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Original Article

In Silico Screening of Bioactive Compounds from *Syzygium cumini* L. and *Moringa oleifera* L. Against SARS-CoV-2 via Tetra Inhibitors

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ABSTRACT

The global pandemic of COVID-19 has caused disastrous consequences for both humans and the economy. The purpose of this study was to determine the potential of juwet (*Syzygium cumini* L.) and moringa (*Moringa oleifera* L.) as inhibitors of RBD spike, helicase, Mpro, and RdRp activity of SARS-CoV-2 with an *in-silico* approach. Samples were obtained from PubChem and RSCB PDB databases. The drug similarity analysis was determined using Swiss ADME and the Lipinski rule of five. Prediction of antivirus probabilities is carried out with PASS Online. Molecular screening is performed by molecular docking using PyRx. Visualization was used using PyMol and Discovery Studio. The bioactive compounds with the best antiviral potential had the lowest affinity bonds to the target proteins against RBD spike, helicase, Mpro, and RdRp of SARS-CoV-2. Results show that ellagic acid from java plum and myricetin from moringa have the best potential as potential antivirals. However, more research is required to validate the results of these computational predictions.

Key words: SARS-CoV-2, *Syzygium cumini* L., *Moringa oleifera* L, *In silico*, Antiviral agent.

INTRODUCTION

Severe acute coronavirus-2 (SARS-CoV-2) causes coronavirus disease (COVID-19).[1] This disease spread rapidly throughout the world, resulting in a pandemic.[2,3] According to WHO, there are more than 550 million confirmed cases and more than 6.3 million deaths worldwide due to COVID-19 infection as of July 12, 2022.[4] SARS-CoV-2 is an enveloped, positive sense, single-stranded RNA virus that causes human infection. So far, there are seven human coronaviruses have been identified: HCoV-OC43, HCoV-229E, HCoV-HKU1, HCoV-NL63, SARS-CoV, MERS-CoV, and SARS-CoV-2.[5,6] SARS-CoV, MERS-CoV and SARS-CoV-2 have the most widespread spread and infection.[7] Genome analysis showed that SARS-CoV-2 matched 79.5% with the SARS-CoV virus that had become an epidemic in 26 countries by 2003.[8]

SARS-CoV-2 infection in human cells occurs mediated by receptor binding domain (RBD) spike with angiotensin-converting enzyme 2 (ACE-2).[9,10] Viral RNA helixes are involved in RNA replication.[11,12] Furthermore, viral RNA undergoes translations producing pp1a and pp1ab proteins which are then folded by proteolytic enzymes such as Mpro.[13,14] RdRp binds to RNA genome (negative-sense) to form genome and subgenome RNA (positive sense) *via* replication and transcription.[15,16]

Synthesis inhibitors have been discovered in some studies. However, there are some side effects caused to the body after taking the drug. Bioactive compounds derived from medical plants in Indonesia are expected to be able to provide antiviral compounds against SARS-CoV-2.[7] Java plum and moringa are two Indonesian plants that can be used in medicine.

Java plum (*Syzigium cumini* L.) is a plant in the Myrtaceae family. The plant is indigenous to India and distributed in tropical Asia and Australia.[17] In Indonesia, java plum is typically consumed directly or mixed with food. Juwet has been shown to have antiviral activity against avian influenza virus (H5N1).[18] Meanwhile, moringa (*Moringa oleifera* L.) is a plant in the Moringaceae family. Moringa is indigenous to North India and can be cultivated in tropical and subtropical climates.[19] This plant is used in traditional Indonesian drinks and may have antiviral properties against hepatitis B (HBV).[20] However, the potential of the two plants as anti-SARS-CoV-2 remains unclear.

The study of SARS-CoV-2 inhibitor compounds takes a time, but preliminary research to determine the potential of plants as drug candidates can be approached with an *in-silico* approach.[21] As a result, this study aims to determine the potential of java plum and moringa as inhibitors of RBD spike, helicase, Mpro, and RdRp activity of SARS-CoV-2 *in silico*.

MATERIALS AND METHODS

Sample preparation

The components of the bioactive ligands found in juwet and moringa are gallic acid (CID: 370), ellagic acid (CID: 5281855), corilagin (CID: 73568), moringyne (CID: 131751186), myricetin (CID: 5281672), chlorogenic acid (CID: 1794427), vitexin (CID: 5280441), and nirmatrelvir (CID: 155903259) as a control. Ligand structure data were obtained

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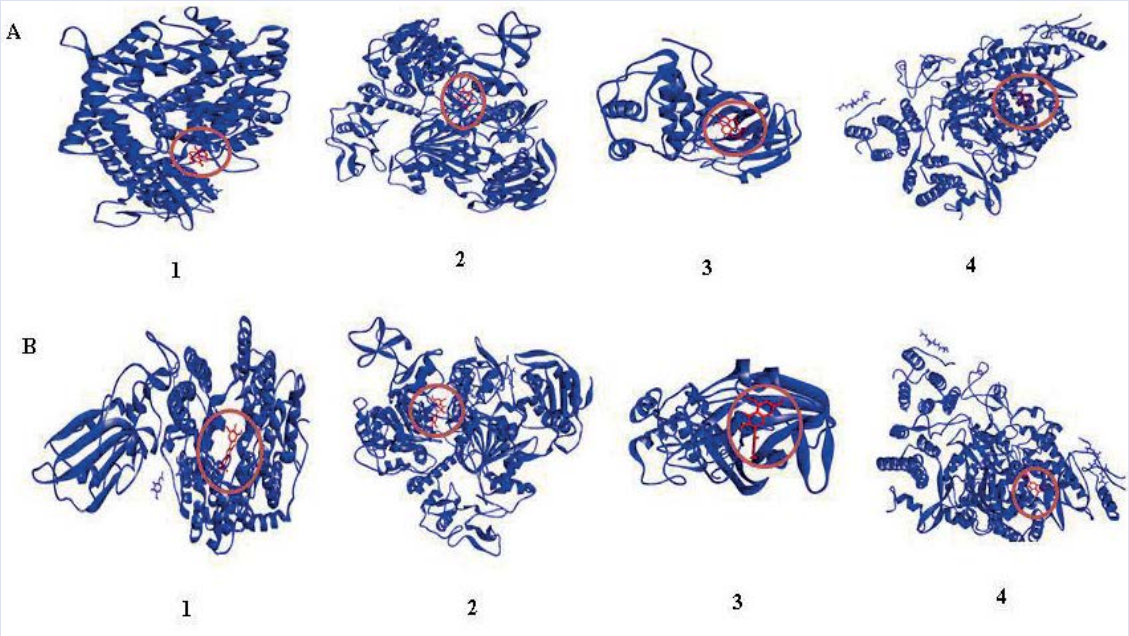

Figure 1: 3D visualization of: A) ellagic acid and B) myricetin targeting: 1) RBD spike, 2) helicase, 3) Mpro, and 4) RdRp of SARS-CoV-2.

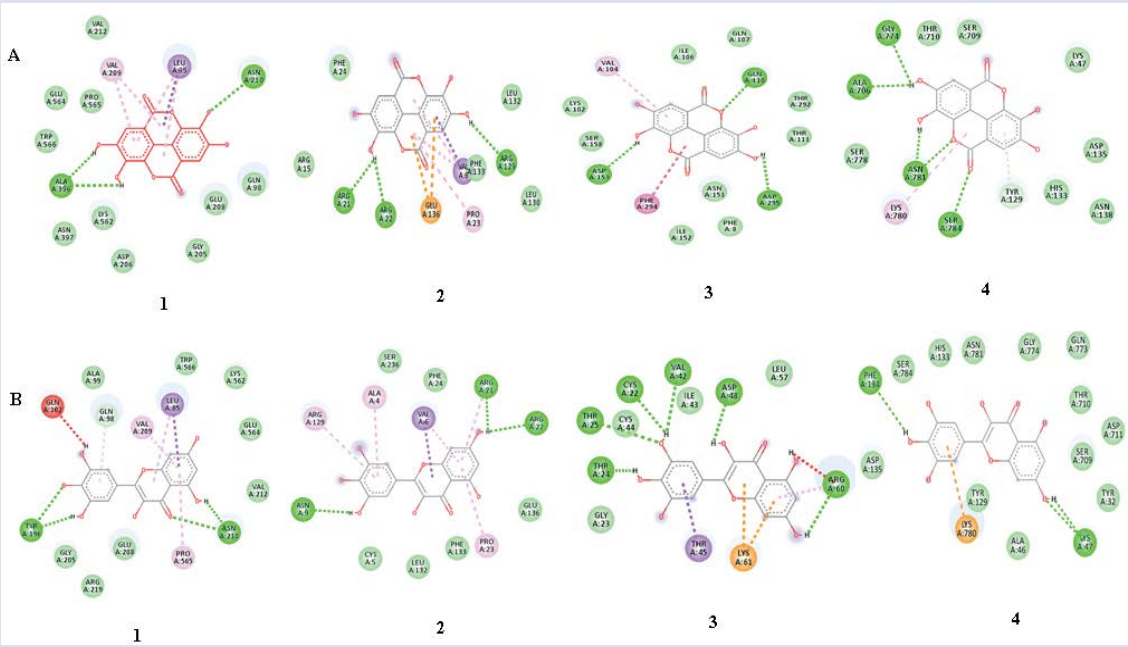

Figure 2: The binding visualization of A) ellagic acid and B) myricetin targeting 1) RBD spike, 2) helicase, 3) Mpro, and 4) RdRp of SARS-CoV-2. Notes: green = hydrogen, light green = van der Waals, pink = pi-alkyl, purple = pi-sigma, orange = pi-cation, and red = unfavorable bonds.

from PubChem. Protein sterilization was performed using AutoDock and Notepad++. Ligand minimization was performed using PyRx. In addition, this study used the target proteins RBD spike (PDB ID: 6LZG), helicase (PDB ID: 6ZSL), Mpro (PDB ID: 7ALH), and RdRp (PDB ID: 6M71) obtained from RSCB PDB. Elimination of water molecules was carried out using PyMol.[22]

Drug-likeness analysis

Bioactive compounds from Moringa and juwet were analyzed for similarities in the drug using the SwissADME web. The Lipinski's rule of was used including molecular weight of <500 Da, hydrogen donor bond (HBD) <5, hydrogen acceptor bond (HBA) <10, high lipopolysis (LogP) <5, and molar refractory (MR) 40-130.[23] Positive predictions were characterized by at least 2 rules. This analysis aimed to determine the probability of a candidate drug molecule passing through the cell membrane if the target is in the cytoplasm and pharmacokinetics.[24]

Antiviral probability prediction

Bioactivity prediction is carried out using the PASS Online web. The category of predictions sought is antiviruses. The potential activity standards used are Pa scores >0.3 and Pa > Pi. This score is favored as computational proof in molecular docking.[25]

Virtual screening

Docking simulations were carried out to determine the intermolecular energy that binds. Molecular docking is carried out with PyRx because of its high accuracy.[26] This was done to determine the activity between ligands and respetors in SARS-CoV-2 which is critical in COVID-19 infection. The purpose of molecular docking is to identify the binding energy of bioactive compounds to target proteins as anti-SARS-CoV-2.[27,28]

Interaction and visualization

Visualization aims to describe the results of docking in more detail. Visualized compounds are the compounds with the lowest binding affinity. Visualization is done using PyMol and Discovery Studio. The result of visualization with PyMol is ligand-target protein complexes.[29] Meanwhile, interactions were visualized with Discovery Studio.

RESULT AND DISCUSSION

Lipinski rule of five is important for determining compounds such as drug candidate molecules. In this study, it was found that there are 5 bioactive compounds that match Lipinski rules of five, namely: chlorogenic acid, gallic acid, elagic acid, moryngine, and myricetin. The PASS Online analysis results show that all drug candidate compounds have good activity (Table 1). However, this prediction still requires *in vivo* and *in vitro* analysis to confirm the antiviral potential of bioactive compounds further.[24]

The molecular docking results aim to determine the stability of the interaction between the ligand and the target protein. The lowest binding affinity indicates the maximum level of stable interaction indicating that the ligand inhibitory activity against the target protein is larger.[31,32] All bioactive compounds have activity against target proteins (Table 2). However, the compounds to be analyzed next are those with the lowest binding affinity and that follow Lipinski rules of five. Myricetin and ellagic acid are examples of such compounds.

The SARS-CoV-2 RBD spike has more extensive amino acid residue mutation than the SARS-CoV one. This results in the formation of van der Waals (vdw) contacts and stronger hydrogen bonds, increasing the potential for transmission of SARS-CoV-2(32). RBD spikes have some conservative residues that can be used as binding key sites in molecular docking such as glutamine (Gln), cysteine (Cys), histidine (His), and aspartic acid (Asp).[33] Myricetin has no hydrogen or hydrophobic bonds to conservative residues. However, it forms hydrogen and hydrophobic bonds with other amino acid residues. Meanwhile, ellagic acid has one vdw hydrophobic interaction with Gln98. Hydrogen bonds cause the resulting binding affinity to be more negative, thus stabilizing the interaction of myricetin and ellagic acid with the SARS-CoV-2 RBD spike.[34] Furthermore, the presence of weak hydrophobic interactions such as Pi-alkyl, Pi-sigma, and vdw bonds aids the stability and turnover of interactions between ligands and target proteins in cellular processes.[35]

SARS-CoV-2 helicase is involved in RNA replication.[11,12] Some helicase segments of SARS-CoV-2 variants show similarities to the 5' RNA NSP13 site, indicating that the part has great potential as a docked part in the development of anti-SARS-CoV-2.[12,36] Myricetin and ellagic acid have a variety bonds, including hydrogen bonds, pi-sigma, pi-alkyl, and vdw interactions. The presence of pi-anion bonds in ellagic acid aids the stability interaction with helicase so that the binding affinity is more negative.[37] Both compounds bind to amino acid residues in domain I of helicase which plays a role in the introduction of nucleic acids.[38]

Mpro is a cysteine protease responsible for viral maturation and protein folding.[13,14,39] SARS-CoV-2 variants are so conserved, there are no homologs in humans, and have low mutation rate.[40] Some of these conserved sites are catalytic residues consisting of asparagine (Asn), glutamine (Gln), and proline (Pro).[41] This position can be used for molecular docking in the development of multivariate anti-SARS-CoV-2. Based on the docking results, myricetin has no binding to catalytic residues so it has a more positive affinity bond than elagic acid. However, there are other hydrogen and hydrophobic bonds to other residual amino acids that stabilize the interaction of myricetin with Mpro. In addition, there is a less preferred bond to Arg60 that requires further research into its role in this interaction.[42] Meanwhile, ellagic acid likely has bonds with some catalytic residues such as hydrogen bonds with Gln110 as well as vdw bonds with Gln107 and Asn151.

RdRp is essential for coronavirus replication and transcription.[15,16,43] RdRp is assisted in this role by other proteins such as nsp7 and nsp8.[44-46]

Table 1: Lipinski rule of five and antiviral probability of selected compounds from java plum and moringa.

Plant	Compound	MW	HBD	HBA	LogP	MR	Antiviral Probability	
							Pa	Pi
Syzygium cumini L.	Gallic acid	170.12	4	5	0.21	39.47	0.342	0.002
	Ellagic acid	302.19	8	4	1.00	75.31	0.322	0.029
	Corilagin	634.45	18	11	-0.55	141.85	0.348	0.023
	Moryngine	312.32	4	7	0.07	75.31	0.345	0.024
Moringa oleifera L.	Myricetin	318.24	6	8	0.79	80.06	0.334	0.026
	Chlorogenic acid	354.31	6	9	-0.38	83.50	0.303	0.035
	Vitexin	634.45	11	18	-0.55	141.85	0.360	0.021

Table 2: Binding affinity (kcal/mol) ligand-protein complexes.

Plant	Compound	Binding Affinity (kcal/mol)			
		RDB Spike	Helicase	Mpro	RdRp
-	Nirmatrelvir	-7.9	-7.9	-6.5	-7.7
Syzygium cumini L.	Gallic acid	-6.2	-5.7	-5.4	-5.8
	Ellagic acid	**-8.7**	**-8.2**	**-8.4**	**-7.9**
	Corilagin	-9.4	-10.1	-9	-10.2
	Moryngine	-7.1	-7.4	-6.7	-6.7
Moringa oleifera L.	**Myricetin**	**-8.5**	**-7.9**	**-7**	**-7.3**
	Chlorogenic acid	-7.7	-7.6	-7.1	-7.8
	Vitexin	-8.8	-8.6	-7.3	-7.9

Many conservative catalytic residues in this protein have the potential to bind to docked bioactive compound ligands.[47-52] The majority of such residues are serine (Ser) and glycine (Gly).[43] According to the results of molecular docking, myricetin has a vdw bond with catalytic residual amino acids Ser709, Gly774, and Ser784. Meanwhile, ellagic acid has hydrogen bonds with Gly774 and Ser784 and vdw bonds with Ser778. The presence of hydrogen bonds in catalytic residues aids in the stabilization of the ligands-target protein complexes, resulting in the desired interaction conformation.

CONCLUSION

The combination of the bioactive compound's java plum (*Syzygium cumini* L.) and moringa (*Moringa oleifera* L.) has the potential to be anti-SARS-CoV-2. Myricetin and ellagic acid are known have the lowest binding affinity to RDB spike, helicase, Mpro, and RdRp of SARS-CoV-2. However, more research is needed to support the results of this study.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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GRAPHICAL ABSTRACT

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