Molecular Docking Studies of Potential *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* as Inhibitor antimalaria

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Molecular Docking Studies of Potential *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* as Inhibitor antimalaria

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Abstract. The purpose of this research is to analysis the potential *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* as an *inhibitor Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* compound for antimalaria. The method used to analysis the potential *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* as an antimalaria was insilico approach by molecular docking using Autodock Vina. Based on the free energy parameter analized ΔG, the value of free energy ΔG is -11.6 kcal /mol with 5 repetisions. The free energy ΔG value from the analysis results was relatively low, this means that *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* is stable to be used as an inhibitor of *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)*. Because the lower the free energy of a molecule the more stable the molecule. Based on hydrogen bond parameters, there were hydrogen bonds in *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* and PfENR receptors. This shows that *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* binding PfENR receptors to strong and stable. Based on the parameters of the analysis of Ligand and Receptor Interactions also showed that *Quercetin 3,4'-dimethyl ether 7-alpha-LArabinofuranosyl-(1-6)-glucoside* compounds were stable used as *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* inhibitors for antimalaria.

1. Introduction

Malaria is a very dangerous disease. 1.2% of people who die due to contracting malaria [1]. Malaria usually threatens the lives of people living in tropical and subtropical regions. Malaria is an infectious disease caused by the genus plasmodium parasite and transmitted by mosquitoes [2]. This disease causes around one to two million deaths every year, or around one hundred fifty to three hundred deaths every hour [3]. Malaria is characterized by symptoms of fever, fatigue, vomiting and headaches. For severe cases, malaria can cause seizures, coma and even death [4].

Clinically malaria is divided into three types, namely tropical malaria caused by plasmodium falciparum, tersiana malaria caused by plasmodium vivax and plasmodium ovale (rare, found outside Africa), and quartane malaria caused by plasmodium malariae [5]. Malaria is transmitted through the bite of a female Anopheles mosquito.

Plasmodium falciparum is the most deadly type of malaria for humans and has the highest priority in finding effective drugs [6]. Clinical symptoms of P. falciparum malaria are generally more severe and more acute than other types, characterized by fluctuating heat, anemia, splenomegaly, and

frequent complications[7]. This malaria attacks all types of red blood cells, which causes cells to become very fragile. The number of red blood cells damaged by parasitic infections disrupts transportation to vital organs and can cause death quickly[7-8].

Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR) is an enzyme that plays an important role in the plasmodium life cycle. This enzyme has an important role in the synthesis process of fatty acids in the body Plasmodium falciparum [9]. This enzyme plays a role in type II fatty acid biosynthesis that takes place in Plasmodium falciparum, with a specific target of *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase* (*PfENR).* Inhibition of the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* is the beginning of the development of antimalarial drugs.

Some natural compounds have the potential to become new lead compounds that can inhibit the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)*. This can be observed if the enzyme compounds are tethered to some plant chemical compounds which are also efficacious as an antimalarial. *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound is a compound derived from the Punicaceae family with plant species of origin namely, *Punica granatum*, *Malum granatum* or commonly known as *pomegranate*. Research on extracts from Punica granatum on antiplasmodial activity that has been carried out suggests that the tannin fraction is useful to be an inhibitor of Plasmodium growth [10].

In this research, molecular docking analysis will be carried out to see the binding ability between the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* against *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl (1-6) -glucoside* enzyme inhibitor using the parameter of the bond free energy value (ΔG) produced. Besides that, hydrogen bonding parameters and interactions between receptors and ligands are also observed to see the stability of the bonds formed.

2. Method

This research uses computer hardware in the form of RAM (Random Access Memory) of at least eight gigabytes. The software used is for the docking simulation process using Autodock vina 1.1.1 while for the preparation and analysis of simulation results performed using the VMD (Visual Molecular Dynamics Program) version 1.9.1, Autodock tools, and Pymol.

The material used in this research is experimental data of X-Ray Diffraction results in the form of three-dimensional structural data of the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR). Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* is used as a receptor. Whereas the Ligand inhibitors used in this research are three-dimensional structures of medicinal plants in Indonesia contained in the Indonesian Medicinal Plants Database namely *Quercetin compound 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) – glucoside*[11].

2.1. Receptor Identification

The protein used as a receptor was the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)*. The three-dimensional structure of *PfENR* downloaded from the Protein Data Bank with the site http://www.rscb.org/pdb [11-12] with the identity of 1NHG in the form of a tetramer. The identification process was done using Discovery Studio Visualizer 4.0 software.

2.2. Ligand Identification

Ligands that are used as inhibitors in this research are three-dimensional structures of medicinal plants in Indonesia that found in the Indonesian Medicinal Plants Database. The ligand compound used as an inhibitor is *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound. The crystal structure of the inhibitor (Ligan) was downloaded from the PubChem Database with the site https://pubchem.ncbi.nlm.nih.gov.

2.3. Geometry Optimization of 3D Receptor Structures

Geometry optimization process is carried out with Pymol software. The initial step is to separate the receptor from the ligand and the solvent and then save it in the .pdb format. Furthermore, the receptor and ligand files are converted back into a file with the extension .pdbqt using Autodock tools (ADT) software. Furthermore, the size of the Grid Box is prepared. Grid Box is a ligand boundary measure for docking receptors. The size is: center_x = 32.336, center_y = 45.963, center_z = 22.641, size_x = 82, size_y = 118 and size_z = 94

2.4. Geometry Optimization of 3D Ligand Structures

The optimization process is carried out by changing the ligand compound data format from the .sdf format file to the .pdb file type. using pymol software. Furthermore, the receptor and ligand files are converted back into a file with the extension .pdbqt using Autodock tools (ADT) software.

2.5. Molecular Docking Process

The molecular docking process is carried out with AutoDock Vina (Scripps Research Institute, USA) and it is assumed that all rotatable bonds (cyclic bonds) of the ligands can rotate (flexible) and the receptors are fixed (rigid) [13]. To run the docking needed, Vina's autodock software, receptor files, ligands and config files. Config file is a file that contains the specified grid box size. After docking is complete, a number of docking modes will be shown along with the value of Affinity (kcal/mol). Repeated 5 times to see the best results and the consistency of the values obtained. Then the docking analysis is performed.

2.6. Molecular Docking Analysis

Docking analysis using pymol and VMD software to see the parameters of free energy gibbs, hydrogen bonds, and the interaction of ligand with receptor.

3. Result and Discussion

3.1. Receptor Identification

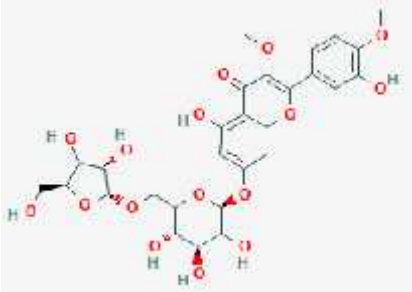
The three-dimensional structure of the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* is downloaded from a protein data bank. The three-dimensional structure of the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* is expressed from bacteria. The enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* was obtained from the results of crystallization using x-ray diffraction. This enzyme has a 1NHG PDB code and has a residual length of 229 residues. Visualization results show that there are 4 chains namely A, B, C and D and there are two natural ligands TCL and NAD.

3.2. Ligand Identification

The ligand used is *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound.

Table 1. *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compounds.

Pubcem CID	44259697
Molecular Formula	$C_{28}H_{32}O_{16}$
Molecular Weight	624.5 g/mol
Hydrogen Bond Donor	8

Count	
Hydrogen Bond Acceptor Count	16
Structure	

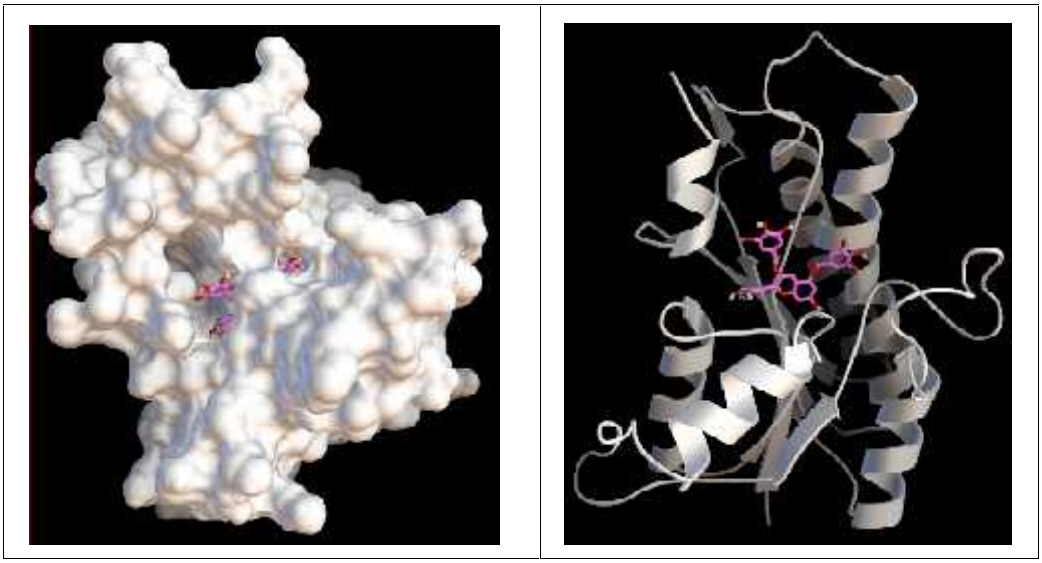
3.3. Bonding Energy (Gibbs free energy)

Gibbs free energy (ΔG binding) is a parameter for determining the stability of a conformation formed between a ligand and a receptor. The lower the free energy of a reacting molecule, the more stable the molecule formed and the reaction that occurs spontaneously. This is in accordance with the law of thermodynamic balance. So, the more negative free energy of a molecule that reacts, the reaction goes spontaneously and the molecule becomes more stable or will quickly form stable conformations[14]. The molecular docking energy for *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound produces a final value of -11.6 kcal / mol consisting of 9 ligand modes. This means that the *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound is stable for use as an inhibitor of the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* because the lower free energy of a molecule, the more stable the molecule is because the reaction goes spontaneously.

Table 2. Gibbs free energy results from molecular docking ligands.

Mode	**Affinity (kcal/mol)**	**dist from best mode**	
		rmsd l.b.	**rmsd u.b**
1	-11.6	0.000	7.948
2	-11.4	4.651	3.187
3	-11.3	2.519	2.397
4	-11.1	1.701	12.405
5	-10.9	9.189	11.231
6	-10.8	8.608	9.618
7	-10.7	6.905	7.530
8	-10.7	5.036	6.845
9	-10.7	3.794	7.948

If analyzed from the value of the free energy of gibbs produced, the *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* compound is possible to be used as an anti-malarial because the free energy is negative. Besides *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* ligand compound is also a compound that has antioxidant and antiplasmodial activity.



(a) (b)

Figure 1. Pose Ligand and receptor (a). Molecular Surface (b). The ribbon.

3.4. Hydrogen Bonding

Hydrogen bonding is an indicator of the stability of a molecule, although the effect is very small. Because the energy produced is relatively small. But if the number of hydrogen bonds is large, then the energy generated from the hydrogen bond parameter becomes large, so that it will be very influential to stabilize a molecule.

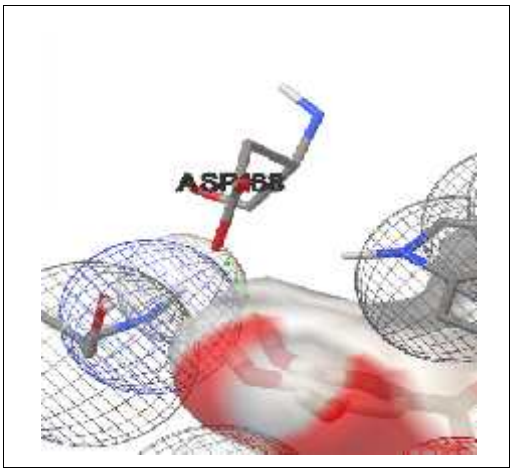


Figure 2. Hydrogen bonding between H atoms and *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl (1-6) –glucoside* ligand.

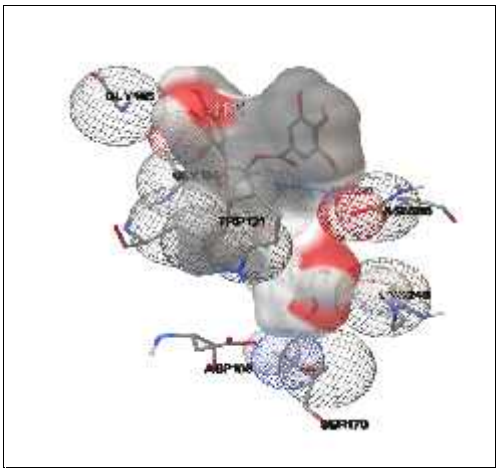


Figure 3. Interaction of receptors and ligands.

Based on the analyzed hydrogen bond parameters, the *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* receptor and ligand have 1 hydrogen bond, which is the bond between the hydrogen atom and the UNK ligand from *Quercetin 3,4'-dimethyl ether 7-alpha-L- Arabinofuranosyl- (1-6) –glucoside* compound (Figure 2). So it can be concluded that in the *Quercetin 3,4'-dimethyl ether 7-alpha-L- Arabinofuranosyl- (1-6) –glucoside* ligand the hydrogen bond does not have a significant effect, because there is only 1 hydrogen bond formed.

3.5. Interaction of Ligands and Receptors

Hydrophobic interactions are interactions that avoid the liquid environment and tend to cluster in the interior of the structure of globular proteins to minimize interactions with water that can damage the structure of proteins and cause enzymes to lose their activity [15].

From hydrophobic interactions, it can be seen that *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* ligand stable to be used as an inhibitor for enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR)* because there is an hydrophobic interaction which will increase stability. The hydrophobic residues from the reacting residues are LEU216, TRP131 while the hydrophilic residues are GLY106, GLY104, ASN218, LYS240, ASP168, SER170. Although the effect of the hydrophobic interaction is small because the residues that interact are only two residues.

4. Conclusion

Based on the analysis of gibbs free energy parameters, it was stated that *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* ligand stable when docked on the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR).* This can be seen from the value of free energy produced by gibbs that is - 11.6 kcal / mol. Negative values indicate that the system is stable. The lower the free energy of a molecule, the more stable the molecule and the reaction runs spontaneously. In addition, based on the parameters of hydrogen bonds and ligand-receptor interactions also stated that the *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* was stable used as an inhibitor for the enzyme *Plasmodium falciparum Enoyl Acyl Carrier Protein Reductase (PfENR).* There is 1 hydrogen bond formed between the ligand and the H atom. For the parameters of the ligand-receptor interaction, there are hydrophobic residues and hydrophilic residues reacting. The hydrophobic residues are LEU216, TRP131 while the hydrophilic residues are GLY106, GLY104, ASN218, LYS240, ASP168, SER170. So that *Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofuranosyl- (1-6) -glucoside* ligand is potentially applied as a candidate for new antimalarial drugs.

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