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In-silico molecular docking study on phytochemical components of *Solanum trilobatum* Linn. against enzyme transport protein.

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ABSTRACT

Aim

Evaluation of cholesterol absorption inhibitory activity of phytoconstituents presentin *Solanum trilobatum* Linn using insilico docking study.

Methodology

The software MolegroVirtual Docker and tools were used formolecular docking v6.0 along with Graphical User Interface, calculate dock score and evaluate conformers. Molegro virtual docker is a discriminatory programme to predict lig and interactions.

Results

The presence of twelve phytochemical constituents from ethanolic extract and aqueous extract were identified by GC- MS. These components undergone *in-silico* molecular docking studies using enzyme transport protein. The lead compounds were selected through the docking score. The compounds of ethanolic extract such as 5,5'-propylenebis[(1H-1,2,4-triazol-3-yl)amine] (-109.174); Benzeneaceticacid, 2-hexenylester, (E)- (-102.673); Ethanol, 2-(9-octadecenyloxy)-,(Z)- (- 100.125) and the compounds of aqueous extract like Oxirane, [(dodecyloxy) methyl] (- 109.374); 13- tetradecenal (-108.323); 3,5-dimethyl benzaldehyde thiocarbamoyl hydrazine (-100.864). Each extract have been shown three lead compounds from insilico molecular docking using standard atorvastatin (-104.402).

Conclusion

Further investigations on the above phytochemical constituents and *in-silico* molecular docking study are necessary to develop potential chemical entities for the prevention and treatment of anti-hypercholesterolemia.

Keywords: Anti-hyper cholesterolemia, Atorvastatin, *Solanum trilobatum*, Molecular docking, 3QNT.

INTRODUCTION

Atherosclerosis generally starts when a person is young and worsens with age. Almost all people are affected to some degree by the age of 65. It is the number one cause of death and disability in the developed world. Though it was first described in 1575, there is evidence that the condition occurred in people more than 5,000 years ago. Arteriosclerosis is a general term describing any hardening (and loss of elasticity) of medium or large arteries [from Greekarteria, meaning 'artery', and sklerosis, meaning 'hardening']; arteriolosclerosis is any hardening of arterioles (small arteries); atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque. The term atherogenic is used for substances or processes that cause formation of atheroma.

Low-density lipoprotein (LDL) particles in blood plasma invade the endothelium and become oxidized, creating risk of cardiovascular disease. A complex set of biochemical reactions regulates the oxidation of LDL, involving enzymes (such as Lp-LpA2) and free radicals in the endothelium. Cholesterol is delivered into the vessel wall by cholesterol- containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process. The process is worsened if there is insufficient high-densitylipoprotein (HDL), the lipoprotein particle that removes cholesterol from tissues and carries it back to the liver. Medical treatments often focus on all eviating symptoms.Howevermeasureswhichfocus on decreasing underlying atherosclerosis as opposed to simply treating symptoms are more effective. Non-pharmaceutical means are usually the first method of treatment, such as stopping smoking and practicing regular exercise.

The plant of *Solanumtrilobatum*, also called assolanum (Tamil:Thuthuvalai) is one of the medicinal plant commonly available in different parts of the world and this plant is used in Indian system of medicine to cure various diseases in human and animals. Thuthuvalai or Climbing Brinjal is a medicinal plant commonly available in Southern India. The plant is full of thorns, including the leaves. It is used traditionally for curing numerous diseases such as asthma, cough and tuberculosis. For medicinal purpose whole plant is used.

MATERIALS AND METHODS

Molecular modeling studies

Molecular docking was performed using the software Molegro Virtual Docker (MVD) v 6.0 (www.molegr.com) along with Graphical User Interface (GUI), Molegro Virtual Docker tools were utilized to generate grid, calculate dock score and evaluate conformers. Molegro virtual docker is a discriminatory programme for predicting-ligand interactions [1-5].

Ligand preparation

The ligands used in this research were prepared using the chemical structure of phytochemical compounds was obtained from PubChem compound database. It was prepared by Chemsketch and MOL SDF format of this ligand was converted to 3D structure of ligand.

Protein preparation

The three-dimensional (3D) structure of transport protein (PDB-ID: 3QNT) was transformed from the RCSB protein Data Bank. Inhibition or depletion of NPC1L1 reduces intestinal cholesterol absorption, resulting in reduction of plasma cholesterol levels. If the reduction of plasma cholesterol level Niemann Pick C1 Like1 protein (NPC1L1). This proteinis an established molecular target for the cholesterol lowering drug atorvastatin.

Structure based

Structure based drug design relies on knowledge of the 3D structure of the biological target obtained through methods such as X-ray crystallography or NMR spectroscopy. If an experimental structure of at argetis not available, it may be possible to create homology model of the target based on the experimental structure of are lated protein.Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may designed using interactive graphics and the intuition of a medicinal chemist. Alternatively, various automated computational procedure may be used to suggest new drug candidates.

RESULTS AND DISCUSSION

The molecular docking analysis were done with the targeted enzyme transport protein (PDB-ID:3QNT) was selected [16-18]. The standard drug atorvastatin (cholesterol lowering drug)was used [6-10] GCMS Analysis of ethanolic extract contains 12 phytochemical compounds are 5- Azacytosine; Ethanol, 2-(9-octadecenyloxy)-,(Z)-; 1-(3,3,3-Trifluoro-2-hydroxypropyl) piperidine; 2-Pentyne, 1-chloro; 5,5'-propylenebis [(1H-1,2,4-triazol-3-yl) amine];Cycloocta- 2,7-dienone,9- octadecenoic acid (Z)-, methyl ester; Hexahydro pentalene-1,6-dione; 2,3- Dimethylhydroquinone; Benzeneacetic acid; 2-hexenylester, (E)-; Cyclohexanamine; N-cyclooctylidene, 2-Myristynoyl-glycinamide. GCMS Analysis of aqueous extract contains 12 phytochemical compounds such as 8- Azabicyclo [3.2.1] octan-3-ol; 8-methyl-, endo-; Oxirane, [(dodecyloxy) methyl]; Cyclohexanone, 2-propyl-; Cyclopropanecarboxamide; 2- cyclopropyl-2-methyl-N-(1-cyclopropylethyl); 13- tetradecenal; 2-butynedioic acid, di-2- propenyl ester, 6- nitro, 3H-quinazolin-4-one; Piperidine,1- hydroxy- 2,2,6,6-tetramethyl-, ion(1-); 4,5,6- trimethyl -2- pyrimidone, 2- benzyl cyclohexanone; Hexahydropyridine,1-methyl-4-[4,5-dihydroxyphenyl]-; 3,5-dimethyl benzaldehyde thiocarbamoyl hydrazine [11-15]. This docking score for all phytochemical compounds were compared with standard drug atorvastatin. From the results, we may observe that for successful docking, intermolecular hydrogen bonding and lipophilic interactions between the ligand and the receptor are very important.

Table 1: Phytochemical compounds of ethanolic extract of whole plant *Solanum trilobatum*

Phytochemical compound names	Mol. Dock Score	Rerank Score	H Bond
5-Azacytosine	-50.8601	-46.756	-2.07252
Ethanol, 2-(9-octadecenyloxy)-,(Z)-	-100.125	-64.5193	-5.0
1-(3,3,3-Trifluoro-2-hydroxypropyl) Piperidine	-64.7489	-63.4478	-1.86734
2-Pentyne, 1-chloro	-60.4205	-47.5812	0
5,5'-propylenebis[(1H-1,2,4-triazol-3-yl)amine]	-109.174	-83.3107	-7.11259
Cycloocta- 2,7-dienone	-64.1657	-54.3633	0
9- octadecenoicacid (Z)-, methyl ester	-90.9785	-38.7517	-1.20362
Hexahydro pentalene-1,6-dione	-82.0347	-66.6682	-4.98148
2,3- Dimethylhydroquinone	-53.9958	-47.9749	-4.53258
Benzeneaceticacid, 2-hexenylester, (E)-	-102.673	-80.3129	0
Cyclohexanamine, N-cyclooctylidene	-83.4299	-65.6181	0
2-Myristynoyl-glycinamide	-84.3653	-65.1961	-0.0188

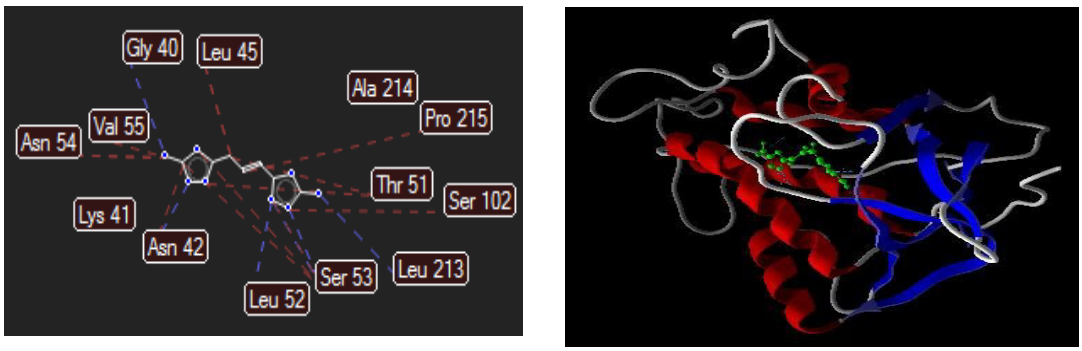

Figure 1: Stearic interaction and docking pose of 5,5'-propylenebis [(1H-1,2,4- triazol-3-yl) amine].

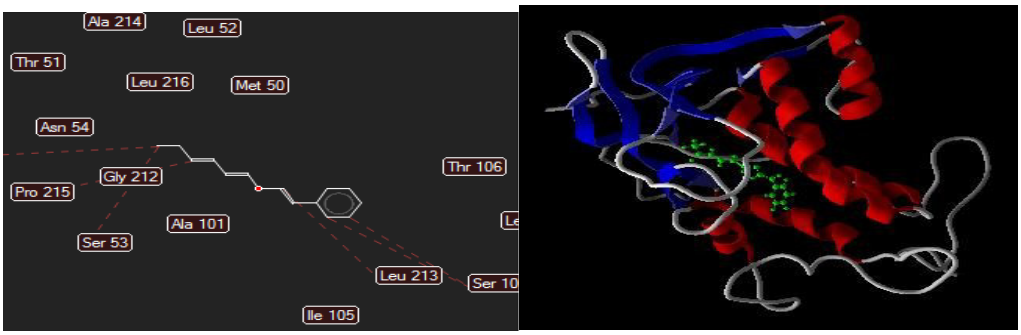

Figure 2: Stearic interaction and docking pose of Benzeneaceticacid, 2- hexenylester, (E)-.

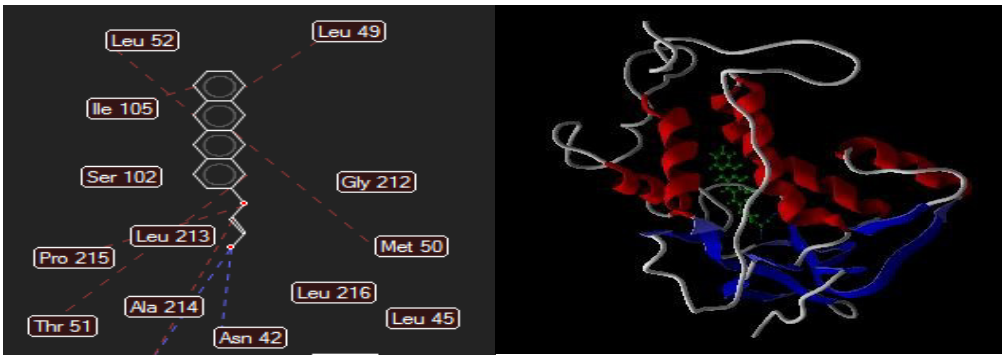

Figure 3: Stearic interaction and docking pose of Ethanol, 2-(9-octadecenyloxy)-, (Z)-.

Table 2: Phytochemical compounds of aqueous extract of whole plant *Solanum trilobatum*

Phytochemical compound names	Mol. Dock Score	Rerank Score	H Bond
8- Azabicyclo [3.2.1] octan-3-ol, 8-methyl-, endo-	-72.0096	-58.9175	-2.5
Oxirane, [(dodecyloxy) methyl]	-109.374	-84.969	-3.22098
Cyclohexanone, 2-propyl-	-65.9024	-55.5693	-0.737332
Cyclopropanecarboxamide, 2-cyclopropyl-2-methyl-N-(1-cyclopropylethyl)	-94.5426	-73.5183	-2.5
13- tetradecenal	-108.323	-80.4829	-1.70715
2- butynedioic acid, di-2-propenyl ester	-92.9436	-66.6601	-4.17544
6- nitro, 3H-quinazolin-4-one	-63.0403	-57.8219	-.4.61553
Piperidine,1- hydroxy- 2,2,6,6-tetramethyl-, ion(1-)	-55.7423	-30.298	-0.645266
4,5,6- trimethyl-2-pyrimidone	-58.312	-50.6013	-2.03812
2- benzylcyclohexanone	-77.9045	-58.9781	-2.12362
Hexahydropyridine,1-methyl-4-[4,5-dihydroxyphenyl]-	-75.7229	-63.37361	-4.71798
3,5-dimethyl benzaldehyde thiocarbamoyl Hydrazine	-100.864	-81.0535	-3.98112

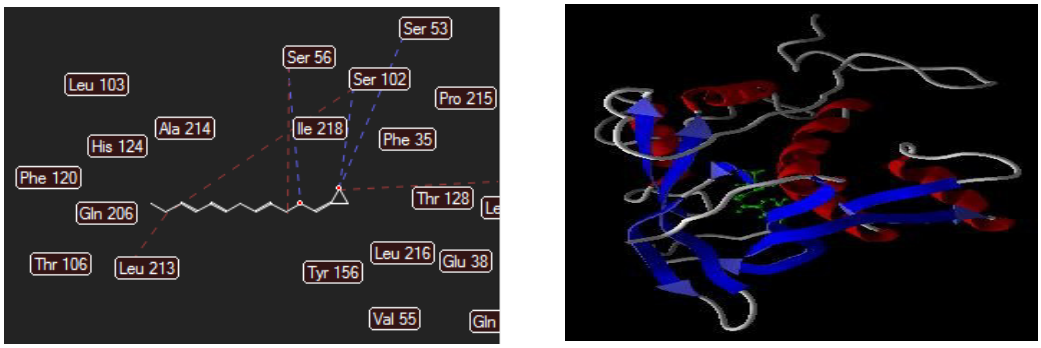

Figure 4: Stearic interaction and docking pose of Oxirane, [(dodecyloxy) methyl].

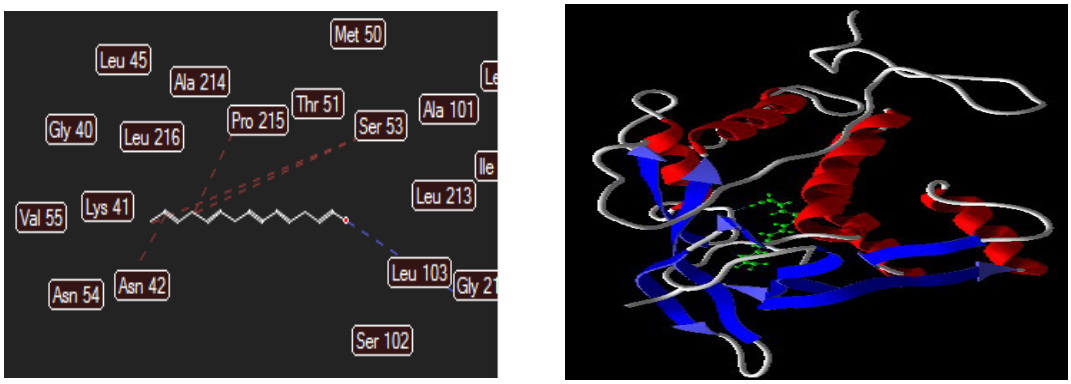

Figure 5: Stearic interaction and docking pose of 13- tetradecenal.

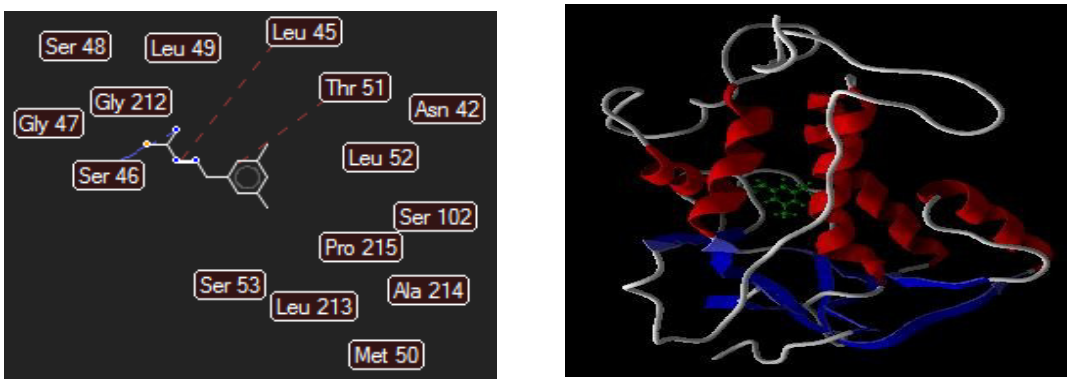

Figure 6: Stearic interaction and docking pose of 3,5-dimethyl benzaldehyde thiocarbamoyl hydrazine.

Table 3: Molecular docking score of standard drug atorvastatin.

Standard drug	Mol. Dock Score	Rerank Score	H Bond
Atorvastatin	-104.402	-555.041	-8.45232

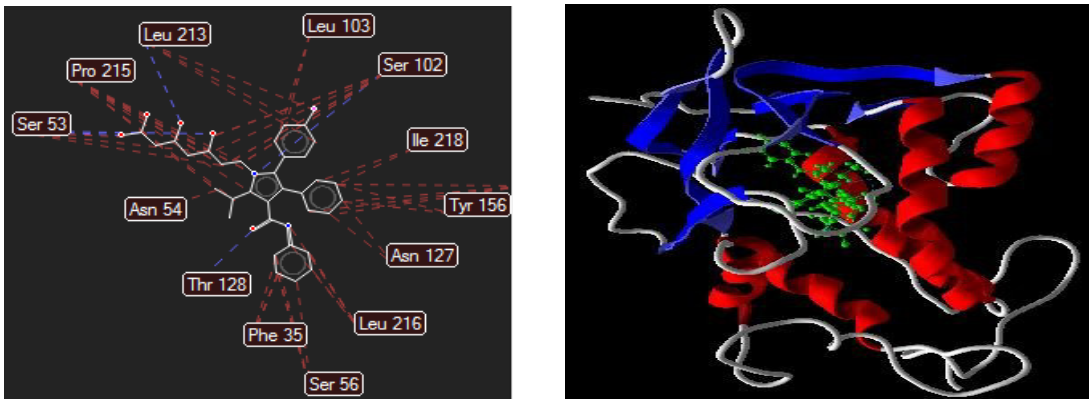

Figure 7: Stearic interaction and docking pose of standard drug atorvastatin.

CONCLUSION

The results of the present research study clearly demonstrated that, molecular docking score are best three phytochemical compounds of *Solanum trilobatum* Linn of ethanolic extract and aqueous extract such as 5,5'-propylenebis [(1H-1,2,4-triazol-3-yl) amine]; Benzene acetic acid, 2-hexenylester, (E)-; Ethanol, 2-(9-octadecenyloxy)-,(Z)- (-100.125); Oxirane, [(dodecyloxy)methyl];13-tetradecenal;3,5-dimethylbenzaldehydethiocarbamoylhydrazine. This docking score for all phytochemical compounds were compared with standard drug atorvastatin. In the excellent binding sites and interactions with transport protein compared to the standard drug. Further investigations on the above phytochemical compounds in *in-silico* molecular docking studies are necessary to develop potential chemical entities for the prevention and treatment of atherogenic activity.

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