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Molecular Docking and Dynamic Simulation of Erythrina fusca lour Chemical Compounds Targeting VEGFR-2 Receptor for Anti-Liver Cancer Activity

Oleh:
Ketua: Dr. apt. Supandi M.Si (0319067801)
Anggota 1: apt. Rosa Adelia, M.Farm (0328128901)

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Mengetahui,
Ketua Program Studi

Dr. apt. Rini Prastiwi**, M.Si.**
NIDN. 0628097801

Ketua Peneliti

Dr. apt. Supandi, M.Si.
NIDN.0319067801

Menyetujui,
Dekan FFS.

Dr. apt. Hadi Sunaryo**, M.Si**
NIDN. 0325067201

Ketua Lemlitbang UHAMKA

Dr. apt. Supandi, M.Si
NIDN. 0319067801

LAPORAN AKHIR

Molecular Docking and Dynamic Simulation of Erythrina fusca lour Chemical Compounds Targeting VEGFR-2 Receptor for Anti-Liver Cancer Activity
Background Liver cancer originates from the liver and is an aggressive tumor often occurring in chronic liver disease and cirrhosis [1]. Globally, in 2020, as many as 905,677 people were diagnosed with liver cancer, and 830,180 died [2]. Vascular Epidermal Factor Receptor-2 (VEGFR-2) PDB code 4ASD. VEGFR-2 is a proangiogenic pathway to increase stages of angiogenesis such as vascular permeability, survival of endothelial cells, proliferation, migration or invasion of surrounding tissue, and formation of capillaries. The mechanism of the VEGFR-2 pathway is to block tyrosine kinase activation [3]. Sorafenib is an anti-angiogenic, its main target is as a multityrosine kinase inhibitor. The Food & Drug Administration (FDA) has approved sorafenib as a systemic therapy for treating liver cancer [4]. Sorafenib is an anticancer mechanism by blocking various growth factor tyrosine kinase receptors, such as VEGF, PDGF, and c-Kit, thereby inhibiting Raf/MEK/ERK signal transduction [5] Giving sorafenib over a long period can cause cancer cells to become resistant to the drug and result in ineffective treatment. New treatment options are needed for treatment therapy in liver cancer. Many discoveries and developments of new anticancer agents are selective in inhibiting cancer cell proliferation pathways [6]. Designing and developing new drugs requires high costs and a long time. In drug development, computer-aided drug design (CADD) is needed to reduce time and costs. CADD or in silico methods can identify essential compounds, such as protease inhibitors and antibiotics. In addition, many anticancer compounds have been identified using the CADD approach [7]. Molecular docking is a structure-based in silico method that can carry out virtual screening of approved drugs, natural products, or compounds that have been synthesized in affordable time [8]. Molecular dynamic simulations can produce suitable conformational states. MD can be used to predict the stability of ligand-receptor complexes with the best results from molecular docking [9]. Erythrina fusca, commonly known as the cangkring plant, can be used as a cancer treatment, especially liver cancer. Bioactivity studies on E. fusca show antibacterial and antimalarial activity, anti-estrogenic and estrogenic activity, potential in treating ischemia, reperfusion injury, and antiherpetic activity. Initial phytochemical screening of the aerial parts (above-ground parts) of E. fusca showed the presence of Alkaloids, Flavonoids, Triterpenes, Steroids, Saponins, Lactones, Coumarins, Reducing Sugars, Carotenoids, Amine and Cardiac Glycosides [10]. This research uses a computational study of the interaction between chemical compounds from the cangkring plant (Erythrina fusca Lour) for liver cancer and the VEGFR-2 receptor using molecular docking and molecular dynamic

methods. The software used for this research was Pymol, AutoDock Tools, Biovia Discovery Studio, and Gromacs.

Objectives

This research aims to find chemical compounds from the cangkring plant (Erythrina fusca) with good potential and conformation in liver anticancer activity against the VEGFR-2 receptor using the in-silico method.

Method

Molecular Docking Preparation of VEGFR-2 Macromolecules Downloading the VEGFR-2 macromolecule from the site https://www.rcsb.org/ ID 4ASD. Separating H2O and sorafenib, then optimizing by adding hydrogen and charge computed gasteiger using Autodock Tools Preparation of native ligands and test ligands Downloading the ligand from the site (https://pubchem.ncbi.nlm.nih.gov/), the ligand is optimized by setting Torsion Tree with choose torsion and set torsion useAutodock Tools. Lipinski analysis number of active Lipinski analysis of the site (http://scfbioiitd.res.in/software/drugdesign/lipinski.jsp#anc hortag) Lipinski terms consist of molecular weight ≤ 500 Da, hydrogen bond acceptor ≤ 10, log P ≤ 5, hydrogen bond donor ≤ 5 Docking Simulation Redocking or molecular docking again with a natural ligand (sorafenib) that has been separated and optimized. Grid box arrangement at grid center x = -24.964, y = -0.497, z = -10.399 with dimensions 40x40x40 Å and spacing = 0.375 Å. Next, save the grid box and save the resulting grid box in (*.gpf) format, then run the grid process with the autogrid.exe binary software. The molecular docking stage involves selecting the receptor and ligand then setting the genetic algorithm parameters then setting the docking parameters 4.2, saving the docking document with Lamarckian GA 4.2 in (*.dpf) format, and then running the docking process with the autodock.exe binary software. Analysis And Visualization Analysis was carried out with bond energy, inhibition constant, and interaction parameters. Visualization in 2D (two dimensions) and 3D (three dimensions) usingBiovia Discovery Studio Visualizer Molecular Dynamic Receptor and Ligand Preparation The VEGFR-2 receptor and ligand were prepared to proceed with the MD simulation. Using a natural ligand (sorafenib) and the best ligand analysis results from docking. The file used results from the complex between the protein and each ligand in (*.pdb) format. 3 Borneo Journal of Pharmacy, Vol x Issue x, Month Year, Page x – x e-ISSN: 2621-4814 4 S ystem Setup Complex ligand-receptor format (*pdb) files are input on CHARMM-GUI

(https://www.charmmgui.org/). At this stage, the topology, water box, ion addition, and selection force field are created. System Minimization System minimization (energy reduction) is carried out to ensure that the system does not experience inappropriate collisions. The structural complex needs to be loosened by reducing the potential energy in the system.

Results and Discussion

The Lipinski analysis process (Ro5) is carried out on test ligands and natural ligands. Lipinski analysis was carried out to predict the physicochemical properties of the native and test ligands. Lipinski's Ro5 is a rule for designing drugs expected to penetrate membranes when administered orally. Lipinski's rule consists of a molecular weight (BM) of no more than 500 g/mL, a partition coefficient (logP) value of less than 5, the number of hydrogen bond donors less than 5, and the number of hydrogen bond acceptors less than 10. Based on these rules showed that the positive control Sorafenib and 25 of 36 test ligands met the four criteria of Lipinski's rule. Physicochemical criteria for acceptable drug absorption and permeability constitute the first step in oral drug bioavailability [11]. The receptor's binding or active site is also determined [12]. Determination of the binding site was carried out using PyMOL by inputting the GDP file of the original ligand and then typing 'center of mass' on the PyMOL command line to obtain the x, y, and z values (x = -24.964; y = 0.497; z = -10.399). Next, the grid box is set at the grid center x = -24.964, y = -0.497, z = -10.399 with dimensions of 40x40x40 Å and spacing = 0.375 Å. The grid box is used as a reference for the molecular docking process of the compound to be tested. The redocking results were analyzed with PyMOL, producing an RMSD (Root Mean Square Deviation) value of 1.136 Å. These results indicate that the docking procedure is valid because it produces an RMSD < 2 Å. The greater the RMSD value, the greater the deviation that occurs. The smaller the RMSD value, the closer the docking result of the ligand pose to the natural ligand pose [13].

Figure 1. RMSD Result Docking results in documents in (*.dlg) format were analyzed using AutoDock Tools with binding energy parameters (ΔGbind), inhibition constants (Ki), and visualization results by analyzing ligand and amino acid interactions. The binding energy value and inhibition constant are parameters of the conformational stability of the compound in terms of affinity with the receptor [14]. The binding energy value is obtained through the interaction of the ligand compound with the receptor, which shows the suitability between the shape and size of the ligand and the binding site on the receptor [15]. Based on the molecular docking results of the native ligand Sorafenib, it produces ΔGbind -11.51 kcal/mol, and the inhibition constant (Ki) value is 3.67 nM. The test ligand Isobavachalcone has the smallest ΔGbind value and is close to Sorafenib, namely 11.45 kcal/mol with an inhibition constant (Ki) value of 4.05 nM. Ligand interactions with stable receptors tend to have low binding energy values, which indicate the best affinity. The smaller the inhibition constant value, the better the inhibitory activity [14]. The more negative the binding energy value, the lower the inhibition constant (Ki) value. The relationship between these two parameters tends to be directly proportional [16]. The results of the bond energy (ΔGbind) and inhibition constant (Ki) can be seen in Table I.

Table I. ΔGbind results and ligand inhibition constants against the VEGFR-2 macromolecule

Ligand	ΔGbind (kkal/mol)	Inhibition Constant (Ki)
Sorafenib	**-11,51**	**3,67 nM**
Isobavachalcone	**-11,45**	**4,05** nM
Vestitone	-8,94	281,56 nM
Erythraline	-8,92	290,19 nM
8-prenyldaidzein	-8,9	299,61 nM
Isoliquiritigenin	-8,87	317,46 nM
Erysodine	-8,83	336,63 nM
Lonchocarpol A	-8,7	417,45 nM
Wighteone	-8,65	459,55 nM
Liquiritigenin	-8,61	490,49 nM
Lupinifolin	-8,61	490,15 nM
Eryvarin D	-8,27	872,18 nM
Scandenone	-8,22	944,67 nM
Erysotrine *N*-oxide	-8,15	1,06 nM
Erythrisenegalone	-8,11	1,14 nM
Genistein	-8,07	1,22 nM

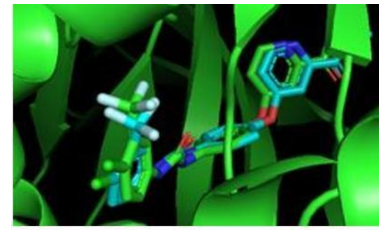

Figure 1. RMSD Result

Identification of interaction results using Biovia Discovery Studio software, which displays visualizations in 2D (two dimensions) and 3D (three dimensions), can be seen in Figure I. The visualization results are in the form of interactions of amino acid residues with ligands. The resulting amino acid interactions indicate the possibility of contact between the ligand and the protein so that it has inhibitory activity. The binding area is where the protein binds to the ligand, which will affect the conformation and function of the protein. The binding site shows amino acid residues which play a role in forming interactions between macromolecules and ligands such as hydrogen bonds, hydrophobic bonds, and electrostatic bonds [17]

Next is the molecular dynamics process. Test ligands are selected by selecting the best test ligand based on the results of molecular docking of compounds in cangkring plants (E.fusca), namely Isobavachalcone. The results of docking in the format (*.dlg) are input into AutoDock Tools for analysis and then the analysis results. The protein-ligand complex is made and saved in (* .pdb) format. Next, the file can be used for the molecular dynamics simulation stage, which begins with system preparation using the CHARMM-GUI website.

Topology, waterbox, ion addition, and force field selection are carried out at this stage. The topology is automatically formed after complex file input. The water box is formed automatically with a rectangular box and cubic crystal type. Solvation or addition of 13737 water molecules for the Sorafenib complex and 13702 water molecules for the Isobavachalcone complex, water molecules are added to the system in the box. Furthermore, adding NaCl ions (Na+ = 39, Cl- = 38) with a concentration of 0.15 M. Biological systems generally contain several salts. So, MD simulations are carried out in electroneutral conditions to model relevant conditions or as closely as possible to biological systems conditions [20]. Before minimization, the overall charge of the system is neutralized by adding ions [21]. Force field selection is done by selecting the CHARMM36 (C36) force field and selecting hydrogen mass repartitioning. The selected generator input, GROMACS, and temperature setting to 310oK. Complex heterogeneous systems with C36 FF can be easily accessed in various simulation packages, including GROMACS [22]. The CHARMM36 force field was optimized using the standard TIP3P (Transferable Intermolecular Potential Three-Point) solvent model for proteins [23]. TIP3P is part of the CHARMM simulation package and is frequently used to simulate biological systems [24]. Minimization is carried out with n steps of 5,000 steps and can stop if the maximum force is <10 kJ/mol. Based on the minimization results on sorafenib, the potential energy value is 7.2752488e+05, the maximum force is 9.0506854e+02 on 4913 atoms, and the normal force = 1.7884336e+01. Meanwhile, minimizing the isobavachalcone, the potential energy value is -7.1923694e+05, the maximum force is 9.5177234e+02 on 4913 atoms, and the normal force = 1.5471794e+01. The equilibration process was carried out with 125,000 steps and 125 ps. The Parrinello-Rahman barostat method functions to maintain constant pressure in the system, and this method is generally recommended for NVT/NPT production simulations [25]. The Molecular Dynamic (MD) production stage is run with 5,000,000 steps and a time of 20

nanoseconds (ns). The time required for one simulation of the production of the native ligand Sorafenib as a positive control is 18 hours 46 minutes, while the duration for Isobavachalcone is 18 hours 33 minutes. After the production process, several parameters can be analyzed: RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuation), Radius of Gyration, and Hydrogen Bond. The results of the MD simulation are in the form of a trajectory that can be analyzed with the help of visualization from xmgrace [26]. The MD results are analyzed to determine the stability of the interaction between the ligand and the receptor over space and time [27]. RMSD aims to determine the magnitude of changes in binding pose over time. This analysis can assess the stability of interactions between ligands and proteins [20]. The graphical representation of the RMSD value explains the possible variations that occur during the simulation [26]. Overall, it can be concluded that the protein-BAX complex and the protein-ISB complex have an RMSD range of around 0.1750.225 nm. The RMSD value of both complexes is less than 3Å (0.3 nm), which shows that the entire system (complex) has good stability [28]. For the binding residues, the RMSF values were in the range of 0.0394-0.0730 nm for the positive control complex and 0.0392-0.1026 nm for the Isobavachalcone complex. An RMSF value of less than 3Å (0.3 nm) indicates that the entire system (complex) has good stability [28]. The radius of gyration value ranges between 1.95-2.0 nm during the simulation time (20000 ps). Based on the graph, it shows that the compactness of the two ligand-protein complexes is stable.

Conclusion

The results of molecular docking of the chemical components of cangkring plants show that the binding energy value of the best test ligand, namely Isobavachalcone, is -11.45 kcal/mol. The comparison ligand (Sorafenib) is -11.51 kcal/mol. The chemical components of cangkring plants interact with the amino acid residues of the VEGFR-2 receptor through hydrogen bonds,

(Sorafenib). Molecular dynamics simulations produce RMSD, RMSF, Radius of Gyration, and hydrogen bond parameters. The Isobavachalcone and Sorafenib complex meets the RMSD and RMSF value requirements of less than 3Å (0.3 nm). The Radius of Gyration value is stable until the end of the simulation, and the movements of the ligand-protein complexes resemble each other. The results of the hydrogen bond interactions between the two complexes are relatively stable per unit of time. Hydrogen bonds have an essential role in the formation of receptor-ligand complexes.

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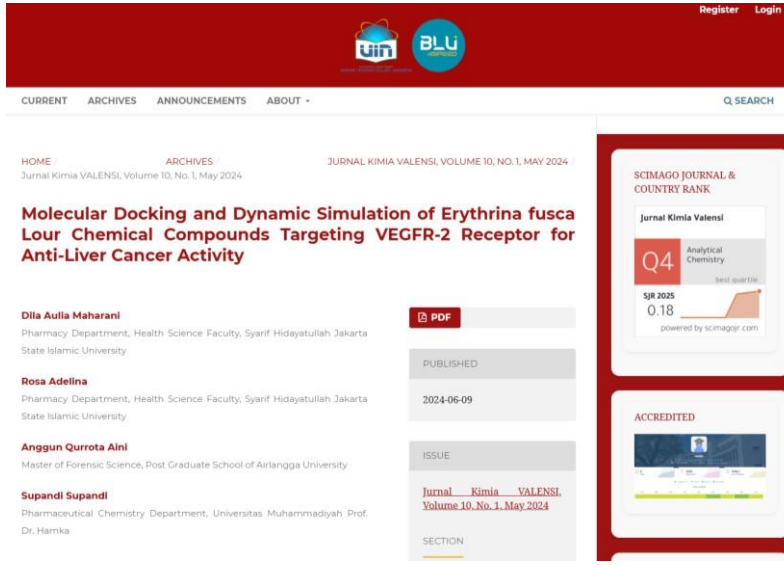

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