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IN SILICO DOCKING APPROACH FOR ANTIATHEROSCLEROTIC ACTIVITY OF PHYTOCONSTITUENTS OF METHANOLIC EXTRACT OF *SOLANUM MELANOGENA*

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ABSTRACT

OBJECTIVE: Atherosclerosis is a chronic inflammatory disease characterized by changes in lipid metabolism within the arterial wall. Liver X alpha receptor is highly expressed in liver may control the metabolism of cholesterol and suppress the inflammatory genes, thus preventing atherosclerosis from being triggered. The *Solanummelongena*possess anti-atherosclerotic property by stimulating the intrahepatic metabolism of cholesterol, produces a marked drop in blood cholesterol level. The objective of the present study is to investigate the anti-atherosclerotic activity of the *methnolic extract of Solanummelongena peel* against Liver X alpha receptor by using iGEMDOCK. **METHODS:** Liver X alpha (Protein Date Bank ID – 3IPQ) 3 Dimensional structure was retrieved using the Protein Data Bank. Phytochemical molecules have been extracted from the Pubchem database and 2D chemical structures have been developed with a Chemsketch program from the Smiles Notation.Comparative molecular docking simulation of the screened phytochemicals was carried out mainly with iGEMDOCKv2.1. **RESULTS:** Among the 13 phytochemicals, Catechin and Naringeninwas found to be the top compound with highest docking score of -100.741kcal/mol and -92.7765 kcal/mol, respectively. **CONCLUSION:** Our analysis indicates phytochemicals derived from *methnolic extract of Solanummelongena peel* can serve as leads and atherosclerosis can be prevented.

Keywords: Atherosclerosis, *Solanummelongena* ,Liver X alpha receptor and iGEMDOCKv2.1.

INTRODUCTION

Atherosclerosis, being a chronic inflammatory condition, is becoming the leading cause of death in most developed countries.[1]Cardiovascular diseases (CVDs) such as myocardial infarction (heart attack), acute coronary syndrome, or stroke occur from plaque and lesion formation within the arteries[2,3]Hypercholesterolemia, hypertension, and obesity give the high risk of development of CVDs.Statins are commonly used as a Clinical treatment for atherosclerosis because of their excellent effectiveness in reducing the degree of low lipoprotein density (LDL).[4,5] Statins inhibit competitively the HMG-CoA reductase enzyme, which plays a major role in catalyzing the rate limiting step in cholesterol biosynthesis.[6] Increased expression of hepatic LDL receptors is caused by decreased

concentration of hepatocyte cholesterol and helps clear LDL from circulation.[7,8]

The liver X receptors (LXRs) are nuclear receptors regulated by endogenous oxysterols, which are oxidized cholesterol derivatives. This has two LXR isoforms, LXRa (NR1H3) and LXRβ (NR1H2). All LXRα and LXRβ control gene expression by binding to target gene-associated DNA sequences as heterodimers with retinoid X receptor (RXR), RXRα (NR2B1), RXRβ (NR2B2) and RXR:/ (NR2B3) isoforms.LXRs function as cholesterol sensors: when cellular oxysterols accumulate due to elevated cholesterol concentrations, LXR induces the transcription of genes that protect cells from overloading cholesterol.LXR's functions in cholesterol homeostasis regulation include bile acid synthesis and metabolism / excretion function, reverse cholesterol transport, cholesterol biosynthesis and uptake, and cholesterol absorption / excretion in the intestines. Often explored are the overlapping and distinct functions of the isoforms LXRα and LXRβ and the possible use of LXRs as desirable targets for cardiovascular disease treatment[9]

Nonetheless, statin intake causes adverse health effects such as hepatic damage and muscle toxicity.[10,11]Additional side effects include myopathy, rhabdomyolysis and acute renal insufficiency.[12] Therefore, attention is now centered on plant-derived natural products which have antiartherosclerotic activity and can promote human health.It can potentially avoid potential health consequences due to long-term statin consumption.Over the last decades, several studies on bioactive compounds and their potential medicinal properties have been studied.[13,14]

Solanummelongena belongs to the Solanaceae family and is an important flowering plant. There are 75 genera and over 2000 species within the family.[15]Members are predominantly herbaceous plants, and the fruit is berry and the seeds have a large endosperm and are primarily cultivated for food and medicine purposes.[16]Solanummelongena Linn (Garden egg) is a culinary vegetable that has been in use since ancient times in the Indian medicinal system. Specific parts of the plant are used in the treatment of inflammatory disease, heart failure, neuralgia, ulcer in nose and cholera. It also has analgesic, anticonvulsant, antipyretic, hypolipidemic activity[15], anti-inflammatory activity.The plant can also be used to treat bronchitis and asthma.

The organic products of Solanummelongena are considered to contain distinctive groups of phenolic phytochemicals (flavones, phenolic acids and anthocyanins) that can have beneficial effects on human health.By HPLC, it was identified that methanolic extract contains distinguishing proof of the diverse phenolic phytochemicals such as Gallic Acid, Catechin, Coffeic Acid, Syringic Acid, Rutin, Coumaric Acid, Vanillin, Ferulic Acid, Naringenin, Querectin, Cinnamic Acid, Propyl Gallate,andDihydroxyisoFlavone.[16]

Hence, this research investigated the molecular association between the phytochemicals in the methnolic extract of *Solanummelongena* peel and the LXRα to prevent atherosclerosis by using iGEMDOCK[17] via insilico docking.

METHODS

LXRα retrieval

The 3-Dimensional structure of LXRα (Protein Date Bank [PDB] ID – 3IPQ) was obtained using Protein Data Bank which could serve as the target molecular docking molecules. The structure was presented using Swiss PDB Viewer to build a deeper understanding of the molecule to use it as a target for the drug.

Building of herbal compounds

Thirteen phytochemicals identified from ethanol extract of *Solanummelongena*peel were screened against LXRα. List of phytochemicals identified are shown in Table 1. The phytochemical molecules were obtained from a pubchemic database and 2-D chemical structures were produced using the Chemsketch program from the SMILES notation. The structure was then converted to 3D, its geometries optimized and saved with an open babel server in MDL mol file format.

Primary docking simulation-IGEMDOCK.

Simulation of the phytochemicals was achieved using the docking module iGEMDOCK-v2.1.[18]Using a generic evolutionary method algorithm, iGEMDOCK performs integrated scanning, docking, and post analysis. The binding site was prepared by iGEMDOCKtool to determine LXRα binding site . For both protein and ligand inputs the program needs .pdb file. Other parameters such as population size, generations and number of solutions were set at 200, 70 and 2 for Standard docking, respectively.The scoring function of iGEMDOCK can be illustrated as follows.

Fitness = vdW + EHydrogen bond + EElectrostatic

Where, vdW is Vander waal's energy (kcal/mol), H-bond is hydrogen bond energy (kcal/mol) and Elec is electrostatic forces

(kcal/mol) between the ligand and receptor protein .

The interaction profile tool in iGEMDOCK has performed post-analysis of the docked poses. The strength, forces of Vander waal, hydrogen bond energy, electrostatic force energy and interacting residues were obtained and tabulated.[19]For further redock analysis, the top eight compound hits were selected based on total overall fitness and H-bond energies.

RESULTS AND DISCUSSION

Molecular docking studies of the Thirteen phytochemical compounds from the methanolic extract of *Solanummelongena* peel were performed primarily using iGEMDOCK v2.1 to establish binding free energy, energy split-up, and interactions between the ligands and the active site residues of LXRα.Among the studied ligands, Catechinand Naringenin were ranked in the first and second place with total binding energies of -100.741kcal/mol and -92.7765kcal/mol, respectivelyCatechinexhibit hydrogen bond energies of -21.3993kcal/mol andshowed hydrogen bond interactions with Ser-264, Met-298,Thr-302,Arg-305, Lys-317respectively. Querectin and Propylgallate shows significant binding energy of -89.1416kcal/moland -81.0235kcal/molwith hydrogen bond energies of -18.69171416kcal/mol and -19.9087 kcal/mol. Querectinshows three hydrogen bond interaction with His-397,Pro-398 and Arg-401aminoacid. andPropylgallate exhibit one hydrogen bond interaction with ARG-305 respectively.

The remaining phytochemicals Gallic Acid, Coffeic Acid, Syringic Acid, Rutin, Coumaric Acid, Vanillin, Ferulic Acid, CinnamicAcid,andDihydroxyisoFlavone displayed total biniding energies from -56.673 kcal/mol to -83.8911 kcal/mol without have any hydrogen bond energies.

Table 1: Primary Docking Results Illustrating Total Binding Energy, Energy Split Up And Interacting Residues Of Control And Test Ligands

Compound name	Primary Docking Analysis				
	Total binding energy kcal/mol	Vander Wall's Energy Kcal/mol	Hydrogen bond energy kcal/mol	Electrostatic bond energy kcal/mol	Interacting residues
Gallic Acid	-67.7006	-67.7006	0	0	Leu-260 ,Ser- 264,Arg-305,Phe-315
Catechin	-100.741	-79.3418	-21.3993	0	Ser-264,Met-298,Thr-302,Arg-305,Lys-317,Leu-260,Ser-264,Glu-267,Arg-305,Phe-315,Leu-316
Coffeic Acid	-73.1332	-73.1332	0	0	Leu-260,Ala-261,Ser-264,Arg-305,Phe -315
Syringic Acid	-71.378	-71.378	0	0	Leu-260,Ala-26,Ser-264,Met-298,Arg-305,Phe-315
Rutin	-71.378	-71.378	0	0	Gln-221,Arg-304,Arg-304,Arg-305,Lys-317,Asp-353,Arg-304,Arg-305,Arg-305,Thr-314,Leu-316,Lys-317
Coumaric Acid	-65.3699	-65.3699	0	0	Phe-257,Leu-260,Ala-261,Phe-315
Vanillin	-56.673	-56.673	0	0	His-390,Val-393, Ser-394,Ile-395,his-396,His-397,Pro-398,his-399,Asp-400,Arg-401,-Leu-402,Met-403,Phe-404,Pro-405
Ferulic Acid	-70.6109	-70.6109	0	0	Leu-260,Ser-264,Arg-305,Phe-315
Naringenin	-92.7765	-92.7765	0	0	Phe-257,Leu-260,Ala-261,Ser-264,Met-298,Arg-305,Phe-315
Querectin	-89.1416	-70.4499	-18.6917	0	His-397,Pro-398,Arg-401,His-390,Ser-394,Pro-398,Asp-400,Arg-401
Cinnamic Acid	-56.8387	-56.8387	0	0	Phe-257,Phe326,Phe-335,Ile-339
Propyl Gallate	-81.0235	-61.1148	-19.9087	0	Arg-305,Leu-260,Ser-264,Phe-315
DihydroxyisoFlavone	-83.8911	-83.8911	0	0	Phe-257,Leu-260,Ala-261,Ser-264,Arg-305,Phe-315

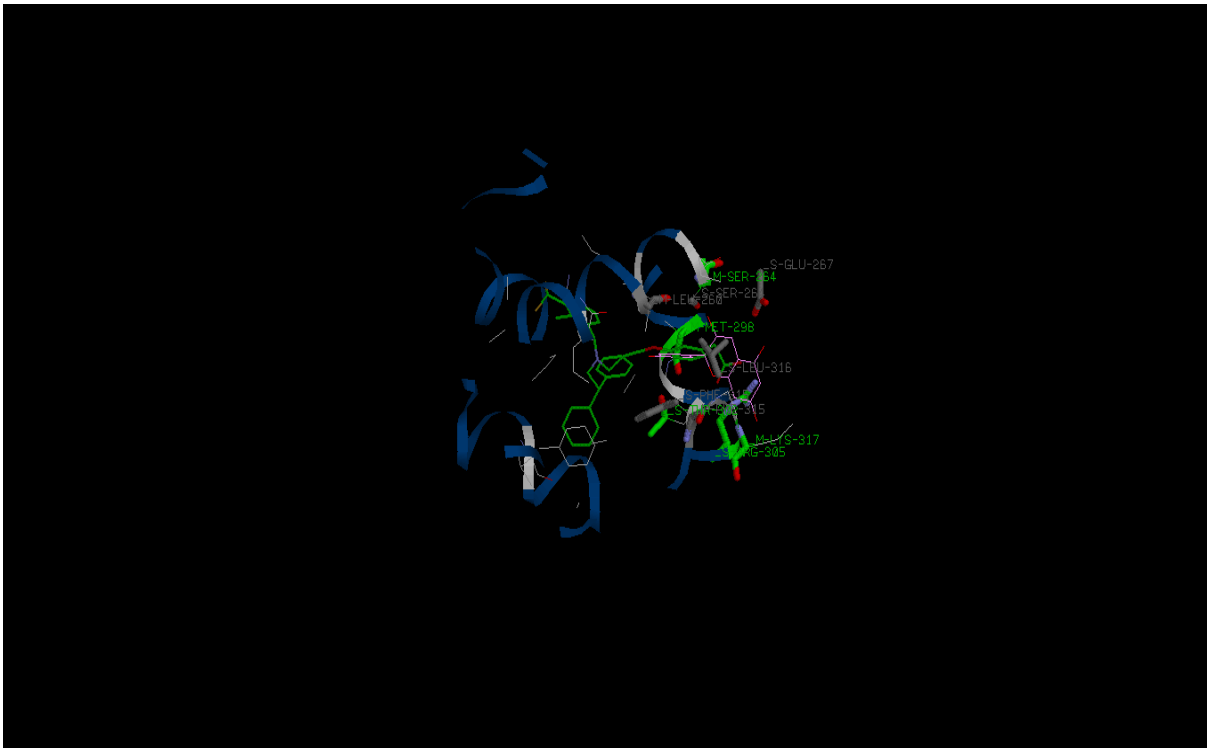

Fig .1: Interaction between LXRα and Catechin

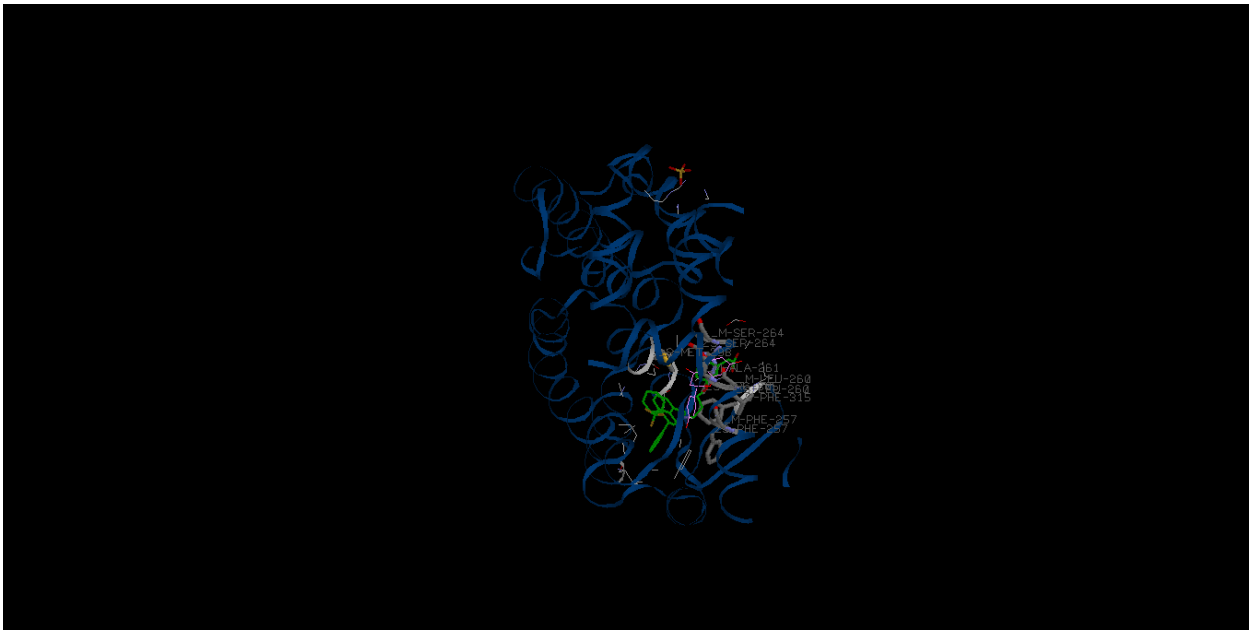

Fig. 2: Interaction between LXRα and Naringenin

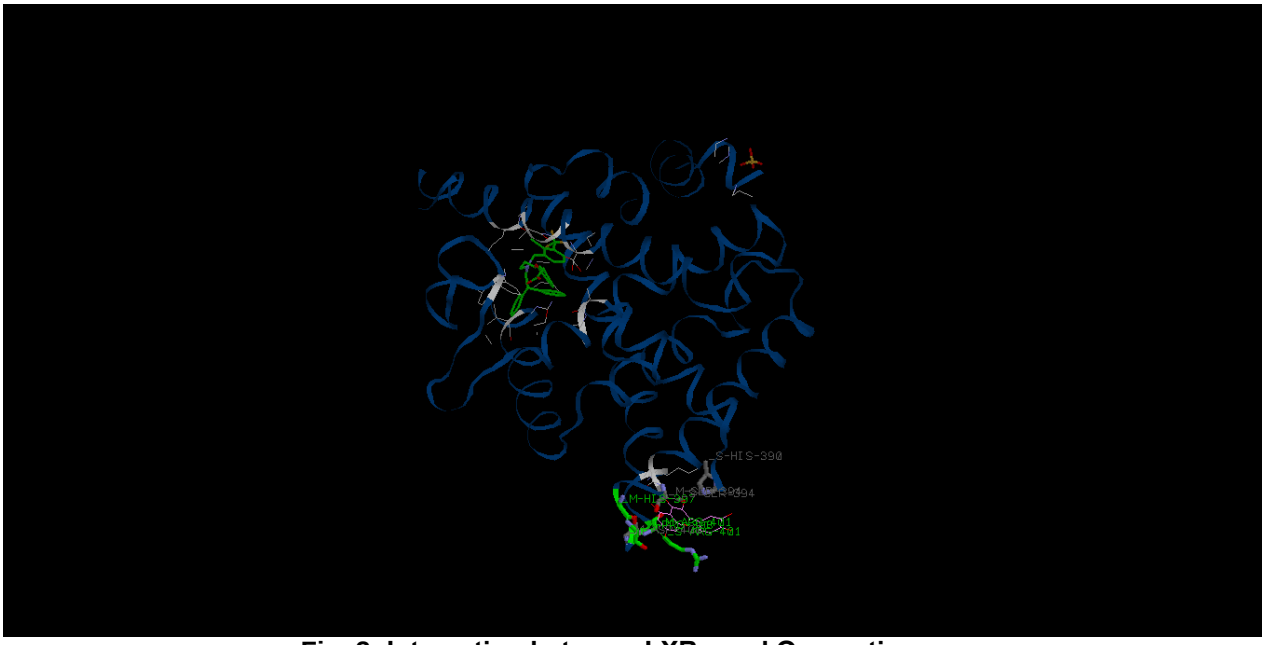

Fig. 3: Interaction between LXRα and Querectin

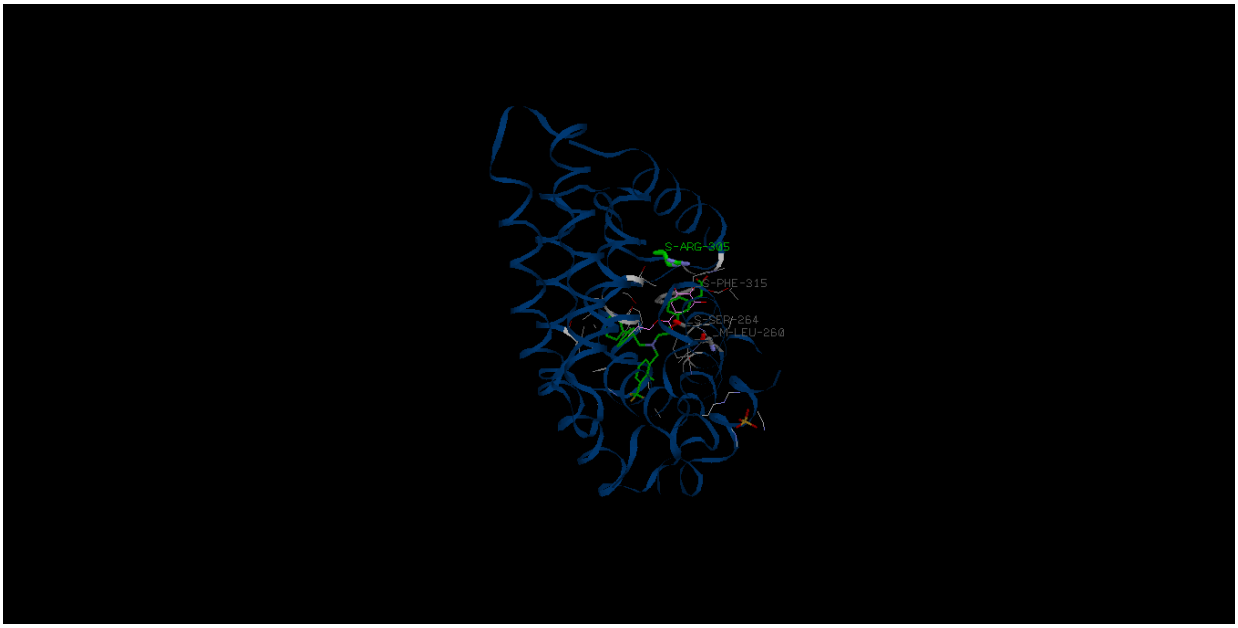

Fig. 4: Interaction between LXRα and Propylgallate

CONCLUSION

Catechin, Naringenin, Querectin and Propylgallatefrom *Solanummelongena* were the best compound hits among the studied compounds. From the different interactions exhibited by these three compounds with the binding site residues of the LXRαIt can be concluded that these compounds will structurally alter the expression of genes involved in the synthesis of hepatic bile and fatty acids, glucose metabolism and sterol efflux after binding with LXRα.

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