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Computational studies of plant derived natural compounds with HMG-CoA enzyme through *in silico* analysis

M. Sellappan [1*], M. Rajasekara Pandian[1], A. Krishnamoorthi[1], S. Senthilnathan[1]
[1]*Department of Zoology, Arignar Anna Government arts college, Namakkal, Tamilnadu, India*
**Corresponding Author: Dr. M. Sellappan*

Abstract: *Plant products have always been well thought-out for many important metabolic disorders due to its abundant medicinal properties. This study was aimed to identify potent compounds with anti-dyslipidemic property from selected plants and analyse them for their efficiency in binding with HMG-CoA reductive. The 3D structure of HMG-CoA protein was retrieved from protein data bank (PDB ID:3CCZ). Totally four plant derived compounds were selected for docking studies such as 6-gingerol, guajavarin, hesperetin and phloretin. Based on the present study, the maximum docking energy was observed at -100.092kcal/mol with guajavarin and the protein binding sites were identified. The docking H-bond results indicate that the guajavarin was an efficient compound with HMG-CoA reductase protein. Our study identified guajavarin as a promising lead compound which could be further developed into an anti-dyslipidemic molecule.*

Key Words*: HMG-CoA, Docking, Guajavarin, Phytocompounds*

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I. Introduction

Current learning in our laboratory reported that AA improves the level of plasma insulin decreases glucose level, reverses the changes in the levels of the key carbohydrate metabolizing enzymes with as well prevents lipid peroxidation and improves antioxidant status in rats with streptozotocin-induced diabetes (Ramachandran and Saravanan 2013). Constant although, satins therapy is helpful in lowering the serum low-density lipid levels (Kavalipati et al., 2015), they often lead to adverse side effects including liver toxicity. Also, indiscriminate use of statins results in side effects (Kiortsis et al., 2007). The reduction of blood cholesterol level is one of the guidelines of the European Society of Cardiology (ESC) to reduce the risk of developing cardiovascular diseases. One of the highest causes of death in Europe and also around the world. Atherosclerosis is a disease in which atheromatous plaques are formed inside arteries, triggering their hardening and narrowing, limiting, the blood flow. These plaques are formed essentially by triacylglycerols, lipoproteins, cholesterol and foam cells (Bentzon et al., 2014).

This possibly will be alive achieved by decreasing diet cholesterol intake, as some studies reported correlations between diet cholesterol intake and blood cholesterol level (Dehghan et al., 2012), which can contribute for atherosclerosis-related diseases (Niki, 2011). Also a healthy diet (Reiner et al., 2011) cholesterol levels can be decreased by reducing its bio-synthesis through inhibition of the enzyme HMG-CoA reductase (HMGR), involved in the cholesterol biosynthetic pathway (Istvan and Deisenhofer, 2001), which is the approach taken clinically by statins. A new approach is the reduction in dietary cholesterol absorption through the blockage of the cholesterol protein transporter in intestinal cells which can be accomplished by the drug ezetimibe (Vrablik et al., 2014).

Cardiovascular disease (CVD) is the major cause of death in developed and developing countries (Leeder et al., 2004). It is well known that three major risk factors for CVD are hypercholesterolemia, smoking and hypertension (Stocker and Keaney, 2004). Several studies have established that elevated blood cholesterol along with triglyceride (TG) level is a major cause and initial risk factor of atherosclerosis and subsequent CVD (Steinberg, 2002). Endogenous cholesterol biosynthesis in the liver is mainly controlled by rate limiting enzyme like 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonic acid. Drugs that lower cholesterol level mainly work by inhibiting the HMG-CoA reductase activity (Carbonell and Freire, 2005).

II. Materials and Methods

Protein Ligand Preparation

The 3D structure of the targeted protein HMG-CoA was retrieved from protein data bank (www.rcsb.org/pdb, PDB ID: 3CCZ). Structure and active sites of the protein was visualized through pyMOL viewer. Totally five plant derived natural compounds were selected and retrieved from pubchem online database for this study. The compounds are 6-gingerol, guajavarin, hesperetin, phloretin and guajavarin were screened. According to Lipinski's rule of five, a compound having not more than five hydrogen bond donors (OH an NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition co-efficient log P of less than five and rotatable bonds of less than ten is taken as drug molecules and docking procedure was carried out (Lipinski et al., 2001) against the HMG-CoA protein. The H atoms were added to the structure and minimizations were performed using Swiss pdb viewer. Hydrogen atoms were added to all the structures and gasteiger atomic partial charges were computed. A geometry optimization of all the compounds was completed using chimera (Pettersen et al. 2004) for flexible conformations of the compounds during the docking.

Active site identification

The pubchem database was used for retrieving the phytochemical molecules; the database is maintained by NCBI. The selected chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the MarvinSketch Software. The predicted ligand binding site residues are listed in Table 1, 2 and 3; Figure 1-5.

The molecular docking was completed using Argus Lab, extensively distributed public domain molecular docking software. The inhibitor and target protein was geometrically optimized using docked engine Argus dock. The catalytic binding site was a small region, where lead molecules can bind to stimulate the target protein and produce the desirable effect. Thus, recognizing the catalytic binding site residues in the protein structure was more importance in computer-aided drug designing. In the present study, Qsite (Laurie and Jackson, 2005) finder was employed for locating the active sites in selected plant derived natural compounds.

III. Results and Discussion

The present study, we selected five plant derived phytocompounds and the protein used in docking. The best binding poses for each ligand molecule into target protein was determined and the one having lowest binding energy among the different poses generated. The lower energy scores represent better binding protein and ligand affinity compared to energy value. Docking of HMG-CoA (Protein-3ccz) with guajavarin, was found to be least binding energy (-100.092kcal/mol). Four hydrogen bonds were formed with the residues and amino acids SER 684 (3.2Å), LYS692 (2.4 Å), ASP 690 (2.7 Å) and LYS 691 (3.1 Å) respectively. The guajavarin compound have more stable ligand–receptor complex amongst other compounds.

Hepatic HMG-CoA reductase is the key enzyme in cholesterol synthesis. Some inhibitors of HMG-CoA reductase can inhibit cholesterol synthesis and lower cholesterol levels. The increased of mevalonate ratio or decreased of HMG-CoA indicates the increased activity of the enzyme. The previous study reported that organophosphates may phosphorylate and inhibit the HMG-CoA reductase, the key enzyme in cholesterol synthesis (Senthilraja et al., 2011). A number of phytochemicals have been reported to possess hypoglycemic effects and the possible mechanism suggested for such hypoglycemic action could be through an increased insulin secretion from L-cells of islets of Langerhans or its release from bound insulin or such hypoglycemic effects of triterpenoids could also be because of their insulin-like actions (Ramachandran et al., 2014).

There has been considerable interest in the use of natural food materials like functional foods to treat hypercholesterolemia. In general, plant foods are considered beneficial to prevention of cardiovascular diseases due to their low fat content and the presence of bioactive compounds with different chemical compositions, which may sometime be considered cholesterol lowering agents through different mechanisms (Chen et al., 2008).

Table1. Physico-chemical properties of selected ligand molecules

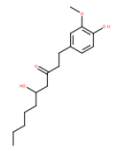
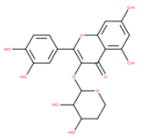
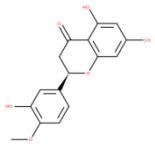
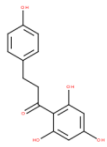
S. No	Compounds	PubChem ID	Structure	M-Formula	M-Weight g/mol	H-Bond Donor	H- Bond Acceptor
1.	GINGEROL	442793		$C_{17}H_{26}O_4$	294.391	2	4
2	GUAJAVARIN	5481224		$C_{20}H_{18}O_{11}$	434.353	7	11
3	HESPERETIN	72281		$C_{16}H_{14}O_6$	302.282	3	6
4	PHLORETIN	4788		$C_{15}H_{14}O_5$	274.272	-NO	-NO

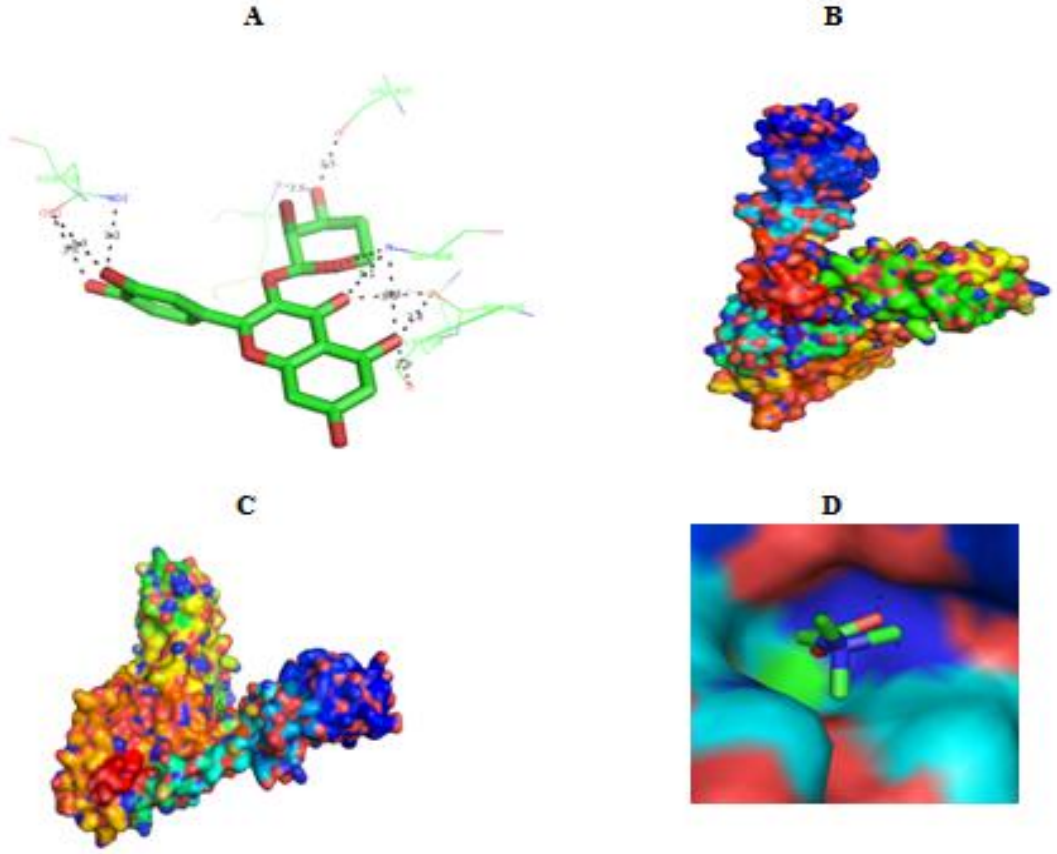
Table 2. Docking Results of different ligand molecules interact with target protein

S. No	Ligands	Binding Energy Kcal/mol	Amino acid Residues	Atom and H-bond distance= A^0
1	GINGEROL	-55.2315	GLY 765 GLY 808 GLY 656 MET 659 ASN 658	GLY 765;O---ND2→2.6 GLY 808;ND2---O→3.1 MET 659;ND2---O→3.2 ASN 658;ND2---O→2.6 GLY 656;ND2---O→3.2
2	GUAJAVARIN	-100.092	ASN 658 MET 655 GLN 766 GLY 765 GLY 608 VAL 805	ASN 658;ND2---O→3.2 ASN658;OD1---O→3.0 ASN 658;OD1---O→3.3 MET 655;ND2---O→2.8 VAL 805;OD1---O→2.5 GLY 808;ND2---O→3.5 GLY 808;ND2---O→3.3 GLY 765;OD1---O→3.0 GLY 765;OD1---O→2.8 GLN 766;OD1--O→2.9
3	HESPERETIN	-54.4792	MET 659 ASN 658 MET 655 GLY 803 VAL 805 GLN 766	MET 659;N---O→2.7 ASN 658;N---O→3.0 MET 655;N---O→2.6 VALL 805;OE1---O→3.2 GLY 803;OE1---O→3.1 GLN 766;OE1---O→2.8 GLN 766;N---O→3.1 GLN 766;OE1---O→3.3
4	PHLORETIN	-63.9635	GLN 766 GLY 765 GLY 803 GLY 656 MET 657 ASN 658	MET 659;ND2---O→3.1 ASN 658;ND2---O→3.1 ASN 658;ND2---O→3.0 GLY 656;ND2---O→3.1 GLY 803;ND2---O→3.2 GLN766;OE1---O→3.0 GLN 766;OE1---O→3.0 GLN 766;OE1---O→2.7 GLY 765;OE1---O→3.1

Table 3. Number of H-bonds interacted with different ligand molecules

S. No	Ligands	Number H-bonds
1	GINGEROL	6
2	GUAJAVARIN	11
3	HESPERETIN	7
4	PHLORETIN	4

Figure 1. Docking of HMG Co-A(3ccz) with GUAJAVARIN



The HMG Co-A (3ccz) with GUAJAVARIN was found to be binding energy -35.2201 respectively. Leven hydrogen bonds were formed with the residues ASN 658 (3.2 Å, 3.0Å, 3.3 Å), MET 655 (2.8Å), GLY 803 (3.5Å, 3.2Å), VAL 805 (2.5Å), GLN 766 (2.9Å) and GLY 765 (3.0 Å, 2.8 Å).

IV. Conclusion

The results obtained from this study would be useful in both understanding the inhibitory mode of plant derived compounds as well as in rapidly and accurately predicting the activities of recently designed inhibitors on the basis of docking scores. Here we concluded that guajavarin compound could be novel chemical interaction with HMG CoA protein preventing the uncontrolled lipid metabolism. Further research is needed for refinement to enrich the activity of the ligands and destroying mechanism, especially in the animal model system, and also to determine the dosage of safety levels, in order to explore this promising avenue to ensure the healthy humans.

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