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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 aims to measure the biological activity of flavonols in the leaves of *Sterculia foetida* as an antihyperlipidemic drug. The chemical structure of flavonols contained in the leaves of Sterculia foetida was taken from the literature. The target protein used was *3-hydroxy 3-methylglutaryl coenzyme A reductase* and the control was simvastatin. Water molecules have been removed with PyMol v2.5.2 Software. Docking between the target protein and flavonols was performed using PyRx-Python Prescription 0.8 Software. The results showed that flavonol compounds have greater potential for antihyperlipidemia compared to control compounds. The equivalent affinity of *3-hydroxy 3-methylglutaryl coenzyme A reductase* for flavonols is -8.3, and the affinity of *3-hydroxy-3-methylglutaryl coenzyme A reductase* for simvastatin is -7.9. Flavonol toxicity studies have shown that flavonols are not potentially carcinogenic and did not cause mutations. The absorption of flavonols in water was higher than that of the control compound.

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Antihyperlipidemia; Sterculia foetida; Flavonol; *3-hydroxy-3-*methylglutaryl; coenzyme *A reductase*

Introduction

Hyperlipidemia is a condition characterized by an increase in total blood cholesterol level (1). It can cause a variety of chronic diseases such as atherosclerosis, coronary artery disease, diabetes, cancer and stroke. (2) The World Health Organization (WHO) showed that in 2008, the incidence of hyperlipidemia in adults increased globally by 37% in men and 40% in women. While in Indonesia, the incidence of hyperlipidemia is 32.8% for men and 37.2% for females. (3)

By inhibiting the activity of *3-hydroxy 3-methylglutaryl coenzyme A reductase* enzyme with simvastatin, the risk of complications of hyperlipidemia can be reduced. However, this drug can cause gastrointestinal disorders and myopathy. Therefore, researchers wanted to discover a natural ingredient that could replace the function of simvastatin. One of the plants that may replace the function of simvastatin is *Sterculia foetida*. (4) (5)

The leaf extract of *Sterculia foetida* contains various compounds that are beneficial to the body, such as flavonoids, coumarins, organic acids and steroids. (6). The most common

types of flavonoids found in the leaves of Sterculia foetida are flavonols and quercetin, which can act as antioxidants and antihyperlipidemic. (7) (8).

Materials and Methods

Ligand Preparation

The chemical structure of flavonol compounds was collected from published literature. The 3D chemical structure and SMILES of flavonol ligands were obtained 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. Ligand and stereoscopic (3D) of the chemical structure were sketched in Avogadro and stored in PDB format.

Target selection

The target protein for docking was generated using published literature and validated using Uniport (https://www.uniprot.org). Proteins collected and validated using PDB (Protein Data Bank https: ///www.rcsb.org/pdb) are cleaned 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 PDB code was 2Q1L, an enzyme involved in cholesterol formation in the body. (3)

Molecular Docking

Molecular docking experiments were performed using PyRx0.8 software. The docking process was performed using the Vina Wizard feature built into the PyRx 0.8 software. This function responded to the natural flavonol compound, the target protein 3 hydroxy 3 methylglutaryl coenzyme A reductase, and the control compound simvastatin.

Visualization of Interactions Between Molecules and Small Molecules

A control ligand (flavonol) for the target protein (*3 hydroxy 3 methylglutaryl coenzyme A reductase*) and a control ligand (sinvastatin) for the target protein (*3 hydroxy 3 methyl glutaryl coenzyme A reductase*). Interactions were visualized and analyzed using PyMol software v 2.5. 2.

Compound Properties and ADMET Prediction

Using AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2/), predictors and importance of compound physicochemical properties, lipophilicity, pharmacokinetics, and drug-like properties Predicted descriptors.

Results and Discussion

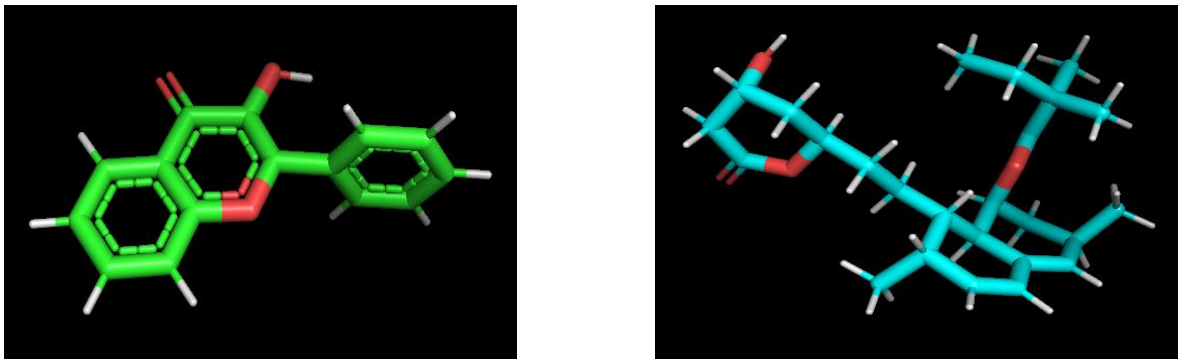
Flavonols and quercetin are compounds of the flavonoid group most commonly found in Sterculia foetida leaf extracts. Flavonol compounds can be used as antihyperlipidemic and antioxidants. As an antihyperlipidemia, flavonols can lower total cholesterol levels and prevent lipid peroxidation through multiple processes. First, it inhibits the formation of mevalonic acid by inhibiting the activity of *3-hydroxy 3-methylglutaryl coenzyme A reductase* (*HMG-CoA reductase*), which is an enzyme involved in the formation of cholesterol in the body. The second mechanism is to reduce the need for NADPH for the formation of fatty acids and cholesterol. The final mechanism is to increase the LDL receptor and chelate cholesterol

acyltransferase (LCAT). This also increases LDL uptake and can convert free cholesterol to HDL. (4) (9)

The structures of plant compounds, control compounds, and target proteins were taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and visualized in 3D by the PyMol application. (Figure 1). The results of docking with the PyRx application showed that flavonols could interact with the target protein, demonstrating that flavonols could be used as an antihyperlipidemic drug. Docking showed that the binding affinity of flavonol compounds was lower than that of simvastatin. This means that flavonols require less energy to bind to the target protein than simvastatin.

HMG-CoA reductase is responsible for the converting of HMG-CoA to mevalonic acid (8). Inhibition of HMGCoA 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

Figure 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

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.

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