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IN SILICO TESTING ON THE ACTIVITY OF FLAVONOL IN *STERCULIA FOETIDA* LEAF AS NATURAL ANTI HYPERLIPIDEMIA COMPOUNDS

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Abstract. This study aimed to determine the bioactivity of flavonol in *Sterculia foetida* leaf as an antihyperlipidemic drug. The chemical structure of the flavonol contained in *Sterculia foetida* leaf was taken from the literature. The target protein used was *3-hydroxy-3-methylglutaryl-coenzyme A reductase*, while the control was simvastatin. Water molecules were removed using PyMol v2.5.2 Software. Docking between the target protein and flavonol was performed using PyRx-Python Prescription 0.8 Software. The results showed that flavonol compounds had greater potential as antihyperlipidemic compared to control compounds. The comparative affinity of *3-hydroxy-3-methylglutaryl-coenzyme A reductase* with flavonols is -8, 3 while the affinity for *3-hydroxy-3-methylglutaryl-coenzyme A reductase* with simvastatin is -7.9. Toxicity test of flavonol showed that the flavonol was not potentially carcinogenic and did not cause mutations. The absorption of flavonol in water was higher than in the control compound.
Keywords: anti hyperlipidemia, *sterculia foetida*, flavonol, *3-hydroxy-3-methylglutaryl-coenzyme A reductase*

1. Introduction

Hyperlipidemia is a condition characterized by excess levels of total cholesterol in the blood(1). This can trigger various chronic diseases such as atherosclerosis, coronary heart disease, diabetes mellitus, cancer, and stroke. (2)

The World Health Organization (WHO) in 2008 showed that there was an increase in the incidence of hyperlipidemia in adults in the world, 37% in men and 40% in women. Whereas in Indonesia, the incidence of hyperlipidemia is 32.8% in men and 37.2% in women.(3)

The risk of complications of hyperlipidemia can be reduced by inhibiting activity *3-hydroxy-3-methylglutaryl-coenzyme A reductase* enzyme using simvastatin. However, this drug can induce digestive tract disorders and myopathy. So, researchers intended to discover natural ingredients that can replace simvastatin function. One of the plants that have the potential to replace simvastatin function is *Sterculia foetida*.(4) (5)

Sterculia foetida leaf extract contains various compounds that are beneficial to the body, such as flavonoids, coumarins, organic acids, and steroids.(6). The most common types of flavonoids in *Sterculia foetida* leaf are flavonol and quercetin which can benefit as antioxidants and anti hyperlipidemia.(7)(8)

2. Materials and Methods

2.1. Ligand Preparation

The chemical structure of the flavonol compound was collected from the published literature. The chemical 3D structure and SMILES of flavonol ligands were taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with ID number: CID:11349 and Canonical Smile:C1=CC=C(C=C1)C2=C(C(=O)C3=CC=CC=C3O2)O. The chemical structures of the ligands and three-dimensional (3D) were sketched using Avogadro and saved in PDB format.

2.2. Target Selection

Target proteins for docking were prepared using published literature and validated using Uniport (https://www.uniprot.org). Proteins collected and validated by using PDB (Protein Data Bank https:///www.rcsb.org/pdb) then the protein was prepared as a clean protein by removing water molecules from the structure using PyMOL v2.5.2 Software. In this study, the target protein was *3-hydroxy-3 methylglutaryl-coenzyme A reductase*, and the code from PDB was 2Q1L which is an enzyme that plays a role in the process of cholesterol forming in the body. (3)

2.3. Molecular Docking

Molecular docking experiments were conducted by using PyRx 0.8 software. The docking process was carried out using the Vina Wizard feature integrated into the PyRx 0.8 software which reacted to natural flavonol compounds, target proteins *3-hydroxy-3-methylglutaryl-coenzyme A reductase* and the control compound which was simvastatin.

2.4. Visualization of Molecule and Small Molecule Interaction

The interaction between ligands (flavonols) of the target protein (*3-hydroxy-3-methylglutaryl-coenzyme A reductase*), and a control ligand (simvastatin) with a target protein (*3-hydroxy-3-methylglutaryl-coenzyme A reductase*) were visualized and analyzed using PyMol Software v 2.5.2.

2.5. Compound's Properties and ADMET Prediction

AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2/) was used to predict predictors and significant descriptors of the Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds.

3. Results and Discussion

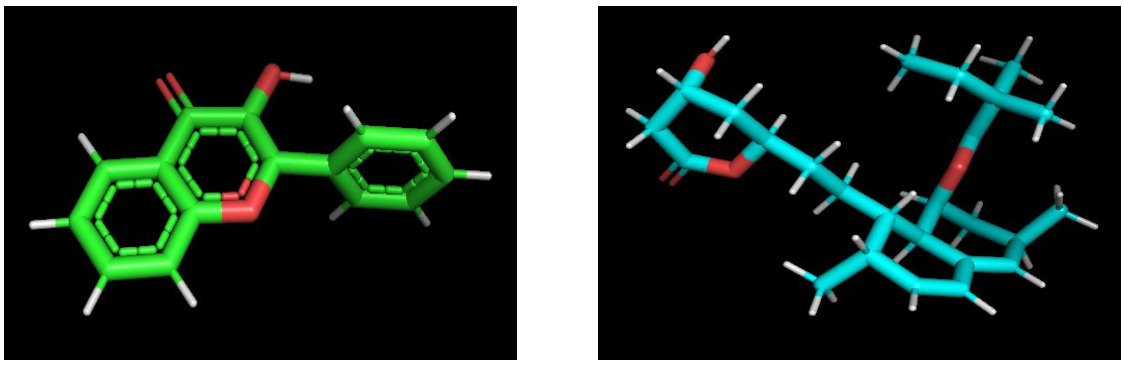
Flavonol and quercetin are compounds of the flavonoid group that are most commonly found in *Sterculia foetida* leaf extract. Flavonol compounds can be used as anti hyperlipidemia and antioxidants. As an antihyperlipidemic, flavonol can reduce total cholesterol levels and prevent lipid peroxidation through several processes. First, it inhibits the formation of mevalonate by inhibiting the activity of *3-hydroxy-3-methyl glutaryl-coenzyme A reductase* (HMG CoA reductase) as an enzyme for cholesterol

formation in the body. The second mechanism is to reduce the need of NADPH for fatty acids and cholesterol formation. The last mechanism is to increase the LDL receptor and chelate cholesterol acyltransferase (LCAT) so that LDL uptake also increases and free cholesterol can be converted into HDL. (4)(9)

The structure of herbal compounds and control compounds as well as target proteins were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) then visualized in 3D through the PyMol application (Fig. 1). The results of docking using the PyRx application exhibited that flavonol could interact with the target protein, which proved that flavonol could be used as antihyperlipidemic agents. The docking showed that the binding affinity of flavonol compounds was smaller than simvastatin which means the energy required by flavonols to bind the target protein was smaller than the simvastatin.

HMG-CoA reductase is responsible for the conversion of HMG-CoA to mevalonic acid (8). Inhibition of HMG-CoA reductase causes a decrease in cholesterol synthesis and an increase in the number of LDL receptors present in the cell membranes of the liver and extrahepatic tissues, resulting in a decrease in total and LDL cholesterol levels in plasma. (10)

Toxicity tests which had been carried out through ADMET predictions presented that flavonol compounds had no carcinogens or mutagens potential. The absorption rate by the body was higher than simvastatin as a control. However, it is not recommended to extract this compound because it is potentially toxic.



(a) (b)

Figure 1. (a) 3D structure of flavonol compounds, (b) 3D structure of simvastatin control compounds

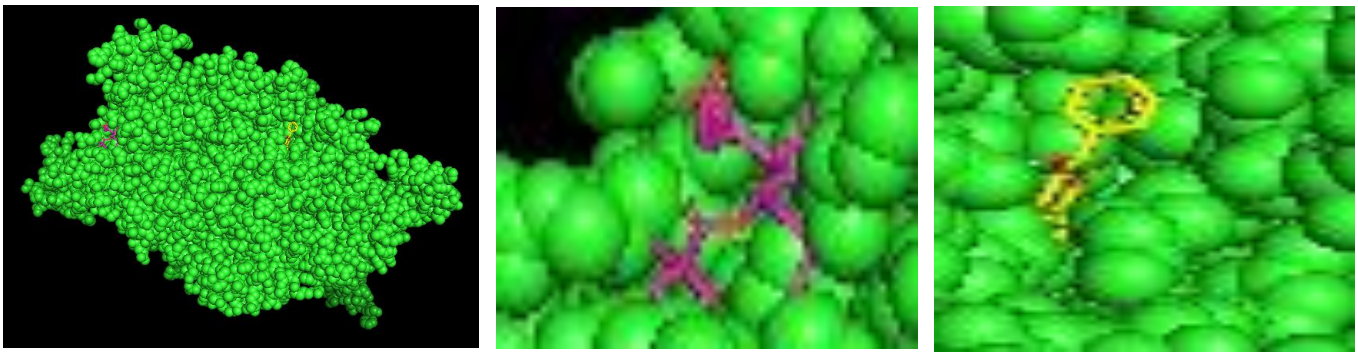


Fig.2. results of docking simvastatin (purple) and flavonol (yellow) with *protein-3 hydroxy-3-methylglutaryl-coenzyme A reductase*

Table.1. results of docking between flavonol compounds and simvastatin with target proteins

Origin of Compound	Ligand	Binding Affinity (kcal/mol)
Sterculia foetida	Flavonol	-8.3
Control	Simvastatin	-7.9

4. Conclusion

Based on the intermolecular interactions and their affinity levels, it can be concluded that the flavonol compounds in *Sterculia foetida* leaf can be used as antihyperlipidemic drugs.

References

1. Heryani R. EFFECT OF RED DRAGON FRUIT EXTRACT ON BLOOD LIPID PROFILE INTRODUCTION. 2016;1:8–17.
2. Permatasari AAAP, Widhiantara IG. Testosterone Therapy Increases Leydig Cell Number and Spermatogenesis of Mice (Mus Musculus) Experiencing Hyperlipidemia. Junal Media Science. 2017;1(22):77–83.
3. Susilawati E. Effect of Ethanol Extract of Rambutan Leaves (Napaleum Lappaceum L.) Against Ldl and Hdl Levels in Male Rats. J Pharmacopolium. 2019;1(3):143–8.
4. Sutejo IR, Rasyada I, Yuniar A. Antihyperlipidemic and Atheroprotective activity of Kepuh (Sterculia foetida) Leaves Ethanolic Extract on High-Fat-Diet Rat Models. J Agromedicine Med Sci. 2017;3(1):44.
5. Normaidah, Nurmansyah D. In Silico Study of Hylocereus polyrhizus and Allium sativum Compounds on HMG-CoA Reductase Enzymes. 2021;(October).
6. S'adah diamond nur. EFFECTIVENESS OF KEPUH (Sterculia foetida L.) LEAF ETHANOL EXTRACT ON SGOT AND SGPT LEVELS OF MALE WISTAR STRAIGHT RATS INDUCED BY HIGH FAT DIET. 2017. 1–55 p.
7. Permatasari TA. Effectiveness of Kepuh Leaf (Sterculia foetida) Ethanolic Extract Against Malondialdehyde Levels In Rat Serum Induced by High Fat Diet. 2017;
8. Zulviyati. Antioxidant and Antihyperlipidemic Activity Test of Kepuh Leaf Extract (Sterculia foetida): DPPH Method and In Vitro Lipase Inhibition. Jember Univ. 2015;
9. Chen T., Liu J., Chang M., Tsai M., Heish PC. The in vitro inhibitory effect of the flavonoid astilbin on 3-hydroxy-3methylglutaryl coenzyme a reductase on vero cells. Zhonghua Yi Xue Za Zhi. 2000;(March 2014):114.
10. Fajrin, Fifteen A. AKTIVITAS EKSTRAK ETANOL KETAN HITAM UNTUK MENURUNKAN KADAR KOLESTEROL. Over Rim. 2017;6:191–9.