caenorhabditis elegans* from *Pseudomonas aeruginosa* infection through the attenuation of quorum sensing regulated virulence factors

V.T. Anju [a], Siddhardha Busi [b,**], Sampathkumar Ranganathan [c], Dinakara Rao Ampasala [c], Sandeep Kumar [a], Kitlangki Suchiang [a], Ranjith Kumavath [d], Madhu Dyavaiah [a,*]

[a] Department of Biochemistry and Molecular Biology, School of Life Sciences, Pondicherry University, Puducherry, 605014, India
[b] Department of Microbiology, School of Life Sciences, Pondicherry University, Puducherry, 605014, India
[c] Centre for Bioinformatics, School of Life Sciences, Pondicherry University, Puducherry, 605014, India
[d] Department of Genomic Science, School of Biological Sciences, Central University of Kerala, Kerala, 671316, India

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ABSTRACT

Pseudomonas aeruginosa is an opportunistic pathogen emerging as a public health threat owing to their multidrug resistance profiles. The quorum sensing systems of *P. aeruginosa* play a pivotal role in the regulation of virulence and act as the target for the development of alternative therapeutics. The study discussed about anti-quorum sensing and antibiofilm properties of lignans (sesamin and sesamolin) found in *Sesamum indicum* (L.) against *P. aeruginosa*. The effect of lignans, sesamin and sesamolin on LasR/RhlR mediated virulence factor production, biofilm formation and bacterial motility were studied. To elucidate the mechanism of action of lignans on QS pathways, QS gene expression and in depth *in silico* analysis were performed. Both the lignans exerted anti-quorum sensing activity at 75 μg/ml without affecting the growth of bacteria. SA and SO exhibited decreased production of virulence factors such as pyocyanin, proteases, elastase and chitinase. The important biofilm constituents of *P. aeruginosa* including alginate, exopolysaccharides and rhamnolipids were strongly affected by the lignans. Likewise, plausible mechanism of action of lignans were determined through the down regulation of QS regulated gene expression, molecular docking and molecular simulation studies. The *in vitro* analysis was supported by *C. elegans* infection model. SA and SO rescued pre-infected worms within 8 days of post infection and reduced the colonization of bacteria inside the intestine due to the anti-infective properties of lignans. The lignans exhibited profound action on Las pathway rather than Rhl which was elucidated through *in vitro* and *in silico* assays. *In silico* pharmacokinetic analysis portrayed the opportunities to employ ligands as potential therapeutics for human use. The deep insights into the anti-QS, anti-biofilm and mechanism of action of lignans can contribute to the development of novel anti-infectives against pseudomonal infections.

1. Introduction

World Health Organization has declared *Pseudomonas aeruginosa* as one of the antibiotic resistant 'priority pathogens' in 2017. Among these, carbapenem resistant *P. aeruginosa*, is categorized as critical and priority level 1 pathogen which demands urgent anti-bacterial interventions [1]. *P. aeruginosa* is a ubiquitous gram negative opportunistic pathogen not only causing infection in humans but also causes in plants and animals [2]. This is a notorious pathogen of the group 'ESKAPE' (*Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella* spp., *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* spp.) causing variety of infections such as burn wound infections, sepsis, ventilator associated pneumonia and lung infections especially in cystic fibrosis patients. This bacterium causes multitude of infections in humans owing to their antimicrobial resistance (AMR) and multi drug resistance (MDR). *P. aeruginosa* is regarded as an alarming global public threat owing to their AMR profiles [3].

The growing scenario of MDR is a greatest threat to the public well-being. This emerging threat hinders the use of traditional antibiotics and elevates the ineffectiveness of antimicrobial therapy [2]. The emergence

* Corresponding author.
** Corresponding author.
E-mail addresses: siddhardha.busi@gmail.com (S. Busi), madhud14@yahoo.co.in (M. Dyavaiah).

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