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DRUG REPURPOSING: IN SILICO MODELING OF INFLUENZA AND MALARIA

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ABSTRACT: Drug repurposing is a novel tool that brought new mechanism to reposition old drugs with a different therapeutic target. The major reason behind the drug repurposing was that, a drug can hit different targets and receptor in the same time or even it may active different signaling pathways. Drug repurposing holds the potential to bring medications with know safety profiles to new patients population. Numerous examples exist for the identification of new indication of new indication for existing molecules, most steaming from serendipitous findings or focused recent efforts specifically limited to the mode of action of a specific drug.In recent years , the need for new approaches to drug research and development, combined with the advent of big data repositories and associated analytical methods , has generated interest in development of systemic approaches to drug repurposing. We present a docking-based screening using a quantum mechanical scoring of a library built from approved drugs and compounds that Carvacrol, Curcumin, Quercetin, HCQ, Indinavir, Allyl Isothiocyanate, with Proteins with PDB id's 4WAT, 6E11, 6OHG, 6S8T, 1EA3, 2N70 could display antiviral activity against Influenza and malaria. Clearly, these compounds should be further evaluated in experimental assays and clinical trials to confirm their actual activity against the disease. We hope that these findings may contribute to the rational drug design against Influenza and malaria.

Keywords: Drug repurposing, virtual screening, drug research, influenza, malaria.

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1. INTRODUCTION

Influenza and malaria continues being one of global leading causes of death. Influenza viruses still constitute a real public health problem today. To cope with the emergence of new circulating strains, but also the emergence of resistant strains to classic antivirals, it is necessary to developed new antiviral approaches. Malaria, being the main global cause globally in the 5 - to 14 - year-old population and the third caused among children below five. Drug repurposing involves findings novel medical uses for existing drugs, including approved, investigation, discontinued and shelved therapeutics. Repurposing a drug has several advantages in compare to de novo drug design drug discovery, since the new therapeutic indication is built on already available. Repurposing a drug has several advantages in comparison to de novo drug discovery. 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 time frame. As of late, various endeavors were made to plan novel inhibitors or utilize drug repurposing ways to deal with recognition hostile to medications. [3,26,33,34,35,53]

2. MATERIALS AND METHODS

Procedure:

ligand Screening [40,41,42,43,45]

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. 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 (Lipinski2004).

Protein Preparation and Active site Determination [44,46,47,48,49,50]

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

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. **Using a web server called Deep Site** Active Pockets of the proteins were calculated. 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. https://academic.oup.com/bioinformatics/article/33/19/3036/3859178 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. **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

1. In silico Docking Using Auto dock Vina [51,52,53,54,55]

Auto dock Vina (Version 1.1.2) along with UCSF Chimera (Version 1.14) was used for molecular **Docking Studies**. Center values and size of the grid of different scores were used from **DEEPSITE** calculations done above.

1. 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)
- **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. 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 below.

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

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 Auto dock vina in the form of Dock score for all the three proteins docked with above mentioned ligands.

Malarial Protein Docking Results

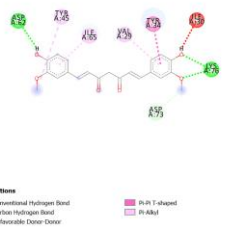
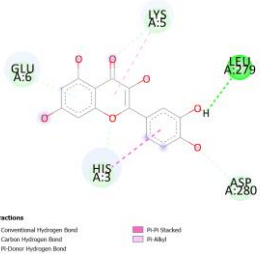
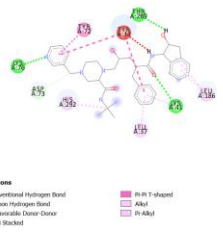
PDB-ID 4WAT [1,2,3,4,5,6,7]

For 4WAT, four active sites were selected out of which the 4thactive site was selected with a Deep site score of 0.997. 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 Result for 4WAT

Ligands	Dock score
Carvacrol	-6.1
Curcumin	-7.6
Quercetin	-6.8
HCQ	-5.4
Indinavir	-9.2
Allyl Isothiocyanate	-3.3

Table 2 - Docking Result for 4WAT with iteraction

Ligands	Dock score	Interactions
Curcumin	-7.6	
Quercetin	-6.8	
Indinavir	-9.2	

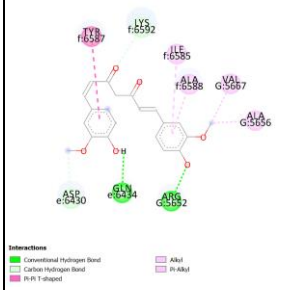
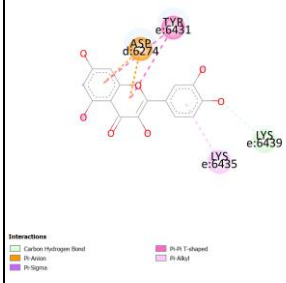
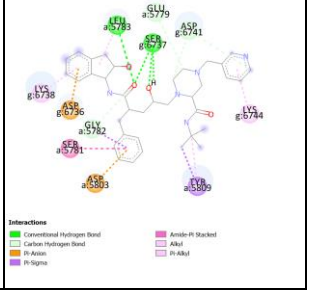
PDB-ID 6E11 [8,9,10,11,12,13,14,15,16]

For 6E11 Chain A, out of the three active sites the 3rd active site was selected with a Deep site score of 0.980. 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 scores with Ligand Protein Interactions.

Table 3 - Docking Result for 6E11

Ligands	Dock score
HCQ	-6.9
Indinavir	-9.7
Allyl Isothiocyanate	-3.3
Carvacrol	-6.7
Quercetin	-8.2
Curcumin	-7.6

Table 4 - Docking Result for 6E11 with interaction

Ligands	Dock score	Interactions
Curcumin	-7.6	
Quercetin	-8.2	
Indinavir	-9.7	

PDB-ID 6OHG [17,18,19,20,21,22,23,24,25,26,27,28,29]

For 6OHG, three active sites were selected out which 1st active site was selected with Deep site score of 0.999, the selection was made on the basis of highest binding energy of ligand-receptor, docking results before statistics are shown in Table 5, No further Statistics studies were performed because of Low standard (max score <(-)7) docking results.

Table 5 - Docking Result for 60HG

Ligands	Dock score
HCQ	-5
Indinavir	-6.4
Allyl Isothiocyanate	-2.8
Carvacrol	-4.5
Quercetin	-5.9
Curcumin	-5.4

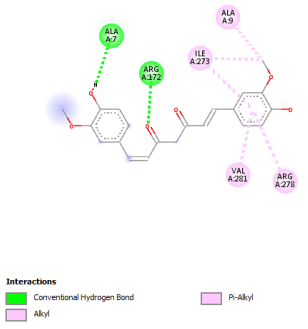
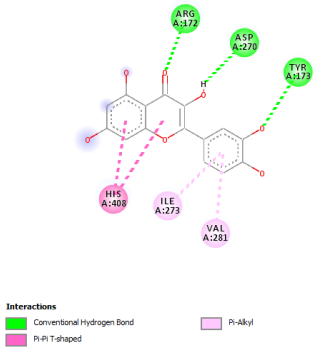
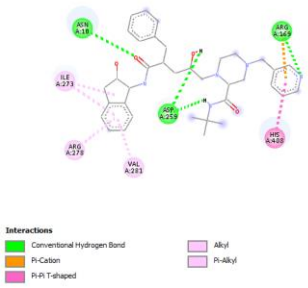
PDB-ID 6S8T [30,31,32,33,34,35,36,37,38]

For 6S8T, three active sites were selected out which 1st active site was selected with Deep site score of 0.999, the selection was made on the basis of highest binding energy of ligand-receptor, docking results before statistics are shown in Table 6 and Table 7 shows the post statistical docking scores with Ligand Protein Interactions.

Table 6 - Docking Result for 6S8T

Ligands	Dock score
HCQ	-6.2
Indinavir	-8.3
Allyl Isothiocyanate	-4
Carvacrol	-6.2
Quercetin	-7.5
Curcumin	-6.5

Table 7 - Docking Result for 60HG with interaction

Ligands	Dock score	Interactions
Curcumin	-6.5	
Quercetin	-7.5	
Indinavir	-8.3	

Influenza Protein Docking Results

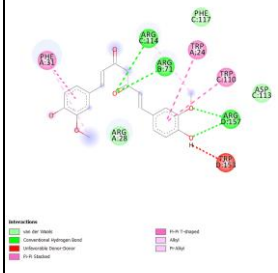
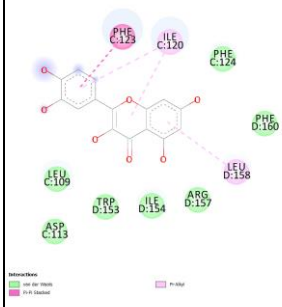
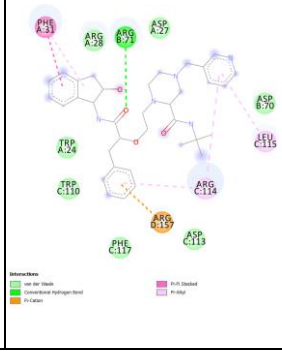
PDB-ID 2N70 [39,40,41]

For 2N70, two active sites were selected out which 1st active site was selected with Deep site score of 0.997, the selection was made on the basis of highest binding energy of ligand-receptor, docking results before statistics are shown in Table 8 and Table 9 shows the post statistical docking scores with Ligand Protein Interactions.

Table 8 - Docking Result for 2N70

Ligand	Dock Score
Allyl Isothiocyanate	-3.8
Carvacrol	-5.7
Curcumin	-6.6
HCQ	-5.9
Indinavir	-7.6
Quercetin	-6.4

Table 9 - Docking Result for 2N70

Ligands	Dock score	Interactions
Curcumin	-6.6	
Quercetin	-6.4	
Indinavir	-7.6	

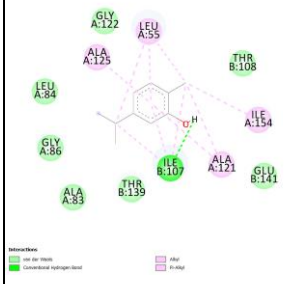
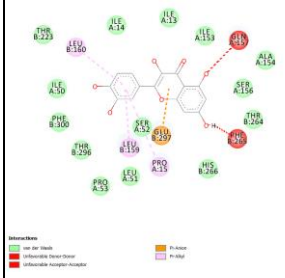
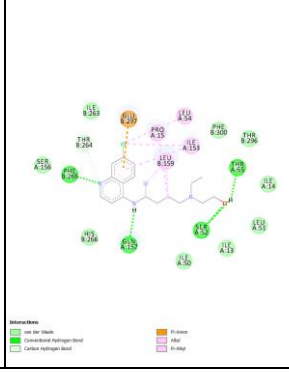
PDB-ID 1EA3 [42,43]

For 2N70, one active sites were selected with Deep site score of 0.987, the selection was made on the basis of highest binding energy of ligand-receptor, docking results before statistics are shown in Table 10 and Table 11 shows the post statistical docking scores with Ligand Protein Interactions.

Table 10 - Docking Result for 1EA3

Ligand	Dock Score
Allyl Isothiocyanate	-3.3
Carvacrol	-6.7
Curcumin	-9
HCQ	-7.2
Indinavir	-6.6
Quercetin	-8.6

Table 11 - Docking Result for 1EA3

Ligands	Dock score	Interactions
Carvacrol	-6.7	
Quercetin	-8.6	
HCQ	-7.6	

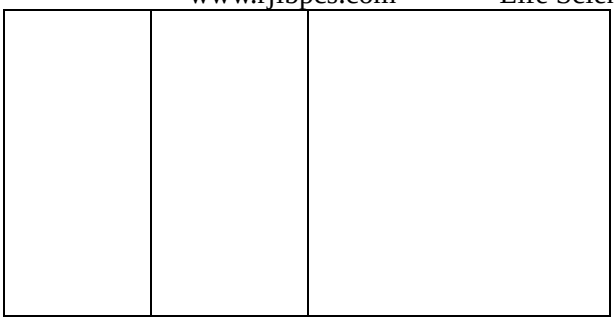


Table 12 summarizes the results showing ligands and their interacted proteins that were considered in the study for the targeted diseases.

Ligand	Proteins Interacted	Target Disease(s)
Allyl Isothiocyanate	-	-
Carvacrol	1EA3	Influenza
Curcumin	4WAT, 6E11, 6S8T, 2N70	Influenza, Malaria
HCQ	1EA3	Influenza
Indinavir	4WAT, 6E11, 6S8T, 2N70	Influenza, Malaria
Quercetin	1EA3,4WAT, 6E11,6S8T,2N70	Influenza, Malaria

4. CONCLUSION

All six ligands were studied using bioavailability radar. Our results proposed Curcumin, Quercetin, Indinavir showed best docking result for Malarial Proteins with PDB id's 4WAT, 6E11, 6S8T. For Influenza protein with PDB id 2N70, Curcumin, Quercetin, Indinavir showed standardized results, whereas, other influenza protein included in study with PDB id 1EA3 showed best docking results with Quercetin, HCQ and Carvacrol. Allyl Isothiocyanate didn't show standardized results with any of the proteins included in the study, on the other hand 6OHG protein didn't produce any standardized results in this study. To find the effectiveness and to propose the exact mechanism in-vitro studies can be encouraged on Curcumin, Quercetin, Indinavir, HCQ and Carvacrol targeting respective diseases that are discussed above to understand the mechanism and a potential cure for Malaria and Influenza.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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