EasyChair Preprint

№ 7201

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December 9, 2021

IN-SILICO TEST OF ACTIVITY QUERCETIN AS A NATURAL COMPOUND IN REDUCING HYPERTENSION

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Abstract

Syzygium polyanthum is one of the herbal plants that contains active compounds, specifically quercetin, which has traditionally been used as a hypertension medication. Based on reverse docking studies, this study aimed to discover the bioactivity of the Quercetin compound from Syzygium Polyanthum for hypertension. The structures of Syzygium polyanthum chemical constituents (quercetin) were gathered from published literature. Phosphoinositide 3-kinase is the Target Protein.PyMOL v1.7.4.5 Software (Schrödinger) was used to remove the water molecule and ligands. The PyRx 0.8 software was used to conduct the molecular docking experiments.
Based on its binding affinity and intermolecular interactions, the results showed that quercetin has a greater potential for lowering hypertension. Quercetin has a binding affinity of -7.6 with Phosphoinositide 3-kinase protein, while Phosphoinositide 3-kinase has a binding affinity of -4,6 with the control compound Amlodipine. The AMES test revealed that quercetin is not a carcinogen. The absorption of quercetin in water is higher than in the control compound.

1. Introduction

Hypertension according to WHO data in 2015 showed that around 1.13 billion people in the world suffer from hypertension, which means that every 1 in 3 people in the world is diagnosed with hypertension. The number of people with hypertension in the world continues to increase every year. It is estimated that in 2025 there will be 1.5 billion people affected by hypertension and every year 9.4 million people die from hypertension and complications. Hypertension is an important public health issue that rarely causes symptoms or significant limitations on the functional health of patients. (1). Hypertension is a major risk factor for coronary heart disease, heart failure, and stroke (2)

In addition to pharmacological and non-pharmacological drugs for the treatment of hypertension, there are also medicines derived from herbal ingredients, namely medicinal plants.

One of them is the bay leaf, which is deliberately planted to take the leaves, this leaf is then used as one of the traditional medicines, and one of the spices in various Indonesian specialties.

Salam (Syzgiyum polyanthum) is the name of a leaf-producing tree that is widely used in Indonesian cuisine. This traditional medicine is empirically efficacious in the treatment of hypertension. Bay leaves grow spread in Southeast Asia and are often found in the yard of the house. Apart from being a kitchen spice, bay leaves have many health benefits, for example, to treat diabetes mellitus, gastritis, pruritus, diarrhea, drunkenness due to alcohol, and hypertension (3)

Syzygium polyanthum contains flavonoid compounds, which flavonoids contain quercetin. Quercetin contained in flavonoids has an effect as a vasodilator, antiplatelet, and antiproliferative and lowers blood pressure, the result of oxidation and repair of body organs that have been damaged due to hypertension. (4) It is concluded that the flavonoids contained in many vegetables and fruits can be used to reduce the risk of myocardial infarction and stroke.

In this study, we found bioactivity to reduce hypertension based on Reverse Docking.

2. Materials and Methods

2.1 Ligand Preparation

The chemical structure of Quercetin was collected from the published literature. The 3D chemical structure and SMILES ligand (Quercetin) were taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with ID number: CID 5280343 and Canonical Smiles: C1=CC(=C(C=C1C2 =C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O. Two-dimensional (2D) and three-dimensional (3D) ligand chemical structures were sketched using Avogadro and Discovery Studio and saved in PDB format.

2.2 Target Selection

Potential protein target candidates for docking were prepared using 3 data banks, namely: Pharmmapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Prediction (www. swisstargetprediction). .ch) and validation using Uniport (https://www.uniprot.org). Collected and validated proteins with PDB (Protein Data Bank https:///www.rcsb.org/pdb) rather than proteins were prepared using clean protein to remove water molecules from the structure. Water molecules and ligands were removed using PyMOL Software v1.7.4.5 (Schrödinger). In this study, the target protein used was Phosphoinositide 3-kinase with code 1E8Y from PDB. Phosphoinositide 3-kinase inhibition could be a new tool to modulate

calcium influx into vascular smooth muscle cells, thereby relaxing arterial resistance and lowering blood pressure.

2.3 Molecular Docking

Molecular docking experiments were carried out using PyRx 0.8 software. The docking process is carried out using the Vina Wizard feature integrated into the PyRx 0.8 software which reacts to the natural compound quercetin, the target protein Phosphoinositide 3-kinase and the control compound is Amlodipine.

2.4. Molecular and Small Molecule Interaction Visualization

The interaction between the target protein-ligand (quercetin) (Phosphoinositide 3-kinase), and control ligand (amlodipine) with known target protein (Phosphoinositide 3-kinase) was visualized and analyzed using PyMol v 2.5.2 Software.

2.5. Compound Properties and Prediction of ADMET

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

3. Results and Discussion

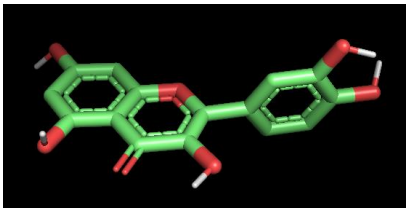
Quercetin is one of the biologically very strong flavonoid classes of active substances. If vitamin C has an antioxidant activity of 1, then quercetin has an antioxidant activity of 4.7. Quercetin is believed to protect the body from several types of degenerative diseases by preventing the fat peroxidation process (5)

Flavonoids (quercetin) act as natural antioxidants that protect blood vessels and inhibit cell oxidation by capturing active oxygen and free radicals. In a study conducted (6), it was found that quercetin can reduce blood pressure in subjects with hypertension. The high content of quercetin in food can modulate the activity of platelets to prevent cardiovascular disease (7). These compounds produce the ability to reduce oxidative stress, inhibit the activity of angiotensin-converting enzymes, increase vascular endothelial relaxation, regulate cell signaling and gene expression.

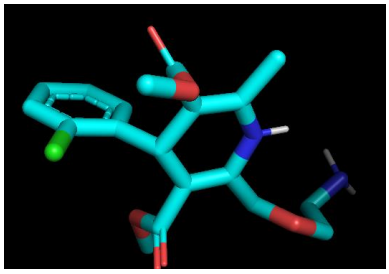
Intracellular signaling pathway involving the enzyme Phosphoinositide 3-kinase has an important role in cell proliferation and is considered a good therapeutic target in reducing hypertension. The research that has been done shows that quercetin can inhibit the activity of Phossphoinositide 3-kinase (8). Quercetin acts as an antioxidant by releasing or donating hydrogen

ions to peroxy free radicals to make them more stable. This activity blocks the oxidation reaction of bad LDL cholesterol which causes the blood to thicken thereby preventing the deposition of fat on the walls of blood vessels. The molecular structure of antioxidants not only can release hydrogen atoms but also converts radicals into low activity so that no reaction with fat occurs. Antioxidants consist of endogenous antioxidants produced by the body itself and exogenous antioxidants derived from food (9). An exogenous antioxidant diet prevents cellular damage through reactions carried out by free radicals. (10)

Toxicity tests have been carried out through ADMET predictions showing that quercetin compounds have no potential carcinogens or mutagens. The rate of absorption by the body was higher than with amlodipine as a control. However, it is not recommended to extract this compound because it is potentially toxic.

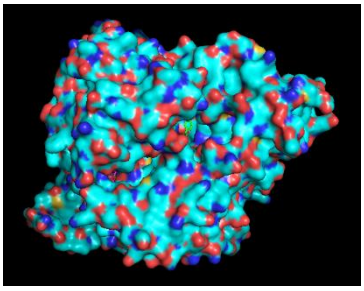


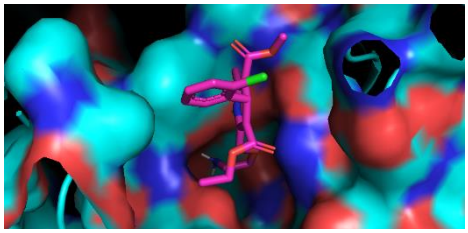
(a)



(b)

Figure 1. (a) 3D structure of quercetin compound, (b) 3D structure of amlodipine control compound





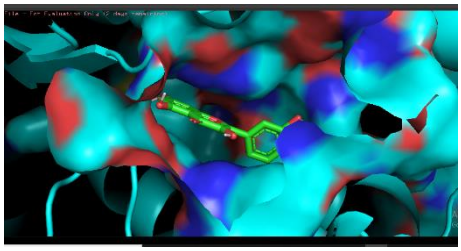


Fig.2. docking results of Amlodipine (purple) and Quercetin (green) with 3 Phossphoinositide 3-kinase protein

Table.1. results of docking between quercetin and amlodipine compounds with target proteins

Ligand	Binding Affinity (kcal/mol)
Quercetin and Phossphoinositide 3-kinase	-7,6
Amlodipine and Phossphoinositide 3-kinase	-4,6

4. Conclusion

Based on the results of an intramolecular interaction and its affinity level, it can be concluded that the quercetin compound in *Syzygium Polyanthum* can be used as a drug in reducing hypertension.

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