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The Potential of Flavonoid Derivative Compounds as Inhibitors of the HMG-CoA Reductase Enzyme for Candidate of Hypercholesterolemia Drugs

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Abstract: Cardiovascular disease (CVD) is a disease that causes death in the world. Behavioral risk factors are crucial in dealing with CVD disease. High levels of cholesterol in the blood are associated with hypercholesterolemia. It can increase the risk of CVD disease. The HMG-CoA reductase enzyme is an enzyme that plays a role in cholesterol synthesis. It will convert the HMG-CoA compound into the mevalonate. Inhibition of this enzyme can reduce cholesterol synthesis because it inhibits the formation of mevalonate, which is the initial stage of cholesterol synthesis. Herbal compounds are compounds produced by plants. It has good benefits for the body. Flavonoid compounds can be beneficial for health. Molecular docking is a method used to determine the binding affinity and interaction values of the enzyme protein interaction with the ligand to be bound. The results of Apigenin binding affinity values is -7.7 kcal/mol, Luteolin is -8 kcal/mol, Quercetin is -8.2 kcal/mol, Kaempferol is -7.4 kcal/mol, Phloretin is -6.8 kcal/mol, Chalconaringenin is -6.9 kcal/mol, Cyanidin is -7.9 kcal/mol, Delphinidin is -7.8 kcal/mol, Hesperetin is -7.7 kcal/mol, Narigenin is -7.8 kcal/mol, Daidzein is -6.8 kcal/mol, Genistein is -7 kcal/mol, Rutin is -9.2 kcal/mol, Taxifolin is -8 kcal /mol, Diosmetin is -7.6 kcal/mol, and its native ligand Rosuvastatin is -8.5 kcal/mol. Flavonoid derivative compounds can bind to the HMG-CoA reductase enzyme. They can be candidates for antihyperlipidemia drugs.

Keywords: Cardiovascular diseases; Flavonoid; HMG-CoA reductase; Hypercholesterolemia; Mevalonate

Introduction

Cardiovascular disease (CVD is the most common cause of death in the world. It caused the deaths of 13 million people worldwide in 2010, which is a quarter of the total deaths in the world (Namara et al., 2019). CVD involves heart coronary, cerebrovascular disease, rheumatic heart disease, and other conditions (Kumar et al., 2020; McAloon et al., 2016). Heart attacks and strokes are the most common diseases. It caused four out of five deaths. Cardiovascular diseases such as Ischemic heart disease and cerebrovascular diseases such as stroke cause 17.7 million deaths (McAloon et al., 2016).

Behavioral risk factors are essential in dealing with CVD. Consumptive behavior by eating high-cholesterol foods can increase lipid levels in the blood. It worsened by consuming cigarettes and alcohol (Akinosun et al., 2021; McAloon et al., 2016). Poor effects of behavior can cause hypertension, increased blood glucose levels, increased blood cholesterol levels, and overweight or obesity (Alhabib et al., 2020; Cherfan et al., 2020).

The body needs cholesterol in sufficient quantities. If cholesterol reaches abnormal levels, it can disrupt body health (Schade et al., 2020). High levels of cholesterol in the blood are associated with hypercholesterolemia. It can increase the risk of CVD

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(Trinder et al., 2020). Lipids and lipoproteins in the body are the cause of CVD. High levels of lipids in the blood can increase the uptake of cholesterol by macrophages and will cause the formation of foam cells. It can trigger plaque formation in blood vessels. Eventually, it results in the narrowing of the blood vessels and inflammation (Linton et al., 2019; Soppert et al., 2020). It also can increase the risk of aortic aneurysm and stroke. The chief cause of the increase in atherosclerotic lesions is high levels of Low-density lipoprotein (LDL) in the blood (Khatana et al., 2020).

The HMG-CoA reductase enzyme is an enzyme that plays a role in cholesterol synthesis. It converts the HMG-CoA into a mevalonate (Zhang et al., 2021). Inhibition of this enzyme can reduce cholesterol synthesis because it inhibits mevalonate production, which is the initial stage of cholesterol synthesis (Zechner et al., 2022).

Statins are commercial cholesterol-lowering drugs. It plays a role in targeting the active site of the HMG-CoA reductase enzyme to prevent binding with the natural ligand, namely HMG-CoA, and will prevent the formation of mevalonate compounds (Hopkins & Young, 2019). This enzyme inhibition mechanism with statins can be the basis for developing hypercholesterolemia drugs, especially herbal medicine, which has many benefits and fewer side effects. Long-term statin consumption can contribute to myopathy or rhabdomyolysis, which can be detrimental (Safitri et al., 2021; Tournadre, 2020).

Herbal compounds are compounds produced by plants (Tran et al., 2020). One of the herbal compounds is flavonoid. It has many benefits for health (Muflihah et al., 2021). Flavonoid compounds themselves consist of several types, namely Apigenin, Luteolin, Quercetin, Kaempferol, Phloretin, Chalconaringenin, Cyanidin, Delphinidin, Hesperetin, Narigenin, daidzein, Genistein, Rutin, Taxifolin, diosmetin (Chanu et al., 2023).

Flavonoid derivative compounds in many natural ingredients need to be researched and developed into medicines that are useful for humans (Panche et al., 2016). Insilico research aims to test drug candidates based on the binding affinity values and interactions formed. It could be an initial step for drug candidate development that has potential as antihyperlipidemia drugs with an inhibitory mechanism for the HMG-CoA Reductase enzyme.

Method

The method used in this research is molecular docking. First, we bound the ligand to the target protein, and then we observed the amount of energy and the interactions formed between the ligand and the protein. Before carrying out molecular docking, compounds and proteins must be prepared first.

Protein/Macromolecule

The targeted protein in this research is HMG-CoA reductase. The structure of 1HWL (GDP: 1HWL) was obtained from the Protein Data Bank (PDB) database (www.rcsb.org) using the X-ray crystallography method to determine the structure of 1HWL and has a resolution of 2.10 Å (Istvan et al., 2001). Based on the data obtained, the 1HWL structure consists of two chains, namely chain A and chain B. Each chain contains an inhibitory ligand, namely 7-[4-(4-FLUORO-PHENYL)-6-ISOPROPYL-2 (METHANESULFONYL-METHYL-AMINO)-PYRIMIDIN-5-YL] -3,5-DIHYDROXY-HEPTANOIC ACID which has another name, Rosuvastatin. The 1HWL PDB structure was prepared by the Pymol application (https://pymol.org/2/), and then the docking was carried out.

Ligand Compound

The ligand compounds used in this research are Apigenin, Luteolin, Quercetin, Kaempferol, Phloretin, Chalconaringenin, Cyanidin, Delphinidin, Hesperetin, Narigenin, Daidzein, Genistein, Rutin, Taxifolin, and Diosmetin. We used Swiss ADME (http://www.swissadme.ch/) to analyze Lipinski's Rule of Five of ligand compounds. The human intestine absorption analysis is carried out by PREADMET predictions (https://preadmet.webservice.bmdrc.org/) to determine the ability of a compound to be absorbed. The collected ligands were prepared by Avogadro software (https://avogadro.cc/) (Snyder et al., 2021).

Molecular Docking

Molecular docking of 16 types of compounds to the 1HWL protein was carried out using PyRx v.0.8 software (https://pyrx.sourceforge.io/downloads) (Trott et al., 2010). The molecular binding target areas are Center X: 2.7145, Y: -11.196, Z: -11.195. The dimensions are X: 14.713, Y: 15.201, Z: 16.482. This location is the binding area of the native ligand rosuvastatin, a 1HWL inhibitor, that has passed phase 3 testing and has been widely used. The binding active site on 1HWL was viewed using the Computed Atlas of Surface Topography of Proteins (CASTP) (sts.bioe.uic.edu/castp/index.html?3kcz) (Tian et al., 2018). The results were visualized and analyzed using PyMol 2.5 (https://pymol.org/2/) and Discovery Studio R17 (https://discover.3ds.com/discovery-studio-visualizer-download). The visualization results then identify the amino acid residues that bind to the ligand compound.

Result and Discussion

Table 1 shows the results of Lipinski's rule of five analysis. It shows that the default ligand compound for the HMG-CoA reductase enzyme, Simvastatin, received the highest HIA value, 90.48%. This result is close to perfect for being absorbed by the body. Figure 3 shows the flavonoid candidates. Flavonoid derivative compounds, like Apigenin, Hesperetin, Narigenin, Daidzein, Genistein, and Diosmetin obtained more than 80% HIA values. Meanwhile, flavonoid derivative compounds like Rutin got the lowest HIA value, 2.86%. It shows that this compound is not potent for absorption by the body.

Lipinski's rule of five test aims to see the molecular weight of a compound with a molecular weight of less than 500 Da, an H-acceptor value of less than 10, and an H-donor of less than 5. The molecular weight of a compound can affect the density, size, and volume of a therapeutic agent that enters the cell to bind to the receptor (Chagas et al., 2018). The H-acceptor and H-donor values can be used for membrane transport analysis, drug interactions with proteins, distribution, and solubility in water (Magalhães et al., 2022).

Based on Table 1, Rutin has a molecular weight value of more than 500 Da, but its H-donor and H-acceptor values do not comply with Lipinski's rule of five. This assessment is in line with the results of the HIA analysis, where Rutin received a low value (2.86%). The delphinidin compound is a compound that does not comply with Lipinski's rule of five because the H-donor value is more than 5.

Table 1. Lipinski's Rule of Five Analysis Results

Compound	Molecular Formula	HIA (%)	Da (g/mol)	H-Donor	H-Acceptor	LogP	Binding Affinity (Kkal/mol)
Apigenin	$C_{15}H_{10}O_5$	88.12 %	270.24	3	5	2.11	-7.7
Luteolin	$C_{15}H_{10}O_6$	79.42 %	286.24	4	6	1.73	-8
Quercetin	$C_{15}H_{10}O_7$	63.48 %	302.24	5	7	1.23	-8.2
Kaempferol	$C_{15}H_{10}O_6$	79.44 %	286.24	4	6	1.58	-7.4
Phloretin	$C_{15}H_{14}O_5$	78.98 %	274.27	4	5	1.93	-6.8
Chalconaringenin	$C_{15}H_{12}O_5$	80.61%	272.25	4	5	1.90	-6.9
Cyanidin	$C_{15}H_{11}O_6^+$	72.50%	287.24	5	6	0.32	-7.9
Delphinidin	$C_{15}H_{11}ClO_7$	54.22%	338.70	6	7	1.22	-7.8
Hesperetin	$C_{16}H_{14}O_6$	87.19%	302.28	3	6	1.91	-7.7
Narigenin	$C_{15}H_{12}O_5$	87.31%	272.25	3	5	1.84	-7.8
daidzein	$C_{15}H_{10}O_4$	92.65%	254.24	2	4	2.24	-6.8
Genistein	$C_{15}H_{10}O_5$	88.12%	270.24	3	5	2.04	-7
Rutin	$C_{27}H_{30}O_{16}$	2.86%	610.52	10	16	0.46	-9.2
Taxifolin	$C_{15}H_{12}O_7$	60.16%	304.25	5	7	0.51	-8
Diosmetin	$C_{16}H_{12}O_6$	88.18%	300.26	3	6	2.19	-7.6
Rosuvastatin	$C_{22}H_{28}FN_3O_6S$	90.48%	481.54	3	9	2.26	-8.5

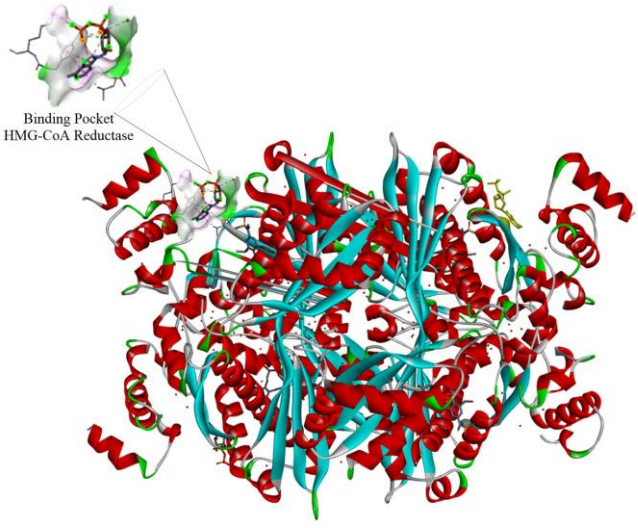


Figure 1. The visualization of HMG-CoA reductase (1HWL)

Rosuvastatin attached to the HMG-CoA reductase enzyme (Figure 1) can be an adequate example of a hyperlipidemia drug development model. Based on the research results, Rosuvastatin obtained a binding affinity value of -8.5 kcal/mol, and the Statin has active site residues on GLU559 (Figure 2). The interactions visualization shows hydrogen bonds that are important for comparing bonds in each candidate hyperlipidemia drug (Istvan et al., 2000). Rouvastatin in Figure 1 has an active site containing residue LYS691. It forms hydrogen bonds that contribute to the bond strength, symbolized by the binding affinity value of the molecule (Istvan et al., 2001).

In this research, the lowest binding affinity value for flavonoid derivative compounds was Rutin, which obtained -9.2 kcal/mol for binding affinity value. This result was lower than the binding affinity of the default ligand, Rosuvastatin, with a binding affinity of -8.5 kcal/mol. Based on Table 2, Rutin was able to bind with

the active site of the HMG-CoA reductase enzyme at residue GLU559, which forms hydrogen bonds. Hydrogen bonds are bonds formed involving hydrogen atoms by covalent bonds (van der Lubbe et al., 2019). It contributes to the binding affinity value in a receptor binding with a ligand (Chen et al., 2016). Hydrogen bonds formed in ASP690, ARG590, LEU562, SER684, and LYS692 residues contribute to low binding affinity values. Apart from the binding affinity value, we need to understand Lipinski's rule of five to see drug candidates. It will be difficult for Rutin to reach the HMG-CoA reductase enzyme due to the low HIA value and the huge molecular weight of Rutin (Basant et al., 2016).

The Quercetin compound is a subclass of flavonoid compounds (Singh et al., 2021). It has anticarcinogenic, anti-inflammatory, and antiviral benefits (Alizadeh et al., 2022). Quercetin can bind to the active site of the HMG-CoA reductase enzyme and obtains a binding affinity value of -8.2 kcal/mol. The visualization of the Quercetin interaction shows that it can bind to the GLU559 residue, the active site of the HMG-CoA reductase enzyme. It will bind to two aromatic rings to form a Pi-Pi anion bond, a non-covalent interaction bond formed by the Pi electrons of aromatic rings that react with each other (Martinez et al., 2012). The HIS752 residue will bind to the aromatic ring in the quercetin compound and form a Pi-Pi bond, while the GLY560, ALA751, LYS735, ASN686, and SER684 residues form hydrogen bonds. The ARG590 residue can bind aromatic rings and form pi-anion bonds.

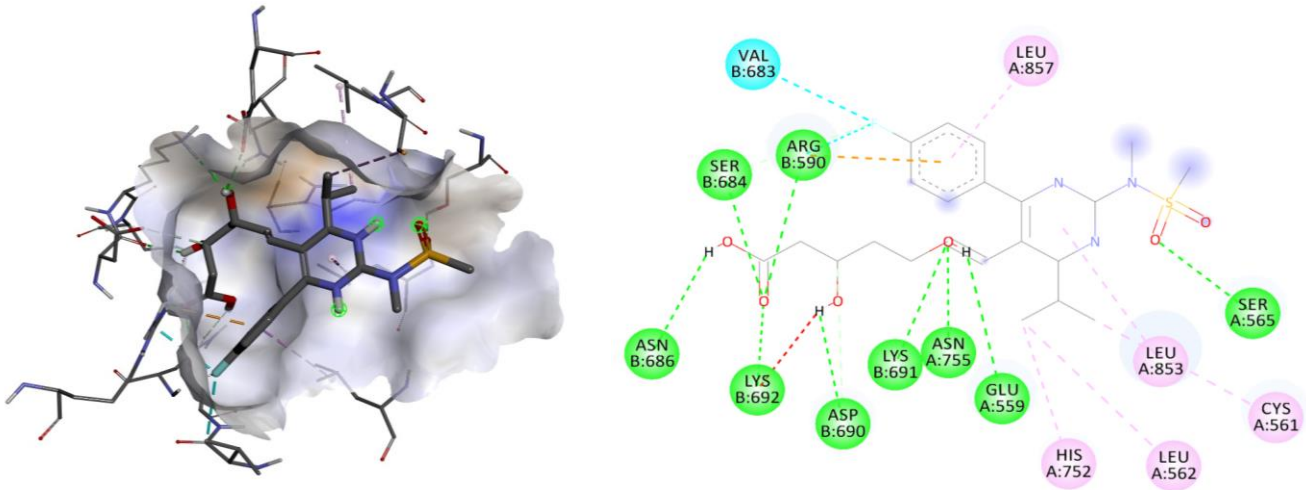


Figure 2. Rosuvastatin, a native ligand, can bind to the active site of the HMG-CoA reductase enzyme and form hydrogen bonds (marked in green) and pi-alkyl (marked in pink)

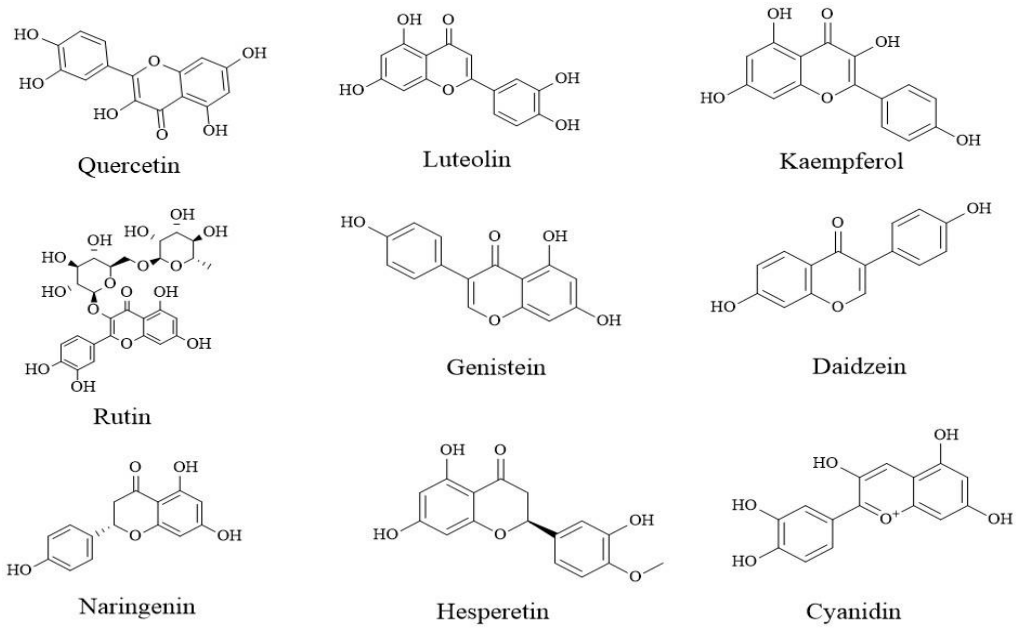
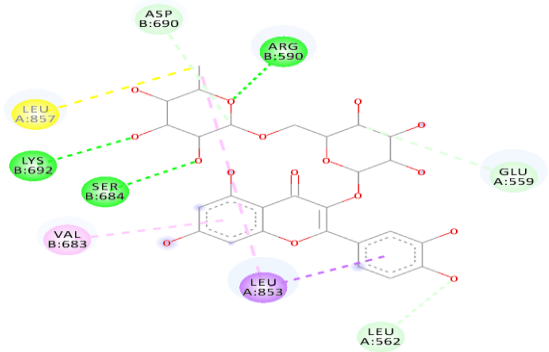
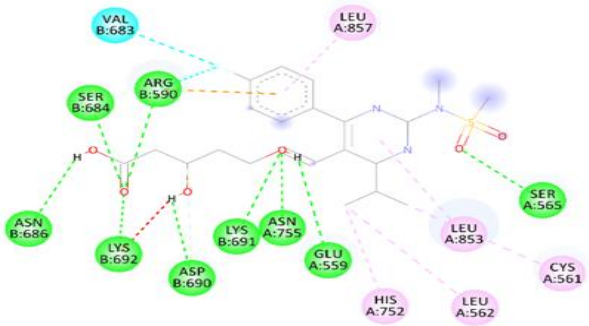
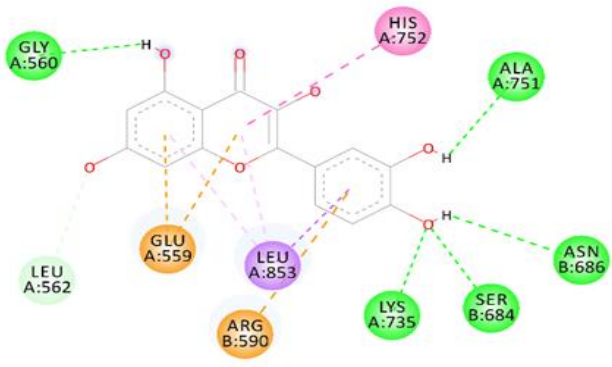


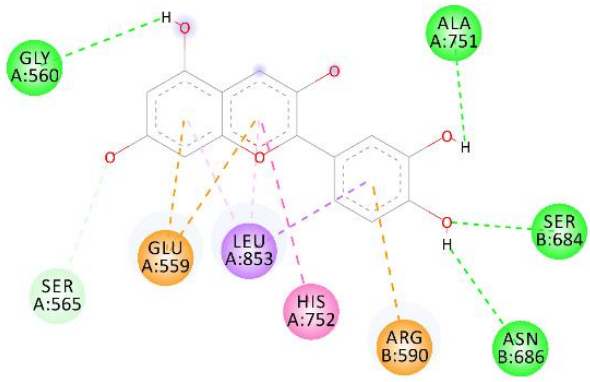
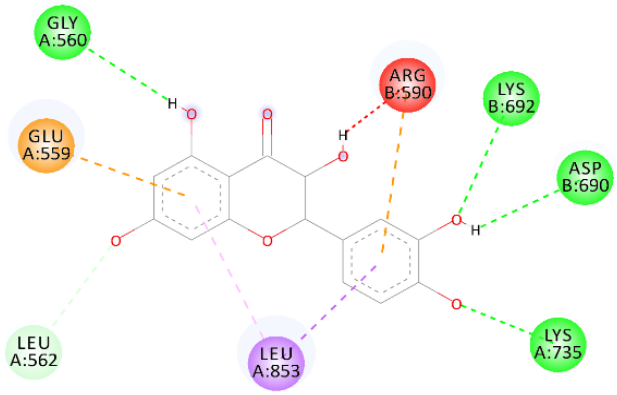
Figure 3. Molecular structure of Flavonoid derivatives

The Cyanidin compound binds to HMG-CoA reductase. It resulted in a binding affinity value of -7.9 kcal/mol. Based on interaction visualization, Cyanidin can bind to GLU559 residue, the active site of the Statin enzyme. The binding is between two aromatic rings of Cyanidin and forms a Pi-Pi bond. Apart from that, Cyanidin binds to SER684 and ASN686 residues and forms hydrogen bonds. LEU853 residue binds two aromatic rings far from Cyanidin to form a Pi-sigma bond. The HIS752 residue binds to the aromatic ring to form a stacked Pi-Pi bond.

The Taxifolin produces a binding affinity value of -8 kcal/mol. It can bind to the GLU559 residue, the active site of the HMG-CoA reductase enzyme, but this bond forms a Pi-cation bond. Another interaction is between the ARG590 residue with a hydrogen atom and the aromatic ring of the Taxifolin. LEU853 residue binds two aromatic rings far apart to form a Pi-sigma bond. GLY560, ASP690, and LYS735 residues bind oxygen atoms and form hydrogen bonds. The ASP690 residue binds hydrogen atoms in the taxifolin compound to form hydrogen bonds.

Table 2. Molecular Interactions with Flavonoid Ligands

Compound	Residue	Interactions	Visualization
Rutin	ASP 690	Hydrogen Bond	
	ARG590	Hydrogen Bond	
	GLU559	Hydrogen Bond	
	LEU562	Hydrogen Bond	
	LEU853	Pi-Sigma	
	VAL683	Pi-Alkyl	
	SER684	Hydrogen Bond	
	LYS692	Hydrogen Bond	
Rosuvastatin	VAL683	Halogen (Fluorine)	
	LEU857	Pi-Alkyl	
	SER565	Hydrogen Bond	
	CYS561	Pi-Alkyl	
	LEU853	Pi-Alkyl	
	LEU562	Pi-Alkyl	
	HIS752	Pi-Alkyl	
	GLU559	Hydrogen Bond	
	ASN755	Hydrogen Bond	
	LYS691	Hydrogen Bond	
	ASP690	Hydrogen Bond	
	LYS692	Hydrogen Bond	
	ASN686	Hydrogen Bond	
	SER684	Hydrogen Bond	
	ARG590	Hydrogen Bond	
Quercetin	GLY560	Hydrogen Bond	
	HIS752	Pi-Pi	
	ALA751	Hydrogen Bond	
	ASN686	Hydrogen Bond	
	SER684	Hydrogen Bond	
	LYS735	Hydrogen Bond	
	LEU853	Pi-Sigma	
	ARG 590	Pi-Anion	
	GLU559	Pi-Anion	
	LEU562	Hydrogen Bond	

Compound	Residue	Interactions	Visualization
Cyanidin	GLY560	Hydrogen Bond	
	ALA751	Hydrogen Bond	
	SER684	Hydrogen Bond	
	ASN686	Hydrogen Bond	
	ARG590	Pi-Anion	
	HIS752	Pi-Pi Stacked	
	LEU853	Pi-Sigma	
	GLU559	Pi-Cation	
		Pi-Anion	
	SER565	Hydrogen Bond	
	GLY560	Hydrogen Bond	
Taxifolin	ARG590	Unfavorable Donor	
	LYS692	Hydrogen Bond	
	ASP690	Hydrogen Bond	
	LYS735	Hydrogen Bond	
	LEU853	Pi-Sigma	
	LEU562	Hydrogen Bond	
	GLU559	Pi-Cation	

Conclusion

Flavonoid compounds can bind to the HMG-CoA reductase enzyme to become candidates for hypercholesterolemia drugs. Inhibition of the enzyme in the active site can suppress the formation of mevalonate compounds and prevent an increase in cholesterol levels in the blood. Rutin compounds cannot meet Lipinski's rule of five and have low reabsorption values. Nevertheless, it has binding affinity values and can bind to the HMG-CoA reductase enzyme. The compounds Quercetin, Cyanidin, and Taxifolin are capable of being candidates for antihyperlipidemia drugs because they can fulfill Lipinski's rule of five regulations and have almost the same interactions as Rosuvastatin, which is a commercial drug to treat hyperlipidemia conditions.

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Author Contributions
Conceptualization and methodology, I Putu Bayu Agus Saputra (Saputra, P.B.A), formal analysis, I Putu Dedy Arjita (Arjita, P.D) investigation, Saputra, P.B.A, writing— original draft preparation, Saputra, P.B.A writing—review and editing Arjita, P.D, and Saputra, P.B.A Visualization. Arjita, P.D, and Saputra, P.B.A authors have agreed to the published version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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