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In Silico Testing on the Activity of Quercetin in the Skin of Onion *Allium Cepa* L as A Natural Antihypertensive Compound

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Abstract

This study aims to determine the bioactivity of the compound quercetin in the peel of Onion (*Allium cepa* L) as a natural antihypertensive compound. The chemical structure of the quercetin compound found in Allium cepa L peel was taken from the literature. The target protein used was Angiotensin-Converting Enzyme (ACE), while the control compound was lisinopril. Water molecules were removed using PyMol v2.5.2 Software. Docking between the target protein and the compound was carried out using PyRx-Python Prescription 0.8 Software. The results showed that the quercetin compound had more significant potential as an antihypertensive compared to lisinopril as a control compound. The affinity ratio of the Angiotensin-converting enzyme with quercetin is -8.1, while the affinity value of the Angiotensin-converting enzyme with lisinopril is -7.1.

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Introduction

The circulatory system illness known as hypertension raises blood pressure above normal ranges, which makes the heart work harder to circulate blood throughout the body. (Haryanto Susanto, Rehmadanta Sitepu FX, 2021). Blood pressure is checked twice, with a five-minute gap, at a peaceful time (Putri, 2020). The World Health Organization (WHO) defines adults over the age of 18 as having mild hypertension if their systolic pressure is between 140 and 159 mmHg and their diastolic pressure is between 90 and 99 mmHg, moderate hypertension if those numbers are between 160 and 179 mmHg and 100 to 109 mmHg, and severe hypertension if those numbers are above 180 mmHg (Harfiantoko & Kurnia, 2013).

According to WHO, by 2025, there will be approximately 1.5 billion people affected by hypertension each year (Pharmaceutical et al., 2019). Patients withhypertension tend

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to increase year after year, with an estimated 600 million worldwide, and have become a very serious health problem known as "the silent killer." (Rahajeng and Tuminah, 2019). If not controlled, it can lead to coronary heart disease, stroke, kidney disease, peripheral arterial disease, and blindness (Rahajeng & Tuminah, 2019;Perez-Vizcaino et al., 2009).

Both drug-based and non-drug approaches can be used to treat hypertension. On the other hand, because the treatment is prolonged, it may be risky and result in negative side effects (Putri, 2020). Lisinopril and other medications in the ACE Inhibitor class are frequently used for hypertension, but according to Braghi, they can occasionally cause taste alterations and cause side effects such a dry cough, which affects roughly 5-20% of Europeans and 40% of Asians. (Rehmadanta Sitepu, FX Haryanto Susanto 2021). Due to its lower cost and lower number of adverse effects, herbal medicine is utilized as an option to treat hypertension (Chaudhary et al., 2020). One of the naturally occurring herbal substances that can be utilized as an ACE inhibitor is the quercetin found in the peel of onions (*Allium cepa* L), which is beneficial as a natural antioxidant and antihypertensive. (Amin et al.2018).

According to earlier studies, giving obese prehypertensive patients 54 mg of quercetin three times a day for six weeks decreased their systolic and mean arterial blood pressure. (Brühl et al. 2015). Smokers' systolic and diastolic blood pressure decreased when given 100 mg of quercetin a day for 10 weeks (Lee et al. 2011).

Onions are widely utilized as herbal medications since they contain elements that are incredibly useful to human health (Sari, 2016). The highest quercetin level was found in onions (*Allium Cepa* L), particularly when compared to garlic, in a survey of 28 different types of vegetables and fruits by Holman et al. (Crystal et al. 2003; Patil et al.1995). Quercetin is the major component of onion skin, which is typically discarded (Setiawan et al., 2021). The flavonoid flavonol 25—which is a member of the flavonoid family and has potential as an antihypertensive, antioxidant, antibacterial, anticancer, anticholesterol, and hypoglycemic agent—belongs to quercetin (Sari, 2016).

Materials and Methods

Ligand Preparation

The PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) was used to obtain the quercetin chemical structure in the form of a 3D chemical structure and SMILES. The molecule's ID number is CID:5280343, and its Canonical Smiles are C1=CC(=C(C=C1C2C3=C(C=C3O2)O)O)O)O)O. Three-dimensional (3D) and the chemical structures of the ligands were drawn using Avogadro and saved in PDB format.

Target Selection

The target protein was prepared for docking using the published literature and the protein data bank, namely www.swisstargetprediction.ch and http://prediction.charite.de, and then confirmed using Uniport (https://www.uniprot.org). Proteins were gathered and verified with PDB (Protein Data Bank; http://www.rcsb.org/pdb), after which the protein was cleaned up for use by eliminating water molecules from the structure using PyMOL v2.5.2 software. Angiotensin-converting enzyme, with the PDB code 1R42, was the target protein in this investigation. Angiotensin II is produced by the conversion of angiotensin I and induces

the constriction of blood vessels and the release of vasoconstrictors, which raises blood pressure.

Molecular Docking

We carried out molecular docking tests with PyRx 0.8 program. The target protein Angiotensin-Converting Enzyme (ACE), the natural chemical quercetin, and lisinopril as a control compound are all reacted to during the docking process utilizing the Vina Wizard tool built into the PyRx 0.8 software (O. Trott AJ.Olson, 2010).

Visualization of Interactions Between Molecules and Small Molecules

PyMol Software version 2.5.2 was used to visualize and evaluate the interaction of the control ligand (lisinopril) and the target protein's ligand (quercetin), angiotensin- converting enzyme.

Compound Properties and Prediction of ADMET

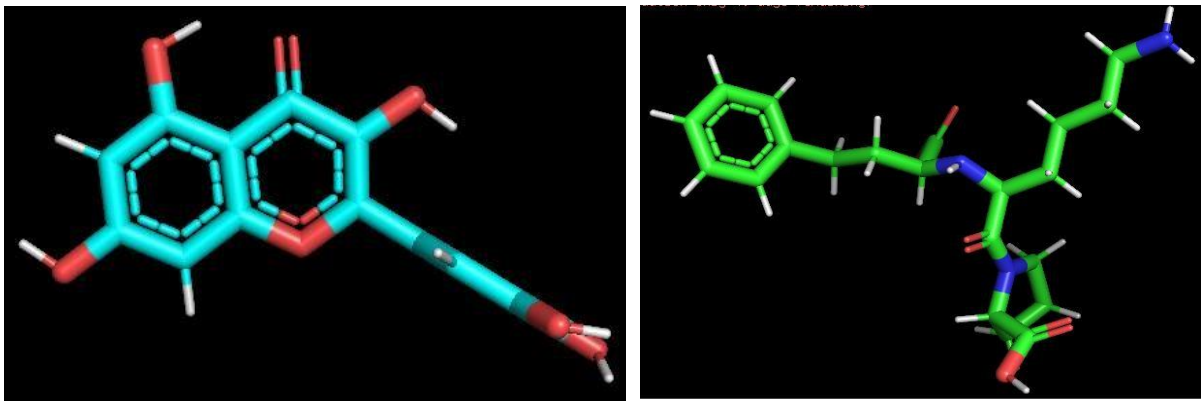
To predict and significant characteristics of the compounds' physicochemical, lipophilicity, pharmacokinetic, and druglikeness features, AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2/) was utilized.

Results and Discussion

Length-frequency analysis

The PubChem website (https://pubchem.ncbi.nlm.nih.gov/) was used to retrieve the structures of herbal compounds, control compounds, and target proteins, which were then visualized in 3D using the PyMol program (Fig. 1). Quercetin can interact with the target protein angiotensin-converting enzyme (ACE), according to the results of docking using the PyRx program, suggesting that it can be utilized as an antihypertensive drug.

The docking results showed that quercetin had a lower binding affinity than lisinopril, the control molecule, indicating that quercetin needed less energy to bind to the target protein. Lisinopril needed more energy to bind to the target protein.



(a) **(b)**

Figure 2. 3D structure of quercetin compound, (b) 3D structure of control compound lisinopril

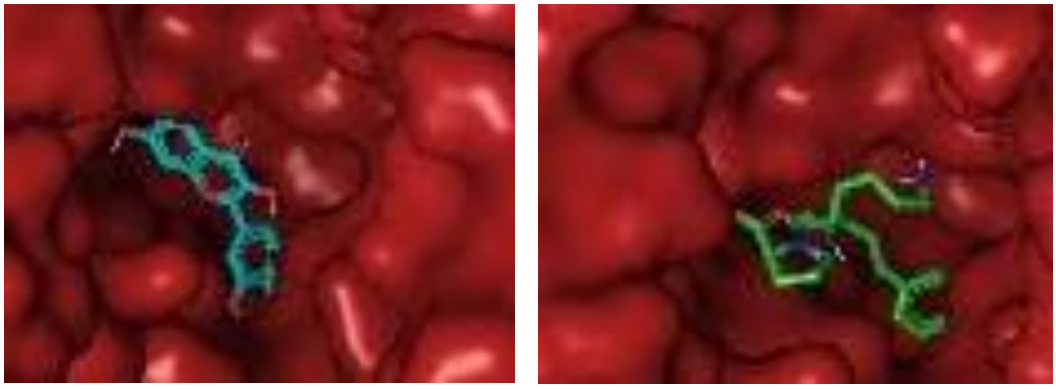


Figure 2. results of docking quercetin (blue) and lisinopril (green) with protein Angiotensin-converting enzyme (ACE)

Table 1. results of docking between quercetin and lisinopril compounds with the target protein

Origin of Compound	Ligand	Binding Affinity (kcal/mol)
Allium Cepa L	**Quercetin**	**-8.1**
Control	**Lisinopril**	**-7.1**

It has been demonstrated that quercetin lowers both systolic and diastolic blood pressure in numerous antihypertensive studies. (Edwards et al.2007). Regarding antihypertensive drugs, quercetin works through a number of mechanisms, including reduced oxidative stress, compromised renin-angiotensin-aldosterone system (RAAS), and improved vascular function via endothelial cells. (Larson et al.2012)

The antihypertensive mechanism of quercetin as an ACE inhibitor is by inhibiting the activity of Angiotensin-Converting Enzyme (ACE), thereby inhibiting the process of Angiotensin II formation. Angiotensin II in circulating blood plasma can cause blood vessel constriction and facilitate the occurrence of natriuretics (Garciá-Saura et al., 2005). As a result, the absence of Angiotensin II eliminates vasoconstriction and has a negative effect on blood pressure levels (Putri, 2020).

Endothelial cells produce nitric oxide (NO) as endothelium-derived relaxing factor (EDRF) more frequently when quercetin increases the activity of nitric oxide synthase in those cells. Nitric oxide causes blood vessel walls to enlarge and lowers blood pressure by relaxing the smooth muscles in blood vessels (Ozarowski et al., 2018; Perez- Vizcaino et al., 2009; Putri, 2020). Quercetin produces vasorelaxation in blood vessels in addition to the endothelium mechanism by acting directly on vascular smooth muscle and obviating the endothelium.Larson et al.2010). According to earlier research on mouse coronary arteries, circulation levels of 10-7 moles/l quercetin will have a vasodilating impact because of elevated amounts of endogenous vasoactive molecules from the coronary artery wall. (Lee et al.2011)

Quercetin also acts as an antioxidant, preventing LDL oxidation reactions by releasing hydrogen ions, which help to stabilize free radicals. This prevents blood coagulation, which

can lead to fat deposition on blood vessel walls. As a result, atherosclerosis, one of the causes of hypertension, is avoided (Putri, 2020).

Quercetin compounds are not potentially carcinogenic, according to toxicity studies performed using ADMET projections. It is not advised to extract the chemical directly due to its potential for toxicity.

Conclusion

It is feasible to draw the conclusion that the chemical quercetin present in onion skin (*Allium cepa* L) can serve as a natural antihypertensive based on the results of intermolecular interactions and affinity.

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