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ANTIHYPERLIPIDEMIC DOCKING STUDY OF CYCLOARTENOL COMPOUND FROM *MUSA BALBISIANA* COLLA WITH SOME TARGETS RELATED WITH HYPERLIPIDEMIA

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ABSTRACT

Objective: Computational chemistry through the molecular docking method has become an important stage in research. This method was as a virtual screening of the discovery of natural active compounds that were active and effective against specific receptors. The aimed of this study to investigate the mechanism of interaction between cycloartenol compounds from the *Musa balbisiana* Colla plant with the receptors that responsible for antihyperlipidemic activity. This study used 3 receptor targets that were closely related to the antihyperlipid mechanism Farnesiod X-Receptor (FXR), Lanosterol 14α-Demethylase (LDM), and Niemann Pick C_1 Like$_1$ Protein (NPC_1L_1). **Materials and Methods:** The molecular docking step included the preparation of target receptors and ligands using the Pyrx program, and Avogadro. Docking simulation was done using AutoDock Vina software and visualization of 2D molecular interactions with Discovery Studio Visualizer. The results of docking were carried out by evaluating the value of the binding affinity between the ligand and the receptor, and the type of bond formed. **Results:** Cycloartenol binding affinity score for target FXR receptors -7.3 kcal/mol, LDM -9.7 kcal/mol, and NPC_1L_1 2.3 kcal/mol. **Conclusions:** Based on the binding affinity score, it can be concluded that the cycloartenol compound from the M*usa balbisiana* Colla plant had antihyperlipidemic activity through the LDM receptor inhibition mechanism.

KEYWORDS: Molecular docking, antihyperlipidemic, cycloartenol, M*usa balbisiana* Colla, FxR, LDM, NPC_1L_1.

INTRODUCTION

The condition of hyperlipidemia is characterized by increased blood lipid levels, including cholesterol and triglyceride values. These clinical parameters contribute to an increased risk of atherosclerosis and coronary heart disease. This disease causes death and major morbidity in almost all countries.[1,2] Heart attacks and strokes are caused by blood clots. Enforcement of treatment for this disease condition is by means of prevention. An approach that is oriented towards a healthy lifestyle, and regular exercise is the best prevention solution. In addition, the use of drugs to lower cholesterol can be used, although it has quite large side effects.[3]

Medicinal plants are currently the main alternative solution compared to modern drugs, due to aspects of better tolerance for each patient, lower toxicity, and relatively avoidable side effects.[4]

The *Musa Balbisiana* Colla plant has been widely known by the public as one of the most commonly consumed banana species. In addition, Cycloartenol compound from this plant is known to have many properties including: Antibacterial Activity.[5,6] Hypo-testicular Activity[7], Antioxidant Property.[8]

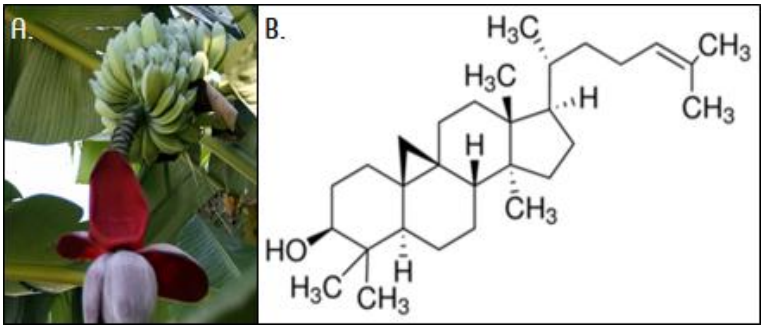

Figure 1: (a) M*usa balbisiana* Colla*; (*b) Cycloartenol.

The molecular docking method has become an important research stage in the search for active molecules that are predicted to have activity against certain receptors. Approach through evaluation based on their free binding energy and the type of bond formed.[9] This method has advantages in terms of more economical costs, shorter time because it can reduce errors in laboratory research.[10] The active compound cycloartenol from the *Musa balbisiana* Colla plant will be used as a target ligand that will interact with receptors responsible for lipid

metabolism Farnesiod X-Receptor (FXR), Lanosterol 14α-Demethylase (LDM), Niemann Pick C_1 Like$_1$ Protein (NPC_1L_1).[11]

The target FXR receptor (PDB code ID: 1OSH) responds to the bile acid (BA) sensor. This receptor has an important role in maintaining the balance of cholesterol metabolism, plays a role in the process of lipid homeostasis, and absorption of fats and proteins. In addition, FXR is also known to be able to reduce plasma triglyceride levels.[12,13] Another receptor that plays an important role in lipid metabolism is LDM (PDB ID code: 3LD6) through the mechanism of catalytic reduction of the l4αgroup-methyl group of lanosterol in cholesterol biosynthesis. LDM has a role as a therapeutic agent in the treatment of hypercholesterolemia.[14,15] NPC_1L_1has been known to have a mechanism for the direct transfer of sterol compounds in the intestine. This receptor (PDB code ID: 3QNT) becomes a molecular target for the drug ezetimibe.[16,17]

MATERIALS AND METHODS

Software and Tools

AutoDock Vina 1.1.2, PyRx, MGL tools, Discovery Studio Visualizer, Avogadro.

Ligand Preparation

Scientific data on cycloartenol compounds and other ligands are listed in table 1.

Table 1: Ligands used in the study.

No	Ligand	Molecular Formula	REFERENCES
1	Cycloartenol	$C_{30}H_{50}O_5$	[7]
2	Fexaramine	$C_{32}H_{36}N_2O_3$	[12]
3	Ketoconazole	$C_{26}H_{28}Cl_2N_4O_4$	[15]
4	Ezetimibe	$C_{24}H_{21}F_2NO_3$	[10]

Target Receptor and Ligand Preparations.

Targeted receptor proteins related to lipid metabolism were obtained from the protein data bank (http://www.rcsb.org); Farnesiod X-Receptor (FXR) (PDB code ID: 1OSH), Lanosterol 14α-Demethylase (LDM) (PDB ID code: 3LD6), Niemann Pick C_1 Like1 Protein (NPC_1L_1) (PDB code ID: 3QNT).

Docking simulation and Parameter Evaluation

Docking simulations of cycloartenol compounds and native ligands were carried out using AutoDock Vina 1.1.2 software. Grid box setup is done with a distance of 1 Å, this is so that

the ligand can move flexibly in finding the best position to bind to the amino acid on the active side of the receptor. The evaluation of the docking simulation was obtained from the parameter scoring of the binding affinity value and also the number and type of bonds formed.

2D visualization of ligand and receptor interactions was carried out with the Discovery studio visualizer program. This visualization illustrates the types of bonds formed, and provides information on which amino acids have an important role in the formation of bonds.

RESULTS AND DISCUSSION

Ligand and Protein Preparation

Cycloartenol as the target ligand and native ligands of each receptor went through the initial stage of energy minimization, then converted the file format into PDBQT form. The physicochemical properties, 3D structure of the ligands are summarized in table 2, and figure 2.

Table 2: Physiochemical parameters of ligand.

No	Ligand	Molecular Weight (Da)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	XLogP3-AA	Minimize Energy
1	Cycloartenol	426.7	1	1	9.8	1143.01
2	Fexaramine	496.6	0	4	6.9	588.08
3	Ketoconazole	531.4	0	7	4.3	2482.04
4	Ezetimibe	409.3	2	3	4.0	1170.81

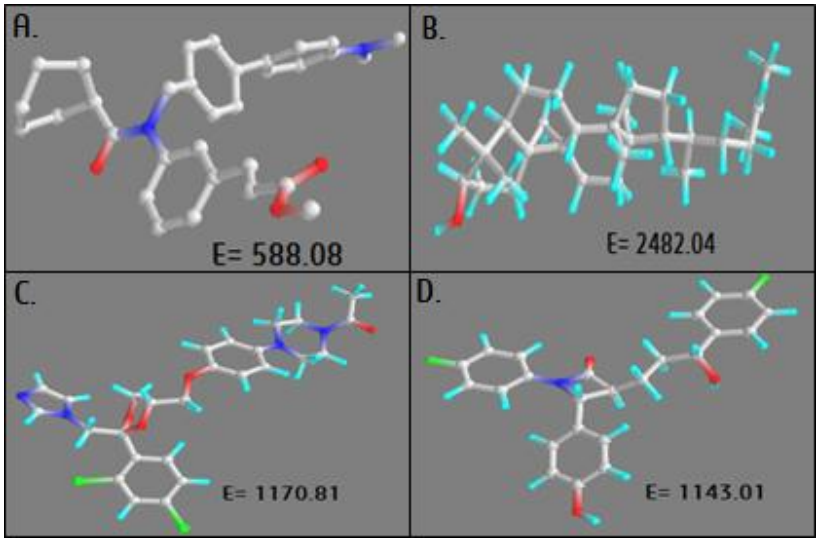

Figure 2: 3D ligand structure and energy minimized results. (A). Fexaramine, (B). Ketoconazole, (C). Ezetemibe, (D). Cycloartenol.

After the receptor protein was converted to PDBQT file format, docking simulations were performed for each native ligand and the binding affinity values of the cycloartenol target ligands were compared with the binding affinity values of each native ligand at each target receptor. 3D structure of the target receptor protein in figure 3.

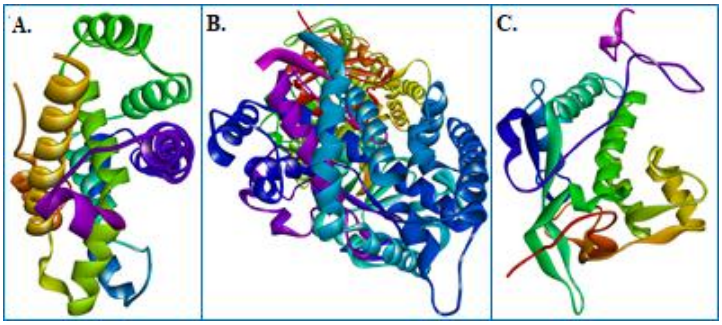

Figure 3: 3D structure of receptor, (A) FXR; (B) LDM; (C) NPC1L1.

Docking Analysis Simulation

Molecular Docking of Cycloartenol Compound with FXR Receptor

Simulation results of docking between Fexaramine , and Cycloartenol to the FXR receptor had the same amino acids in bond formation at Thr 292, Ile 356, Ile 361, Met 369, Met 294, Leu 291, Ala 395. Cycloartenol had no hydrogen bonds with amino acids at the FXR receptor, but form van der Walls, pi-Sigma, Alkyl, and pi-Alkyl bonds.

Docking analysis was carried out by comparing the binding affinity values where the native ligand was Fexaramine (-10.9 kcal/mol), and Cycloartenol (-9.0 kcal/mol).

Molecular docking of Cycloartenol compound with LDM Receptor

Molecular docking between the native ketoconazole ligand and the cycloartenol target ligand against the LDM receptor target showed differences in the formation of bonds with amino acids. Ketoconazole forms 2 hydrogen bonds with the amino acids Pro376, and Met 487, while cycloartenol has no hydrogen bonds.

The binding affinity value of ketoconazole ligand (-10.5 kcal/mol), and cycloartenol (-9.7 kcal/mol).

Molecular docking of Cycloartenol compound with NPC1L1 Receptor.

Docking simulations of native Ezetimibe and cycloartenol ligands against the target NPC1L1 receptor showed a significant difference, where there was no similarity of amino acids that

form bonds. The bond formed between cycloartenol and the receptor is a weak vand der Walls bond.

Scoring of the binding affinity value of ezetimibe (-7.0 kcal/mol) was better than cycloartenol (2.3 kcal/mol).

The interaction of 2D ligands with the target receptor, and the binding affinity values for all ligands are summarized in Figure 4, and Table 3

Table 3: Comparative binding affinity of different ligands with receptors.

No.	Receptor	Ligand	Binding Affinity (kcal/mol)
1	**Farnesiod X-Receptor**	Fexaramine Cycloartenol	-10.9 -7.3
2	Lanosterol 14α-Demethylase (LDM)	Ketoconazole Cycloartenol	-10.5 -9.7
3	Niemann-Pick C1 Like-1 (NPC1L1)	Ezetimibe Cycloartenol	-7.0 2.3

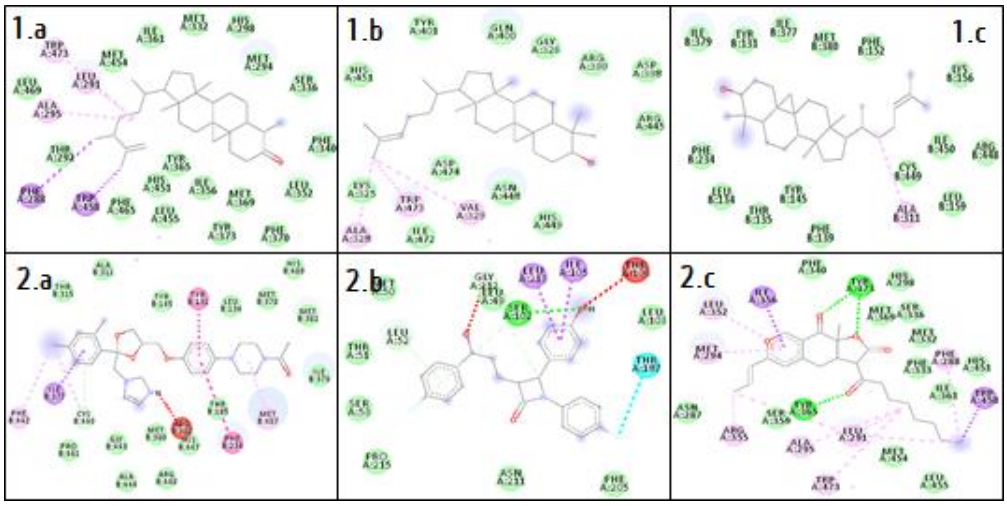

Figure 4: Interaction of ligands and target receptors. (1.A) Fexaramine bound to FXR, (1.B) Cycloartenol bound to FXR, (2.A) Ketoconazole bound to LDM, (2.B) Cycloartenol bound to LDM, (3.A) Ezetimibe bound to NPC1L1, (3.B) Cycloartenol bound to NPC1L1.

CONCLUSIONS

Molecular docking studies of the active compound cycloartenol from the *Musa balbisiana* Colla plant showed that it has potential as an antihyperlipidemic through the mechanism of inhibition of the LDM receptor.

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