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Original Article

Bioactive Compounds from Mangosteen (*Garcinia mangostana* L.) as an Antiviral Agent via Dual Inhibitor Mechanism against SARS-CoV-2: An *In Silico* Approach

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19 which is responsible for respiratory illness infection in humans. The virus was first identified in China in 2019 and later spread to other countries worldwide. This study aims to identify the bioactive compounds from mangosteen (*Garcinia mangostana* L.) as an antiviral agent via dual inhibitor mechanisms against two SARS-CoV-2 proteases through the *in silico* approach. The three-dimensional structure of various bioactive compounds of mangosteen from the database was examined. Furthermore, all the target compounds were analyzed for drug, antiviral activity prediction, virtual screening, molecular interactions, and three-dimensional structure visualization. It aimed to determine the potential of the bioactive compounds from mangosteen that can serve as antiviral agents to fight SARS-CoV-2. Results showed that the bioactive compounds from mangosteen have the prospective to provide antiviral agents that contradict the virus via dual inhibitory mechanisms. In summary, the binding of the various bioactive compounds from mangosteen results in low binding energy and is expected to have the ability to induce any activity of the target protein binding reaction. Therefore, it allows various bioactive compounds from mangosteen to act as dual inhibitory mechanisms for COVID-19 infection.

Key words: Antiviral agent, COVID-19, *Garcinia mangostana* L., *In silico* approach, SARS-CoV-2.

INTRODUCTION

Coronavirus disease-2019 or COVID-19 pandemic which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had lead many disadvantages in the economy and health sector.[1] The newest data reveal until October 2021 has been stated that approximately 245 million people and 5 million death has occurred across the world. Furthermore, more than 4.2 million people have been infected, with a total death of more than 140 thousand people happening in Indonesia.[2]

COVID-19 pandemic is the third noteworthy coronavirus outbreak in the twenty-first century, following the SARS and the Middle East respiratory syndrome (MERS) epidemics in 2002/2003 and 2012.[3,4] In contrast to the extremely contagious and pathogenic SARS-CoV, MERS-CoV, and SARS-CoV-2, four more coronaviruses can infect human, including HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43, which caused only mild respiratory sickness like the common cold.[5] Additionally, rapid vaccination processes are still endlessly occurring by WHO and other various countries, including Indonesia.[6,7] Yet, the discovery of an effective medicine in order to fight against SARS-CoV-2 is still barely reaching a satisfactory result.[8]

SARS-CoV-2 is a virus that has 29,903 bp genome in length (NCBI Reference Sequence: NC_045512.2) and has ssRNA as their genetic material.[9] It has four structural proteins, which are envelope protein (E), membrane glycoprotein (M), nucleocapsid phosphoprotein (N), and spike glycoprotein (S).[10] Furthermore, a number of non-structural proteins has been mapped.[11] In addition, two SARS-CoV-2 proteases: main protease (M^{pro}) and papain-like protease (PL^{pro}), have an essential function in the discovery of antiviral therapy candidates. PL^{pro} had a role in the maturation and the cleavage of viral proteins, destroys of the host response, as well as in the replicase-transcriptase complex incorporation. Another protease, M^{pro} is used to induce the maturation and the cleavage of viral proteins throughout the process of virus replication.[12,13]

Indonesia is a nation enriched in biodiversity; there are roughly 40,000 plant species, of which around 7,500 are medicinal plants, whether native or introduced species, cultivated or wild.[14] For ages, their worth has been recognized over the world for use as medications and cosmetics, as well as in traditional and modern applications.[15] *Garcinia mangostana* L. or mangosteen is a member of the Clusiaceae family and the genus *Garcinia*.[16] *Garcinia* is a vast genus with 400 species native to East India, the Malay Peninsula, and Southeast Asia, including Indonesia. In truth, mangosteen is a tropical fruit that has been used as a traditional medicine for hundreds of years globally.[17,18]

Many researchers reported antiviral activity of mangosteen against chikungunya virus (CHIKV), porcine reproductive and respiratory syndrome virus (PRRSV), dengue virus (DENV), and avian pox

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virus.[19-22] However, the potency of mangosteen against SARS-CoV-2 is remains unclear. Therefore, this study aimed to identify the potency of bioactive compounds derived from mangosteen as an antiviral agent via dual inhibitor mechanisms towards two SARS-CoV-2 proteases with *in silico* approach.

MATERIALS AND METHODS

Sample retrieval

The chemical compound of mangosteen which consisted of α-mangostin (CID: 5281650), β-mangostin (CID: 5495925), and γ-mangostin (CID: 5464078) were collected from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) (Figures 1A, 1B, and 1C). Meanwhile, the targeted protein on SARS-CoV-2 which consisted of two non-structural proteins including main protease (M^{pro}; PDB ID: 7ALH) and papain-like protease (PL^{pro}; PDB ID: 7CMD) were obtained from the PDB (https://www.rcsb.org/) (Figures 1D and 1E).

Drug likeness analysis

Bioactive compounds such as α-mangostin, β-mangostin, and γ-mangostin were used for further drug-likeness analysis using Lipinski's rule of five in SCFBIO web server (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). It considered as a positive prediction with two minimum rules which followed. This analysis aimed to determine the probability of the medicine molecule candidate to get through the cell membrane if the target were in the cytoplasm environment and pharmacokinetic.[23]

Antiviral probability prediction

Probability prediction of biological activity as an antivirus agent on the bioactive compounds of α-mangostin, β-mangostin, and γ-mangostin was performed by using the PASS web server (http://way2drug.com/PassOnline/). The threshold prediction with probability activation (Pa) score >0.3 was considered as potential antivirus.[23,24]

Virtual screening

In this study, we performed molecular docking methods to know the activity of dual inhibitors on α-mangostin, β-mangostin, and γ-mangostin compounds when they bind to target proteins (SARS-CoV-2 M^{pro} and PL^{pro}). The molecular docking was performed by using PyRx 0.9.9 software (Scripps Research, USA) with an academic license. The compound with the most negative affinity score on both targeted proteins was considered to have the ability to trigger the biologic response on the proteins as dual inhibitor. The binding ability in the molecular docking showed by the binding affinity score (kcal/mol), which formed within complex protein molecules and ligand.[23]

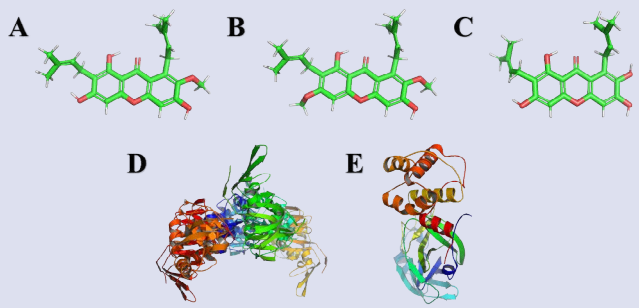

Figure 1: The chemical compound from mangosteen: A) α-Mangostin (CID: 5281650); B) β-Mangostin (CID: 5495925); C) γ-Mangostin (CID: 5464078); and targeted protein on the SARS-CoV-2: D) Main protease (M^{pro}) (PDB ID: 7ALH); E) Papain-like protease (PL^{pro}) (PDB ID: 7CMD).

Chemical interaction and 3D molecular visualization

Compound with the most negative binding affinity score was addressed for further analysis to find its position and chemical binding interaction type by using Discovery Studio Visualizer™ v.16.1 (Dassault Systèmes SE, France). The visualization process was performed by using PyMOL software v.2.5.2 (Schrödinger, Inc., USA) with an academic license.[23,24]

RESULTS AND DISCUSSION

Lipinski's rule of five is important in determining a medicine compound candidate as a drug-like molecule; those rules are consisted of molecule mass <500 Dalton, LogP <5, the hydrogen binding donor <5, hydrogen binding donor <10, and molar refractivity between 40-130.[25] According to the drug-likeness prediction, those three compounds, such as α-mangostin, β-mangostin, and γ-mangostin, could comply all the Lipinski's rule of five. Therefore, it could be considered as drug-like molecule (Table 1).

The analyses result of the PASS web server, a compound with Pa score greater than Pi score, was predicted to have potential as antiviral. The Pa score >0.3 mean that the query compound has been more activated and it proved computationally.[23] Antiviral analyses probability on this research was using threshold Pa >0.3. Compounds with Pa score >0.3 are considered to have potency as antiviral agents. Results showed that all the compounds were considered as antivirus agents. However, their potential is stills need to be examined through further analysis by using *in vitro* or *in vivo* (Table 1).

The molecular docking for M^{pro} was conducted by using grid position with center (Å) X: -26.28 Y: 12.59 Z: 57.04; dimensions (Å) X: 51.37 Y: 66.97 Z: 63.44, while molecular docking for PL^{pro} was using grid position with center (Å) X: 12.29 Y: 7.07 Z: 17.99; dimensions (Å) X: 60.13 Y: 88.85 Z: 65.73. Binding affinity is defined as stable binding energy formed between protein-ligand complex. The level of binding affinity score may influence by biological activity when it binds to the targeted protein domain. The biological activity calculated is the inhibition response to the targeted protein.[26] This inhibition of the targeted protein activity may decrease viral load SARS-CoV-2 production.[27] Regarding the molecular docking simulation, the γ-mangostin compound has the most negative binding energy on both targeted proteins, and it may have potential as antiviral via dual inhibitor (Table 2).

The activity of M^{pro} and PL^{pro} when SARS-CoV-2 has performed a replication on the host cell depends on the catalytic site, based on Cys145 and His41 (M^{pro}) as well as Pro248, Thr301, and Asp286 (PL^{pro}).[28] The position and chemical binding type showed that γ-mangostin may interact on the catalytic site of M^{pro} at position Cys145 and His41 through Pi bonding and it also had interaction with PL^{pro} with amino acid residue Pro248 and Thr301 along with the hydrogen bond and Pi (Figure 2). Moreover, the non-covalent interaction was also formed within the protein-ligand complex and it is considered to be able to trigger a specific biological response, such as inhibition. The inhibitor could induce the response on the target protein when the interaction resulted by hydrogen bonding. Then, the molecule flexibility may also influence by the Pi binding.[29]

Plants, used to treat illnesses, are both valuable and useful. They are defined as potential plants with therapeutic benefits based on their secondary metabolites compounds which had health-related effects, regardless of whether their utilization has been shown clinically. These plants can be collected from the wild or grown in a lab for benefit as food or cosmetics agents. Various plant components, extracts, and sophisticated products had been used to cure sickness for a long time. In brief, around the world, there are more than 50,000 higher plant species are regarded to be used for medicinal purposes.[30]

Former studies have been described the potential of mangosteen as an antiviral agent. The α-mangostin is a potential natural antiviral

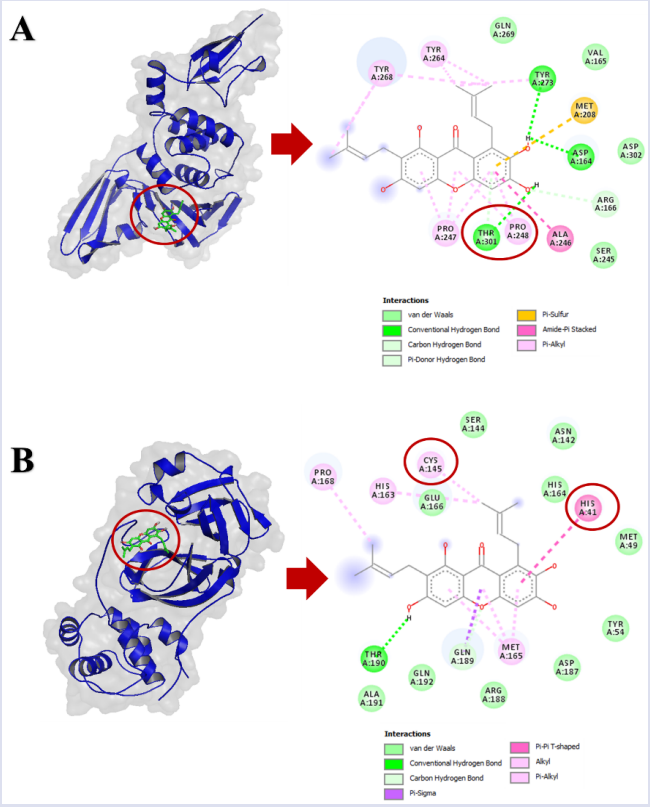

Figure 2: The binding visualization of γ-mangostin on the targeted protein: A) M^{pro} and B) PL^{pro}.

Table 1: Analysis result of Lipinski's rule of five and prediction of antiviral activity.

Compounds	MW (<500 Da)	HBD <5	HBA <10	LogP	MR (40-130)	Antiviral Probability	
						Pa	Pi
α-mangostin	410	3	6	5.16	114.20	0.423	0.026
β-mangostin	424	2	6	5.46	119.09	0.428	0.024
γ-mangostin	396	4	6	4.86	109.31	0.453	0.018

Note: Molecular weight (MW); Hydrogen bond donor (HBD); Hydrogen bond acceptor (HBA); High lipophilicity (LogP); and molar refractivity (MR).

Table 2: Binding affinity of complex compounds and protein.

Compounds	PubChem ID	Binding Affinity (kcal/mol)	
		M^{pro}	PL^{pro}
α-mangostin	5281650	-7.5	-7.3
β-mangostin	5495925	-6.8	-6.9
γ-mangostin	5464078	-7.6	-7.6

agent to fight the chikungunya virus (CHIKV) through *in vitro* and *in vivo* experiments.[19] Arjin *et al.* stated that Thai medicinal herbs, including mangosteen, were tested *in vitro* for antiviral efficacy against the porcine reproductive and respiratory syndrome virus (PRRSV).[20] Previously, the ethanol extract of mangosteen was reported to inhibit HIV-1 protease with a high potency level.[21] Mangosteen ethanolic extract also inhibits avian poxvirus replication *in vivo*.[22] Furthermore, another study, Panda *et al.* reported that *in vitro* and *in silico* data of α-mangostin had the capacity to reduce DENV-2 production at various phases of its replication cycle. It is suggesting that it might be used as a DENV-2 prophylactic/therapeutic drug.[23] Additionally, in DENV-infected immature monocyte-derived dendritic cells, α-mangostin significantly inhibited cytokine/chemokine (IL1β, TNF-α, IL6, CCL4, IL10, CCL5, CXCL10, and IFN-α) production. These findings point to the possibility of developing α-mangostin as a new anti-DENV medication.[31]

Presently, the possibility of various medicinal plants for antivirus to fight against SARS-CoV-2 has been reported by many researchers globally. In Asia, the Chinese herbal medicine tested to encounter SARS-CoV-2 by several researchers using *in silico*,[32,33] The traditional Himalayan medicinal plants also had been tested against SARS-CoV-2 which reported by Natesh *et al.*[34] Moreover, the Indian traditional medicine were also having a good antiviral potential towards the SARS-CoV-2 *in silico* analysis.[35,36] Another research, including Brazilian, Peruvian, and Mexican herbal medicines from the American continent were also reported for having potential against SARS-CoV-2.[37-39] Another point of view, numerous African medicinal plants were reported by researchers.[40-43] Our former study revealed that an herbal combination of *Moringa oleifera* and *Curcuma longa* could be an antiviral agent via dual inhibitors pathway for SARS-CoV-2.[23]

M^{pro} and PL^{pro} are two SARS-CoV-2 proteases that had an essential role as antiviral candidates. Both of the proteins contributed to the function of protein maturation, cleavage of viral proteins, binding complex of replicase-transcriptase, and the interfering for the host cells. Some of the studies explained that M^{pro} facilitated the discovery of the antiviral candidate obtained from medicinal plants.[44-47] Moreover, PL^{pro} was also had been reported as the target to discover the antiviral candidate agents based on the herbal material.[48-51] On another part, RdRp was also tested as an antiviral target candidate based on a herbal compound reported by Ahmad Mir *et al.*[52] The result of the whole research may be used for support towards the development of the antiviral agent candidate. However, further analysis should be performed to confirm and uncover the further potential.

CONCLUSION

In summary, various bioactive compounds from mangosteen, such as α-mangostin, β-mangostin, and γ-mangostin had low binding energy towards the targeted protein, M^{pro} and PL^{pro}. It is expected to have the ability to induce that protein activity. Furthermore, those bioactive compounds have demonstrated the ability to be developed as an antiviral drug which is depicted by Lipinski's rule of five and antiviral activity prediction. Therefore, the bioactive compounds from mangosteen are considered as dual inhibitory mechanisms for COVID-19 infection.

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DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

ABBREVIATIONS

CHIKV: Chikungunya virus; COVID-19: Coronavirus disease-2019; DENV-2: Dengue virus serotype 2; HIV-1: Human immunodeficiency virus 1; M^{pro}: Main protease; MERS: Middle East respiratory syndrome; PL^{pro}: Papain-like protease; PDB: Protein Data Bank; PRRSV: Porcine reproductive and respiratory syndrome virus (PRRSV); SARS-CoV: Severe acute respiratory syndrome coronavirus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization.

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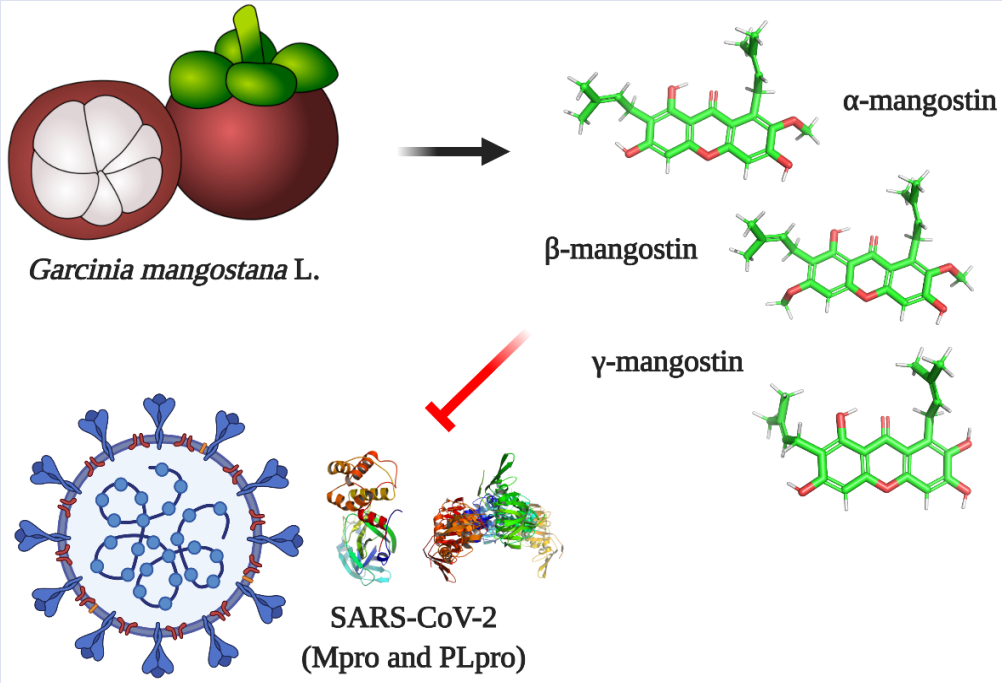
GRAPHICAL ABSTRACT



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