Molecular Docking of Turmeric Active Compounds (*Curcuma long*a L.) against Main Protease in Covid-19 Disease

Nadhiefa Rahmadania Hasnaa[1], Rosario Trijuliamos Manalu[2]* , Subaryanti[3]
[1]Faculty of Pharmacy, National Institute of Science and Technology Jakarta.

ABSTRACT: CoronaVirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has become a global epidemic since late 2019. From the results of the analysis, it was found that curcumin compounds have good pharmacokinetics and potential as drugs. The result of visualization of protein-ligand complex showed that curcumin compound had good stability interaction. The molecular docking method for predicting the structure of protein-compound complexes is called protein-ligand docking. Curcumin compounds have a higher affinity than bisdemethoxycurcumin and oseltamivir. The purpose of the study was to find the active compounds contained in the turmeric plant (*Curcuma longa* L.) which have antiviral activity by inhibiting the SARS-CoV-2 protein.

Keywords*: Docking, Turmeric, Antiviral, Covid-19*

INTRODUCTION

The novel coronavirus infection (COVID-19) epidemic that started in China in late 2019 has been growing rapidly and cases have been reported worldwide. Coronavirusis one of the main pathogens that attack Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS)-CoV which have previously been characterized as agents that pose a major threat to public health.SARS-CoV-2 is a virus from the *Coronaviridae* family that has an envelope(R. T. Manalu et al., 2021). This envelope structure in viruses is involved in important aspects of the viral life cycle (Schoeman & Fielding, 2019). SARS-CoV-2 infection causes tissue damage and decreased lung function, and in some cases causes lung failure (Prajapat et al., 2020).

Efforts to overcome the COVID-19 outbreak, such as the development of vaccines that are recognized as successful so far, then several drugs that are considered to have a good effect on the recovery of COVID-19 patients, as well as several metabolites from medicinal plants. which have been observed to give outstanding results in treatment. Commonly used antivirals often show limited efficacy and serious side effects, herbal extracts have been used for medicinal purposes since ancient times and are known for their antiviral properties and more tolerable side effects (Ben-Shabat et al., 2020). Thus, nature-based pharmacotherapy can be an appropriate alternative to treat viral diseases.

The mechanism of action of active herbal compounds can be analyzed using an in-silico study using the molecular docking method. Dockingprocess has 3 goals main that is predict binding side active from a ligand, identify a new ligand use virtual screening, and predict affinity bond Among compounds and parts active of the ligands that have is known. Docking often used in Thing predict bond candidate drug molecular small against target proteins with predict activity molecules and their affinities(Mukesh & Rakesh, 2011).

A molecular docking study was designed to evaluate the effect of Food and Drug Administration (FDA)approved antiviral drugs and plant-based antiviral agents on the protein structure of the COVID-19 main protease virus from SARS-COV-2 (Peele et al., 2020).PLANTS® (Protein-Ligan ANT System) is one of the docking applications which is a free application that has the same quality as other paid docking applications. In addition, the advantage of practical PLANTS® is that it is simple and easy. However, PLANTS® does not provide protein preparation, ligand, and visualization functions, so additional applications are needed (Leach et al., 2006).

One of the herbal plants that are efficacious as medicine is turmeric because it contains curcumin and essential oils which is efficacious for treating gallbladder disease, colds, coughs, diabetes, rheumatism, sinusitis, skin diseases, parasitic infections and inflammation (Suprihatin et al., 2020). Current research indicates that turmeric has a variety of antiviral properties, by interfering with virus adsorption, entry, replication, and even viral budding. (Praditya et al., 2019). Curcumin, which is commonly found in the rhizomes of the genus Curcuma, has also been reported to inhibit the 3CLpro enzymatic activity of SARS-CoV(Sun et al., 2017). Therefore, this study aims to analyze the potential of various active compounds contained in the turmeric plant and their role in the SARS-CoV-2 protein.

METHODOLOGY

The research method used is in silico based with molecular docking technique.Receptor StructureCovid-19 target protein structure (code: 6LU7) obtained from PDB (http://www.rcsb.org/pdb/home/home.do).Ligand Structure the active

compounds of the turmeric plant as many as 56 compounds were obtained through the Pubchem page (https://pubchem.ncbi.nlm.nih.gov/).

Receptor preparation (target protein)

The protein structure used is the SARS-CoV-2 protein (code 6LU7) with a PDF document format downloaded via the database pageProtein Data Bank http://www.rcsb.org/pdb/home/home.do.Then the selection of the target protein to be used is based on its structure and organism. Protein macromolecules are prepared by separating them from solvents and non-standard ligands or residues. The separation of macromolecules from unnecessary molecules is done using the YASARA.

Preparation of Ligand Structure

The ligand structure is downloaded on the PubChem database page in 2D. Protonation was converted at pH 7.4 using Marvin Sketch, the data obtained were saved in .mrv format. Files that have been saved in.mrv format are opened and searched for conformation with the same software and then saved in .mol2 format.

Lipinski's Five Rule Analysis

Lipinski's Five Rule is defined in designing orally active drugs.Analysiswas carried out with compound files saved and then uploaded to Lipinski's Rule ofFive web serverhttp://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp

Docking Validation

Prior to the mooring action, validation was carried out which was useful for determining the root mean square deviation (RMSD) value. Validation using the YASARA program by entering certain ligands and receptors in .mol2 format. A protocol is accepted if the RMSD atomic weight is less than 2.0 Angstroms.

Molecular Docking

Molecular docking is performed on Windows operating system with PLANTS software. The ligand and receptor preparation results are transferred in .mol2 format. In the next step to find the binding site obtained with the command code. To run the docking process, enter the command code and wait for it to finish.

Docking Analysis and Visualization

The docking results are expressed in terms of the free bond energy and the type of interaction involved in the test ligand and native ligand. To see the relationship between ligands and receptors using Discovery Studio 2021 which is able to visualize the structure in two or three dimensions so that analysis is easier to do.

Pre-ADMET

Prediction of pharmacokinetic properties (ADME: absorption, distribution, metabolism, and excretion) and toxicity of compounds was carried out using the pkCSM online tool webserver. Predictions are made by copying the compound canonical SMILES from PubChem and pasting them on the pkCSM web server page http://biosig.unimelb.edu.au/pkcsm/prediction.

PASS (Activity Spectrum Prediction for Substances)

PASS (Prediction of Activity Spectra for Substances) is a web server tool designed as a tool to evaluate the general biologic potential of organic drug-like

molecules http://way2drug.com/passonline/. PASS provides simultaneous prediction of various types of biological activity based on the structure of organic compounds. Thus, PASS can be used to estimate the biological activity profile for virtual molecules, prior to their chemical synthesis and biological assays.

RESULTS

Table1. The result of drug-like molecule prediction from *Curcuma long*a L

No.	Compound	MW	LogP	HBD	HBA	MR
1.	4S-Dihydrocurcumenone	236.000	3.563	1	2	76.568
2.	8-Hydroxycadalene	214.000	3.028	1	1	69.099
3.	Alpha Atlantone	218.000	3.649	0	1	73.410
4.	Alpha Turmerone	218.000	3.659	0	1	73.355
5.	Alpha Cadinol	222.000	3.897	1	1	78.160
6.	Alpha Calacorene	200.000	3.542	0	0	70.499
7.	Acetoxyneocurdione	294.000	3.884	0	4	86.513
8.	Alpha Curcumene	202.000	3.788	0	0	72.613
9.	Aerugidiol	250.000	3.209	1	3	75.085
10.	Alismoxide	238.000	3.597	2	2	79.039
11.	Ar-Turmerone	216.000	3.445	0	1	71.076
12.	Bisacumol	218.000	3.670	0	1	73.300
13.	Bisacurol	220.000	3.751	0	1	74.824
14.	Bisacurone	252.000	3.295	2	3	77.282
15.	Bisacurone B	252.000	3.295	2	3	77.282
16.	Bisacurone C	252.000	3.295	2	3	77.282
17.	Bisacurone epoxide	268.000	3.326	1	4	77.941
18.	Bisdemethoxycurcumin	308.000	2.298	2	4	80.435
19.	Cadalenequinone	228.000	2.844	0	2	67.479
20.	Calarene	204.000	3.961	0	0	75.112
21.	Curcolone	246.000	2.748	1	3	70.692
22.	Curcolonol	264.000	2.674	2	4	73.795
23.	Curcumadiol	238.000	3.607	2	2	78.984
24.	Curcumadione	234.000	3.509	0	2	74.206
25.	Curcumalactone	236.000	3.734	0	2	76.430
26.	Curcumanolide A	234.000	3.509	0	2	74.206
27.	Curcumanolide B	234.000	3.509	0	2	74.206
28.	Curcumenol	234.000	3.338	1	2	74.344
29.	Curcumenolactone C	264.000	3.084	0	4	72.694
30.	Curcumenone	234.000	3.509	0	2	74.206
31.	Curcumin	368.000	3.105	2	6	92.754
32.	Curcumol	236.000	3.563	1	2	76.568
33.	Curcuphenol	218.000	3.489	1	1	73.492
34.	Curdione	236.000	3.723	0	2	76.485
35.	Curlone	218.000	3.526	0	1	72.600

Table1. The result of drug-like molecule prediction from *Curcuma long*a L

No.	Compound	MW	LogP	HBD	HBA	MR
36.	Curmadione	234.000	3.509	0	2	74.206
37.	Curzeone	228.000	2.834	0	2	67.534
38.	Curzerene	216.000	3.403	0	1	71.296
39.	Curzerenone	230.000	3.059	0	2	69.758
40.	Cyclocurcumin	368.000	3.056	2	6	93.470
41.	Dehydrocurdione	234.000	3.509	0	2	74.206
42.	Demethoxycurcumin	338.000	2.701	2	5	86.595
43.	Oxycurcumenol	250.000	3.369	0	3	75.003
44.	Turmerone	218.000	3.649	0	1	73.410
45.	Turmeronol A	232.000	3.145	1	2	71.955
46.	Turmeronol B	232.000	3.145	1	2	71.955
47.	Wenjine	282.000	2.667	0	5	75.197
48.	Xanthorrhizol	218.000	3.489	1	1	73.492
49.	Zederone	246.000	2.950	0	3	70.390
50.	Zedoalactone A	266.000	2.899	2	4	76.019
51.	Zedoalactone B	280.000	2.565	2	5	74.427
52.	Zedoarol	246.000	2.940	0	3	70.445
53.	Zedoarolide A	296.000	2.607	1	6	75.031
54.	Zedoarolide B	282.000	2.780	2	5	76.706
55.	Zedoarondiol	252.000	3.253	2	3	77.502
56.	Zingiberene	204.000	4.003	0	0	74.892

Note: MW: Molecular Weight; HBD: Hydrogen Bond Donors; HBA: Hydrogen Acceptors;
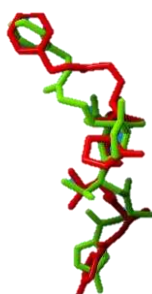LOGP: High lipophilicity; MR: Molar refractivity

Figure 1. The docking validation of the native ligand 17 conformation with an RMSD value of 1.8052 (Armstrong).

Table 2. Molecular Docking result

Compounds	Molecular Formula	Docking Score
	Native Ligands	
N3		-122.030
	Comparative Ligands	

Table 2. Molecular Docking result

Compounds	Molecular Formula	Docking Score
Remdesivir	$C_{27}H_{35}N_6O_8P$	-111.408
Oseltamivir	$C_{16}H_{28}N_2O_4$	-81.70
Test Ligands		
4S-Dihydrocurcumenone	$C_{15}H_{24}O_2$	-60.68
8-Hydroxycadalene	$C_{15}H_{18}O$	-66.53
Alpha Atlantone	$C_{15}H_{22}O$	-57.90
Alpha Turmerone	$C_{15}H_{22}O$	-65.33
Alpha Cadinol	$C_{15}H_{26}O$	-61.77
Alpha Calacorene	$C_{15}H_{20}$	-68.00
Acetoxyneocurdione	$C_{17}H_{26}O_4$	-67.32
Alpha Curcumene	$C_{15}H_{22}$	-71.11
Aerugidiol	$C_{15}H_{22}O_3$	-66.32
Alismoxide	$C_{15}H_{26}O_2$	-67.78
Ar -Turmerone	$C_{15}H_{20}O$	-66.91
Bisacumol	$C_{15}H_{22}O$	-70.15
Bisacurol	$C_{15}H_{24}O$	-72.82
Bisacurone	$C_{15}H_{24}O_3$	-67.87
Bisacurone B	$C_{15}H_{24}O_3$	-67.50
Bisacurone C	$C_{15}H_{24}O_3$	-61.37
Bisacurone epoxide	$C_{15}H_{24}O_4$	-62.67
Bisdemethoxycurcumin	**$C_{19}H_{16}O_4$**	**-87.37**
Cadalenequinone	$C_{15}H_{16}O_2$	-61.70
Calarene	$C_{15}H_{24}$	-57.22
Curcolone	$C_{15}H_{18}O_3$	-66.11
Curcolonol	$C_{15}H_{20}O_4$	-54.68
Curcumadiol	$C_{15}H_{26}O_2$	-64.62
Curcumadione	$C_{15}H_{22}O_2$	-62.83
Curcumalactone	$C_{15}H_{24}O_2$	-49.94
Curcumanolide A	$C_{15}H_{22}O_2$	-58.78
Curcumanolide B	$C_{15}H_{22}O_2$	-61.61
Curcumenol	$C_{15}H_{22}O_2$	-57.99
Curcumenolactone C	$C_{15}H_{20}O_4$	-59.24
Curcumenone	$C_{15}H_{22}O_2$	-58.99

Table 2. Molecular Docking result

| Compounds	Molecular Formula	Docking Score
Curcumin	**$C_{21}H_{20}O_6$**	**-88.81**
Curcumol	$C_{15}H_{24}O_2$	-58.98
Curcuphenol	$C_{15}H_{22}O$	-75.38
Curdione	$C_{15}H_{24}O_2$	-44.87
Curlone	$C_{15}H_{22}O$	-74.33
Curmadione	$C_{15}H_{22}O_2$	-67.11
Curzeone	$C_{15}H_{16}O_2$	-61.70
Curzerene	$C_{15}H_{20}O$	-61.02
Curzerenone	$C_{15}H_{18}O_2$	-58.89
Cyclocurcumin	$C_{21}H_{20}O_6$	-80.22
Dehydrocurdione	$C_{15}H_{22}O_2$	-53.83
Demethoxycurcumin	$C_{20}H_{18}O_5$	-79.42
Oxycurcumenol	$C_{15}H_{22}O_3$	-57.93
Turmerone	$C_{15}H_{22}O$	-67.20
Turmeronol A	$C_{15}H_{20}O_2$	-73.83
Turmeronol B	$C_{15}H_{20}O_2$	-69.70
Wenjine	$C_{15}H_{22}O_5$	-54.14
Xanthorrhizol	$C_{15}H_{22}O$	-77.19
Zederone	$C_{15}H_{18}O_3$	-53.15
Zedoalactone A	$C_{15}H_{22}O_4$	-58.52
Zedoalactone B	$C_{15}H_{20}O_5$	-64.66
Zedoarol	$C_{15}H_{18}O_3$	-55.77
Zedoarolide A	$C_{15}H_{20}O_6$	-60.85
Zedoarolide B	$C_{15}H_{22}O_5$	-69.67
Zedoarondiol	$C_{15}H_{24}O_3$	-57.93
Zingiberene	$C_{15}H_{24}$	-64.87
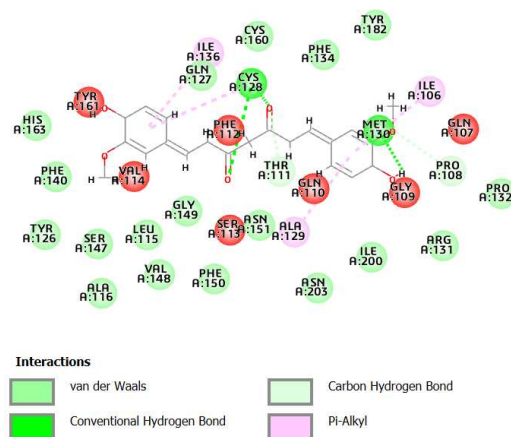
Figure 2. Visualization of the interaction of curcumin with protein

Table3.ADMET prediction using pkCSM

Prediction Test		Value Prediction
Absorption	Water solubility	-4.01
	Caco2 permeability	-0.093
	Intestinal absorption (human)	82.19
	Skin Permeability	-2.764
	P-glycoprotein substrate	Yes
	P-glycoprotein I inhibitor	Yes
	P-glycoprotein II inhibitor	Yes
Distribution	VDss (human)	-0.215
	Fraction unbound (human)	0
	BBB permeability	-0.562
	CNS permeability	-2.99
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP1A2 inhibitior	Yes
	CYP2C19 inhibitior	Yes
	CYP2C9 inhibitior	Yes
	CYP2D6 inhibitior	No
	CYP3A4 inhibitior	Yes
Excretion	Total Clearance	-0.002
	Renal OCT2 substrate	No
Toxicity	AMES toxicity	No
	Max. tolerated dose (human)	0.081
	hERG I inhibitor	No
	hERG II inhibitor	No
	Oral Rat Acute Toxicity (LD50)	1.833
	Oral Rat Chronic Toxicity (LOAEL)	2.228
	Hepatotoxicity	No
	Skin Sensitisation	No
	T.Pyriformis toxicity	0.494
	Minnow toxicity	-0.081

Table 6.Prediction of potential drug compounds with PASS online

Pa	Pi	Activity name
0,159	0,15	*Antiviral*

DISCUSSION

1. Lipinski's Five Rule

This molecular anchoring research aims to design a drug molecule to find new drug compounds that can interact effectively with the target receptor so that it can cause biological activity. Lipinski's Rule of Five also known as Rule of five is a rule of thumb for evaluating a drug or determining whether a chemical compound with a particular pharmacological or biological activity has properties that make it an orally administered drug in humans.These rules describe molecular properties that are important for drug pharmacokinetics in the humanbody, includingabsorption, distribution, metabolism, and excretion. Based on these rules, 56 active compounds of the turmeric plant were investigated to determine whether or not they matched the requirements of Rule Five using the Lipinski webserver. From the screening results, the test ligands used for molecular binding showed that all the compounds used met the five criteria, so they tended to be clinically active if given orally because of their good absorption.

2. Docking Validation

The validation of the docking method was carried out by re-docking the conformation of the original ligand to the binding site, where the RMSD (Root Mean Square Deviation) value was 1.8052Å. The obtained RSMD value states that the method has a high or low validity value (RMSD value <2 indicates a high validity value), meaning that the ligand copy position is similar to the active compound.

3. *Docking Analysis and Visualization*

From the results of analysis and visualization using the Discovery Studio software, it is known that the hydrogen bonding in the best test ligand, curcumin, obtained bound amino acid residues, namely, ALA116, ARG131, SER147, VAL148, LEU115, TYR126, GLY149, PHE150, ASN151, ASN203, ILE200, PRO132, PHE140, HIS163, GLN127, CYS160, PHE 134, TYR182 with van der Waals interactions. Forms hydrogen bonds with the amino acids CYS128 and MET130. PRO108 and THR111 carbon hydrogen bonds. As well as forming the type of interaction with Pi-Alkyl namely ALA129 and ILE106. Other residues are unfavorable amino acids. Hydrogen bonds are quite important for biological activity. Hydrogen bonding is an interaction that can stabilize ligand bonds and receptor binding. Other interactions between ligands and receptors that can increase conformational stability are electrostatic interactions and van der Walls interactions (R. Manalu, 2021)

4. ADMET Prediction

The predictive value of curcumin in the water solubility absorption test states that curcumin compounds are difficult to dissolve in water, have good CaCo2 permeability and good absorption intensity. According to Chander et al., (2017), a compound is said to have good absorption if its absorption value is >80%, and its absorption is bad if it is <30%. The intestine is the main site of absorption of drugs given orally. Single layer cell permeability is often used as an in vitro model of the

intestinal mucosa so that it can predict oral drug absorption. Skin permeability parameters are very important in drug delivery.

According to Pires et al., (2015), a compound is said to have relatively low skin permeability if it has a log value of Kp> -2.5. From these results, it can be seen that the Skin Permeability value (log Kp) of curcumin compound (-2.764) means less than -2.5, so it can be predicted that this compound has the potential to be developed in topical dosage forms because it is topical. Has good skin permeability. Prediction results of substrates and inhibitors of P-glycoprotein I and II stated "Yes". This means that these compounds will be absorbed through P-glycoprotein and P-glycoprotein inhibitors I and II.

Prediction of volume of distribution at steady state or volume of distribution is a theoretical volume prediction which states the total concentration of homogeneous drug circulating in blood plasma. In this case, the volume of distribution is small if <0.71 L/kg or <-0.15 log L/kg), and the volume of distribution is large if >2.81 L/kg or >0.45 log L/kg. Not bound to the fraction of drug in plasma. Able to penetrate BBB (Blood Brain Barrier) if BB log value > 0.3. The compound is predicted to be able to penetrate the drug through the bloodstream in the brain. CNS or Central Nervous System Permeability is the ability of a drug to penetrate the central nervous system. This is important to reduce side effects and toxicity or can increase the efficacy of drugs for the purpose of treating the central nervous system. These compounds are predicted to penetrate the CNS, this is said by Pires et al., (2015), the compound penetrates the CNS if the log PS is >-2. Meanwhile, if the PS log <-3 is considered not to penetrate the SSP.

Polymorphisms in the CYP family may have the greatest impact on the fate of therapeutic drugs. The CYP2D6, 2C19, and 2C9 polymorphisms are the most frequent variations in phase I drug metabolism, as nearly 80% of currently used drugs are metabolized by these enzymes. Prediction of the metabolism of this compound, among others, tends to have the property of inhibiting cytochrome 450 enzymes. Prediction of the rate of drug clearance in the body which is a combination of hepatic clearance (liver metabolism and bilinary clearance) and kidney clearance. If it has a more negative value, the harder it is to remove.

AMES toxicity in this compound states that it is not mutagenic. This compound is classified as low in the estimated safe dose limit for humans because it has a value of < 0.447. Inhibition of the potassium channel encoded by hERG (human ether-a-go-go gene) is a major cause of the development of long QT syndrome - leading to fatal ventricular arrhythmias. The toxicity of T. pyriformis was stated to be low because the IG50 value was < -0.5. Predictions of chemicals that induce liver cell damage were also not found. Toxicity prediction based on minnow (fish) mortality based on LC50 value. LC50 is the concentration of the substance causing the death of the minnow fish population as much as 50%. LC50 value < 0.5 mM or (log LC50 < -0.3) is considered to have high acute toxicity (Pires et al., 2015).

5. *PASS (Prediction of Activity Spectra for Substances*

Based on the prediction results using the online PASS webserver, there are various kinds of potentials possessed by curcumin compounds, one of the results used as the basis for searching is antivirus with the results Pa>Pi: 0.159> 0.150. If the Pa value < 0.5 then the compound has a low activity value on a laboratory scale (Chelliah, 2008). This means that with this value the curcumin compound has the possibility of being a good compound, but has a low possibility of compound activity as an antiviral.

CONCLUSIONS AND RECOMMENDATIONS

The compound curcumin with a docking score of -88.81 and bisdemethoxycurcumin with a docking score of -87.37 had a better interaction than oseltamivir with a docking score of -81.70 against the SARS-CoV-2 protein receptor.Curcumin has good potential to exert antiviral effect on SARS-CoV-2 protein in the treatment of COVID-19.It is necessary to conduct in silico research on other medicinal plants in handling COVID-19 and to conduct in vitro and in vivo tests to determine the activity of turmeric plant compounds as an antiviral for COVID-19.

FURTHER STUDY

Research can be developed to determine the activity of curcumin compounds and their derivatives as other antivirals.

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