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In Silico Screening of Natural Compounds as Potential Inhibitors of SARS-CoV-2 Main Protease: Targets for COVID-19

Nursilawati L[1]*, Siswandono[2], Mumpuni E[3]

[1, 3]Faculty of pharmacy Universitas Pancasila, Jakarta , Indonesia.

[2]Faculty of pharmacy Universitas Airlangga, Surabaya , Indonesia

[1]Corresponding Author E-mail: *lusinsys[at]gmail.com*

Abstract: ***Historically, plants have been sought after as bio-factories for the production of diverse chemical compounds that offer a multitude of possibilities to cure diseases. To combat the current pandemic coronavirus disease 2019 (COVID-19), plant-based natural compounds are explored for their potential to inhibit the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the cause of COVID-19. The present study is aimed at the investigation of antiviral action of several groups of phytoconstituents against SARS-CoV-2 using a molecular docking approach to inhibit Main Protease. Virtual screening of phytochemicals was performed through molecular docking, simulations, in silico drug-likeness prediction to identify the potential hits that can inhibit the effects of SARS-CoV-2. Considering the published literature on medicinal importance. The docking score was calculated by preferring the conformation of the ligand that has the lowest binding free energy (best pose). The results are indicative of better potential of Curcumin and Quercetin as Mpro inhibitors. Thus, phytochemicals like curcumin and Quercetin hold potential to be developed as treatment options against COVID-19.***

Keywords: In silico, curcumine, quercetin, COVID-19

1. Introduction

At the end of December 2019, the coronavirus outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei, China,1 leading to the rapid spread of 2019 novel coronavirus (COVID-19) into a pandemic responsible for the current global health crisis(2,3). In May 2020, there have been approximately 5 million confirmed cases of COVID-19 and more than 30 thousand deaths worldwide, as reported by the WHO(4) In this review, we aim to report historical records on the antiviral activity of a particular diet and herbal medicine on influenza virus, SARS-CoV-1, and SARS-CoV-2. This will promote the use of dietary therapy and herbal medicine as complementary COVID-19 prevention therapies, given the current absence of an effective drug and/or vaccine against COVID-19/SARS-COV-2. Several doctors and researchers have already attempted to use herbal medicines on clinical trials against SARS-CoV-2.5 The longstanding use of dietary therapy and herbal medicine to prevent and treat diseases cannot be overemphasized, as several herbs exhibit antiviral activity.6 Using dietary therapy and herbal medicine to prevent SARS-CoV2 infections could be a complementary COVID-19 therapy, while drugs remain under development. In this study, docking studies were performed over binding pocket of COVID-19 to find the potential small molecule to combat life threatening corona virus disease.

2. Material and Methods

2.1 Instrumentation

Computational chemistry calculations using a computer with an Intel (R) processor type Core i7-5500U CPU @ 2.40GHz with a 500 GB Hard disk and 12 GB RAM. Programs used include Molegro Virtual Docker 6.0 (Molegro ApS), SMILES Translator, pkCSM, Chem offi ce 2016, and GDP

2.2 Methods

Ligand Structure Preparation. The research began by downloading or preparing 6LU7, and 6M0J ligand-receptor structures. These ligands are obtained by downloading for free on the RCSB PDB website. Preparation of 3 Dimensional Structures of Active Compounds (Test Compounds).

3D structural preparation was carried out on Quercetin and Curcumine which were made in the Chem3D 16.0 program, after obtaining the stereochemical form of compounds and the most stable form, the structure was stored in the form of SYBYL.mol2.

Docking Analysis Process. Docking is done using the Molegro Virtual Docker (MVD) program of all compound structures in the form of 3-dimensional images and smile names. There are several steps to the docking process the first is downloading ligand-receptors, which is the structure of enzymes involved in the reactions that occur for the drug's target work at the RCSB PDB site. Choose the structure of the enzyme that binds to the drug which is the comparison of the active substance of the compound to be investigated in

this case, 6LU7, and 6M0J then the receptor containing the downloaded compound comparative ligand is imported into MVD, seen its cavities and interactions between the bonds.

The second stage is detection of the position of the receptor, where the drug will be bound (interacting), where it is in the form of holes (cavities) in the ligand-receptors.

The third stage is the structure of the quinine alkaloid active compound which is then imported into MVD as well as the test compound ligand which is then seen by the interaction between bonds (ligand map), then the detection of pharmacophore groups and determine the 3 points (compound atoms) where the drug will interact (bond) with the ligand receptor.

The fourth stage is to place the ligand structure of the test compound into the selected hole of the ligand-receptor by putting the structure of the compound in the hole, in the MVD program it is done by "allign" i.e attaching three atoms of the compound to the pharmacophore group to the same three atoms in the existing ligand in the receptor. Fifth, look at the picture (view) the position of compounds in receptor holes (cavities).

The last stage, when it has bonded and the bonds are in the cavities, then docking compounds are then performed on the receptor, which is done automatically with the MVD program. Things to consider in this process are the selection of docking compounds and the cavity in which the drug will interact. The parameters measured in the docking process are the energy values involved, in the form of MolDock Score, Rerank Score, and Hbond, and RMSD (Root Mean Square Deviation) values. To measure the strength of drug-receptor bonds, a parameter often used is the Rerank Score (RS)

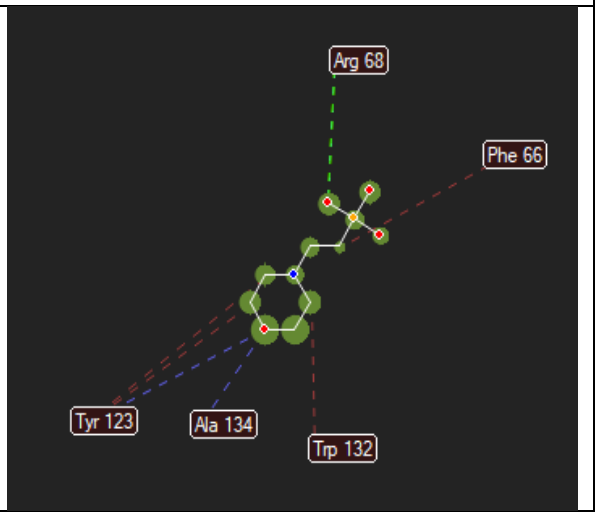
3. Results and Discussion

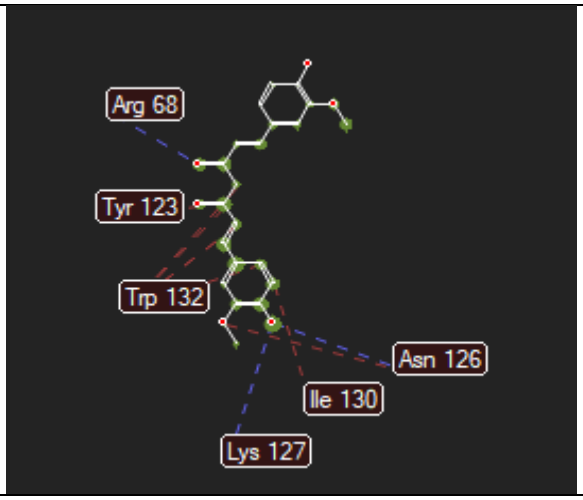
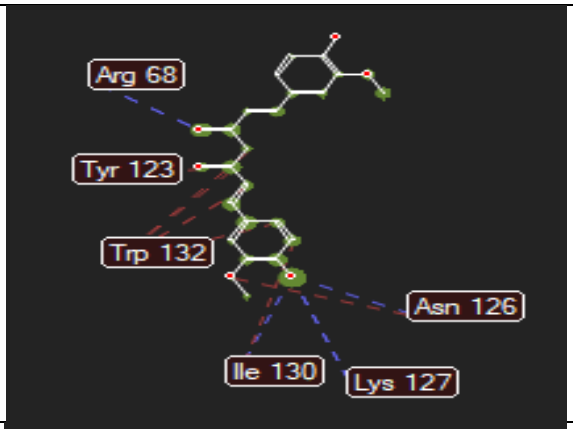
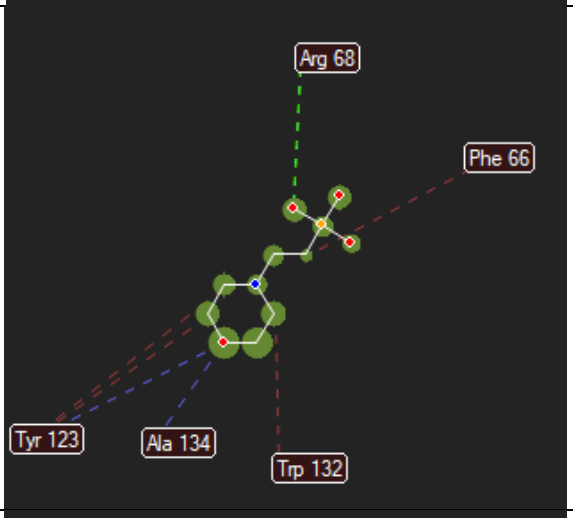
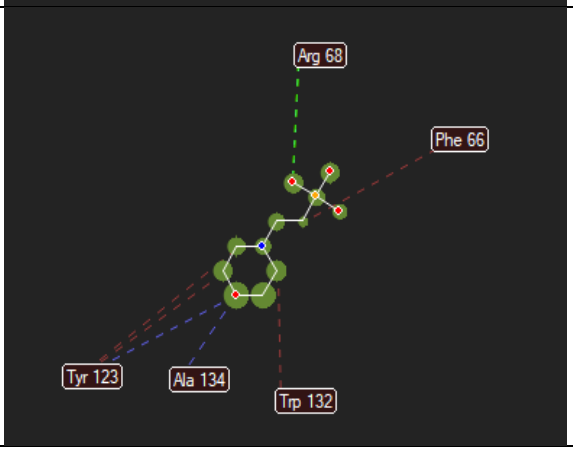
Ligand Structure Preparation. In Figure 1 you can see the structure of the ligand-receptor in which a pharmacophore group is attached to which the drug binds to the amino acid bonds that are present in the ligand-receptor which is a protein. However, the downloaded protein must have a ligand so that it can bind to the comparison drug in this case simvastatin which has activity as an antiatherosclerosis indirectly. Both of these ligand-receptors are seen in the cavities so that when docking is done with the test compound the docking compound must enter.

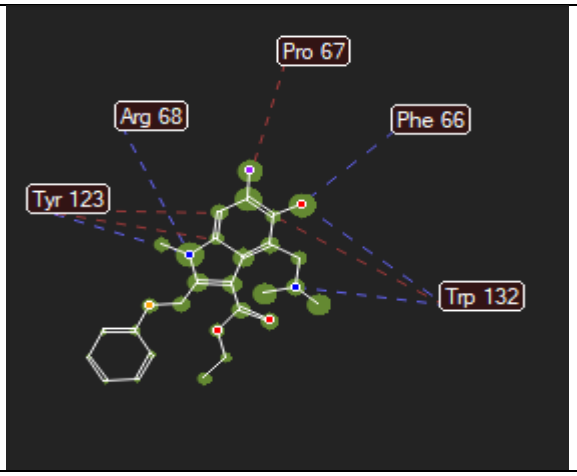
Docking Analysis Process

No	Nama Senyawa	*Rerank Score*
	Uji	
1.	Quercetin_Conformer3D_CID_5280343	-70.4146
2.	Curcumin_Conformer3D_CID_969516	-56.3819
	Pembanding	
1.	Favipiravir_Structure2D_CID_492405	-57.3877
2.	Oseltamivir_Structure2D_CID_65028	-71.0225
3.	Lopinavir_Structure2D_CID_92727	-60.9005
4.	Umifenovir_Structure2D_CID_131411	-76.7798

RMSD (Angstrom)	MolDock Optimizer	MolDock SE	Iterated Simplex	GPU Screening (CUDA)
MolDock Score	0.06	0.16	0.64	0.30
MolDock (Grid) Score	0.06	0.06	0.01	0.54
PLANTS Score	0.07	0.58	0.92	0.97
PLANTS (Grid) Score	0.07	0.08	0.04	0.06

No	Chemicals compound	*Visualisasi*
	sample	
1.	Quercetin_Conformer3D_CID_5280343	

2.	Curcumin_Conformer3D_CID_969516	
	Reference	
3.	Favipiravir_Structure2D_CID_492405	
4.	Oseltamivir_Structure2D_CID_65028	
5.	Lopinavir_Structure2D_CID_92727	

6.	Umifenovir_Structure2D_CID_131411	

Docking analysis results test compounds with their receptors, obtained the re rank score (RS) that illustrate. ligand bonds with receptors. Based on the hospital prediction of the activity of the compound can be obtained test when it has been bound to the receptor seen the lower the RS, the more stable it will be the bond between the ligand and the receptor so that activity compound can be said to be higher compared with compounds that have a higher RS.As you know, the value of RS is a value reflect the bond energy needed for form a bond between the ligand and its receptor, thus the activity of a can be predicted compound

4. Acknowledgement

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5. Conflict of Interest

The authors declare no conflict of interest.

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