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In silico molecular docking analysis of few plant compounds as aldose reductase inhibitors

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ABSTRACT

Various proteins play important roles in diabetes and a number of plants have been tested for their efficacy in modulating the disease. In our study, protein - ligand interaction studies were performed on 133 compounds from different parts of four plants (Allium sativum, Dacus carota, Eucalyptus globus and Lycopersicon esculentum) against aldose reductase enzyme. Molegro Virtual Docker software was used as docking program and the 2D molecules are energy minimized using Tsar (Tools for structure activity relationships) software. Further, docking and re-scoring of compounds using Molegro, MEDock and Patchdock followed by rank-sum technique revealed high binding affinity of compound Eriodictyol-7-neohesperiodoside from Allium sativum against aldose reductase, 1AH3. The docked pose of compound Eriodictyol-7-neohesperiodoside exactly fits into the active site region and the ligand formed more number of H-bond interactions than the co-crystallized ligand.

Key Words: Docking, Molegro, MEDock, Patchdock, Diabetes, Aldose Reductase, 1AH3

INTRODUCTION

Diabetes Mellitus is a disease in which the body does not produce sufficient amount of insulin or the cells do not respond to the insulin produced [1]. As a result of this sugar accumulates in the blood leading to various complications such as cataract, retinopathy, nephropathy and neuropathy [2].

High intake of plant foods may help to treat diabetes and the advantages can be linked to the presence of specific compounds in plants. Various plants have been tested for their efficacy in modulating diabetes, however, few reports were found to contain computer-aided docking studies on compounds from plants vs. proteins. Virtual screening studies reported in literature stated the importance of dataset, algorithms and scoring functions. This provided us the rationale to screen plant based compounds using Molegro software. In this paper we report screening various compounds from four plant sources (*Allium sativum, Dacus carota, Eucalyptus globulus* and *Lycopersicon esculentum*) against aldose reductase (PDB ID: 1AH3).

Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process.

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Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure [3]. Some recent studies have focused on certain factors such as the size and diversity of the ligand dataset, wide range of targets and the evaluation of docking programs [4].

However, in general, it is important to visualize the docked poses of high-scoring compounds because many ligands are docked in different orientations and may often miss interactions that are known to be important for the target receptor. This study becomes more difficult as the size of the dataset increases. Therefore, another approach is to eliminate unpromising compounds before docking by restricting the dataset to drug-like compounds; by filtering the dataset based on appropriate property and sub-structural features and by performing diversity analysis [5].

MATERIALS AND METHODS

Dukes Ethnobotany [6] was used to obtain chemical compound names from each plant and the respective structures were obtained from literature. The 2D structures of 133 compounds from four plants (*Allium sativum, Dacus carota, Eucalyptus globules and Lycopersicon esculentum*) were drawn using ISISDraw software [7] and are converted to 3D by opting corina

3D analysis tool in Tsar software [8]. The geometries of these compounds were optimized and the charges were added.

Receptor X-ray structure

The X-ray crystal structure of aldose reductase protein, 1AH3, in complex with inhibitor Fidarestat was obtained from the Protein Data Bank [9]. Default parameters are used in the molecular docking program Molegro and a consensus scoring was employed using Molegro, MEDock and Patchdock and ranking was employed to generate classes using Tsar Software.

MEDock

The MEDock [**M**aximum-**E**ntropy based **Dock**ing] web server is aimed at providing an efficient utility for prediction of ligand binding site [10]. MEDock accepts ligands in PDBQ format. To generate the format, PRODRG [11] server was utilized.

PATCHDOCK

Patchdock [12] is an algorithm for molecular docking. The input is two molecules of any type: proteins, DNA, peptides, drugs.

Before screening the 133 plant compounds dataset, the docking protocol was validated. 1AH3 protein with bound ligand were docked individually into their corresponding binding pockets to obtain the docked pose and the RMSD of all atoms between these two conformations in each case are 0.873, 0.872 and 0.670 A˚ indicating that the parameters for docking simulation are good in reproducing the X-ray crystal structure.

Consensus scoring and ranking

Generally, docking programs predict the protein - ligand complex structures with reasonable accuracy and speed. The ability to predict the binding mode of a ligand to differentiate poses is based on reliable scoring functions. However, combinations of various scoring functions would reduce the errors in single scoring schemes and improve the probability of identifying true hits [13]. Thus, it has been demonstrated that consensus scoring is generally more effective than single scoring for molecular docking [14] and represented an effective way in getting improved hit rates in various virtual database screening studies [15].

In our study, we tested three different scoring functions such as MolDock score of Molegro, MEDock and Patchdock softwares. The scores generated by the programs are ranked by using the Tsar and generated 4 classes, of which, the compounds in class1 represents the top rank and given high score.

RESULTS AND DISCUSSION

Docking analysis of all compounds on 1AH3 using Molegro Virtual Docker resulted in few best compounds that were evaluated based on the binding compatibility (kcal/mol) with the receptor. In each case, binding energies greater than the co-crystallized ligand are selected.

Dock scores of co-crystallized ligand run in triplicates are within -99.39 to -110.49 kcal/mol range and therefore any molecule from the dataset that resulted in the scores higher than the range are considered more appropriate. Therefore initially, virtual screening with docking and scoring resulted in few best hits. In the second step, consensus scoring was applied to generate different scores for these compounds. Likewise, re-scoring docking poses with independent functions is another valuable approach which gained prominence in recent studies. Therefore, re-scoring of best docked poses based on their interaction energies with respective protein active site residues was done using MEDock and Patchdock.

In all the above cases, ranking was done individually by clustering best scored compounds into equally split four classes using Tsar software, of which compounds in Class1 represents the highest class or top rank. Classes were generated for all scoring functions and instead of taking an average, rank-sum technique [16] was employed to retrieve best compounds. The ranks obtained from each of the individual scoring functions were added to give a rank-sum (Table1). Finally, from top rank-sum classes, compound Eriodictyol-7-neohesperiodoside from *Allium sativum* was found to be the most potential ligand against aldose reductase.

Binding modes

Active site of 1AH3 offers different binding modes for these compounds as they are strongly dependent on the attached substituent. Compound Eriodictyol-7-neohesperidoside (Figure 1) from *Allium sativum* formed more number of H-bond interactions (Figure 2) with Thr113(2), His110, Val47(3), Gln49(2) respectively.

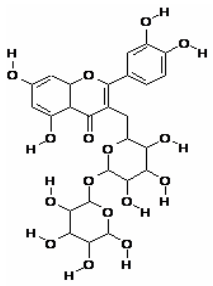

Figure 1. Structure of Eriodictyl-7-o-neohesperiodoside

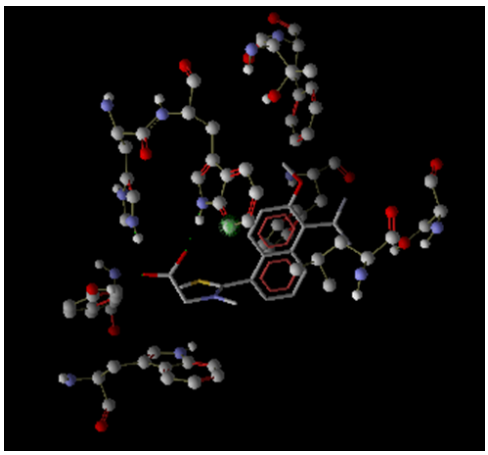

Figure 2. H-bond interactions of Eriodictyl-7-o-neo hesperiodoside with active site residues of 1AH3.

Table 1: Optimized dock scores of best compounds that scored higher than respective original ligands against aldose reductase, 1AH3 and their respective classes.

Plant	Compounds	Molegro (kcal/mol)	MEDock (kcal/mol)	Patchdock (kcal/mol)	Classes			
					Molegro	MEDock	Patch dock	Sum
Allium sativum	Eriodictyol-7-neohesperiodoside	-140.11	**-11.99**	**5742**	**3**	**4**	**3**	**10**
Eucalyptus globulus	Engeletin	-157.047	-9.47	6503	4	3	1	8
Eucalyptus globulus	Ellagitannin	-147.024	-4.17	6186	3	1	2	6
Eucalyptus globulus	Eriocitrin	-136.329	-9.39	5668	1	3	3	7
Lycopersculum esculentum	Neoxanthin	-145.147	-9.14	6642	3	3	1	7
Dacus carota	Neoxanthin	-145.147	-9.14	6642	3	3	1	7
Dacus carota	Antherexanthin	-140.709	-8.32	6390	2	3	1	6
Dacus carota	Daucosterol	-133.241	-7.32	6404	1	3	1	5

CONCLUSION

Virtual screening methods are extensively used in drug discovery process to reduce the time spent on the research as well as expenditure. The approach utilized in this study resulted in identifying compound Eriodictyol-7-neohesperidoside with high binding affinity towards aldose reductase. The docked pose of compound Eriodictyol-7-neohesperidoside revealed more number of H-bond interactions than the co-crystallized ligand. Therefore, this study states the importance of small molecules from various plant sources as docking agents. This approach to screen compounds from plants depends on various parameters such as size and shape of the compound and pharmacophoric groups attached on the compounds, among others. Further, work can be extended to study the receptor-ligand interactions experimentally and evaluation of their biological activity would help in specific isolation and effective treatment of diseases.

REFERENCES

1. Brownlee M (2001). Biochemistry and molecular cell biology of diabetic complications. Nature. 414: 813-820
2. Understanding diabetic retinopathy by Pardianto G et al., in Mimbar Ilmiah Oftalmologi Indonesia.2005, 2: 65-66
3. Jalaie M, Shanmugasundaram V (2006) Virtual screening: are we there yet? Mini Rev Med Chem 6: 1159-1167
4. Warren GL, Andrews CW, Capelli AM et al. (2006) A critical assessment of docking programs and scoring functions. J Med Chem 49: 5912-5931
5. Waszkowycz B (2008) Towards improving compound selection in structure- based virtual screening. Drug Discov Today 13: 219-226
6. http://www.ars-grin.gov/duke/
7. www.mdli.com
8. www.accelrys.com
9. www.rcsb.org/pdb
10. http://medock.csbb.ntu.edu.tw/step1.html.
11. http://davpc1.bioch.dundee.ac.uk/prodrg/
12. http://bioinfo3d.cs.tau.ac.il/PatchDock/
13. Kitchen DB, Decornez H, Furr JR et al. (2004) Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov 3: 935-949
14. Wang Z, Canagarajah BJ, Boehm JC et al. (1998) Structural basis of inhibitor selectivity in MAP kinases. Structure 6: 1117- 1128
15. Charifson PS, Corkery JJ, Murcko MA, Walters WP (1999) Consensus scoring: A method for obtaining improved hit rates from docking databases of three-dimensional structures into proteins. J Med Chem 42: 5100-5109
16. Clark RD, Strizhev A, Leonard JM, Blake JF, Matthew JB (2002) Consensus scoring for ligand/protein interactions. J Mol Graph Model 20: 281- 295

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