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Analysis of Molecular Interactions of 8-Gingerol Compounds in Ginger (*Zingiber officinale*) as ACE Inhibitor

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Background: Hypertension is a disease with increasing characteristics of blood pressure. The ACE gene has a role in the conversion of ATI to ATII in hypertensive conditions. Healing is done by using the 8-gingerol content contained in ginger. The purpose of this study was to analyze the molecular interaction between 8-gingerol and ACE. **Method:** ACE model proteins (ID: 3bkk) was obtained from Protein Data Bank (PDB), and 8-gingerol ligands (CID: 168114) was obtained from the PubChem database. ACE and 8-gingerol were docked by Discovery Study Client 4.1 software. Analysis of amino acid residues, binding energy, van der Waals forces, and hydrogen bonds was performed by using Discovery Studio Client 4.1. **Result:** The interaction between 8-gingerol and ACE showed that seven amino acid residues interacted with 8-gingerol, also found hydrogen bonds, hydrophobic and Van der Waals forces that strengthen and stabilize these bonds. **Conclusion:** the interaction of 8-ginger with the playful side of ACE was determined as an ACE inhibitor, the inhibition was a significant effect on the obstruction of ACE conversion.

Analisis interaksi molekuler Senyawa 8-gingerol dalam Jahe (*Zingiber officinale*) sebagai ACE inhibitor

Kata kunci:
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A B S T R A K

Background: Hipertensi merupakan penyakit dengan karakteristik tingginya tekanan darah yang disebabkan beberapa faktor salah satunya secara genetik. Gen ACE memiliki peran dalam konversi ATI menjadi ATII dalam kondisi hipertensi. Penyembuhan dilakukan dengan menggunakan kandungan 8-gingerol yang terkandung dalam jahe. Tujuan penelitian ini adalah menganalisis interaksi molekuler yang terjadi antara 8-gingerol dan gen ACE. **Metode:** Protein model ACE (ID: 3bkk) diperoleh dari database Protein data Bank (PDB) sedangkan ligan 8-gingerol (CID: 168114) diperoleh dari database PubChem. Docking ACE dan 8-gingerol menggunakan perangkat lunak Discovery studio Client 4.1. Analisis residu asam amino, energi yang berikatan, gaya van der Waals, dan ikatan hidrogen yang terbentuk menggunakan Discovery Studio Client 4.1. **Hasil:** Interaksi antara 8-gingerol dan ACE menunjukkan adanya tujuh residu asam amino yang berinteraksi dengan 8-gingerol, ditemukan juga ikatan hidrogen, hidrofobik dan gaya van der Walls yang menguatkan dan menstabilkan ikatan tersebut. **Kesimpulan**: Interaksi 8-gingerol dengan sisi aktif ACE berpotensi sebagai ACE inhibitor, penghambatan tersebut berdampak terhadap terhambatnya konversi ACE.

Introduction

Hypertension defined as a high blood pressure condition, namely 140/90 mmHg (Dipiro et al., 2017). Increased blood pressure causes cardiovascular disease (Chobanian, 2004). In Indonesia, hypertension is the disease with the third-highest total mortality (Tarigan et al., 2018). Some of the risk factors that can cause hypertension are genetic factors, being overweight, excess sodium intake, dyslipidemia, lack of physical activity, and vitamin D deficiency (Dharmeizar, 2012). In T2DM, a

different amount of band protein was obtained during inflammatory conditions than normal (Bare et al., 2018). Therefore, handling specific handling. One of the genetic risk factors for hypertension is the activation of the Angiotensin-converting enzyme (ACE) gene. The ACE gene has a role in regulating the renin-angiotensin system, which is transforming angiotensin-I (ATI) to angiotensin-II (ATII); this gene also has a role as a hydrolyzer and a vasodilator protein (Ouwerkerk et al., 2017). ACE activation must be in order to reduce and inhibit hypertension.

Hypertension treatment is carried out by providing synthetic drugs, but it is predicted to have side effects. Therefore, it is necessary to research by looking for ingredients from natural anti-hypertensive drugs with records that can inhibit angiotensin-converting enzymes, angiotensin receptor blockers, and beta-block or calcium channel blockers. The treatment system uses natural ingredients that do not have small toxicity when compared to synthetic drugs; these compounds can increase physiological activity and have a good effect on users because the interactions that occur reduce the effect on the body (Krisnamurti et al., 2020; Sari & Bare, 2020).

Ginger (*Zingiber officinale*) is a home garden plant in Sikka Regency known as "Lea." According to the stories of the Sikka people, they believe that ginger can treat various diseases. A literature study found that ginger's polyphenol content has pharmacological properties (Mao et al., 2019). The ginger rhizome with the largest polyphenol component consists of 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerol, 12-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, fl flavonoids (Mao et al., 2019). Several research studies of ginger as a medicine are the content of 6-gingerol, 6-shogaol, and 8-shogaol compounds as JNK inhibitors (Bare et al., 2020; Tiring et al., 2019). This study examines JNK inhibitors, and there is no information on the study of molecular interactions between 8-gingerol and the ACE gene. Therefore, this study aims to analyze the activity of 8-gingerol in ginger as an ACE inhibitor in reducing the prevalence of hypertension in Indonesia.

Methods

ACE and 8-gingerol Data Collection

The ACE model protein (ID: 3bkk) was obtained from the Protein Data Bank (PDB). ACE is cleaned of water molecules and binding ligands using PyMol software. The 8-gingerol ligand (CID: 168114) was obtained from the PubChem database. The 8-gingerol ligand energy was minimized using PyMol Open Babel, and then the ligand file was converted into pdb form.

ACE docking and 8-gingerol

ACE docking and 8-gingerol contained in ginger were analyzed using the Discovery studio Client 4.1 server. Energy calculations are performed with each of these servers. The 3D visualization of the docking results was viewed using the Discovery Studio and PyMol programs to analyze amino acid residues, binding energies, van der Waals forces, and hydrogen bonds formed (Bare et al., 2019).

Results

The interaction between 8-gingerol and ACE (Figure 1a) resulted in seven amino acid residues, namely THR166, HIS353, THR372, GLU162, ALA354, VAL380, and ASN167 (Figure 1c-d). The analysis showed that the 8-gingerol-ACE complex formed hydrogen bonds with conventional hydrogen bond types on the amino acid residues THR166, HIS353, and THR372, Pi-Anion type electrostatic bonds were formed on the amino acid residue GLU162, hydrophobic bonds type Pi-Pi T -shaped on the HIS353 amino acid residue and the Pi-Alkyl type on the ALA354 and VAL380 amino acid residues and the unfavourable type unfavourable bump on the ASN167 amino acid residue (Figure 1c-d). In addition, the analysis results also showed the presence of van der Waals in the amino acid residues THR302, ALA170, PRO163, LYS511, TRP279, GLN369, ASP377, GLU376, ASN374, ASN285, and THR171 (Figure 1c-d). The energy produced is -302.9 cal/mol (Table 1).

The light blue indicated the shallow hydrophobicity level between the ligand and the protein to the dark blue of the large part of the ligand surface (Figure 2a). The amino acid residues formed to act as donors and acceptors to the ACE model protein (Figure 2b). The interaction formed shows a neutral state with a value of 0 because most of the surface is covered in grey, indicating 0 (Figure 2c-d). The solvent-accessible surface (SAS) value on the 8-gingerol surface shows a very high value, indicated by most of the surface covered by green (Figure 2e).

Discussions

Research by Bare, et al., (2019) found seven amino acid residues that bind to chlorogenic acid-ace compounds, namely the amino acid residues LYS118, ILE204, MET223, ARG124, ALA207, GLU123, and SER219. Interestingly, the interactions that occur between 8-gingerol and ACE also produce seven amino acid residues that interact with different ligands but are active. Hydrogen bonds also support the interactions that occur in the amino acid residues THR166, THR372, and HIS353 and the hydrophobic groups on the amino acid residues HIS353, ALA354, and VAL380.

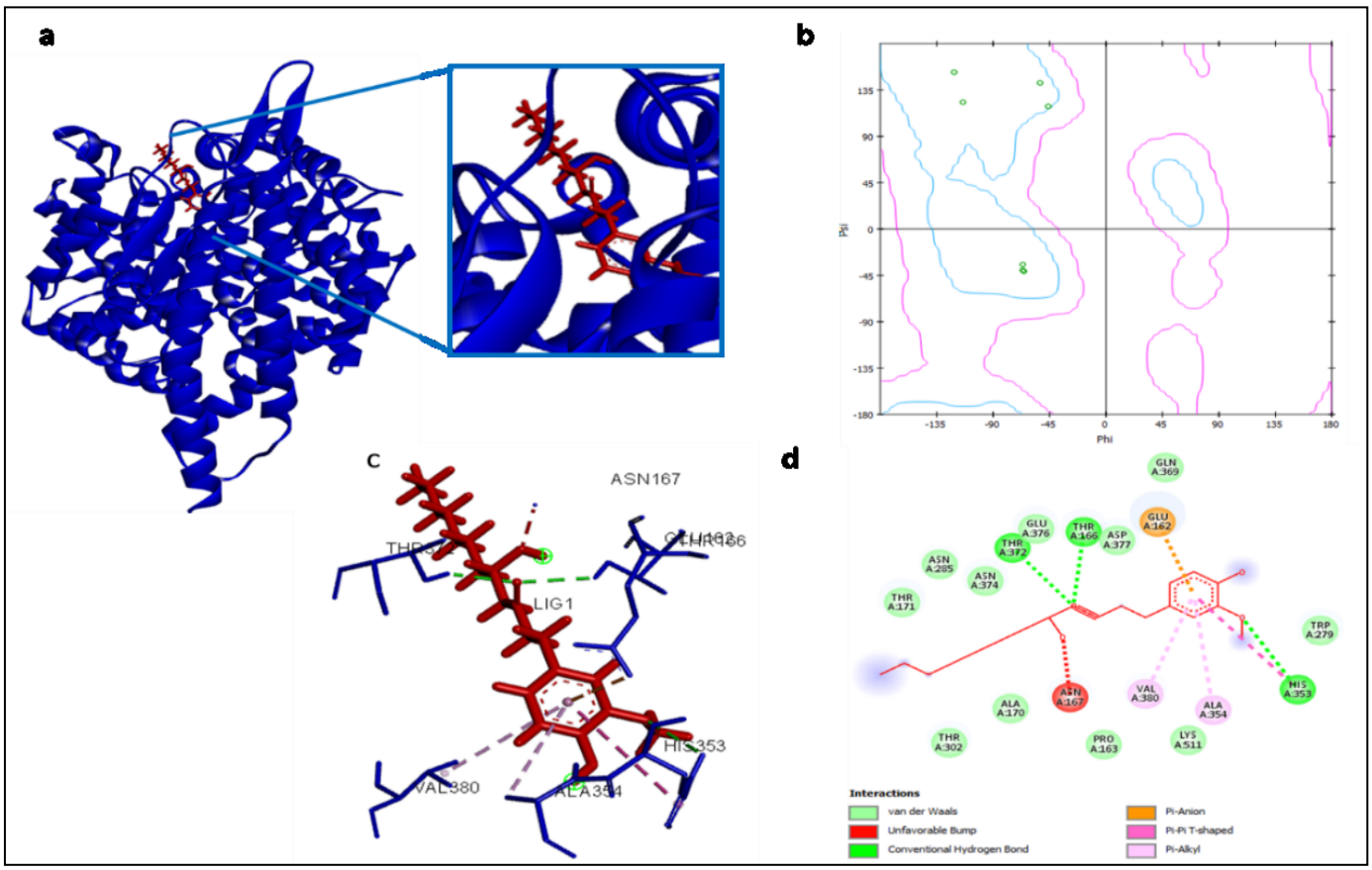

Figure 1. Interaction between 8-Gingerol-ACE (a), 8-Gingerol-ACE interaction, (b), Ramachandran plot 8-Gingerol-ACE (c), 3D of 8-Gingerol-ACE (d), 2D of 8-Gingerol-ACE

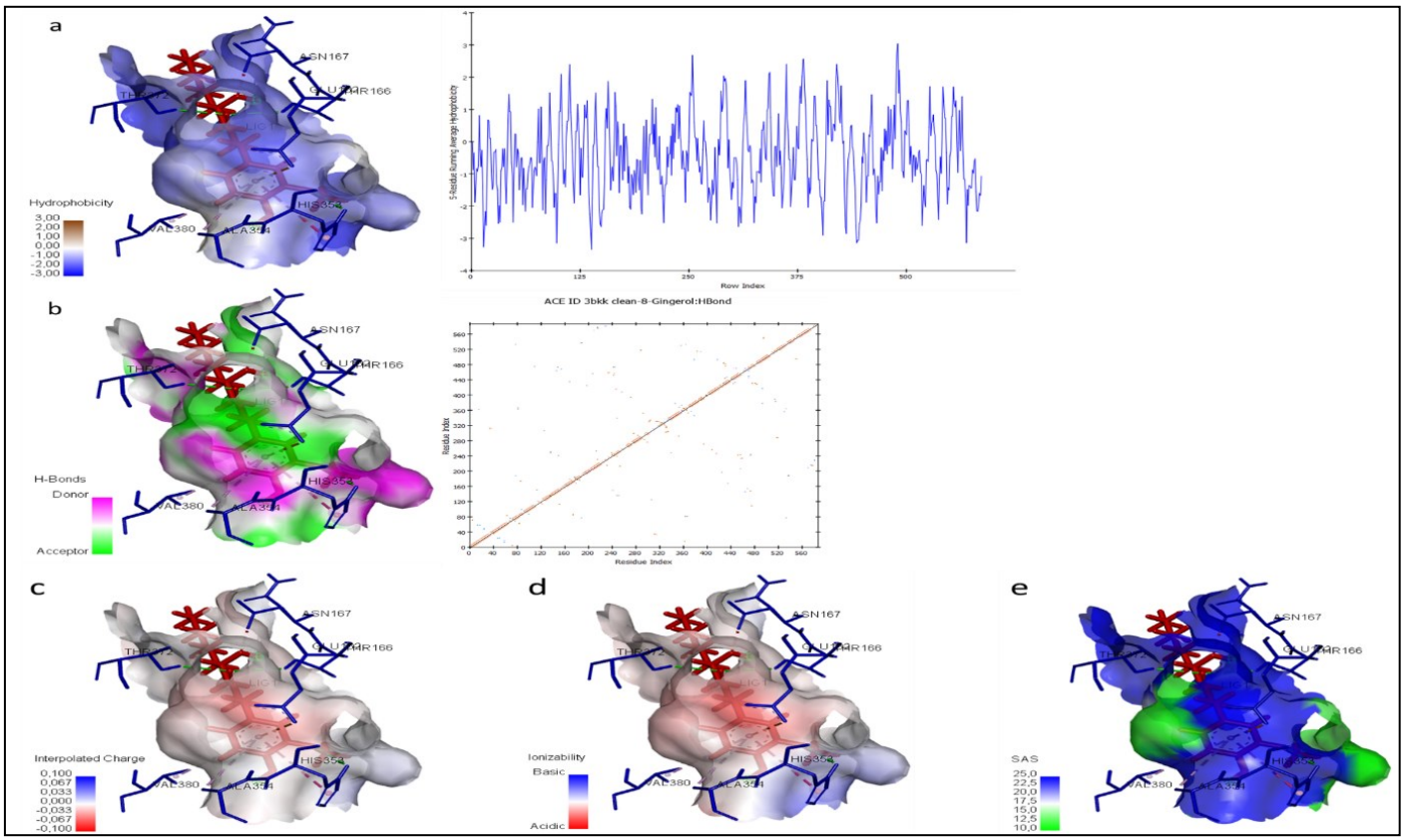

Figure 2. Physochemstry complex of 8-Gingerol-ACE, (a), hydrophobicity and hydrophobicity plot 8-Gingerol-ACE (b), hydrogen bond and 8-Gingerol-ACE bond plot (c), active side charge 8-Gingerol-ACE (d), ionization (e), solvent accessible surface (SAS).

Table 1. Interaction 8-Gingerol and *Angiotensin converting enzyme* I (ACE)

Interaction	Energy (cal/mol)	Name	Distance	Category	Type	Donor	From Chemistry	Acceptor	To Chemistry
ACE-8-Gingerol	-302.9	A:THR166:HG1 - :LIG1:O	2.7386	Hydrogen Bond	Conventional Hydrogen Bond	A:THR166:HG1	H-Donor	:LIG1:O	H-Acceptor
		A:HIS353:HD1 - :LIG1:O	3.0023	Hydrogen Bond	Conventional Hydrogen Bond	A:HIS353:HD1	H-Donor	:LIG1:O	H-Acceptor
		A:THR372:HG1 - :LIG1:O	2.47277	Hydrogen Bond	Conventional Hydrogen Bond	A:THR372:HG1	H-Donor	:LIG1:O	H-Acceptor
		A:GLU162:OE2 - :LIG1	3.09313	Electrostatic	Pi-Anion	A:GLU162:OE2	Negative	:LIG1	Pi-Orbitals
		A:HIS353 - :LIG1	5.73448	Hydrophobic	Pi-Pi T-shaped	A:HIS353	Pi-Orbitals	:LIG1	Pi-Orbitals
		:LIG1 - A:ALA354	5.31979	Hydrophobic	Pi-Alkyl	:LIG1	Pi-Orbitals	A:ALA354	Alkyl
		:LIG1 - A:VAL380	5,.4049	Hydrophobic	Pi-Alkyl	:LIG1	Pi-Orbitals	A:VAL380	Alkyl
		A:ASN167:OD1:B - :LIG1:O	2.12018	Unfavorable	Unfavorable Bump	A:ASN167:OD1:B	Steric	:LIG1:O	Steric

The seven amino acid residues found in the previous study were different from the seven amino acid residues in this study. The active site that binds to the two ligands at different amino acid residues shows the other potential of the 8-gingerol content of the ACE gene. This bond's presence causes an increase in bond strength and maintains the interaction between ligands and proteins (Kataria & Khatkar, 2019; S et al., 2020). Van der Waals forces formed on eleven amino acids (THR302, ALA170, PRO163, LYS511, TRP279, GLN369, ASP377, GLU376, ASN374, ASN285, and THR171) provide additional strength, which affects the energy of the bonds formed. Efficient binding of ligand-protein is supported by various binding types and binding energy (Choi et al., 2000; Jia et al., 2019; Krisnamurti et al., 2021).

Based on the interactions and bonds formed on the amino acids' active site (Figure 1, Table 1), the 8-gingerol compound found in ginger is predicted to have the potential as an ACE inhibitor. Inhibition using ACE inhibitors is thought to play an essential role in treating hypertension (Mao et al., 2019). ACE inhibitor therapy is correlated with health effects Bhullar et al., (2014), because the content comes from nature, making it safer to consume. 8-gingerol compound needs to be combined with other ingredients from ginger to get the best ACE inhibition results. The combination of phytochemical components carries out synergistic activities that impact increasing their biological activity in the body system (Phan et al., 2018; Van Bergen et al., 2013). Treatment systems that inhibit ACE have the potential to inhibit the regulation of the renin-angiotensin system. Seven amino acids were found to have the potential to inhibit angiotensin-I regulation from transforming into angiotensin-II.

Conclusions

The 8-gingerol compound contained in ginger is predicted to have ACE inhibitor properties. There are seven amino acid residues from the ACE protein that can bind to the 8-gingerol compound. The bonds formed between 8-gingerol and Angiotensin-converting enzyme (ACE), namely hydrogen bonds, van der Waals forces, and hydrophobic bonds, are indicated to increase these strengths with energy of -302.9 cal/mol.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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