In Silico Screening of Bioactive Compounds from *Garcinia mangostana* L. Against SARS-CoV-2 via Tetra Inhibitors

Nur Sofiatul Aini[1], Viol Dhea Kharisma[2], Muhammad Hermawan Widyananda[2,3], Ahmad Affan Ali Murtadlo[2], Rasyadan Taufiq Probojati[2,4], Dora Dayu Rahma Turista[5], Muhammad Badrut Tamam[6], Vikash Jakhmola[7], Elsa Yuniarti[8,9], Saddam Al Aziz[8,10], Muhammad Raffi Ghifari[8,11], Muhammad Thoriq Albari[8,11], Riso Sari Mandeli[8,12], Muhammad Arya Ghifari[8,11], Devi Purnamasari[8,13], Budhi Oktavia[8,14], Amalia Putri Lubis[8,14], Fajriah Azra[8,14], Fadhilah Fitri[8,15], ANM Ansori[16], Maksim Rebezov[17,18,19], Rahadian Zainul[8,14,*]

[1]Faculty of Mathematics and Natural Sciences, State University of Surabaya, Surabaya, INDONESIA.

[2]Division of Molecular Biology and Genetics, Generasi Biologi Indonesia Foundation, Gresik, INDONESIA.

[3]Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, INDONESIA.

[4]Faculty of Agriculture, Universitas Kadiri, Kediri, INDONESIA.

[5]Biology Education Department, Faculty of Teacher Training and Education, Mulawarman University, Samarinda, INDONESIA.

[6]Department of Biology, Faculty of Sciences and Technology, Universitas Muhammadiyah Lamongan, Lamongan, INDONESIA.

[7]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, INDIA.

[8]Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMP-BIOTICS), Universitas Negeri Padang, Padang, INDONESIA.

[9]Department of Biology, Faculty of Mathematics and Natural Sciences Universitas Negeri Padang, Padang, INDONESIA.

[10]Department Mathematics Education, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, INDONESIA.

[11]Department of Information Technology, Faculty of Computer Sciences, Universitas Brawijaya, Malang, INDONESIA.

[12]Environmental Science, Postgraduate Programme, Universitas Negeri Padang, Padang, INDONESIA.

[13]Department of Radiology Engineering, Universitas Awal Bros, Pekanbaru, INDONESIA.

[14]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, INDONESIA.

[15]Department of Statistics, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, INDONESIA.

[16]Professor Nidom Foundation, Surabaya, INDONESIA.

[17]Department of Scientific Research, Russian State Agrarian University - Moscow Timiryazev Agricultural Academy, Moscow, RUSSIAN FEDERATION

[18]Faculty of Biotechnology and Food Engineering, Ural State Agrarian University, Yekaterinburg, RUSSIAN FEDERATION

[19]Department of Scientific Research, K.G. Razumovsky Moscow State University of Technologies and Management (The First Cossack University), Moscow, RUSSIAN FEDERATION

Correspondence

Rahadian Zainul

Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMP-BIOTICS), Department of Chemistry, Faculty of Mathematics and Natural Sciences Universitas Negeri Padang, Padang, INDONESIA.

E-mail: rahadianzmsiphd@fmipa.unp.ac.id

Phcogj.com

ABSTRACT

The global COVID-19 pandemic caused by SARS-CoV-2 has been the resulted of massive human deaths since early 2020. The purpose of this study was to determine the potential of mangosteen (*Garcinia mangostana* L.) as an inhibitor of RBD spike, helicase, Mpro, and RdRp activity of SARS-CoV-2 with an *in silico* approach. The samples were obtained from PubChem and RCSB PDB. Analysis of the similarity of the drug was carried out with the Swiss ADME on the basis of Lipinski rule of five. Prediction of antivirus probabilities was carried out using PASS Online. Molecular screening was performed using PyRx through molecular docking. Discovery Studio was used for visualization. The bioactive compounds with the highest antiviral potential were indicated with the lowest binding affinity to the targeted proteins RBD spike, helicase, Mpro, and RdRp of SARS-CoV-2. The results indicated that mangiferin has the greatest potential as a potential antiviral. However, more research is required to validate the results of these computational predictions.

Key words: SARS-CoV-2, *Garcinia mangostana* L., *In silico*, Antiviral agent.

INTRODUCTION

The COVID-19 pandemic is caused by positive-sense beta-coronavirus RNA, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] Covid-19 cases were first reported in Wuhan, Hubei China in late December 2019 and have since spread into a global pandemic.[2] Currently, SARS-CoV-2 is responsible for 6 million deaths from SARS-CoV-2.[3] According to genome analysis, SARS-CoV-2 had a 79.5% resemblance to SARS-CoV which had caused an epidemic in 26 countries in 2003.[4] SARS-CoV-2 spreads uncontrollably through aerosols. Furthermore, this virus also causes fever, cough, respiratory failure, septic shock, and organ failure.[5,6]

SARS-CoV-2 infection in human cells occurs mediated by receptor binding of the spike domain in the terminal C domain (SARS-CoV-2-CTD) with angiotensin-converting enzyme 2 (ACE-2).[7,8] Viral RNA helicase plays a role in the replication and folding of RNA in the target cell.[9] Furthermore, viral RNA is translated into pp1a and pp1ab proteins then folded by proteolytic enzymes such as Mpro into nonstructural proteins (nsps).[10,11] RdRp binds to genome RNA (negative-sense) to form genome and subgenome RNA (positive sense) *via* replication and transcription.[12]

Several therapeutic strategies of antiviral drugs have been developed today including lopinavir, baricitinib, remdesivir, and favipiravair.[13] In addition, nanotechnology is now widely applied as an anti-SARS-CoV-2.[14] Indonesia is known as megabiodivesity country with numerous medicinal plants.[15] The bioactive of medicinal plants are expected to provide antiviral compounds for SARS-CoV-2.[16] Some Indonesian plants that can be used in medicine are various groups of mangosteen.

Garcinia mangostana L. is a member of the Guttiferae family.[17] The plant grows primarily in tropical Asia including Indonesia and its fruits are widely used in food and traditional medicine.[18,19] Mangosteen peel has been shown to have antimetabolic poperties.[20,21] SARS-CoV-2 inhibitor compounds studies take a long time, but preliminary research to determine the potential of plants as drug candidates can be done with an *in silico* approach.[22] Therefore, this study aims to determine the potential of *G. mangostana* L. as inhibitors of RBD spike, helicase, Mpro, and RdRp activity of SARS-CoV-2 *in silico*.

MATERIALS AND METHODS

Sample preparation

The bioactive ligand components found in *G. mangostana* L. are mangostanol (CID: 10048103), gartinin (CID: 5281633), calabaxanthone (CID: 341188), mangiferin (CID: 5281647), mangostenol (CID: 5495927), and epicatechin (CID: 72276). Ligand structure data were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Protein sterilization was performed using AutoDock and Notepad++. Ligand minimization was carried out using PyRx. The target proteins used were RBD spike (PDB ID: 6LZG), helicase (PDB ID: 6ZSL), Mpro (PDB ID: 7ALH), and RdRp (PDB ID: 6M71) obtained from RCSB PDB (https://www.rcsborg/). Elimination of water molecules was carried out using PyMol.[23]
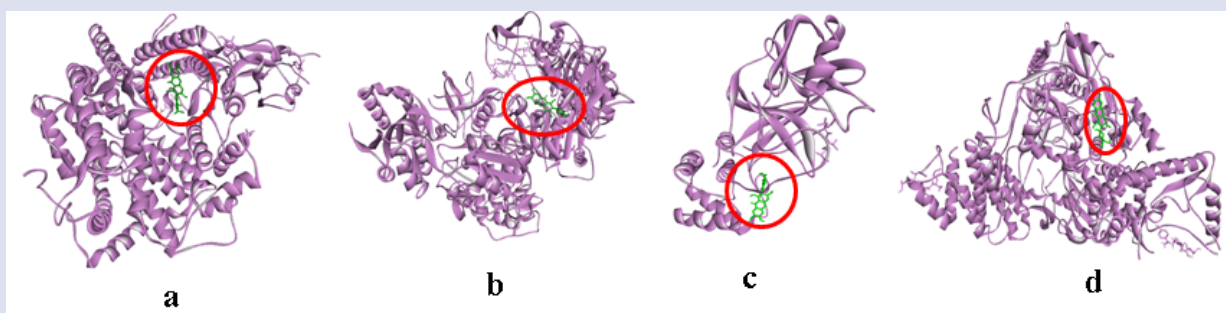
Figure 1: 3D visualization of mangiferin targeting: a) RBD spike, b) helicase, c) Mpro, and d) RdRp of SARS-CoV-2.
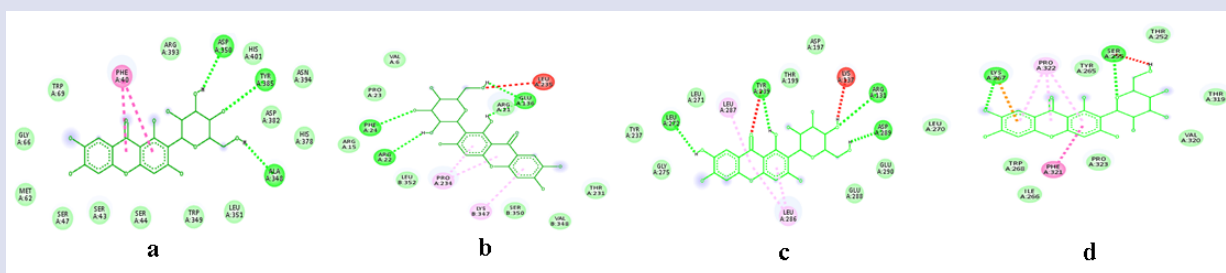
Figure 2: The binding visualization of mangiferin targeting a) RBD spike, b) helicase, c) Mpro, and d) RdRp of SARS-CoV-2.

Table 1: Lipinski rule of five and antiviral probability of selected compounds from mangosteen.

Compound	MW	HBD	HBA	LogP	MR	Antiviral Probability	
						Pa	Pi
Mangostanol	426.46	3	7	3.77	119.36	0.306	0.034
Gartinin	396.43	4	6	4.31	115.52	0.206	0.090
Calabaxanthone	392.44	1	5	4.78	116.35	0.173	0.130
Mangiferin	422.34	8	11	-0.81	100.70	0.367	0.019
Mangostenol	426.46	4	7	3.62	121.15	0.302	0.036
Epicatechin	290.27	5	6	0.85	74.33	0.378	0.017

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

Compound	Binding Affinity			
	RDB Spike	Helicase	Mpro	RdRp
Mangostanol	-7.8	-8.7	-7.6	-7.7
Mangiferin	**-7.7**	**-8.6**	**-8**	**-8.1**
Mangostenol	-8.1	-8.4	-6.9	-7.4
Epicatechin	-8.1	-7.6	-7	-7.2

Drug-likeness analysis

The bioactive compound mangosteen was analyzed for drug similarities using SwissADME (http://www.swissadme.ch/index.php). The Lipinski's rule of five used includes a molecular weight (MW) 500 Da, hydrogen binding donor (HBD) 5, hydrogen binding acceptor (HBA) 10, high lipopolycity (LogP) 5, and molar refractory (MR) 40-130.[24] Positive prediction was defined by the fulfillment of at least 2 rules.[25]

Antiviral probability prediction

Bioactivity prediction was carried out using the PASS Online (http://way2drug.com/PASSOnline/) web. The category of predictions sought was antiviral. The potential activity standards used are Pa > 0.3 and Pa > Pi. The score is preferred as computational evidence in molecular docking.[26]

Virtual screening

Docking simulations were carried out to calculate the binding energy. Molecular docking is performed with PyRx due to its high accuracy.[21] The purpose of molecular docking was to identify the binding energy of bioactive compounds to target proteins as anti-SARS-CoV-2.[27]

Interaction and visualization

The goal of visualization is to provide more detailed description of the docking results. The most negative affinity compounds were displayed. Visualization of the target ligand-protein complex and its interaction was performed using Discovery Studio. The result of PyMol visualization is a complex structure of ligand-targeted proteins.[28,29]

RESULT AND DISCUSSION

Lipinski rule of five is important for determining drug candidate compounds by being treated as drug-like compounds.[30] Based on the drug similarity analysis, it was determined that 6 bioactive compounds meet the Lipinski rule of five so that they can be interpreted as drug-like compounds. Meanwhile, an antiviral probability analysis performed using PASS Online revealed that mangostanol, mangiferin, mangostenol, and epicatechin had Pa > Pi and Pa > 0.3[26] (Table 1). The score indicates that the bioactive compounds have higher activation potential than the inactivation as antivirals. As a result, these compounds are preferred in bioinformatics studies.[31] However, the results of this prediction still require *in vitro* and *in vivo* studies. Compounds docked against the next four targeted SARS-CoV-2 proteins satisfy Lipinski rule of 5 and have high antiviral probability.

The molecular docking results are used to determine the stability of the interaction between the ligand and targeted protein complexes. The highest level of stability interaction is indicated by the low binding affinity, indicating the inhibitory activities of the ligands to the targeted protein are greater.[6] Table 2 shows that all bioactive compounds have binding activity against targeted proteins. However, the compound to be visualized is that has the lowest binding affinity, mangiferin.

SARS-CoV-2 RBD spike has more extensive mutation than SARS-CoV RBD spike. This results in the formation of vdw (van der Waals) interactions and hydrogen bonds when binding to ACE2 is greater, increasing the potential for SARS-CoV-2 transmission.[7] Gln, Cys, His, and Asp are some conservative residues in RBD spike that can be used in molecular docking.[32] Mangiferin forms chemical bonds with conservative residues such as hydrogen bonds to Asp350 and vdw bonds to His378, Asp382, and His401. Hydrogen bonds cause smaller binding energy so that the ligand-targeted protein complexes interactions are stable.[33] Furthermore, the presence of hydrophobic interactions such as pi-pi T-shaped and vdw bonds aids the interaction stability and ligand turnover to the targeted protein in cellular processes.[34]

SARS-CoV-2 helicase is involved in RNA replication and folding.[9] Some helicase segments of SARS-CoV-2 variants show similarities to NSP13 5' RNA site, suggesting that it has great potential in the *in silico* anti-SARS-CoV-2 development *in silico*.[35] Mangiferin forms various bonds to helicase, including hydrogen, pi-alkyl, and vdw bonds. The pi-alkyl bond is formed from the interaction of the aromatic cloud from the aromatic group with the electron cloud from the alkyl group.[36] The presence of weak bonds such as pi-alkyl and vdw bonds affect ligand activity against targeted proteins in viral entry inhibition, maturation, and protein folding.[37] In addition, there is an unfavorable acceptor-acceptor bond to Leu235. This bond is a less preferred inhibitor in docking due to several factors such as the presence of induced fit bonds, irrelevant binding modes, critical cell activity, and unpredictable bonding models at other binding sites.

Mpro is a cysteine protease responsible for viral maturation and protein folding.[10,11] Various SARS-CoV-2 variants are so conserved that their mutation rates are low.[38] Some of these conserved sites are catalytic residues include Asn, Gln, and Pro.[39] This position can be used as a molecular docking position in the development of anti-SARS-CoV-2. Mangiferin indicates the presences of hydrogen bonds, pi-alkyl, vdw, donors are disliked, and acceptors are not liked. The existence of an unfavorable donor-donor bond causes the binding energy to be more positive. More *in vitro* and *in vivo* research is required to determine the significance of these bonds.[40]

RdRp is an essential component of coronavirus replication and transcription because it plays a role in the formation of genomic and non-genome RNA.[41,12] In the role, RdRp is assisted by other proteins such as nsp7 and nsp8.[1] RdRp contains a large number of conservative

catalytic residues, the majority of which are Ser and Gly.[12] Molecular docking results show that mangiferin has a hydrogen bond to Ser255. The presence of hydrogen bonds in catalytic residues aids stabilize ligand complex bonds with targeted proteins resulting in the desired interaction conformation.[42] There are also pi-cation, pi-alkyl, pi-stacked amide, vdw, and unfavorable donor-donor bonds that form a relatively negative binding affinity.[43-50]

CONCLUSION

Mangosteen (*Garcinia mangostana* L.) has an anti-SARS-CoV-2 potential. The bioactive compound mangiferin from mangosteen is known to have the lowest binding energy 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

Garcinia mangostana L.

SARS-CoV-2

ABOUT AUTHORS

Nur Sofiatul Aini is a student in general biology at State University of Surabaya, Indonesia. Her research focuses on ethnobotany, enzymology, food additive microbiology, and bioinformatics.

Rahadian Zainul has completed a Bachelor of Educational Chemistry in IKIP Padang, then continued his studies and obtained a Master of Chemistry at Universitas Andalas, and earned a Doctoral Chemistry degree at Universitas Andalas. He is a researcher on the design and modification of copper oxide for inactivation SARS-CoV-2 by stimulated indoor lights and a researcher on the design and modification of copper oxide by computation approach with DFTB+. He is also the Head of Cambiotics Research Center, Universitas Negeri Padang. The author has published 41 manuscripts in Scopus-indexed journals and also 8 h-index.