BIOAVAILABILITY AND MOLECULAR DOCKING PREDICTION OF SECONDARY METABOLITE OF *Curcuma zedoaria* AS POTENTIAL MPRO SARS COV-2 INHIBITOR

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ABSTRACT

Almost all countries worldwide have been exposed to the COVID-19 pandemic, which can cause respiratory diseases. Therefore, it is necessary to identify and develop drugs for the treatment of COVID-19. White turmeric (Curcuma zedoaria) is very popular because it is effective as an anticancer and antiviral agent. This study used the in silico method to predict the secondary metabolite compounds contained in C. zedoaria as inhibitors of Mpro (main protease) SARS-CoV-2. Of the 30 secondary metabolite compounds identified, 26 compounds had good bioavailability prediction, and three compounds (curcumadiol, curcumin, and desmethoxycurcumin) were predicted to have potential as SARS-COV-2 Mpro inhibitors because they have low inhibition constants and numerous ligand-protein interactions. Curcumadiol have binding energy: -8.34 kcal/mol; pKi: 0.77 µM; hydrogen bond: Glu166, Thr190, and Gln192; and hydrophobic bond: Met165 and Gln189. Curcumin have binding energy: -8.28 kcal/mol; pKi: 0.85 µM; hydrogen bond: Leu141, Gly143, Ser144, and Thr190; and hydrophobic bond: Cys145, Met165, and Gln189. Desmethoxycurcumin have binding energy: -7.83 kcal/mol; pKi: 1.84 µM; hydrogen bond: Asp187, Thr190, and Gln192; and hydrophobic bond: Met165.

***Keywords**: Curcuma zedoaria, SARS-CoV-2, bioavailability, molecular docking*

INTRODUCTION

Almost all countries worldwide have been exposed to the COVID-19 pandemic, which can cause respiratory diseases. It was first detected in December 2019 in Wuhan, China (Rathinavel *et al.*, 2020). Based on the COVID-19 case data collected by the *World Health Organization* (WHO), 767,726,861 cases and 6,948,764 deaths due to SARS-Cov-2 were confirmed as of July 9, 2023 (WHO, 2023). This virus is named *Severe Acute Respiratory Syndrome Coronavirus* 2 (SARS-CoV-2), and the disease caused by it is named *Coronavirus Disease-2019* (COVID-19) (Sukur *et al.*, 2020).

SARS-CoV-2 is thought to spread primarily through respiratory droplets produced by coughing or sneezing (Kementerian Kesehatan RI, 2020). These sparks can result from sneezing and normal breathing. In addition, the virus can spread by touching the surfaces of contaminated objects (Rothan and Byrareddy, 2020). The high total number of cases and deaths means that the disease must be given special attention that must be addressed immediately. To date, the number of infected patients continues to grow, and no effective drugs have been approved for the treatment of COVID-19 (Hanggoro *et al.*, 2020). Therefore, it is necessary to identify and develop drugs for the immediate treatment of COVID-19.

Indonesia is the world's largest archipelagic country. The abundance of biodiversity in Indonesia can be used to develop medicinal plants (Lestari, 2016). Riset

Tumbuhan Obat dan Jamu (Research on Medicinal Plants and Herbs), carried out by the Balai Besar Penelitian dan Pengembangan Tanaman Obat dan Obat Tradisional (Center for Research and Development of Medicinal Plants and Traditional Medicines), has produced an ethnopharmacological knowledge database in the form of information on traditional medicinal herbs, as many as 33,000 herbs that are empirically proven to be able to maintain public health, consisting of 2,800 species of medicinal plants (Makani, *et al*, 2022). One of the medicinal plant families that is often used is the zingeberecae family (Larasati, *et al* 2019). White turmeric (*Curcuma zedoaria*) belongs to the *Zingiberaceae* family and can grow up to 2 meters (M and Irawan, 2020). *C. zedoaria* is very popular because it is effective as an anticancer and antiviral agent (Fitria, 2019). *C. zedoaria* has been used traditionally to treat various diseases, including abdominal pain, blood stagnation, diarrhea, skin disorders, and rheumatism. The chemical ingredients contained in the rhizomes and leaves of white turmeric are curcumin, zedoarin, gum, resin, starch, saponins, flavonoids, polyphenols, and essential oils such as cineol, camphene, zingiberene, borneol, and camphor (Qamariah, 2020).

Based on the data above, this study used an *in silico* method to predict the secondary metabolite compounds contained in *C. zedoaria* as inhibitors of Mpro (main protease*)* SARS-CoV-2. This research was conducted by examining compound interactions and free energy values (Suhadi, *et al*, 2019). *In silico* testing is used for computational testing. This test could be an early method for developing new herbal medicines to support the development of the pharmaceutical industry (Basuki, *et al*, 2017). Through this test, we can predict, hypothesize, and progress the latest treatment discoveries.

RESEARCH METHODS

Tools

The software used in this study was AutoDock PyRx series 0.8, Biovia Discovery Studio 2020, Avogadro series 1.2.0. The databases used in this study are PDB the Protein Data Bank (PDB) webserver, Dr. Duke Phytochemical and Ethnobotanical Databases webserver, SwissADME webserver, PubChem webserver, and Proteins.plus webserver.

Materials

In this study, the target protein Mpro was used with the code 6LU7 from the PDB webserver (Pandey *et al.*, 2020), and secondary metabolites of *Curcuma zedoaria* were obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases webserver (U.S.). Department of Agriculture, 2016).

Bioavailability Prediction

Data on *Curcuma zedoaria* bioactive chemicals were obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases. The data collected from the database were supplemented by the data obtained by accessing the PubChem chemical compound library portal. The simplified molecular-input line-entry system (SMILES) codes of *Curcuma zedoaria* secondary metabolites were input into the *SwissADME* webserver to obtain good bioavailability data based on the *Boiled-Egg* method (Daina and Zoete, 2016; Daina *et al*, 2017). Compounds that enter the *boiled-egg* area proceed to the next stage.

Molecular Docking

Before molecular docking, proteins were prepared using *Biovia Discovery Studio2020* to separate proteins and ligands. This method was validated by docking ligand compounds with protein targets. Molecular docking was performed on the *Grid Box* specified at coordinates x = -10.5679, y = 11.8096, and z = 68.1165, with a size of 60 × 60 × 60 and a distance of 0.375 Å.

Secondary metabolite compounds of *Curcuma zedoaria* that passed *Boiled-Egg* were prepared using Avogadro and the MMF94s method. The test compound was docked with Mpro using *AutoDock PyRx series 0.8.* The parmeter used by *the Lamarckian genetic*

algorithm has a running number of 100, a maximum number of evaluations of 2,500,000, a position size of 150, and a maximum generation of 27,000 (Muchlisin *et al*., 2022).

Ligand-Protein Interaction Prediction

The interaction between secondary metabolite compounds of *Curcuma zedoaria* and Mpro was analyzed using *the Protein.plus web server*.

RESULTS AND DISCUSSION

Secondary Metabolite Compounds of *C. zedoaria*

From Dr. Duke's Phytochemical and Ethnobotanical Databases webserver and PubChem webserver, 30 lists of secondary metabolite compounds in *C. zedoaria* plants are shown in **Table I.**

Table I. List of Secondary Metabolite Compounds of *C. zedoaria*

No	Compound Name	Compound Code
1	1.4-cineole	Mol 1
2	1.8-cineole	Mol 2
3	Alpha-pinene	Mol 3
4	Curcumadiol	Mol 4
5	Curcumanolide-A	Mol 5
6	Curcumanolide-B	Mol 6
7	Curcumenol	Mol 7
8	Curcumenone	Mol 8
9	Curcumin	Mol 9
10	Curcumol	Mol 10
11	Curdione	Mol 11
12	Curzerenone	Mol 12
13	D-alpha-pinene	Mol 13
14	D-borneol	Mol 14
15	D-camphene	Mol 15
16	D-camphor	Mol 16
17	Dehydrocurdione	Mol 17
18	Desmethoxycurcumin	Mol 18
19	Epicurzerenone	Mol 19
20	Ethyl-p-methoxycinnamate	Mol 20
21	Furanodiene	Mol 21
22	Furanodienone	Mol 22
23	Germacrone-4.5-epoxide	Mol 23
24	Isocurcumenol	Mol 24
25	Isofuranodienone	Mol 25
26	Isofuranogermacrene	Mol 26
27	Procurcumenol	Mol 27
28	Pyrocurzerenone	Mol 28
29	Zederone	Mol 29
30	Zingiberene	Mol 30

Bioavailability Prediction

The bioavailability of a drug is an important parameter in determining the amount and speed of drug absorption in the body (Lena *et al*., 2023). Therefore, the determination of bioavailability was very important in this study. Bioavailability predictions were carried out using SwissADME and the Boiled-Egg method (Daina and Zoete, 2016; Daina *et al*, 2017). This method used an image model to classify the absorption of a compound **Figure 1.**

Boiled-Egg is a reliable predictive model that analyzes the polarity (TPSA) and lipophilicity (WlogP) of small compounds (Muchlisin *et al.*, 2022). Boiled-egg can be used in various contexts, including screening chemical libraries during the preliminary stages of drug discovery and assessing potential drug candidates. The egg white region shows the ability of the compound to be absorbed in the gastrointestinal tract, while the yolk region can penetrate the blood-brain barrier (Sugiura *et al.*, 2016). The secondary metabolites of *C. zedoaria*, located in the white circle, were predicted to have good bioavailability. These compounds become inclusion compounds that are docked with the target protein. Of the 30 known compounds, were 26 predicted to have a high bioavailability **Table II.**

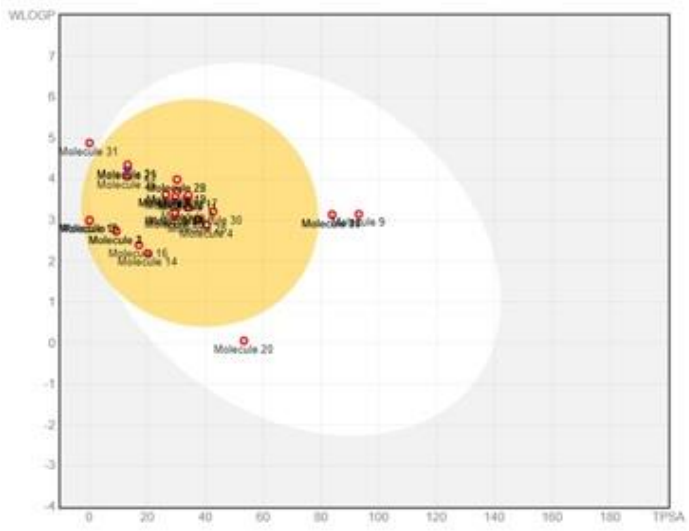


Figure 1. Boiled Egg model

Table II. List of Secondary Metabolite Compounds of *C. zedoaria* that Pass the Boiled-Egg Classification and Lipinski's Rule

No	Bioavailability Prediction	Total Compounds	Compound Code
1	High	26	Mol 1, Mol 2, Mol 4, Mol 5, Mol 6, Mol 7, Mol 8, Mol 9, Mol 10, Mol 11, Mol 12, Mol 14, Mol 16, Mol 17, Mol 18, Mol 19, Mol 20, Mol 21, Mol 22, Mol 23, Mol 24, Mol 25, Mol 26, Mol 27, Mol 28, Mol 29
2	Low	4	Mol 3, Mol 13, Mol 15, Mol 30

Molecular Docking Prediction

The docking process was carried out to predict the affinity and interaction of secondary metabolite compounds of *C. zedoaria* with the target protein 6LU7. Antiviral drugs inhibiting Mpro (the main protease) SARS-CoV-2 were chosen for comparison: oseltamivir, favipiravir, and lopinavir. The lower the binding energy, the greater the binding efficiency and, hence, the augmented inhibition (C. *et al.*, 2022). In addition, the predicted value of the inhibition constant (pKi) also influences the strength of the interactions. The lower the pKi value, the stronger is the interaction (Muchlisin *et al.*, 2022). The inhibition constant is the half-maximal inhibition of an enzyme by a chemical compound. It is used to estimate the potential of a substrate/inhibitor to enhance or inhibit the biological function of enzymes. Compounds with an inhibition constant of less than 100 µM are considered potential inhibitors, whereas those with inhibition constants of more than 100 µM are non-potent inhibitors (C. *et al.*, 2022).

The results of docking against the main protease (6LU7) lopinavir (binding energy: -9.01 kcal/mol; pKi: 0.25 µM) exhibited the best binding conformations with Mpro in the current study compared to oseltamivir (-6.85 kcal/mol; 9.54 µM) and favipiravir (-4.29 kcal/mol; 715.76 µM). Based on the data obtained, 24 secondary metabolite compounds of *C. zedoaria* had a pKi value of less than 100 µM, indicating their potential as Mpro inhibitors. Compound code mol 4 (-8.34 kcal/mol; 0.77 µM), mol 7 (-7.81 kcal/mol; 1.89 µM), mol 9 (-8.28 kcal/mol; 0.85 µM), mol 18 (-7.83 kcal/mol; 1.84 µM), and mol 24 (-7.47 kcal/mol; 3.34 µM) exhibited the best binding energy and pKi with Mpro in the current study **Table III.**

Table III. The Docking Results and Secondary Metabolite Compounds of *C. zedoria* Against Mpro (6LU7)

No	Compound Code	ΔG (Kcal/mol)	Inhibition Constant Prediction (pKi) (µM)
1	Mol 1	-5.87	50.10
2	Mol 2	-5.80	56.49
3	Mol 4	-8.34	0.77
4	Mol 5	-6.23	27.09
5	Mol 6	-6.16	30.74
6	Mol 7	-7.81	1.89
7	Mol 8	-6.51	16.84
8	Mol 9	-8.28	0.85
9	Mol 10	-5.95	43.35
10	Mol 11	-6.81	10.25
11	Mol 12	-6.51	16.99
12	Mol 14	-5.23	146.12
13	Mol 16	-5.54	87.27
14	Mol 17	-6.39	20.82
15	Mol 18	-7.83	1.84
16	Mol 19	-6.68	12.59
17	Mol 20	-4.52	486.04
18	Mol 21	-6.72	11.94
19	Mol 22	-6.04	37.69
20	Mol 23	-6.33	22.75
21	Mol 24	-7.47	3.34
22	Mol 25	-6.49	17.45
23	Mol 26	-6.21	27.84
24	Mol 27	-6.91	8.67
25	Mol 28	-6.68	12.74
26	Mol 29	-6.31	23.69
27	Oseltamivir	-6.85	9.54
28	Favipiravir	-4.29	715.76
29	Lopinavir	-9.01	0.25

Ligand-Protein Interaction Prediction

The analysis of ligand-protein interactions is also essential to review the ability of the secondary metabolite of *C. zedoaria* to interact with the ligand-binding domain (LBD) of the target protein (Hidayat *et al.*, 2021). Several things can be observed, namely, hydrogen bonds and hydrophobic bonds. Hydrogen bonding is a bond that occurs between hydrogen atoms in one molecule and one element (N, O, F) in another molecule, which is the strongest dipole-dipole force. Hydrogen bonds are essential for determining the structure, properties, and functions of a molecule (Vinsiah, 2018). The higher the number of hydrogen bonds, the higher is the binding efficiency and inhibition (C. *et al.*, 2022). Meanwhile, hydrophobic

interactions are interactions that avoid the liquid environment and are more clustered in the inner part of the globular structure of proteins to minimize interactions with water, which can damage protein structures and cause enzymes to lose their activity (Imanudin, *et al* 2022). Hydrophobic interactions are residual interactions of nonpolar amino acids (Elfi, *et al*, 2021).

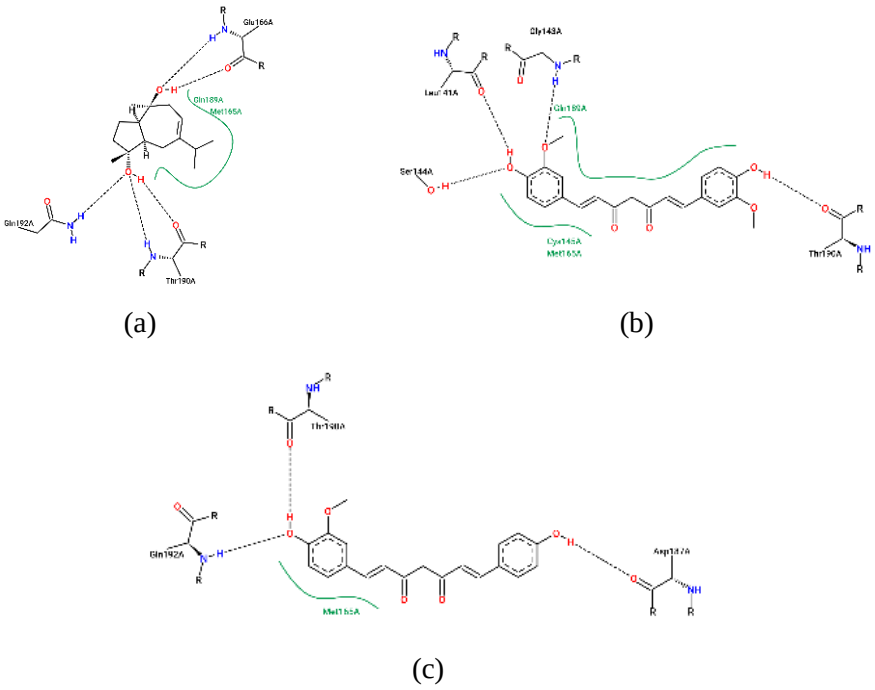
Table IV. Bonds Formed between Positive Control and Secondary Metabolite Compounds of White Turmeric Plant (*Curcuma zedoaria*) Against Mpro (6LU7)

No	Compound Code	Amino Acid Interaction	
		Hydrogen Bonding	Hydrophobic Bonding
1	Mol 1	No interaction	No interaction
2	Mol 2	No interaction	No interaction
3	Mol 4	Glu166, Thr190, Gln192	Met165, Gln189
4	Mol 5	Gly143, Ser144	No interaction
5	Mol 6	Glu166	His41, Gln189
6	Mol 7	Glu166	Met165, Gln189
7	Mol 8	His163	Met165
8	Mol 9	Leu141, Gly143, Ser144, Thr190	Cys145, Met165, Gln189
9	Mol 10	Asn142	No interaction
10	Mol 11	Glu166	His41, Met165, Gln189
11	Mol 12	No interaction	No interaction
12	Mol 14	Leu141	No interaction
13	Mol 16	No interaction	No interaction
14	Mol 17	His163	Cys145
15	Mol 18	Asp187, Thr190, Gln192	Met165
16	Mol 19	Gln189	No interaction
17	Mol 20	His164	No interaction
18	Mol 21	No interaction	No interaction
19	Mol 22	Gly143	No interaction
20	Mol 23	Glu166	His41
21	Mol 24	Glu166	Met165, Gln189
22	Mol 25	No interaction	No interaction
23	Mol 26	No interaction	No interaction
24	Mol 27	His163, Glu166	Glu166
25	Mol 28	Glu166	His41, Met49, Met165, Gln189
26	Mol 29	Glu166	Met165
27	Oseltamivir	His163A, Glu166A	Met165A, Glu166A
28	Favipiravir	Phe140A, Asn142A, His163A	No interaction
29	Lopinavir	His41A, Gly143A, Cys145A, His164A	His41A, Met49A, Asn142A, Met165A, Glu166A, Asp187A, Gln189A

The analysis showed that the three compounds have many hydrogen and hydrophobic bonds: mol 4, mol 9, and mol 18 **Table IV; Figure 2**. Mol 4 has hydrogen bonds (Glu166, Thr190, and Gln192) and has hydrophobic bonds (Met165 and Gln189). Mol 9 has hydrogen bonds (Leu141, Gly143, Ser144, and Thr190) and has hydrophobic bonds (Cys145, Met165, and Gln189). Mol 18 has hydrogen bonds (Asp187, Thr190, and Gln192) and a hydrophobic bond (Met165). Mol 4, mol 9, and mol 18 show potential as Mpro inhibitors.

The secondary metabolite compounds that have great potential as a main protease inhibitor, which was seen from low pKi and many ligand-protein interactions, are mol 4 (curcumadiol), mol 9 (curcumin), and mol 18 (desmethoxycurcumin).

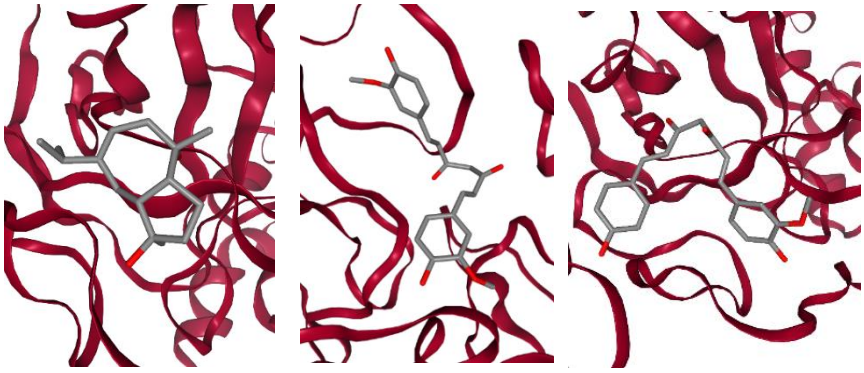
Curcumin is a compound that has antioxidant, anti-inflammatory, and antiviral activities. Curcumin has an antiviral effect by preventing the replication of SARS-COV and inhibiting 3Cl protease in Vero E6 cells. It can significantly inhibit the cytopathogenic effect of SARS-COV (any pathological changes (or lesion) in the host cells that are caused by virus infection) in Vero E6 cells (Ryu, 2017; Prasetyo, *et al*, 2022). Desmethoxycurcumin has anticancer, anti-inflammatory, neuroprotective, anti-Alzheimer, and antioxidant activities (Abdurrahman, 2019). Demethoxycurcumin exhibits anti-inflammatory activity based on its ability to stabilize red blood cell membranes (Sa'adah, 2019). In comparison, the activity of curcumadiol has not yet been studied.



(a) (b)

(c)

Figure 2. Visualization of secondary metabolite compounds of *C. zedoaria* in two-dimensional structure: (a) curcumadiol, (b) curcumin, (c) desmethoxycurcumin



(a) (b) (c)

Figure 3. Visualization of secondary metabolite compounds of *C. zedoaria* in three-dimensional structure: (a) curcumin, (b) curcumadiol, (c) desmethoxycurcumin

CONCLUSION

Curcumadiol, curcumin, and desmethoxycurcumin are predicted to have potential as SARS-COV-2 Mpro inhibitors because they have low energy binding and inhibition constants prediction and numerous ligand-protein interactions.

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