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Molecular Docking Study: Identification of Potential Inhibitors in Lavandula Angustifolia Essential Oil Against the Main Protease of Sars-Cov-2

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Abstract. *SARS-CoV-2, also known as, Covid-19 is an almost globally endemic disease that has infected hundreds of millions of people and caused ongoing deaths. Researchers are still trying to search for effective drugs against Covid-19. Currently, with the development of science and technology, the process of drug discovery through simulated environments is becoming increasingly accurate and yielding rapid results. The protease crystal structure of Covid-19 plays a crucial role in viral replication and represents promising primary targets for antiviral drug discovery and therapy. Lavender and N3 compound ligands were used as test ligands. A total of 9 lavender ligand compounds were subjected to testing using the molecular docking method. Molecular docking aims to achieve the optimal conformation of both the protein and ligand, as well as the relative orientation between them. The analysis conducted during molecular docking includes the determination of the inhibition constant and the study of interactions between the protein and ligand.*

Keywords: Covid-19, docking, N3, ligand

Introduction

The Coronavirus Disease 19 (Covid-19) virus outbreak began in Wuhan China in late 2019. The outbreak has spread to all corners of the world very quickly. More than 200 countries have been affected by this virus. The World Health Organization (WHO) has declared this outbreak a pandemic. The pandemic is caused by the β-coronavirus variant SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*). As the name of the virus implies, the disease is transmitted through organ respiration, either direct contact or through splashes from infected individuals [1].

Despite the research efforts of the scientific community, no antiviral or vaccine has been found to be 100% effective for the prevention of SARS-CoV-2. Finding an effective cure is time-consuming and costly. Substantial steps to produce vaccines and drugs are still in clinical studies, while for now covid drugs are a very urgent need. The research procedure for new drugs that can show a

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good antiviral effect takes years, maybe even more than 10 years. Therefore, the fastest method is to use computer simulations to test various drug compounds that have been approved by drug regulatory agencies in treating other diseases and then tested for SARS-CoV-2. In this way, drug discovery will be faster and more effective [2]. With the development of technology in this era, it is not impossible for the world of computer simulation to become the main choice as a research method because of its accuracy and effectiveness that can always be improved. Moreover, the successful discovery of the crystal structure of SARS-CoV-2 will play an important role in the discovery of its inhibitors. According to Choudary et al. (2020) [3] this crystal structure was obtained from the X-ray diffraction results of 3CLpro or Mpro material through mass spectroscopy measurements which is known to have a molecular mass of 33,797 kDa, with a catalytic efficiency of SARS-CoV-2 of 28,500 $M^{-1}S^{-1}$ [4]. The inhibition process carried out against Mpro shows that there is a disturbance in the replication and transcription process of non-structural proteins so that the virus becomes inactive. In the human body, there is no enzyme that resembles the Mpro of the covid-19 virus so that inhibitors of Mpro will not leave toxic effects in the human body [5].

There have been many studies on the process of drug discovery with Mpro targets, one of which was a study conducted by Ullrich and Nitsche (2020) [6] by using N3 as a ligand. The N3 ligand was obtained from the incorporation of drug design through virtual drug screening. This program focuses on identifying existing drug loads by targeting Mpro. Another study revealed that N3 was able to inhibit Mpro from various coronavirus variants including MERS-CoV and SARS-CoV. N3 showed strong antiviral inhibitory activity in inhibiting covid-19 viruses [4]. The purpose of this research was to use molecular docking to obtain the ligand and protein conformations of Mpro SARS-CoV-2, using the reference ligand N3 and lavender essential oil compounds and analysis

Materials and Methods

This research will investigate the interaction of Mpro with N3 ligand and Lavandula Angustifolia (Lavender flower) essential oil compound. The 3-dimensional structure of the protein used is obtained from the PDB (Protein Data Bank) with the site http://www.rcsb.org/pdb/ which has ID 6LU7 and a resolution of 2.16 Å. The protein data obtained previously is a complex protein that must be separated first to be simulated. The 3-dimensional structure of the ligand compounds contained in Lavender essential oil was obtained from PubChem with the site http://www.pubchem.ncbi.nlm.nih.gov/. Some of the content of lavender flower essential oil compounds that will be used as ligand candidates are *linalyl acetate*, *linalool, geraniol*, β-*caryophyllene*, terpinene-4-ol, *lavandulol*, *lavandulyl acetate*, 1,8-cineole, and borneol [7]. Lavender flower compounds were chosen because referring to studies conducted by Abou Bakar *et al* (2021) [7], Lavender essential oil compounds have antiviral properties. Therefore, further studies are needed to observe lavender flower essential oil compounds as SARS-CoV-2 inhibitors. So that it is known whether the results obtained are better or not compared to the N3 ligand.

Broadly speaking, the first stage of this research is to conduct molecular docking with Lavender flower compounds as ligands. The software used in this research are *Autodocktools, PyRx*, dan *Discovery Studio*. This molecular docking is for the determination of ligand candidates which will later be simulated in molecular dynamics as a series of searches for ligand candidates for the drug covid-19. The purpose of molecular docking is to achieve an optimal conformation for both the protein and ligand and the relative orientation between the protein and ligand so that the free energy of the whole system is minimized [8]. The output obtained from the molecular docking

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simulation is the Gibbs energy of nine Lavender flower compounds. The compound that has the most negative Gibbs energy will be used in the next stage. A small Gibbs energy value indicates that the conformation formed is stable, and a large Gibbs energy value indicates that the complex formed is unstable [9].

Results and Discussion

Molecular Docking Simulation

The simulation system contains 9 Lavender essential oil ligands and reference ligand N3 that are docked with the viral Mpro receptor using PyRx software. The system is ready to build a grid box to determine the receptor region that will be docked and use exhaustiveness of 32. The following is a visualization and size of the grid box that will be used in the docking simulation process

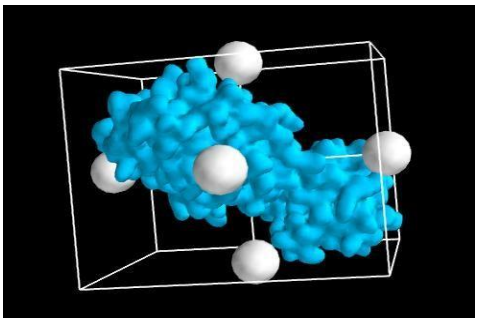

Figure 1. Grid box of Mpro receptor for molecular docking process.

Table 1. Grid box size of docking simulation system

Axis	X (nm)	Y (nm)	Z (nm)
Center	-26.3373	12.6074	58.9274
Size	51.17568	65.6376	58.91751

In figure 1 visualization of the molecular docking grid box, it has been seen that the grid box has been made to cover all parts of the receptor with the sizes available in table 1. Table 1 contains details of the center and size of the grid box on the X, Y and Z axes. The next step is molecular docking simulation. The output of molecular docking is in the form of a .csv file containing the value of the free energy of the bond and the macromolecular file of the receptor and ligand docking in .pdb format. The free energy value of the bond obtained can be used to analyze the magnitude of the inhibition constant on each ligand. Below is a table of molecular docking simulation results and visualization of the system during molecular docking simulation.

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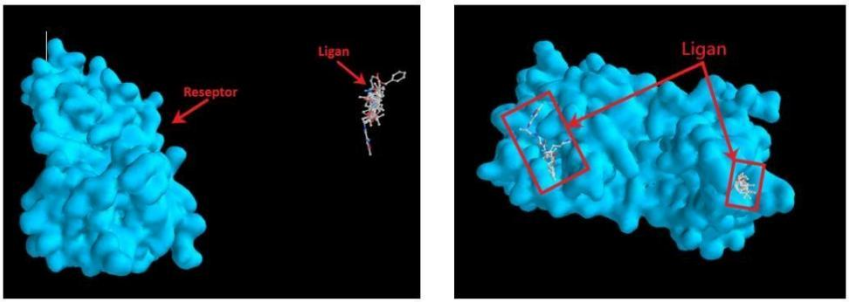

Figure 2. System before and after molecular docking simulation

There are some differences that can be analyzed from the figure before and after the system simulation. In figure 2, before the molecular *docking* simulation is performed, the ligands to be tested are outside of the receptor. These ligands can be outside the receptor and gather in one area because the ligands have not had the best conformational coordinates between each ligand, so they look stuck and overlap in one particular area. While at the time after the *docking* simulation was performed, the test ligands began to stick to the receptor. These ligands are attached according to the grid box area that was previously made. The size of the grid box that was built was deliberately made thorough and reached all parts of the receptor because the active side of the receptor can spread throughout the receptor.

Table 2. Molecular docking simulation results

Compound	ΔG Gibbs energy	Inhibition Constant
Lavender	(kJ/mol)	(µM)
Linalyl Acetate	-4.8	0.9981
Geraniol	-4.5	0.9982
β-*Caryophyllene*	-6.1	0.9975
Terpinene-4-ol	-5.0	0.9980
Lavandulol	-4.8	0.9981
Lavandulyl Acetate	-4.8	0.9981
1,8-*Cineole*	-5.2	0.9979
Borneol	-5.4	0.9978
N3	-7.7	0.9969

Bond free energy is the strength of the interaction between two (or more than two) reversibly bonded molecules. The bond free energy that has the highest negative value is the best value. Based on table 2 of docking simulation results, ligand N3 which is the original ligand of Mpro virus has the lowest value of bond free energy which is -7.7 (kJ/mol). The next lowest value is -6.1 (kJ/mol) owned by β-Caryophyllene compound which is a Lavender essential oil compound. Inhibition constant is an indicator of how strong an inhibitor is. A good inhibition constant value is the lowest value [10]. The lowest value of the inhibition constant is owned by compound N3 with a value of 0.9969 µM. The next lowest inhibition constant value of the lavender compound test

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ligand is the β-Caryophyllene compound with a value of 0.9975 µM. This shows that compound N3 and β-Caryophyllene have a high effectiveness value of inhibitory activity.

Conclusions

The research aimed to obtain ligand and protein conformations of Mpro SARS CoV-19 using the reference ligand N3 and lavender essential oil compounds, has been completed. The results of the molecular docking simulation showed that among the ten lavender essential oil compounds tested, the β-Caryophyllene compound exhibited the most superior inhibition constant and free energy value. However, it is important to note that while the β-Caryophyllene compound demonstrated superior properties compared to the other essential oil compounds, its inhibition constant was not better than that of the reference ligand N3. This suggests that the test ligand has a bond that is easily separated when compared to the reference ligand. Thus, the N3 ligand exhibits greater stability in comparison to the β-Caryophyllene ligand during the docking process.

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