Research Article

Computational Repurposing Model of Curcumin As A Drug

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ABSTRACT

Viral diseases continue to be a public threat on a global scale day by day and the world is in a continuing battle with the novel deadly viral Diseases and with no prompt medicines accessible the scourge brought about by the disease is expanding step by step. The ongoing need to develop new antiviral drugs with fewer side-effects and that are effective against viral pathogens has spurred the research community to invest in various drug discovery strategies, one of which is drug repurposing the methods of finding most promising existing compounds which has able to give best positive effects against viral infections. We present a docking-based screening using a quantum mechanical scoring of drug Curcumin with Proteins with PDB id's 4B3V, 5LK0, 6BM8, 4QUZ, 6SJV, 1JLF, 5EG7, 7K40 could display antiviral activity against Rubella, Hanta, Herpes, Noro, papilloma, HIV, Influenza, COVID19. Clearly, these compounds should be further evaluated in experimental assays and clinical trials to confirm their actual activity against the viral disease. We hope that repurposing of the drug from our recommendation may contribute to the rational drug design against the above viruses.

Keywords: Curcumin, Viral diseases, docking, interactions, active site, ligand, receptor.

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INTRODUCTION

Day by day the use of synthetic drugs has increased continuously which has various side-effects on the human body but plant-based drugs are more suitable in terms of the least side effects. Since ancient times mankind has been dependent on plant drugs for the treatment of various deadly viral diseases, among all plant drugs curcumin is widely used, the principal polyphenol extracted from turmeric. Its medicinal properties are mentioned in Indian Veda's and Chinese medicine. Curcumin has been studied extensively for its pleiotropic activity, including anti-inflammatory, anti-oxidant, and antiviral activity [1,2,6]. These mechanisms involve direct interference of viral replication and suppression of cellular signalling pathways essential for viral replication, such as PI3K/Akt, NF-κB [16,17].

A clinical trial of curcumin in patients with premalignant lesions concluded that curcumin in higher doses does not appear any toxic effects in the patient's body not only that in various clinical trials conducted in humans for various cancers and other health conditions curcumin given promising results suggesting low toxicity of curcumin. One of the main biological functions of curcumin is revoking the infection of viruses, by targeting the viral entry or just attacking the viral components which are essential for viral replication [4,5,24].

Viral diseases have become a critical public issue over the globe since the beginning. It influences individuals worldwide and there is no immunization yet for these infections. we require to identify the main pathways that the treatment should target. These targets can either be the main proteins of the virus involved in the mechanisms used to enter the host cell and replicate, or the host proteins that facilitate the spread of the virus or cause over-reactive dangerous responses, here is a vital need to create a strong enemy of these diseases, specialists for the breaks viral chain contaminations. As of late, various scientists were made to plan novel inhibitors or find to utilize drug repurposing ways to deal with recognition hostile to medications [25,26].

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 [14]. 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** [12,13]. 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 [15]. The results calculated by the web server were in the form of different ids, centres and scores. Scoring in deep site was using neural networking based on following instructions using DCNN architecture. Centre values for the grid were selected keeping score greater than 0.98.

UCSF Chimera (Version 1.14) was used to prepare the receptor using Dock Prep function [7]. **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 Autodock Vina

- **Autodock Vina (Version 1.1.2) along with UCSF Chimera (Version 1.14)** was used for molecular **Docking Studies** [7,8]. Centre values and size of the grid of different scores were used from **DEEPSITE** calculations done above.

Following Parameters were set in autodock 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 Autodock 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 [9]. **Discovery Studio 2020** was used to study the ligand interactions and total number of residues [10]. 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 [11].

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

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.

Docking Results of Rubella Virus Protein:

PDB_ID 4B3V [18]

For 4B3V, five active sites were selected out of which the 1st active site was selected with a Deep site score of 0.993. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 1**.

Docking result of Hantavirus protein:

PDB_ID 5LK0 [19]

For 5LK0, two active sites were selected out of which the 1st active site was selected with a Deep site score of 0.998. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 2**.

Docking result of Herpes Simplex virus protein:

PDB_ID 6BM8 [20]

For 6BM8, three active sites were selected out of which the 1st active site was selected with a Deep site score of 0.998. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 3**.

Docking result of Norovirus protein:

PDB_ID 4QUZ [21]

For 4QUZ, two active sites were selected out of which the 1st active 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 and the 2D interaction diagram is given below in **Table 4**.

Docking result of Human Papillomavirus protein:

PDB_ID 6SJV

For 6SJV, two active sites were selected out of which the 1st active site was selected with a Deep site score of 0.999. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 5**.

Docking result of HIV virus protein:

PDB_ID 1JLF [22]

For 1JLF, three active sites were selected out of which the 1st active site was selected with a Deep site score of 0.999. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 6**.

Docking result of Influenza virus protein:

PDB_ID 5EG7 [23]

For 5EG7, two active sites were selected out of which the 1st active site was selected with a Deep site score of 0.999. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 7**.

Docking result of SARS-CoV2 virus protein:

PDB_ID 7K40 [3]

For 7K40, four active sites were selected out of which the 1st active site was selected with a Deep site score of 0.998. The selection was made on the basis of the highest binding energy of the ligand receptor. The docking results and the 2D interaction diagram is given below in **Table 8**.

Table 1: Docking score and 2D interactions of Curcumin with Rubella Virus viral protein.

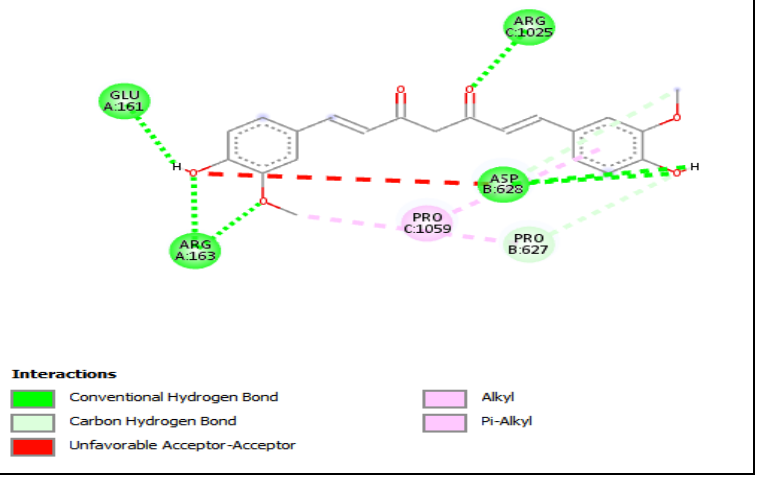
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	4B3V	-8	

Table 2: Docking score and 2D interactions of Curcumin with Hantavirus viral protein.

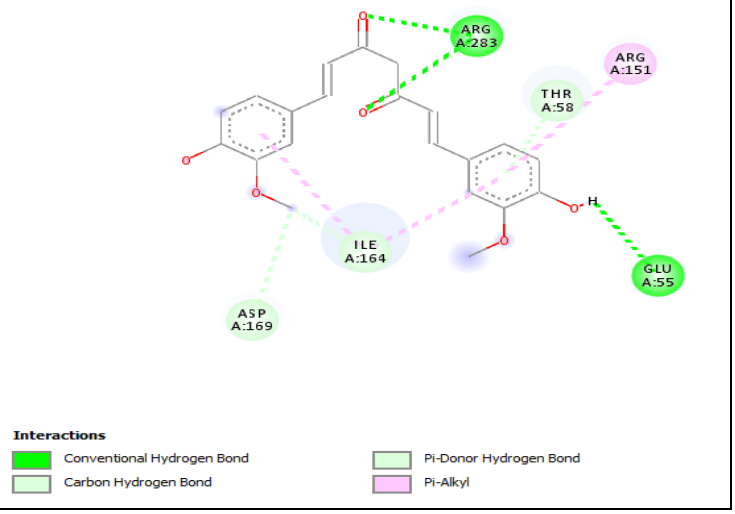
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	5LK0	-7.2	

Table 3: Docking score and 2D interactions of Curcumin with Herpes Simplex virus viral protein.

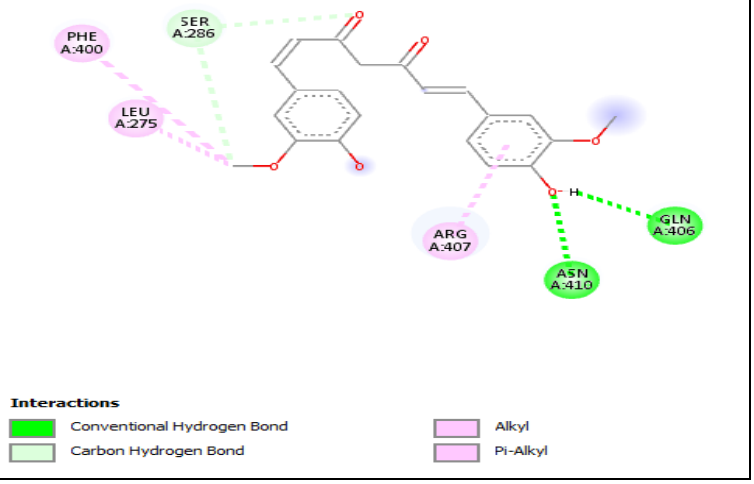
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	6BM8	-7.9	

Table 4: Docking score and 2D interactions of Curcumin with Norovirus viral protein.

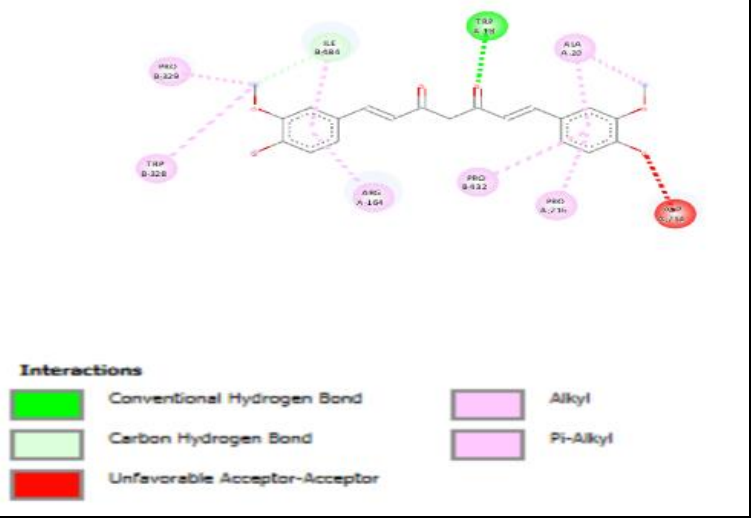
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	4QUZ	-8.5	

Table 5: Docking score and 2D interactions of Curcumin with Human Papillomavirus viral protein.

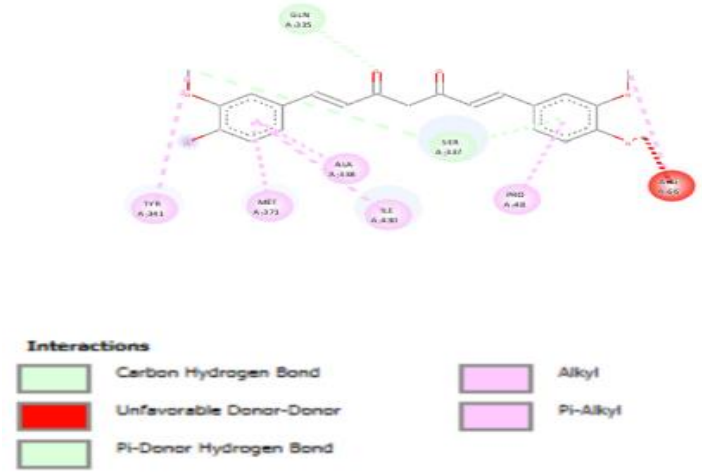
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	6SJV	-8.8	

Table 6: Docking score and 2D interactions of Curcumin with HIV viral protein.

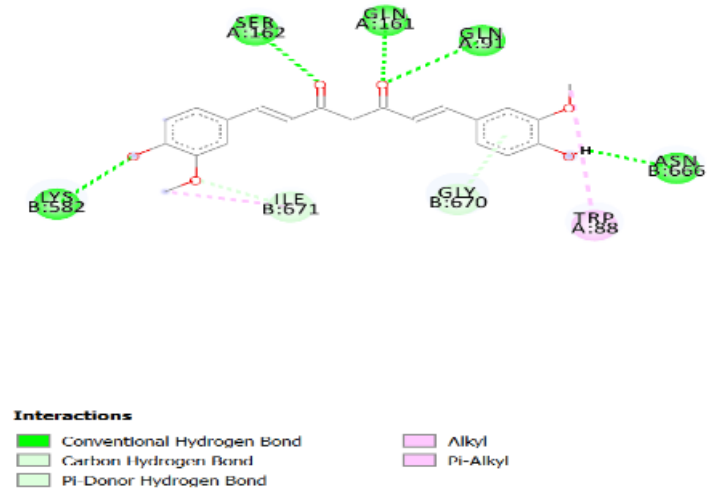
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	1JLF	-8.8	

Table 7: Docking score and 2D interactions of Curcumin with Influenza Virus viral protein.

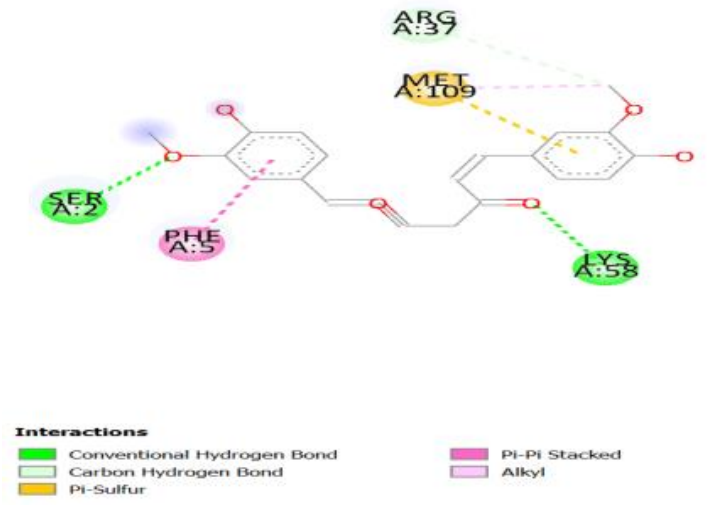
Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	5EG7	-8.3	

Table 8: Docking score and 2D amino acid interactions of Curcumin with SARS-CoV2 Viral protein.

Ligand	Protein	Dock Score	Amino Acid Interactions
Curcumin	7K40	-7.1	

Table 9: Results showing ligands and their interacted proteins that were considered in the study for the targeted diseases

Ligand	Proteins (Pdb-Id)	Targeted Viral Diseases	Dock Score
Curcumin	4B3V	Rubella	-8
Curcumin	5LK0	Hanta	-7.2
Curcumin	6BM8	Herpes	-7.9
Curcumin	4QUZ	Norovirus	-8.5
Curcumin	6SJV	Papillomavirus	-8.8
Curcumin	1JLF	HIV	-8.8
Curcumin	5EG7	Influenza	-8.3
Curcumin	7K40	Coronavirus	-7.1

CONCLUSION

Curcumin was studied using bioavailability radar. Our results proposed Curcumin, showed best docking results for rubella virus, norovirus, papillomavirus, HIV virus and influenza virus Proteins with PDB id's 4B3V, 4QUZ, 6SJV, 1JLF, 5EG7. For Hantavirus, Herpes virus and Coronavirus protein with PDB id's 5LK0, 6BM8, 7K40 Curcumin showed standardized results. To find the effectiveness and to propose the exact mechanism in-vitro studies can be encouraged on Curcumin targeting respective diseases that are discussed above to understand the mechanism and a potential cure for above viral diseases.

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