



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

Andi Ariyandy¹, Nindrahayu², Ami Febriza³, Andi Irwan Muluk⁴, Sulfahri⁵

¹ Department of Physiology, Faculty of Medicine, Hasanuddin University Makassar, Indonesia,

² Hasanuddin University Hospital, Makassar, Indonesia,

³ Department of Physiology, Faculty of Medicine, University of Muhammadiyah Makassar, Indonesia

⁴ Biomedical Sciences, Graduate School, Hasanuddin University, Makassar, Indonesia,

⁵ Biological Sciences, Faculty of Mathematics and Natural Sciences, Hasanuddin University, Makassar, Indonesia

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.

Article History

Received August 13, 2022

Accepted December 14, 2022

Keyword

Quercetin;
Angiotensin-Converting Enzyme (ACE);
Allium Cepa L

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). According to the World Health Organization (WHO), adults over 18 are considered to have mild hypertension if their systolic and diastolic blood pressures are between 140 and 159 mmHg and 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, hypertension would affect over 1.5 billion people annually (Pharmaceutical et al., 2019). With an estimated 600 million cases worldwide, the

number of people with hypertension tends to rise yearly, making it an extremely dangerous health issue known as "the silent killer." (Rahajeng and Tuminah, 2019) If left untreated, it can cause peripheral arterial disease, renal disease, coronary heart disease, stroke, 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).

Because they contain components that are highly beneficial to human health, onions are frequently used as herbal medicines (Sari, 2016). In a study of 28 different types of vegetables and fruits by Holman et al., the highest quercetin level was discovered in onions (*Allium cepa* L), particularly when compared to garlic (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 chemical structure of quercetin was obtained from the PubChem compound database (<https://pubchem.ncbi.nlm.nih.gov/>) as a 3D chemical structure and SMILES. The molecule's Canonical Smiles are C1=CC(=C(C=C1C2C3=C(C=C3O2)O)O)O)O, and its ID number is CID:5280343. The ligands' chemical and three-dimensional (3D) structures were drawn using Avogadro and saved in PDB format.

Target Selection

Using published research and the protein data bank, specifically www.swisstargetprediction.ch and <http://prediction.charite.de>, the target protein was ready for docking. It was then verified using Uniport (<https://www.uniprot.org>). Proteins were collected, validated with PDB (Protein Data Bank; <http://www.rcsb.org/pdb>), and then cleaned up for use by removing water molecules from the structure using PyMOL v2.5.2 software. The target protein in this study was angiotensin-converting enzyme, with the PDB number 1R42. Angiotensin I is converted into angiotensin II, which causes the release of vasoconstrictors and the constriction of blood vessels, hence increasing 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.

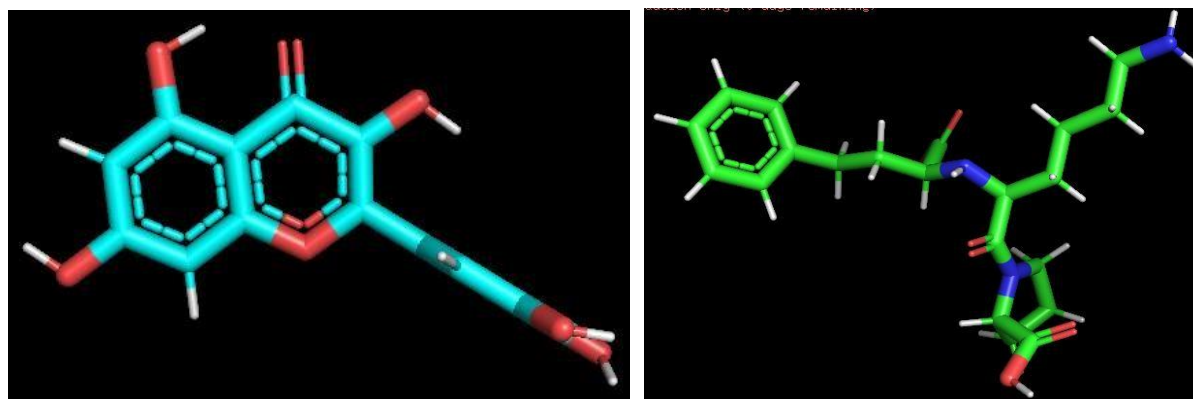
Results and Discussion

Length-frequency analysis

The structures of herbal compounds, control compounds, and target proteins were retrieved from the PubChem website (<https://pubchem.ncbi.nlm.nih.gov/>), and then visualized in 3D using the PyMol program (Figure 1).

According to the results of docking using the PyRx program, quercetin can interact with the target protein angiotensin-converting enzyme (ACE), which suggests that it can be used as an antihypertensive medication.

According to the docking results, quercetin required less energy to connect to the target protein than the control chemical, lisinopril, which had a higher binding affinity. In order to bind to the target protein, lisinopril required additional energy.



(a)

(b)

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

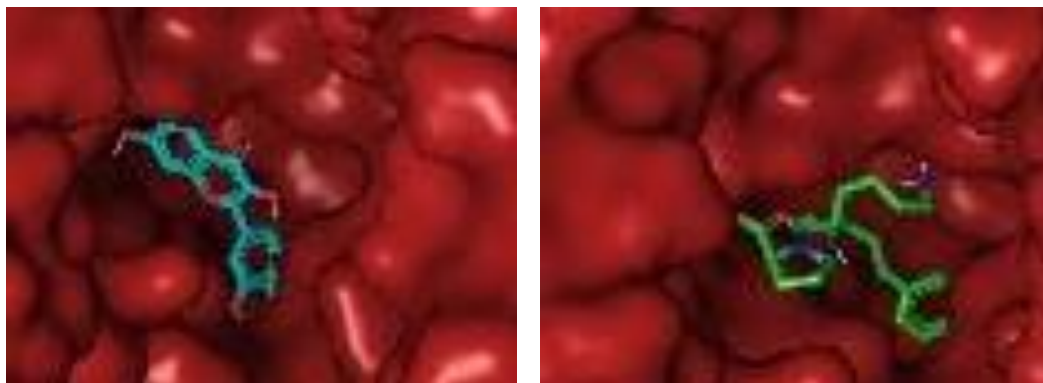


Figure 2. results of docking quercetin (blue) and lisinopril (green) with protein Angiotensin-converting enzyme (ACE)

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

Origin of Compound	Ligand	Binding Affinity (kcal/mol)
<i>Allium Cepa L</i>	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 (García-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.

References

- Amin, M., Putra, KS, Amin, IF, Earlia, N., Maulina, D., Lukiati, B., & Lestari, U. (2018). Quercetin: the bioactive compound from *Allium cepa* L. as anti-inflammation based on in silico screening. *Biology, Medicine, & Natural Product Chemistry*, 7(1), 27–31. <https://doi.org/10.14421/biomedich.2018.71.27-31>
- Brüll, V., Burak, C., Stoffel-Wagner, B., Wolfram, S., Nickenig, G., Müller, C., Langguth, P., Alteheld, B., Fimmers, R., Naaf, S., Zimmermann, BF, Stehle, P., & Egert, S. (2015). Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: A randomized double-blinded placebo-controlled cross-over trial. *British Journal of Nutrition*, 114(8), 1263–1277. <https://doi.org/10.1017/S0007114515002950>
- Chaudhary, N., Sabikhi, L., Hussain, SA, & Kumar MH, S. (2020). A comparative study of the antioxidant and ACE inhibitory activities of selected herbal extracts. *Journal of Herbal Medicine*, 22(November 2018), 100343. <https://doi.org/10.1016/j.hermed.2020.100343>
- Crystal, S., Lombard, KA, Peffley, EB, & Liu, WX (2003). Genetic Analysis of Quercetin in Onion (*Allium cepa* L.) 'Lady Raider. *Texas Journal of Agriculture and Natural Resources*, 16(0), 24–28.
- Edwards, RL, Lyon, T., Litwin, SE, Rabovsky, A., Symons, JD, & Jalili, T. (2007). Quercetin reduces blood pressure in hypertensive subjects. *Journal of Nutrition*, 137(11), 2405– 2411. <https://doi.org/10.1093/jn/137.11.2405>
- Pharmacy, PS, Nahdlatul, U., Sunan, U., Bojonegoro, G., & Antihypertensive, O. (2019). Garcíá-Saura, MF, Galisteo, M., Villar, IC, Bermejo, A., Zarzuelo, A., Vargas, F., & Duarte, J. (2005). Effects of chronic quercetin treatment in experimental renovascular hypertension. *Molecular and Cellular Biochemistry*, 270(1–2), 147–155. <https://doi.org/10.1007/s11010-005-4503-0>
- Harfiantoko, MN, & Kurnia, E. (2013). Degree of Hypertension (According to WHO) Affects Sleep Quality and Psychosocial Stress. *Stikes Journal*, 6(2), 1–12.
- Larson, AJ, David Symons, J., & Jalili, T. (2012). Therapeutic potential of quercetin to decrease blood pressure: Review of efficacy and mechanisms. *Advances in Nutrition*, 3(1), 39–46. <https://doi.org/10.3945/an.111.001271>
- Larson, AJ, Symons, JD, & Jalili, T. (2010). Quercetin: A treatment for hypertension? - A review of efficacy and mechanisms. *Pharmaceuticals*, 3(1), 237–250. <https://doi.org/10.3390/ph3010237>
- Lee, KH, Park, E., Lee, HJ, Kim, MO, Cha, YJ, Kim, JM, Lee, H., & Shin, MJ (2011). Effects of daily quercetin-rich supplementation on cardiometabolic risks in male smokers. *Nutrition Research and Practice*, 5(1), 28–33. <https://doi.org/10.4162/nrp.2011.5.1.28>
- O. Trott, AJ Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, *Journal of Computational Chemistry* 31 (2010)455-461

- Ożarowski, M., Mikołajczak, PL, Kujawski, R., Wielgus, K., Klejewski, A., Wolski, H., & Seremak-Mrozikiewicz, A. (2018). Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: Review of in vitro, in vivo, and clinical studies. *Evidence-Based Complementary and Alternative Medicine*, 2018. <https://doi.org/10.1155/2018/7421489>
- Patil, BS, Pike, LM, & Yoo, KS (1995). Variation in the quercetin content in different colored onions (*Allium cepa* L.). *Journal of the American Society for Horticultural Science*, 120(6), 909–913. <https://doi.org/10.21273/jashs.120.6.909>
- Perez-Vizcaino, F., Duarte, J., Jimenez, R., Santos-Buelga, C., & Osuna, A. (2009). Antihypertensive effects of the flavonoid quercetin. *Pharmacological Reports*, 61(1), 67– 75. [https://doi.org/10.1016/S1734-1140\(09\)70008-8](https://doi.org/10.1016/S1734-1140(09)70008-8)
- Putri, SD (2020). Quercetin in Parasite Tea as Hypertension Therapy. *Medulla*, 10, 307–311.
- Rahajeng, E., & Tuminah, S. (2019). Hypertension Prevalence and its Determinants in Indonesia Hypertension Prevalence and its Determinants in Indonesia. Center for Biomedical and Pharmacy Research Institute for Health Research, Ministry of Health, Jakarta Abstract:, 59(12), 581–590.
- Rehmadanta Sitepu FX Haryanto Susanto, ES (2021). Evaluation of the Use of Ace Inhibitor Lisinopril Antihypertensive Drugs on the Occurrence of Dry Cough in Hypertensive Patients in the Church Community in Malang Regency. *Wijata Journal*, 8(2), 51–57.
- Sari, AN (2016). Various Spice Plants As A Source Of Natural Antioxidants. *Elkawnie*, 2(2), 203. <https://doi.org/10.22373/ekw.v2i2.2695>
- Setiawan, AYD, Putri, RI, Indayani, FD, Widasih, NMS, Anastasia, N., Setyaningsih, D., & Riswanto, FDO (2021). Chemical Content and Potential of Shallots (*Allium cepa* L.) as an Inhibitor of SARS-CoV-2. *Indonesian Journal of Chemometries and Pharmaceutical Analysis*, 1(3), 143–155.