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, Murrayykoneigii, 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, eHTS, 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) Murrayyakoneigii [31 Compounds]; (v) Eucalyptus, [26 Compounds]; (vi) Calendula officinalis [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.
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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 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 was used. Classes were generated using Tsar Software and the sum of the classes for each compound is shown in Table 2 (see supplementary material).

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 eHiTS) 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)      |