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In Silico Study: Prediction the Potential of Caffeic Acid As ACE inhibitor

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Abstract

Hypertension is an abnormal increase in blood pressure. Regulating blood and cardiovascular function have correlated with the ACE pathway. To decrease blood pressure can use the ACE inhibitor. This paper aims to predict potential of Caffeic Acid as anti-hypertension by blocking the ACE pathway. The method in this research used in silico study. The protein was obtained from Protein Data Bank (PDB) and the ligand was obtained from PubChem. Molecular docking was performed by using HEX and visualization analysis was analyzed by using Discovery Studio. The interaction of caffeic acid and ACE has a functional as anti-hypertension roles. The evidence by twelve amino acid, which bind with the caffeic acid (ASP377, ASN277, ASN285, GLU376, ALA170, ASN167, ASN374, THR372, THR166, CYS370, GLU162 and PRO163). The chemistry bond was formed are hydrogen bond, van der Waals and electrostatics in amino residue ASP377. This binding could stop the synthesis of AT-I to AT-II which pathway to hypertension. Caffeic acid has a potential role as anti-hypertension by inhibiting ACE.

1. INTRODUCTION

Hypertension is an abnormal increase in blood pressure, both systolic blood pressure and diastolic blood pressure. Someone was called hypertension, if systolic/diastolic blood

pressure more than 140/90mmHg (normal 120/80mmHg) (Liang & Kitts, 2015).

Hypertension closely related to changes in lifestyle, consumption of foods, decreased physical activity, cholesterol, and stress and others (Suyono, 2006). Ministry of Health Indoensia (2013) reported hypertension become number 3 cause of death after stroke and tuberculosis, where the proportion of deaths reaches 6.7% of the population of deaths at all ages in Indonesia (Tarigan, Lubis, & Syarifah, 2018).

Treatment hypertension by the blocking of angiotensin converting enzyme (ACE) which located in the surface of the vascular endothelium. ACE has functional in regulating blood pressure and cardiovascular function (Upadhyay & Mohan Rao, 2013). Hypertension is one of factor to Type 2 Diabetes Mellitus. In Case of high glucose showed has different profile protein compare with normal conditions (case of Type 2 Diabetes Mellitus) (Bare & Fatchiyah, 2018; Bare, Marhendra, Sasase, & Fatchiyah, 2018).

Phenolic compounds from plant leaves are a potential resource of ACE inhibitors. Oboh et al., (2014) found phenolic extracts from jute leaf and sandpaper leaf exhibited inhibitorye ffecton ACE in vitro as well as in high cholesterol diet fed rats. This mechanism highlight anti-hypertensive property, which could lay credence to its use in traditional medicine.

Chlorogenic acid one of group phenolic compounds that contained in Robusta green coffee (Adriana, 2012). Caffeic acid and quinat acid were hydrolyzed from chlorogenic acid when coffee roasted process (Aziz, 2009). Bare, Kuki, Rophi, Krisnamurti, & Lorenza, (2019) found quinat acid has a potential as an inhibitor in COX-2.

In this papers, we concern to investigate and analysis of potential chemical compound caffeic acid as an anti-hypertension by to inhibit ACE by molecular docking analysis.

2. MATERIALS AND METHODS

Procedures

3D structure ACE (ID: 3bkk) was taken from database Protein Data Bank (www.rscb.org), whereas chemical structure of caffeic acid (CID: 1794427) was taken from the database of PubChem.com. Structure of caffeic acid was minimized of energy by PyRx Virtual screening tool Open Babel tool. Removing water molecules, which incorporated ACE used Discovery studio. Caffeic acid, which formed SDF file format, converted to PDB format by in PyRx Virtual screening software.

Data analysis

Interaction between caffeic acid and ACE were docked. Moleculer docking ligand and protein were established by using the Hex 8.0.0 software. Visualization and analysis data from the molecular interactions of caffeic acid and ACE in the Discovery Studio Client 4.1 software (Meidinna & Fatchiyah, 2019)

3. RESULTS

Interaction between caffeic acid and ACE showed binding site amino acid residue. We found amino acid residues that interacted with the caffeic acid were ASP377, ASN277, ASN285, GLU376, ALA170, ASN167, ASN374, THR372, THR166, CYS370, GLU162 and PRO163 domain A (Figure 1). Hydrogen bond showed in THR372, GLU162, ASN167, and THR372 with the type of conventional hydrogen bond, carbon hydrogend bond and Pi-Donor Hydrogen Bond. . Van der Waals interactions in residue amino acid ASN277, ASN285, GLU376, ALA170, ASN374, THR166, CYS370, and PRO163. These interactions make stronger the binding of caffeic acid and ACE was performed. Interestingly, we found one electrostatics in amino residue ASP377 (Figure 1). Energy binding was formed -203.28 cal/mol.

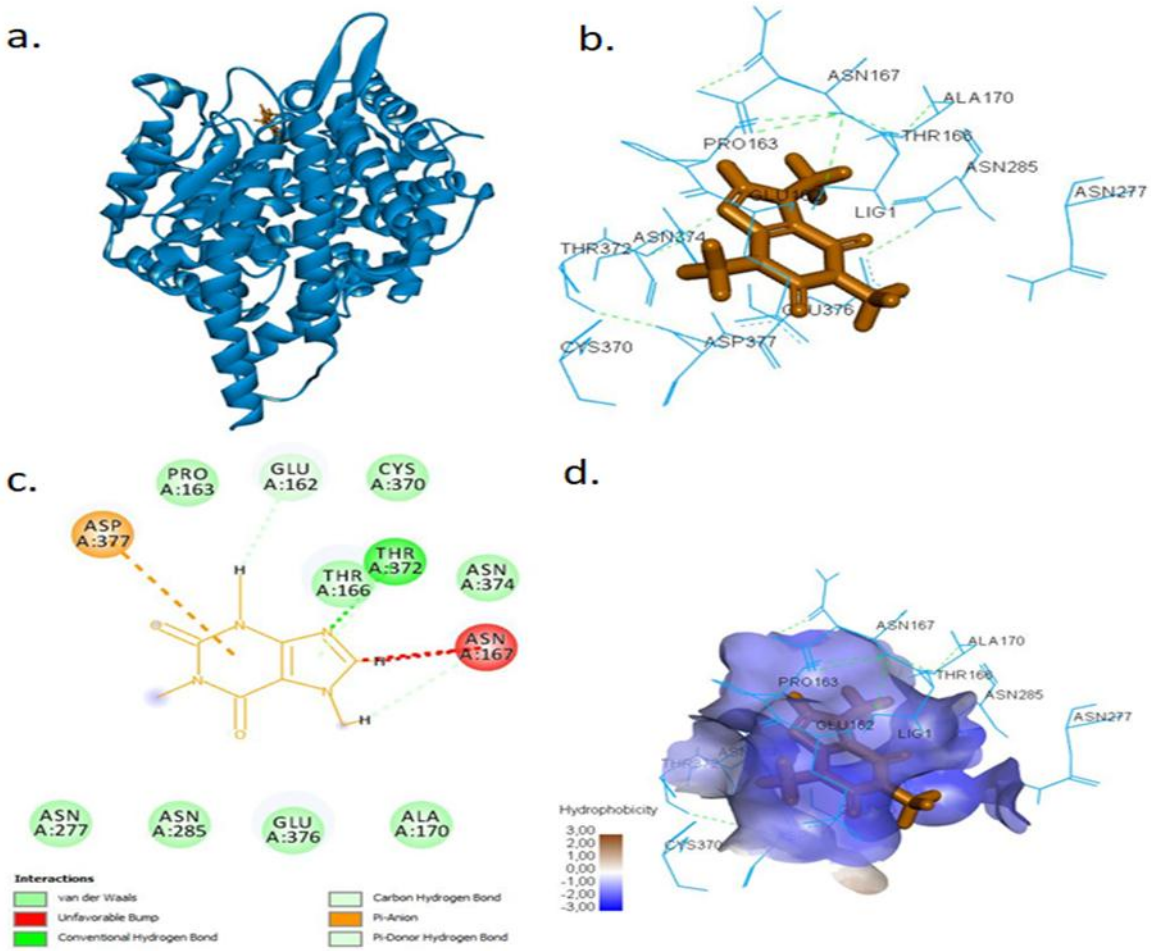

Figure 1. Molecular interaction between Caffeic Acid and ACE. a. Ligand and Protein interactions, b. 2D structure interaction, c. 3D structure interaction, d. Hydrophobicity complex

4. DISCUSSION

Caffeic acid has role to inhibit ACE. This inhibition correlated with ACE function. ACE inhibitors have been widely developed to prevent angiotensin II production in cardiovascular diseases. Angiotensin II, an important oxidant, alters the binding of LDL-C to its receptors and increases endothelial uptake of LDL-C. Therapy with ACE inhibitors appears to eliminate this untoward effect (Oboh et al., 2014).Hydrogen bond formations, which formed between ligan-protein, most important for proper binding of ligand within the enzyme (Kataria & Khatkar, 2019).

Table 1. Interaction Caffeic Acid and ACE protein

Complexes	Energy (cal/mol)	Name	Distance	Category	Types	from chemistry	to chemistry
Caffeic acid-ACE	-203.28	A:THR372:HG1 - :LIG1:N	2,25929	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		:LIG1:H -	2,22174	Hydrogen	Carbon	H-Donor	H-

A:GLU162:OE1		Bond	Hydrogen Bond		Acceptor
:LIG1:H - A:ASN167:OD1:B	2,90338	Hydrogen Bond	Carbon Hydrogen Bond	H-Donor	H-Acceptor
A:ASP377:OD1 - :LIG1	4,52364	Electrostatic	Pi-Anion	Negative	Pi-Orbitals
A:THR372:HG1 - :LIG1	2,94261	Hydrogen Bond	Pi-Donor Hydrogen Bond	H-Donor	Pi-Orbitals
A:ASN167:OD1:B - :LIG1:C	2,20159	Unfavorable	Unfavorable Bump	Steric	Steric
:LIG1:H - A:ASN167:OD1:B	1,72546	Unfavorable	Unfavorable Bump;Carbon Hydrogen Bond	Steric;H-Donor	Steric;H-Acceptor

Phenolic compounds have the potential to inhibit the activity of ACE with varying doses. Agunloye & Oboh, (2018) reported dosage caffeic acid for ACE inhibitory effect is IC50=24.23±0.14µg/mL. The inhibition carried out by caffeic acid in ACE activity is the result of interactions between the phenolic hydroxyl groups and enzymes' active site amino acids via hydrogen bonds. In this research, we found three hydrogen bonds were formed by caffeic acid and ACE interaction. The smaller distance of hydrogen between ACE and caffeic acid to the acceptor lead the hydrogen bond will be stronger than other bonds (Santoso, Atmajaya, & Tirtodiharjo, 2016).

Caffeic acid shows properties which have the function to inhibit ACE by interaction 4 residues amino acid which bind with caffeic acid. They are THR372, GLU162, ASN167, and THR372. Result of the interaction is to obstruct synthesis angiotensin I to angiotensin II. Some analyzed that these effects were due to the blocking of metabolic pathways involved in the process like JAK/STAT cascade or Ras/Raf signaling (Li et al., 2005). Caffeic acid blocked oxidative stress which contributed to the generation of ROS and lead to become hypertension (Actis-Goretta, Ottaviani, & Fraga, 2006; Laiz & Rodrigo, 2016).

5. CONCLUSION

TCaffeic acid has a potential role as anti-hypertension by inhibiting ACE. In this research showed twelve residues amino acid which interactions with the caffeic acid. This binding have potential to block the synthesis of AT-I to AT-II, therefore can reduce the hypertension.

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