

Scopus 3

by Suswandari Suswandari

Submission date: 02-Jun-2023 03:51PM (UTC+0700)

Submission ID: 2107344370

File name: 3.pdf (1.3M)

Word count: 2619

Character count: 14201

Original Article

Docking Studies and Molecular Dynamics Simulation of *Ipomoea batatas* L. Leaves Compounds as Lipoxygenase (LOX) Inhibitor

Yeni Yeni¹, Supandi Supandi¹, Lusi P. Dwita¹, Suswandari Suswandari², Maizatul S. Shaharun³, Nonni S. Sambudi³

¹Department of Pharmacy, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia, ²Department of Postgraduate Social Science Education, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia, ³Department of Fundamental & Applied Sciences, Universiti Teknologi PETRONAS, Perak, Malaysia

Submitted : 03-Feb-2020
Revised : 01-Jun-2020
Accepted : 08-Jul-2020
Published : 05-Nov-2020

INTRODUCTION

Inflammation is a local protective response caused by injury or tissue damage, and it serves to destroy, reduce, or localize both the injured agent and the tissue. In recent years, research has shown that arachidonic acid metabolites are essential mediators of inflammation. Arachidonic acid can be metabolized through two different means, which are cyclooxygenase (COX) pathway that produces prostaglandin and

thromboxane, and lipoxygenase (LOX) pathway, which produces leukotriene.^[1]

In treating inflammation, a group of drugs widely used are nonsteroidal anti-inflammatory drugs (NSAIDs).

ABSTRACT **Background:** Inflammatory mediators produced by cyclooxygenase (COX) and lipoxygenase (LOX) pathways are responsible for many human diseases, such as cancer, arthritis, and neurological disorders. Flavonoid-containing plants, such as *Ipomoea* *atas* leaves, have shown potential anti-inflammatory activity. **Objectives:** This study aimed to predict the actions of 10 compounds in *I. batatas* leaves, which are YGM-0a [cyanidin 3-O-sophoroside-5-O-glucoside], YGM-0f [cyanidin 3-O-(2-O-(6-O-(E)-p-coumaroyl-β-D-glucopyranoside)-5-O-β-D-glucopyranoside)], YGM-1a [cyanidin 3-(6,6'-caffeyl-p-hydroxybenzoylsophoroside)-5-glucoside], YGM-1b [cyanidin 3-(6,6'-dicaffeylsophoroside)-5-glucoside], YGM-2 [cyanidin 3-(6-caffeylsophoroside)-5-glucoside], YGM-3 [cyanidin 3-(6,6'-caffeyl-ferulylsophoroside)-5-glucoside], YGM-4b [peonidin 3-(6,6'-dicaffeylsophoroside)-5-glucoside], YGM-5a [peonidin 3-(6,6'-caffeylphydroxybenzo-ylsophoroside)-5-glucoside], YGM-5b [cyanidin 3-6-caffeylsophoroside)-5-glucoside], and YGM-6 [peonidin 3-(6,6'-caffeylferulylsophoroside)-5-glucoside] as LOX inhibitors, and also predict the stability of ligand-LOX complex. **Materials and Methods:** The compounds were screened through docking studies using PLANTS. Also, the molecular dynamics simulation was conducted using GROMACS at 310 K. **Results:** The results showed that the most significant binding affinity toward LOX was shown by YGM-0a and YGM-0a, and the LOX complex in molecular dynamics simulation showed stability for 20 ns. **Conclusion:** Based on Docking Studies and Molecular Dynamics Simulation of *I. Batatas* Leaves compounds, YGM-0a was shown to be the most probable LOX inhibitor.

KEYWORDS: Anti-inflammatory, docking, *Ipomoea batatas* L., lipoxygenase, molecular dynamics

Address for correspondence: Dr. Supandi Supandi, Department of Pharmacy, Universitas Muhammadiyah Prof. DR. HAMKA, Jl. Delima 2/4 Jakarta Timur, Indonesia. E-mail: supandi@uhamka.ac.id

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Yeni Y, Supandi S, Dwita LP, Suswandari S, Shaharun MS, Sambudi NS. Docking studies and molecular dynamics simulation of *Ipomoea batatas* L. leaves compounds as lipoxygenase (LOX) inhibitor. J Pharm Bioall Sci 2020;12:5836-40.

8 Access this article online

Quick Response Code:	Website: www.jpbonline.org
	DOI: 10.4103/jpbs.JPBS_103_20

The therapeutic effects of NSAIDs are related to the inhibition of COX enzyme. Other anti-inflammatory drugs commonly used are corticosteroids, which work by reducing the activity of phospholipase A2 and binding to LOX enzyme, thereby reducing the production of leukotriene. One of the anti-inflammatory drugs that have the same mechanism of action as corticosteroid is zileuton.^[2,3]

Ipomoea batatas leaves contain flavonoids and annins.^[4] The flavonoids are YGM-0a, YGM-0f, YGM-1a, YGM-1b, YGM-2, YGM-3, YGM-4b, YGM-5a, YGM-5b, and YGM-6. These compounds can inhibit COX or LOX enzyme, and also inhibit leukocyte accumulation to become an anti-inflammatory drug. However, inadequate information about traditional medicine has limited its use.^[5]

Docking studies that dominate the computer-aided drug design (CADD) are conducted for virtual screening or drug optimization. These studies can predict ligand orientation when bound to protein receptors or enzymes. Also, molecular dynamics simulations are used to understand the structure and function of biological macromolecules. In these simulations, proteins have a dynamic model with internal movements and conformational changes.^[6]

MATERIALS AND METHODS

The applications used were Protein Data Bank (PDB), PubChem, Marvin Beans, YASARA, PLANTS, Discovery Studio Visualizer, GROMACS, GRACE, and VMD. The material was a 3D structure of LOX enzyme with native ligand Fe (II) ion obtained from PDB with code 3V98. The 3D structure of zileuton and its ligand were obtained from PubChem.

The docking studies were carried out using PLANTS,^[7] and the 3D structure of compounds contained in *I. batatas* L. leaves and zileuton was docked to a receptor. In this case, the LOX enzyme had been separated from its native ligand using YASARA. Hence, before docking the receptor compound redocking was performed between the receptor and its native ligand Fe (II) ion to obtain root-mean-square deviation (RMSD) $\leq 2 \text{ \AA}$.^[8]

The ligand structure from PubChem was prepared using Marvin Beans software precisely with Marvin sketch. This structure was cleaned by changing the 3D shape into 2D. The protonation was then checked at a pH of 7.4. After this procedure, the best conformation search was conducted using YASARA to proceed to the simulation stage.^[9] The ChemPLP score was obtained from the results, and a more negative value indicated

a higher affinity for the receptor. The results were visualized using Discovery Studio, and a compound the most negative ChemPLP score was selected.

The simulations were conducted using GROMACS on the selected compound-receptor complex, which was carried out for 20 ns at a temperature of 310 K. The analysis of structural changes can be seen from RMSD value, RMSF, and potential energy. Also, visualization of molecular dynamics simulations can be seen through VMD.

RESULTS

Data collection

The receptor used in this study was 5-lipoxygenase (5-LOX) enzyme and native ligand Fe (II) ion obtained from PDB with PDB code 3V98^[10].

The drug used for comparison was zileuton.^[11] The 3D structure of zileuton and the compounds contained in *I. batatas* L. leaves were obtained from PubChem and edited using Marvin Sketch.

Docking study

Redocking 5-LOX with native ligand Fe (II) produced an RMSD value of 0 Å. The result showed YGM-0a had the highest affinity and lowest ChemPLP score of $-19,9046 \text{ kcal/mol}$ [Figure 1]. This was lower than zileuton, and there were about 26 hydrogen bonds in the complex.

Molecular dynamics simulation

Simulations were conducted on the YGM-0a and 5-LOX complex [Figure 2]. There were two hydrogen bonds of the complex after simulations. Also, the stability of the ligand-receptor complex can be seen from RMSD and the simulation time. The RMSD value of YGM-0a and LOX complex was not more than 0.03 nm or 0.3 Å.

RMSF graph showed fluctuation of the receptor atoms. The most fluctuating atoms were the 1st (N from serine), 263rd (C from glycine), 4421st (C from glycine), 4431st (C from glycine), and 5119th (C from glycine) with 0.0373, 0.0309, 0.0304, 0.0311, and 0.0307 RMSF, respectively. The average potential energy was $1,85956 \times 10^6 \text{ kcal/mol}$.

DISCUSSION

In *I. batatas* leaves, some flavonoids have the potential to be used as anti-inflammatory drugs.^[5] In this research, the prediction of their activity was conducted through docking studies. Docking is a term used in computational schemes to determine the interactions between two molecules (receptors and

ligands). From the docking obtained, the coordinates of atomic molecules predicted the interaction between receptor and ligand. The purpose of docking software

is to understand and predict molecular recognition by determining the binding sites between two molecules.^[12,13]

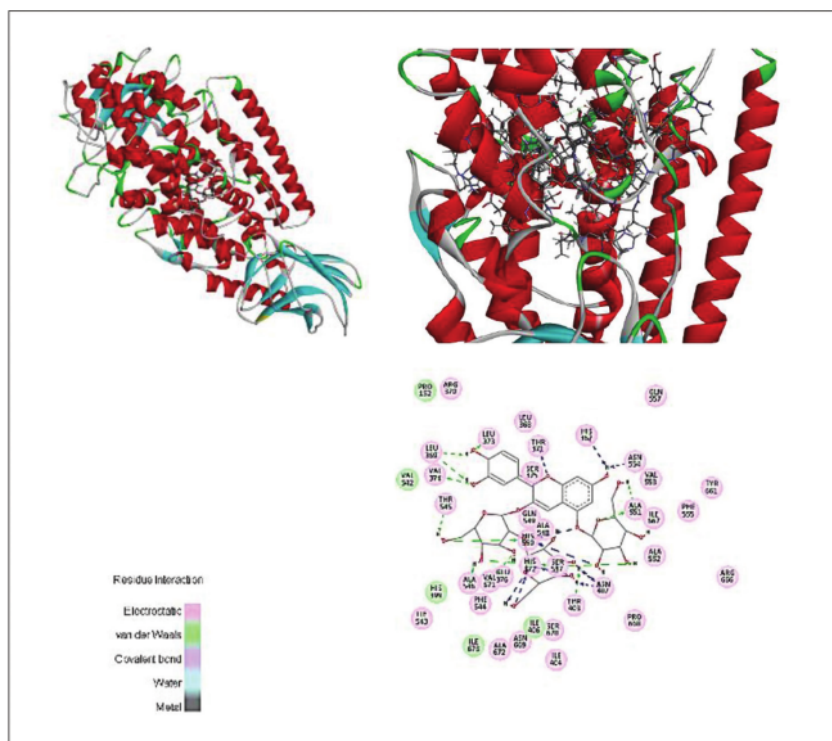


Figure 1: Visualization of docking result of YGM-0a with 5-lipoxygenase complex

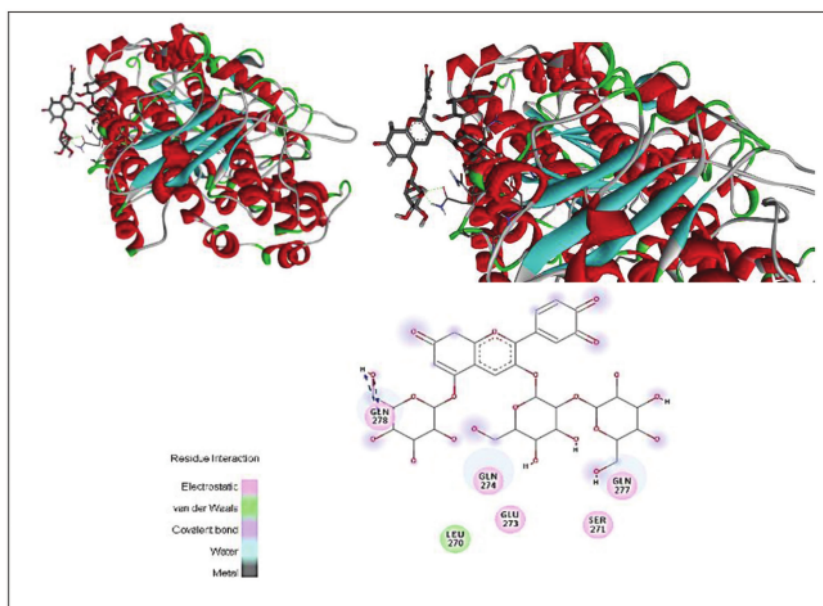


Figure 2: Visualization of molecular dynamics results of YGM-0a with 5-lipoxygenase complex

The docking study was conducted using PLANTS on 10 3D structures of compounds contained in *I. batatas* leaves and zileuton as a comparison drug. Zileuton is a 5-LOX inhibitor used for treating asthma, and as a selective tool to evaluate the role of 5-LOX and leukotrienes.^[11] The receptor used in this study was 5-LOX enzyme, which plays a major role in inflammation.^[10]

There were three docking methods, namely: rigid body, flexible ligand, and flexible. In rigid-body docking, the receptors and ligands were in a rigid state. In flexible ligand, the receptor remained rigid, but the ligand was flexible. Meanwhile, in flexible docking, the receptors and ligands were in a flexible state.^[13] The method used in PLANTS software was flexible ligand docking.^[14-16]

Redocking was first conducted using PLANTS and its native ligand Fe (II) ion before docking the compounds to receptor. This process aimed to determine whether the method used was acceptable. The redocking process also analyzed the binding site coordinates of the receptor used. The results were default native ligand and receptor. After obtaining the default binding site, it was then used in virtual screening of the 10 compounds.^[9] The RMSD value of redocking 5-LOX enzyme with native ligand Fe (II) was 0 Å. This showed that the method could be used for virtual screening.^[17]

In the docking result, YGM-0a has the highest affinity and lowest ChemPLP score of -19,9046 kcal/mol.^[14-16] This value showed its affinity for 5-LOX was higher than zileuton. Therefore, YGM-0a has better anti-inflammatory activity compared to zileuton, and can be used as an anti-inflammatory drug.

ChemPLP is used to model steric complementarity between proteins and ligands by considering hydrogen and metal bonds.^[15]

Molecular dynamics simulations were conducted on YGM-0a and 5-LOX complex, in which the ligands and receptors were in a flexible state.^[18] This simulation aimed to determine the stability of the ligand-receptor complex, which was conducted for 20 ns at a normal human temperature of 310 K.

The stability of the ligand-receptor complex can be seen from RMSD and simulation time. The RMSD value of YGM-0a and 5-LOX complex was not higher than 3 Å. This indicated that the whole system has good stability.^[19]

Movement of atoms can be seen from RMSF values during simulation.^[17,18,20] The RMSF graph showed that receptor atoms fluctuate the most; this implied that

YGM-0a atoms were stable during simulation (RMSF <3 Å).

Also, potential energy showed stability during simulation.^[20] Also, graph of YGM-0a and LOX showed stability, with an average potential energy of $1,85956 \times 10^6$ kcal/mol.

CONCLUSION

The compound in *I. batatas* L. leaves that have the highest affinity in inhibiting 5-LOX was YGM-0a with the most negative ChemPLP value of -19,9046 kcal/mol. This value showed that its affinity for 5-LOX was higher than zileuton. Also, the stability of YGM-0a and 5-LOX complex showed stable results for 20 ns with RMSD and RMSF value not more than 3 Å. Also, the average potential energy was $1,85956 \times 10^6$ kcal/mol.

Financial support and sponsorship

This study was funded by a grant from Universitas Muhammadiyah Prof Dr Hamka (Uhamka)-Universitas Teknologi Petronas Malaysia (UTP).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abbas A, Lichtman A, Pillai S. Basic immunology. 4th ed. Philadelphia, PA: Elsevier; 2014.
2. Laidlaw TM, Fuentes DJ, Wang Y. Efficacy of zileuton in patients with asthma and history of aspirin sensitivity: a retrospective analysis of data from two phase 3 studies. *J Allergy Clin Immunol* 2017;139:384-90.
3. Sinha S, Doble M, Manju SL. Design, synthesis and identification of novel substituted 2-amino thiazole analogues as potential anti-inflammatory agents targeting 5-lipoxygenase. *Eur J Med Chem* 2018;158:34-50.
4. Rihsyah Y, Mulqie L, Choesrina R. Uji aktivitas antiinflamasi ekstrak etanol Daun Ubi Jalar Ungu. *Prosidi Penel SPeSIA* 2015;12:630-6.
5. Ramadhani N, Sumiwi SA. Aktivitas antiinflamasi berbagai tanaman diduga berasal dari flavonoid. *Farmaka* 2016;14:111-22.
6. Chen YC. Beware of docking! *Trends Pharmacol Sci* 2015;36:78-95.
7. Exner TE, Korb O, Ten Brink T. New and improved features of the docking software PLANTS. *Chem Cent J* 2009;3:4150.
8. Kiszka E. A pre-docking filter based on image recognition. *arXiv: Biomolecules* 2014;1:1-6.
9. Purnomo H. Kimia Komputasi Untuk Farmasi dan Ilmu Terkait: Uji In-Silico Senyawa Antikanker. Yogyakarta, Indonesia: Pustaka Pelajar; 2013.
10. Gilbert NC, Rui Z, Neau DB, Waight MT, Bartlett SG, Boeglin WE, et al. Conversion of human 5-lipoxygenase to a 15-lipoxygenase by a point mutation to mimic phosphorylation at serine-663. *Faseb J* 2012;26:3222-9.
11. Liu Y, Wang W, Li Y, Xiao Y, Cheng J, Jia J. The 5-lipoxygenase inhibitor zileuton confers neuroprotection against glutamate

- oxidative damage by inhibiting ferroptosis. *Biol Pharm Bull* 2015;38:1234-9.
12. Morris GM, Lim-Wilby M. Molecular docking. *Methods Mol Biol* 2008;443:365-82.
 13. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des* 2011;7:146-57.
 14. Capoferri L, Verkade-Vreeker MC, Buitenhuis D, Commandeur JN, Pastor M, Vermeulen NP, et al. Linear interaction energy based prediction of cytochrome P450 1A2 binding affinities with reliability estimation. *PLoS One* 2015;10:e0142232.
 15. Korb O, Stützel T, Exner TE. An ant colony optimization approach to flexible protein-ligand docking. *Swarm Intel* 2007;1:115-34.
 16. van Dijk M, Ter Laak AM, Wichard JD, Capoferri L, Vermeulen NPE, Geerke DP. Comprehensive and automated linear interaction energy based binding-affinity prediction for multifarious cytochrome P450 aromatase inhibitors. *J Chem Inf Model* 2017;57:2294-308.
 17. Havener KE, Ball DM. Validation of molecular docking programs for virtual screening against dihydropteroate synthase. *J Chem Inf Model* 2009;49:444-60.
 18. Abraham M, Hess B, Spoel D, Lindahl E. GROMACS user manual version 2016.5. Stockholm, Sweden: The Royal Institute of Technology and Uppsala University; 2018.
 19. Manna A, Dian M, Hudyanti D, Siahaan P. Molecular docking of interaction between e-cadherin protein and conformational structure of cyclic peptide ADTC3 (Ac-CADTPC-). *J Kimia Sains Dan Apl* 2017;20:30-6.
 20. Ajao A, Kannan M, Yakubu S, Vj U, Jb A. Homology modeling, simulation and molecular docking studies of catechol-2, 3-dioxygenase from *Burkholderia cepacia*: involved in degradation of petroleum hydrocarbons. *Bioinformation* 2012;8:848-54.

Scopus 3

ORIGINALITY REPORT

17%

SIMILARITY INDEX

14%

INTERNET SOURCES

11%

PUBLICATIONS

5%

STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Universitas Airlangga Student Paper	3%
2	Nadia Plata, Izabela Konczak-Islam, Shalini Jayram, Kylie McClelland, Tracey Woolford, Philip Franks. "Effect of methyl jasmonate and p-coumaric acid on anthocyanin composition in a sweet potato cell suspension culture", Biochemical Engineering Journal, 2003 Publication	2%
3	link.springer.com Internet Source	2%
4	juriskes.com Internet Source	1%
5	perakgateway.utp.edu.my Internet Source	1%
6	www.jstage.jst.go.jp Internet Source	1%
7	Ferreira, Leonardo, Ricardo dos Santos, Glaucius Oliva, and Adriano Andricopulo.	1%

"Molecular Docking and Structure-Based Drug Design Strategies", Molecules, 2015.

Publication

8	pt.scribd.com Internet Source	1 %
9	gchron.copernicus.org Internet Source	1 %
10	jurnal.ugm.ac.id Internet Source	<1 %
11	Vikky Awasthi, Yash Gupta, Rubika Chauhan, Prakasha Kempaiah, Jyoti Das. "Growth inhibition of plasmodium falciparum by Nano-molar concentrations of 1-(4-hydroxy-3-methoxyphenyl) decan-3-one (6-paradol); is a cure at hand?", Phytomedicine Plus, 2022 Publication	<1 %
12	a.iium.edu.my Internet Source	<1 %
13	docplayer.fr Internet Source	<1 %
14	git.embl.de Internet Source	<1 %
15	jrms.mui.ac.ir Internet Source	<1 %
16	jurnal.unpad.ac.id Internet Source	<1 %

17	loop.frontiersin.org Internet Source	<1 %
18	123dok.co Internet Source	<1 %
19	Submitted to Universidad San Francisco de Quito Student Paper	<1 %
20	static.frontiersin.org Internet Source	<1 %
21	theses.hal.science Internet Source	<1 %
22	www.frontiersin.org Internet Source	<1 %
23	Marc van Dijk, Antonius M. ter Laak, Jörg D. Wichard, Luigi Capoferri, Nico P. E. Vermeulen, Daan P. Geerke. "Comprehensive and Automated Linear Interaction Energy Based Binding-Affinity Prediction for Multifarious Cytochrome P450 Aromatase Inhibitors", Journal of Chemical Information and Modeling, 2017 Publication	<1 %

Exclude quotes On

Exclude matches Off

Exclude bibliography On

