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IN SILICO APPROACH OF ANTIHYPERCHOLESTEROL COMPOUNDS FROM *ALLIUM SATIVUM* THROUGH DOCKING ANALYSIS AND ADMET PREDICTIONS

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Abstract

Allium Sativum (Allicin) is one of the herbs traditionally used as a drug for the hypercholesterol. This study aimed to discover bioactivity of the Allicin compound from Allium Sativum for level decrease of hypercholesterol based on reverse docking studies. Structures of chemical constituents of Allium Sativum (Allicin) was collected from published literature. The water molecule and ligands were removed by using PyMOL v1.7.4.5 Software (Schrödinger). Molecular docking experiments were performed using the PyRx 0.8 software. Prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds were predicted using Swissadme. The results showed that Allicin has greater potential as an level decrease of hypercholesterol based on its binding affinity and intermolecular interactions. The binding affinity of Allicin with HMG Co-A reductase is -2.6, while binding affinity HMG Co-A reductase with the control compound simvastatin is 16.3. AMES Test showed that Allicin is not potential mutagens and not carcinogens. Druglikeness prediction showed that Allicin fulfil the rules of Lipinski, Ghose, Veber, Egan and Muegge with 0.55 Bioavailability Score.

Keywords: Hypercholesterol, Allium Sativum, Simvastatin, Allicin, HMG Co-A Reductase

1. Introduction

Hypercholesterolemia is an abnormal condition in which there is an increase in blood cholesterol to above normal limits with high cholesterol levels 200 mg/dl. Hypercholesterolemia is caused by several factors such as stress, hypertension, low physical activity, obesity, low fruit and vegetable consumption, alcohol consumption, eating high-fat foods, and smoking. Reducing cholesterol levels in the blood can be done by limiting cholesterol biosynthesis and adjusting diet. Limitation of cholesterol and fat biosynthesis can be done by inhibiting the activity of HMG Co-A reductase (Lachenmeier et al., 2012). Statin drugs are the most effective in reducing lipid levels. They work by inhibiting 3-Hydroxy-3-Methylglutaryl-CoA reductase (HMG-CoA Reductase) by binding to the HMG CoA reductase enzyme, resulting in a conformational change on the active site and a decrease in Low Density levels. Lipoproteins (LDL)(Stone et al., 2014). In animal experiments, garlic was found to have the effect of reducing the activity of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase in the liver. The experimental results are in line with the theory that garlic can lower cholesterol levels (Hewen et al., 2019).

2. Materials and Method

2.1.Ligands Preparation

Structures of the chemical compound of *Allium Sativum* (Allicin) was collected from published literature. Chemical 3D structure and SMILES of ligand (Allicin) taken from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with number ID: CID 65036 and Canonical Smile : C=CCSS(=O)CC=C. The two-dimensional (2D) and the three-dimensional (3D) chemical structures of the ligands were sketched using Avogadro and Discovery Studio and were saved in PDB format.

2.2.Target Selection

The reseptor potential target candidates for docking was prepared using 3 databanks, i.e: Pharmmapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Prediction (www.swisstargetprediction.ch) and validate using Uniport (https://www.uniprot.org). The reseptor that was collected and validated with PDB (Protein Data Bank https:///www.rcsb.org/pdb) than reseptor were prepared using clean reseptor to remove the water molecules from the structure. The water molecule and ligands were removed by using PyMOL v1.7.4.5 Software (Schrödinger). In this study, the target reseptor used was HMG CoA reductase with the 1HW9 code of PDB, because HMG CoA reductase is a compound in the form of an enzyme that plays an essential role in the fidological and pathophysiological processes (Dicky Wahyu Irawan, 2020).

2.3.Molecular Docking

Molecular docking experiments were performed using the PyRx 0.8 software. The reverse docking process was carried out using the Vina Wizard feature integrated into PyRx 0.8 software which reacts to the natural compound Allicin, the target reseptor HMG CoA reductase and the control compound (activator compound HMG CoA reductase). Activator compounds will be a positive control in the docking process (Dicky Wahyu Irawan, 2020).

2.4.Visualization of Molecule and Small Molecule Interaction

The interactions between ligands (Allicin) target reseptor (HMG CoA reductase), and known inhibitors of target reseptor visualized and analyzed using PyMol v1.7.4.5 Software (Schrödinger) (Rose et al., 2021)

2.5. Compound's Properties and ADMET Predictions

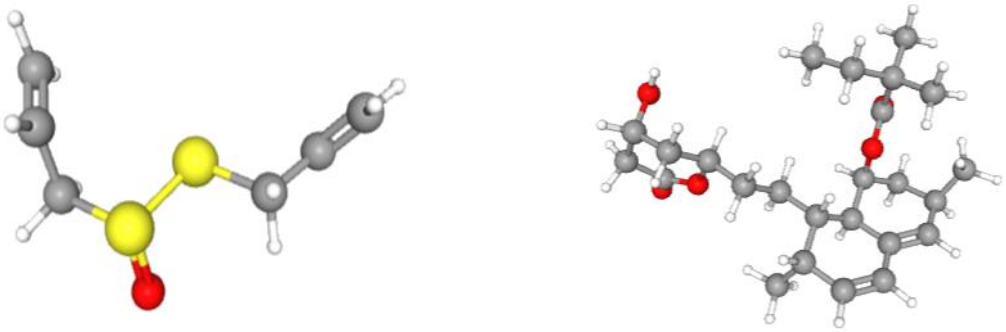
Swissadme (http://www.swissadme.ch) and admetSAR (lmmd.ecust.edu.cn:8000) is used to predict the prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds (Rose et al., 2021).

3. Results and Disscussion

The parameter in the In Silico test is the binding affinity value of the interaction between the ligand compound and its receptor. The bond between the ligand and the receptor can be seen from several bonds that occur during the docking process such as ionic bonds, bonds, hydrogen bonds, Van Der Waals bonds and covalent bonds. In this study, the ligands used were allicin and HMG CoA reductase as receptors. The result of this research is the bond between allicin and HMG CoA reductase. HMG CoA reductase is an enzyme that can control the rate of cholesterol biosynthesis. In the structure of HMG CoA reductase there are 4 amino acids as the main catalytic (glutamate, asparte, lysine and histidine) (Cerqueira et al., 2016).

Based on the results obtained, the binding affinity value of the allicin model formed from the Molecular Docking test. The lowest binding affinity value of Allicin is -2.6 in model 0. The lowest comparative affinity value of simvastatin model is 16.9 in model 0. When the drug has been absorbed in the intestines into the blood circulation, then the drug will be distributed throughout the body tissues by penetrating cell membrane so that the drug can reach its intended target receptor. In the world of pharmacology, it is important to consider the factor of drug distribution throughout the body tissues and through cell membranes so that it can reach the target receptor because drug interactions with the target compound cannot occur if the drug cannot reach its target. (Jadhav *et al*., 2015). The difference in the value of binding affinity for both the compound and the compound model can be influenced by the bond formed between the compound and the target receptor. In this study the compounds tested were squalene and simvastatin compounds as comparisons in this study. Hydrogen bonding can also play an important role in determining the level of binding affinity obtained from Molecular Docking. Hydrophobic bonds can also affect the level of binding affinity value but the effect given by hydrophobic bonds is not as big as the effect given by hydrogen bonds.

In the Molecular Docking test, 2 test compounds were taken against the HMG CoA reductase receptor, namely allicin and simvastatin compounds, each of which was selected on the best model of the two compounds, namely the model with the lowest binding affinity value. The allicin compound in this study acted as the compound tested and then compared with simvastatin as a drug used to treat hypercholesterolemia. In the analysis of the interaction between the two compounds using the discovery studio software, several hydrogen and hydrophobic bonds were formed between the two. In Molecular Docking, allicin compound with HMG CoA reductase receptor which affects the binding affinity value, while in simvastatin the best binding affinity value is 16.9. Comparison of binding affinity values between allicin compounds with a value of -2.6 and simvastatin with a value of 16.9 shows that squalene compounds have not been able to become more effective drugs than simvastatin in treating hypercholesterolemia.



(a) (b)

Figure 1. (a) Chemical 3D Structure of Allicin and (b) Simvastatin were showed by software PyMol

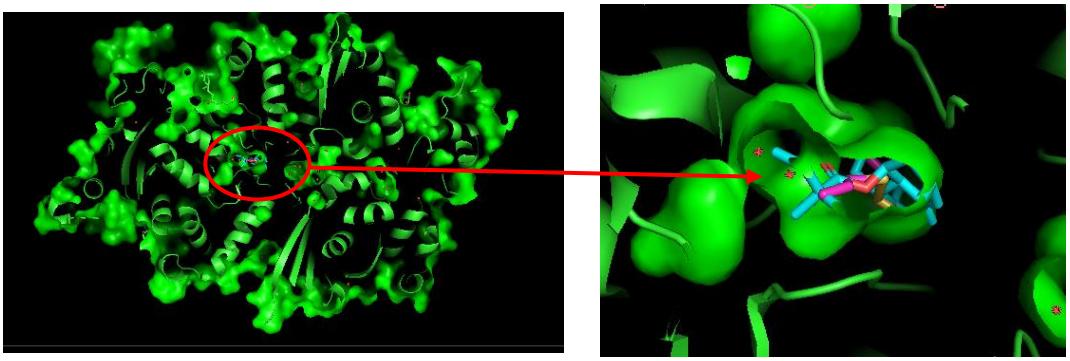


Figure 2. Binding Site of Allicin (purple), Simvastatin (blue) with HMG CoA reductase (green)

Table 1. The result of Reverse Docking NOS3 with ligand and control activator

Ligand	Binding Affinity
HMG CoA reductase and Allicin	-2.6
HMG CoA reductase and Simvastatin	16.3

Most of the drugs have aimed for treating some chronic diseases. Thus, the concentration of a drug must be consistent [18]. The side effect of the α-caesalpin compound for the body has observed by ADMET predictions which were evaluated and linked to cell permeation, metabolism process and bioavailability. As revealed by the result of this study (AMES Test), the result shows that α-caesalpin is not potential mutagens and not carcinogens. The Ligands is considered to have the potential to enter the cell membrane and be absorbed by the body if they meet Lipinski's rules. The search results show that α-caesalpin fulfils the rules of Lipinski, Ghose, Veber, Egan and Muegge with the Bioavailability Score 0.55.

4. Conclussion

This study proved that Allicin has potential as level decrease of hypercholesterol an based on its binding affinity with -2.6 and intermolecular interactions. Allium Sativum contains allicin which is potential hipercholesterol drug according to Lipinski, Ghose, Veber, Egan dan Muegge rule and 0.55 Bioavailability Score.

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