Original Research Paper

Volume-9 | Issue-6 | June-2019 | PRINT ISSN No. 2249 - 555X

Biological Science

QUORUM SENSING AND *IN SILICO* SYSTEM NETWORK STUDIES IN *K. PNEUMONIAE*

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ABSTRACT *Klebsiella pneumoniae* is a gram-negative bacteria and was *an* opportunistic pathogen that secrete type 2 signaling molecules leading to quorum sensing. The protein-protein interactions of pelC, rhlR, luxR and lasR has shown relationships and properties with Polysaccharide biosynthesis, Bioluminescence, Acid tolerance, Rhamnolipid biosynthesis, Virulence factor induction, pyocyanin biosynthesis and Biofilm formation. The analysis is conducted based on the interactions and analysis of KEGG and String databases, the mechanism of genes has been initiated as hybrid method in the present work. The docking result has shown that oxytetracycline has shown beter activity with pelC, rhlR, luxR and lasR receptors may be active against Biofilm formation by *Klebsiella pneumonia*e.

KEYWORDS : quorum sensing, *Klebsiella pneumoniae*, Network studies.

INTRODUCTION

Bacteria use quorum sensing mechanisms holding several clustering behaviors like biofilm formation, antibacterial therapy, host–microbial associations, etc using gene expression programmes [1,2]. *Klebsiella pneumoniae* is a gram-negative, encapsulated, non-motile, facultative anaerobic, lactose-fermenting, rod-shaped bacterium showing quorum sensing mechanisms [3, 4]. *K. pneumoniae* is a best known human pathogen of the respiratory system that causes pneumonia and underlying medical problems like chronic pulmonary disease and often arises as a nosocomial infection [5,6].

The gene/protein network studies are the replica network of the operation of a system. The *in silico* process of the process of the operation for the study of quorum sensing in K. pneumonia is a novel method in Bioinformatics. The key characteristics like functions, behaviour, and physical properties of a system in bacteria like *K. pneumonia* are essential in understanding the pathogenesis causing in humans.

Quorum sensing use by bacteria to have collective behaviours between living species due to expressions of gene expression programmes. Encoding of a putative glycosyltransferase system promotes capsular polysaccharide biosynthesis leading to cell-to-cell communication or quorum sensing [7,8]. Beta-galactosidase acts against autoinducer shows as quorum sensing cascade molecule [9]. Quorum quenching enzymes like lactonase, oxidoreductase**,** acylase and paraoxonase acts as density-dependent intercellular communication agents that coordinates multicellular behavior in prokaryotes [10,11,12]. Many intracellular metabolic functions leads to cell–cell communication by Adenosine deaminase catalyzes the deamination of adenosine with help of lasR [13]. Cefmetazole, Ceforanide, Ertapenem, Oxytetracycline and Ofloxacin are acts as antimicrobial agents for quorum sensing inhibition [14].

MATERIALS & METHODS

The system properties for the present work conducted are as follows: AMD A6-9220 RADEON R4, 5 compute cores 2C-3G 5.50 GHz processor with 4 GB RAM and 64-bit OS, x-64-based processor.

Four proteins name pelC, rhlR, luxR and lasR are selected for the interaction using string database (https://string-db.org). The proteins in *Pseudomonas aeruginosa* has been predicted interactions with pelC, sdiA - annotation not available [a.k.a. rhlR, sdiA_1, AO896_12160] and lasR. The proteins of LuxR and LasR with *Martelella mediterranea* have found interaction.

Based on the interactions and analysis of KEGG and String databases, the mechanism of genes has been initiated as hybrid method in the present work. The receptors (glycosyltransferase, beta-galactosidase, oxidoreductase and adenosine deaminase) have modeled using swissmodel. The sequences were retrieved from string database, submitted to swissmodel and the models with good validation have been selected for docking studies.

The ligands (Cefmetazole, Ceforanide, Ertapenem, Oxytetracyclin and Pefloxacin) were retrieved from Drugbank that are related to quorum sensing.

The docking of the receptors (glycosyltransferase, beta-galactosidase, oxidoreductase and adenosine deaminase) with selected ligands (Cefmetazole, Ceforanide, Ertapenem, Oxytetracyclin and Pefloxacin) from has been analysed for better activity using iGEMDOCK.

RESULTS AND DISCUSSION

The protein protein interactions of pelC, rhlR, luxR and lasR has shown relationships and properties with Polysaccharide biosynthesis, Bioluminescence, Acid tolerance, Rhamnolipid biosynthesis, Virulence factor induction, pyocyanin biosynthesis and Biofilm formation (Figure 1).

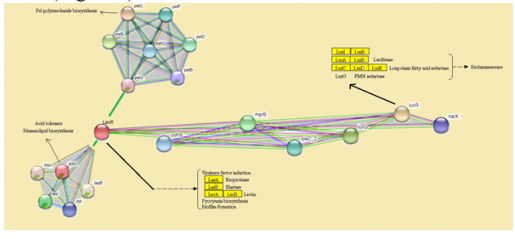

Figure 1: Quorum sensing mechanism using String/ KEGG pathways

The modeled structures from the sequences retrieved from string database have shown good validation shown by ramachandran plot (Figure 2). The ligands were selected from drug bank with term "quorum sensing" (Figure 3).

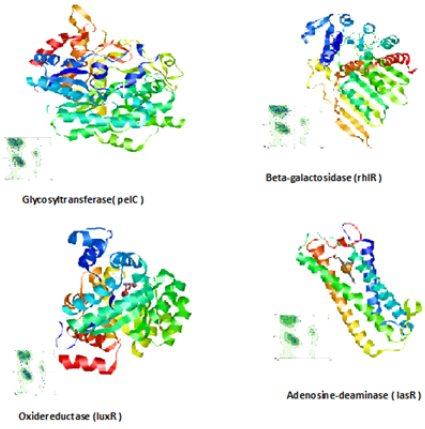

Figure 2: Selected Receptors

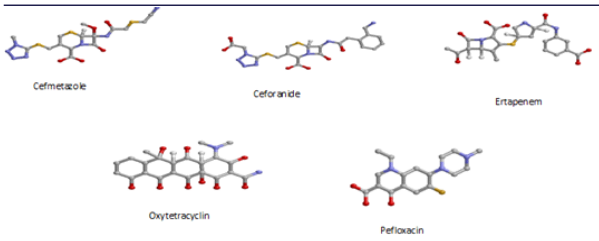

Figure 3: Selected Ligands

The docking result obtain between Glycosyltransferase (Receptor) with Cefmetazole (Ligand) has shown binding energy value of -97.4 K.Cal. The active site of the ligand binding with protein molecule is THR -3.5, ARG –7.9, TYR –9.3, THR -4.1 The Docking Result Obtain Between beta-galactosidase (Receptor) with Cefmetazole (Ligand) has shown binding energy value of -95.8 K.Cal. The active site of the ligand binding with protein molecule is TYR -14, LEU –3.5, GLN -6.5, ARG -3.4, ARG -3.5. the docking result obtain between Oxidoreductase (Receptor) with Cefmetazole (Ligand) has shown binding energy value of -99.3 K.Cal. The active site of the ligand binding with protein molecule is ARG -3.8, ARG –11.7,ARG -3.5, GLN -4.1, GLN -4.1, ASP -4.7, HIS -2.8. The Docking result obtain between Adenosine deaminase (receptor) with Cefmetazole (Ligand) has shown binding energy value of -96.7 K.Cal. The active site of the ligand binding with protein molecule is ASN -3.5, ASP -3.5, GLY -5.6, ASP –2.6, HIS -3.8.

The docking result obtain between Glycosyltransferase (Receptor) with Ceforanide (Ligand) has shown binding energy value of -99.4 K.Cal. The active site of the ligand binding with protein molecule is ARG -2.7, GLU -6, ARG -5.8, GLN -3.5, and ARG -3.5. The docking result obtain between Beta-galactosidase (Receptor) with Ceforanide (Ligand) has shown binding energy value of -107.4 K.Cal. The active site of the ligand binding with protein molecule is ARG -2.7, ARG -2.9, ARG -2.7, ARG -9, ARG -3.5, GLN -2.8, ARG -9.5, and ARG 5.7, HIS 6. The docking result obtain between Oxiderductase (Receptor) with Ceforanide (Ligand) has shown binding energy value of -101.8 K.Cal. The active site of the ligand binding with protein molecule is PHE -3.5, GLU -3.5, ARG -4.6, TYR -5.6, ASP -2.5, ARG -3.5. The docking result obtain between Adenosine Deaminase (Receptor) with Ceforanide (Ligand) has shown binding energy value of -103.3 K.Cal. The active site of the ligand binding with protein molecule is CYS -4.6, VAL -6.3, ASP -7.6, LEU -3.5, GLU -7.4, GLY -2.5, ILE -8.1, THR -2.8.

The docking result obtain between Glycosyltransferase (Receptor) with Ertapenem (Ligand) has shown binding energy value of -98 K.Cal. The active site of the ligand binding with protein molecule is SER -6, HIS –3.5, LEU -2.5, THR -2.5, THR -6.5, THR -2.5. The docking result obtain between beta-galactosidase (Receptor) with Ertapenem (Ligand) has shown binding energy value of -94.8 K.Cal. The active site of the ligand binding with protein molecule is LEU -6, GLY -7.9, ASN -5.9, ALA -2.7, SER -3.5. The docking result obtain between Oxidoreductase (Receptor) with Ertapenem (Ligand) has shown binding energy value of -98.4 K.Cal. The active site of the ligand binding with protein molecule is PHE -3.5, SER -4.2, SER -7, SER -3.8, ARG -5.4. The docking result obtain between Adenosine deaminase (Receptor) with Ertapenem (Ligand) has shown binding energy value of -81.6 K.Cal. The active site of the ligand binding with protein molecule is ALA -2.5, LEU -3.5, ILE -6, THR -4.7..

The docking result obtain between Glycosyltransferase (Receptor) with Oxytetracyclin (Ligand) has shown binding energy value of -115.8 K.Cal. The active site of the ligand binding with protein molecule is GLN -3.9, GLU -5, HIS -3.1, GLU -3.5, SER -7.5, TRP -2.5, LEU -9.8, ASN -8.5. The docking result obtain between Beta-galactosidase (Receptor) with Oxytetracyclin (Ligand) has shown binding energy value of -120.3 K.Cal. The active site of the ligand binding with protein molecule is ASP -3.9, ARG -2.5, ARG -3.5, GLN -5.3, GLN -3.7, ARG -10.6, GLU -9.9. The docking result obtain between Oxidoreductase (Receptor) with Oxytetracyclin (Ligand) has shown binding energy value of -118.3 K.Cal. The active site of the ligand binding with protein molecule is ASP -4.7, ASN -9.5, ARG -3.1, ARG -6, GLU -11.6. The Docking Result Obtain Between Adenosine deaminase (Receptor) With Oxytetracyclin (Ligand) Has Shown Binding Energy Value Of -106.6 K.Cal. The Active Site Of The Ligand Binding With Protein Molecule is ARG -14.1, ASP -2.8, TYR -2.5.

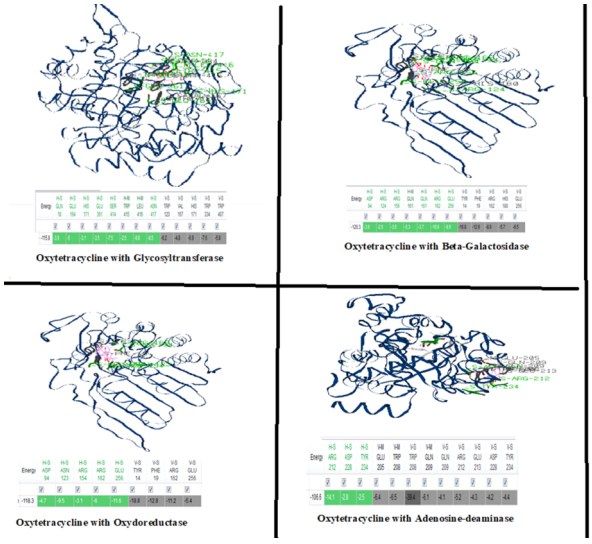

Figure 4: Selected Receptors

The results of the best docked ligand Oxytetracyclin with all the selected receptors are shown in Figure 4.

The docking result obtain between Glycosyltransferase (Receptor) with Pefloxacin (Ligand) has shown binding energy value of -82.4 K.Cal. The active site of the ligand binding with protein molecule is GLN -2.8, GLU -3, ARG -2.5, TRP -2.6. The Docking Result Obtain Between Beta-galactosidase (Receptor) with Pefloxacin (Ligand) has shown binding energy value of -83.3 K.Cal. The active site of the ligand binding with protein molecule is ARG -2.5, ARG -2.5, ARG -4.9, ARG -9.7. The docking result obtain between Oxidoreductase (Receptor) with Pefloxacin (Ligand) has shown binding energy value of -76.7 K.Cal. The docking result obtain between Adenosine deaminase (Receptor) with Pefloxacin (Ligand) has shown binding energy value of -76.7 K.Cal. the active site of the ligand binding with protein molecule is TYR -2.5.

TABLE 1: Docking Result

Ligands	Glycosyl transferase	Beta-Galactosidase	Oxidoreductase	Adenosine Deaminases
Cefmetazole	-97.4	-95.8	-99.3	-96.7
Ceforanide	-99.4	-107.4	-101.8	-103.3
Entrapenem	-98	-94.8	-98.4	-81.6
Oxytetracyclin	-155.8	-120.3	-118.3	-106.6
Pefloxacin	-82.4	-83.3	-76.4	-76.7

Oxytetracyclin has found best molecule as inhibitors of Biofilm formation and Quorum sensing agents. Quorum Sensing is a process of communication in bacteria by using secreted chemical signaling molecules or Autoinducers between the cells. *Klebsiella pneumoniae* is an opportunistic pathogen secretes type 2 signaling molecules plays a major role in biofilm formation in the early stages of microcolonies development [15].

CONCLUSION

The docking result has shown that oxytetracycline has shown beter activity with pelC, rhlR, luxR and lasR receptors may be active against Biofilm formation by *Klebsiella pneumonia*e. Further wetlab methods may provide good support for the activity of controlling biofilm formation from the early stages *klebsiella pneumoniae.*

ACKNOWLEDGEMENT

The author acknowledged to thank management and staff of Atal Bihari Vajpayee University, Bilaspur (CG) in bringing out the research work.

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