Research Article

Computer Aided Drug Screening for Lung Infection

Joydeep Paul*[1], Payel Debnath[1], Ranajit Nath[1], Ratul Bhowmik[2], Sara Farheen[1]

1. Department of Pharmacology, NSHM Knowledge Campus, Kolkata-Group of Institutions, Kolkata, West Bengal, India.
2. Department of Pharmaceutical Chemistry, SPER, Jamia Hamdard, New Delhi, India.

***Corresponding author's E-mail:** bkwatra999@gmail.com

Received: 02-03-2021; **Revised:** 22-04-2021; **Accepted:** 28-04-2021; **Published on:** 15-05-2021.

ABSTRACT

Lung infections are the leading cause of morbidity and mortality worldwide. Most causes of infection are not treatable. In children less than 5 years of age, they are the cause of death. Most infections are caused by viruses and bacteria. We present a docking-screening using a quantum mechanical scoring of a library built from approved drugs and competent that apiin, baicalein, boswellic acid, eugenol, ganoderic acid, quercetin, vasicine, with proteins with PDB id's 1VQQ, 3N26, 7K40, 5EG7 could display antiviral activity against lung infection. Clearly, these compounds should be further evaluated and clinical trials to confirm their actual activity against the disease.

Keywords: Lung infection, phytochemicals, docking, active sites, ligand, receptor.

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DOI: 10.47583/ijpsrr.2021.v68i01.027

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v68i01.027

INTRODUCTION

Lung infection is often considered one of the most common medical conditions around the globe. It is also considered as one of the leading causes of death and disability in the world. It is estimated that lung infection accounts for more than 4 million fatalities annually [14]. Bacteria and viruses are the main causes of acute lower respiratory tract infection. Therefore, there is a pressing need to create an intense enemy of this disease, specialist for the avoidance of the flare – up and stop the bacterial and viral contaminations. Repurposing of realized little particles is by all accounts an exceptionally productive path so as to create strong medications to battle diseases in this brief timeframe[1-5,11,15,16,21,24,26]. As of late, various endeavors are made to plan novel inhibitors or utilize drug repurposing ways to deal with recognition hostile to medication [10,12,18].

PROCEDURE

1. Ligand Screening

For the initial Ligand screening purposes, a web-based tool named SwissADME (https ://www.swiss adme.ch/) was used to eliminate a few compounds according to Lipinski's rule of five parameters [23]. For a compound to qualify as ligand it should Have < 500 Da molecular weight, a high lipophilicity i.e. value of Log P being less than 5, hydrogen bond acceptors being less than 10 and H-bond donors less than 5. Any compound with more than 2 violations was ruled out for further study.

2. Protein Preparation and Active Site Determination.

Required protein in pdb format was downloaded from the website **rcsb.org**, commonly known as the **Protein Data Bank** [28]. 3D conformers of the ligand were downloaded from PubChem [19,20].

Using **PyMOL (Version 2.4.1)** software water molecules as well as native ligands from the protein were removed, defined as cleaning/purification of the protein for further application [29]. **Using a web server called Deep Site** Active Pockets of the proteins were calculated [8]. The results calculated by the web server were in the form of different ids, centers and scores.

Scoring in deep site was using neural networking based on following instructions using DCNN architecture. Center values for the grid were selected keeping score greater than 0.98.

UCSF Chimera (Version 1.14) was used to prepare the receptor using DockPrep function [30]. **Dock Prep** prepared structures for Docking using these functions:

- deleting water molecules
- repairing truncated sidechains
- adding hydrogens
- assigning partial charges
- writing files in Mol2 format

In silico Docking Using Auto dock Vina Autodock Vina (Version 1.1.2) along with UCSF Chimera (Version 1.14) was used for molecular **Docking Studies** [6,30]. Center values

and size of the grid of different scores were used from **DEEPSITE** calculations done above.

Following Parameters were set in auto dock vina.

Receptor options –

- **Add hydrogens in Chimera** (**true**/false) – whether to add hydrogens in Chimera before calling the script. The receptor prep script will check for hydrogens and add them if they are missing. AutoDock Vina needs the polar (potentially H-bonding) hydrogens to identify atom types for scoring purposes.
- **Merge charges and remove non-polar hydrogens** (**true**/false) – note AutoDock Vina does not use charges or nonpolar hydrogens, so this setting is not expected to affect results except for the presence or absence of nonpolar hydrogens in the processed receptor
- **Merge charges and remove lone pairs** (**true**/false) – note AutoDock Vina does not use charges or lone pairs, so this setting is not expected to affect results except for the presence or absence of lone pairs in the processed receptor (and there may not have been any lone pairs to start with)
- **Ignore waters** (**true**/false)
- **Ignore chains of non-standard residues** (**true**/false) – ignore chains composed entirely of residues other than the 20 standard amino acids.
- **Ignore all non-standard residues** (true/**false**) – ignore all residues other than the 20 standard amino acids.

For Ligands

- **Merge charges and remove non-polar hydrogens** (**true**/false) – note Auto Dock Vina does not use charges or nonpolar hydrogens, so this setting is not expected to affect results except for the presence or absence of nonpolar hydrogens in the ligand output files
- **Merge charges and remove lone pairs** (**true**/false) – note AutoDock Vina does not use charges or lone pairs, so this setting is not expected to affect results except for the presence or absence of lone pairs in the ligand output files (and there may not have been any lone pairs to start with)

3. Docking parameters

- **Number of binding modes** (1-10, **10**) – maximum number of binding modes to generate
- **Exhaustiveness of search** (1-8, **8**) – thoroughness of search, roughly proportional to time
- **Maximum energy difference (kcal/mol)** (1-3,**3**) – maximum score range; binding modes with scores not within this range of the best score will be discarded.

The docking results were calculated by Auto dock vina using it's Scoring function and results were displayed in the form of Scores and RMSD values. Docking results with the highest value score accompanied by negative sign and least RMSD values were chosen for further studies.

4. Residue Analysis

PyMOL was used for visualization of interactions of the docked structure at the ligand sites. **Discovery Studio 2020** was used to study the ligand interactions and total number of residues [7]. It was also used to plot the 2D structure of the interactions and residues.

5. Statistical Analysis

Descriptive, estimation and Hypothesis testing with confidence interval of 95% was applied to data using formula 1 given belw.

$$CI = \bar{x} \pm z\frac{s}{\sqrt{n}}$$

CI = confidence interval
$\bar{x}$ = sample mean
z = confidence level value
s = sample standard deviation
n = sample size

Formula 1 used for calculation of confidence interval

RESULTS AND DISCUSSION

Molecular Docking

The docking result was obtained from Autodock vina in the form of Dock score for all the four proteins docked with the above mentioned ligands.

Docking Results of Influenza Virus Protein

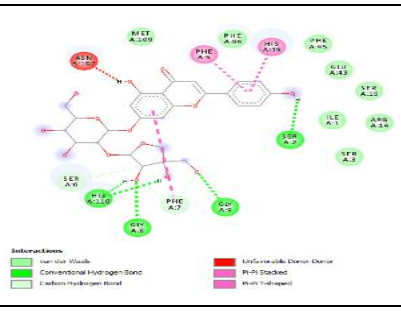
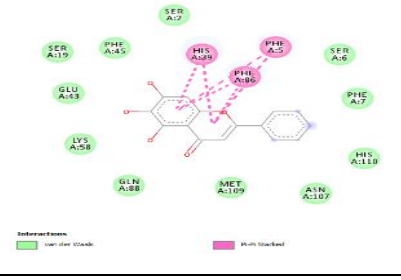
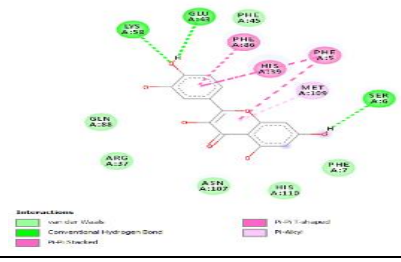
PDB-ID 5EG7 [25,26,27]

For 5EG7, two active sites were selected out of which the first active site was selected with a Deepsite score of 0.99965. The selection was made on the basis of the highest binding energy of the ligand-receptor. The docking results before statistics are shown in **Table 1** and **Table 2** shows the post statistical docking scores with Ligand Protein interactions.

Table 1: Docking score of phytochemicals with Influenza Virus viral protein.

Ligand	Dockscore
Apiin	-8
Baicalein	-8
Boswelic Acid	-7.6
Eugenol	-5.8
Genoderic Acid	-7.2
Quercetin	-8.2
Resveratrol	-7.2
Vasicine	-6.3

Table 2: Docking scores and 2D amino acids interactions of Apiin, Baicalein and Quercetin with Influenza Virus viral protein.

Ligands	Dock score	Interactions
Apiin	-8	
Baicalein	-8	
Quercetin	-8.2	

Docking results of SARS-Cov2 viral protein

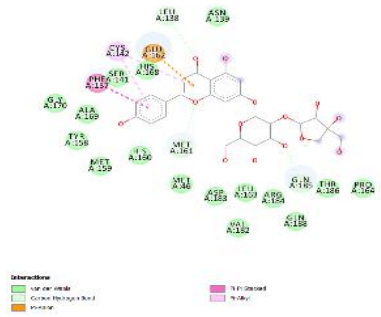
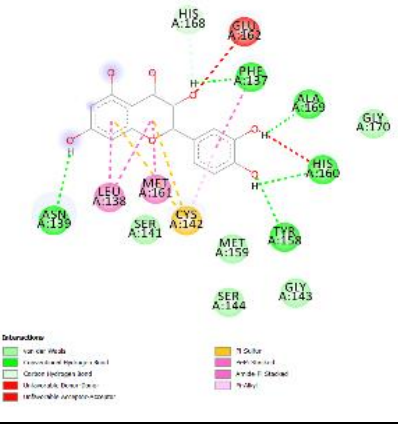
PDB-ID 7K40 [9]

For 7K40, four active sites were selected out of which the second active site was selected with a Deepsite score of 0.988627. The selection was made on the basis of the highest binding energy of the ligand-receptor. The docking results before statistics are shown in **Table 3** and **Table 4** shows the post statistical docking score with Ligand Protein interactions.

Table 3: Docking score of phytochemicals with SARS-CoV2 viral protein.

Ligand	Dockscore
Vasicine	-5.5
Eugenol	-5.3
Apiin	-8.9
Baicalein	-6.8
Resveratrol	-7.6
Quercetin	-7.9
Ganoderic Acid	-7.6
Boswellic Acid	-7.5

Table 4: Docking scores and 2D amino acids interactions of Apiin and Quercetin with SARS-CoV2 viral protein.

Ligands	Dock score	Interactions
Apiin	-8.9	
Quercetin	-7.9	

Docking results of Chlamydia pneumoniae transport protein

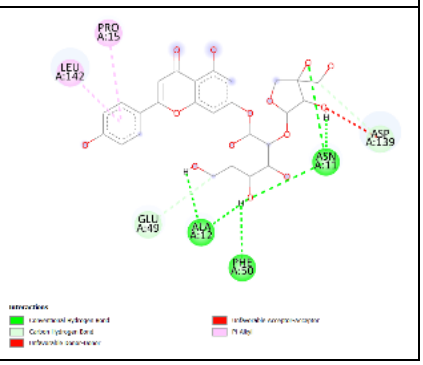
PDB-ID 3N26 [13]

For 3N26, four active sites were selected out of which the first active site was selected with a Deepsite score of 0.999139. The selection was made on the basis of the highest binding energy of the ligand-receptor. The docking results before statistics are shown in **Table 5** and **Table 6** shows the post statistical docking score with Ligand Protein interactions.

Table 5: Docking score of phytochemicals with Chlamydia pneumoniae transport protein.

Ligand	Dock score
Eugenol	-5.2
Vasicine	-5.4
Apiin	-8.4
Baicalein	-6.8
Boswellic Acid	-6.9
Ganoderic Acid	-6.7
Quercetin	-6.9
Resveratrol	-6.8

Table 6: Docking scores and 2D amino acids interactions of Apiin with Chlamydia pneumoniae transport protein.

Ligands	Dock Score	Interactions
Apiin	-8.4	

Docking results of Staphylococcus aureus penicillin binding protein

PDB-ID 1VQQ [17, 25]

For 1VQQ, 2 active sites for chain A and 2 active sites for chain B were selected out of which the first active site of chain B was selected with a Deepsite score of 0.998654. The selection was made on the basis of the highest binding energy of the ligand-receptor. The docking results before statistics are shown in **Table 7** and **Table 8** shows the post statistical docking score with Ligand Protein interactions.

Table 7: Docking score of phytochemicals with Staphylococcus aureus penicillin binding protein.

Ligand	Dock score
Apiin	-8.7
Baicalein	-7.8
Boswellic Acid	-10
Eugenol	-5.4
Genoderic Acid	-7.1
Quercetin	-7.6
Resveratrol	-7.2
Vasicine	-6.1

Table 8: Docking scores and 2D amino acids interactions of Apiin and Boswellic acid with Staphylococcus aureus penicillin binding protein.

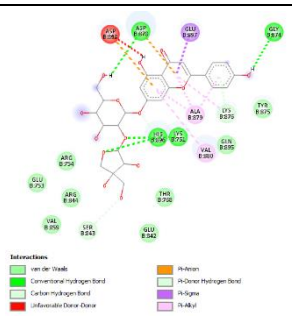
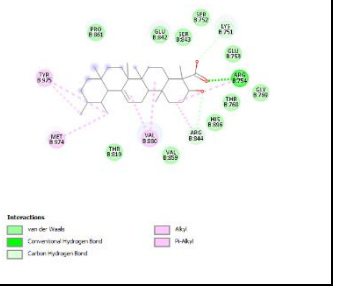
Ligands	Dock score	Interactions
Apiin	-8.7	
Boswellic Acid	-10	

Table 9: It summarizes the results showing ligands and their interacted proteins that were considered in the study for the targeted disease.

Ligands	Proteins Interacted	Target Disease
Apiin Baicalein Boswellic acid Eugenol Ganoderic acid Quercetin Resveratrol Vasicine	1VQQ 7K40 3N26 5EG7	Lung infection caused by Sars-CoV2 (7K40), Influenza Virus (5EG7), Staphylococcus aureus (1VQQ), Chlamydia pneumonia (3N26)

CONCLUSION

All 8 ligands were studied using bioavailability radar. Our results proposed that Apiin, Baicalein and Quercetin showed best docking results with PDB-ID 5EG7. For PDB-ID 7K40, Apiin and Quercetin showed the best docking results. Apiin also showed best docking results with PDB-ID 3N26. For PDB-ID 1VQQ, Apiin and Boswellic acid showed best docking results. To find the effectiveness and to propose the exact mechanism in-vitro studies can be encouraged on Apiin, Baicalein, Quercetin, and Boswellic acid targeting their respective protein of organisms responsible for lung infection that are discussed above to understand the mechanism and a potential cure for lung infection.

Acknowledgement

We would like to thank our supervisor, Bharat Kwatra, from Invenzion Labs Inc. whose expertise was invaluable in formulating the research questions, methodology and drawing conclusions. His insightful feedback and guidance pushed us to sharpen our thinking and brought our work to a higher level.

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Source of Support: None declared.

Conflict of Interest: None declared.