|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2020: 79.44
Original Research Article Volume 6, Issue 04; April: 2022; Page No. 31-41

In-Silico Modeling of Potential Molecules to target Diabetes Type-2

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Article Info: Received 22 January 2022; Accepted 21 March 2022
doi: https://doi.org/10.32553/ijmbs.v6i4.2509
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Conflict of interest: No conflict of interest.

Abstract

By and by, the world is in a battle with Diabetes and its variants with no prompt medicines accessible. The scourge brought about by the disease is expanding step by step. A ton of researchers are continuing for the potential medication up-and-comer that could help the medical care framework in this battle. We present a docking-based screening using a quantum mechanical scoring of a library built from approved drugs and compounds that Curcumin, Delphinidin, Cyanidin-3,5-diglucoside, Diterpenoid Lactones, Glycosides, Alkaloids, with Proteins with PDB id's 3K35 and 3A5J could display antiviral activity against Diabetes types-2. 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 Diabetes type-2.

Introduction

The World Health Organisation (WHO) estimated the global prevalence of diabetes among adults over 18 years of age as 8.5% in 2014. There are estimated 72.96 million cases of diabetes in the adult population of India. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0-7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study). More than 95% of people with diabetes have type 2 diabetes. It influences individuals worldwide and there is no immunization yet for this rapidly spreading as a major threat to worldwide general wellbeing. As of late, various endeavors have been made to plan novel inhibitors or utilize drug repurposing ways to deal with recognition hostile to medications. However no prominent drug has been discovered hitherto for treatment, and this paper intends to find a potential drug in-silico that can effectively act as a solution.

Procedure:

1. Ligand Screening

For the initial Ligand screening purposes, a web-based tool named Swiss ADME (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).

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**. 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

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.

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

Diabetic Protein Docking Results-:

PDB-ID 3A5J

For 3A5J, seven active sites were selected out of which the zeroth active site was selected with a Deep site score of 0.98, Table 1. 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.

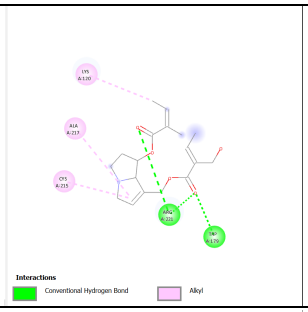
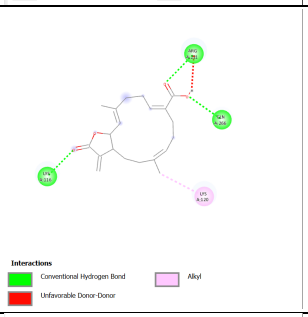
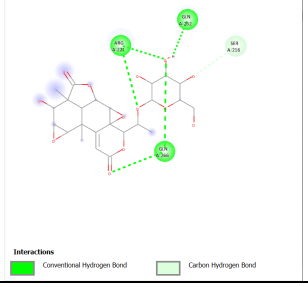
Table 1: shows the selected sites obtained from Deep Site based on DCNN algorithm

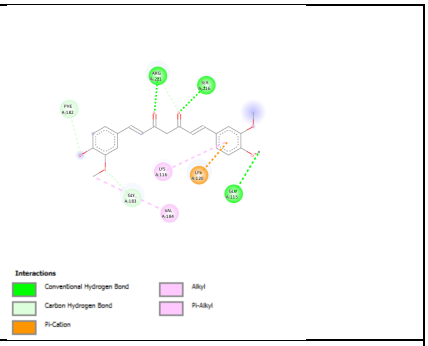
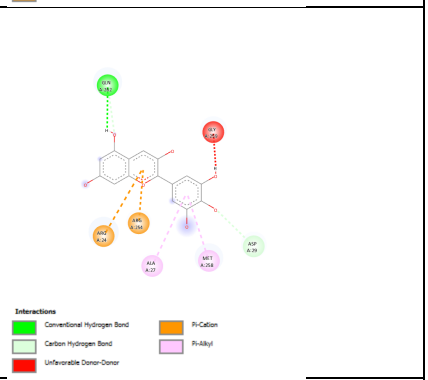
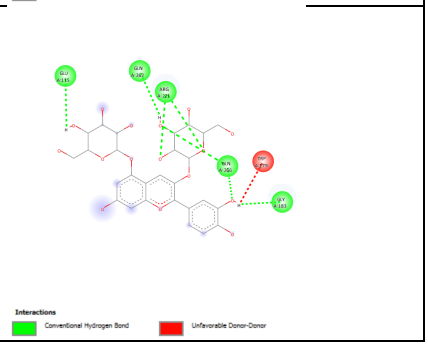
Site	Score	Selected/Not Selected
0	0.98	Selected
1	0.77	Not Selected
2	0.71	Not Selected
3	0.73	Not Selected
4	0.55	Not Selected
5	0.60	Not Selected
6	0.44	Not Selected

Table 2:

Ligands	**Dock score**
Alkaloid A	-7
Cembranoid Diterpene lactone	-7.5
Inumakilactone A Glycoside	-8.6
Curcumin	-7.1
Delphinidin	-7.2
Cyanidin-3,5-diglucoside	-8.1

Table 3:

Ligands	Dock score	Interactions
Alkaloid A	-7	
Cembranoid Diterpene lactone	-7.5	
Inumakilactone A Glycoside	-8.6	

Curcumin	-7.1	
Delphinidin	-7.2	
Cyanidin-3,5-diglucoside	-8.1	

PDB-ID 3K35

For 3K35, six active sites were selected out of which the 0th and 1st active sites were selected with a Deep site score of 0.99 and 0.98, Table 1. 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.

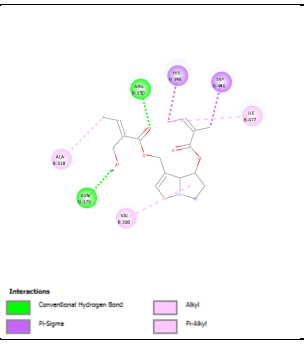
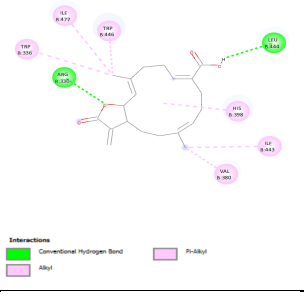
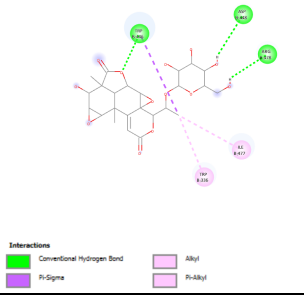
Table 4: shows the selected sites obtained from Deep Site based on DCNN algorithm

site	score	selected/not selected
0	0.99	Selected
1	0.98	Selected
2	0.80	Not Selected
3	0.59	Not Selected
4	0.69	Not Selected
5	0.52	Not Selected

Table 5

Ligands	Dock score corresponding to 0th active site	Dock score corresponding to 1st active site
Alkaloid A	-7.3	-6.2
Cembranoid Diterpene lactone	-8.4	-6.9
Inumakilactone A Glycoside	-8.7	-8.1
Curcumin	-9.2	-8.4
Delphinidin	-8.2	-8
Cyanidin-3,5-diglucoside	-8.8	-8.9

Table 6:

Ligands	Dock score corresponding to 0th active site	Interactions
Alkaloid A	-7.3	
Cembranoid Diterpene lactone	-8.4	
Inumakilactone A Glycoside	-8.7	

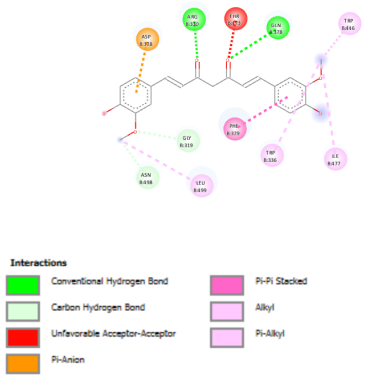
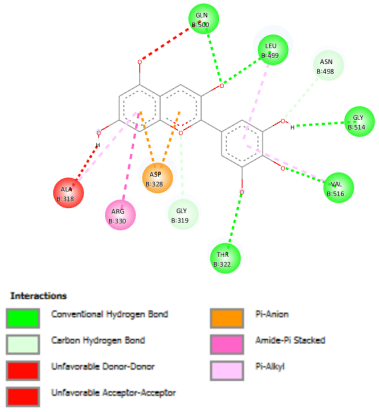
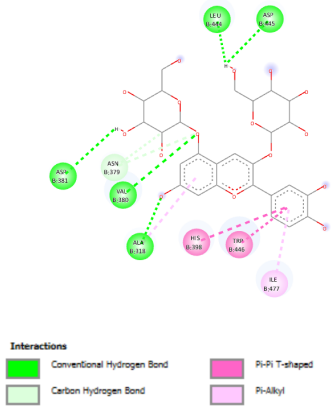
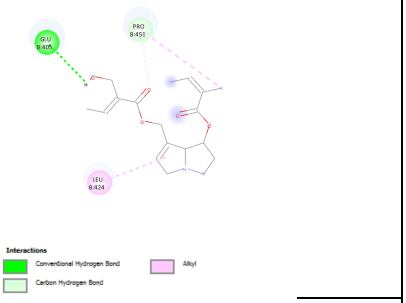
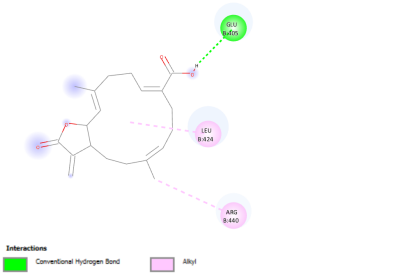
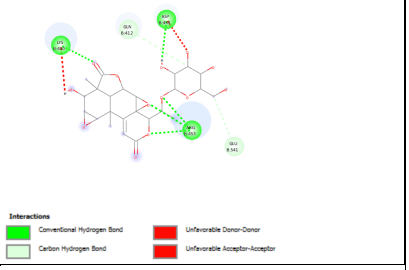
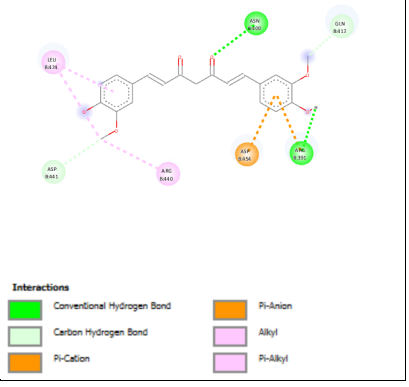
Curcumin	-9.2	
Delphinidin	-8.2	
Cyanidin-3,5-diglucoside	-8.8	

Table 7:

Ligands	**Dock score corresponding to 1st active site**	Interactions
Alkaloid A	-6.2	
Cembranoid Diterpene lactone	-6.9	
Inumakilactone A Glycoside	-8.1	
Curcumin	-8.4	

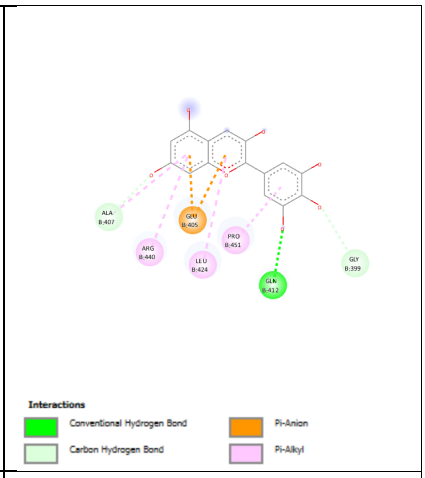
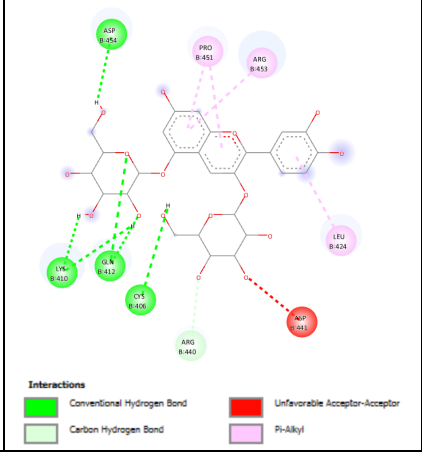
Delphinidin	-8	
Cyanidin-3,5-diglucoside	-8.9	

Table 7 summarizes the results showing ligands and their interacted proteins that were considered in the study for the targeted diseases.

Ligand	Proteins Interacted	Acceptance
Allyl Isothiocyanate	-	-
Alkaloid A		Accepted
Cembranoid Diterpene lactone		Strongly accepted
Inumakilactone A Glycoside		
Curcumin		
Delphinidin		
Cyanidin-3,5-diglucoside		

Conclusion:

All six ligands were studied using bioavailability radar. Our results proposed Cyanidin-3,5-diglucoside, Curcumin and Inumakilactone A Glycoside showed best docking result for diabetic, Proteins with PDB id's 3A5J and 3K35. For Diabetic protein with PDB id 3A5J, Cyanidin-3,5-diglucoside and Inumakilactone A Glycoside showed standardized results, whereas, other diabetic protein included in study with PDB id 3K35 showed best docking results with Cyanidin-3,5-diglucoside and Curcumin. To find the effectiveness and to propose the exact mechanism in-vitro studies can be encouraged on Curcumin, Cyanidin-3,5-diglucoside, Cembranoid Diterpene lactone and Delphinidin targeting respective diseases that are discussed above to understand the mechanism and a potential cure for Diabetes type-2.

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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