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Analysis of Drug-Like Properties and in Silico Screening for the Potential of Flavonoid Compounds in Bay Leaves (*Syzygiumpolyanthum* (Wight) Walp) as Antidyslipidemia

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A B S T R A C T

Dyslipidemia is a metabolic syndrome in lipid metabolism in the body which is characterized by increase of lipid profile levels. The HMG-CoA reductase enzyme plays a role in the process of endogenous cholesterol synthesis in the mevalonate pathway by converting HMG-CoA molecules into mevalonate. Activation of PPARα can increase lipolysis through induction of lipoprotein lipase (LPL) which can catalyze the hydrolysis reaction of triglyceride-rich lipoprotein molecules, causing a decrease in triglyceride levels. Inhibition of the HMG-Coa reductase enzyme and activation of PPARα are targets in the development of antidyslipidemia drugs. Bay leaves (Syzygiumpolyanthum (Wight) Walp) are known to contain flavonoid compounds such as quercitrin, quercetin, retusin, and juncusol. Analysis of drug-like properties, pharmacokinetic profile, and screening of the potential of flavonoids in bay leaves as antidyslipidemia were carried out in Silico using the molecular docking method. Analysis of drug-like properties shows that the compounds quercetin, retusin, and juncusol fulfill drug-like properties according to Lipinski's basic rules. Analysis of the pharmacokinetic profile and molecular docking of the test compounds against the target protein showed that the four test compounds had affinity and formed bonds at the active site of the target protein. The bond energy values for the compounds quercitrin, quercetin, retusin, and juncusol in the HMG-Coa reductase enzyme are -4.99; -4.81; -4.93, and -5.26 kcal/mol. The binding energy values for the compounds quercitrin, quercetin, retusin, and juncusol in PPARα are -5.96; -5.65; -6.05, and -5.86 kcal/mol. The four test compounds were able to inhibit the action of the HMG-Coa reductase enzyme and activate PPARα in silico.

Keywords: antidyslipidemia, quercitrin, quercetin, retusin, juncusol, In Silico, molecular docking

1. Introduction

Dyslipidemia is a metabolic syndrome in lipid metabolism in the body which is characterized by increased levels of the lipid profile (total cholesterol, low density lipoprotein (LDL), and triglycerides) and accompanied by a decrease in high density lipoprotein (HDL) levels (Susanti*et al.*, 2016). Dyslipidemia is related to the process of atherosclerosis formation. Dyslipidemia patients are at risk of suffering from diseases such as coronary heart disease, ischemic cerebrovascular disease, peripheral vascular disease, and pancreatitis (Nirosha*et al.*, 2014). There are several factors that cause dyslipidemia, one of which is food or diet. A diet containing foods high in saturated fat, trans fat and sugar increases the risk of dyslipidemia (Ezeh and Ezeudemba, 2021).

Treatment of dyslipidemia is currently carried out with drugs that act on proteins that play a role in the lipid metabolism process. The enzymes HMG-Coa reductase and PPARα are target proteins in the development of dyslipidemia drugs. The HMG-CoA reductase enzyme plays a role in the process of endogenous cholesterol synthesis in the mevalonate pathway by converting HMG-CoA molecules into mevalonate. Mevalonate is phosphorylated and decarboxylated to form isopentenyl pyrophosphate (IPP). IPP undergoes polymerization and forms farnesyl pyrophosphate (FPP). FPP molecules undergo condensation to form squalene which will be processed into cholesterol (Shi *et* al., 2022). Statin drugs are drugs that work on the HMG-CoA reductase enzyme. Statin binds to the active site of the enzyme causes conformational changes in the enzyme structure and reduces enzyme activity and intracellular cholesterol synthesis. Low intracellular cholesterol concentrations in hepatocytes activate proteases that cleave membrane-bound sterol regulatory element-binding proteins(SREBPs), and then migrate to the nucleus and bind to sterol response elements. This binding results increased transcription of the LDL receptor, which translocates to the liver cell membrane. LDL and VLDL particles in plasma bind to LDL receptors and undergo endocytosis in hepatocytes, then are excreted or recycled. This process increases the catabolism of LDL and VLDL cholesterol and results in a decrease in plasma cholesterol concentration (Stancu and Sima, 2001).

Peroxisome proliferator-activated receptor α(PPARα)is a ligand-activated transcription factor that belongs to the NR1C nuclear receptor subfamily. PPAR α plays a role in lipid metabolism processes as well as cell proliferation and differentiation (Mirza *et al.*, 2019). Activation of PPARα can increase lipolysis through induction of lipoprotein lipase (LPL). LPL catalyzes the hydrolysis reaction of triglyceride-rich lipoprotein molecules into

free fatty acids and monoacylglycerol. This process causes a decrease in triglyceride levels (Pawlak *et al.,* 2015). Fibrate class drugs such as fenofibrate are examples of drugs that work as PPARα agonists.

Bay leaves (*Syzygiumpolyanthum*(Wight) Walp) are empirically used as a medicinal plant in Indonesia. Bay leaves are known to contain flavonoid compounds such as quercitrin, quercetin, retusin, and juncusol (Dewijanti*et al.,* 2020). The interaction of ketone groups in flavonoid compounds and hydroxyl groups in cholesterol forms hemicetal compounds. (Sakaganta and Sukohar, 2021). Flavonoid compounds are known to have the activity of inhibiting the action of the HMG CoA reductase enzyme so that it can reduce cholesterol formation in the liver (Hartanti*et al.,* 2019).

Research for new drugs invention for dyslipidemia still continue. The molecular docking method is one method that can be used in the compound screening process. Molecular dockingcan predict the conformation of a compound in a target protein. This method is able to identify compound conformations, predict binding affinity values, and predict molecular geometry and electronic properties. Evaluation of drug compounds is generally carried out through analysis of druglikenessand pharmacokinetic profile (ADME) of a compound (Nusantoro and Fadlan, 2020).

In this study, analysis of drug-like properties, prediction of ADME properties of drugs, and molecular dockingof flavonoid compounds contained in bay leaves (quercitrin, quercetin, retusin, and juncusol) were carried out on the enzymes HMG-Coa reductase and PPARα.

2. Research Materials and Methods

2.1 Material

Three-dimensional structures of the enzymes HMG-Coa reductase (pdb id: 1HW9) and PPAR α (pdb id: 7C6Q) downloaded from the website https://www.rcsb.org/pdb/home/home.do and three-dimensional structures of the compounds quercitrin, quercetin, retusin, and juncusol.

2.2 Tool

2.2.1 Hardware

The hardware used is an HP Pavilion 14 with AMD Ryzen 5 5000 series processor specifications and Microsoft Windows 11 64 bit operating system.

2.2.2 Software

a. SWISS ADME for predicting drug-like properties.
b. pkCSM to predict the pharmacokinetic (ADME) profile of compounds
c. Chimera App 1.17.3
d. ArgusLab App
e. Autodock 4.2 application

2.3 Work procedures

2.3.1 Analysis of Drug-Like Properties and Pharmacokinetic Profile

Analysis of drug-like properties was carried out with the SwissADME program which can be accessed on the website (http://www.swissadme.ch/). Analysis of drug-like properties was carried out based on Lipinski's basic rules (molecular weight, partition coefficient value (log P), and number of donors and number of hydrogen bond acceptors).

Prediction of the pharmacokinetic profile of the test compound was carried out using the pkCSM program which can be accessed on the website (http://biosig.unimelb.edu.au/pkcsm/). Analysis of drug-like properties was carried out by entering SMILES (Simplified Molecular Input Line Entry Specification) data from the compounds quercitrin, quercetin, retusin and juncusol. Analysis of the pharmacokinetic profile of compounds is carried out by looking at the absorption, distribution, metabolism, excretion and toxicity profiles of the test compounds.

2.3.2 Preparation of Target Protein Structures

Preparation of the target protein structure was carried out by separating the protein (HMG-Coa Reductase and PPARα) from the native ligand. Target protein preparation was carried out using the Chimera 1.17.3 application to provide space so that the size and coordinates of the pocket were known as a docking place for the test compound on the target protein.

2.3.3 Molecular Docking Methods

Validation of the molecular docking method is carried outby redocking the native ligandthat has been separated at the structure preparation stage to the target protein. Method validation was carried out using the Autodock 4.2 application. The method is said to be valid if the RMSD value obtained is ≤ 2Å (Allen and Rizzo, 2014).

2.3.4 Optimization of 3-Dimensional Structure of Test Compounds

The three-dimensional structures of the compounds quercitrin, quercetin, retusin, and juncusol were downloaded from the website https://pubchem.ncbi.nlm.nih.gov/. The three-dimensional structure of the test compound was then optimized using the ArgusLab application. Structural geometry optimization was carried out using the AM1 semi-empirical computing method and energy calculations were carried out on the structure before and after the optimization process.

2.3.5 Docking of Test Compounds on Target Proteins

The three-dimensional structure of flavonoid compounds was dockedwith HMG-Coa reductase and PPARα proteins which had been prepared using the Autodock 4.2 application. Docking oftest compounds is carried out using the coordinates and grid box sizesresulting from method validation. The dockingresults of the test compound will show the conformation and binding energy of the test compound to the target protein.

2.3.6 Data analysis

Conformational data and binding energy values resulting from the results of molecular dockingof the test compound with the target protein are then analyzed. The strength of the bonds formed is assessed by the bond energy. The lower the bond value of the compound to the target protein, the stronger the bond of the test compound to the target protein.

3. Results and Discussion

3.1 Analysis of Drug-Like Properties and Pharmacokinetic Profile

Analysis of the drug-like properties of flavonoid compounds in bay leaves was carried out based on Lipinski's basic rules. A compound has drug-like properties if it meets the requirements for a molecular weight of ≤ 500 Daltons (Da), a log P partition coefficient value of ≤ 5, a number of hydrogen bond donors ≤ 5, and a number of hydrogen bond acceptors ≤ 10 (Lipinski, 2000). The data in table 1 shows that all the flavonoid compounds in bay leaves tested met the requirements for molecular weight parameters and log P partition coefficient values. The compounds quercetin, retusin and juncusol met all the requirements of Lipinski's basic rules. The quercitrin compound does not meet the requirements for the parameters of the number of hydrogen bond acceptors and the number of hydrogen bond donors. From these results it can be concluded that the compounds quercetin, retusin, and juncusol have similar properties to drugs and therefore have the potential to be developed as drugs.

Table 1. Results of analysis of drug-like properties of flavonoid compounds in bay leaves based on Lipinski's rules

Compound	Molecular Mass (Da)	Log P	Number of Hydrogen Bond Acceptors	Number of Hydrogen Bond Donors
Quercitrin	448.36	0.4887	11	7
Quercetin	302,238	1,988	7	5
Retusin	358,346	3,2	7	1
Juncusol	266.34	4.12324	2	2

Prediction of the pharmacokinetic properties of flavonoid compounds contained in bay leaves was then carried out using the pkCSM application. Pharmacokinetic zero prediction includes the properties of absorption, distribution, metabolism, excretion, and toxicity of compounds. The predicted results of the pharmacokinetic properties of flavonoid compounds in bay leaves are shown in table 2.

The compound absorption profile is seen from the percentage of absorption in the gastrointestinal tract and interaction with P-glycoprotein. Compounds have poor absorption in the gastrointestinal tract if they have an absorption percentage of less than 30%, moderate if they have an absorption percentage between 30% to 80%, and high if they have an absorption percentage of more than 80% (Perez *et al.*, 2004). The data in table 2 shows that the compounds quercitrin and quercetin have moderate levels of gastrointestinal absorption, while the compounds retusin and juncusol have high levels of gastrointestinal absorption. P-glycoprotein is a drug transporter that determines the absorption and release of various drugs. The interaction of a compound with P-glycoprotein (Pgp) can reduce the levels of the compound in cells, thereby reducing the effect of the compound (Ahmed *et al.*, 2022). The four test compounds are not substrates of Pgp, so the absorption of the compounds is not affected by Pgp activity.

Table 2. Results of Prediction of Pharmacokinetic Profile of Flavonoid Compounds in Bay Leaves

Compound	Absorption		Distribution		Metabolism		Excretion	Toxicity
	Gastrointestinal absorption	**Pgp Substrate**	**Distribution volume (log L/kg)**	**Free Drug Fraction**	**CYP substrates**	**CYP inhibitors**	**Clearance (mL/min/kg)**	**Hepatotoxic**
Quercitrin	50.142%	No	0.024	0.162	-	-	0.538	No
Quercetin	77.204%	No	1,559	0.206	-	CYP1A2	0.407	No
Retusin	95.257%	No	-0.211	0.138	CYP3A4	CYP1A2 CYP2C19 CYP3A4	0.738	No
Juncusol	92.38%	No	0.45	0	CYP3A4	CYP1A2 CYP2C19 CYP2C9	0.061	Potential

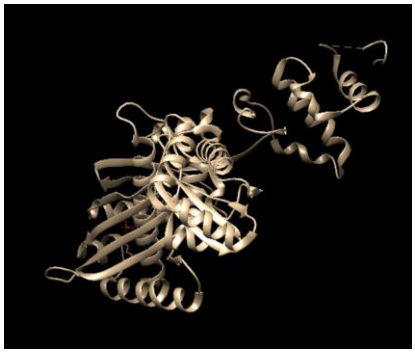
The distribution profile of flavonoid compounds in bay leaves was assessed from the distribution volume and plasma protein binding parameters of the compounds. Volume of distribution (Vd) is a pharmacokinetic parameter that indicates the tendency of a drug to remain in the plasma or be distributed to tissue compartments. A high volume of distribution value indicates that the drug has a tendency to leave the plasma and enter the extravascular compartment of the body, so that a higher dose of the drug is required to reach a certain plasma concentration (Shargel and Yu, 2016). The volume of distribution is considered low if it is below 0.71 L/kg (log VDss<-0.15) and high if it is above 2.81 L/kg (log VDss> 0.45) (Nursanti, 2023). From the table it is known that the retuscin compound has a low volume of distribution so it requires a low dose to reach a certain plasma concentration. Plasma protein binding is the degree of drug binding to proteins in the blood. The greater the binding of the drug to plasma proteins, the better the distribution of the drug compound (Nusantoro and Fadlan, 2020). The compounds quercitrin, quercetin, retusin, and juncusol have plasma protein binding percentages of 83.8%, 79.4%, 86.2%, and 100%, respectively.

Phase I drug metabolism is influenced by the activity of cytochrome P450 enzymes. Several cytochrome P450 substrates can induce the expression and inhibit the action of cytochrome P450. Induction accelerates drug metabolism and reduces its pharmacological effects. In prodrugs, enzyme induction can increase pharmacological effects to the point of causing toxic effects (Katzung*et al.,* 2015). Inhibition of cytochrome P450 enzymes causes a decrease in enzyme activity in metabolizing drugs. Cytochrome P450 inhibitors can increase drug levels in the blood causing toxicity (Almazroo*et al.*, 2017). The compounds quercetin, retusin, and juncusol are substrate compounds for the cytochrome P450 enzyme and can inhibit the enzyme's action. So these compounds can affect phase I metabolism which takes place in the liver.

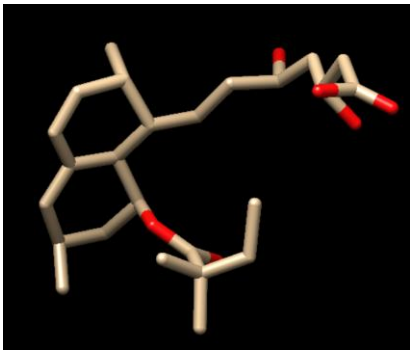
The excretion of flavonoid compounds contained in bay leaves was assessed by the clearance parameters of these compounds from the body. The clearance values for the compounds quercitrin, quercetin, retusin, and juncusol were 0.538; 0.407; 0.738; and 0.061 mL/minute/kg. The toxicity of a compound is assessed by its potential to cause liver damage (hepatotoxic). The juncusol compound is known to have the potential to be hepatotoxic.

3.2 Preparation of Target Protein Structures

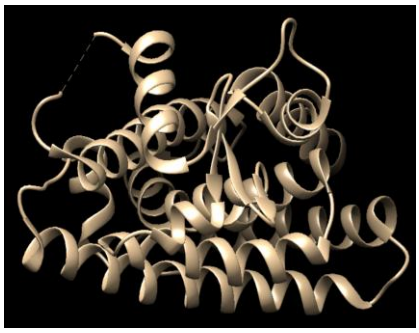
Preparation of target proteins (HMG-Coa Reductase and PPARα) is carried out by separating *the native ligands* contained in the protein structure so that space is available that can be used during the docking process of the test compounds. The HMG-Coa reductase structure used is the structure with pdb id 1HW9. The structure of HMG-Coa reductase has four chains with *the native ligand* simvastatin found in all chains. The chain used in this research is chain A. The PPARα structure used is the structure with pdb id 7C6Q. This structure has one chain with *the native ligand* sanguinarine. Sanguinarine is an alkaloid compound isolated from the *Sanguinaria canadensis*. This compound is a PPARα agonist compound which is known to have antihypertriglyceridemic effects (Tian *et al.,* 2021). The result of the target protein structure preparation process is the protein structure and *native ligand* which are saved in the form of a pdb file. The structures of the target protein and *native ligand* are shown in Figure 1.



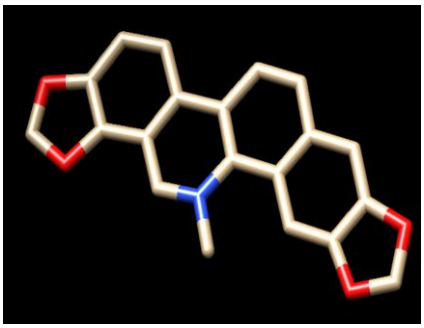
(a) HMG-Coa Reductase



(b) Simvastatin



(c) PPARα



(d) Sanguinarine

Figure 1. Structure of the Target Protein and *Native Ligand*

3.3 Molecular Docking Methods

Table 3. Molecular Docking Method Validation Results

Target Proteins	***Native ligands***	**Bond Energy (kcal/mol**	**RMSD (Å)**	**Amino Acid Residues**	**Atomic Clusters**
HMG-Coa Reductase	Simvastatin (3)	-4.57	1.5	LYS735 : HZ1	O1A, O1B
PPARα	Sanguinarine (9)	-7.54	0,0	TYR334 : HN	O4

Validation of the method was carried out by redocking the target proteins (HMG-Coa reductase and PPARα) with native ligands . The validation parameter for the molecular docking method is the RMSD (Root Mean Square Deviation) value. The RMSD value is a comparison of atomic positions between the experimental structure and the redocked structure of the target protein (Lestari, 2015). The validation results of the molecular docking method can be seen in table 3. The method is said to be valid if the RMSD value obtained is ≤ 2Å (Allen and Rizzo, 2014). The molecular docking method used is valid because it has an RMSD value ≤ 2Å for both target proteins.

3.4 Optimization of Three-Dimensional Structure of Test Compounds

The three-dimensional structures of quercitrin, quercetin, retusin and juncusol compounds were optimized using the ArgusLab application. Three-dimensional structure optimization was carried out to obtain a more stable structure with a lower total structural energy (Nusantoro and Fadlan, 2020). The results of the structural optimization of the compounds quercitin, quercetin, retusin, and juncusol are shown in table 4. Based on the data in table 4, the structure optimization went well with the final total energy results being lower than before carrying out the structure optimization.

Table 4. Test Compound Geometry Optimization Results

Compound	**Initial energy (kcal/mol)**	**Final energy (kcal/mol)**
Quercitrin	-205.1	-238.4

Quercetin	-141.1	-158.0
Retusin	-152.2	-180.8
Juncusol	-97.1	-117.3

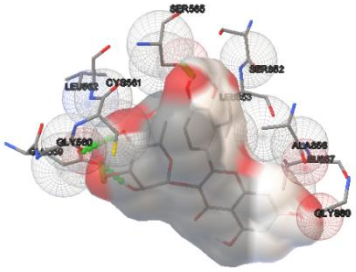
3.5 Docking of Test Compounds on Target Proteins

Docking of flavonoid compounds (quercitrin, quercetin, retusin, and juncusol) on the active site of the target protein (HMG-Coa reductase and PPARα) was carried out using the Autodock 4.2 application with the size and coordinates of the native ligand interaction site . The results obtained from the docking process of the test compound with the target protein are data on the bond energy and hydrogen bonds formed. Binding energy indicates the affinity of the test compound for the target protein. The existence of an affinity between the test compound and the target protein is indicated by a negative bond energy. The smaller the bond energy, the more stable the bond formed (Laksmiani et al., 2016). The binding energy and list of amino acid residues that bind compounds (quercitrin, quercetin, retusin, and juncusol) to the target protein (HMG-Coa reductase and PPARα) are shown in table 5. Visualization of the interactions that occur between the test compound and the target protein is shown in the figure. 2 and figure 3.

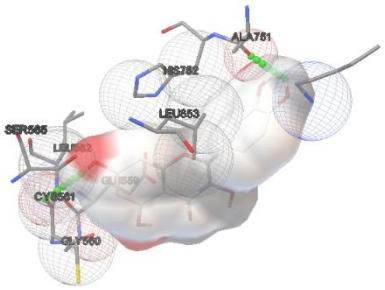
Table 5. Results of Docking of Flavonoid Compounds on Target Proteins

Target Proteins	Compound	Bond Energy (kcal/mol	Amino Acid Residues	Atomic Clusters
HMG-Coa Reductase	Quercitrin (4)	-4.99	SER565 : OG	H20
			GLU559 : OE2	H9
			LEU562 : N	O4
			GLU559 : OE2	H11
	Quercetin (6)	-4.81	ALA751 : O	H10
			LYS735 : NZ	O7
	Retusin (9)	-4.93	GLU559: OE2	H6
	Juncusol (4)	-5,26	GLU559: OE2	H15
PPARα	Quersitrin (1)	-5.96	THR279: OG1	H11
	Quercetin (3)	-5.65	LEU247: O	H10
			LEU247: O	H6
			THR279: OG1	H8
	Retusin (1)	-6,05	TYR334: HN	O2
	Juncusol (3)	-5.86	LEU247: O	H16

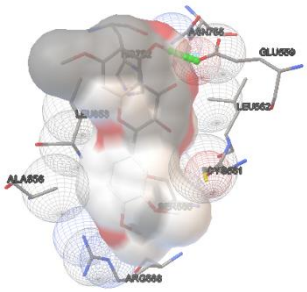
Based on the bond energy values obtained, it shows that the compounds quercitrin, quercetin, retusin, and juncusol have affinity and form hydrogen bonds with the HMG-Coa reductase and PPARα proteins. The four test compounds have a greater affinity for the HMG-Coa reductase protein compared to simvastatin as indicated by a smaller binding energy value. This shows that the four test compounds have the potential to be developed as antidyslipidemia agents. The bond that occurs between the test compound and the HMG-Coa reductase protein is able to inhibit the formation of endogenous cholesterol through the mevalonate pathway in the liver. The binding that occurs between the test compound and the PPARα protein can activate PPARα resulting in the induction of lipoprotein lipase (LPL). LPL catalyzes the hydrolysis reaction of triglyceride-rich lipoprotein molecules, causing a decrease in triglyceride levels (Pawlak *et al.*, 2015).



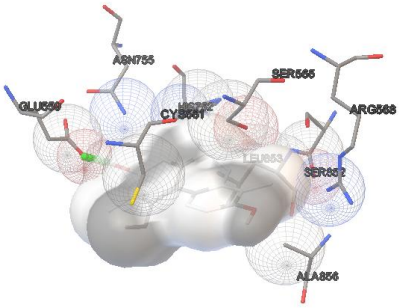
(a) HMG-Coa Reductase-Quercitrin



(b) HMG-Coa Reductase-Quercetin

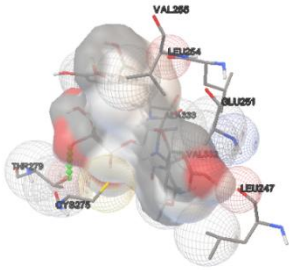


(c) HMG-Coa Reductase-Retusin

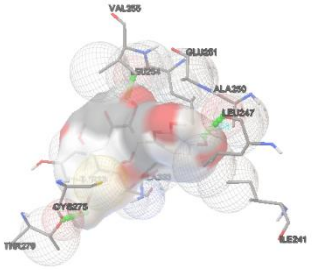


(d) HMG-Coa Reductase-Juncusol

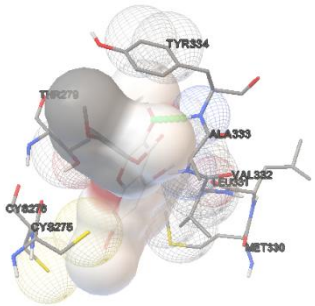
Figure 2. Visualization of HMG-Coa Reductase bonds with flavonoid compounds in bay leaves



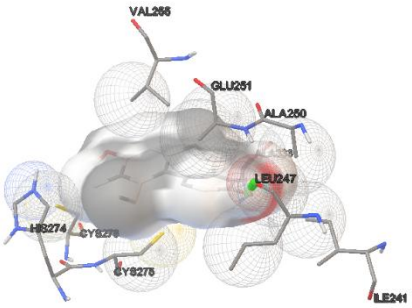
(a) PPAR α-Quercitrin



(b) PPAR α-Quercetin



(c) PPAR α-Retusin



(d) PPAR α-Juncusol

Figure 3. Visualization of PPAR α binding with flavonoid compounds in bay leaves

4. Conclusion

The compounds quercetin, retusin, and juncusol fulfill drug-like properties based on Lipinski's basic rules. Analysis of the pharmacokinetic profile and molecular docking of the test compounds against the target protein showed that the four test compounds had affinity and formed bonds on the active site of the target protein, so they were able to inhibit the action of the HMG-Coa reductase enzyme and activate PPARα in silico.

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