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In-Silico Study Of The Potential Of Neem Leaf Active Compounds (Azadirachta Indica) As A-Amylase Enzyme Inhibitors Through Molecular Docking And ADMET Analysis

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Abstract

Indonesia has reached 20.4 million adults with the fifth highest number of diabetes in the world and is estimated to be 28.6 million by 2050. The use of acarbose has side effects such as digestive problems to potential for the liver and kidneys, so these problems can be overcome with herbal plant treatment, one of which is the active compound of neem leaves (Azadirachta indica). This study aims to analyze the interaction of 20 neem leaf compounds with α-amylase enzymes through the molecular docking approach, ADMET prediction, and modification of potential new compounds as antidiabetic candidates. This research was conducted in silico using PyRx-AutoDock Vina for docking, VegaZZ, PyMOL, and Discovery Studio for optimization and visualization, SwissADME for ADME prediction, and Toxtree for toxicity test. The docking method validation is expressed in RMSD values of <2 Å. The docking results showed that Kaempferol had a ΔGBinding of -7.9 kcal/mol, an RMSD value of 1.229 Å and had a similarity of amino acid residues to the native ligands ASP:197. Kaempferol has a good ADME profile, High (III) category toxicity and is mutagenic and carcinogen. The design of the new compound of Kaempferol i.e. 2-(4-hydroxycyclohexyl)-1-methoxybutane-1,4-diol has amino acid residue similarity to the native ligands ASP A:197, ΔGBinding -5.6, RMSD value 1,704 Å and has good ADME, Low (I) category toxicity. The active compound of neem leaves has the potential to be an inhibitor of the enzyme α-Amylase.

Keywords: A-Amylase, ADME, Molecular Docking, Neem Leaf, Toxicity.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose and/or HbA1c levels due to the pancreas' inability to secrete insulin, act on insulin, or both (PERKENI, 2024). Insulin is a hormone produced by the pancreas that acts as a key to transporting glucose from the food we eat from the bloodstream to the body's cells to produce energy. The body breaks down carbohydrates into glucose in the blood, and insulin helps glucose move into the cells. An ineffective insulin production leads to high blood glucose levels (Tiurma & Syahrizal, 2021).

According to data from the International Diabetes Federation (2024), Indonesia has 20.4 million adults (20-79 years old), the fifth-highest number of diabetics in the world, and it is estimated that this number will reach 28.6 million by 2050. Diabetes mellitus can be managed medically with insulin injections and oral antidiabetic medications. One commonly used medication is acarbose. The use of diabetes medication has several side effects, such as digestive problems, the risk of hypoglycemia, and potential impacts on vital organs like the liver and kidneys. Therefore, these problems can be addressed by using herbal remedies, one of which utilizes the active compounds found in neem leaves (Azadirachta indica) (Lestari et al., 2025).

Neem leaves are empirically used by the community to treat conditions such as diabetes mellitus. Neem is a medicinal plant that has been used for generations, especially in the Indian subcontinent (Lestari et al., 2025). Neem has various biological activities, including anticancer, antifungal, anti-inflammatory, antidiabetic, and other biological activities (Pramita & Murlistyarini, 2020).

In a study by Melinda et al. (2023), the antidiabetic activity of neem (Azadirachta indica) leaf fractions was tested in vitro based on α-amylase enzyme inhibition, demonstrating antidiabetic potential with an inhibitory value of 33.82%. Preliminary testing using an in silico method based on molecular docking is necessary to determine the activity of several neem (Azadirachta indica) leaf compounds as α-amylase enzyme inhibitors.

In silico studies aim to identify candidate active compounds and optimize their conversion into drugs based on their physicochemical properties. These studies can also identify potentially toxic active compounds and those with adverse pharmacodynamic (potency, affinity, selectivity) and pharmacokinetic (absorption, metabolism, bioavailability) characteristics. This facilitates the discovery of potential active compounds before in vitro testing and saves time and costs for further research. Molecular docking can predict the interaction of a compound with a target macromolecule through computational molecular modeling, using a score that reflects the magnitude of binding affinity (Widhanti et al., 2025).

Therefore, based on this background, an in silico study of the potential of active compounds from neem leaves (Azadirachta indica) as α-amylase enzyme inhibitors is necessary using a molecular docking approach and ADMET analysis.

RESEARCH METHODS

Research Methods

The study "In Silico Study of the Potential of Active Compounds of Neem Leaves (Azadirachta indica) as Inhibitors (α-Amylase) Using a Molecular Docking Approach and ADMET Analysis" is planned to be conducted using a quantitative research method with a computer-based pre-experimental approach. The in silico study of active compounds of neem leaves (Azadirachta indica) against the α-Amylase enzyme uses ChemDraw, Chem3D, Discovery Studio Visualizer, VegaZZ, PyRx-Python, AutoDock Vina, PyMOL, Toxtree, and SwissADME software.

Research Variables

Identify the main variables

The main variable in this study is the 3D structure of 20 compounds from neem leaves (Azadirachta indica) which have antidiabetic activity with the α-Amylase receptor.

Classification of main variables

The main variables that have been identified can be classified into various types of variables, namely independent variables, controlled variables, and dependent variables. Independent variables are variables that can be changed to influence the dependent variable (Larosha et al., 2022). The independent variable in this study is the 3D structure resulting from geometric optimization of the composition of neem (Azadirachta indica) leaf compounds. The controlled variables in this study are the geometric optimization method, the docking method, and the optimization and docking parameters. The dependent variable is a variable that cannot be changed and is influenced by the independent variable (Larosha et al., 2022). The dependent variables in this study are the value of the binding free energy (ΔG) and the number of interactions between the composition of neem (Azadirachta indica) leaf compounds and the ADMET parameter value of the composition of neem (Azadirachta indica) leaf compounds.

Operational definition of main variables

The main variable in this study was the three-dimensional structure resulting from geometric optimization of 20 neem (Azadirachta indica) leaf compound structures using the VegaZZ software program. These variables were then examined to determine their effect on the dependent variable, namely the binding free energy (ΔG), the interaction pattern between neem (Azadirachta indica) leaf compounds, and the ADMET parameter values of the neem (Azadirachta indica) leaf compound compositions.

The binding free energy (ΔG) value is a parameter used to determine the spontaneity of a reaction and the stability of ligand interactions (20 neem (Azadirachta indica) leaf compound structures interacting with the receptor (α-Amylase) from docking results to assess a compound's ability as an antidiabetic agent (Lestari et al., 2023).

RESULTS AND DISCUSSION

Downloading of α-Amylase macromolecule

The α-Amylase macromolecule was downloaded from the Protein Data Bank (RSCB PDB) website with the identity code 4W93 in .pdb format. 4W93 was chosen because it has a direct bond with Montbretin-A as a native ligand. A native ligand is a ligand that binds to the target protein (Naufa et al., 2022). Another selection criterion for the 4W93 macromolecule is found in the human organism (homo sapiens). The organism used is as close as possible to the human macromolecule (homo sapiens). The method for determining the macromolecular structure chosen is X-Ray Diffraction because it can be applied to large macromolecular structures (>100 KDa) and complexed with native ligands that have estimated activity similar to the test ligand and are more precise (Pratama et al., 2021). The stability of the macromolecular structure is determined based on the resolution of the crystal structure. A low resolution value indicates a high-resolution structure because the atomic states of the crystal structure are close to their actual state (Ferdian et al., 2021). This macromolecule has a resolution of 1.35 Å, making it stable and a high-resolution structure. This is consistent with research by Ferdian et al. (2021) that found that the crystal structure of a macromolecule is stable if its resolution is less than 2.5 Å.

Preparation of α-Amylase Macromolecules

The protein structure in PDB has bonds with ligands and water molecules. Ligands and water molecules need to be removed because they can disrupt the hydrophobic interactions that occur during the docking process. Proteins with native ligands from the 4W93 macromolecule were separated using Biovia Discovery Studio 2025 software. The macromolecular structure was prepared so that the molecular docking process can take place as closely as possible to the physiological processes found in the human body (Salsabila et al., 2023). This is in line with the research of Listyani et al. (2019) that macromolecules that have been prepared can continue the docking process, so that the results of molecular docking are better because there is nothing that hinders the docking process with the test ligand.

2D and 3D Structure Creation of Test Ligands

The structures of the test compounds contained in neem leaves were obtained from the PubChem website. The 2D structures of the test ligand, positive control, and negative control compounds were created using ChemDraw 15.0, then converted into 3D models using Chem3D 15.0 and saved in .pdb format. The 3D structures are necessary because the entire docking process is carried out in 3D.

Test Ligand Optimization

The test ligands used in this study were 20 active compounds from neem leaves (Azadirachta indica), the structure of Monbretin-A that binds to the 4W93 macromolecule as a reference compound for amino acid residues because it is a native ligand, a positive control in the form of acarbose, an antidiabetic drug that is already on the market, and a negative control in the form of paracetamol that has been optimized using VegaZZ software. Geometry optimization was carried out to produce the lowest molecular energy, thus indicating the stability of the optimized ligand chemical structure, which can produce a structure with a different fold from the initial structure (Pratama et al., 2021). The test ligand was optimized by adding partial gasteiger charges and then adding forcefield autodock. The compound was minimized by 3,000 steps to obtain the most stable conformation (Listyani et al., 2019).

Docking Method Validation

Validation of the docking or redocking method was performed using PyRx software. Validation of the docking method was performed with a native ligand that had been separated from the macromolecule and optimized using VegaZZ. The general principle of docking validation is performed by docking the native ligand to the target macromolecule. The ligand and protein are prepared using the docking method and parameters that will be used for the docking study on the test

ligand. Gridbox settings are performed prior to validation based on the binding site size and the size of the test ligand (Pratama et al., 2021). Gridbox settings aim to determine the ligand binding space for the docking process. Gridbox settings include center_x, center_y, and center_z to determine the position of the parameter box on the macromolecule. Size_x, size_y, and size_z determine the size of the gridbox for the ligand binding space (Sari et al., 2022).

The parameter used for method validation is the Root Mean Square Deviation (RMSD) value. The RMSD value is used to determine whether the predicted binding mode of the test compound is successful and is important for the validation of the docking method. The RMSD value is the conformation of the native ligand, measured crystallographically, expressed in macromolecular values whose gridboxes have been adjusted and then tested with the native ligand (crystallographic results), which is called method validation (Pratama et al., 2021). The ligand resulting from redocking (validation) is visually verified with the native ligand. Based on Table 4.1, there are visualization results showing the overlapping position between the two ligand structures, indicating that the ligand resulting from redocking occupies the same binding space as the native ligand and has a very good bond position match. Based on Table 4.1, the results of the RMSD calculation obtained from the PyMOL software are 1.439 and the results of the RMSD value using the PyRx software are 1.806. These results indicate that the validation method can be used and is declared valid because the RMSD value obtained is less than 2 Å. This is in line with research by Pratama et al. (2021) that stated that the RMSD value is considered good if it is less than 2 Å.

The results of the validation of the docking method on the native ligand montbretin-A with the target macromolecule α-Amylase were visualized using Discovery Studio Visualizer software to observe the interactions of amino acid residues that will be used as a comparison against the test ligand active compound from neem leaves (Azadirachta indica) to determine its activity as an α-Amylase enzyme inhibitor. The visualization results of the montbretin-A compound with the α-Amylase macromolecule are ASP A197, ILE A235, LYS A200, GLU A240, GLU A233, HIS A101, HIS A299, TYR A62, LEU A165, LEU A162.

Molecular Docking Results

The molecular docking process was performed using PyRx software. A total of 20 test ligands were docked with the target macromolecule to observe their interactions with the target macromolecule. The gridbox settings used were the same as those used during docking method validation to maintain a consistent RMSD value and ensure more accurate results (Pratama et al., 2021). Molecular docking results were analyzed based on the Root Mean Square Deviation (RMSD) value, the free energy of binding (Δgbinding), and the interaction between amino acid residues. The free energy of binding indicates the stability of the ligand's interaction with the macromolecule. The more negative the free energy of binding (Δgbinding), the more stable the compound binds to the macromolecule, resulting in a stronger bond and maximum inhibitory activity (Naja et al., 2022).

Table 4.2 shows the results of the molecular docking process of the test ligands with the α-Amylase macromolecule, indicating that the 20 test ligands and three reference ligands produced the best RMSD and Δgbinding values. The docking results obtained a binding free energy value ranging from -4.0 kcal/mol to -8.6 kcal/mol. There is a test ligand from the active compound of neem leaves that has a Δgbinding value equal to Montbretin-A (native ligand), namely gedunin at -8.6 kcal/mol, and Δgbinding values close to native ligands, namely quercitrin (-8.3 kcal/mol), myricetin (-8.0 kcal/mol), kaempferol (-7.9), and isomargolonone (-7.9) which indicates the potential for high binding affinity and the possibility of having activity as an α-Amylase inhibitor. The resulting binding free energy (Δgbinding) value is more negative, the more stable the compound binds to the macromolecule, so that the bond formed is stronger and its inhibitory activity is maximum (Naja et al., 2022).

The RMSD values obtained from the molecular docking process ranged from 1.05 to 2.347. The results of the RMSD values of the test ligands were acceptable. This is in line with the research of Mutiara et al. (2022) where the RMSD values produced below 3 Å are said to be valid and optimal if below 2 Å. Based on the RMSD values obtained for the test ligands, there were 18 compounds that

had RMSD values smaller than the RMSD values for the native ligands. This indicates that the smaller the RMSD value indicates a better predicted ligand position because it is closer to the native conformation (Ischak et al., 2023). The analysis results from the positive control acarbose had a Δgbinding value of -6.9 and an RMSD value of 1.132, while the obtained Δgbinding value and RMSD value for the negative control paracetamol were relatively large, namely -5.1 for the Δgbinding value and 2.192 for the RMSD value. The difference between the two control comparisons can provide a clear basis for comparison to assess the suitability of candidate drug compounds in inhibiting α-Amylase enzyme inhibitors.

Interaction of Test Ligand with Receptor

The interaction of the test ligand with the receptor was observed using Discovery Studio Visualizer software. Visualization and analysis of docking interactions were used to determine the presence of binding between the native ligand and the test ligand used. The visualization results were in the form of interactions between amino acid residues and the ligand (Putri et al., 2024). Chemical interactions that can be formed from the docking results are hydrogen bonds and hydrophobic interactions. Hydrogen bonds are bonds formed between hydrogen atoms of a molecule and another molecule that is more electronegative. Hydrogen bonds have the strongest and most stable type of bond between molecules. Hydrophobic interactions are interactions between non-polar molecules that cannot form hydrogen bonds with water molecules and are classified as weak bonds (Ekawasti et al., 2021). The results of the interaction of 20 active compounds from neem leaves (Azadirachta indica) showed that four compounds had the same amino acid residue interactions with the native ligand and the positive control in hydrogen bonding: kaempferol, rutin, hyperoside, and quercitrin. Based on the obtained Δgbinding value, the gedunin compound has the same Δgbinding value as Montbretin-A (native ligand) which is -8.6 kcal/mol but the RMSD value resulting from the molecular docking process is more than 2 Å which is 2.347 and no amino acid residues were found in terms of the same hydrogen bonds with the ligand and positive control. Some compounds that have Δgbinding values close to the native ligand are quercitrin (-8.3 kcal/mol), myricetin (-8.0 kcal/mol), kaempferol (-7.9), and isomargolonone (-7.9) but of the four compounds myricetin and isomargolonone compounds did not find any amino acid residues in terms of the same hydrogen bonds with the ligand and positive control. The results of the interaction of active compounds of neem leaves that have specific amino acid activity with native ligands are kaempferol, rutin, hyperoside, and quercitrin. Based on the interaction pattern of amino acid residues, a number of test compounds showed compatibility of conventional hydrogen bonds with Montbretin-A as a native ligand and acarbose as a positive control, namely Aspartic Acid (ASP), Isoleucine (ILE), Lysine (LYS), Glutamate (GLU). This means that the ability to mimic some of the standard ligand binding models in the α-Amylase binding site and has the potential to produce similar biological activity. Compounds that have specific amino bond residues with ligands include kaempferol, rutin, hyperoside, and quercitrin. This is in line with the research of Naufa et al (2022) where the similarity of amino acid residues with native ligands indicates that the test ligand is able to inhibit the activity of the target macromolecule and has the same potential activity as the native ligand. Therefore, it can be concluded that the test ligands kaempferol, rutin, hyperoside, and quercitrin have the best inhibitory activity with the α-Amylase enzyme..

ADME Parameter Prediction

Absorption, distribution, metabolism, and excretion (ADME) testing aims to predict the potential of a compound to become an oral drug based on Lipinski's rule of five (Naufa et al., 2022). Lipinski's rule can observe the permeability of compounds through passive diffusion through the lipid bilayer of the target. The requirements for Lipinski's rule of five include a molecular weight of less than 500 g/mol, a partition coefficient (logP) of less than 5, a number of hydrogen bond acceptors of less than 10, and a number of hydrogen bond donors of less than 5 (Indrasari et al., 2022).

Based on the ADME test results for the molecular weight category, 19 compounds met the requirements for Lipinski's rule of five. However, rutin did not meet the requirements because it had a molecular weight above 500 g/mol and is not recommended as an oral drug candidate. Rutin is a

flavonoid compound that contains sugar groups, resulting in a much larger compound structure, which can result in a relatively high molecular weight. This is in line with the research of Pitaloka et al. (2023) stated that test compounds that do not meet the requirements are not recommended for use as oral preparations because they will have difficulty penetrating the digestive membrane (Pitaloka et al., 2023). Molecular weight must be considered for optimal drug absorption because it indicates the compound's ability to penetrate the membrane and thus affect drug action (Lailiyyah & Lisdiana, 2023).

In the lipophilicity category, 16 compounds met the requirements and 6 compounds did not. Compounds that did not meet the partition coefficient (logP) value parameter based on Lipinski's rule of five were phytol, 1-Tridecene, methyl isoheptadecanoate, 2,6,10,14-Tetramethylpentadecane, Hexahydrofarnesyl acetone, and Methyl 14-methylpentadecanoate because they had partition coefficient (logP) values greater than 5. The resulting logP values for these six compounds were >5 because all of these compounds are lipophilic due to their structures being dominated by a long hydrocarbon skeleton. Lipophilicity indicates a molecule's ability to dissolve in fat and its polarity. This is in line with research by Lailiyyah & Lisdiana (2023) that compounds with excessively high logP values (logP>5) are difficult to dissolve in water due to their hydrophobic nature. Compounds with high logP values tend to be toxic because they are stored in fat and take a long time to exit the body.

Other parameters used are hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD). Hydrogen donor and acceptor are measures of hydrogen bond capacity; the greater the hydrogen bond capacity, the more energy is required for the absorption process. The test results obtained showed that rutin, hyperoside, and quercitrin did not meet the criteria for hydrogen bond acceptors because their hydrogen bond acceptor values were greater than 10. Compounds that did not meet the criteria for hydrogen bond donors were myricetin, rutin, hyperoside, and quercitrin because their hydrogen bond donor values were greater than 5. Compounds that did not meet the criteria for hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) in the ADME test were predominantly flavonoids. The presence of several sugar groups in the flavonoid framework increases the number of oxygen atoms (hydroxyl and ether groups) thereby increasing the compound's ability to form hydrogen bonds with water, but at the same time inhibits passive diffusion through lipid membranes. Most of the active compounds in neem leaves meet the criteria characterized by low HBA and HBD counts. This is in line with research by Fakhirah et al (2023) that compounds that show low HBA and HBD counts indicate compounds that are easily absorbed by the body. The results of the water solubility criteria for the compound 2,6,10,14-Tetramethylpentadecane show that it is difficult to dissolve in water..

Other parameters predicted in ADME testing are GI absorption, BBB permeability, P-gp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP3A4 inhibitor, and bioavailability score. Pharmacokinetic profile testing conducted through the SwissADME website with tested parameters include Gastrointestinal Absorption (GI absorption), BBB permeability, P-GP substrate, inhibitors of the enzymes CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Gastrointestinal Absorption (GI absorption) parameters are parameters used to predict drug absorption in the stomach when developed into oral preparations. Most active compounds in neem leaves have high GI absorption values, except for myricetin, rutin, hyperoside, quercitrin, phytol, 4-cymene, α-Terpinene, 1-Tridecene, and 2,6,10,14-Tetramethylpentadecane. High GI absorption values can be influenced by their Topological Polar Surface Area (TPSA) values, which are criteria for compounds readily absorbed in the gastrointestinal tract (Zainuri et al., 2024). Compounds with low GI absorption values are caused by their high molecular weight and TPSA values, which can reduce gastrointestinal permeability. This is consistent with research by Aini et al. (2024) that found that higher molecular weight and TPSA values make it difficult to penetrate membranes, resulting in longer drug absorption and distribution times.

Blood-Brain Barrier (BBB) parameters require high penetration for most drugs entering the central nervous system. First, the molecule must cross the blood-brain barrier by passive diffusion and/or active transport. BBB penetration should be minimized for non-Central Nervous System (Non-CNS) drugs to reduce the possibility of unwanted pharmacological effects and potential neurotoxicity (Listyani & Azizah, 2025). The results showed that compounds capable of penetrating the BBB, indicated by a "yes" result, were nimbiol, margolonone, isomargolonone, 4-cymene, α-terpinene, terpinene 4-ol, m-Toluylaldehyde, methyl 14-methylpentadecanoate, and 2-ethyl-5-methylfuran. This is unfavorable because these compounds have the potential to penetrate the blood-brain barrier due to their similar lipophilic properties. This is in line with research by Kartika et al. (2024) who stated that compounds that are good for therapy are those that cannot penetrate the blood-brain barrier because the distribution process is better because they will not affect the brain's central nervous system, so they can reach target tissues and tend to be easily excreted.

P-glycoprotein (P-GP) functions as a biological barrier by removing toxins from cells. This parameter is used to predict the possibility of a compound being a P-glycoprotein substrate/inhibitor or not. Compounds included in P-GP substrates cannot penetrate the brain making it difficult to treat diseases involving the central nervous system (Listyani & Azizah, 2025). Based on the results of the compounds gedunin, rutin, margolonone, phytol, isomargolonone, 2,6,10,14-tetramethylpentadecane, hexahydrofarnesyl acetone that can be absorbed into the brain are characterized by a yes assessment result, this condition is less favorable because the compound has the potential to experience efflux in intestinal epithelial cells. This is in line with the research of Latif et al (2018) that ideally in drug development compounds should not be P-glycoprotein substrates, especially oral preparations because they have the potential to experience efflux in intestinal epithelial cells, thus inhibiting the absorption of some drugs administered orally.

Metabolic parameters are based on the activity of the enzymes CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. The metabolic process of drug compounds is generally metabolized in the liver. Cytochrome P450 3A4 (CYP3A4) is often observed because most drugs are metabolized by CYP3A4. The CYP1A2 enzyme is located in the endoplasmic reticulum and its expression is induced by several polycyclic aromatic hydrocarbons (PAHs). The endogenous substrate of this enzyme is unknown, but it is capable of metabolizing several PAHs into carcinogenic substances. The CYP2C19 enzyme is characterized by a neutral or weakly basic compound with 2 to 3 hydrogen bond acceptors, which are generally proton pump inhibitors. The pharmacokinetic effects of this enzyme have been reported to metabolize several antidepressants, antifungals, and antimalarials. The CYP2C9 enzyme has the characteristics of a weakly acidic compound with hydrogen bond acceptors such as NSAIDs. Several studies have shown that this enzyme can metabolize sulfonyl urea compounds such as glibenclamide, tolbutamide, and glimepiride. CYP2D6 is an enzyme that functions as a catalyst for basic compounds with a 4-7Å protonated nitrogen atom, such as compounds containing alkaloids and antidepressants (Listyani et al., 2022).

Pharmacokinetic testing results showed 17 compounds with a positive result and 3 compounds with a positive result of CYP1A2, namely 1-tridecene, methyl isoheptadecanoate, and methyl 14-methylpentadecanoate. Compounds that do not form CYP1A2 enzyme substrates due to the characteristics of this enzyme substrate include planar, aromatic, polyaromatic, heterocyclic amides, and amines. This enzyme is induced by several polycyclic aromatic hydrocarbons (PAHs) and is part of the cytochrome P450 family, an enzyme that catalyzes the oxidation of various exogenous drugs and carcinogens, including endogenous compounds, steroid hormones, and neuroactive amino acids (Pratama et al., 2023). Compounds that test yes have the ability to inhibit CYP1A2 enzyme activity and potentially affect the metabolism of other drugs (Pramudiyawati et al., 2024). Therefore, the 17 compounds that test no exhibit more stability and minimize changes in other drug levels.

Pharmacokinetic testing results showed 18 compounds with no results and two compounds with yes results, namely nimbiol and kaempferol, were CYP2C19 enzyme inhibitors. Compounds that are CYP2C19 and CYP2C9 inhibitors can increase plasma concentrations and sometimes cause side

effects (Hartanti et al., 2022). The CYP2C19 and CYP2C9 enzymes can cause potential drug interactions when used together with other drugs metabolized by these enzymes (Wilapangga & Arif, 2025). This means that 18 compounds that showed no results indicate that these compounds do not inhibit the activity of the CYP2C19 enzyme, thereby reducing drug interactions when used together. The ADME prediction results showed 14 compounds with no results and 6 compounds showing CYP2C9 enzyme inhibitors with yes results, namely nimbiol, and kaempferol, myricetin, phytol, 2,6,10,14-tetramethylpentadecane, and hexahydrofarnesyl acetone. Compounds that are not CYP2C9 enzyme inhibitors indicate that the compounds do not inhibit the activity of the CYP2C9 enzyme, thereby reducing drug interactions when used together and improving the clinical safety profile.

Pharmacokinetic testing results for CYP2D6 inhibitor criteria included 18 compounds with a "no" result, and two compounds with a "yes" result, namely nimbiol and 4-cymene. Eighteen compounds did not inhibit CYP2D6, thus minimizing the risk of drug interactions. This is in line with research by Nugraha (2025), who found that the CYP2D6 enzyme can cause potential drug interactions when used concurrently with other drugs metabolized by this enzyme. Furthermore, compounds that do not inhibit CYP2D6 have a low metabolic interaction profile. This is in line with research by Wang et al. (2022), who stated that compounds that do not inhibit CYP2D6 generally have a more stable metabolic profile, making them more advantageous in the development of new drug candidates.

Pharmacokinetic testing results for CYP3A4 inhibitor criteria indicated that all compounds were not CYP3A4 inhibitors. CYP3A4 is one of the enzymes most involved in liver metabolism, accounting for nearly 50% of the drug's activity. In drug metabolism, if a compound acts as an inhibitor that inhibits cytochrome P450 activity, it can increase the bioavailability of other compounds, potentially causing toxicity (Mutiara et al., 2022). All compounds are predicted not to inhibit the main cytochrome P450 enzymes, thus minimizing the risk of drug interactions. This is in line with research by Nugraha (2025) that the CYP3A4 enzyme can cause potential drug interactions when used concurrently with other drugs metabolized by this enzyme. Bioavailability prediction is a parameter used to determine whether a compound can be used as a drug candidate capable of being absorbed into the body, making it crucial. Bioavailability testing is performed on the SwissADME website using the Boiled-Egg method, which includes lipophilicity, particle size, solubility, flexibility, and saturation. The Boiled-Egg method is used in new drug development by predicting gastrointestinal absorption and blood-brain barrier penetration (Fauzi et al., 2024). The bioavailability scores indicated that all tested ligands had good bioavailability, with values ranging from 0.17 to 0.85, with the majority scoring 0.55. This is consistent with research by Sulistiyani et al. (2023) that compounds with scores above 0.10 can be predicted to be effective drug candidates if they meet safety requirements through toxicity prediction.

Toxicity Parameter Prediction

Based on the toxicity test that has been carried out using the Toxtree application on 20 active compounds of neem leaves (Azadirachta indica) which were analyzed according to the Cramer Rules parameters, they are categorized into three classes, namely I, II, and III. Compounds included in the Low category (Class I) are compounds with a simple, efficient or easily absorbed structure, and if consumed orally have a low level of toxicity (Istiqomah et al., 2023). Compounds included in the Low category (Class I) are Nimbiol, Margolonone, Phytol, Isomargolonone, 4-cymene, α-Terpinene, m-Toluylaldehyde, 1-Tridecene, Methyl isoheptadecanoate, 2,6,10,14-Tetramethylpentadecane, and Methyl 14-methylpentadecanoate. Compounds in the Intermediate category (Class II) are compounds that have a medium level of toxicity if based on their structure (Istiqomah et al., 2023). Hexahydrofarnesyl acetone is a compound classified as Intermediate (Class II). Eight compounds, including kaempferol, gedunin, myricetin, rutin, hyperoside, quercitrin, terpinene 4-ol, and 2-ethyl-5-methylfuran, are classified as High (Class III), indicating their high toxicity. Class III compounds contain reactive functional groups, are considered unsafe for consumption, and exhibit significant toxicity (Deviana & Diniatik, 2021).

Cramer's rules parameter prediction results show a range of toxicity categories, from Low (Class I), Intermediate (Class II), to High (Class III), which provides a structural warning that these compounds have the potential to cause significant toxicity. Therefore, the predicted toxicity values serve as a reference for dosage and drug potency, based on their toxicity (Capritasari et al., 2025).

Carcinogenicity parameters (genetox and nongenotox) and mutagenicity rulebase by ISS are tests conducted to predict carcinogenicity in test compounds (Listyani et al., 2024). Carcinogenic toxicity testing aims to determine compounds that can cause cancer or tumors (Indrasari et al., 2022). The results of the "Structural alert for genotoxic carcinogenicity" indicate the presence of a structural warning that has the potential to be genotoxic carcinogenic (Listyani et al., 2024). Chemical compounds that act as mutagens can disrupt DNA and protein synthesis and cause chromosomal aberrations (Rahayuningsih et al., 2022). Compounds included in the "Structural alert for genotoxic carcinogenicity" are Kaempferol, Gedunin, Myricetin, Rutin, Hyperoside, Quercitrin, and m-Toluylaldehyde. Meanwhile, "Negative for genotoxic carcinogenicity" indicates that the test compound did not contain any harmful functional groups recorded as triggers of DNA mutations, and "Negative for nongenotoxic carcinogenicity" results indicate that the compound is classified as having no indication of triggering cancer through non-DNA pathways such as hormonal disruption or uncontrolled cell proliferation (Istiqomah et al., 2023). Therefore, overall, this profile supports that the candidate compound has a low carcinogenic risk based on toxicological predictions.

The in vitro mutagenicity (Ames test) alert parameter by ISS is used to describe the ability of a test compound to trigger mutations in the bacterial DNA structure. This test was conducted on Salmonella typhimurium bacteria (Anastasya et al., 2023). In the in vitro mutagenicity (Ames test) alert results by ISS, the "Structural alert for S. typhimurium mutagenicity" result indicates that the test compound is predicted to cause mutagenicity in S. Typhimurium bacteria and the "No alert for S. typhimurium mutagenicity" result indicates there is no warning for mutagenicity in S. Typhimurium. This may be because the test compound does not have a substructure that causes mutagenicity (Listyani et al., 2024). Based on these results, there are 13 compounds that show "No alert for S. typhimurium mutagenicity", namely Nimbiol, Margolonone, Phytol, Isomargolonone, 4-cymene, α-Terpinene, Terpinene 4-ol, 1-Tridecene, Methyl isoheptadecanoate, 2,6,10,14-Tetramethylpentadecane, Hexahydrofarnesyl acetone, Methyl 14-methylpentadecanoate, and 2-ethyl-5-methylfuran, thus indicating that the test compounds do not have the potential to cause mutations in S. typhimurium bacteria.

Modification of New Compounds

Modifications were made to create a new compound design that could improve toxicity levels. Modifications were made to the new compound kaempferol. This compound was chosen because it is a mutagen and carcinogen, is classified as high or class 3, and is unsafe if consumed excessively, and has significant toxicity activity. Therefore, modifications were necessary to reduce the toxicity effects.

The new compound design was drawn using ChemDraw. The name of the new compound design was obtained from ChemDraw by converting structure to name, resulting in the new design name, 2-(4-hydroxycyclohexyl)-1-methoxybutane-1,4-diol. The optimized structure of the new compound design was then docked with the target macromolecule, α-Amylase. The amino acid residues were analyzed using Discovery Studio Visualizer software. The toxicity and ADME parameters were tested (Wardani & Listyani, 2024).

The results of compound modification with the presence of the OH group significantly increased the binding energy activity. The interaction of the new compound design with the target macromolecule amino acid residues has similarities with the amino acid residues of the comparison control (native ligand and acarbose) in terms of hydrogen bonds, namely ASP A:197, which means that the test compound has the ability to mimic some of the standard ligand binding models in the α-Amylase binding site and has the potential to produce similar biological activity (Naufa et al., (2022). One of the amino acid residues that acts as a catalytic residue of the α-amylase enzyme is ASP197. The ASP197 residue acts as a catalytic nucleophile in the hydrolysis reaction carried out by the α-

amylase enzyme on polymeric substrates such as carbohydrates (Klara et al., 2023). The results of molecular docking tests on the new compound have changes in the Δgbinding and RMSD values. The Δgbinding value of the new compound is from -7.9 kcal/mol to -5.6 kcal/mol and the original RMSD value is 1.229 Å to 1,704.

The ADME test results showed good physicochemical parameters and met Lipinski's rule of five. The resulting molecular weight was 218.29 g/mol and a log P value of 0.87, indicating excellent solubility, small molecular size, and moderate lipophilicity. The CYP2C19 and CYP2C9 enzyme parameters for kaempferol showed a "yes" result, while the new compound did not. In a study by Wilapangga & Arif (2025), CYP2C19 and CYP2C9 inhibitors can cause drug interactions. Therefore, the profile of the new compound, which does not inhibit these enzymes, is safe for the development of new drug compounds. The toxicity test results for the new compound design showed low Cramer's rule parameters and no carcinogens or mutagens, suggesting that the resulting new compound design can be used as a new drug candidate.

Overall, the modification of the new compound, including the reduction of the benzene ring and aromatic chain, resulted in a good ADME and toxicity profile. It also boasts high water solubility and reduces the risk of drug interactions.

CONCLUSION

Based on the research that has been conducted, it can be concluded that:

1. Four active compounds from neem leaves (Azadirachta indica) share amino acid residue bonds with the control compounds: kaempferol, rutin, hyperoside, and quercitrin, with Δgbinding values of -7.9, -7.8, -7.1, and -8.3, respectively, and RMSD values of 1.229, 1.053, 1.06, and 1.231, respectively.
2. In the ADME prediction test, 10 compounds did not meet Lipinski's rule of five: myricetin, rutin, hyperoside, quercitrin, phytol, 1-tridecene, methyl isoheptadecanoate, 2,6,10,14-tetramethylpentadecane, hexahydrofarnesyl acetone, and methyl 14-methylpentadecanoate.
3. In the toxicity prediction test using Cramer's rules low parameters, eight compounds had High Class III toxicity, namely kaempferol, gedunin, myricetin, rutin, hyperoside, quercitrin, terpinene 4-ol, and 2-ethyl-5-methylfuran.
4. The design of a new kaempferol compound, namely 2-(4-hydroxycyclohexyl)-1-methoxybutane-1,4-diol, has a ΔG binding value of -5.6, an RMSD value of 1.704, the same amino acid residues as the comparison control (ASP A:197), ADME predictions according to Lipinski's rule of five, low Cramer's rules toxicity predictions, and the absence of carcinogens and mutagens.

REFERENCES

Agustin, N. E., Majid, D. F. A., & Rahmawati, N. (2023). Potensi Daun Mimba (*Azadirachta Indica* Juss.) sebagai Kandidat Antivirus Penyebab Penyakit Mulut dan Kaki pada Hewan Ternak Berdasarkan Analisis *In Silico*. *JURNISMIO : Jurnal Inspirasi SMAMIO*, *1*(5), 30–45.

Aini, N., Permana, F. H., Zaenab, S., & Fatmawati, D. (2024). Studi in Silico Potensi Antikanker Senyawa Quercetin, Kaempferol, dan Pelargonidin terhadap Reseptor Histamin 1. *Chimica et Natura Acta*, *12*(2), 74–84.

Amin, S., Aliansyah, L. A., Adlina, S., & Prasetiyo, A. (2024). *Pencarian Kandidat Obat Baru sebagai Inhibitor Main Protase SARS-CoV-2 dari Senyawa Aktif Tanaman Andrographis Paniculata: Studi in-Silico*.

Anastasya, G., Wensa, L., Permata, S., Amatulloh, A., Fath, Z. T. A., & Zuhrotun, A. (2023). *In Silico Study of Klabet Seed Compounds (Trigonella foenum-gracum L.) as Alpha Estrogen Inhibitors In Breast Cancer*. *Indonesian Journal of Viological Pharmacy*, *3*(3), 183–193.

Asis, D. A. D. (2023). *Uji Aktivitas Penghambatan Enzim alpha-Glukosidase Fraksi N-Heksan dan Etil Asetat Rimpang Lempuyang Gajah (Zingiber zerumbet L.)*.

Capritasari, R., Akrom, Setianto, A. budi, Putri, M., & Hasna, E. R. (2025). Prediksi Toksisitas, Analisis ADME dan *Docking* Molekuler *Asiaticoside* Terhadap Penghambatan Angotensin Converting Enzyme Inhibition. *JFL Jurnal Farmasi Lampung*, *14*(1), 82–93.

Deviana, K. Z., & Diniatik. (2021). Analisis Penambatan Molekuler dan Prediksi Toksisitas dan ADME Penghambat Enzim Dipeptidil Peptidase IV dari Senyawa Aktif *Momordica charantia* L. sebagai Antidiabetes. *Pharmaceutical Journal of Indonesia*, *18*(02), 361–370.

Ekawasti, F., Sa'diah, S., Cahyaningsih, U., Dharmayanti, N. L. P. I., & Subekti, D. T. (2021). Molecular Docking Senyawa Jahe Merah dan Kunyit pada Dense Granules Protein-1Toxoplasma gondii dengan Metode *In Silico*. *Jurnal Veteriner*, *22*(4), 474–484.

Fakhirah, M. A., Banowati, N. D., Nurjanah, Y., Nurulaini, S. N., Athaya, S., Muchtaridi, M., Rusdin, A., & Mardisanutol, H. T. (2023). *In Silico Study of Black Pepper (Piper nigrum L.) Bioactive Compounds as Acetylcholinesterase (AChE) Enzyme Inhibitors in Alzheimer's Disease. Indonesian Journal of Biological Pharmacy*, *3*(2), 106–119.

Fauzi, F. M., Wutsqa, Y. U., & Rohmatika, N. A. (2024). Studi Bioavailabilitas dan Molecular *Docking* Senyawa Fenolik *Ocimum sanctum* L. Sebagai Inhibitor Reseptor Estrogen Alfa Pada Sel Kanker Payudara. *Journal Akfarindo*, *9*(1), 49–56.

Ferdian, P. R., Elfirta, R. R., Ikhwani, A. Z. N., Kasirah, Haerul, Sutardi, D., & Ruhiat, G. (2021). Studi *In Silico* Senyawa Fenolik Madu Sebagai Kandidat Inhibitor Mpro SARS-CoV-2. *Media Penelitian Dan Pengembangan Kesehatan*, *31*(3), 213–232.

Hartanti, I. R., Putri, A. A., Auliya AS, N. N., Triadenda, A. L., Laelasari, E., Suhandi, C., & Muchtaridi, M. (2022). Molecular *Docking* Senyawa Xanton, Benzofenon, dan Triterpenoid Sebagai Antidiabetes dari Ekstrak Tumbuhan Garcinia Cowa. *Jurnal Kimia*, *16*(1), 72–83.

Indrasari, T., Herowati, R., & Harmastuti, N. (2022). Studi Biokemoinformatika Metabolit Daun Kersen (*Muntingia calabura* L.) sebagai Agen Kanker Kolorektal. *Pharmaceutical Journal of Indonesia*, *19*(02), 251–262.

Ischak, N. I., Musa, W. J. A., Aman, L. O., Alio, L., Kilo, A. La, & Saleh, S. D. (2023). Studi Molecular *Docking* dan Prediksi ADME Senyawa Metabolit Sekunder Tumbuhan Obat Tradisional Gorontalo terhadap Reseptor HER-2 sebagai Antikanker Payudara. *Jamb.J.Chem*, *5*(1), 90–103.

Istiqomah, N., Fatikasari, S., & Hutuba, A. H. (2023). Kajian in Silico Daun Sungkai (*Peronema canescens*) dalam Menghambat Enzim lanosterol 14-α demethylase Jamur *Candida albicans*. *Indonesian Journal of Pharmaceutical Education*, *3*(1), 131–142.

Kartika, W. A., Silalahi, A. A., Athaillah, Rambe, R., & Fattara, F. P. (2024). Molecular Docking Meniran (*Phillanthus niruri* L.) Terhadap Penghambatan Enzim Tyrosine Kinase Sebagai Antikanker. *Indonesian Journal of Pharmaceutical and Clinical Research*, *07*(02), 14–024.

Klara, I. K., Purwono, R. M., & Achmadi, P. (2023). Analisis *In Silico* Senyawa Flavonoid Kayu Secang (*Caesalpinia sappan* L.) pada Reseptor *α-Amilase* Sebagai Antihiperglikemik. *Acta Veterinaria Indonesiana*, *11*(3), 210–219.

Lailiyyah, H., & Lisdiana, L. (2023). Uji Aktivitas Antibakteri Senyawa Aktif Temu Kunci (*Boesenbergia rotunda*) terhadap *Mycobacterium tuberculosis* secara *In Silico*. *Lentera Berkala Ilmiah Biologi*, *12*(2), 132–149.

Larosha, S., Dwilda, E., & Wardhana, M. P. (2022). Hubungan Antara Efektivitas Pelayanan *Antenatal Care* Dengan Tingkat Kepuasan Ibu Hamil Pada Masa Pandemi Covid-19 Di Puskesmas Kota Banjarbaru. *Jurnal Ilmiah Indonesia*, *7*(12), 20169–20180.

Latif, M. S., Rusdiana, T., & Gozali, D. (2018). Artikel Tinjauan : Pengaruh P-Glycoprotein (P-GP) Terhadap Bioavaibilitas Atorvastatin. *Farmaka*, *15*(3), 1–6.

Lestari, I. N., Renada, E., Juliana, D., Iswara, K., & Sukmara, S. (2023). *Molecular Docking Study of Antidiabetic Compounds on PPAR-γ Receptors from Ciplukan (Physalis angulata Linn.) Plants. Indonesian Journal of Biological Pharmacy*, *3*(1), 1–9.

Lestari, N. W., Safutri, W., & Safitri, O. S. (2025). *Narrative Riview* : Potensi Terapeutik dan Fitokimia Daun Mimba (*Azadirachta indica*) dalam Pengobatan Tradisional. *Jurnal Farmasi Universitas Aisyah Pringsewu*, 51–58.

Lestari, Zulkarnain, & Sijid, ST. A. (2021). *Diabetes Melitus: Review Etiologi, Patofisiologi, Gejala, Penyebab, Cara Pemeriksaan, Cara Pengobatan dan Cara Pencegahan*. 237–241.

Listyani, T. A., Addawiyyah, M., & Raharjo, D. (2024). Uji *In Silico* Toksisitas Senyawa Derivat Flavonoid Beserta Modifikasi Senyawa Baru. *MEDFARM : Jurnal Farmasi Dan Kesehatan*, *3*(2), 197–210.

Listyani, T. A., & Azizah, D. (2025). Pendekatan *Docking* Molekuler dan Prediksi ADME: Potensi Derivat Flavonoid Rosela (*Hibiscus sabdariffa* L.) Sebagai Agen Antiobesitas Melaui Modulasi Reseptor IL-10. *Duta Pharma Journal*, *5*(2), 141–157.

Listyani, T. A., Fauzi, F., Ariyanti, & Wardani, T. S. (2022). *In Silico ADME and Toxicity Studies of Derivate Phthalimide Compounds as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitor. Global Health Science Group*, *3*(1), 17–26.

Listyani, T. A., Herowati, R., & Djalil, A. D. (2019). Analisis *Docking* Molekuler Senyawa Derivat Phthalimide sebagai Inhibitor *Non-Nukleosida* HIV-1 Reverse Transcriptase. *Jurnal Farmasi Indonesia*, *15*(2), 123–134.

Listyani, T. A., Muniroh, A., Raharjo, D., & Chyang, P. J. (2025). *Docking and Structural Modification of Flavonoid Derivative Compounds as Cycloxygenas-2 Enzyme Inhibitors. Indonesian Journal of Global Health Research*, *7*(1), 311–322.

Melinda, N. A., Kusumo, D. W., & Sari, D. I. K. (2023). Aktivitas Antidiabetes Beberapa Fraksi Daun Mimba (*Azadirachta indica*) Secara *In Vitro* Berdasarkan Penghambatan Enzim *α-Amilase*. *Original Article Majalah Farmasi Dan Farmakologi*, *27*(3), 82–87.

Mutiara, Y. M., Wahjudi, M., & Kok, T. (2022). Studi *In Silico* Potensi Piperine, Piperlongumine, dan Thymoquinone Sebagai Obat Alzheimer. *Indonesian Journal of Biotechnology and Biodiversity*, *6*(3), 77–87.

Naja, A. P., Andika, & Mi'rajunnisa. (2022). Studi *In Silico* Senyawa Metabolit Sekunder Daun Sirih Hijau (*Piper betle* L) Sebagai Inhibitor Enzim Main Protease (Mpro) Pada SARS-CoV-2. *Medical Sains : Jurnal Ilmiah Kefarmasian*, *7*(2), 343–356.

Naufa, F., Mutiah, R., & Indrawijaya, Y. Y. A. (2022). Studi *in Silico* Potensi Senyawa Katekin Teh Hijau (*Camellia sinensis*) sebagai Antivirus SARS CoV-2 terhadap Spike Glycoprotein (6LZG) dan Main Protease (5R7Y). *Journal of Food Pharmaceutical Sciences*, *10*(1), 584–596.

Nugraha, R. V. (2025). Evaluasi In Silico Kaempferol Sebagai Potensial Inhibitor Tirosinase : Molecular *Docking* dan Prediksi ADMET. *Jurnal Kesehatan Tambusai*, *6*(4), 14506–14514.

PERKENI. (2024). *Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia 2024*.

Pitaloka, A. D., Nurhijriah, C. Y., Kalina, Musyaffa, H. A., & Azzahra, A. M. (2023). *Molecular Docking of Chemical Constituents of Dayak Onion (Eleutherine palmifolia (L.) Merr) towards VHR Receptors as Candidates for Cervical Anticancer Drugs. Indonesiam Journal of Biological Pharmacy*, *3*(2), 83–95.

Pramita, V. L., & Murlistyarini, S. (2020). Tinjauan Literatur Peran *Azadirachta indica* A. juss.) Sebagai Terapi Anti Skabies. *JDVA40*, *1*(1), 40–48.

Pramudiyawati, A., Putri, D. E., Nurfadilah, & Wilapangga, A. (2024). Skrining Studi *in Silico* Potensi Farmakokinetika dan Toksisitas Senyawa 6,10,14-trimetil-2-pentadekanon dari Ekstrak Daun Ekaliptus. *Indonesian Journal of Pharmaceutical Education*, *4*(1), 39–46.

Pratama, A. B., Herowati, R., & Ansory, H. M. (2021). Studi *Docking* Molekuler Senyawa Dalam Minyak Atsiri Pala (*Myristica fragrans* H.) dan Senyawa Turunan Miristisin Terhadap Target Terapi Kanker Kulit. *Majalah Farmaseutik*, *17*(2), 233–242.

Pratama, J. P., Kurniawati, N., & Erikania, S. (2023). Uji *In Silico* Senyawa Daun Belimbing Wuluh (*Averrhoa bilimbi* L.) Sebagai Antikanker Kolorektal Serta Prediksi Profil Farmakokinetik dan Toksisitas. *Prosiding Seminar Informasi Kesehatan Nasional (SIKesNas)*, 25–40.

PubChem. (2024). *National Library of Medicine*. National Library of Medicine.

Putri, T. Z. A. D., Findrayani, R. P., Isrul, M., & Lolok, N. (2024). Studi Molecular Docking Senyawa Kimia dari Herba Putri Malu (*Mimosa pudica*) Terhadap Inhibisi Enzim *A-Glukosidase* Sebagai Antidiabetes Melitus. *Jurnal Pharmacia Mandala Waluya*, *3*(4), 225–233.

Rahayuningsih, S. R., Mayanti, T., & Gunawan, F. H. (2022). Sitotoksisitas dan Genotoksisitas Ekstrak N-Heksana dan Etanol Daun Api-Api (*Avicennia marina* (Forks.) Vierh) dengan Indikator Indeks Mitosis dan Aberasi Kromosom Akar Bawang (*Alium cepa* Linn.). *Journal of Marine Research*, *11*(3), 337–346.

Salsabila, A. S., Safira, R. Z., Sari, W. A., Nugraha, A. R., Wulandari, D., & Qaivani, R. (2023). *In Silico Study of Moringa leaves Compound (Moringa oleifera L.) as Protein Kinase C Alpha Inhibitor in Breast Cancer. Indonesian Journal of Biological Pharmacy*, *3*(3), 154–173.

Sari, B. L., Elfrieda, N. S. A. L., Marsuan, K., Sapitri, P., & Hafidh, A. (2022). Aktivitas Antioksidan dan Studi *In Silico* Ekstrak Buah Pala (*Myristica fragrans* Houtt). *Jurnal Farmamedika*, *7*(1), 28–40.

Sulistiyani, Firdaus, M. F., Sigiro, R. H., Nawangsih, A. A., Purwanto, U. M. S., & Andrianto, D. (2023). Potensi Ekstrak Maggot Lalat Tentara Hitam *Hermetia illucens* (Linnaeus) dalam Regulasi Mekanisme Antioksidan Selular dan Antiradang : Kajian *In Silico*. *Jurnal Entomologi Indonesia*, *20*(3), 223–239.

Tiurma, J. R., & Syahrizal. (2021). Obesitas Sentral dengan Kejadian Hiperglikemia pada Pegawai Satuan Kerja Perangkat Daerah. *Higeia Journal of Public Health Research and Development*, *5*(3), 354–364.

Wang, Y., Li, Q., Chen, X., & Zhao, Y. (2022). *Quercetin and related flavonoids as α-amylase inhibitors: Structure–activity relationship and in silico analysis. Journal of Food Biochemistry, 46*(10).

Wardani, T. S., & Listyani, T. A. (2024). *Docking Molekuler dalam Pencarian dan pengembangan Pengobatan Human Immunodeficiency Virus (HIV)*. Lontar Mediatama.

Widhanti, A. A., Darwinata, A. E., Tarini, N. M. A., & Dwija, I. B. N. (2025). Uji *In Silico* Potensi Senyawa Aktif pada Daun Cempaka Putih (*Magnolia Alba*) Berbasis Molecular Docking Sebagai Antituberkulosis. *Jurnal Locus: Penelitian & Pengabdian*, *4*(12), 11355–11369.

Wilapangga, A., & Arif, M. (2025). Analisis Prediksi Potensi Farmakokinetik dan Toksisitas Pada Senyawa Kurkumin dari Extrak *Curcuma Aromatica* Secara *In Silico*. *Journal Of Pharmacy UMRI*, *2*(2), 156–165.

Wulandari, M. T. (2020). *Uji Aktivitas Antidiabetes Ekstrak Daun Kepel (Stelechocarpus burahol) Secara In Vitro Menggunakan Metode Inhibisi Enzim α-amilase*.

Zainuri, W., Muhammad, R., Wahyuningsih, S., Niliandari, D. A., Azzahra, M. F., & Sukiman, A. (2024). Analisis Senyawa Kurkumin Pada Tanaman Kunyit (*Curcuma Longa*) Sebagai Obat Herbal Gastritis Menggunakan Analisis Pass, Swiss Adme Dan Docking. *Jurnal Biologi Dan Pembelajarannya*, *11*(2), 161–172.