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Potential of Prenylated Flavonoid Derivatives from Jackfruit Roots (*Artocarpus heterophyllus* Lam.) as Liver Anticancer Candidates: *In Silico Study*

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Abstract

Hepatocellular carcinoma (HCC), or liver cancer, is the fourth largest cancer in Indonesia, with 21,392 new cases and around 20,920 deaths. One of the standard drugs for liver cancer patients is lenvatinib, but lenvatinib has dangerous side effects such as hypertension. Previous studies reported that jackfruit root extract (*Artocarpus heterophyllus* Lam.) contains prenylated flavonoid compounds known to have anticancer activity. This study aims to find compounds that have the potential to the anticancer liver from jackfruit root by understanding the interaction between prenylated flavonoid derivative compounds against the VEGFR2 receptor (PDB ID: 3WZE) in silico. The methods include toxicity and pharmacokinetic screening, drug scanning, docking, and molecular dynamics simulation. The toxicity, pharmacokinetic, and drug scans of cycloartocarpesin are better than lenvatinib. The docking cycloartocarpesin compound showed ΔG -8.49 kcal/mol and Ki 0.59967 M lower than lenvatinib by forming the same hydrogen bond at residue Glu885. The molecular dynamics simulation of the cycloartocarpesin compound in the MM-GBSA calculation method resulted in a ΔG_{total} of -56.641 kcal/mol. The cycloartocarpesin compound is predicted to be used as a candidate for liver anticancer drugs because it has better stability and affinity than lenvatinib.

1. Introduction

Hepatocellular carcinoma (HCC) is a primary liver cancer due to abnormal hepatocyte cell growth. HCC is one of the cancers with the highest prevalence and incidence globally [1]. The incidence of hepatoma in 2020 reached 905,677 cases, so it ranks sixth in the world in terms of cancer, and the third leading cause of cancer death is as many as 830,180 cases [2]. HCC in Indonesia is in the top four cancer cases, with 21,392 new cases in 2020, and around 20,920 dying [3].

One of the standard drugs for patients with liver cancer or hepatocellular carcinoma is lenvatinib; however, side effects of lenvatinib have been reported, such as hypertension, diarrhea, decreased appetite, and weight loss [4].

One of the plants known to have antioxidant activity is the jackfruit (*Artocarpus heterophyllus* Lam.). Empirically jackfruit root treats skin diseases, asthma, fever, and diarrhea [5]. Secondary metabolites in *Artocarpus heterophyllus* are phenolic compounds, especially flavonoids with hydroxy groups known to have antioxidant and anticancer activities [6]. *Artocarpus heterophyllus* root ethanol extract contains flavonoid compounds (free 6- or 8-prenylated substituted flavones, free 8-geranyl substituted flavones, and free 3-prenylated substituted flavones) [7].

Prenylated flavonoid compounds have an extraordinary spectrum of pharmacological activities such as antioxidant, antibacterial, cytotoxic, and estrogenic, most notably their potential role as anticancer [8]. Vascular endothelial growth factor

receptor (VEGFR) tyrosine kinase is a promising therapeutic target in cancer treatment. VEGF/VEGFR2 is considered a major proangiogenic pathway to promote all processes of angiogenesis, including vascular permeability, endothelial cell survival, proliferation, migration or invasion into surrounding tissues, and capillary vessel formation. Cancer progression is always associated with VEGF expression, and the VEGF/VEGFR2 signaling pathway is often considered an essential mediator of cancer therapy [9].

Based on this statement, this study aims to find compounds that have the potential to the liver anticancer from jackfruit root (*Artocarpus heterophyllus* Lam.) by knowing the in silico interactions between prenylated flavonoid derivatives and VEGFR2 receptors (PDB ID: 3WZE).

2. Methodology

This research was conducted in silico by conducting physicochemical screening through toxicity prediction, pharmacokinetics, Lipinski's rule of five analysis (drug scan), molecular docking, and molecular dynamics of 45 prenylated flavonoid derivatives against VEGFR2 receptors.

2.1. Equipment and Materials

This research used Intel® Core™ i3-3110U CPU @ 2.40GHz 2.40GHz hardware, 4.00 GB RAM, 64-bit operating system x64-based processor. For the Molecular Dynamics process, a PC (Personal Computer) was used with the Linux Ubuntu 18.04.5 LTS 64-bit operating system, Processor Intel® Core™ i5-8400 CPU @ 2.80GHz x 6, Gnome 3.28.2, Disk 245,1 GB.

The materials were the 2D structure of 45 prenylated flavonoid derivatives [10] drawn using Chemdraw and protonated with Marvin Sketch. VEGFR2 protein was downloaded via http://www.rscb.org/pdb/ with PDB code 3WZE.

2.2. Preparation of Ligands and Proteins

Ligands were drawn in two dimensions using ChemDraw software. Geometric optimization was performed with the help of the MarvinSketch 5.2.5.1 program by protonating at pH 7.4 according to body pH and performing a conformational search [11]. The receptor was downloaded from the Protein Data Bank (PDB) website, separated from water molecules, standard ligands, and other residues, and added hydrogen atoms [12].

2.3. Prediction of Toxicity Aspects, Pharmacokinetics, and Lipinski's Rule of Five (Drug Scanning)

Prediction of toxicity aspects was performed through Toxtree software [13], and prediction of pharmacokinetic aspects was carried out using the PreADMET program, which can be accessed online using the site http://preadmet.bmdrc.kr/ [14]. Drug scanning was used to observe the similarity of drugs with existing drugs (Drug Likeness) and was carried out using the rule of good medicine (Lipinski's rule of five) and oral ligand bioavailability. The parameters used include molecular weight < 500 g/mol, lipophilicity < 5, hydrogen donor < 5, hydrogen acceptor < 10, and refractory molar between 40-130 [15].

2.4. Validation of Molecular Docking Method

The docking stage was validated by re-docking the receptor with natural ligands that had been previously prepared. The docking method can be valid if the obtained RMSD value is < 2 Å [16].

2.5. Docking of Test Ligand

The test ligand was docked using the virtual screening method with the help of the PyRx 0.8 program with the exact coordinates for docking grid box (x,y,z), box dimension, and spacing as the results of receptor validation in AutoDock. Virtual screening was performed on 45 test ligands and one comparison ligand simultaneously with one receptor, and coordinates were adjusted by activating the docking menu and conformational run as 100 [17].

2.6. Molecular Dynamics Analysis

Simulations were conducted on the test ligands with the best values and the comparison ligands using the AMBER 16 program. The parameters used in molecular dynamics were Root Mean Square Fluctuation (RMSF), Root Mean Square Deviation (RMSD), and Molecular Mechanism-Generalized Born Surface Area (MM-GBSA) [18]. The compounds with the lowest binding energies were subjected to molecular dynamics (MD) simulations. MD simulations were conducted using AMBER ff14SB force field for proteins. The ligands were given the general AMBER force field (GAFF), and TIP3P water was added with the size of 10 × 10 × 10 Å. After applying a constrained electrostatic potential to balance the ligands' charges, topology data were created (RESP). The minimization, heating, and equilibration were done using the Amber 16 module.

Before starting the molecular dynamics simulations, a heating device allowed the ligands and receptors to interact with the previously provided force field. Three heating steps—from 0 to 310 K at regular intervals—were applied to approach the body's physiological temperature. After that, the system was stabilized through equilibration, reaching a steady state before molecular dynamics simulations were generated. Moreover, the RMSD and RMSF were computed. The dynamics simulation was carried out using a supercomputer equipped with Intel VR Xeon CPU E5-2620 2.40 GHz and Nvidia VR GeForce GTX TITAN X SSE2 [12].

3. Results and Discussion

3.1. Prediction of Toxicity Aspects, Pharmacokinetics, and Lipinski's Rule of Five (Drug Scanning)

Toxicity testing was done to identify the toxic effects of the test compounds and determine the toxicity level of a compound using Toxtree software. The parameters observed include Cramer' s Rule, the Kroes TTC decision tree, and the Benigni/Bossa rulebase.

Table 1. Toxicity aspect prediction results

Compound	Cramer's rule	Benigni/Bossa rulebase	Kroes TTC
Lenvatinib	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Albanin A	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
14-Hydroxyartonin E	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Artonin E	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Cyclocommunol	Class III	Structural Alert for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	Negligible risk (low probability of a lifetime cancer risk greater than 1 in 10^6)
Artoindonesianin Q	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Artoindonesianin R	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Artonol E	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Heteroflavanone C	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Cycloartocarpesin	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Morusin	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern
Artocarpin	Class III	Negative for genotoxic carcinogenicity Negative for nongenotoxic carcinogenicity	The substance would not be expected to be a safety concern

Description:
Green color: meet the requirements of toxicity testing
Red color: does not meet the requirements of toxicity testing
Purple color: still allowed with adjusted dose

The Cramer's Rule parameters to determine the level of toxicity were identified based on their functional groups. The Kroes TTC decision tree was used to evaluate the threshold for describing drug compounds in humans or predicting the risk of harm. In contrast, the Benigni/Bossa rulebase parameter was employed to identify compounds that can be potentially carcinogenic and mutagenic [19]. The prediction result of toxicity aspects can be seen in Table 1.

Based on Table 1, from 45 prenylated flavonoid derivative compounds, ten test compounds and one comparison compound met the test requirements. In the Cramer's Rule parameter, all prenylated flavonoid-derived compounds from jackfruit root are classified as high toxicity (class III), which means these compounds have a high level of toxicity due to the presence of reactive groups, such as heterocyclic and lactones or cyclic diethers. Nevertheless, it can still be used as a candidate drug with adjusted doses of 1.5 g/kg BW/day to minimize toxic effects [20].

According to the Kroes TTC decision tree parameters, the ten compounds are not expected to threaten their safety or are still within the safe threshold for human consumption and safe if present in the body. These compounds include albanin A, 14-hydroxyartonin E, artonin E, artoindonesianin Q, artoindonesianin R, artonol E, heteroflavanone C, cycloartocarpesin, morusin, artocarpin, and lenvatinib (comparative compound).

According to the Benigni/Bossa rulebase parameter, the compounds that passed the test showed negative results, or there was no possibility of causing carcinogenicity, either through genotoxic or non-genotoxic mechanisms due to the absence of an alert structure for carcinogenicity.

Table 2. Pharmacokinetic aspect prediction results

Compound	Parameter		
	$CaCo_2$	HIA (%)	PPB
Lenvatinib	18.993 [b]	93.212 [c]	88.933 [b]
Albanin A	17.648 [b]	85.301 [c]	100 [a]
14-Hydroxyartonin E	10.604 [b]	81.658 [c]	89.853 [b]
Artonin E	10.849 [b]	88.431 [c]	88.647 [b]
Artoindonesianin Q	16.845 [b]	91.079 [c]	87.45 [b]
Artoindonesianin R	16.845 [b]	91.081 [c]	87.527 [b]
Artonol E	19.822 [b]	92.453 [c]	88.554 [b]
Heteroflavanone C	35.408 [b]	94.488 [c]	82.537 [b]
Cycloartocarpesin	17.312 [b]	90.600 [c]	89.976 [b]
Artocarpetin A	18.925 [b]	90.897 [c]	92.093 [a]

Description:
$CaCo_2$: <4→ Low [a], 4-70→ Medium [b], >70→ High [c]
HIA : 0-20% → Bad [a], 20-70% → Medium [b], 70-100% → Good [c]
PPB : >90%→ Firmly bound [a], <90%→ Weakly bound [b]
Black color = meet the ADME test criteria
Red color= does not meet the ADME test criteria

Compounds that pass the selection were then predicted for several pharmacokinetic aspects of molecular design using the PreADMET program, a web-based application aiming to predict the absorption, distribution, metabolism, and excretion processes in the human body in silico. The parameters observed included

Caco-2, HIA (Human Intestinal Abortion), and PPB (Plasma Binding Protein). Predictions of pharmacokinetic aspects can be seen in Table 2.

Table 2 shows seven test compounds met the ADME test criteria, including 14-hydroxyartonin E, artonin E, artoindonesianin Q, artoindonesianin R, artonol E, heteroflavanone C, cycloartocarpesin, and lenvatinib (comparison compound). The comparison compound (lenvatinib) and all prenylated flavonoid derivative compounds in jackfruit root were predicted to have a moderate permeability value of 4–70. The absorption rate in the human intestine is in a good range from 70% to 100%. Some compounds' blood protein binding level is > 90%, indicating strong binding to plasma proteins. However, the compounds lenvatinib (88.933%), 14-hydroxyartonin E (89.853%), artonin E (88.647%), artoindonesianin Q (87.45%), artoindonesiani R (87.527%), artonol E (88.554%), heteroflavanone C (82.537%), and cycloartocarpesin (89.976%) had low blood protein binding level of < 90% which indicated weak binding to plasma proteins which meant that these compounds could be distributed well. This is consistent with the idea that drugs bound to plasma proteins are inactive. Only free, unbound drugs can act on their targets to create a biological response and enter the elimination process [21].

Table 3. Drug scanning test results according to Lipinski's rule of five

Compound	Lipinski's				
	BM	Hydrogen Donor	Hydrogen Acceptor	Log P	Refractory Molar
	< 500 g/mol	< 5	< 10	< 5	40-130
Lenvatinib	426	4	8	4.071	113.515
14-Hydroxyartonin E	452	5	8	4.008	120.622
Artonin E	436	4	7	5.035	119.210
Artoindonesianin Q	398	3	7	4.163	106.908
Artoindonesianin R	398	3	7	4.163	106.908
Artonol E	448	3	7	5.046	122.221
Heteroflavanone C	414	2	7	4.338	111.321
Cycloartocarpesin	352	3	6	3.603	94.554
Styracifolin D	520	4	8	4.798	138.441
Isocycloheterophyllin	502	3	7	6.559	140.251

Description:
Black color: meet Lipinski's test criteria
Red color: does not meet Lipinski's test criteria

Lipinski's test is a qualitative prediction of pharmacokinetic aspects related to the ability to absorb and distribute drugs in the body through oral administration. It can help distinguish between drug-like and non-drug-like molecules by considering their absorption rate and permeability through the lipid bilayer in the human body. The data on the results of the compound test using Lipinski's rule can be seen in Table 3.

Table 3 shows four compounds that fulfill Lipinski's rule of five criteria: artoindonesianin Q, artoindonesianin R, heteroflavanone C, cycloartocarpesin, and the comparison compound lenvatinib. They can potentially be given orally. However, the artoni E, artonol E, styracifolin D, and isocycloheterophyllin do not fulfill Lipinski's rule of five criteria on parameters log P, molecular weight, and refractory molar.

3.2. Docking of Test Ligands and Visualization of Interaction on Receptors

Lenvatinib is one of the standard drugs for patients with liver cancer or hepatocellular carcinoma. The choice of lenvatinib as a comparison compound was based on its mechanism of action, which can inhibit the tyrosine kinase receptor VEGFR-2 from preventing the development of cancer cells and angiogenesis. The receptor used in the molecular docking simulation was VEGFR2 with PDB code 3WZE. Docking validation results can be seen in Table 4 and Figure 1.

Table 4. Docking validation results

PDB code	Center Grid Box	Box Dimension	Space	RMSD (Å)	Binding Affinity (kcal/mol)	Ki (µM)
3WZE	X = 21.492 Y = 25.278 Z = 35.952	X = 40 Y = 40 Z = 40	0.375	0.412	-12.49	699.95 pM (0.00069995 µM)

The result of receptor validation (redocking) produced free energy (ΔG) of -12.49 kcal/mol and its inhibition constant (Ki) of 0.00069995 with an RMSD value of 0.412 Å which means the validation method is called valid because the resulting RMSD value is 2 Å. The lower the RMSD value, the closer the position of the natural ligands from docking to the natural ligands from crystallography; hence, the method is better. The molecular docking parameters can be used because they meet the criteria and can be trusted for further research on the test compounds. The results of the molecular binding of test compounds and lenvatinib against VEGFR2 receptors are in Table 5.

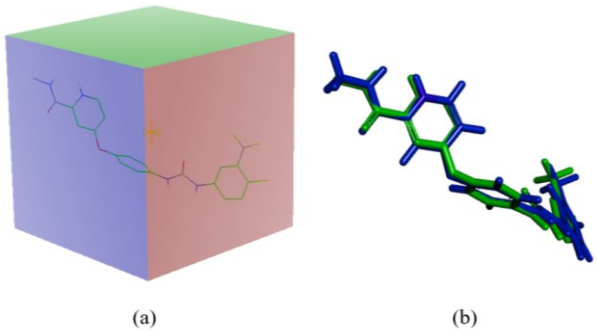

Figure 1. (a) Native ligand position in a grid box, (b) Overlay visualization of native ligand overlap after validation (green) with before validation (blue) at the 3WZE receptor

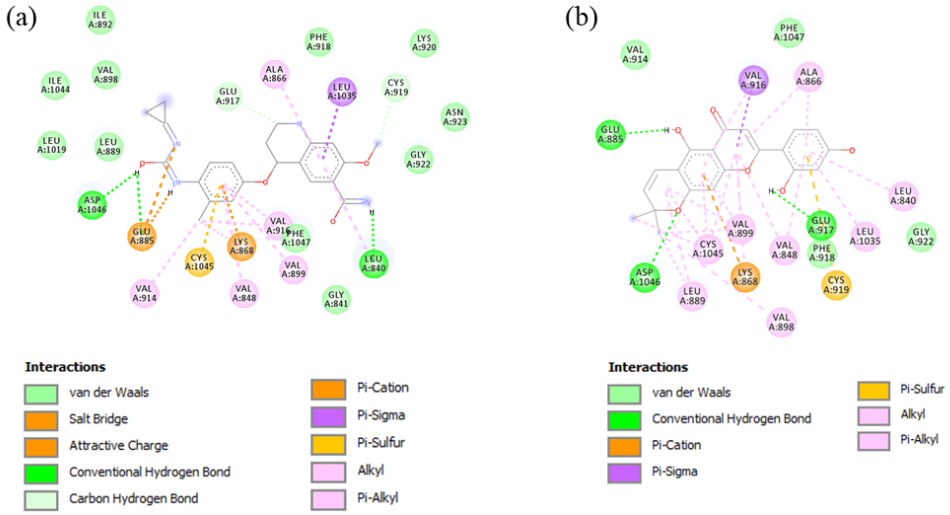

Figure 2. (a) Visualization results of the interaction of lenvatinib with the VEGFR2 receptor, (b) Visualization results of the interaction of cycloartocarpesin with the VEGFR2 receptor

Table 5. The binding affinity of lenvatinib and selected compounds against VEGFR2

Compound	Binding Affinity (ΔG) (kcal/mol)	Ki (μM)
Lenvatinib	-7.03	7.08
Artoindonesianin Q	-6.28	24.96
Artoindonesianin R	-7.31	4.42
Artoindonesianin B	-2.78	9.200
Heteroflavanone C	-7.04	6.90
Styracifolin D	+59.24	-
Cycloartocarpesin	-8.49	0.59967
Artonin B	+12.86	-
Cudraflavone A	-6.90	8.80
Artocarpin	-6.69	12.48

Description:
Green color: meet docking requirements (value is smaller than the comparison compound)
Black color: does not meet the docking requirements

Based on Table 5, the prenylated flavonoid derivatives contained in jackfruit root obtained three compounds with lower ΔG and Ki values than the comparison drug lenvatinib, specifically artoindonesianin R, heteroflavanone C, and cycloartocarpesin compounds. This indicates that the level of affinity of the three compounds to the receptor is higher than the comparison compound, so the three compounds may have acted as an anticancer agent against liver cancer.

The bonds formed from the interaction between the reference drug compound (Lenvatinib) and the target protein were hydrogen bonds at residues of Asp1046, Leu840, and Glu885, as well as contact with the hydrophobic part with 11 residues consisting of Leu1019, Leu889, Ile1044, Val898, Ile892, Phe918, Lys920, Asn923, Gly922, Gly841, and Phe1047. Moreover, the bonds formed from the interaction between the cycloartocarpesin compound and the target protein were hydrogen bonds at residues Glu885, Asp1046, and Glu917, as well as hydrophobic contact with four residues consisting of Val914, Phe1047, Gly922, and Phe918.

The amino acid residue that formed hydrogen bonds between the reference drug and the test compound with the best affinity was the Glu885 residue, so it is possible that the cycloartocarpesin test compound has the same biological activity and has a stable interaction with the comparison drug compound because it binds to the same amino acid residue.

3.3. Molecular Dynamics Simulation

The interactions that occur in the molecular docking method were then retested by molecular dynamics with a time of 20 ns (20000 ps), producing Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) values. RMSD was used to compare conformational or three-dimensional (3D) molecular changes during the simulation.

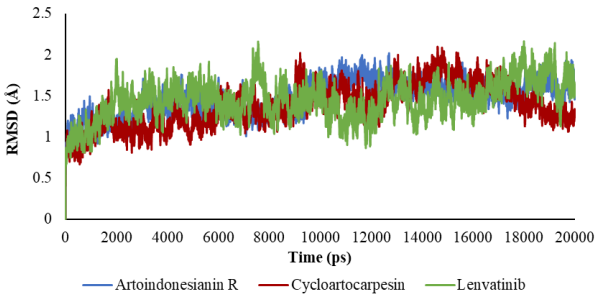

Figure 3. RMSD values of lenvatinib, artoindonesianin R, and cycloartocarpesin compounds

Based on Figure 3, during the molecular dynamics simulation in progress, there was an increase in the RMSD value, which indicated that the ligand was ready to form bonds with the opened protein structure. The highest RMSD value of the artoindonesianin R test compound was ± 2.02 Å at 12 ns, the highest RMSD value of the cycloartocarpesin test compound was ± 2.09 Å at 14 ns, and the highest RMSD value of the comparison drug (lenvatinib) was ± 2.16 at a time of 7 ns. Then an evaluation was carried out using the Discovery Studio Visualizer program to see the ligand and protein positions' stability during the simulation.

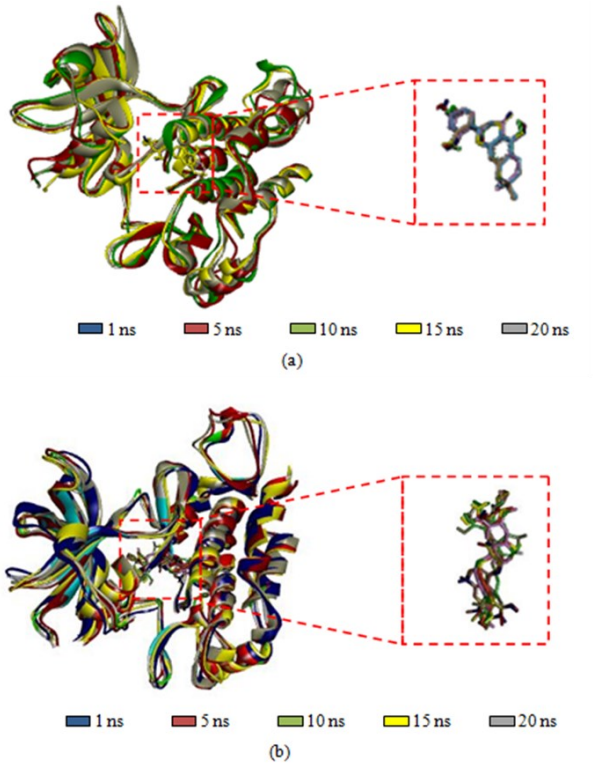

Figure 4. (a) Complex Superimposition Overlay on the results of the molecular dynamics simulation of the cycloartocarpesin test compound, (b) the comparison compound lenvatinib

Based on Figure 4, it can be predicted that the time needed for cycloartoarpesin to reach a stable conformation, in general, is when the simulation runs until the simulation time ends. In contrast, the comparator lenvatinib has not reached a stable condition until the simulation ends, so extending the analysis time in the molecular dynamics simulation is necessary. The stability level of the comparator compound was achieved at 16 ns with an RMSD value of 1.5 Å, the stability level of the test compound artoindonesianin R was achieved at 14–16 ns with an RMSD value of 1.4Å, and the stability level of the cycloartocarpesin compound was reached at 2–4 ns with a value of RMSD 1.3 Å.

Unlike RMSD, RMSF was calculated for each residue that arranges the protein and determines the extent of protein flexibility when the simulation system is in progress [13]. It is considered stable when the fluctuation is low and less stable when it is high (Figure 5).

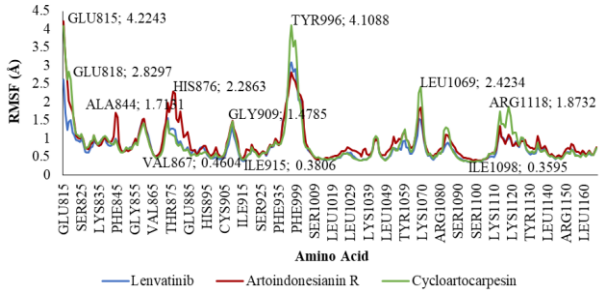

Figure 5. RMSF values of lenvatinib, artoindonesianin R, and cycloartocarpesin compounds

The residue that experienced the highest fluctuation was in the compound artoindonesianin R with the amino acid residue Glu815 (4.2 Å), while the residue that experienced the lowest fluctuation was in the compound cycloartocarpesin with the amino acid residue Ile1098 (0.3 Å).

The RMSD and RMSF analysis results were continued by calculating the complex energy using the Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) calculation method. In the MM-GBSA method, free energy (ΔG) indicates the affinity of a compound to bind to the receptor. The smaller the value of free energy (ΔG) produced, the greater the ability of a compound to bind to the receptor.

Table 6. The system bond energy calculation using the MM-GBSA method

Energy component (kcal/mol)	System		
	Lenvatinib	Artoindonesianin R	Cycloartocarpesin
van der Waals (vdW) Interaction	-56.3839	-54.222	-53.5874
Electrostatic Energy (EEL)	-22.1495	-72.3192	-45.7468
Electrostatic Contribution to Solvation-Free Energy (E_{GB})	56.2957	77.7401	48.4219
Non-polar Contribution to the Solvation-Free Energy (E_{SURF})	-6.5164	-6.6831	-5.7287
ΔG gas (vdW+EEL)	-78.5334	-126.5412	-99.3342
ΔG solv (E_{GB}+E_{SURF})	49.7793	71.057	42.6932
ΔG TOTAL (vdW+EEL+E_{GB}+E_{SURF})	**-28.7541**	**-55.4842**	**-56.641**

Table 6 shows that the cycloartocarpesin system has a lower ΔG_{Total} value of -56.641 kcal/mol compared to the compound artoindonesianin R (-55.4842 kcal/mol) and the comparator drug lenvatinib (-28.7541 kcal/mol). This shows that the cycloartocarpesin compound has a better affinity for the VEGFR2 receptor (PDB 3WZE), so the compound can be predicted to have good potential as a liver cancer drug than the comparison drug lenvatinib by forming a stable bond.

4. Conclusion

Prenylated flavonoid derivatives with stable interactions with the VEGFR2 receptor in silico was cycloartocarpesin because it had the same biological activity and stable interactions with the comparison drug, so it bound to the similar amino acid residue, namely the amino acid Glu885. The selected compound cycloartocarpesin is predicted to provide activity as a liver anticancer with a value of ΔG_{Total} -56.641 kcal/mol. Therefore, the compound is predicted to be used as a candidate for liver anticancer drugs.

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