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In Silico Screening of Two Selected Ligands, Curcumin, And Cinnamaldehyde, From the Compound Database for Antidiabetic Activity and Validation of Activity by Re-Docking.

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ABSTRACT

This study aims to perform in silico screening of two ligands selected from the compound database based on a literature review for predicting their antidiabetic activity on human sodium-glucose co-transporter 2 receptors. The receptor is in complex with the ligand Empagliflozin and was downloaded from the protein database. The ligands used for this study were Cinnamaldehyde and Curcumin. PyRx molecular docking software was used to perform the analysis. The study was validated using a re-docking technique using ligand Empagliflozin. Highly promising activity was predicted due to good docking score for curcumin (-10.2) and Cinnamaldehyde (-6.9). The redocking score was (-7.5). The values are above the benchmark. The root main square value showed the reproducibility of this method. The finding gives insight into Insilco docking for antidiabetic activity and further exploration of phytochemicals for Insilco screening.

Keywords: Docking, PyRx, Curcumin, Cinnamaldehyde, Diabetes, Redocking

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INTRODUCTION

In ancient times, drugs were discovered by identifying the active ingredients from traditional medication or by chance. Classical pharmacology was used for the investigation of chemical libraries [1]. Now, screening of hit compounds and optimization to decrease possible side effects and increase drug likeliness and selectivity are part of drug discovery. A target can be used to find out whether a molecule is druggable [2]. There are several targets on which antibiotic drugs act like selective peroxisome proliferator-activated receptor (PPAR)-r modulators [3]. Normal antidiabetic agent pioglitazone, rosiglitazone binds to this receptor [4]. Nonsteroid glucocorticoid receptor modulators Glycogen-like peptide -1- receptor agonist, sodium–glucose – co-transfer 2 is a molecule target of antidiabetic drugs [5,6]. Sodium-glucose transporter incorporation glucose (SGLT) is expressed specifically in the intestines and lowers blood glucose concentration via glucose excretion in urine due to depression of (SGLT) function. It also boosts insulin secretion from β cells of islets of Langerhans. SGLT inhibition is a novel class of antidiabetic agents Sotagliflozin is a dual SGLT inhibitor. Thus, SGLT inhibitors are Dapagliflozin, canagliflozin empagliflozin [7].

Turmeric (Curcuma longa) is a spice, food coloring agent. The ethnopharmacological action is the treatment of biliary disorders, anorexia, cough, diabetic women, Hepatic disorders, Rheumatism, and sinusitis. The main bioactive component of turmeric is Curcumin. It exhibits anti-inflammatory, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, and antiviral activity [8]. Cinnamaldehyde has been shown to possess antimicrobial activity [9,10]. The present study aims to screen the antidiabetic action of Curcumin and Cinnamaldehyde on Sodium-Glucose Co- Transporter 2 receptors, establish the action mechanism and rank them in terms of activity. The software used was PyRx.

MATERIALS AND METHODS

Prepared protein

PyRx software written in Python programming can be downloaded and run on any computer with memory configuration

Hardware: Dell intel core 15V pro 8th Generation with 8GB RAM, Windows 10 with HD graphics

Input files

- PubChem database was used to download 3D structures in sdf format for ligands.
- For Receptor sodium Glucose Co- Transporter in complex with empagliflozin.

Experimental

Protein preparation

The crystal structure of Sodium-Glucose Co-Transporter (7VSI) was downloaded and prepared using Biovia discovery studio. The Het atom, water molecules, ligand groups, and unwanted chains were removed, and polar hydrogen was added and saved on the PDB file.

Ligand preparation

3D structures of the Cinnamaldehyde and Curcumin in sdf. format was downloaded, and energy minimization was done and saved as a pdbqt file using the open babel tool in PyRx.

Ligand for redocking

The 3D structure of Empagliflozin in sdf format was downloaded from the PubChem database, and energy minimization was done using the open babel tool in PyRx and converted into a pdbqt file. Auto dock vina tool was used to perform a docking with the target 7VSI. Binding affinity was obtained.

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Molecular docking simulation

Running docking using auto dock vina found the most likely binding mode and binding affinity.

Interaction studies

The docked compounds with minimum binding energy were selected. Discovery Studio was used to visualize and study the interaction between ligands and targets. The amino acids and Residues involved in binding were also studied.

RESULTS AND DISCUSSION

Figure 1: Docked Image of Empagliflozin

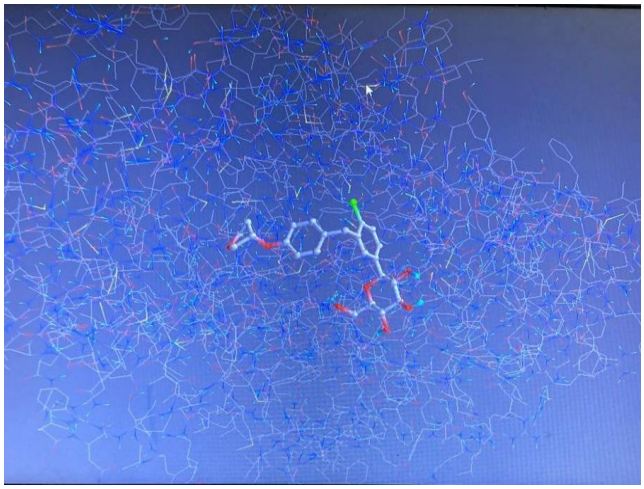

Figure 2: Curcumin

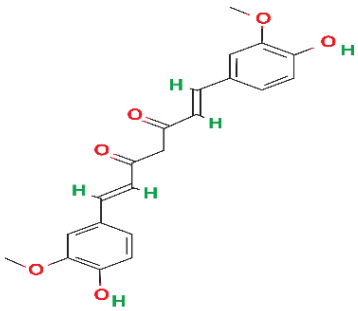

Figure 3: Cinnamaldehyde

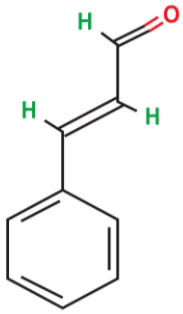

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Table 1: Docking Data

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Ligand Cid 11949646 Empagliflozin	-7.5	0	0
	-7.4	9.443	5.424
	-7.3	43.107	39.698
	-7.2	10.887	5.687
ligand Cid- 637511 Cinnamaldehyde	-6.1	0	0
	-6.1	3.139	2.432
	-6.1	4.15	2.805
	-5.9	3.115	2.634
Ligand Cid 969516 Curcumin	-10.2	0	0
	-9.2	2.804	1.575
	-9	8.889	1.505

A molecular docking study was performed with auto dock tools. The phytochemicals, Cinnamaldehyde and Curcumin, were docked with a target of PBID -7VSI Curcumin was found to possess the best score of -10.1 Kcal/mol Cinnamaldehyde - 6.9 Kcal/mol. The docking score was – 7.5 Kcal/mol. All scores are comparable; Curcumin was the best. Have the highest interaction. It can be considered a lead compound for antidiabetic drug development. Developing new drugs from lead compounds is an important step. New medications with fewer side effects will be useful for maintaining a healthy life. The Sodium-glucose co-transporter 2 is an important receptor in glucose reabsorption from the kidney and intestine. The inhibitors of the receptors will be effective antidiabetic drugs.

CONCLUSION

The docking results showed that phytochemical Curcumin had a higher binding affinity than the standard ligand Empagliflozin for Sodium-glucose co-transporter 2 receptor. The other phytochemical with the good binding affinity was Cinnamaldehyde. Mechanism through which Sodium-glucose co-transporter acts is by reducing renal glucose reabsorption. Curcumin is predicted to act by inhibiting glucose reabsorption

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