Volume 16
Number 1
JUNE 2024

Journal of
The Indonesian Society of Integrated Chemistry
Published by Jambi University, Chemistry Education Study Program

P-ISSN 2085-1715 & E-ISSN 2621-5543

JISIC

In Silico Study of Bioactive Compounds of Putat Leaf Extract (Planchonia valida) as Anti-Cancer Against the VEGFR2 Receptor

Anisa Bela[1], Tribuana Tungga Dewi[1], Satria Prabawa[1], Alfi Khatib[2], Yusnaidar[1], Madyawati Latief[1,3], Indra Lasmana Tarigan[1,3*]

1 Chemistry Study Program, Department of Mathematics and Natural Sciences, Faculty of Science and Technology, Jambi University. Jambi – Ma. Bulian Road, Mendalo Indah, Muaro Jambi, Jambi, Indonesia.
2 Department of Pharmaceutical Chemistry, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Malaysia.
3 Natural Product and Bioactive Compoud Laboratory, Fakultas Sains dan Teknologi, Universitas Jambi.

ABSTRACT

Cancer is the process of forming new tissue that is abnormal and malignant. Efforts to discover anti-cancer drug compounds continue to be made to minimize the toxic effects of chemotherapy, so it is necessary to look for other alternatives to treat cancer. This research aims to determine the anti-cancer activity of putat plant bioactive compounds through identification of receptor targets and interaction studies using the molecular docking method against the VEGFR2 (Vascular endothelial growth factor receptor-2) receptor. The results showed that in the test of eight putat plant bioactive compounds the best results were obtained for the compound 3-oxo-N-(1,3-thiazol-2-yl) butanamide with a binding free energy value of -9.86 kcal-mol-1 with an inhibition constant value of 1.47 µM. The best docking result has an inhibition constant value that is higher than the native ligand and has a binding free energy that is almost close to the binding free energy of the native ligand with an inhibition constant value of 42.38 µM and a binding free energy value of 10.06 kcal-mol-1. Therefore, the results of the docking of the bioactive compound 3-oxo-N-(1,3-thiazol-2-yl) butanamide with the VEGFR-2 receptor are considered capable of being an alternative as a candidate for anti-cancer drugs.

Keyword: Anti-cancer, Docking, Prediction, Toxicity, VEGFR2.

Received: March 8, 2024;
Accepted: June, 19 2024

* coresponding author: Indra Lasmana Tarigan
indratarigan@unja.ac.id
DOI: https://doi.org/10.22437/jisic.v16i1.32049

INTRODUCTION

Cancer is a disease that can threaten human life and is characterized by uncontrolled cell proliferation or cell division. According to Globocan data in 2020, it is estimated that there were 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and nearly 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) in 2020 (Putram et al., 2017). According to World Health Organization (WHO) estimates in 2019, the cancer burden is expected to continue increasing until 2040. Cancer is the first or second leading cause of death before the age of 70 in 112 out of 183 countries and ranks third or fourth in 23 countries. Most medicinal plants in Indonesia play a very important role, especially for people in rural

areas where healthcare facilities are still very limited. Communities around forest areas use medicinal plants as raw materials for medicine based on knowledge about the use of medicinal plants that is passed down from generation to generation. One medicinal plant is the putat plant (Khafid et al., 2023).

The putat plant, scientifically known as Planchonia valida of the family Lecythidaceae, lives in the forests of Malaysia, Sumatra, Kalimantan, Java, Sulawesi, Bali, Lombok, Sumba, Sumbawa, Komodo Island, and Timor. This species is commonly found in humid areas, along riverbanks, or in alluvial plains and mountainous regions at altitudes ranging from 0 to 1000 meters, with an average annual rainfall of 1100 mm to 3800 mm (Supriningrum et al., 2019). Putat leaves can be used to treat skin diseases such as itching by pounding the leaves and applying them to the itchy area. Putat leaves are also used as a bath mixture after childbirth. In addition to being used as medicine, putat leaves can be mixed with cooling powder and used to protect the skin from sun exposure when working in the fields, and they can remove dark spots on the face (Syamsudin et al., 2022).

One of the efforts to develop existing medicines is through drug design. The aim of drug design is to obtain new drugs with better activity and lower toxicity through structural modifications. Changes in the structure of a compound will alter the physicochemical properties of the compound, including its lipophilic, electronic, and steric properties, and these changes in physicochemical properties will lead to changes in the biological activity of the compound (Handoyo et al., 2022). Drug development is a dynamic process that evolves rapidly and is facilitated by computers (Machine Learning). Modeling the interactions between chemicals and biological targets facilitates the development of new pharmacophores. The results of this modeling include ligand and receptor interaction studies to predict effects and processes in the body based on chemical structure (Putra et al., 2020).

In silico testing is widely used today and is popular in the field of computation. In silico studies using molecular docking techniques are a method that can be used to predict the bioactivity of a compound before conducting experimental analysis in the laboratory. This method has advantages, including reducing the excessive use of tools and materials and saving on experimental costs. The in-silico method can also be used to predict compound activity by examining the amount of binding free energy formed in its interaction with the active site of the involved protein (Dona et al., 2019).

Based on research conducted by Dewi et al. (2023), 27 active compounds are contained in putat, and 8 active compounds have potential as anti-cancer agents. This study will conduct in silico testing of 8 active compounds that have potential as anti-cancer agents by examining the interactions of ligands and receptor/target proteins used. This study uses the VEGF/VEGFR2 receptor with the PDB code: 3WZE. Vascular endothelial growth factor receptor (VEGFR) tyrosine kinases are clinically validated drug targets for cancer therapy. VEGF/VEGFR2 is considered the most important pro-angiogenic pathway to enhance all stages of angiogenesis, including vascular permeability, endothelial cell survival, proliferation, migration or invasion into surrounding tissues, and capillary tube formation. Cancer development is often associated with VEGF expression, and the VEGF/VEGFR2 signaling pathway is generally considered the main mediator of tumor angiogenesis, making

VEGF/VEGFR2 a target system for therapeutic intervention in cancer (Kesuma et al., 2018).

This study aims to identify the receptor target of the ligand (quercetin) as an anti-cancer candidate in silico by identifying the target protein VEGFR based on its pharmacophore and studying its interaction through the reverse docking method. Based on this method, predictions of the interaction between test ligands and receptors can be obtained.

METHODS

Equipment and Materials

The primary materials in this study are the 3D structures of eight bioactive compounds from the putat plant stored in PDB format, and the receptor structure (target protein) VEGFR2 with the PDB code 3WZE, stored in PDB format on their respective webserver databases. The hardware used in this study includes a computer and the software used includes PyRx, ChemDraw Ultra version 22.0, Chem 3D version 22.0, AutoDockTools, Discovery Studio Visualizer 2021, and UCSF Chimera. The web server used is The Research Collaboratory for Structural Bioinformatics Protein Data Bank.

Ligand Structure Preparation

Ligand preparation was carried out by converting the 2-dimensional (2D) molecular structures of eight bioactive compounds from the putat plant, drawn using ChemDraw Ultra version 22.0, into 3-dimensional (3D) structural models using Chem3D version 22.0 and saved in PDB format. Hydrogen ions were then added to the ligands using Discovery Studio 2021 and saved in PDB format. Optimization of the ligands was performed using AutoDockTools, followed by setting the number of torsional bonds on the ligands and saving them in PDBQT format.

Macromolecule Preparation

The three-dimensional macromolecule VEGFR-2 was downloaded from the Protein Data Bank (PDB) at https://www.rcsb.org, using the receptor VEGFR2 with the PDB code 3WZE. The macromolecule was separated from solvents and native ligands or non-standard residues using UCSF Chimera. Unnecessary native ligands and residues were removed by selecting the residues, choosing all nonstandard, and then deleting them using the actions feature. The macromolecule (receptor) file was saved in PDB format. The macromolecule was then optimized using Auto Dock Tools by adding hydrogen ions and Kollman charges, and saved in PDBQT format.

Validation of Molecular Docking Parameters

The validation of the molecular docking method was performed using Auto Dock Tools. This was done through the re-docking method (re-docking) of the native ligand of each macromolecule (receptor). The parameter used was Root Mean Square Deviation (RMSD). The outcome of this process included the grid box parameters and RMSD values. The docking method is considered valid if it has an RMSD value < 2 Å, indicating that the protocol is accepted and docking can be performed (Nursamsiar et al., 2020).

Molecular Docking

The molecular docking process was performed using PyRx software based on Auto Dock Tools. The optimized structures

of the macromolecule (receptor) and ligands were saved in a single folder. The docking process used the grid box and energy minimization parameters as per the validation results. Grid box parameters were set using the grid box coordinates determined based on the ligand coordinates from the receptor used in the docking validation process. Docking was then performed using PyRx software with the Auto Dock wizard feature. Docking data displayed included binding affinity values and amino acid residue interactions. The docking results were saved in PDB format.

Visualization and Analysis of Docking Results

Visualization was conducted to observe the interactions occurring in the docking results between the receptor and ligands. The docking results were visualized using Discovery Studio Visualizer 2021.

RESULTS AND DISCUSSION

The prediction of physicochemical properties was carried out using Lipinski's Rule of Five to evaluate the bioavailability of a compound, thereby enabling optimal selectivity. Lipinski's criteria estimate solubility and permeability, developed through both experimental and computational approaches. Consequently, ligands that meet Lipinski's criteria are assumed to have the potential to penetrate the body's cell membranes, be absorbed by the body, and tend to exhibit better stability during testing. According to Lipinski et al. (1997), a compound does not comply with Lipinski's rules if it has more than one violation. Permeability refers to a compound's ability to penetrate membranes. The molecular weight value of the first Lipinski rule criterion is that all ligands must be less than 500 Daltons. If the molecular weight exceeds 500 Daltons, the body will have difficulty absorbing it efficiently as it cannot diffuse across cell membranes. A Log P value greater than 5 can cause the drug compound to exhibit a higher level of toxicity because the drug compound will be retained in the phospholipid bilayer for a longer time and be distributed more widely in the body. This reduces the selectivity of binding to the target enzyme. A Log P value that is too negative or less than -4 is also unfavorable as the compound cannot pass through the phospholipid bilayer (Afladhanti et al., 2022). The third criterion is the number of hydrogen bond acceptors (HBA), which should be less than 10. All tested ligands showed values of less than 10. If the HBA count exceeds 10, it will interfere with the hydrogen bonding between the ligand compound and the receptor. The fourth criterion is the number of hydrogen bond donors (HBD), which should be less than 5. In this study, the HBD count for all ligands was less than 5. Similar to HBA, if the HBD count does not conform to Lipinski's rules, it will affect the hydrogen bonding formed between the ligand and the receptor.

Hydrogen bond donors and acceptors are related to the biological activity of drug compounds (Fransiska et al., 2022). The greater the number of hydrogen bond donors and acceptors, the higher the energy required for the absorption process to occur (Akkoç et al., 2021). The number of hydrogen bond donors and acceptors indicates that the energy needed for the absorption process increases with the increase in hydrogen bonding capacity. If a ligand meets Lipinski's criteria without any violations, it is considered drug-like or a potential candidate for a drug (Hasan et al., 2022). Based on the screening results, eight active

compounds from the putat plant have potential as anti-cancer agents out of the 27 active compounds identified in the putat plant. The bioactive compounds from the putat plant that have been screened are listed in Table 1 and meet Lipinski's rules, indicating high potential bioavailability in the body.

Table 1. Screening Results of Test Ligands

Ligands	Log P Coefficient	Molecular Weight (MW) (g/mol)	HBA	HBD
Thiouracil Acid	0.8105	170.19	2	3
Propofol glucuronide	1.1540	354.39	7	4
(3,3-Dimethoxycyclobutane-1,1 diyl) bis (methylene) dimethane sulfonate	1.8697	332.39	8	0
3-oxo-N-(1,3-thiazol-2-yl) butanamide	1.0607	184.22	4	1
Methane;2-(2-nitropyridin-3-yl) ethyl methane sulfonate; sulfuryl dichloride	4.0149	397.25	8	0
2-[[1-[(3,5-dimethylphenyl) methyl] triazol-4-yl] methyl]-4-(4-hexylpiperazin-1-yl)-1,2-thiazolidine 1,1-dioxid	3.7359	488.69	7	0
2-methyl-N-propyl-N-pyrrolidin-3-ylpentane-1-sulfonamide; hydrochloride	3.6811	312.90	4	0
3-chloro-N-[2-(diethylamino) ethyl]-2-methyl-N-(2-methylpropyl) propane-1-sulfonamide	3.5811	326.9	4	0

Ligand Structure Preparation

A ligand is a signaling molecule that binds to a binding site on a target protein. This binding occurs through intermolecular forces such as ionic bonds, hydrogen bonds, and van der Waals forces. The goal of ligand preparation is to create ligand flexibility by increasing the number of rotatable bonds. The preparation of test ligands involves removing water molecules to facilitate the molecular docking process by simplifying the mathematical calculations. Additionally, hydrogen atoms need to be added to simulate the docking process under physiological pH conditions and to restore hydrogen atoms in the molecule, allowing for the observation of hydrogen bonds that appear in the interaction between the ligand and the target receptor (Hasan et al., 2022).

Macromolecule Preparation

A receptor is a cellular protein macromolecule that specifically binds directly with ligands (hormones, neurotransmitters, and drugs). Particularly in molecular therapy, receptors are often used as drug action targets with precise efficacy results. The 3D structure of VEGFR2 (3WZE) was obtained from the PDB databank and is the result of crystallization using X-ray diffraction with a resolution of 1.90 Å (Figure 1). The smaller the resolution of the protein structure obtained from X-ray crystallography, the closer the structure is to the actual structure within the cell. Additionally, the receptor must originate from the species Homo sapiens to ensure that the docking results are as close to the actual conditions as possible (Kalontong et al., 2022). VEGFR-2 is a type of protein that acts as a tyrosine kinase receptor. This protein plays a crucial role in regulating angiogenesis, which is the formation of new blood vessels. VEGFR2 is found on the surface of endothelial cells, which line blood vessels. The kinase core of VEGFR-2 has a spatial structure consisting

of two lobes that form an active center between the two lobes (Wang et al., 2020) (Figure 2).

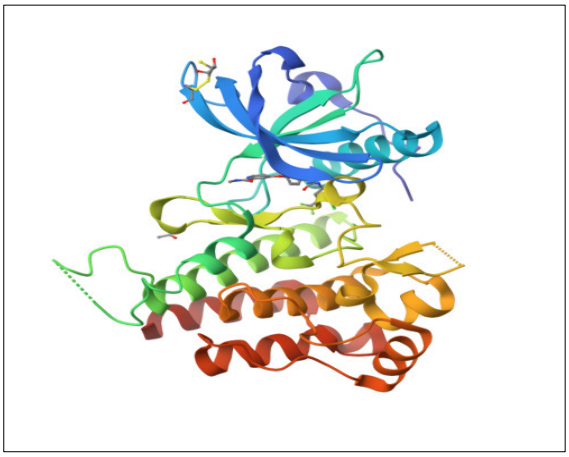


Figure 1. Structure of Vascular Endothelial Growth Factor Receptor-2 Protein (PDB ID: 3WZE)

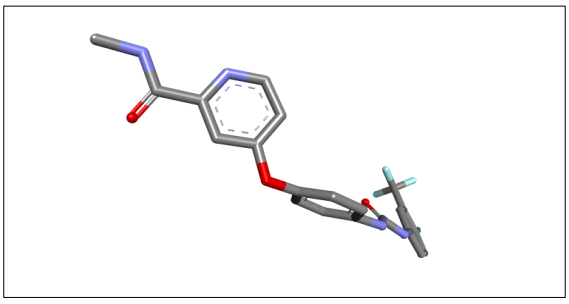


Figure 2. Structure of the Native BAX Ligand from VEGFR-2 Protein (PDB ID: 3WZE)

Analysis Parameters

The analysis parameter used to demonstrate that the VEGFR-2 complex has good quality is represented by a Ramachandran plot. The Ramachandran plot provides information related to conformational stability and the quality of the protein structure to be used in the molecular docking process. This plot depicts the amino acid residues in the enzyme structure in two dimensions, with the φ (phi) angle as the x-axis and the ψ (psi) angle as the y-axis, divided into four quadrants or regions (Hooft et al., 1997). These four regions are (1) the most favored region, (2) the additional allowed region, (3) the generously allowed regions, and (4) the disallowed region. A good protein structure has more than 90% of the residue plot values in the most favored region and less than 0.8% in the disallowed regions (Carugo, 2013). The visualization results show that VEGFR-2 has a Ramachandran plot value of 93.4% in the most favored region, 6.2% in the additional allowed region, 0.4% in the generously allowed regions, and 0.0% in the disallowed region. This indicates that the protein structure used has a good number of amino acid conformations as it meets the criteria of the Ramachandran plot analysis parameters, ensuring that the phi-φ and psi-ψ torsion angles in the protein structure are appropriately formed. The torsion angles represent the rotation of the polypeptide around two bonds formed by the Cα atom, namely the phi (φ) torsion angle and the psi (ψ) torsion angle, making the combination of these two axes a basis for assessing the stereochemical quality of a protein model (Suprianto et al., 2020).

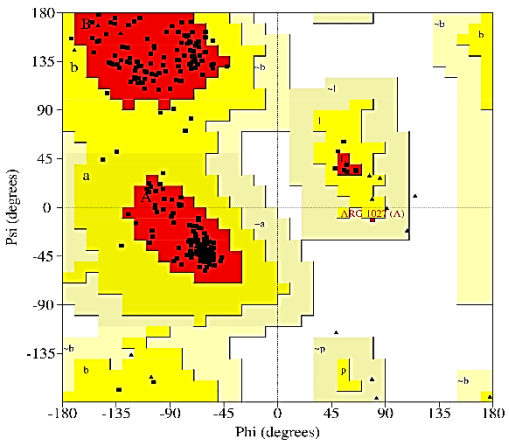


Figure 3. Ramachandran Plot of VEGFR-2 Protein

Toxicity Prediction

The prediction of the toxicity properties of compounds is essential in the discovery of various drugs, serving as a foundation for assessing the potential hazards of a compound to humans and the environment. The toxicity properties of the eight compounds (ligands) were predicted virtually using the admetSAR 2.0 webserver, with seven control parameters: Ames toxicity, carcinogenicity, hepatotoxicity, acute toxicity, skin sensitization, human ether-a-go-go related gene (hERG), and nephrotoxicity. Generally, toxicity can be categorized into short-term/acute toxicity tests and long-term toxicity tests. The Ames toxicity test is a method used to assess the mutagenic potential of compounds using bacteria. According to the criteria set by the US Environmental Protection Agency (EPA), there are four categories of oral toxicity: a) Category I with a value of ≤50 mg/kg, considered highly toxic; b) Category II with a value of 50<x≤500 mg/kg, considered moderately toxic; c) Category III with a value of 500<x≤5000 mg/kg, considered slightly toxic; and d) Category IV with a value of >5000 mg/kg, considered non-toxic (Li et al., 2014).

Carcinogenicity refers to the property of a compound where normal cells transform uncontrollably into cancer cells due to genetic abnormalities (Rahmawati, 2021). The Ames mutagenicity test is widely used to assess the mutagenic potential of compounds using bacteria (Kesuma et al., 2018). The Ames test identifies mutagenic compounds that can trigger the formation of cancer cells. The inhibition of the human Ether-a-go-go-Related Gene (hERG) involves a gene channel associated with the human ether-a-go-go gene, playing a critical role in cardiac repolarization by regulating potassium flow. Blockage or reduction of hERG channel currents can cause long QT syndrome (LQTS), a cardiac side effect that can lead to sudden death (Lamothe et al., 2016). According to Table 2, compounds with low toxicity include Thiourocanic acid and Propofol glucuronide in Category 3 and N-2 Acetoacetanide in category 2.

Table 2. Toxicity Tests

Compound	Toxicity								
	AMES Toxicity (Probability)	Carcinogenesis		Hepatotoxicity (Probability)	Acute Oral Toxicity		Skin Sensitisation (Probability)	hERG Inhibition (Probability)	Nephro-toxicity
		Group	Category		Probability	Category			
Thiourocanic acid	- (0.8700)	Non-required (0.8500)	Non-Carcinogenic (0.4973)	- (0.5500)	0.4732	III	- (0.8674)	- (0.7879)	- (0.7699)
Propofol glucuronide	- (0.6847)	Non-required (0.6816)	Non-Carcinogenic (0.9311)	- (0.6197)	0.7284	III	- (0.8217)	- (0.4922)	- (0.7404)
(3,3-Dimethoxycyclobutane-1,1-diyl)bis(methylene) dimethanesulfonate	+ (0.7500)	Non-required (0.6000)	Carcinogenic (0.7489)	- (0.5618)	0.6184	III	- (0.7321)	- (0.7041)	+ (0.7089)
3-oxo-N-(1,3-thiazol-2-yl)butanamide	- (0.6100)	Non-required (0.4639)	Non-Carcinogenic (0.7900)	+ (0.6875)	0.448	II	- (0.8947)	- (0.6229)	+ (0.5207)
Methane;2-(2- nitropyridin-3-yl)ethyl methanesulfonate;sulf uryl dichloride	+ (0.7000)	Non-required (0.5573)	Carcinogenic (0.6200)	+ (0.6875)	0.5539	III	- (0.7929)	- (0.5753)	+ (0.6834)
2-[[1-[(3,5-dimethylphenyl)methyl]triazol-4-yl]methyl]- 4-(4-hexylpiperazin-1- yl)-1,2-thiazolidine 1,1-dioxid	- (0.7700)	Non-required (0.5841)	Non-Carcinogenic (0.6800)	+ (0.5875)	0.6083	III	- (0.8319)	+ (0.7388)	- (0.8124)
(3-chloropropyl) (dibutylsulfamoyl)methylamine	- (0.5900)	Non-required (0.4493)	Carcinogenic (0.5596)	- (0.5199)	0.4691	III	- (0.8069)	- (0.5511)	+ (0.7208)
2-methyl-N-propyl-N-pyrrolidin-3-ylpentane-1-sulfonamide;hydrochloride	- (0.6800)	Non-required (0.5810)	Non-Carcinogenic (0.6104)	- (0.5783)	0.5486	III	- (0.8243)	- (0.4584)	+ (0.5000)

Molecular Docking Validation

Validation of the molecular docking method is a preliminary test and is crucial before conducting molecular docking on test ligands. At this stage, the process involves re-docking the native ligand to the target protein, which has been removed, using AutoDock Tools. This validation process aims to observe the deviations between the native ligand's conformation before and after re-docking. The validation parameter used for docking is the RMSD (Root Mean Square Deviation) value. RMSD indicates the fit between the ligand's crystallography coordinates and the tested ligand's coordinates and is used to determine the success of the binding prediction, making it important for docking program validation. According to Nursamsiar et al. (2020), an acceptable RMSD value is < 2 Å. The greater the deviation, the higher the error in predicting the ligand's interaction with the protein (Nurjannah et al., 2023).

In molecular docking validation, the grid box is configured to provide space for the native ligand to form a conformation during docking with the target protein. The grid box is where the ligand interacts with the amino acid residues on the target protein. Determining the grid box is essential to find the coordinate points at the binding site area of a protein. As shown in Table 3, the results of the re-docking process of the native ligand on the VEGFR2 receptor indicate an RMSD value of 0.82 Å, thus validating the method used.

Table 3. Molecular Docking Validation

Native Ligand	Binding Free Energy (kkal-mol^{-1})	Inhibition Constant (μM)	RMSD (Å)	Amino Acid Residues
VEGFR2 (3WZE)	-10,06	42,38	0,82	CYS 919, ASP 1046, GLU 885, HIS 1026, GLU 917, ILE 1044, LYS 868, CYS 1045, PHE 1047, VAL 898, LEU 1019, ILE 1044, LEU 889, VAL 848, LYS 868, VAL 916, VAL 848, ALA 866, LEU 1035

Molecular Docking Analysis

Molecular docking is used as an approach to predict how two different molecules, such as a drug compound and a target protein, can bind to each other by providing information about their interactions, the binding distance, and modeling the optimal position and orientation of the molecules when bound (Rahman, 2023). This is crucial in drug discovery as it helps in selecting compounds most likely to interact with specific biological targets, thus accelerating the development of new drugs. Docking analysis allows for the early identification of potential anti-cancer target molecules from natural compounds.

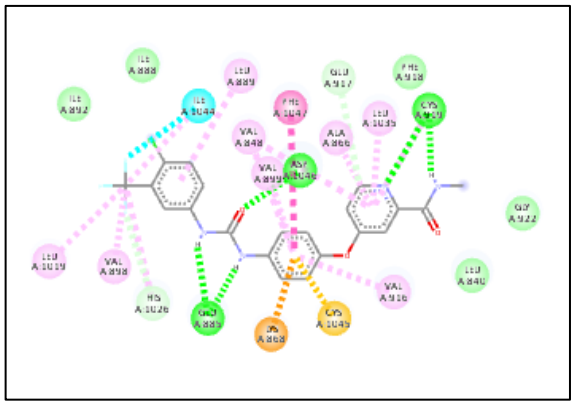
Molecular docking on the test ligands was conducted similarly to the validation process, using the same grid box size and position. The molecular docking in this study was performed using PyRx software with the AutoDock wizard feature. The docking results can be visualized in 2D and 3D using Discovery Studio 2021. The following are the 2D and 3D molecular docking results (Figure 4).

Two-dimensional visualization aims to identify the types of bonds between the ligand and receptor during interaction, which helps predict the bond strength. The

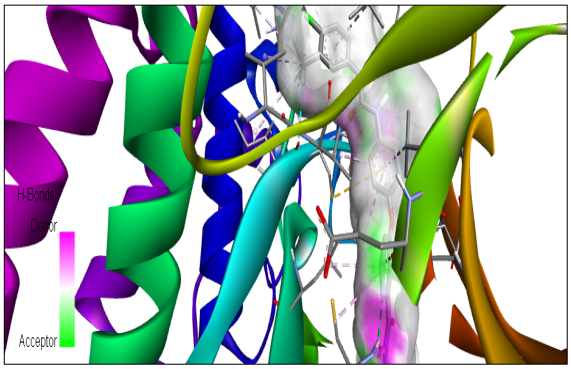
parameters observed for determining ligand affinity to the receptor are binding free energy (ΔG), predicted inhibition constant (ki), amino acid residues, and the number of hydrogen bonds. Ligand affinity to the receptor is determined by the ΔG and ki values. The more negative the ΔG value and the smaller the ki value, the higher the ligand affinity (Pratama, 2016). Test ligands with amino acid residues and hydrogen bonds similar to the native ligand indicate similar interaction types, reflecting comparable biological activity.

Visualization is performed by obtaining docking data or scoring values. Molecules with the lowest scoring values indicate good affinity and stability, and can be visualized using software. The smaller the docking result, the more stable the protein-ligand complex, making the compound better and more potential as a drug candidate (Akbar et al., 2022). Visualization of docking results can be performed using Discovery Studio Visualizer 2021 software. The purpose of visualization is to observe interactions between the ligand and amino acid residues on the receptor. Visualization of ligand-receptor interactions shows the amino acid residues of the receptor that play a crucial role in the binding site area. In the molecular docking test with eight bioactive compounds from the putat plant with the VEGFR-2 receptor, potential anti-cancer activity can be observed from the comparison ligand used as a control, which is the native ligand on the test receptor. A test compound with a lower affinity value is predicted to bind more stably compared to the reference compound (Suhadi et al., 2019). The interaction of amino acid residues can also determine whether a compound has the same biological activity as the reference or native ligand.

The docking results of the eight bioactive compounds from the putat plant can be seen in Table 4. The docking results include binding energy and types of interactions (hydrogen bonds). The scoring function of ligand conformations formed on a macromolecule at equilibrium is known as binding free energy. Binding free energy will be more stable if the value is negative. Binding free energy is also directly proportional to the inhibition constant. The larger the negative value of the ΔG of a compound, the more spontaneous its ability to interact with the target receptor. The inhibition constant can be considered strong if it has a value ≤ 100 µM and weak if ≥ 100 µM (Putri et al., 2023). Low binding free energy indicates a stable ligand-protein complex. Based on this, the test compound conformation with the lowest binding energy and interaction with amino acid residues at the binding site is selected (Susanti et al., 2019).

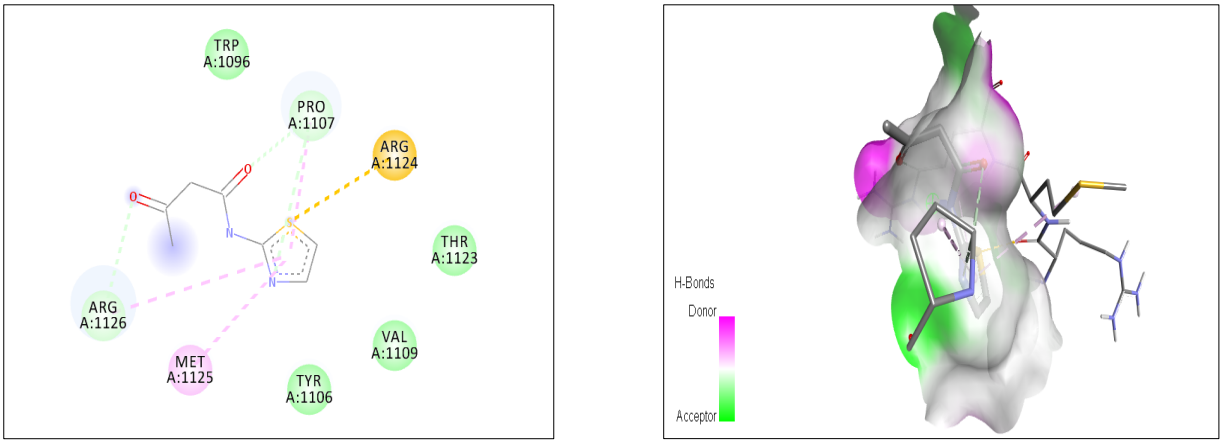


(a)



(b)

Figure 4. Visualization of Native Ligand Docking Results for VEGFR-2. (a) Native Ligand VEGFR-2 in 2D Form (b) Native Ligand VEGFR-2 in 3D Form



(a) (b)

Figure 5. Visualization of Docking Results for Ligand 3-oxo-N-(1,3-thiazol-2-yl) butanamide. (a) Ligand 3-oxo-N-(1,3-thiazol-2-yl) butanamide in 2D Form (b) Ligand 3-oxo-N-(1,3-thiazol-2-yl) butanamide in 3D Form.

Table 4. Docking Results of Ligands with VEGFR2 Receptor

Ligands	Binding Free Energy (kkal-mol^{-1})	Inhibition Constant (μM)	Hydrogen Bonds	Hydrogen Bond Distance (Å)	Amino Acid Residues
Native Ligand	10.06	42.38	ASP 1046 LYS 868 ILE 1044	3.16358 2.47912 2.89431	CYS 919, ASP 1046, GLU 885, HIS 1026, GLU 917, ILE 1044, LYS 868, CYS 1045, PHE 1047, VAL 898, LEU 1019, ILE 1044, LEU 889, VAL 848, LYS 868, VAL 916, VAL 848, ALA 866, LEU 1035
Thiouranic acid	-3.58	2.39	LYS 1062 ASP 1079 PHE 1078	2.6562 2.15312 1.83007	LYS 1062, ARG 1080, PHE 1078, ASP 1079
Propofol glucuronide	-5.18	159.59	ASP 1046 GLU 885	3.17364 2.15869	ARG 1027, HIS 1026, CYS 1024, ILE 1025, ASP 1046, ILE 892, LEU 1019, VAL 898, ILE 1044, CYS 1045, VAL 899, LEU 889, GLU 885, LYS 868, ILE 888
(3,3-Dimethoxycyclobutane-1,1 diyl)bis(methylene)dimethanesulfonate	-2.10	4.58	ARG 1126 TYR 1106 MET 1125 ARG 1124	2.40614 3.16714 3.14128 2.99478	MET 1125, TRP 1096, TYR 1106, PRO 1107, ARG 1126, VAL 1109, THR 1123, ARG 1124
3-oxo-N-(1,3-thiazol-2-yl)butanamide	-9.86	1.47	PRO 1107 ARG 1126	3.58191 3.16139	VAL 1109, ARG 1118, PHE 1115, LEU 1119, THR 1123, TYR 1106, ARG 1124, ARG 1126, PRO 1107, MET 1125
Methane;2-(2-nitropyridin-3-yl)ethyl	-5.09	186.78	HIS 1026	3.68148	LEU 889, VAL 899, CYS 1045, ILE 1044, VAL 898, LEU 1019, ILE 892, ILE

Ligands	Binding Free Energy (kkal-mol^{-1})	Inhibition Constant (μM)	Hydrogen Bonds	Hydrogen Bond Distance (Å)	Amino Acid Residues
methanesulfonate; sulfuryl dichloride					1025, HIS 1026, CYS 1024, GLU 885, ASP 1046, ARG 1027, ILE 888
2-[[1-[(3,5-dimethylphenyl)methyl]triazol-4-yl]methyl]-4-(4-hexylpiperazin-1-yl)-1,2-thiazolidine 1,1-dioxid	-8.51	580.07	ASP 1046 GLU 885 ASP 1046	3.22266 2.72587 3.00689	ARG 1027, ILE 1025, HIS 1026, ILE 888, VAL 914, LEU 889, PHE 1047, CYS 1045, VAL 848, ALA 866, VAL 916, LEU 1035, VAL 899, LEU 840, ASN 923, GLY 922, LYS 868, GLU 885, ASP 1046, ILE 892
2-methyl-N-propyl-N-pyrrolidin-3-ylpentane-1-sulfonamide;hydrochloride	-6.06	36.38			GLU 885, ASP 1046, ILE 892, VAL 898, VAL 899, CYS 1045, ILE 1044, LEU 1019, HIS 1026, ILE 1025, ARG 1027, LEU 889, ILE 888
3-chloro-N-[2-(diethylamino)ethyl]-2-methyl-N-(2-methylpropyl)propane-1-sulfonamide	-4.51	490.52	ARG 1124 GLY 1145	2.97641 3.54752	GLY 1145, LEU 1119, LYS 1120, ARG 1124, GLU 1121, GLY 1122, GLU 1146, HIS 1144

CONCLUSION

The molecular docking of eight bioactive compounds from the putat plant with the VEGFR-2 (Vascular Endothelial Growth Factor Receptor-2) receptor resulted in the best docking outcome for the compound 3-oxo-N-(1,3-thiazol-2-yl) butanamide. This compound exhibited a binding free energy value of -9.86 kcal/mol, an inhibition constant of 1.47 μM, and formed two hydrogen bonds with PRO 1107 and ARG 1126. Based on these results, the bioactive compound 3-oxo-N-(1,3-thiazol-2-yl) butanamide with the VEGFR-2 receptor is considered a potential candidate for anti-cancer drug development.

ACKNOWLEDGEMENTS

We would like to thank the NPBC Laboratory, Faculty of Science and Technology, University of Jambi, for their support with instrumentation and software during this research.

REFERENCES

Afladhanti, P. M., Romadhan, M. D., Hamzah, H. A., Putri, S. N., & Angelica, E. C. (2022). *M*olecular Docking Study of Gingkgo biloba Compounds as Potential Inhibitors of SARS-CoV-2. *SCRIPTA SCORE*: *Scientific Medical Journal,* 4(1), 30–43.

Akbar, N. A., Amin, S., & Wulandari, W. T. (2022). Studi In Silico Senyawa yang Terkandung dalam Tanaman Daun Sirih Merah (*Piper crocatum* RUIZ & PAV) sebagai Kandidat Anti SARS CoV-2. *Prosiding Seminar Nasional Diseminasi Hasi Penelitian Program Studi S1 Farmasi.* 2, 378–391.

Akkoç, S., Tüzün, B., Özalp, A., & Kökbudak, Z. (2021). Investigation of structural , electronical and in vitro cytotoxic activity properties of some heterocyclic compounds. *Journal of Molecular Structure 1246*. https://doi.org/10.1016/j.molstruc.2021.131127

Carugo, O. (2013). Half a century of Ramachandran plots. *Acta Crystallographica.* D69.1333–1341. https://doi.org/10.1107/S09074449130115 8X

Dewi, T.T, A. Bela, S. Prabawa, M. Latief, Yusnaidar, I. L. Tarigan et al. (2023). *Analisis LC-MS/MS Senyawa Metabolite dan Prediksi Senyawa Hasil Isolasi Tanaman Putat (Planchonia valida) Sebagai Kandidat Obat Antikanker*. Laporan Hasil Penelitian Fakultas Sains dan Teknologi, Universitas Jambi.

Dona, R., Frimayanti, N., Ikhtiarudin, I., Iskandar, B., Maulana, F., & Silalahi, N. T. (2019). Studi In Silico, Sintesis, dan Uji Sitotoksik Senyawa P-Metoksi Kalkon terhadap Sel Kanker Payudara MCF-7. *Jurnal Sains Farmasi & Klinis*, *6*(3), 243. https://doi.org/10.25077/jsfk.6.3.243-249.2019.

Fransiska, A. N., Pratama, A. A., Nurayuni, T., Wulanbirru, P., Cordova, D. M., Advaita, C. V., Malau, J., & Mulki, M. A. (2022). *Jurnal Pendidikan dan Konseling Review : Target Aksi Obat Terhadap Reseptor Dopamin*. *4*, 8706–8716.

Handoyo, M. O. M., Yuliani, Y., & Purnama, E. R. (2022). Uji in Silico Senyawa Phytol Hasil Ekstrak Daun Zodia (Evodiasuaveolens) sebagai Antikanker. *Berkala Ilmiah Pendidikan Biologi (BioEdu)*, *11*(2), 368–373. https://doi.org/10.26740/bioedu.v11n2.p368-373

Hasan, R., Cholashotul I'anah, F., & Bahi, R. R. (2022). Docking Molekuler Senyawa Potensial Daun Kelor (*Moringa oleifera*) Terhadap Reseptor Folat. *Journal of Innovation Research and Knowledge*, *2*(2), 519–526.

Hooft, R. W. W., Sander, C., & Vriend, G. (1997). *Objectively judging the quality of a protein structure from a Ramachandran plot*. Bioinformactics, 13(4), 425–430. https://doi.org/10.1093/bioinformatics/13.4.425.

Kalontong, P. K., Safithri, M., & Tarman, K. (2022). Penambatan Molekul Senyawa Aktif Spirulina Platensis Sebagai Inhibitor TMPRSS2 Untuk Mencegah Infeksi Molecular Docking SARS-COV-*2. Jurnal Pengolahan Hasil Perikanan.* 25, 253–267. DOI: 10.17844/jphpi.v25i2.40645.

Kesuma, D., Siswandono, S., Purwanto, B. T., & Hardjono, S. (2018). Uji in silico Aktivitas Sitotoksik dan Toksisitas Senyawa Turunan N-(Benzoil)-N'- feniltiourea Sebagai Calon Obat Antikanker. *JPSCR : Journal of Pharmaceutical Science and Clinical Research*, *3*(1), 1. https://doi.org/10.20961/jpscr.v3i1.16266

Khafid, A., Wiraputra, M. D., Putra, A. C., Khoirunnisa, N., Putri, A. A. K., Suedy, S. W. A., & Nurchayati, Y. (2023). UJi Kualitatif Metabolit Sekunder pada Beberapa Tanaman yang Berkhasiat sebagai Obat Tradisional. *Buletin Anatomi dan Fisiologi*, *8*(1), 61–70. https://doi.org/10.14710/baf.8.1.2023.61-70

Lamothe, S. M., Guo, J., Li, W., Yang, T., & Zhang, S. (2016). The Human Ether-a-go-go-related Gene (hERG) potassium channel represents an unusual target for protease-mediated damage. *Journal of Biological Chemistry*, *291*(39), 20387–20401. https://doi.org/10.1074/jbc.M116.743138

Li, X., Chen, L., Cheng, F., Wu, Z., Bian, H., Xu, C., Li, W., Liu, G., Shen, X., & Tang, Y. (2014). In silico prediction of chemical acute oral toxicity using multi-classification methods. *Journal of Chemical Information and Modeling*, *54*(4), 1061–1069. https://doi.org/10.1021/ci5000467

Molekuler, P., Aktif, S., Merah, S., & Antialzheimer, K. (2023). *ALCHEMY Jurnal Penelitian Kimia*. *19*(1), 68–85. https://doi.org/10.20961/alchemy.19.1.59676.68-85

Nurjannah, S., Arum, D., Tarigan, I.L., Latief, M. (2023). Anti-Inflammatory Prediction of Peronemin Compounds from Sungkai *(Peronema canescens* Jack) and Their Derivates. *Al Ulum: Jurnal Sains dan Teknologi*. 9(2). 59-66. DOI: http://dx.doi.org/10.31602/jst.v9i2.11338

Nursamsiar, N., M. Mangande, M., Awaluddin, A., Nur, S., & Asnawi, A. (2020). In Silico Study of Aglycon Curculigoside A and Its Derivatives as α-Amilase Inhibitors. *Indonesian Journal of Pharmaceutical Science and Technology*, *7*(1), 29. https://doi.org/10.24198/ijpst.v7i1.23062

Putra, P. P., Fauzana, A., & Lucida, H. (2020). In Silico Analysis of Physical-Chemical Properties, Target Potential, and Toxicology of Pure Compounds from Natural Products Analisis Sifat Fisika-Kimia, Potensi Target dan Toksikologi Senyawa Isolat Murni dari Bahan Alam dengan Metode In Silico. *Indonesian Journal of Pharmaceutical Science and Technology Journal Homepage*, *7*(3), 107–117. http://jurnal.unpad.ac.id/ijpst/UNPAD

Putram, N. M., Setyaningsih, I., & Tarman, K. (2017). Anticancer Activity from Active Fraction of Sea Cucumber. *Jurnal Pengolahan Hasil Perikanan Indonesia*, 20(1), 53. https://doi.org/10.17844/jphpi.v20i1.16399

Rahman, A. (2023). Studi Doking Molekuler Perbandingan Evektivitas Senyawa Dari Buah Morinda Citrifolia L . Sebagai Antikanker. *CHEMVIRO: Jurnal Kimia dan Ilmu Lingkungan.* 1(2), 57–65.

Rahmawati, S. (2021). Peran Onkogen dan Tumor Suppressor Gene pada Karsinogenesis. *Jurnal JK Unila*, *5*(1), 61.

Pratama, M. R.F. (2016). Studi Docking Molekular Senyawa Turunan Kuinolin Terhadap Reseptor Estrogen-α. *Jurnal Surya Medika*,2(1).1-7

Suhadi, A., Docking, M., & Ursolat, A. (n.d.). Simulasi Docking Senyawa Aktif Daun Binahong Sebagai Inhibitor Enzyme Aldose Reductase. *SEL: Jurnal Penelitian Kesehatan,* 6(2):45-65. https://doi.org/10.22435/sel.v6i2.1651

Suprianto, T., Wijayanti, W., & Wardana, I. N. G. (2020). Synergistic effect of curcumin and activated carbon catalyst enhancing hydrogen production from biomass pyrolysis. *International Journal of Hydrogen Energy*. 46(10): 7147-7164. https://doi.org/10.1016/j.ijhydene.2020.11.211

Supriningrum, R., Fatimah, N., & Purwanti, Y. E. (2019). Karakterisasi Spesifik dan Non Spesifik Ekstrak Etanol Daun Putat (*Planchonia valida*). *Al Ulum Jurnal Sains Dan Teknologi*, *5*(1), 6. https://doi.org/10.31602/ajst.v5i1.2468

Syamsudin, S., Alimuddin, A. H., & Sitorus, B. (2022). Isolasi Dan Karakterisasi Senyawa Fenolik Dari Daun Putat (*Planchonia valida* Blume). *Indonesian Journal of Pure and Applied Chemistry*, *5*(2), 85.

Wang, X., Bove, A. M., Simone, G., Ma, B., & Odell, A. (2020). Molecular Bases of VEGFR-2-Mediated Physiological Function and Pathological Role. *Frontier in Cell and Developmental Biology.* 8(599281), 1–12. https://doi.org/10.3389/fcell.2020.599281