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RESEARCH ARTICLE

Molecular Docking: Analysis of Mahogany Plant Compounds (*Swietenia macrophylla* King) against the ACE2 Enzyme of SARS-CoV-2

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ABSTRACT

Various treatment approaches have been attempted to tackle severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. One approach to develop new drugs is through the utilization of medicinal plants. Mahogany (*Swietenia macrophylla* King) is one of the plants that is thought to have potential as an inhibitor of SARS-CoV-2. This study aims to determine the anti-SARS-CoV-2 potential of compounds in mahogany plants that have good interactions and interaction patterns with angiotensin-converting enzime 2 (ACE2) receptors. A total of ten mahogany plant compounds were tested for drug-likeness based on Lipinski screening which will then be docked to the ACE2 molecular target, using the molecular docking method. The parameters observed were binding energy values and amino acid residues. The results of molecular docking showed that the compounds predicted to have the highest binding affinity and have similar interaction patterns with natural ligands to the ACE2 molecular target were secomahoganin and stigmasterol. The secomahoganin and stigmasterol compounds are predicted to have good interactions with the ACE2 receptor.

Keywords: ACE2, molecular docking, SARS-CoV-2, *Swietenia macrophylla*

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus infection, is a respiratory illness that was first detected in Wuhan, China, in December 2019. In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. The disease spreads rapidly through various means, including direct contact, aerosols, and droplets [1], [2]. As of May 2025, globally there have been approximately 774 million positive cases of COVID-19 with more than 7.06 million deaths, while in Indonesia there were approximately 6.92 million cases and 162,000 deaths [3].

Various treatment approaches have been pursued to address SARS-CoV-2 infection. One of the drugs used is remdesivir, which has proven effective in inhibiting the virus infection. Apart from remdesivir, nafamostat, which is known as a middle east respiratory syndrome coronaviruses (MERS-CoV) inhibitor, also plays a role in preventing membrane fusion and inhibiting SARS-CoV-2 infection [4]. However, based on existing studies, the use of antivirals such as favipiravir, remdesivir, and hydroxychloroquine has not shown adequate efficacy in the treatment of COVID-19 [5], [6]. While the SARS-CoV-2 virus continues to mutate and form new variants. Therefore, the development of new drugs that have the potential to treat COVID-19 is crucial. One way to achieve this is by utilizing medicinal plants [7]. Natural-based medicine is a form of traditional medicine that has developed rapidly in various countries [8]. The WHO has recognized the importance of herbal medicine as an integral part of the healthcare system, where about 11% of the 252 existing drugs are derived from plants. Medicinal plants are known to play a role in pharmacology, such as having antioxidant, antiviral, anticancer, antimicrobial, antifungal, and antiparasitic properties [9]. Medicinal plants are a rich source of secondary metabolites, which have chemical and taxonomic diversity with diverse functions [9], [10].

Many active compounds derived from natural materials have shown potential as antivirals [11]. One of the plants of interest is mahogany (*Swietenia macrophylla* King). This plant is rich in polyphenols, which are believed to have a variety of benefits, including antioxidants, anti-inflammatory, antiviral, and antibacterial [12]. In addition, mahogany also contains limonoids, which are triterpenoid derivatives, known to have antiviral, antifungal, antibacterial, anticancer, and antimalarial activities [13]. Based on previous research, a molecular review of mahogany was suspected to have potential as a SARS-CoV-2 inhibitor in papain-like protease (PLpro) receptor [14].

Therefore, this study was conducted using in silico methods to explore the potential of mahogany as an antiviral. In silico research utilizes computer-based simulations and computational modeling to analyze and predict interactions between various molecules [14]. This approach allows researchers to test various compounds efficiently, without the need to conduct complicated and time-consuming laboratory experiments [15]. In silico assays can be performed through molecular docking, which serves to predict the activity of compounds on target cells [16]. Molecular docking is one of the techniques in bioinformatics used to analyze the possibility of forming specific bonds between ligand molecules and receptors [17]. This study aims to analyze the molecular docking of compounds from mahogany plants that serve as test ligands against SARS-CoV-2 virus proteins.

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Materials and Methods

Materials

In this study, the materials used consisted of the SMILES codes of the test ligands taken from PubChem, then converted to three-dimensional (3D) structures using the VegaZZ application. For macromolecules, the 3D structure of ACE2 (1R4L) was downloaded from the RCBS Protein Data Bank (PDB).

Methods

1. Test Ligand Preparation

The ligands used in this study include secomahoganin, swietenolide, γ-himachalene, roxburghiadiol A, 7-deacetoxy-7-oxogedunin, cadina-1,4-diene, swietenine, swietemacrophyllanin, β-sitosterol, and stigmasterol. These ligands were used because they were available in the database (http://ijah.apps.cs.ipb.ac.id/). As well as in previous studies, these ligands have met the Lipinski standard in drug-likeness screening [18]. Drug-likeness tests were performed again to ensure these compounds were viable as test ligands, using SwissADME. The drug-likeness profile assessment aims to determine whether the compounds meet Lipinski's Rule of Five criteria as oral drug candidates [19]. The 3D structures of the ligands were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and then processed using VegaZZ software to minimize its energy. The ligand was then pretreated using AutoDockTools (ADT) to add hydrogen and charge assignment.

2. Macromolecule Preparation

The target protein in this study was the ACE2 enzyme, which was obtained from the RCBS PDB (https://www.rcsb.org/). The selection of this protein was based on certain criteria, namely having a 3D structure generated through X-ray crystallography techniques with adequate resolution.

3. Validation of Molecular Docking

The conformation of the natural ligand (MLN-4760) to the receptor, based on the experimental crystallographic structure, will be compared with the conformation of the redocked natural ligand using ADT. This redocking process is performed by setting the grid box at x, y, z coordinates, and by centering it at x, y, z with default spacing. The results of this comparison will be expressed as the root mean square deviation (RMSD) value. The docking method is considered valid if an RMSD value of ≤ 2 Å is obtained.

4. Molecular Docking

The molecular docking process was performed by utilizing AutoDock 4.0 (AD4.0) and ADT. The protein and ligand structures which had been optimized separately, were stored in the same folder. Before starting the docking process, the grid parameter file was prepared. This step aimed to set the active side of the test ligand to match the active side of the natural ligand, with the x, y, and z dimensions adjusted to 40 × 40 × 40 and a spacing of 0.375 Å. The docking process itself utilized the Lamarckian Genetic Algorithm (LGA), where the Genetic Algorithm (GA) parameters were set to perform 100 runs with a population of 150 individuals.

Result

Screening of Test Ligands

The result of drug-likeness prediction can be seen in **Table 1**.

Table 1. Drug-likeness prediction results

Compounds	Lipinski filters				
	BM ≤ 500	MlogP ≤ 4,15	N or O ≤ 10	NH or OH ≤ 5	Desc
Secomahoganin	×	✓	✓	✓	*Yes*
Swietenolide	✓	✓	✓	✓	*Yes*
γ-Himachalene	✓	×	✓	✓	*Yes*
Roxburghiadiol A	✓	×	✓	✓	*Yes*
7-deacetoxy-7-oxogedunin	✓	✓	✓	✓	*Yes*
Cadina-1,4-diene	✓	×	✓	✓	*Yes*
Swietenine	×	✓	✓	✓	*Yes*
Swietemacrophyllanin	✓	✓	✓	×	*Yes*
β-Sitosterol	✓	×	✓	✓	*Yes*
Stigmasterol	✓	×	✓	✓	*Yes*

Description: Yes = Eligible (violates 1 rule), No = not eligible (violates > 1 rule), ✓= meets Lipinski rule, × = does not meet Lipinski rule

Validation of Molecular Docking Methods

The result of gridbox parameters and RMSD value of redocking can be seen in **Table 2** and **Table 3**.

Table 2. Grindbox parameters

Macromolecule Code	Gridbox					
	Center			Dimensions (Å)		
	X	Y	Z	X	Y	Z
1R4L	40.336	6.024	29.006	40	40	40

Table 3. RMSD value of redocking result

Target Protein Name	Natural ligan	PDB code	RMSD (Å)	Condition
ACE2	MLN-4760	1R4L	0.978	< 2 Å

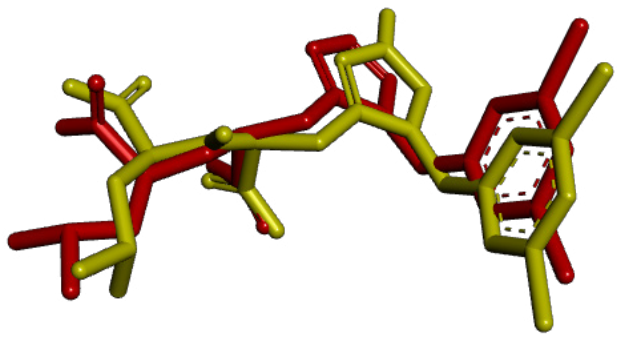

Figure 1. Overlay results of crystallographic ligands (red) and redocked ligands (yellow)

Molecular docking result

The results of molecular docking of compounds to ACE2 protein can be seen in **Table 4**.

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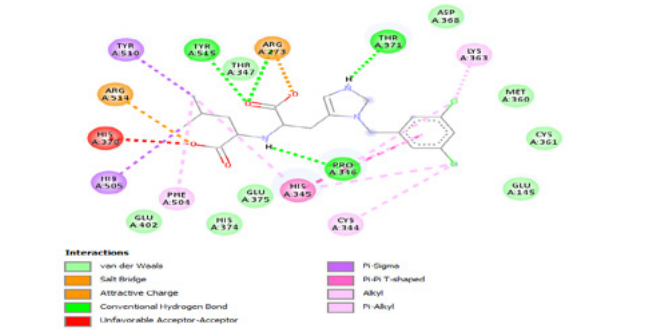
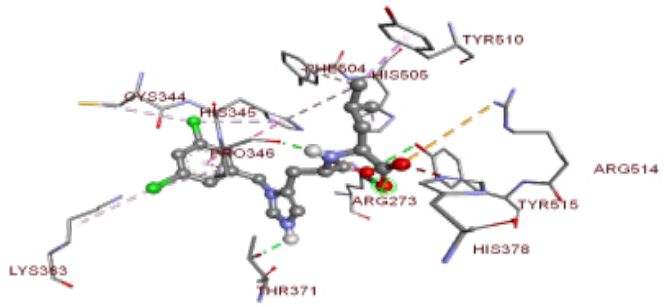
Table 4. Results of molecular docking of compounds to ACE2 protein

Compounds	Bond energy (kkal/mol)	Amino acid residues involved in the rnteraction	
		Hydrogen bonding	other than Hydrogen bonding
MLN-4760 (natural ligands)	-7.10	Tyr515, Thr371, Pro346	Arg273, Asp368, Lys363, Met360, Cys361, Glu145, Cys344, His345, Glu375, His374, Phe504, Glu402, His505, His378, Arg514, Tyr510
Secoma-hoganin	-10.50	Arg518, **Lys363**, Tyr127	**His505, Tyr515, Arg273,** Phe274, **Asp368**, Asp367, **Cys361, Met360, Pro346, Glu145**, Asn149, Trp271, **His345, Thr371, Phe504, Glu375, His374**, Glu406
Stigmas-terol	-10.34	-	Ser128, **Cys344, Glu145, His345**, Tyr127, **Cys361, Lys363, Asp368, Pro346, Met360,** Asp367, Thr371, Phe274, Glu406, Arg518, **Arg273**, Trp271, Leu144, Asn149

*Bold: similarity of amino acids that interact with natural ligands



(A)



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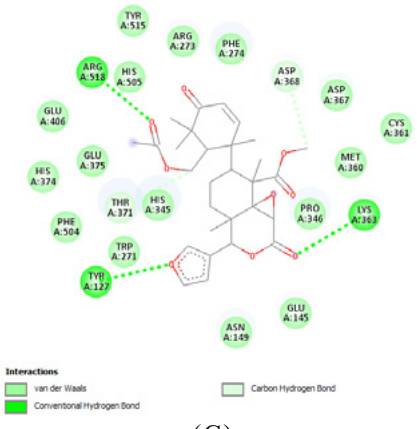
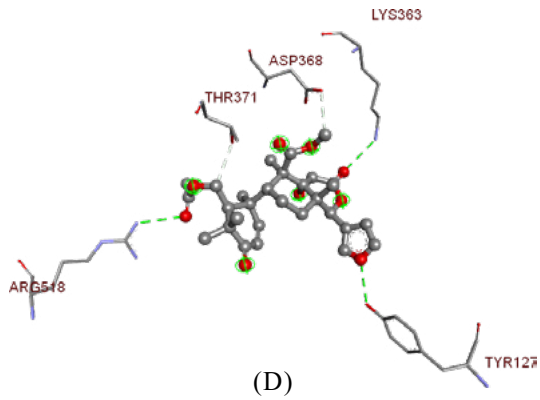


(C)



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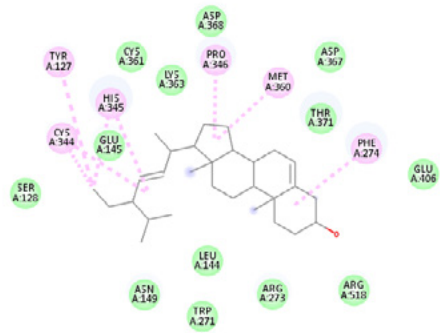
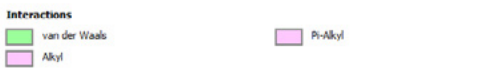
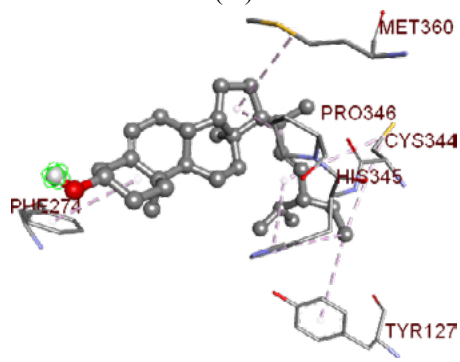




(E)



(F)

Figure 2. Interaction diagram of the test ligand compared to the natural ligand. The MLN-4760 (natural ligand) dimension (A) and (B), the secomahoganin dimension (C) and (D), the stigmasterol dimension (E) and (F)

Discussion

This study has tested ten compounds for Drug-likeness screening. This screening aims to qualitatively assess the likelihood of a molecule to function as an oral drug, considering bioavailability aspects through the use of the SwissADME website. The website provides five Drug-likeness filters, namely Lipinski, Ghose, Veber, Egan, and Muegge. In this study, we focus on the application of the Lipinski filter. The Lipinski rule is designed to evaluate chemical compounds that have pharmacological activity and can function effectively when administered orally to humans. If a compound meets the criteria set by the Lipinski rule, it is considered to have the potential to penetrate cell membranes and be absorbed by the body. According to Lipinski, a compound is said to be

eligible if the drug-likeness screening results do not violate more than one of the four predetermined criteria, so that further molecular docking will be performed [20], [21]. The results of the ten compounds tested for drug-likeness showed that the compounds were predicted to have the opportunity to become oral drugs because each compound only had one parameter that did not meet so that it could continue for molecular docking.

Canonical SMILES codes for ten compounds found in mahogany plants have been retrieved from PubChem, then, their 3D structures were created using the VegaZZ application. For the target protein, the 3D structure was taken from the RCBS PDB code 1R4L and has a resolution of 0.978 Å. This macromolecule met the criteria of having a 3D structure generated through the crystallographic X-ray diffraction method with a resolution that meets the standard (< 2 Å) [22], [23].

Validation of the molecular docking method was performed using ADT. Method validation is an important step to ensure that the molecular docking technique used is reliable. This process is done by comparing the conformation of the natural ligand obtained through crystallography with the natural ligand that has undergone the redocking process against the target protein. In the validation step, it is very important to determine the gridbox or center coordinate which is the location of the interaction between the ligand and the protein, known as the active site of the protein. Generally, the center of the gridbox is determined based on the center of mass of the natural ligand, while the dimensions of the gridbox are adjusted to the size of the ligand as well as the binding sites on the protein that contain amino acids vital for protein activity [22], [23]. The centers and gridbox dimensions of the macromolecules used in this study can be found in **Table 3**. During the validation process, the parameters observed include the RMSD value as well as the interaction between the ligand obtained from crystallography and the ligand generated through redocking with the amino acid residues of the target protein. The RMSD value serves to assess the success of the binding mode prediction and has a very important role in validating the docking program [24]. A molecular docking protocol is considered valid when the RMSD value of the redocking superposition is below 2 Å. The smaller the RMSD value, the closer the ligand position is to the natural ligand conformation. Conversely, if the RMSD value exceeds 2 Å, this indicates a more significant deviation from the calculation results, so the docking results obtained cannot be used as a reliable reference [7], [22], [23].

Table 3 and **Figure 1** show the RMSD values as well as the overlay of the redocking results of the natural ligands on their target proteins. From these observations, it can be seen that the position of the redocked ligand is very close to the location of the crystallographic ligand and occupies the same active site. This indicates an interaction between the ligand and the amino acids that are also involved in the crystallographic ligand interaction. This redocking process is very important, as it serves to validate the docking method and evaluate its level of accuracy. In the context of molecular docking, redocking is the stage when the tested ligand is placed back on the active site of the target protein, after calculation of its initial energy and placement. If the redocking results show that the ligand is close to the position of the crystallographic ligand and fills the same active site, and interacts with amino acids involved in the crystallographic ligand interaction, this indicates consistency between the docking results and the crystallographic structure [25], [26]. These results indicate that the docking method used has been well verified, so the docking process between the protein and the test ligand can be performed using ADT.

A total of ten compounds in mahogany plants were tethered to target proteins using the molecular docking method, ADT. Molecular docking is a method used to analyze the interaction between drug candidate compounds and protein targets. In this way, we can predict the potential activity or inhibition that may occur in an enzyme [27], [28]. Molecular docking involves the assessment of several factors in evaluating test ligands which will play a role in the selection of ligands that have the potential to bind to the target protein specifically and effectively. These factors are free binding energy and amino acid residue similarity to the natural ligand [25]. A small docking score value indicates the free bond energy to be lower. The lower the free binding energy, the higher the stability of the bond between the ligand and the receptor so that it can be predicted that the resulting activity will be greater [29], [30]. The similarity of amino acid residues between the test ligand and the natural ligand on the target protein can increase the possibility of forming an optimal binding complex. This is due to the binding of the natural ligand to the target protein which is determined by specific interactions between the ligand and amino acid residues in the active site of the protein [31].

Table 4 presents two compounds that show lower binding energies compared to the other test compounds, as well as having smaller free bond energy values compared to the natural ligand. MLN-4760, which is the natural ligand of 1R4L, interacts with the amino acid residues on the active side through various types of bonds, including hydrogen, van der Waals, π-alkyl, alkyl, π-sigma, and salt bridges (**Figure 2**). Based on Towler *et al.* [32], there are several amino acid residues of the same natural ligand with redocked results, namely His374, His378, Glu402, Arg273, His505, His345, Pro346, Thr371, Tyr515, Glu375, Tyr510, Arg514, Phe504, Met360, Cys344, Cys361, Asp368, Glu145, and Lys363. For ACE2, the stability of the carboxyl anion most likely occurs through the phenolic group of Tyr515. Secomahoganin has the lowest binding free energy value on TMPRSS2 protein followed by stigmasterol. Both test ligand values are smaller when compared to MLN-4760 (**Table 4**). Secomahoganin has 14 amino acid residues in common with the natural ligand, while 3β-hydroxy-stigmast-5-en-7-one has ten amino acid residues in common.

Based on the molecular docking results, the best two test ligands from each target protein have potential interactions with SARS-CoV-2 target proteins and merit further investigation, because the test ligands interact with the same amino acid residues as the natural ligand of the target protein. Until now, there has been no related research regarding molecular or in vitro and in vivo inhibition studies of compounds in mahogany plants against SARS-CoV-2.

The molecular docking results show that several compounds from mahogany plants have interactions with the tested molecular targets. Some of them have better free-binding energy values than natural ligands. A compound can be known to have activity against the target protein by observing two parameters, namely binding energy and interaction pattern. If a compound shows an optimal binding energy value but does not interact effectively with amino acid residues similar to the natural ligand, then the compound does not have an ideal

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interaction pattern. Thus, the compound cannot be confirmed to have activity equivalent to the natural ligand [33].

Conclusion

Based on the results of the research that has been done, it can be concluded that among the compounds tested in mahogany plants that show the best docking results and have interaction patterns that resemble native ligands against ACE2 target molecules are secomahoganin and stigmasterol compounds.

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