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Virtual screening of plant derived compounds for aldose reductase inhibition using molecular docking

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Abstract:
The role of the aldose reductase in type 2 diabetes is widely described. Therefore, it is of interest to identify plant derived compounds to inhibit its activity. We studied the protein-ligand interaction of 267 compounds from different parts of seven plants (Allium sativum, Coriandrum sativum, Dacus carota, Murrayyakoneigii, Eucalyptus, Calendula officinalis and Lycopersicon esculentum) with aldose reductase as the target protein. Molecular docking and re-scoring of top ten compounds (using GOLD, AutoDock Vina, eHiTS, PatchDock and MEDock) followed by rank-sum technique identified compound allium38 with high binding affinity for aldose reductase.

Keywords: Computer aided drug design, Type 2 diabetes, Molecular docking, Aldose reductase

Background:
There are several protein targets known to be linked with type 2 diabetes. However, effective ligands are not available for many such protein targets in relation to type 2 diabetes. The role of the aldose reductase in type 2 diabetes is widely described. Literature survey shows that the average docking score of the existing ligands, inhibitors for aldose reductase is -126.048 Kcal/mol **[1].** Hence, it is of interest to screen for compounds with improved inhibitory effects.

The role of food sourced from plants in controlling abnormal blood pressure and insulin activity is a subject intense debate and speculation. Hence, these benefits are often associated with plant specific compounds. Various plants and their parts have been tested for their efficacy in modulating diabetes. However, information of compounds isolated from such plants with protein targets associated with type 2 diabetes is limited **[2].** Hence, it is of interest to virtually screen hundreds of compounds. Therefore, we used the x-ray crystal structure of aldose reductase (PDB: 1AH3; http://www.rcsb.org/pdb/) for molecular docking with plant derived compounds. Here, we describe the computed binding of potential molecules with the target protein using docking methods.

Methodology:

Plant derived compounds

Details of 267 compounds from 7 plants is summarized as: (i) Allium sativum [42 Compounds]; (ii) Coriandrum sativum [50 Compounds]; (iii) Dacus carota [74 Compounds]; (iv) Murrayya koneigii, [31 Compounds]; (v) Eucalyptus, [26 Compounds]; (vi) Calendula officinali [14 Compounds]; (vii) Lycopersicon esculentum [30 Compounds].

Protein target

Protein coding genes related to diabetes are selected using the gene cards website. We selected aldose reductase because its structure was solved and co-ordinates made available.

Target protein structure

We used the x-ray crystal structure of aldose reductase (PDB: 1AH3; http://www.rcsb.org/pdb/).

Virtual Screening

Virtual screening (VS), is a productive and cost-effective technology in search for novel lead compounds **[3].**

Plant derived compound structures

267 compounds, selected based on the property and sub-structural features, from 7 plants were drawn using ISIS Draw software (www.mdli.com). The 2D structures are converted into 3D structures by using corina 3D analysis tool in Tsar. The geometries of these compounds were optimized using cosmic optimize 3D module and the charges were added. All molecules were written as mol2 files.

Molecular visualization and analysis

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 sort of study becomes more difficult as the size of the dataset increases. Therefore, an alternative 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 **[4].** Consensus scoring combines information from different scores to balance errors in single scores and improve the probability of identifying 'true' ligands **[5]**. In our study, we tested six different scoring functions such as (i) GOLD; (ii) Patchdock; (iii) eHITS; (iv) Molegro; (v) MEDock; (vi) Autodock Vina.

Molecular docking

Molegro Virtual Docker (MVD) was used to dock compounds to generate an ensemble of docked conformations and each scoring function is applied to generate classes based on the obtained dock scores followed by ranking the best conformations. During ranking, signs of some scoring functions are changed to make certain that a lower score always indicates a higher affinity

Rank-sum technique

Ranking was done individually by clustering best scored compounds into equally split four classes using the Tsar software, of which compounds in Class4 represents the highest class or top rank. Classes were generated for all scoring functions and instead of taking an average, rank-sum technique **[6]** was employed to retrieve best compounds. The ranks obtained from each of the individual scoring functions were added to give a rank-sum. The advantage of a sum over an average is that the contribution from each individual score can more easily be split out for illustrative purposes in the former instance.

Discussion:

The 267 plant compounds from 7 different plants were docked with the aldose reductase protein structure (PDB ID: 1AH3) and the Docking Scores for all the 267 plant compounds were recorded. The dock score of the top 10 compounds out of the 267 compounds from 7 different plants are shown in the **Table 1 (see supplementary material)**. The top 10 compounds were further docked against aldose reductase using 5 others docking programs GOLD, PatchDock, eHits, MEDock and Autodock Vina. The docking scores of the 10 best compounds attained using different software are listed in **Table 2 (see supplementary material)**. Each docking program is listing different compound as best docking score. To find the best compound, rank sum technique was used. Classes were generated using Tsar Software and the sum of the classes for each ligand is shown in **Table 3 (see supplementary material).** The rank-sum technique resulted in Allium38 with the highest score. The structure of the allium 38 is shown in **(Figure 1).** The hydrogen bond interactions for the best compounds were visualized using Molegro Virdual Docker (MVD). The Mol Dock Scores, number of interactions and the interacting residue list are given in **Table 4 (see supplementary material).**

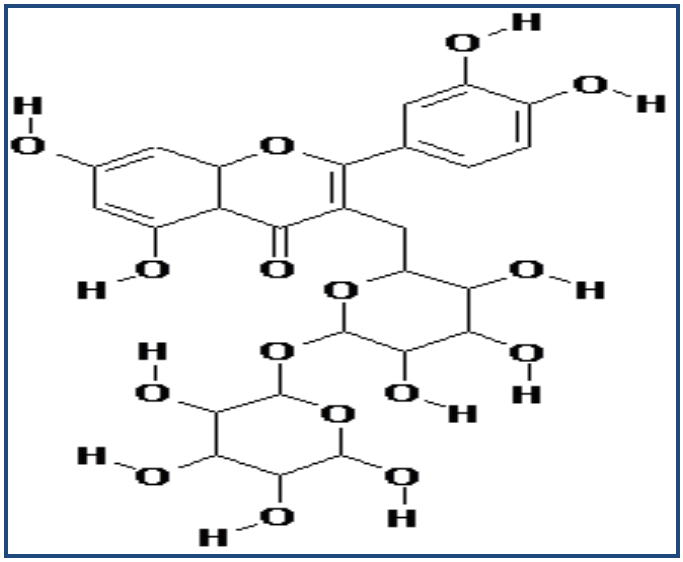

Figure 1: Schematic structure of allium38 compound

Conclusion:

Consensus scoring is a widely used approach to improve the scoring reliability and hit rate in virtual screening and four standalone programs (GOLD, Molegro, AutoDock and e-HiTS) and two online servers (PatchDock and MEDock) are utilized to rank top hits. Allium38 ranked high and reported to be the best compound that can bind with high affinity to aldose reductase enzyme. Allium38 resulted in best hits with a better binding energy than the original co-crystallized ligand described in PDB ID: 1AH3. This observation is interesting and promising in the context of a potential inhibitor for aldose reductase.

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Supplementary material:

Table 1: Table showing the docking scores of top ten compounds from the database

S. No	Compound	Affinity(kcal/mol)
1	Euc12	-157.047
2	Euc15	-147.024
3	Allium38	-146.111
4	Neoxanthin	-145.147
5	Cor23	-142.029
6	Antherexanthin	-140.709
7	6-Mar	-140.136
8	Allium34	-139.003
9	Euc18	-136.329
10	Daucosterol	-133.241

Table 2: Comparison of scores for the top 10 compounds in the database obtained using different docking software(s)

S. No	Compound	Molegro (kcal/mol)	Ehits (kcal/mol)	Vina (kcal/mol)	Gold (kcal/mol)	MEDock (kcal/mol)	Patchdock Score
1	Euc12	-157.047	-5.5231	-9.2	55.08	-9.47	5198
2	Euc15	-147.024	-1.5166	-7.8	11.9	-4.17	6186
3	**Allium38**	**-146.111**	**-5.6216**	**-8.7**	**42.14**	**-11.99**	**5742**
4	Neoxanthin	-145.147	-0.4137	-9.6	1.04	-9.14	6642
5	Cor23	-142.029	-4.833	-8.9	52.02	-10.1	5104
6	Antherexanthin	-140.709	-0.6743	-9.8	16.76	-8.32	6390
7	6-Mar	-140.136	-5.4752	-8	10.9	-7.45	5450
8	Allium34	-139.003	-4.0861	-5.4	92.1	-4.06	4738
9	Euc18	-136.329	-4.2477	-9.1	47.37	-9.39	5668
10	Daucosterol	-133.241	-3.3719	-8.7	42.47	-7.32	6404

Table 3: Classes generated using TSAR software

S. No	Compound	Molegro	Ehits	Vina	Gold	MEDock	Patchdock	Sum
1	Euc12	4	4	4	3	3	1	19
2	Euc15	3	1	3	1	1	4	13
3	**Allium38**	**3**	**4**	**4**	**2**	**4**	**3**	**20**
4	Neoxanthin	3	1	4	1	3	4	16
5	Cor23	2	4	4	3	4	1	18
6	Antherexanthin	2	1	4	1	3	4	15
7	6-Mar	2	4	3	1	2	2	14
8	Allium34	1	3	1	4	1	1	11
9	Euc18	1	3	4	3	3	2	16
10	Daucosterol	1	3	4	2	2	4	16

Table 4: Hydrogen bond interactions with inhouse plant database

Compound	Mol Dock Score	No. of Interactions	Interacting residues
Allium38	-146.111	8	OG1 - Thr113(2) NE2 - His110 O - Val47(3) NE2 - Gln49(2)