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Virtual Screening of 8-Gingerol in *Zingiber officinale* Towards Cox-2 Gene

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Abstract. Ginger rhizome has polyphenol component which is 8-gingerol. Recent research showed that the compound has role as anti-inflammation and antioxidant. This study aim to analyze the role of 8-gingerol which interacts with COX-2. This study used in silico analysis. Protein model COX-2 (ID: 6cox) was taken from Protein Data Bank (PDB) database while 8-gingerol (CID: 168114) from PubChem. Docking and visualization of interaction between COX-2 and 8-gingerol using Discovery Study Client 4.1 software. We found 8-gingerol has the potential as an inhibitor of the COX-2 gene as evidenced by the 3 amino acid residues that interact with the ligands on the active site and are supported by van der Waals forces and a bond energy of -340.3 cal/mol.

Keyword: 8-gingerol; anti-inflammation; COX-2; zinger

INTRODUCTION

Inflammation in the body will increase for people with Type 2 Diabetes Mellitus (T2DM). This happened because some of their protein absent compare to health person (Bare et al. 2018). The inflammation that occurs also increases organ damage. One of the genes as a promotror in inflammation of T2DM is COX-2. COX-2 acts as an inflammatory mediator. COX-2 will activate prostaglandin G2 into prostaglandin H2 which can increase inflammation in the body (Kellogg, Cheng, and Pop-Busui 2008). The more protlaglandin H2 is produced, the higher the level of organ damage, therefore it is necessary to do inhibition at the genetic level. Some research showed that natural chemicals compound that inhibit COX-2 by in silico study (Bare, Kuki, et al. 2019; Bare, Sari, et al. 2019; Tiring et al. 2019). Ginger rhizome has the largest polyphenol component consisting of its ingredients, one of which is 8-gingerol (Ghasemzadeh et al. 2018; Mao et al. 2019). Rhizome of ginger (*Zingiber officinale*) is a traditional herbs from Indonesia and known for the potential. It categorized as a medicinal herb because it can treat several health problems such as pain, fever, coughs, cancer, asthma, and has anti bacteria, anti-inflammatory, anti-oxidant properties, hypoglycemic, and hypolipidemic (Bare, Maulidi, et al. 2019; Imtiyaz et al. 2013; Mao et al. 2019; Mohammed et al. 2019; Njobdi, Gambo, and Ishaku 2018; Rehman et al. 2011; Saiah et al. 2017). This study analyzes the active side of 8-gingerol which interacts with COX-2 as a step in inhibiting COX-2 performance.

METHODS

Protein model COX-2 (ID: 6cox) was obtained from Protein Data Bank (PDB) database while 8-gingerol (CID: 168114) from PubChem database. Docking COX-2 and 8-gingerol using Discovery Study Client 4.1 software. The 3D visualization of the docking results was viewed using the Discovery Studio and PyMol programs.

RESULTS AND DISCUSSION

The interaction between 8-Gingerol and COX-2 produces twenty-five amino acid residues that interact with the ligands.

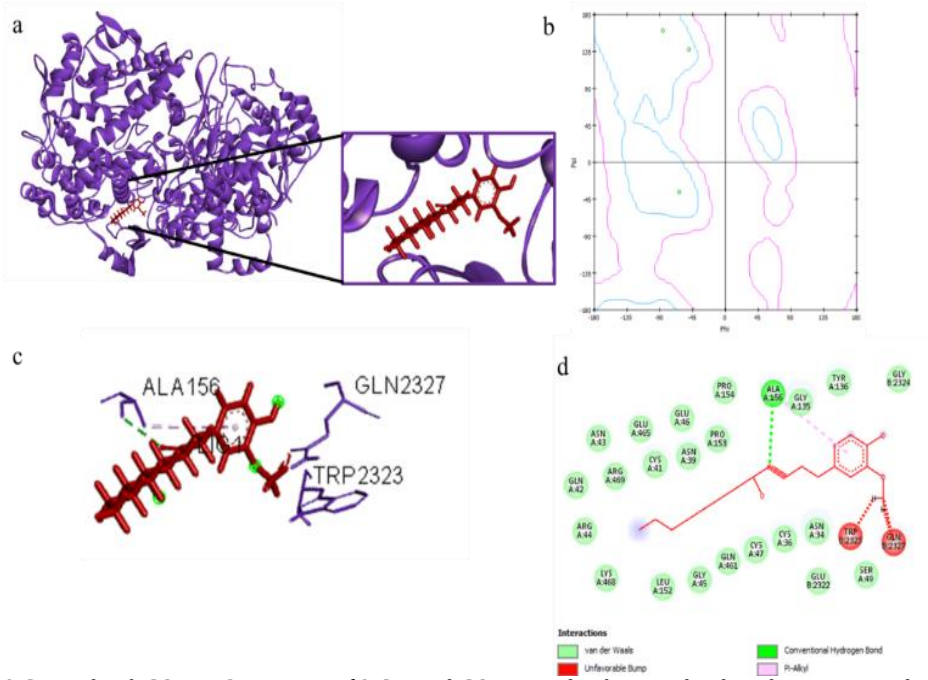

Figure 1. Interaction of 8-Gingerol with COX2, a 3D structure of 8-Gingerol-COX2 complex, b. Ramachandran plot, green triangle shows the active side of COX2 which binds to the bioactive compound Ginger, c. 3D structure of the interaction of the bioactive compounds of ginger and COX2, d. 2D structure.

We found three amino acid residues that binding with 8-gingerol, they divided in some kind of bonds Unfavorable Bump (GLN2327 and TRP2323), and Conventional Hydrogen Bond (ALA156). These interaction formed energy binding 340,3 cal/mol (Table 1). Van der Waals force (ARG44, GLN42, ASN43, ARG469, GLU465, CYS41, ASN39, PRO153, PRO154, GIY135, TYR136, GLY2324, SER49, GLU2322, ASN34, CYS36, CYS47, GLN461, GLY45, LEU152, and LYS468) give some effort to make strength the interaction.

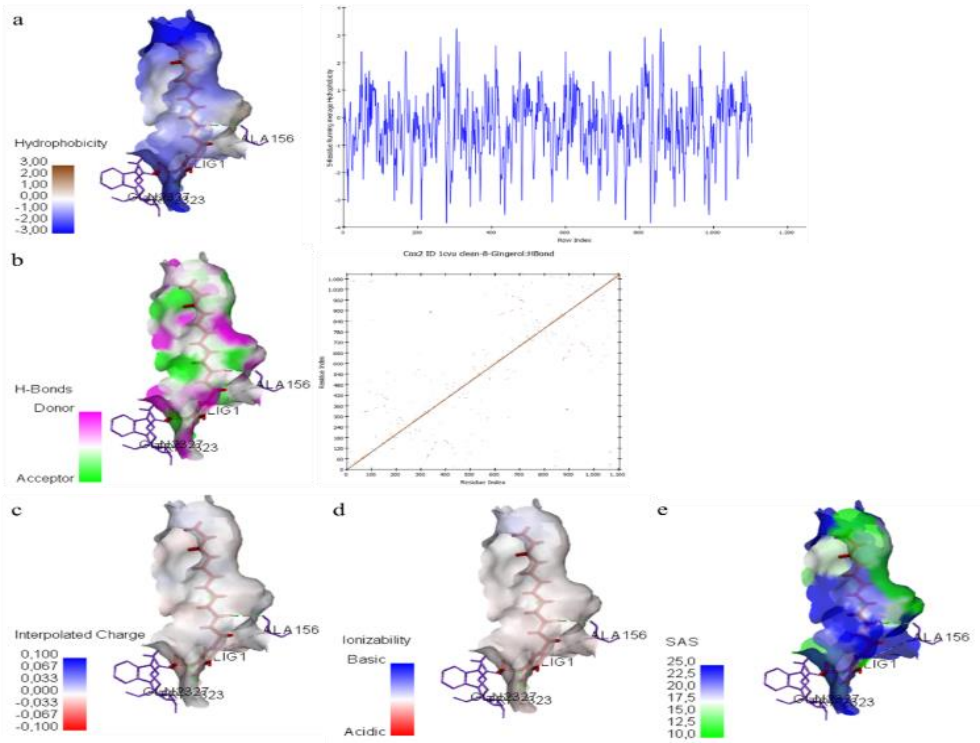

Figure 2. Pharmacochemical characters of the active site of cox2 on the 8-Gingerol-COX2 complex, a Hydrophobicity and hydrophobicity graph of the active COX2 site, b. hydrogen bonding and hydrogen interaction plots, c. COX2 active side load, d. Ionization of the active side of COX2, e. solvent accessible surface.

The interaction between 8-Gingerol and COX2 showed a neutral level of hydrophobicity at the ligand surface (Figure 2a). 8-Gingerol compound functions as a COX-2 donor and acceptor in GLN2327 (Figure 2b and table 1). 8-gingerol compounds tend to be neutral so that the ligands are filled with 0 (Figure 2c and 2d). The absorption of 8-gingerol is quite high (Figure 2e).

Tabel 1. The interaction between 8-gingerol and COX2

Interactions	Energy (cal/mol)	Name	Distance	Category	Types	From Chemistry	To Chemistry
COX2-8 Gingerol	-340.3	A:ALA156:HN - :LIG1:O	3,00022	Hydrogen Bond	Conventional Hydrogen Bond	H-Donor	H-Acceptor
		:LIG1 - A:ALA156	5,45218	Hydrophobic	Pi-Alkyl	Pi-Orbitals	Alkyl
		B:TRP2323:HD1 - :LIG1:H	1,33585	Unfavorable	Unfavorable Bump	Steric	Steric
		B:GLN2327:OE1 - :LIG1:C	2,05648	Unfavorable	Unfavorable Bump	Steric	Steric
		:LIG1:H - B:GLN2327:OE1	1,033	Unfavorable	Unfavorable Bump;Carbon Hydrogen Bond	Steric;H-Donor	Steric;H-Acceptor

The combination or superimpose of those compounds show higher potency as the inhibitor. This research we found GLN2327, TRP2323 and ALA156 that bind with the 8-gingerol. Those compound form a complex binding to the proteins and posed an optimal inhibition the protein. The complexity of these binding also consist of several Van der Waals force that support the interaction and also improve the binding stabilization. In the result also showed that the complex of 8-gingerol has different binding region in COXs. Role of COXs enzyme is essential in metabolism and inflammation in human body. The COX-2 enzyme is one essential factor of inflammation (Ricciotti and FitzGerald 2011; Smyth et al. 2009). High selectivity to COX-2 is a key property for an inflammation drug. The COXs inhibition occurred near the heme-binding or peroxidase site (Simmons 2004), which might indirectly prevent the prostaglandin synthesis (Zarghi and Arfaei 2011). Commonly, reducing pain and inflammation has been done by NSAIDs, such as acetaminophen.

CONCLUSION

8-gingerol has the potential as an inhibitor of the COX-2 gene as evidenced by the 3 amino acid residues that interact with the ligands on the active site and are supported by van der Waals forces and a bond energy of -340.3cal / mol.

REFERENCE

Bare, Yohanes, Agustina Dua Kuki, Apriani Herni Rophi, and Gabriella Candrakirana. 2019. "Prediksi Asam Kuinat Sebagai Anti-Inflamasi Terhadap COX-2 Secara Virtual Virtual Prediction of Quinic Acid As Anti-Inflammation of COX-2." *Biota: Jurnal Ilmu-Ilmu Hayati* 4(3):124–29. doi: https://doi.org/10.24002/biota.v4i3.2516.

Bare, Yohanes, Agung Marhendra, Tomohiko Sasase, and Fatchiyah Fatchiyah. 2018. "Differential Expression of IL-10 Gene and Protein in Target Tissues of Rattus Norvegicus Strain Wistar Model Type 2 Diabetes Mellitus (T2DM)." *Acta Informatica Medica* 26(2):87–92. doi: 10.5455/aim.2018.26.87-92.

Bare, Yohanes, Andri Maulidi, Dewi Ratih Tirto Sari, and Sri Sulystyaningsih Natalia Daeng Tiring. 2019. "Studi in Silico Prediksi Potensi 6-Gingerol sebagai inhibitor c-Jun N-terminal kinases (JNK)." *Jurnal Jejaring Matematika dan Sains* 1(2):59–63. doi: 10.36873/jjms.v1i2.211.

Bare, Yohanes, Dewi Ratih Tirto Sari, Yoga Tribakti Rachmad, Gabriella Candrakirana Krisnamurti, and Agustina Elizabeth. 2019. "In Silico Insight the Prediction of Chlorogenic Acid in Coffee through Cyclooxygenase-2 (COX2) Interaction." *Biogenesis: Jurnal Ilmiah Biologi* 7(2):100–105. doi: 10.24252/bio.v7i2.9847.

Imtiyaz, Shaikh, Khaleequr Rahman, Arshiya Sultana, Mohd Tariq, and Shahid Shah Chaudhary. 2013. "Zingiber Officinale Rosc.: A Traditional Herb with Medicinal Properties." *Tang [Humanitas Medicine]* 3(4):26.1-26.7. doi: 10.5667/tang.2013.0009.

Kellogg, Aaron, Hsinlin Cheng, and Rodica Pop-Busui. 2008. "Cyclooxygenase-2 Pathway as a Potential Therapeutic Target in Diabetic Peripheral Neuropathy." *Current Drug Targets* 9(1):68–76. doi: 10.2174/138945008783431691.

Mao, Qian Qian, Xiao Yu Xu, Shi Yu Cao, Ren You Gan, Harold Corke, Trust Beta, and Hua Bin Li. 2019. "Bioactive Compounds and Bioactivities of Ginger (Zingiber Officinale Roscoe)." *Foods* 8(6):1–21. doi: 10.3390/foods8060185.

Mohammed, Ammar, Ahmed Ali, Mawahib Elamin Mohamed El-nour, Owais Mohammad, and Sakina Mohamed Yagi. 2019. "In Vitro Anti-Inflammatory Activity of Ginger (Zingiber Officinale Rosc.) Rhizome, Callus and Callus Treated with Some Elicitors." *Journal of Medicinal Plants Research* 13(10):227–35. doi: 10.5897/JMPR2019.6758.

Njobdi, Sani, Maryam Gambo, and Gali Adamu Ishaku. 2018. "Antibacterial Activity of Zingiber Officinale on Escherichia Coli and Staphylococcus Aureus." *Journal of Advances in Biology & Biotechnology* 19(1):1–8. doi: 10.9734/jabb/2018/43534.

Rehman, Riazur, M. Akram, Naveed Akhtar, Qaiser Jabeen, Tariq Saeed, S. M. Ali Shah, Khalil Ahmed, Ghazala Shaheen, and H. M. Asif. 2011. "Zingiber Officinale Roscoe (Pharmacological Activity)." *Journal of Medicinal Plant Research* 5(3):344–48.

Ricciotti, Emanuela, and Garret A. FitzGerald. 2011. "Prostaglandins and Inflammation." *Arteriosclerosis,*

Thrombosis, and Vascular Biology 31(5):986–1000. doi: 10.1161/ATVBAHA.110.207449.

Saiah, Wassila, Hanane Halzoune, Rabah Djaziri, Khadidja Tabani, Elhadj Ahmed Koceir, and Naima Omari. 2017. "Antioxidant and Gastroprotective Actions of Butanol Fraction of Zingiber Officinale against Diclofenac Sodium-Induced Gastric Damage in Rats." *Journal of Food Biochemistry* 42(1):1–12. doi: 10.1111/jfbc.12456.

Simmons, D. L. 2004. "Cyclooxygenase Isozymes: The Biology of Prostaglandin Synthesis and Inhibition." Pp. 387–437 in *Pharmacological Reviews*. Vol. 56.

Smyth, Emer M., Tilo Grosser, Miao Wang, Ying Yu, and Garret A. FitzGerald. 2009. "Prostanoids in Health and Disease: Fig. 1." *Journal of Lipid Research* 50(Supplement):S423–28. doi: 10.1194/jlr.R800094-JLR200.

Tiring, Sri Sulystyaningsih Natalia Daeng, Yohanes Bare, Andri Maulidi, Mansur S, and Fitra Arya Dwi Nugraha. 2019. "Studi In Silico: Prediksi Potensi 6-Shogaol Dalam Zingiber Officinale Sebagai Inhibitor JNK." *Al-Kimia* 7(2):147–53. doi: 10.24252/al-kimia.v7i2.10638.

Zarghi, Afshin, and Sara Arfaei. 2011. "Selective COX-2 Inhibitors: A Review of Their Structure-Activity Relationships." Pp. 655–83 in *Iranian journal of pharmaceutical research : IJPR*. Vol. 10.