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MOLECULAR DOCKING STUDIES ON SELECTED PHYTOCOMPOUNDS AGAINST PCSK9 LDL RECEPTORS [HOMOSAPIENS] FOR CORONARY ARTERY DISEASE

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Abstract-Coronary artery disease is the angina product or myocardial infection, is one of our widespread public disease. That is present in blood flow through the arteries. Due to this disease, the heart muscle may not receive enough oxygen and chest pain (called angina) may be felt. It is estimate that more than 16 million Americans have suffering from Coronary artery disease and 8 million have had a myocardial infarction (MI). Based on data from Framingham trail nearly 50% of male and 30% of female over the age of 40 will develop Coronary artery disease. However some research paper shoes that natural compound i.e. Flavonoid, Queratin, Ellagic, Resveratrol, has been regarded as a promising drug target against Coronary artery disease. In this study the docking had been done the LDL-Receptor protein (PDB ID-4LKC) using Auto dock 4.2 against the Flavonoid, Queratin, Ellagic, Resveratrol. The result show that among four phytocomound, the ellagic compound (pubchem id-5280343) showed good docking score (-7.96), and intermolecular energy (-9.15) against LDL-Receptor then the hydrogen bonding interaction (ILE-118,ALA-152,ALA-152,SER-142,THR-146,ALA-152,LYS-208,THR-150,SER-142) with active site residue. However this lead molecule has to be evaluated further before they are suggested as the best potential lead molecule.

1. INTRODUCTION

The heart is a muscular organ about the size of a fist, located just behind and slightly left of the breastbone. The heart pumps blood through the network of arteries and veins called the cardiovascular system. The cardiovascular system is important to our body in the blood circulation through the arteries and veins. Arteries are the blood vessels that carry blood away from the heart, while most arteries carry oxygenated blood and veins are blood vessels that carry blood toward the heart. Most veins carry deoxygenated blood from the tissues back to the heart. Due to the defect of arteries that result in the heart disease that is the Conditions. Heart disease (HD) is a general term for a variety of cardiovascular heart disease (CVD) is the leading cause of death worldwide. Cardiovascular disease (CVD) [1] is a general term that describes a disease of the heart or blood vessels.

Smoking tobacco also results in increased exposure to carbon monoxide (CO), a color less, order less gas which is produced from the incomplete burning of combustible products. CO is the fourth most common chemical of the 4,000 different constituents of tobacco smoke and can make up 3-5% of its volume. When levels of CO in the blood increase the ability of the body to carry oxygen is significantly decreased. Blood pressure is measured as two numbers, written one over the other and recorded in millimetres of the top (higher) number is the systolic pressure, the pressure in the arteries as the heart is contracting and the bottom (lower) number is the diastolic pressure [2]. The pressure in the arteries when the heart is relaxed between beats. Diabetes is defined as having a fasting plasma glucose value of 7.0 mmol/l (126 mg/dl) or higher. The risk of cardiovascular events is from two to three times higher in people with type 1 or Type 2 diabetes and the risk are disproportionately higher in women. Raised blood cholesterol increases the risk of heart disease and stroke. Globally, one third of ischemic heart disease is attributable to high cholesterol [3]. The prevalence of raised total cholesterol noticeably increases, according to the income level of the country. In low-income countries, around 25 per cent of adults have raised total Cholesterol, while in high-income countries; over 50 percent of adults have raised total Cholesterol. High dietary intakes of saturated fat, trans-fats and salt and low intake of fruits, vegetable and fish are linked to cardiovascular risk.

Due to different cause there is several type of cardiovascular disease happen Coronary heart disease (CAD) [4] is a type of disease of the blood vessels supplying the heart muscle that can lead to a heart attack. The brain is responsible for heart attack. Blood must flow to and through the brain for it to function. If this flow to a part of the brain is blocked or interrupted, that part of the brain is deprived of oxygen and nutrients and begins to die. Coronary artery disease (CAD) is the most common type of heart disease. It is the leading cause of death in the United States in both men and women's. The most important part of cardiovascular disease is coronary artery disease. That is more harmful than the other heart disease. Coronary artery disease (CAD) is present; blood flow through the arteries can be reduced. When this happens, the heart muscle may not receive enough oxygen [5].

Coronary artery disease (CAD) is in which a waxy substance called plaque (plak) builds up inside the coronary arteries [6]. These arteries supply oxygen-rich blood to your heart muscle. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows the arteries, reducing blood flow to your heart muscle. When plaque builds up in the arteries, the condition is called atherosclerosis (ATH-er-o-skler-O-sis). Atherosclerosis is a process that can involve many of the body's blood vessels with a variety of presentations [7] [8]. When it involves the coronary arteries it results in coronary artery disease (transient ischemic attack), the cerebral arteries; Cardiovascular disease (stroke), the aorta; aortic aneurysms, the ileo-femoral and poplitealarteries; peripheral vascular disease, the mesenteric arteries; intestinal ischemia. Half of all deaths in the developed world and a quarter of deaths in the developing world are due to Cardiovascular Disease, which are comprised of hypertension and the diseases caused by atherosclerosis.

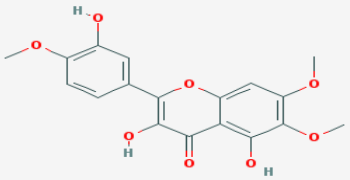
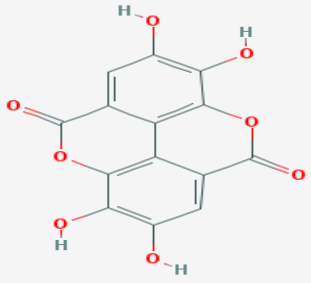
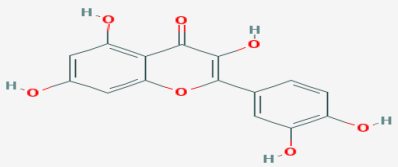
Hardening of the arteries (atherosclerosis) is the predominant cause of acute coronary artery disease. Atherosclerosis primarily attacks the innermost layer of the artery wall, the intima, which is made up of endothelial cells. Initially, a storing of blood fats (lipids) occurs between the endothelial cells, where inflammatory cells, macrophages, ingest the fat.

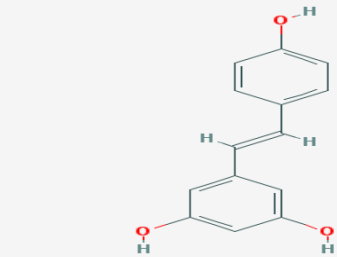
Atherosclerosis is the main cause of coronary artery disease. The process begins as disruption of endothelial function due to the accumulation of lipoprotein droplets in the intima of the coronary vessels [9]. Water insoluble lipids are carried in the bloodstream attached to water soluble apolipoproteins (lipoproteins). High concentrations of low density lipoprotein (LDL) [10] can permeate an already disrupted or dysfunctional endothelium where it undergoes oxidation and, in diabetics, glycation. Modified LDL attracts leukocytes into the intima and can be scavenged by macrophages leading to the formation of foam cells. These cells replicate giving rise to one of the earliest. A heart attack occurs when blood flow to an area of your heart muscle is completely blocked. This prevents oxygen-rich blood from reaching that area of heart muscle, causing it to die. This condition is called angina.

2. METHODOLOGY

Three dimensional structure of c-terminal domain of pcsk9 lower LDL cholesterol protein with PDB ID 4KLC was retrieved from RCSB Protein Data Bank. Four different phytochemical compounds like Flavonoid, Queratin, Ellagic and Resveratrol were retrieved from pubchem database. The chemical molecules are optimized and saved.

Table 1.1: Phytochemical compound infofmation that download from pubchem

S. No.	Plant Name	Drug ID	Chemical Formula	IUPAC NAME	Structure
1	Flavonoids plant	9997719	$C_{18}H_{16}O_8$	3,5-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) -6,7-dimethoxychromen-4-one	
2	vegetables	5281855	$C_{14}H_6O_8$		
3	Onion plant	5280343	$C_{15}H_{10}O_8$	2-(3,4-dihydroxyphenyl) -3,5,7-trihydroxychromen-4-one	

4	Eucalyptus, spruce, and lily plant	445154	$C_{14}H_{12}O_3$	5-[(E)-2-(4-hydroxyphenyl)ethenyl] benzene-1,3-diol	

After retrieving both protein 4lkc and four ligands like chemicals compound, the Auto Dock 4.2 was used for docking analysis. That is a Graphical user interface called auto dock tool or ADT that helps the user to set up the two molecules for docking study. ADT works with the combination of two methods to achieve these goals. Rapid grid based energy evaluation and efficient search of tensional freedom. Here the Lamarckian genetic algorithm and empirical free energy scoring function is typically providing the docking result for ligand with approximately 10 fixable conformations. Pymol visualization tools in structural biology are used for the visualization of three dimensional structures. It used for the conformation analysis and manipulating the structure of docking result, it also gives the energy information and bond distance about the structure.
Hydrogen bond interaction, docking score, intermolecular energy and tensional energy of the each binding conformation within the 10 was analyzed and the best conformation was selected according to docking score. Finally each conformation has different docking result and the lowest docking score is the best conformation result in the molecular docking experiment.

3. RESULTS AND DISCUSSION

The docking analysis was done for Flavonoid, Ellagic, Queratin and Resveratrol compound with target protein 4lkc using the autodock 4.2 docking software. The image was taken using the PyMol software. That aim to identify the detail information about hydrogen bond interaction between receptor and ligand.

3.1 Best Pose in Docking Result

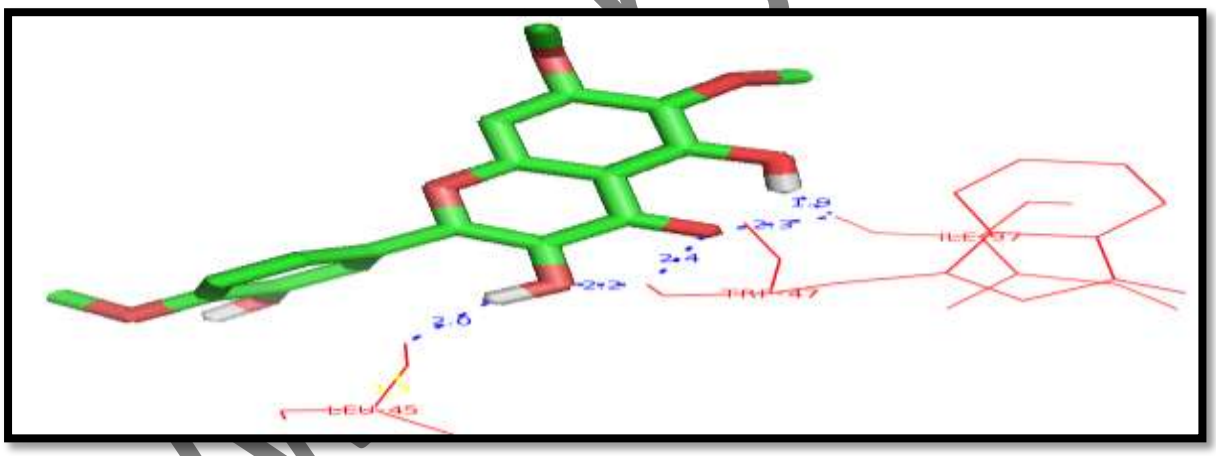


Fig. 3.1Screenshort PyMol Result of Best Pose Docking Result of Protein 4lkc With Compound Flavonoid

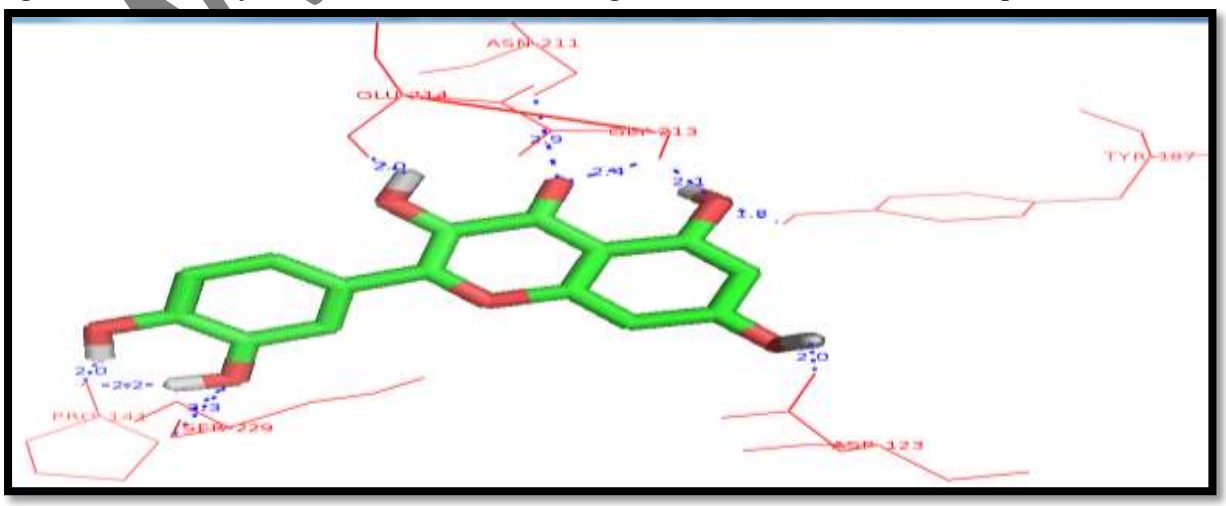


Fig. 3.2 Screenshort PyMol Result of Best Pose Docking Result of Protein 4lkc With Compound Queratin

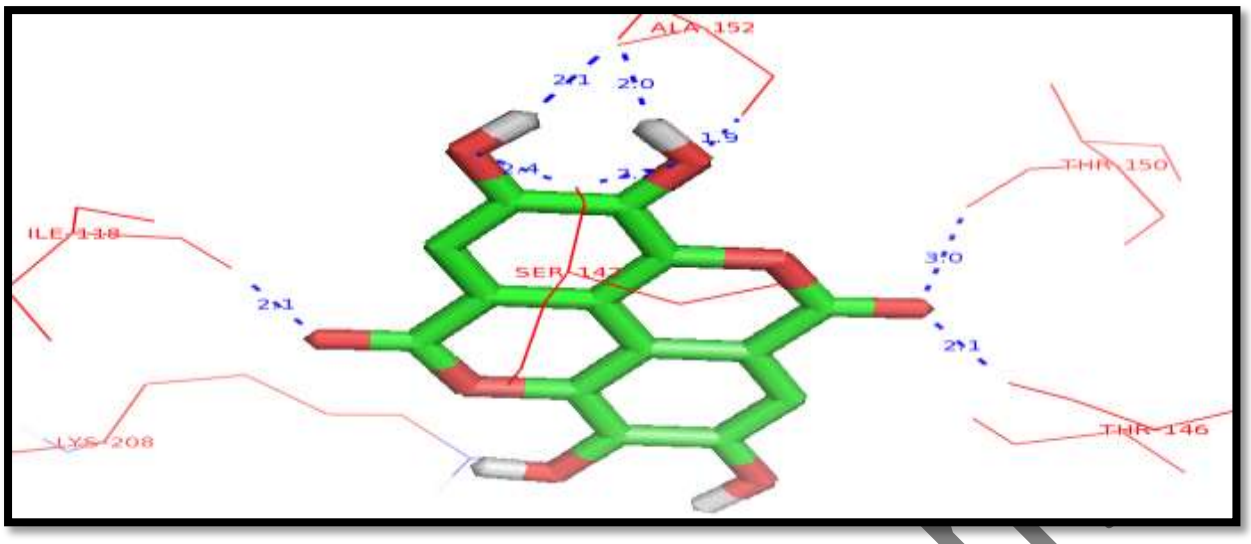


Fig. 3.3 Screenshort PyMol Result of Best Pose Docking Result of Protein 4lkc With Compound Ellagic

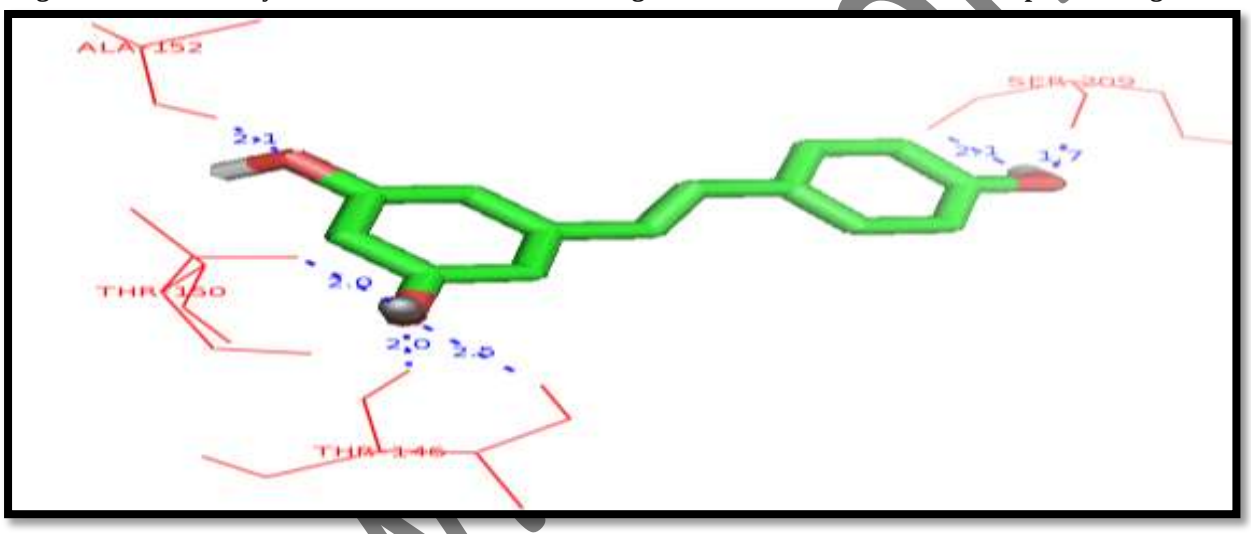


Fig 3.4 Screenshort PyMol Result of Best Pose Docking Result of Protein 4lkc With Compound Resveratrol

Table-3.1 Detail Information About Docking Score With H-bond Interaction in Protein 4lkc With Compound Ellagic

pose number	H- bond intraction	distance	Docking score	Intermolecular energy	Tersional energy
1	O---H-N (LYS-208)	1.9	-7.86	-9.05	1.19
	O---H-N (ILE-118)	2.0			
	O---H-N (SER-142)	2.4			
	O---H-O (THR-150)	2.9			
	O---H-N (THR-146)	2.2			
	O---H-N (ALA-152)	1.8			
	(ALA-152) O---H-O	2.0			
	(ALA-152) O---H-O	2.0			
2	O---H-N (TRP-47)	2.1	-5.3	-6.49	1.19
	O---H-O (SER-62)	2.3			
	O---H-N (SER-62)	2.5			
	O---H-N (PHE-99)	2.4			
	O---H-N (PHE--99)	2.8			
	(PHE-99) O---H-O	2.2			
3	**O---H-N (ILE-118)**	**2.1**	**-7.96**	**-9.15**	**1.19**
	(ALA-152) O---H-O	**2.1**			

	(ALA-152) O---H-O	**2.0**			
	O---H-N (SER-142)	**2.7**			
	O---H-N (SER-142)	**2.4**			
	O---H-N (ALA-152)	**1.9**			
	O---H-N (LYS-208)	**1.8**			
	O---H-O (THR-150)	**3.0**			
	O---H-N (THR-146)	**2.1**			
4	(ASP-56) O---H-O	2.0	-6.38	-7.57	1.19
	(ASP-56) O---H-O	2.0			
	O---H-O (TYR-95)	3.1			
	(PHY-92) O---H-O	2.1			
	(PHY-92) O---H-O	1.9			
5	O---H-O (THR-146)	1.9	-7.68	-8.87	1.19
	O---H-N (THR-146)	1.8			
	O---H-O (LYS-144)	3.3			
	O---H-N (SER-142)	2.3			
	(ALA-152) O---H-O	2.1			
	O---H-N (ALA-152)	2.1			
	O---H-O (ILE---118)	3.0			
	O---H-N (ILE-118)	1.8			
	O---H-N (LYS-208)	2.7			
6	O---H-N (THR-123)	2.1	-5.31	-6.51	1.19
	O---H-O (THR-123)	2.4			
	O---H-O (THR-123)	3.0			
	O---H-O (GLU-163)	3.3			
	O---H-N (LEU-11)	2.3			
	(PRO-217) O---H-O	2.1			
7	(ASP-61) O---H-O	2.4	-5.53	-6.27	1.19
	O---H-N (ASP-61)	2.0			
	O---H-O (ILE-97)	2.9			
	(ILE-97) O---H-O	2.0			
	O---H-N (TRP-47)	2.2			
	O---H-O (GLU-46)	3.5			
8	O---H-N (TRP-47)	2.3	-5.48	-6.67	1.19
	O---H-N (TRP-47)	2.7			
	(LEU-45) O---H-O	2.2			
	O---H-O (ILE-97)	3.1			
	(ILE-97) O---H-O	1.7			
	O---H-O (GLU-46)	3.3			
	O---H-N (ASP-61)	2.0			
9	(ASP-56) O---H-O	2.1	-6.12	-7.32	1.19
	(ASP-56) O---H-O	2.3			
	O---H-O (TRY-95)	3.1			
	(PHE-92) O---H-O	2.2			
	(PHE-92) O---H-O	1.9			
10	O---H-O (ILU-11)	2.7	-5.77	-6.96	1.19
	(LEU-11) O---H-O	2.2			
	(PRO-217) O---H-O	1.9			
	O---H-N (THR-123)	2.2			
	O---H-O (THR-123)	2.7			
	O---H-O (THR-123)	3.2			
	O---H-O (GLU-163)	3.3			

DISCUSSION

In this present experiment to find out some plant photochemical compound that is character to cure the CAD. . So that the in vivo studies had been done the *LDL-receptor* protein (PDB structural ID 4LKC) using Auto dock 4.2 against the compound are flavonoid, ellagic, resveratrol, queretin was downloaded from PubChem having PubChem ID- 9997719, 5281855, 445154, 5280343 respectively.

The similarity of docked structures was measured by computing the root mean square deviation (RMSD) between the coordinates of the atoms and creating clustering of the conformations based on the RMSD values. Interaction energies between ligand-receptor are calculated with a free energy-based expression. The lowest binding energy conformation in all cluster were considered as the most favourable docking pose. Binding energies that are reported represent the sum of the total intermolecular energy, total internal energy and torsional free energy minus the energy of the unbound system. The docking score were generated by auto dock module and shown in above table. From this study, the lowest docked energy structure was analyzed in detail in an effort to know the common pharmacophore for LDL-receptor inhibitors.

In the docking result, the figure 2 shows the low energy docked structures of flavonoid with human LDL-receptor protein (4lkc). The docked energies of the ten poses were in the range of -6.03 to -3.85 kcal/mol and five no. of hydrogen bond interactions that are ILE-97, ILE-97, TRP-47, TRP-47, and LUE-45. The figure 3 shows the low energy docked structures of Queratin with human LDL-receptor protein (4LKC). The docking energies of the ten poses were in the range of -6.85 to -4.56 kcal/mol. The lowest docked energy structure is -6.85 kcal/mol with nine hydrogen bond interactions i.e. TYR-187, GLY-213, GLY-213, SER-229. GLU-214, PRO-141, PRO-141, ASP-123, and ASN-211. The figure 4 shows the low energy docked structures of Ellagic with human LDL-receptor protein (4LKC). The docked energies of the ten poses were in the range of -7.96 to -5.3 kcal/mol. The lowest energy docked structure (-7.96) interacted with human LDL-receptor and formed nine hydrogen bonds interactions, that are ILE-118,ALA-152,ALA-152,SER-142,THR-146,ALA-152,LYS-208,THR-150,SER-142. In the docking result, the figure 5 shows the low energy docked structures of Resveratrol with human LDL-receptor protein (4lkc). The docked energies of the ten poses were in the range of -6.77 to -4.94 kcal/mol. Lowest docked energy of Resveratrol is -6.77 kcal/mol. The lowest energy docked structure interacted with human LDL-receptor protein with six strong hydrogen bond interactions that are SER-209, SER-209, THR-146, THR-150, THR-146, ALA-152.

In docking results, Ellagic compound showing best docking energy (-7.96) Intermolecular Energy (9.15), & active site hydrogen bond interaction compare to other three which having docking energy (-6.03,-6.85 and -6.77) Intermolecular Energy (-8.17,-8.64 and-8.26), & active site hydrogen bond interaction. The best pose docking result images were taken using PYMOL. So it is concluded that Ellagic compound shows a greater inhibition of the enzyme activity compare to Flavonoid, queratin and resveratrol compound & suggests that further in vitro and in vivo testing can be done for the above compounds against coronary artery disease(CAD) protein.

CONCLUSION

The natural product Flavonoid, Ellagic, Queratin, resveratrol compound represents a potential lead for new type coronary artery disease drugs. An Antibody Against the C-terminal Domain of PCSK9 lowers LDL Cholesterol Levels protein (PDB ID-4LKC) was downloaded from protein data bank & the phytochemicals compound was downloaded from pubchem database for docking studies. In docking results, Ellagic compound showing best docking energy (-7.96) Intermolecular Energy (9.15), & active site hydrogen bond interaction compare to other three which having docking energy (-6.03,-6.85 and -6.77) Intermolecular Energy (-8.17,-8.64 and-8.26), & active site hydrogen bond interaction. The best pose docking result images were taken using PYMOL. So it is concluded that Ellagic compound shows a greater inhibition of the enzyme activity compare to Flavonoid,queratin and resveratrol compound & suggests that further in vitro and in vivo testing can be done for the above compounds against coronary artery disease(CAD) protein .

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