

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

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Original Article

Docking Studies and Molecular Dynamics Simulation of *Ipomoea batatas* L. Leaves Compounds as Lipoygenase (LOX) InhibitorYeni Yeni¹, Supandi Supandi¹, Lusi P. Dwita¹, Suswandari Suswandari², Maizatul S. Shaharun³, Nonni S. Sambudi³

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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 batatas* 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-(2-O-(6-O-(E)-p-coumaroyl-β-D-glucopyranosyl)-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'-caffeylphydroxybenzoylsophoroside)-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

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).

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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 on 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

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.

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Conflicts of interest

There are no conflicts of interest.

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