

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

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ABSTRACT

This study is a continuation of a previous study that analyzed the interaction of bioactive compounds from mahogany (*Swietenia macrophylla* King) with the SARS-CoV-2 Angiotensin-Converting Enzyme 2 (ACE2) using a molecular docking approach. This study aims to evaluate the dynamic stability of the ligand-protein complex through molecular dynamics simulation using YASARA Dynamics software with the AMBER14 force field for 100 ns. The parameters analyzed include Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF). The results show that the ACE2-secomahoganin and ACE2-stigmasterol complexes experienced relatively high RMSD fluctuations, indicating global conformational changes in the protein structure during the simulation. Although RMSF analysis shows relatively low fluctuations in several active site residues such as His374, His378, Glu402, and Tyr515, the overall variability indicates that the system does not exhibit uniform stability. These findings provide preliminary computational insights into the dynamic interactions of mahogany compounds with ACE2, with stigmasterol showing relatively more consistent behavior than secomahoganin and may be potential candidates for further research against SARS-CoV-2, although further computational and experimental validation is required.

Keywords: ACE2; Molecular Dynamics Simulation; SARS-CoV-2; *Swietenia macrophylla*

INTRODUCTION

The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has had a major impact on the global health system. Angiotensin-Converting Enzyme 2 (ACE2) protein plays an important role as the main receptor that mediates the entry of the virus into host cells through interaction with the spike protein (1,2). Due to its central role, current therapeutic strategies are aimed at blocking the interaction between the spike protein and ACE2, without inhibiting the enzymatic activity of ACE2 itself (3,4).

In silico approaches such as molecular docking and molecular dynamics simulation (MD) are an efficient tool for predicting molecular interactions between active compounds and target proteins, and serves as a complementary method to guide and prioritize further experimental validation (5,6). In a previous study, Amrulloh & Khairani (7) reported that two compounds from mahogany plants, namely secomahoganin and stigmasterol, had binding energies of -10.50 and -10.34 kcal/mol against ACE2, respectively, indicating high binding affinity.

Many substances found in nature can be identified as active ingredients in the manufacture of antiviral drugs. One approach that has been widely developed in many countries is natural product-based drug discovery using bioactive compounds derived from natural sources (8). Mahogany plants, belonging to the Meliaceae family, are rich in secondary metabolites such as limonoids, triterpenoids, and flavonoids, which have antiviral, anti-

inflammatory, and antioxidant activities (9,10). Amrulloh's (11) research also reported that mahogany compounds show stability in binding with the SARS-CoV-2 PLpro protein. This reinforces the potential of mahogany as a source of natural antiviral bioactive compounds. However, molecular docking results are static and do not reflect the actual dynamics of biological systems (12,13). Therefore, MD is needed to evaluate the stability of ligand-protein interactions under physiological conditions (14,15).

This study aims to assess the stability of the complex between ACE2 and two selected mahogany compounds, namely secomahoganin and stigmasterol, through RMSD and RMSF analysis using MD to provide a preliminary assessment of the structural stability and flexibility of the protein-ligand complex, acknowledging that additional parameters may further strengthen the analysis. The results of this study are expected to further evaluate the stability of the protein-ligand interactions observed in previous docking studies and support the development of mahogany compounds as candidate molecules targeting ACE2 against SARS-CoV-2.

METHODS

Tool

TOSHIBA dynabook B35/Y with specifications: Intel(R) Core(TM) i5-5200U processor, 8.0 gigabytes of RAM, 500 gigabytes SSD hard drive, Intel(R) HD Graphics 5500 graphics card, and YASARA Dynamics.

Materials

The SMILES code of the test ligand obtained from PubChem and the three-dimensional structure of the macromolecule, namely ACE2 (PDB ID: 1R4L), downloaded from the Protein Data Bank (RCSB PDB).

Detailed Procedure

Structure Preparation

The ACE2 protein structure was obtained from the Protein Data Bank (PDB ID: 1R4L) with a crystal X-ray resolution of 3 Å (16). Prior to simulation, the protein structure was prepared by removing crystallographic water molecules and other non-essential heteroatoms. The prepared structure was then subjected to initial energy minimization to relieve steric clashes and optimize geometry. The secomahoganin and stigmasterol ligands were taken from previous research (7), while the co-crystal ligand MLN-4760 was used as a comparison.

Molecular Dynamics (MD) Simulation

Molecular dynamics simulations were performed using YASARA Dynamics version 15.1.1 with the AMBER14 force field for 100 ns. The system was prepared under physiological pH conditions (pH 7.4). The protein-ligand complex was solvated in an explicit water model using TIP3P water molecules within a cubic simulation box with periodic boundary conditions applied. The box size was defined to ensure a minimum distance of 10 Å between the complex and the box edges. To mimic physiological ionic strength, Na⁺ and Cl⁻ ions were added to achieve a concentration of 0.15 M NaCl. The simulation was conducted at a temperature of 298 K and a pressure of 1 bar using a time step of 2.5 fs, and trajectories were recorded every 200 ps. The choice of temperature was based on standard computational conditions, although it may not fully represent physiological temperature.

Trajectory Analysis

The analysis focused on two primary parameters, namely Root Mean Square Deviation (RMSD) to assess the global stability of the protein-ligand system, and Root Mean Square Fluctuation (RMSF) to evaluate the local flexibility of amino acid residues at the active site of the ACE2. While these parameters provide initial insights into structural stability, they are not sufficient to evaluate binding affinity. Therefore, additional analyses such

as MM/GBSA or MM/PBSA calculations would be required to more accurately assess ligand binding and identify key contributing residues.

RESULT AND DISCUSSION

Root Mean Square Deviation (RMSD)

The RMSD parameter describes the conformational stability of the protein-ligand complex during molecular dynamics simulations. Based on Figure 1 and Table 1, the ACE2-MLN-4760 complex (co-crystal ligand) showed an average RMSD value of 2.68 ± 0.50 Å, indicating a relatively stable conformation throughout the 100 ns simulation, as the ligand remained within the binding pocket of ACE2 (16). In contrast, ACE2-secomahoganin and ACE2-stigmasterol exhibited significantly higher RMSD values of 30.09 ± 11.79 Å and 13.23 ± 2.54 Å, respectively. These elevated RMSD values suggest substantial conformational changes, which may indicate structural instability of the complexes, possible ligand dissociation from the binding site, or limitations in the simulation or analysis setup. Therefore, these results should be interpreted with caution, and further analyses are required to confirm the stability of these interactions.

The high RMSD values observed for secomahoganin and stigmasterol suggest substantial conformational changes, which may indicate ligand displacement from the binding site or overall instability of the protein-ligand complex within ACE2. According to Salmaso & Moro (13), an increase in RMSD can be caused by changes in the secondary structure of proteins due to the relaxation of the system towards a thermodynamic equilibrium state. Based on the graph and average results, it can be seen that the stability of the Secomahoganin and Stigmasterol ligand bonds with the ACE2 protein is very poor because the graph and average RMSD are more than 5 Å. As is well known, an RMSD value above 5 Å indicates a significant conformational change and a large structural change and indicates low stability (14). The high RMSD values observed for the two test ligands indicate significant conformational deviations that may reflect instability of the protein-ligand complex, potentially due to unfavorable interactions within the binding site. (17,8).

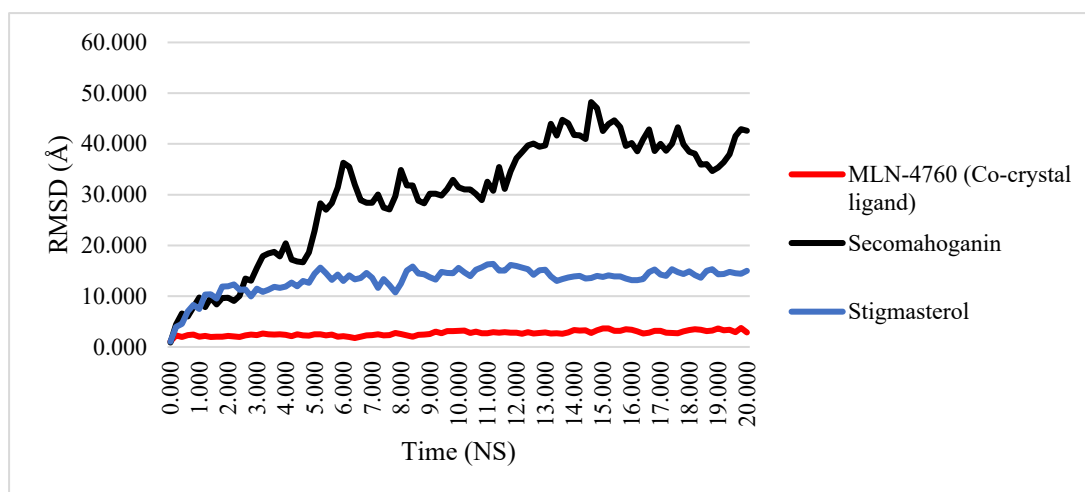


Figure 1. Comparison of root mean square deviation (RMSD) graphs between MLN-4760 (red), Secomahoganin (black), and Stigmasterol (blue)

Table 1. Average RMSD and RMSF Values

	Average (Å)		
	Co-crystal ligand	Secomahoganin	Stigmasterol
RMSD	2.68 ± 0.50	30.09 ± 11.79	13.23 ± 2.54
RMSF	1.57 ± 0.86	1.88 ± 2.43	1.40 ± 0.93

Root Mean Square Fluctuation (RMSF)

Based on Figure 2 and Table 1, the RMSF profiles of secomahoganin and stigmasterol are relatively similar to that of the co-crystal ligand. The ACE2-MLN-4760 (co-crystal ligand) complex shows an average RMSF value of 1.57 ± 0.86 Å, while ACE2-secomahoganin and ACE2-stigmasterol reach 1.88 ± 2.43 Å and 1.40 ± 0.93 Å, respectively. Although the average RMSF values appear comparable, the notably high standard deviation observed for secomahoganin indicates significant residue fluctuation, suggesting localized flexibility rather than uniform stability within the ACE2 structure. These results imply that while several amino acid residues, including Tyr515, Thr371, Pro346, Arg273, Asp368, Lys363, Met360, Cys361, Glu145, Cys344, His345, Glu375, His374, Phe504, Glu402, His505, His378, Arg514, and Tyr510, exhibit relatively low fluctuations, other regions may experience higher mobility, particularly in the secomahoganin complex. These residues are located within or near the binding region of the ACE2, suggesting their potential involvement in ligand-protein interactions. However, detailed visualization and interaction analysis are required to clearly identify the binding mode and key interacting residues.

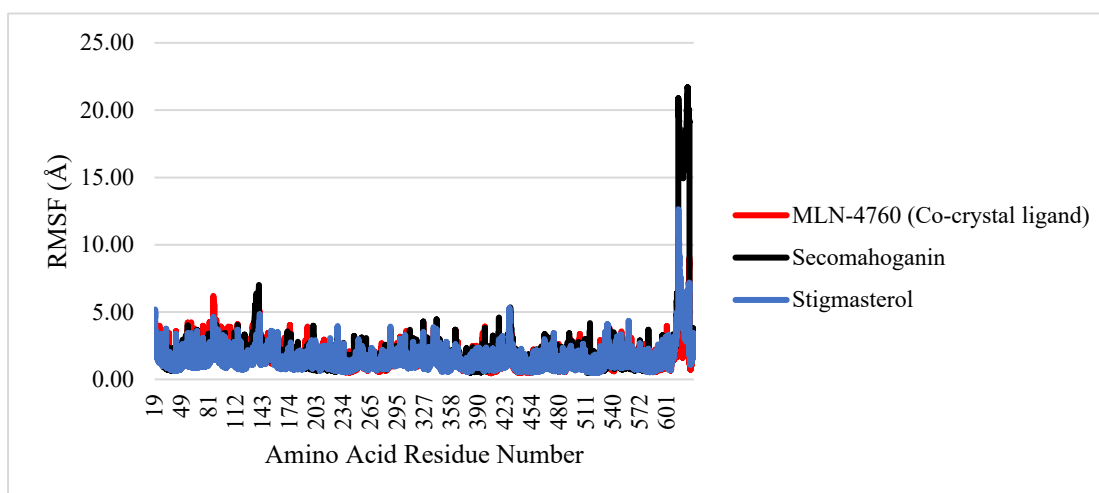


Figure 2. Comparison of root mean square fluctuation (RMSF) graphs between MLN-4760 (red), Secomahoganin (black), and Stigmasterol (blue).

The combination of high RMSD fluctuations and relatively low RMSF in active residues suggests that the system experiences significant conformational changes, although no clear evidence of convergence toward a stable state is observed. This phenomenon is characteristic of large protein systems with deep binding pockets (14). Therefore, secomahoganin and stigmasterol can be categorized as potential ligands with the ability to maintain long-term binding to ACE2, supporting their role as natural SARS-CoV-2 inhibitor candidates.

CONCLUSION

Molecular dynamics (MD) simulations indicate that the active compounds from mahogany, namely secomahoganin and stigmasterol, exhibit high RMSD values, suggesting notable conformational deviations during the simulation. Although RMSF analysis shows relatively low fluctuations in several active site residues of ACE2, the high variability, particularly in the secomahoganin complex, indicates that the system does not exhibit uniform stability. These findings provide preliminary computational insights into protein-ligand interactions and suggest that stigmasterol may still be considered for further investigation. However, the results should be interpreted with caution due to the limited scope of analysis, and additional computational and experimental validation is required to confirm these observations in the context of SARS-CoV-2.

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