Microbiological Research 226 (2019) 19–26

Contents lists available at ScienceDirect

Microbiological Research

journal homepage: www.elsevier.com/locate/micres

Anti-quorum sensing and anti-biofilm activity of 5-hydroxymethylfurfural against *Pseudomonas aeruginosa* PAO1: Insights from *in vitro*, *in vivo* and *in silico* studies

Jobina Rajkumari[a], Subhomoi Borkotoky[b], Dhanasekhar Reddy[c], Saswat Kumar Mohanty[d], Ranjith Kumavath[c], Ayaluru Murali[b], Kitlangki Suchiang[d], Siddhardha Busi[a,*]

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

ARTICLE INFO

Keywords:
P. aeruginosa
5-hydroxymethylfurfural
Quorum sensing
C. elegans
Docking
qRT-PCR

ABSTRACT

Pseudomonas aeruginosa is one of the most common pathogens associated with nosocomial infections and a great concern to immunocompromised individuals especially in the cases of cystic fibrosis, AIDS and burn wounds. The pathogenicity of *P. aeruginosa* is largely directed by the quorum sensing (QS) system. Hence, QS may be considered an important therapeutic target to combat *P. aeruginosa* infections. The anti-quorum sensing and anti-biofilm efficacy of aromatic aldehyde, 5-hydroxymethylfurfural (5-HMF) against *P. aeruginosa* PAO1 were assessed. At the sub-inhibitory concentration, 5-HMF suppressed the production of QS-controlled virulence phenotypes and biofilm formation in *P. aeruginosa*. It was also able to significantly enhance the survival rate of *C. elegans* infected with *P. aeruginosa*. The *in silico* studies revealed that 5-HMF could serve as a competitive inhibitor for the auto-inducer molecules as it exhibited a strong affinity for the regulatory proteins of the QS-circuits i.e. LasR and RhlR. In addition, a significant down-regulation in the expression of QS-related genes was observed suggesting the ability of 5-HMF in mitigating the pathogenicity of *P. aeruginosa*.

1. Introduction

Numerous pathogenic microorganisms are known to utilize the cell-density dependent bacterial communication system known as quorum sensing (QS) to regulate numerous virulence phenotypes, contributing to its pathogenicity. In *P. aeruginosa*, the QS system constitutes of two major intertwined circuits, LasI/LasR and RhlI/RhlR. The synthase protein, LasI and RhlR synthesize the autoinducers, 3-oxododecanoyl-L-homoserine lactone (3-oxo-C_{12}-AHL) and N-butanoyl homoserine lactone (C_4-HSL) which binds to their cognate transcriptional regulators, LasR and RhlR respectively. The LasR/3OC_{12}-HSL and RhlR/ C_4-HSL complexes, in turn, regulate the expression of genes related to virulence factor production (Kalia, 2013). QS also amplifies bacterial virulence by stimulating biofilm formation which leads to the development of antibiotic resistance. The biofilm forming ability of *P. aeruginosa* has been implicated for causing severe chronic infections in individuals with cystic fibrosis and burn wounds (Solano et al., 2014). Hence, targeting the QS circuit may serve as one of the most effective ways to counteract the infections caused by *P. aeruginosa*.

Numerous compounds have been extensively studied for their ability to interrupt and/or disrupt the bacterial QS system. Unlike classical antibiotics which target the basic cellular metabolic processes, the quorum sensing inhibitors (QSIs) are thought to hamper the bacterial communication without exerting selective pressure on the bacteria, thereby decreasing the chance for the appearance of MDR strains. It has also been proposed that a potential QSI should be highly specific for the QS regulator and efficiently reduce the QS-regulated gene expression without exerting a bactericidal effect on the pathogen or causing an adverse effect on the host cell (Kalia, 2013). Natural compounds are extensively being investigated for their ability to curtail the bacterial QS circuit and attenuate pathogenicity, without causing a harmful side-effect. 5-hydroxymethylfurfural (5-HMF, $C_3H_6O_3$) is an aromatic aldehyde naturally present in honey, dried fruits, wine, fruit juices, and coffee. Earlier reports have demonstrated the potential use of 5-HMF in the prevention or treatment of sickle-cell anemia and type I allergic reactions. It has also been reported to possess anti-oxidant, anti-

* Corresponding author at: Department of Microbiology, School of Life Sciences, Pondicherry University, Puducherry, 605014, India.
E-mail address: siddhardha.busi@gmail.com (S. Busi).

https://doi.org/10.1016/j.micres.2019.05.001
Received 31 October 2018; Received in revised form 3 May 2019; Accepted 4 May 2019
Available online 07 May 2019
0944-5013/ © 2019 Elsevier GmbH. All rights reserved.