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Sophisticated in Silico Molecular Analysis of Tomato (*Solanum lycopersicum L.*) Extract for Modern Hypertension Therapy

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ABSTRACT

Introduction: Hypertension is a dangerous disease and is called the "Silent Killer" because it can make people who suffer from it experience death. It's a line with medication of hypertension can cause many serious side effects.
Methods: The research sample is obtained through the extraction of Oleic acid amide and Lycopene from tomatoes. After which the tomato fruit extract will be tested for its content using phytochemical tests and GCMS. Then an analysis of the compounds shown in the extract was carried out using the in silico method to decide the prediction of the interaction between the ligand and the active site of the target protein.
Results: Based on the phytochemical and GC-MS tests, it shows that tomato extract has three dominant metabolites. They are lycopene 10.93 RT^{-1} (min), oleic acid amide (Andogen 73) 28.75%, 9-octadecenoic acid 27.59 RT^{-1} (min) and etc. The docking results showed oleic acid amide has bigger binding affinity was 16.3 (kcal/mol). The results of the docking of oleic acid and captopril showed the best binding affinity values, namely -6.3 kcal/mol and -6.0 kcal/mol, respectively. The results show that more amino acid residues from oleic acid amide bonds with ACE are produced, indicating that the ligand is suitable for binding to the active site of the target protein. Consequently, oleic acid amide of tomato interacted more with the target protein as an antihypertensive than captopril. In other hand, lycopene was contributing to be anti-aggregation properties of hypertension patients.
Conclusion: It can be concluded that the oleic acid amide and lycopene in tomatoes has the potential to be a modern therapy for hypertensive patients. This aims to determine which metabolite compounds in tomato extract are more evidence at binding to target proteins as candidates on treating hypertension

Keywords: In Silico, Oleic Acid Amide, Lycopene, Tomato, Hypertension.

INTRODUCTION

Hypertension is a dangerous disease and is called the "Silent Killer" because this disease can make people who suffer from it experience death and even tend to experience no symptoms at all. Hypertension is a type of non-communicable disease with a very high

level of morbidity and mortality.[1] This situation occurs when a person's blood pressure is above normal, more than 140 mmHg for systolic and 90 mmHg for diastolic. Globally, based on data from the World Health Organization (WHO) in 2019, it was noted that the prevalence of hypertension in the world reached 22% of the total population in the world. It turns out that Southeast Asia is in third place with the highest prevalence of hypertension cases, which is 25%.[2]

Hypertension is still a frightening terror for the entire world's population, and it is estimated that its prevalence continues to increase every year. Hypertension does not only affect old people, but the disease does not look at age, even based on existing data, one of the highest causes of death at a young age is due to hypertension. This disease tends to have a high prevalence in developing countries[3]

In Indonesia, based on data from the Ministry of Health, the prevalence of hypertension in Indonesia is 34.1%, which has increased from the previous year. Cardiovascular disease if not treated immediately can cause more severe complications to other vital organs and can even cause death.[4]

Hypertension occurs due to the formation of angiotensin II from angiotensin I by Angiotensin 1 Converting Enzyme (ACE) which plays an important physiological role in regulating blood pressure. Basically hypertension is not a disease that can be transmitted because it is a non-communicable disease, but this disease can be passed down through genetic pathways. However, someone who has hereditary hypertension can prevent it by continuing to control blood pressure and maintain a healthy lifestyle.[5]

When viewed from the lifestyle of adolescents and young people who are currently in a productive period, there are many of them who ignore the importance of maintaining a healthy body, starting from the habit of smoking, staying up late, eating fast food, even the habit of being lazy can also be a risk factor for someone suffering from diabetes. hypertension. So it's no wonder that the prevalence of hypertension cases continues to increase and is increasing every year and is a disease with the highest cause of death in the world.[6]

Not only that, someone who has been diagnosed with hypertension must regularly take medication that aims to keep the sufferer's blood pressure stable. Based on the Ministry of Health (KEMENKES) regarding the prevalence of hypertension, 13.3% of patients diagnosed with hypertension did not take medication. From these data it shows that almost the majority of hypertensive patients are not compliant in taking medication so they do not get optimal treatment.

There are many factors for a person to become non-adherent in taking antihypertensive drugs.[7] Some of the reasons why people with hypertension do not take medication include because people with hypertension feel they have no symptoms, forget to take their medicine, are afraid of side effects, and are bored with the habit of taking medication so that most people with hypertension are disobedient in taking medication which can cause complications and even death.[8] Based on the problems above, we present a solution to help reduce hypertension rates and create antihypertensives by tomato (*solanum lycopersicum l.*),

Tomatoes contain lycopene which can help lower blood pressure. In a meta-analysis study concluded that lycopene can lower blood pressure and is considered efficient for the treatment of high blood pressure.[9] The tomatoes used as a source of lycopene in this study contained most of the lycopene compounds in them. In one study, the effective lycopene requirement for reducing hypertension was greater than 15 mg. Tomatoes contain very high lycopene compounds, up to 30-150 mg of lycopene in them, so they are considered effective as antihypertensives.[10]

The purpose of this research is to analyze and prove the content of the tomato fruit,

which can be used as a therapy for patients with hypertension.

MATERIALS & METHODS

The research was conducted on August 7th-21st, 2023 at Natural Materials Laboratory, Faculty of Mathematics and Natural Sciences and Bioinformatics Laboratory, Faculty of Medicine, Andalas University.

Research Material

The samples used in this study were fresh tomatoes obtained from the Raya market in Padang, West Sumatra. Samples were washed and cut into small pieces, then dried in an oven at 60°C until dry. After drying, the sample is blended until smooth and forms a powder.

Product Equipment & Materials

The tools used in this study included: glassware, bowl, analytical scales, oven, stirrers, blenders, spoons, knife, filters, erlenmeyer, beaker glasses, and rotary evaporator.

The materials used in this study included: tomato extract/ tomato powder, and stevia.

Research Methods

1. Extraction of tomato (*Solanum lycopersicum L.)*

The extraction process is carried out in several stages. These stages include (1) sorting, (2) simplicia production, (3) tomato extraction using the 96% ethanol maceration method, and (4) distillation using a rotary evaporator.

2. Phytochemical screening of tomato extract

a. Alkaloids Test

Extract was mixed with 1% alkaline ammonia water and chloroform in the test tube. The chloroform layer (bottom layer) was absorbed and HCl added. Divide the blank into three parts and do the rest with Meyer's reagent and Dragendorff's reagent, respectively. A positive result is mixed with Mayer's reagent to give a white color and Dragendorf's reagent to give a cloudy and orange color.

b. Tannin Test

Extract in a test tube with a small amount of distilled water, heat in a water bath, and add dropwise a 1% (1:1) gelatin solution. The formation of a white precipitate indicated the presence of tannins.

c. Carotenoid Test

Extract was mixed with 10 mL of chloroform solution in a test tube and shaken vigorously. The resulting mixture was then filtered and added to an 85% H2SO4 solution. A blue-colored solution formed on the surface indicates the presence of carotenoids.[11]

d. Flavonoids Test

Extract was taken into a test tube and mixed with a few magnesium powders, and concentrated HCl was added dropwise. The best result indicating the presence of flavonoids is the attractive yellow-red color.

e. Saponin Test

The extract is dissolved in 10 ml of distilled water and heated in a water bath. After cooling, the solution in the tube is shaken for ± 30 seconds. After adding 1 drop of dilute HCl, continuous foam will be formed, and the formation of stable foam even after 30 minutes was taken as an indication of the presence of saponins.

3. GC-MS Analysis

Gas chromatography-mass spectrometry (GC-MS) is a combination of two methods for analyzing different compounds contained in analyte samples based on the separation of a volatile substance.[12] GC-MS analysis was carried out using a GC-MS QP2010 plus equipped with a hydrogen ionization detector (FID). The extract was injected in split mode at 250°C for 3 minutes using an internal 0.75 mm inlet to reduce the maximum pressure. Chromatographic separation was carried out on a 30 m 0.25 mm DB-WAX analytical column (J&W Scientific, Folsom, CA) with helium as carbon monoxide at a constant rate of 0.8 ml/min. The oven temperature was set at 60°C for 5 minutes, then increased from 100°C per minute to 280°C (10 minutes). The FID temperature is set at 250°C.[13]

4. Molecular Docking

a. Ligand Preparation

From the results of the GC-MS test, researchers chose the five most abundant compounds contained in tomatoes, including lycopene (CID: 446925); captopril (CID: 44093); oleic acid amide (CID: 5283387); cis-9 octadecenoic acid (CID: 445639); 3,5-dimethyloctane (CID: 139989); and 9-octadecenoic acid (CID: 445639). These compounds were obtained from the PubChem database in SDF format. The energy of ligands were minimized and converted to the data format from SDF to PDB format with PyRx software.

b. Protein Preparation

The protein structure was obtained from the Protein Data Bank as ACE (PDB ID: 1UZF). The protein was then prepared using BIOVIA Discovery Studio 2019 to remove the ligands and water molecules.

c. Docking & Visualization

Docking was performed by PyRx software to estimate binding energy and possible ligand-receptor interactions. Placement results are shown after using BIOVIA Discovery Studio version 19.

RESULT

1. Phytochemical Test

Phytochemical analysis of tomato extracts aimed to identify secondary metabolites found in onion skin. The results of the phytochemical analysis of onion skin are shown in table 1.

Table 1. Result of phytochemical test

No	Metabolites	Result
1	Alkaloids	+
2	Flavonoids	+
3	Tannin	+
4	Carotenoid	+
5	Saponin	+

Ex: Detected (+)
Not detected (-)

From the result of 96% ethanol extract phytochemical tests, it can be seen that tomatoes contain secondary metabolites which are alkaloids, flavonoids, tannins, carotenoid, and saponins.

2. Screening of Metabolites by GC-MS

The results of GC-MS analysis on tomato extract obtained the following chromatographic spectra.

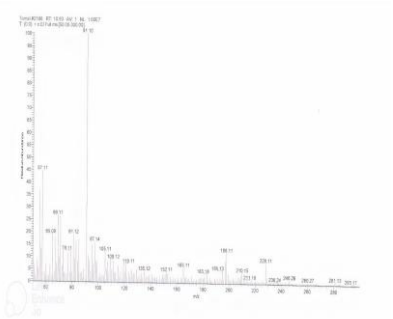


Figure 1. GCMS analysis results of tomato extract

According to the spectral chromatography results above, several fragments were identified with a retention time of 10.93. The pattern of these fragments resembles one of the basic dihydroxy lycopene fragments with the highest peak of the molecular ion m/z 91. This molecular ion is a fragment of an acyclic carotenoid compound that exhibits the characteristics of a lycopene compound with a maximum of 100%.[14]

In addition to the lycopene compound contained in tomato extract. The GC-MS results for other fragment compounds are also reflected in the chromatograms. In a study by Ibrahim *et al.*, the volatile profile of tomato fruit was determined from GC-MS results, so that twenty-eight metabolites were identified in tomato extract. Out of the results, the five dominant metabolites are listed in Table 2, as below.[15]

Table 2. Result of GC/MS analysis of tomatoes extract

RT^{-1} (min)	Volatile metabolites
6.34	3,5-Dimethyloctane
10.93	Lycopene
27.09	Cis 9-Octadecenoic acid
27.59	9-Octadecenoic acid
28.75	Oleic acid amide (Adogen 73)

3. Docking Test

In an in silico analysis study conducted. We took several ligands to be used for molecular docking. This aims to determine which metabolite compounds in tomato

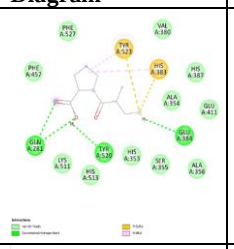
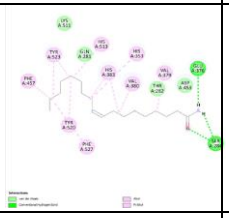
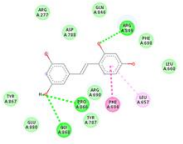
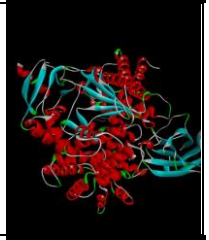
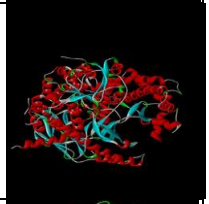
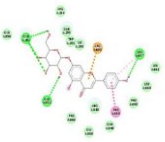
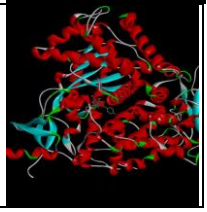
extract are more effective at binding to target proteins as candidates for treating hypertension. For the blood pressure-lowering pathway, we used the protein angiotensin-converting enzyme (ACE) for specific ligand targeting. Some secondary metabolites can lower blood pressure by inhibiting the activity of the angiotensin-converting enzyme (ACE). The following results of molecular docking are listed in table 3.

Table 3. Molecular docking results.

Compound Name	Binding Affinity (kcal/mol)
Captopril	-6.0
3,5-Dimethyloctane	-4.9
Lycopene	-2.5
Oleic acid amide	-6.3
Cis 9- Octadecenoic acid	-5.9
9- Octadecenoic acid	-5.9

The molecular docking performed is useful for predicting the molecular mechanism that occurs between the ligand and ACE so that it can act as a blood pressure-lowering agent. The binding energy calculated from the docking results predicts the strength of the bond between the ligand and the ACE protein. The strength of the interaction between two or more molecules is measured by binding energy. The lower the affinity between the receptor and ligand, the higher the binding energy value. On the other hand, the lower the binding energy value, the higher the affinity between the receptor and the ligand (Kastritis and Bonvin, 2012).[16]
The docking results between lycopene, the most abundant compound contained in tomatoes and the ACE target protein resulted in a high binding affinity of -2.5 kcal/mol. This value is greater than the value of the other five compounds. However, the best docking results show a lower binding affinity for larger binding energies. Meanwhile, the results of the docking of oleic acid and captopril showed the best binding affinity values, namely -6.3 kcal/mol and -6.0 kcal/mol, respectively. Docking between oleic acid and ACE produces eleven amino acid residues consisting of two types of bonds. One hydrogen bond occurs in the amino acids Ser284 and Glu376, while the hydrophobic bonds with the Pi-Alkyl type produce nine amino acid residues, namely Val379, Val380, His353, His383, Phe457, His513, Tyr520, Tyr523, and Phe527. Compared with the results of the ligand comparator, namely captopril, it produces five amino acid residues when it binds to ACE. Hydrogen bonds occur in the amino acids Tyr520, Glu384, and Gln281, while other bonds, namely hydrophobic bonds with the pi-sulfur type, produce residues of the amino acids His383 and Tyr523. The results of the docking visualization can be seen in Table 4 below.

Table 4. Molecular Docking Visualization

Ligand	2D Protein-Ligand Interactions Diagram	Binding Location
Captopril (Drug control)		
Oleic acid amide		
Oxyresveratrol (Drug control)		
Hesperidin		
β- Pinene		

Between these two ligands, there are several differences in the binding activity of the active site on ACE. This is compared to captopril as a control drug, which produces almost the same amino acid residues as oleic acid amide. The oleic acid amides have a lower binding affinity (-6.3 kcal/mol) than the control drugs (-6.0 kcal/mol). The results show that more amino acid residues from oleic acid amide bonds with ACE are produced, indicating that the ligand is suitable for binding to the active site of the target protein. The more amino acid residues produced, the better the position of the ligand at the ACE active site. When a compound or ligand has the same residual interaction activity as the native ligand, it will have a lower binding affinity value so that it is more tightly bound to the target protein.[17]

Table 5. Result comparison between comparator ligands and

Ligand	Binding Affinity (kcal/mol)	Chemical Interaction	Amino Acid Residue
Captopril (Drug control	-6.0	Hydrogen bond	Tyr520, Glu384, Gln281
		Hydrophobic bond	His383, Tyr523
Oleic acid amide	-6.3	Hydrogen bond	Ser284, Glu376
		Hydrophobic bond	Val379, Val380, His353, His383, Phe45, His513, Tyr520, Tyr523, Phe527

DISCUSSION

Hypertension is defined as two measurements in which systolic blood pressure is greater than 140 mmHg and diastolic blood pressure is greater than 90 mmHg.[18] One of the largest risk factors for heart disease is high blood pressure. 18.6 million fatalities worldwide are attributable to heart disease. Additionally, this fatality represents a third of all fatal infections.[19]

Several studies indicate that oral supplements containing extracts of tomatoes significantly decrease blood pressure.[20] The content contained in tomatoes has the effect of reducing blood pressure. Tomato (*Solanum lycopersicum*) contains various bioactive compounds, such as carotenoids, vitamin A, calcium, and gamma-aminobutyric acid, which play a role in preventing cardiovascular diseases such as hypertension and other complications.[21] One of the rich ingredients in tomatoes is lycopene. Lycopene is a type of carotenoid pigment that causes a red color. It is not only responsible for its red color-giving pigment but also has health-promoting properties.[22] Effect of giving a tomato nutritional complex containing 15 mg and 30 mg of lycopene to reduce systolic blood pressure in hypertensive patients.[23]

Based on phytochemical tests, tomato extract contains alkaloids, flavonoids, tannins, saponins, and carotenoids. Flavonoid compounds contained in tomatoes can act as antioxidants and also play a role in lowering blood pressure.[24-25] In addition, the carotenoid found in tomatoes, namely lycopene compounds, is one of the compounds that also plays a role in reducing blood pressure. In this study, we chose lycopene as the main compound in the docking test because of its abundance in tomatoes. We use ACE as the main target. However, the docking results showed that lycopene has a higher binding affinity than other compounds. This means that the strength of the interaction between the ligand and the protein is low. We assume that the ligand in the form of a lycopene compound cannot be targeted to the ACE pathway, but there are other pathways that play a role in lowering blood pressure.

Lycopene is an antioxidant that can absorb single oxygen molecules (free radicals) two times better than alpha-tocopherol. Through this pathway, lycopene lowers blood pressure through its role as an antioxidant. Lycopene prevents free radicals from causing oxidative stress, which then triggers the production of nitric oxide in the

endothelium and improves vascular function, causing systolic blood pressure to decrease.[26]

Research conducted by Engelhard et al. found a significant reduction in systolic and diastolic blood pressure in patients with type 1 hypertension who received short-term treatment with 250 mg of tomato extract.[27] The bioactivity of lycopene compounds in tomatoes proves that this fruit has anti-platelet aggregation properties. In a randomized trial study, tomato extract was able to reduce ADP and collagen-induced platelet aggregation.[28] Lycopene contributes to its anti-aggregation properties and has the potential to reduce lipid levels, lower blood pressure, and reduce the risk of cardiovascular disease.[29]

Apart from lycopene, the content contained in tomatoes is oleic acid amide, as indicated by the GC-MS results. After molecular docking analysis, the interaction between oleic acid amide and the ACE pathway protein showed a better prediction of the binding of ligands and proteins to lower blood pressure. A study has been conducted to examine the effect of a dose of tomatoes plus olive oil, which also contains oleic acid.[30] The results show that the intervention can reduce plasma cholesterol and triglycerides. Tomato extract added to olive oil produces maximum effect due to increased lycopene bioavailability, which is improved by oleic acid. The addition of olive oil to tomato juice makes lycopene easier to absorb because it facilitates lycopene's movement towards the lipophilic phase, making it more bioavailable. More optimal absorption of lycopene results in a greater reduction in blood pressure.[31]

CONCLUSION

Hypertension is one of the causes of death from cardiovascular disease in the world. This is because hypertension, with its nickname “The Silent Killer” is a disease that is silently deadly. It is likely that sufferers are asymptomatic, but in fact, it actually worsens their condition. Every year, this case increases, and regardless of age, it attacks various age groups. Lycopene can be a solution to existing problems because the activity of lycopene in tomatoes can be antihypertensive. Not only that, after carrying out the in-silico test, it turned out that tomatoes also contain oleic acid, which turns out to also have a role as an antihypertensive. Therefore, researchers believe that lycopene and oleic acid can be one of the efforts to reduce the incidence and death due to hypertension.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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