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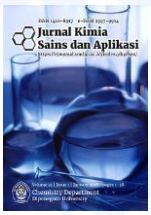

Docking and Molecular Dynamic Simulations Study to Search Curcumin Analogue Compounds as Potential Inhibitor Against SARS-CoV-2: A Computational Approach

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Abstract

Coronavirus is a pandemic in the world. It requires researchers and scientists to work hard to find a vaccine or drug to inhibit the development of the coronavirus. Many drugs have been used, such as remdesivir, lopinavir, and chloroquine. However, how effective is the use of these drugs for inhibiting the coronavirus's growth? There is no research has been done. Curcumin is now known as one of the compounds that have some biological activities, and it is also can potentially be used as a CoV-2 inhibitor. The computational study, i.e., molecular docking and molecular dynamic, can help researchers to predict which compounds have the potential as an inhibitor against the CoV-2 coronavirus. In this study, lopinavir was used as a positive control. Lopinavir and 45 curcumin analog compounds were docked against the main protease protein with 6LU7 PDB ID. Based on the docking results, it was discovered that compound **1**, compound **2**, and compound **4** have the same binding orientation as lopinavir. Molecular dynamic simulation with the lowest binding free energy conformation was used to check these compounds' stability. Only compound **4** was maintained to observe hydrogen bonding with Lys5 and Lys137 with a distance of 2.9 Å. The distance of hydrogen bonds and binding free energy over simulation time is essential to elucidate the potential compound's affinity. For then, compound **4** can be used as a potential inhibitor against the CoV-2 coronavirus.

1. Introduction

Corona Virus (CoV-2) or known as Covid-19, first appeared in the China City of Wuhan, Hubei Province in December 2019 [1, 2]. WHO (World Health Organization) has declared that CoV-2 has become a pandemic, a plague that has spread in a short time throughout the world. Covid-19 has been categorized as an infectious disease and has a continuous infection line. From March until the beginning of June 2020, the number of cases has been confirmed as many as 6.515.796 positive people of Covid-19, and the number of dead as many as 387.298 people [3]. Countries with the most three cases are the United States of America with a positive population of 1.987.335 cases, 112.060 died, and 746.980 recovered then Brazil 671.460 cases, 35.919 died, and 302.080 recovered. Russia has 458.690 cases, 5.725 died, and 221.390 recovered [3].

Covid-19 is an infectious disease caused by a newly discovered coronavirus. Coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a wide variety of infections in mammals, including humans. Currently, SARS-CoV-2, a highly infectious and pathogenic coronavirus, has become a global concern. Since SARS-CoV-2 is a novel pathogenic coronavirus, to date, no effective antiviral therapy is available. Preventive and supportive therapies are a primary approach for the management of Covid-19. Around the globe, researchers are endeavoring for the

development of effective prevention and treatment strategies for Covid-19 [4, 5].

Curcumin is a derivative of turmeric secondary metabolite with immense biological properties. It is one of the most commonly used and highly researched in multi-targeting phytochemicals [6]. Curcumin also has been reported to bind with various proteins of viral and human origin. Since the corona's pandemic, a report has been published about Curcumin as a potential inhibitor against CoV-2 using computational studies through molecular docking and molecular dynamic [6].

Drug design and computational approaches is a suitable combination for searching for new inhibitor against viruses. This combination can create a significant impact since they are cost-efficient, speedy, and are almost universally applicable across a wide range of the target. Computational approaches can aid in drug design in various ways, such as molecular docking and molecular dynamics.

In this study, molecular docking and molecular dynamic simulation have been used to examine the binding interaction of curcumin analog compounds with the protein 6LU7. The complex protein-ligand's best possess can be used to explore the binding free energy and the spatial arrangement based on lopinavir's orientation as a positive control [7]. Also, docking results and MD simulation can predict whether the compound can attack the virus target. Furthermore, the estimated active Curcumin was then chosen as the reference for the next stage in the drug design.

2. Material and Methods

2.1. Ligand Preparation

Lopinavir and 45 curcumin analog compounds [7] were used as ligands. In this study, lopinavir was used as a positive control [8]. The molecular structures of the ligands, as depicted in Table 1, it was sketched using ChemBioDraw Ultra 13.0 software packages. These ligands were converted into *PDB format using Discovery Studio Visualizer (DSC) for then each ligand was input one by one into MOE 2019_0101 (Chemical Computing Group) software package.

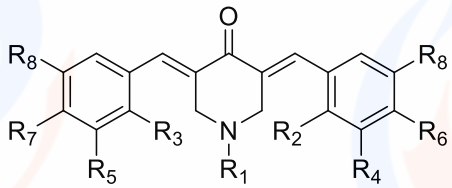

Table 1. Molecular structure of curcumin analog

Cpd	R1	R2	R3	R4	R5	R6	R7	R8
1	H	Cl	Cl					
2	H			Br	Br			
3	H					Cl	Cl	
4	CH_3	Cl	Cl					
5	CH_3			Br	Br			
6	CH_3					Cl	Cl	
7	C_6H_6	Cl	Cl					
8	C_6H_6			Br	Br			
9	C_6H_6					Cl	Cl	
10	H	OH	OH					
11	H			OH	OH			
12	H					OH	OH	
13		OH	OH					
14				OH	OH			
15						OH	OH	
16	C_6H_6	OH	OH					
17	C_6H_6			OH	OH			
18	C_6H_6					OH	OH	
19	H	OCH_3	OCH_3					
20	H			OCH_3	OCH_3			
21	H					OCH_3	OCH_3	
22		OCH_3	OCH_3					
23				OCH_3	OCH_3			
24						OCH_3	OCH_3	
25	C_6H_6	OCH_3	OCH_3					
26	C_6H_6			OCH_3	OCH_3			
27	C_6H_6					OCH_3	OCH_3	
28	H	OCH_3	OCH_3	OCH_3	OCH_3			
29		OCH_3	OCH_3	OCH_3	OCH_3			
30	C_6H_6	OCH_3	OCH_3	OCH_3	OCH_3			
31	H	OCH_3	OCH_3					OCH_3
32		OCH_3	OCH_3					OCH_3
33	C_6H_6	OCH_3	OCH_3					OCH_3
34	H			OCH_3	OCH_3	OCH_3	OCH_3	
35				OCH_3	OCH_3	OCH_3	OCH_3	
36	C_6H_6			OCH_3	OCH_3	OCH_3	OCH_3	
37	H	OCH_3	OCH_3			OCH_3	OCH_3	OCH_3
38		OCH_3	OCH_3			OCH_3	OCH_3	OCH_3
39	C_6H_6	OCH_3	OCH_3			OCH_3	OCH_3	OCH_3
40	H			OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
41				OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
42	C_6H_6			OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
43	H					C_2H_7N	C_2H_7N	
44						C_2H_7N	C_2H_7N	
45	C_6H_6					C_2H_7N	C_2H_7N	

A new database consisted of all ligands was created in MOE 2019_0101 (Chemical Computing Group), for then molecular docking was performed using this database as ligands source.

2.2. Protein Preparation

Protein protease was downloaded from a protein data bank with PDB ID 6LU7. The ligand was removed, then all the hydrogen atoms were added. A minimization process followed it. It minimized the energy using

CHARMM27 force field, alpha-carbon minimized, heavy atom minimized, and backbone minimized. Finally, the minimized protein should be saved in PDB format in MOE 2019_0101 (Chemical computing group) software package.

2.3. Molecular Docking

Docking was constructed through a simulated annealing method using CHARMM27 forcefield. Molecular docking was performed using MOE_2019.0101 (Chemical computing group) software package with a grid box measuring 25.86 Å × 27.81 Å × 23.36 Å dimension along x, y, and z axes, respectively. Upon the docking process was finishing, the lowest energy was selected as the best conformation. The complex enzyme ligand was minimized to a gradient of 0.01 kcal/mol/ Å.

2.4. Molecular Dynamic Simulation (MD)

NAMD (NAnoscale Molecular Dynamics program v 2.9) was used to perform the MD simulation. MD simulation was constructed under the periodic boundary condition with the NVT scheme. For the heating step, each simulated system was gradually heated from 0 to 300 K for 100 ps. MD simulations were conducted on a 50 ns time scale for each system in an isothermal, isobaric ensemble (NPT) with periodic boundary conditions. The coupling of temperature and pressure parameters was set on 1.0 ps. The coordinates were saved at every 0.1 ps during the sampling process. The simulations have generated the conformations for then they were used for further binding free energy calculations and decomposition process [7].

3. Results and Discussion

3.1. Molecular Docking

Lopinavir (i.e., positive control) and Curcumin were docked into the protein to study binding interaction between the ligands and protein [9]. Specifically, we predicted the bound conformations of the studied compounds inside a serine protease's active site. Lopinavir performed the hydrogen bonding with Lys5, van der Waals interaction with Glu288, Glu290, hydrophobic interaction with Val125. This compound has a binding free energy value of -45.98 kcal/mol, and RMSD is less than 2.0. The best docking results were selected according to the lowest binding free energy and the lowest RMSD value.

Furthermore, root-mean-square deviation (RMSD) can be used as an essential parameter for predicting potentially bioactive compounds that ideally should be less than 2 [10]. Based on this, it is presumed that lopinavir becomes active as an inhibitor against the CoV-2 coronavirus. The spatial arrangement of lopinavir is presented in Figure 1.

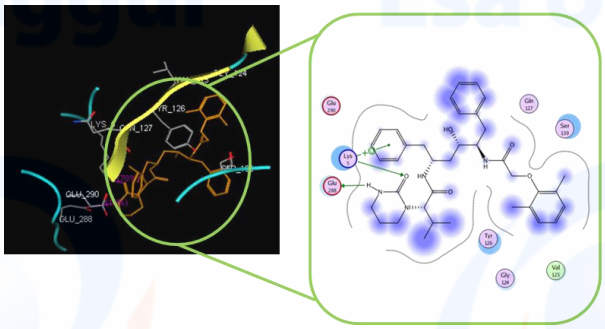

Figure 1. The spatial arrangement of lopinavir

Several docking criteria can be used to predict which compound will be the active inhibitor, such as the same bond orientation and type with the positive control, the lowest bond-free energy with RMSD less than 2.0. Generally, root means square deviation (RMSD) is used to validate the docking protocol. Validation of docking protocols means that we have to consider the crystallography of complex ligand and protein inside it and perform the same complex docking.

Table 2 is presented the docking results. Compound **1** has the same orientation as lopinavir with the binding free energy value of -41.67 kcal/mol. The more negative binding free energy means a stronger binding. This compound's binding free energy is close to the positive control, and it also has hydrogen bonding interaction with Lys5. Compound **1** also performed a van der Waals interaction with Glu288 and Glu290, but it does not have a hydrophobic interaction with an amino acid in the active site.

The number of hydrogen bonds formed by protein and ligand complexes was calculated by docking. It can be used to predict which compounds will become more active as inhibitors of CoV-2 coronavirus. A measure of the compound's probability under test bound to the same amino acid residue used by the control compound: lopinavir, binds). For compound **2,** there are two hydrogen bonding between this compound with amino acid residue Lys5, Arg131. Van der Waals interaction was observed with Glu290. The binding free energy value of -41.09 kcal/mol. The spatial arrangement of compound **1** and compound **2** are presented in Figure 2.

Table 2. Docking Results

Compound	Interactions			Binding free energy (kcal/mol)	RMSD
	Hydrogen bond	Van der Waals	Hydrophobic		
Lopinavir	Lys5	Glu288, Glu290	Val125	-45.98	0.00
Cpd 1	Lys5	Glu288, Glu290,	-	-41.67	0.00
Cpd 2	Lys5, Arg131	Glu290,	-	-41.09	0.00
Cpd 4	Lys5, Lys137	Glu288, Asp289 Glu290	Leu286	-41.93	0.00

Compound **4** engaged in two hydrogen bonds with Lys5 and Lys137, located at the active site. We predict compound **4** to be the active compound of all the Curcumin. It has the other interaction with the active

site. Regarding other types of interaction between compound **4** and the protein, we assumed the van der Waals interaction with Glu288, Asp289, Glu290. Hydrophobic interactions were also assumed between the compound **4** ligand and residues Leu286. Figure 3 is presented the spatial arrangement of compound **4**.

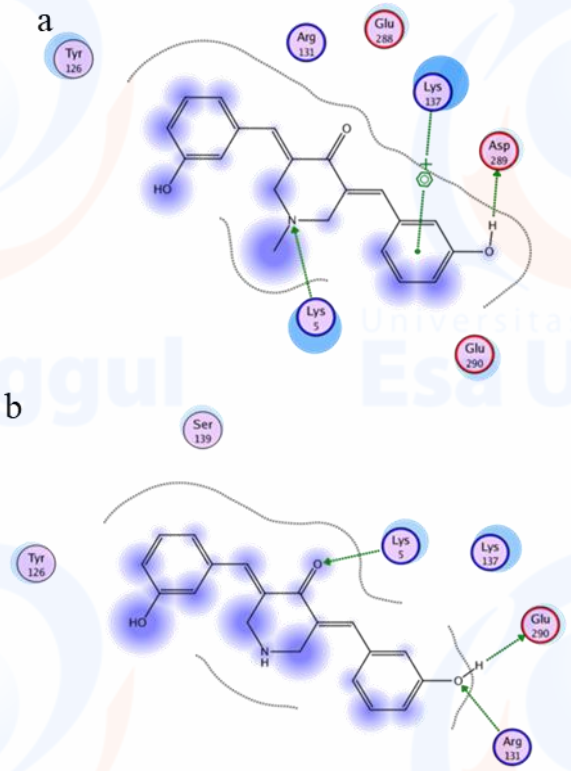

Figure 2. The spatial arrangement of **(a)** compound **1** and **(b)** compound **2**

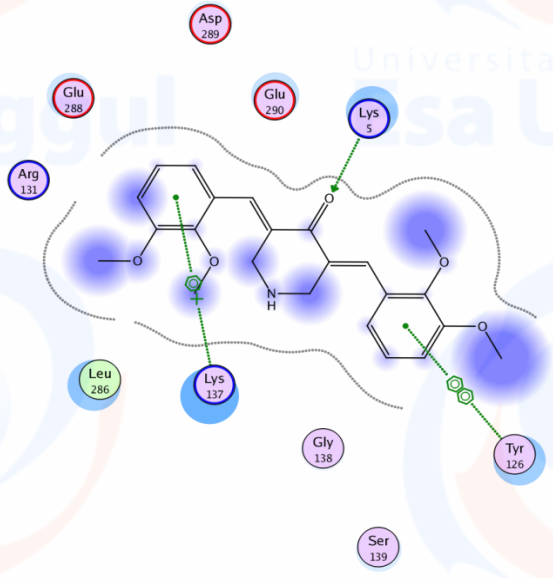

Figure 3. The spatial arrangement of compound **4**

As shown in Table 2, it appears that compound **4** has immense potential against the CoV-2 coronavirus because it maintains bonds with the same amino acid-like lopinavir, which were Lys5, Glu288, and Glu290. This compound is binding via two hydrogen bonds and with two Van der Waals interactions with the binding free energy value is close with lopinavir as a positive control. It may cause that this compound becomes active and assume it can be used as an inhibitor against the CoV-2 coronavirus.

The best pose of lopinavir and compound **1**, compound **2**, and compound **4** were then superimposed as depicted in Figure 4. Superimpose was performed to check lopinavir's orientation and compound **1**, compound **2**, compound **4** simultaneously. It seems that all three of these compounds have the same orientation to bind with the protein, wherein, in both cases, the benzyl ring flipped slightly. However, other parts' backbones (i.e., rings A and B) maintained their orientations.

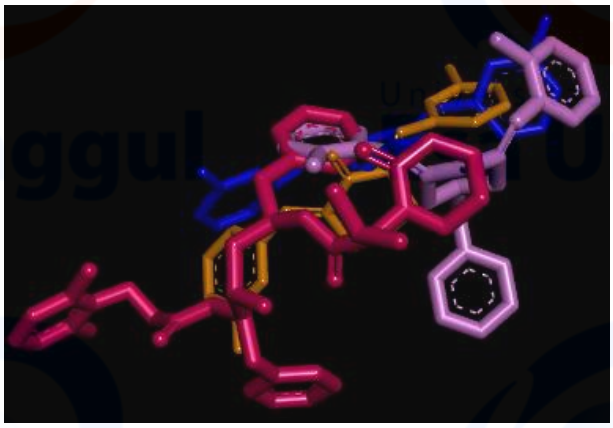

Figure 4. Superimposition of lopinavir (pink), compound **1** (blue), compound **2** (orange), compound **4** (purple)

3.2. Molecular Dynamic (MD)

Each system was simulated under the periodic boundary condition with an isothermal-isobaric (NPT) scheme. The nonbonded interaction was set to 10Å, and the electrostatic interaction was managed using the mesh Ewald method [10]. MD studies have currently been widely used in the design of drugs to understand the gene pathways and drug-receptor interactions [8]. The primary purpose of MD simulation is to explore the first stage of docking by assessing the binding of predictive poses. MD simulations can also be used to provide helpful information about the complimentary docking predictions [9]. The stable minimum energy is the beginning of the MD simulation, the system fluctuates around the initial conformation, and the ligand continues to have an initial binding mode [11]. In this study, MD simulations were carried out at 300 K for 50 ns to see the ligand's affinity to the binding site. The binding energy confirmation from the MD simulation is presented in Table 3.

Table 3. MD simulation results

No	Binding energy (kcal/mol)	Number of hydrogen bonding	Hydrogen bonding distance (Å)
Cpd 1	-401.78	-	-
Cpd 2	-398.13	-	-
Cpd 4	-447.85	Lys5, Lys137	2.9
Lopinavir	-453.20	Lys5	2.9

As a positive control, lopinavir has the lowest binding free energy, which shows that the lopinavir-protein complex is more flexible and stable [8]. The conformational value of free energy binding to compound **4** is -447.85 kcal/mol, which is relatively close to lopinavir. Thus, the compound 4-protein complex does not change during the MD simulation. Also, hydrogen bond distance and free energy of binding over simulation time are essential to elucidate potential compounds' affinity [12]. The hydrogen bonding distance of lopinavir with Lys5 was observed at 2.9 Å, and the hydrogen bonding of compound **4** with Lys5 and Lys137 was observed at the distance of 2.9Å. As illustrated in Figure 5, it seems that the conformation of compound 4 is maintained to bind well to critical residues after MD simulation. Thus, it is indicated that compound **4** has a tremendous potency as an inhibitor for the CoV-2 coronavirus.

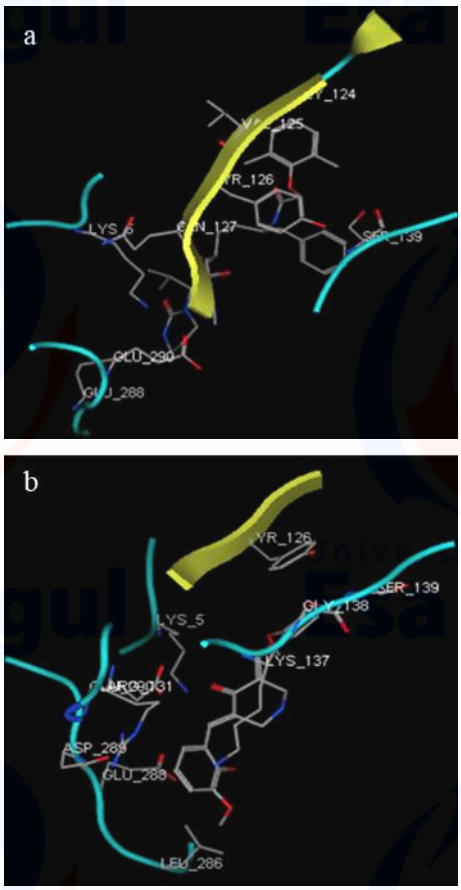

Figure 5. Binding mode visualization of compound **4**

A different case like compound **4** After the MD simulation, compound **2** and compound **3** were utterly changed. Both compounds were constructed in another binding orientation. The hydrogen bonds that were initially constructed in the docking results, after the MD simulation, almost all the hydrogen bonds were broken. This is also supported with high binding energy values were observed for compound **2** and compound **3** with a value of -401.78, -398.13, respectively. It is indicated that both complexes (i.e., compound **1**-protein and compound **2**-protein) were not flexible and not stable. Thus, compound **1** and compound **2** may not become active inhibitors against the CoV-2 coronavirus.

4. Conclusions

Molecular docking and MD simulation have been done for lopinavir and 45 curcumin analog compounds. Based on docking results, it was discovered that compound **1**, compound **2**, and compound **4** has the same binding orientation as lopinavir. Molecular dynamic simulation with the lowest binding free energy conformation was used to check these compounds' stability and flexibility. The hydrogen bonding of compound **4** is maintained to bind with Lys5 and Lys137. It was observed at a distance of 2.9Å. The distance of hydrogen bond and free energy of binding over simulation time is essential to elucidate the potential compound's affinity. For then, compound **4** can be used as a potential inhibitor against the CoV-2 coronavirus. Furthermore, the estimated active Curcumin (i.e., compound **4**) was then chosen as the reference for the next stage in the drug design.

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