APPLYING BIOACTIVE COMPOUNDS OF *PSEUDOMONAS* SPP. FOR MEDICINE SUBSTANCE DEVELOPMENT

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Infectious diseases are still a worldwide important problem. This fact has led to the characterization of new biomarkers that would allow an early, fast and reliable diagnostic and targeted therapy. In this context, *Pseudomonas aeruginosa* can be considered one of the most threatening pathogens since it causes a wide range of infections. Antibiotic treatment is not trivial given the incidence of resistance processes and the fewer new antibiotics that are placed on the market. With this scenario, relevant *quorum sensing* (QS) molecules that regulate the secretion of virulence factors

and biofilm formation can play an important role in diagnostic and therapeutic issues [Winstanley et al., 2009].

P. aeruginosa is an opportunistic nosocomial human pathogen, which causes a broad spectrum of acute and chronic infections such as bloodstream infections in intensive care units, burn and chronic dermal wound infections, surgical site infections, hospital-acquired pneumonia and respiratory and urinary tract infections [Williams et l., 2009].

P. aeruginosa expresses an arsenal of virulence traits that are powerful weapons damaging host cells. Secreted virulence factors comprise a series of cytotoxins such as those of the type 3 secretion system which include several protein toxins that play important roles on the pathogenesis of this bacterium. The expression of many of these virulence factors is regulated by the QS network. This system is controlled and synchronized by RhlR, LasR and PQS regulators, which are involved in a series of events related to the production of biofilm, toxins and pigments, as well as to the development of antimicrobial resistance [Jakobsen et al., 2013].

About 50 pigmented, heterocyclic nitrogen-containing secondary metabolites are synthesized by some strains of *Pseudomonas* spp. and a few other bacterial genera. Fluorescent pseudomonads are the best studied phenazine producing microorganisms, including strains of *P. fluorescens*, *P. chlororaphis* and *P. aeruginosa* [Bell et al., 2015].

Phenazine derivatives could be used as prodrugs due to biological activities, for which pharmacologists and chemists have committed themselves to make them into patent medicines. For example, Clofazimine (Lamprene®) is successfully applied in clinic as widely used antileprosy and antitubercular drug due to antimicrobial activity and immunosuppressive properties [Makgatho et al., 2017].

Phenazines (i.e. pyocyanin, PYO) are pigmented bacterial metabolites that have a function on microbial competition and virulence and are secreted in high amounts during the early colonization phase to ensure the establishment of the infection. Phenazines exert a large number of effects on host cells [Hall et al., 2016] including direct damage mainly triggered through formation of reactive oxygen species, alteration of cytokine production, ciliary motion inhibition in human nasal ciliated epithelium and interruption of cell signaling. In addition, they have a crucial role on apoptosis, cell cycle arrest and they induce premature senescence [Bell et al., 2015]. Thus, phenazines play an important role on *P. aeruginosa* virulence, as it has been found in PYO deficient mutants that cause attenuated acute and chronic lung infection in mouse, with respect to wild-type *P. aeruginosa* strains. Moreover, phenazines can exert a toxic effect on other cells but instead benefit their producers by mediating extracellular electron transfer and survival in anoxic environments [Costa et al., 2015].

The most studied *P. aeruginosa* phenazines are PYO, 1-hydroxyphenazine (1-OHphz) and phenazine-1-carboxylic acid (PCA). Bioactivities of these compounds are linked to their ability to redox-cycle [Dietrich et al., 2008], which leads to generation of reactive oxygen species that cause host cell damage.

PYO production is associated with a high percentage of *P. aeruginosa* isolates. Thereby, Wilson et al. [Wilson et al., 2008] identified by HPLC 2 phenazine pigments, PYO and 1-OHphz, in the sputum of 9 from 13 (70 %) cystic fibrosis and bronchiectasis patients colonized by *P. aeruginosa*. Concerning infected burn patients, Muller et al. [Muller et al., 2009] examined 7 samples of wound dressings detecting PYO presence just in 4 of them (57 %).

PCA is also called tubermycin B (Mupirocin®) due to its antibiotic activity against *Mycobacterium tuberculosis*. It is widely distributed in various microorganisms as a precursor of many natural phenazine derivatives. Gorantla et al. firstly reported its antifungal activity against major human pathogen, *Trichophyton rubrum*, which could be responsible for causing athlete's foot, jock itch, ringworm and fingernail fungus infections [Gorantla et al., 2014].

According to reports in recent years, phenazine derivatives possessed antiproliferative activities against various cancer cell lines [Lu et al., 2017]. Additionally, phenazine derivatives are candidates to be developed as inhibitors of disease-related targets and so on [Lu et al., 2017].

Thus, the ability of *P. aeruginosa* to raise disease depends on the production of virulence factors. This fact points them as potential biomarkers of infection. Moreover, the concentration of these molecules is found in direct proportion to the bacterial load. In this context, PYO emerges as a very interesting target for developing new detection techniques. At the same time, many phenazines have shown great pharmacological activity in various fields, such as antimicrobial, antiparasitic, neuroprotective, insecticidal, anti-inflammatory and anticancer activity. Researchers continue to investigate these compounds and hope to develop them as medicines.