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FURANONE COMPOUNDS: POTENTIAL QUORUM QUENCHERS FOR INHIBITING PATHOGENIC INFECTIONS

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ABSTRACT: Pathogenicity of the gram negative bacteria depends on the amount of autoinducer n-acyl homoserine lactone (AHL). Reduction in AHL could interfere with virulence to lower the infection. The halogenated furanone, 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone obtained from red macro alga *Delsia pluchra* showed structural similarity to that of AHL and thereby competitively inhibited AHL binding to its receptors. To identify compounds that are structurally similar to halogenated furanones literature survey has been performed on some plants and fungal species having known antibacterial activity. GC-MS and related analysis data reveled the potential species having furanone compounds in their extracts. The study done here uses online available cheminformatics tools (ChemMine) to identify furanone compounds structurally similar to 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)- furanone. This study suggests, a novel compound 2,5-dimethyl-4-hydroxy-3(2H)-furanone obtained from Ananas comosus as a potential candidate for reducing AHL levels. Both the compounds are found to be structurally similar and thus 2,5-dimethyl-4-hydroxy-3(2H)-furanone could be a potential quorum quencher which can ultimately inhibit bacterial virulence.

Key words: - quorum sensing, quorum quenching, AHL, GC-MS, ChemMine.

INTRODUCTION :

Cell to cell communication in bacteria requires generation of certain diffusible molecules namely autoinducers. These autoinducers help the bacterial cells to communicate with one another to identify cell density and modify its behavior (Parsek and Greenberg 2000). This process of cell to cell communication is known as Quorum Sensing. The autoinducer systems differ in gram negative and gram positive bacteria. And their role in bioluminescence, virulence, biofilm formation, sporulation etc. has been extensively studied. Since QS is responsible for virulence in the clinically relevant bacteria, inhibition of QS appears to be a promising strategy to control these pathogenic bacteria. With indiscriminate use of antibiotics, there has been an alarming increase in the number of antibiotic resistant pathogens. Antibiotics are no longer the magic bullets they were once thought to be and therefore there is a need for development of new antibiotics and/or other novel strategies to combat the infections caused by multidrug resistant organisms. Quorum sensing inhibition or quorum quenching has been pursued as one of such novel strategies. Interestingly, ethnobotanically known plants have been showed antibacterial potential on various bacterial species. However, very limited studies have been done to observe their anti- quorum sensing potential or quorum quenching ability.

Two decades ago, in an exciting study it has been found that red macro-alga, *Delisea pulchera* contained halogenated furanones which structurally resembled the autoinducer found in marine bacteria i.e. n-acyl homoserine lactone (AHL). The chemical name of this furanone was for 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone. The halogenated furanones are similar in structure to AHL, except that furanones have a furan ring instead of homoserine lactone ring. Due to the

same structure instead of AHL, furanone binds to Lux-R type signal receptor and blocks the pathway (Manefield *et al.,* 1999). Other mechanisms of inhibiting AHL includes some Quorum Quenching enzymes such as; AHL-lactonases, acylases, oxidoreductase and paraoxonases (PONs), which breakdown AHL signals.

In this review, we focused on identifying furanone compounds in the extracts of well-known antibacterial medicinal plants and fungal species. For studying the same, ethnobotanically known antibacterial plants and fungal species were approached in the literature and further their phytochemicals were searched for furanone containing compounds. To confirm the sturctural similarity between the identified compounds pubChem similar structure search was performed for 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone (https://pubchem.ncbi.nlm.nih.gov/). Also, tanimoto similarity coefficient is obtained using ChemMine similarity workbench (https://chemminetools.ucr.edu/similarity/) for furaone containing compounds. The tanimoto coefficient varies from 0 to 1, 0 indicating no similarity whereas 1 indicating completely identical compounds.

Potential antibacterial

Ocimum sanctum has been extensively studied to find its antibacterial potential on various bacteria. Both gram negative and gram positive bacteria are inhibited by the use of leaf extracts. Also, the use of leaf extract has been shown to develop protective immunity against salmonella specie (Goel, Kumar, and Bhatia 2010; Rathnayaka 2013). These evidences makes it a potential candidate to study its quorum quenching activity. Another such plant is *Azadirachta indica* (Neem) which have been shown to inhibit the growth of pathogenic bacteria like *Klebsiella pneumonia* and *Salmonella typhimurium* (Banna, Parveen, and Jalaluddin Iqbal 2014). Ethanolic extracts of *Ananas comosus* fruit and peel has been studied for antibacterial property on pathogenic bacterial isolates and found effective against multi drug resistant bacteria as well (Nahid Hasan, Saha, and Ahmed 2021). *Warburgia salutaris* also known as Pepperbark is one of the most valuable plant of the natural African environment and the stem and leaves have been used to treat yeast, fungal, bacterial and protozoal infections for centuries. Plant has been shown to possess antimicrobial potential against skin pathogens and respiratory tract pathogens (Khumalo *et al.,* 2019). Not only plants but some fungal species have also been known to have antibacterial potential. *Lactarius helvus*, a mushroom commonly known as fenugreek milkcap, is a member of the large milkcap genus Lactarius in the order Russulales. This is commonly used and cooked mushroom in the north American culture. Lactarius mushrooms showed antibacterial activity at 0.5-5 µg/ml for gram positive and negative bacteria (Vidari and Vita-Finzi 1995).

Phytochemicals as quorum quenchers

In order to understand if these known antibacterial plant and fungal species have furanone containing phytochemicals, an extensive survey is performed to identify the phytomolecules present in their extracts. Tulsi seed extracts contained phthalic acids, Hexadecanoic acid, and other compounds (Walvekar and Deasi 2021). Caryophyllene and Eugenol obtained as a bioactive compounds in leaves of *Ocimum sanctum* (Iqbal *et al.,* 2020). Volatile compounds extracted from flower spikes, flower with nectar, and leaves of Tulsi using HS-SPME/GC-MS showed presence of ocimene, eugenol, germacrene etc. (Yamani *et al.,* 2016). However, no furanone containing compound were observed in any of the GC-MS analysis.

Similar search was performed for *Azadirachta indica* and some furan containing compounds are found in the ethanolic extracts of leaves of Neem. Furanmethanol, (+-)-4-Amino-4,5-dihydro-2(3H)- furanone, 2,4-Dihydroxy-2,5-dimethyl3(2H)-furan-3-one, 2(4H)-Benzofuranone, 5,6,7,7atetrahydro-4,4,7a-trimethyl, and 5-Isopropyl-3,3-dimethyl-2-methylene-2,3-dihydrofuran are among the few compounds isolated from the neem extracts. However, their concentration was very low. Also, no structural similarity was observed between these furan containing compounds with halogenated furanone obtained from *Delsia pulchra*.

Another furanone containing plant was *Ananas comosus* (pineapple). Among the volatile compounds found in fruit pulp of pineapple includes 2,5-dimethyl-4-hydroxy-3(2H)-furanone which also contributes to the pineapple aroma. Interestingly, a pubChem similarity search identifies similarity between the furanone compound observed in *Delsia pulchra* and *Ananas comosus* (Figure 1a). Also, ChemMine structure similarity search (https://chemminetools.ucr.edu/similarity/) reveals that 2,5-dimethyl-4-hydroxy-3(2H)-furanone is similar to that of 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone with tanimoto coefficient of 0.13 (Figure 1b). Usually, Tanimoto coeff. of >0.85 considered for two similar compounds. But, here the two compounds have also been found structurally similar by the structural similarity search tool on ChemMine https://chemminetools.ucr.edu/tools/view_job/1725615/) (Figure 2).This indicates that *Ananas comosus* fruit extracts which are known antibacterial agents can also inhibit AHL similar to that of halogenated furanone found in *Delsia pulchra*.

ChemMine structural similarity search tool was used for other furanone compounds as well. For example, (5Aα, 9Aα, 9Bβ)-5, 5A, 6, 7, 8, 9, 9A, 9B-Octahydro-6, 6, 9A-trimethylnaphtho[1, 2c] furan-1-(3H)-one (drimenin) has been obtained from heartwood, bark and leaf extract of *Warburgia salutaris* (Mohanlall and Odhav 2009). Although this compound was found similar to halogenated furanone i.e. 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone on pubChem search for similar structures, the structure similarity search on ChemMine could not reveal its similarity and tanimoto coefficient was also very low. Studies done on *Lactarius helvus* showed 3-Amino-4,5-dimethyl-2 (5H)- furanone as one of the bioactive compound. But, ChemMine search could not reveal its similarity with halogenated furanone.

Overall, this cheminformatics study suggests 2,5-dimethyl-4-hydroxy-3(2H)-furanone found in *Ananas comosus* as a potential quorum quencher based on its structural similarity with halogenated furanone found in *Delsia pulchra*. Halogenated furanone i.e. 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone found in *Delsia pulchra* has already been showed to restrict the interaction of quorum sensing molecule AHL in gram negative bacteria with is corresponding receptor and thereby affect the virulance. Thus, any structurally similar molecule can be expected to show similar effects. However, to prove the same, experimental evidences are required.

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Figure 1: Furanone compound of *Ananas comosus*: a) result of pubchem search reveling the structural similarity between halogenated furanone of *Delsia pulchra* and furanone compound obtained from pineapple. b) Compound similarity obtained by ChemMine similarity workb0000000.0.ench between the two furanone compound having CID 10309 for 2,5-dimethyl-4-hydroxy-3(2H)-furanone and CID 57169946 for 4-bromo-5-(bromomethylene)-3-(1′-hydroxybutyl)-2(5H)-furanone. Also a maximum common substructure is indicated (bottom left).

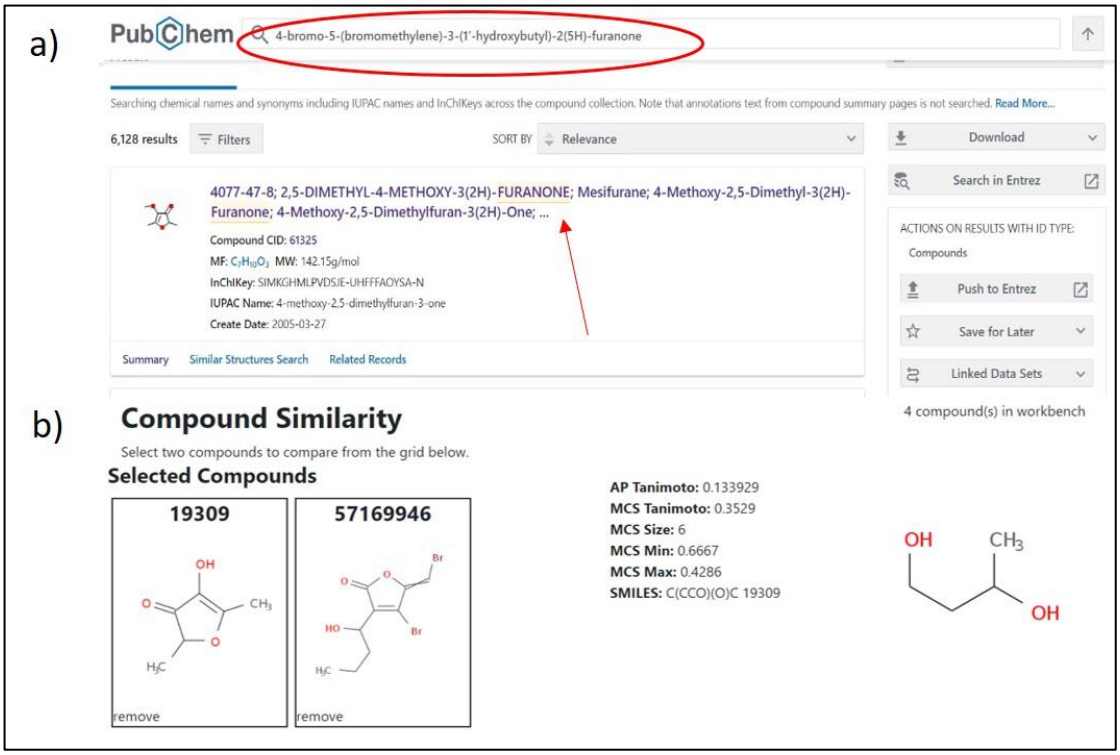

Figure 2: Structural similarity search for halogenated furanone compound; ChemMine tool reveals only one similarity of halogenated furanone with 2,5-dimethyl-4-hydroxy-3(2H)-furanone with similarity cutoff value of 0.5.