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Molecular Docking Studies of Phytoconstituents Identified in *Acorus calamus* Linn. on HMG-CoA reductase- An Enzyme Target for Antihyperlipidemic Activity

Akshay R. Yadav* & Prashant S. Salunkhe

Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon,
Dist-Sangli, Maharashtra, India-415404

ABSTRACT

The phytoconstituents of the medicinal plants have been collected from the chemical database pubchem. 3-hydroxy-3-methylglutaryl-coenzyme A is the target for the docking analysis (HMG CoA reductase). Obesity refers to the accumulation of abnormal or unnecessary fat in the human body, resulting in a health risk. The study of in-silico docking was performed using Molegro virtual docker (MVD). In-silico docking studies have taken the place of the new version of GLIDE Software v5.5, built by Schrödinger. These findings showed that the binding energy in all active components ranged from -2.5 to -8.6 kcal/mol. If compared to the standard (-9.2 kcal/mol). Due to their structural parameters, the inhibitors of HMG-CoA reductase are excellent, as are Calamol and 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl) indene acid. It was found that, as opposed to the standard drugs, the investigated phytoconstituents showed potent inhibiting activity as the MolDock score directly represents possible binding to the enzyme.

Keywords: *Acorus calamus*, In-silico docking, Phytoconstituents, HMG-CoA reductase.

INTRODUCTION

In adults, obesity is generally described as a $[BMI > 30\text{kg/m}^2]$ body mass index¹. The main risk factors for insulin-resistance and type 2 diabetic mellitus, cardiovascular and non-alcoholic liver fat conditions include weight gain and obesity, and an increase in risk of

impairment. The obesity of all causes is associated with a modestly increased risk of death. Docking studies play a significant role in designing new chemical entities for the treatment of various diseases. Vacha is a typical Indian herb used for various diseases including neurology, gastrointestinal problems, respiratory, metabolic, renal disease and liver problems. The herb of Vacha is also known for its use as a medicine herb²⁻³. The purpose of in-vivo experimentations is to evaluate the effects of plant species on the docking studies and to evaluate the effects of phytoconstituents⁴⁻⁸. The target was selected as 3-hydroxy-3-methylglutaryl-coenzymeAA for the docking studies (HMG CoA reductase)⁹⁻¹⁵. It was therefore planned to explore the impact of different phytoconstituents on the HMG CoA reductase enzyme as a target protein using Schrödinger-built software v5.5 on the Red Hat Enterprise Linux5 workstation¹⁶⁻²⁸. The phytoconstituent docking score is compared with the regular drugs, i.e. atorvastatin, obtained from the drug data bank²⁹⁻³⁹. Molecular docking is an appealing scaffold for understanding medicinal biomolecular interactions in rational drug design as well as in the mechanical analysis in order, primarily noncovalently, to insert the molecule (ligand) into the favorite binders of the particular target area of the DNA/protein (receptor)⁴⁰⁻⁵². The information gathered from the docking method can be used to demonstrate the binding energy, free energy and complex stability. The docking are currently used to forecast the preliminary ligand-receptor complex binding parameters. The present study aims to carry out a reverse pharmacological assessment of the antiobesity impact of selected phytoconstituents of medicinal plants suggested in folk medicine. Furthermore, in Ayurvedic literature, the routine use of coriander seed decoction is considered to be effective in reducing the amount of blood lipids⁵³⁻⁵⁹.

MATERIAL AND METHODS

Molecular Modeling Studies:

Schrödinger has also been used for molecular modelling studies by GLIDE v5.5 on the Red Hat Enterprise Linux5 workstation. In the preparation of ligand, protein and HTVS, all steps involved, Maestro v9.5 Graphical User Interface (GUI) workspace was used (High Throughput Virtual Screening)⁶⁰⁻⁶¹.

Ligand Preparation:

The ligands used in this study have been developed with the Schrödinger Suite 2013 LigPrep module v2.3. LigPrep follows the energy minimization force fields in OPLS-AA (Optimized Potential Liquid Simulations for All Atoms)⁶².

Protein Preparation:

Thermodynamic and structure guided design of statin HMG-CoA reductase inhibitor (PDB Code=3CCT) with 2.12Å resolution. Only high atoms, water, cofactors and metal ions can be used in a standard PDB structure, and multimerical structures can be used. GLIDE software protein preparation Wizard for the processing and preparation of protein was used. This is also in line with the optimized power potentials in the energy reduction fields for liquid simulations-all atoms (OPLS-AA)⁶³⁻⁶⁴.

Docking Protocol:

The GLIDE Extra Precision (XP) mode was used for all docking calculations. The binding site for which various energy grids have been determined and stored. For those atoms with absolute partial loads below 0.15 (scale factor of 0.8) and 1.0 electrons of the ligand and proteins, respectively, the scale factor for van der Waals radii was added. In the initial calculation process, the maximum number of poses produced by the max keep variable was set at five thousand and the best hold variable was set at one thousand. The E-model, which comes from a combination of gscore, coulombic, van der Waals and the ligand strain energy, is another scoring feature used by GLIDE⁶⁵⁻⁶⁶.

RESULTS AND DISCUSSION

Statins are evident in generating a number of adverse effects that are confirmed by findings from multiple Randomized Controlled Trials. The GLIDE norm score for Atorvastatin was found to be -9.2. This demonstrates that potential drugs for the production of anti-diabetic activity drugs could be the chemical component of the plant. The GLIDE score may be used as a semi-quantitative descriptor to describe ligands which bind to a certain conformation of a protein receptor. In general, a high affinity of the ligand to the receptor for a low GLIDE score can be predicted. In particular, with a docking score of -8.6 and -2.5 respectively, the compounds Calamol and 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl) indene acid were found to be potent. The role of the docking inhibitor and the crystal protein structures is well decided upon. GLIDE-led docking studies have confirmed that the inhibitors referred to above fit into the protein binding site. The phytoconstituent responsible for the highest MolDock ranking, namely Calamol and 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl) indene acid, may therefore have a free radical scavenging mechanism for exhibiting anti-hyperlipidemic activity compared to standard drugs.

Table 1: Glide score of Phytoconstituents of *Acorus calamus* Linn.

Sr. no	Phytochemical constituents	Glide score
1	α -Asarone	-2.5
2	β -Asarone	-4.9
3	γ -Asarone	-5.2
4	Eugenyl acetate	-1.9
5	Calamol	-8.6
6	Cinnamaldehyde	-5.1
7	2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3 (2,4,5-trimethoxyphenyl) indene	-7.8
8	Atorvastatin	-9.2

CONCLUSION

In conclusion, our findings strongly support the medicinal use of *Acorus calamus* Linn. phytoconstituents as a possible herb that can be eaten to avoid hyperlipidaemia over the commonly prescribed pitavastatin and atorvastatin in our day-to-day lives, where these phytoconstituents are free of any side/adverse effects. Further research may be performed to determine the exact mechanism of action by which antihyperlipidemic activity was exhibited by the medicinal plants.

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