SRIWIJAYA JOURNAL OF MEDICINE

Molecular Docking Study of *Garcinia mangostana* (Mangosteen) Compounds as SARS-CoV-2 Potential Inhibitors

Putri Mahirah Afladhanti*, Muhammad Despriansyah Romadhan, Haidar Ali Hamzah, Qherine Bhelqis

Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
E-mail: mahirah.afladhanti@gmail.com

Abstract

COVID-19 pandemic poses a challenge for researchers all over the world to find effective drugs. Previous studies had identified the role of Mpro, TMPRSS2, RdRp, and ACE2 which are useful as promising drug targets to inhibit SARS-CoV-2. This study aimed to identify the potential compounds derived from *Garcinia mangostana* (mangosteen) as potential SARS-CoV-2 inhibitors using a molecular docking study. A total of 6 compounds of mangosteen such as 8-desoxygartanin, α-mangostin, β-mangostin, Y-mangostin, garcinon e, and gartanine were used in this study. N-acetylcysteine (NAC), nafamostat, remdesivir, and lopinavir were also used as comparative drugs. Compounds and comparative drugs were docked on Mpro, TMPRSS2, RdRP, and ACE2 using AutodocTools 1.5.6 and Autodock Vina. The visualization of molecular interactions was carried out by Discovery Studio v16. All compounds met the criteria as drugs based on Lipinski's solubility test and were safe to use based on toxicity test with admetSAR. Docking results showed that all compounds had an affinity to all receptor targets. 8-Desoxygartanin showed strong molecular interactions compared to the comparative drugs with binding energies of -8.0, -9.6, - 7.8, and -8.6 kcal/mol for Mpro, TMPRSS2, RdRp, and ACE2, respectively. All compounds have the potential to be developed as potential inhibitors through inhibiting Mpro, TMPRSS2, RdRp, and ACE2. Therefore, in vitro and in vivo investigations are needed to bring these compounds to the clinical setting.

Keywords: 8-Desoxygartanin, *Garcinia mangostana,* Molecular Docking, SARS-CoV-2

1. Introduction

Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) has emerged globally as a serious infectious disease at the end of 2019. SARS-CoV-2 has been identified as an enveloped non-segmented positive sense RNA virus in β-coronavirus group. This virus can be spread by human-to-human transmission via droplet or aerosol from infected people.[1] It attacks human body systems such as respiratory, digestive, and nervous systems with a rapid transmission and a fairly high mortality rate.[2] The latest report from World Health Organization (WHO) cited until the 1st of October 2021 there have been 233,503,524 confirmed cases with 4,777,503 deaths. Meanwhile, Indonesia reported 4,216,728 confirmed cases and 142,026 deaths.[3,4]

The life cycle of SARS-CoV-2 begins with the attachment of S protein to Angiotensin Converting Enzyme 2 (ACE2) as a host cell receptor. Virus that enters the cell will release mRNA in the cytoplasm that is facilitated by Transmembrane Serine Protease 2 (TMPRSS2) and is translated into structural and non-structural proteins. In addition, several proteins such as the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) also play an important role in the assembly of new virus.[5] Based on the role of these

proteins in the virus life cycle, studies have shown that these proteins were potential as protein targets for COVID-19 treatment development.[6] However, until now there is no specific antiviral therapy for COVID-19 patients and primary care is only symptomatic treatment.[7] Hence, further research related to the discovery of compounds for antivirus drug in inhibit SARS-CoV-2 is required.

Garcinia mangostana (mangosteen) is a tropical tree cultivated principally in Indonesia, Philippines, Thailand, and Malaysia.[8] Based on phytochemical screening, the pericarp of mangosteen fruits are rich in bioactive compounds with xanthones as the main compound. Several xanthone derivatives that are commonly found in mangosteen are 8-desoxygartanin, α-mangostin, β-mangostin, Y-mangostin, garcinone E, and gartanin.[9,10] Previous researches had identified the role of xanthones as anti-inflammatory, antioxidant, antifungal, antimicrobial, and antiviral.[11,12,13] The latest studies proved that mangosteen pericarp could against RNA and DNA virus including chikungunya, hepatitis C, and dengue virus.[8,14,15] Randomized control trial study in HIV patients conducted by Amanah et al. reported that mangosteen peel extract increased the number of $CD4^+$ T cells and decreased the level of CD38 expression compared with control group.[14] Another research conducted by Gopalakrishnan et al. reported one of xanthones derivatives, 8-desoxygartanin from mangosteen showed antifungal activity against *Fusarium oxysporum vasinfectum*, *Alternaria tenuis*, and *Dreschlera oryzae.*[9]

Currently, there is no study reporting on the potential of mangosteen compounds against SARS-CoV-2. Therefore, this study aims to identify six potential compounds of mangosteen as SARS-CoV-2 inhibitors using molecular docking to inhibit the protein targets of Mpro, TMPRSS2, RdRp and ACE2.

2. Method

2.1. Prediction of drug-likeness and ADMET properties

Drug-likeness prediction was performed using SwissADME, a free online website tool (http://www.swissadme.ch/).[16] Meanwhile, to assessed ADMET properties of the compounds, we used admetSAR, a free online website tool (http://lmmd.ecust.edu.cn/admetsar2).[17]

2.2. Selection of protein target and ligands

We used the term ligand as a compound in mangosteen or a comparative drug. A total of 6 compounds (ligands) were selected and Lopinavir, Nafamostat, Remdesivir, and N-acetylcysteine (NAC) were used as comparative drugs. We selected the ligands through online screening based on previous literatures with a compound that has been proven to be potential in medicinal effect was selected. The structure of ligands were downloaded from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) whereas Mpro (PDB ID: 5HYO), RdRp (PDB ID: 6XQB), ACE2 (PDB ID: 7C8D), and TMPRSS2 (PDB ID: 5AFW) as protein targets were downloaded from Protein Data Bank (http://www.rcsb.org).

2.3. Preparation of protein target and ligands

We used Autodock and Discovery Studio software to perform the preparation. The preparation of protein target was carried out by removing water molecules, adding polar hydrogen atoms, and removing a natural ligand structure. After the preparation, we saved the file in pdbqt format. Meanwhile, the preparation of ligands were performed by creating all bonds being all rotatable then saved the file in pdbqt format.[18]

2.4. In-Silico molecular docking

We executed docking using Autodock Vina software. A protein target site was set with the help of a grid box parameters shown in **Table 1**. The best binding affinities (more negative value) was selected from a set of 9 conformation poses after running docking. A compound showing the best hits was selected to be visualized its molecular interaction.

Table 1. Coordinate value and grid box size

	ACE2	Mpro	TMPRSS2	RdRp
Center (Å)				
x	53,788	-11,824	4,565	141,009
y	59,483	14,735	52,510	139,028
z	25,267	74,152	71,669	149
Box dimension (Å)				
x	92	40	74	30
y	68	40	90	30
z	74	40	90	30

2.5. Visualization analysis

We performed visualization analysis to assess the binding sites of the ligand and observed chemical bonds formed between ligands and protein target. The visualization analysis was carried out using Discovery Studio software and depicted in 3D and 2D format.

3. Results

3.1. Drug-likeness and ADMET properties

Drug-likeness and ADMET properties were assesed using lipinski rules and admetSAR to determine the toxicity of the compound. Based on Lipinski's Rule of Five that showed in **Table 2**, all compounds used in this study have complied with Lipinski's Five of Rule so that all compounds used in this study are considered drug-like compounds. In a meantime, based on admetSAR shown in **Table 3**, all compounds in this study have a "-" value on carcinogenecity, which means non-carcinogenic and have an LD_{50} > 500 mg/kg for acute oral toxicity, categorized in III, which means non-toxic. Meanwhile, the ames-mutagenesis show that most of the compounds in this study have a "-" value means non-mutagenic.

3.2. In-Silico molecular docking

In this study, six mangosteen compounds and four comparative drugs were chosen. Crystal structures of Mpro, TMPRSS2, RdRp, and ACE2 were used. The docking results in this study are presented in **Table 4**. Lopinavir, nafamostat, remdesivir, and NAC showed the binding energies of -7,1, -9,1, -7,7, -4,0 kcal/mol. 8-Desoxygartanin had the highest binding affinities compared to the comparative drugs with binding energies of -8.0, -9.6, -7.8, and -8.6 kcal/mol for Mpro, TMPRSS2, RdRp, and ACE2, respectively. α-Mangostin, β-mangostin, Y-mangostin, Garcinone E, and Gartanin had binding energy values below nafamostat on TMPRSS2, which a value of -9.1 kcal/mol. In addition, α-mangostin, β-mangostin, Y-mangostin, and garcinone E had the binding energy value below remdesivir on RdRp, which was -7.7 kcal/mol. When compared with lopinavir to Mpro and NAC to ACE2, all compounds in mangosteen had higher binding energy value than the comparative drugs.

Table 2. Molecular docking results

Compounds	Mpro	TMPRSS2	RdRp	ACE2
8-Desoxygartanin	-8,0	-9,6	-7,8	-8,6
α-Mangostin	-7,4	-9.0	-6.9	-7,9
β-Mangostin	-7,1	-8.1	-7.1	-7,7
Y-Mangostin	-7,7	-8.8	-7.4	-7,9
Garcinone E	-8,0	-8.7	-8,0	-8,9
Gartanin	-7,9	-8.2	-7,7	-8,3
Comparative drugs				
Lopinavir	-7,1			
Nafamostat		-9,1		
Remdesivir			-7,7	
NAC				-4,0

3.3. Visualization analysis

The visualization analysis yield that 8-desoxygartanin had five hydrophobic and seven hydrogen interactions. There were 14 amino acid residues such as Met165, Met49, Glu166, His41(4), Leu27, Cys145(4), Gly143, and Ser144. Moreover, lopinavir showed three hydrophobic and four hydrogen interactions with amino acid residues such as Met49(2), Glu166(2), Gln189, His41(2), Asn142, Cys145, and Leu27. On the interaction with TMPRSS2, 8-desoxygartanin had five hydrophobic and hydrogen interactions respectively with 14 amino acid residues such as Tyr455(2), Asp623(2), Cys622(2), Arg553(4), Arg555(2), Thr556, and Asp452. Besides, nafamostat had four hydrophobic and five hydrogen interactions with amino acid residues such as Lys621, Arg553, Thr556, Tyr455, Ala558, Arg624, Ser682, Asp623(2), Asp760(2), Cys622, and Asn691. 8-Desoxygartanin also bound in RdRp with amino acid residues of Arg356, Leu158(2), Ala100, Ala50, Val35(3), Ile79, Ala172, Phe97(2), Lys52, Asp173, and TYR32(3). The interaction with RdRp had 14 hydrophobic and two hydrogen interactions. Moreover, remdesivir had seven hydrophobic and one hydrogen interactions with amino acid residues of Arg157(2), Tyr153, Pro158, Pro194(2), Phe5, Phe195, and Tyr162. On the interaction with ACE2, 8-desoxygartanin had five hydrophobic and two hydrogen interactions with amino acid residues of Ala348, Trp349(2), Asp350, Arg393, Phe390, Phe40, and Asn394. Besides, NAC only showed four hydrogen interactions with amino acid residues of His493, Trp478(2), Glu489, and Arg482.

Table 3. Lipinski rule of five results

No.	Compounds	MW <500 (g/mol)	H-donor	H-acceptor	LogP	Molar Refractivity
1.	8-Desoxygartanin	380.43	3	5	5.43	113.50
2.	α-Mangostin	410.46	3	6	5.52	119.99
3.	β-Mangostin	424.49	2	6	6.08	124.46
4.	γ-Mangostin	396.43	4	6	4.96	115.52
5.	Garcinon E	464.55	4	6	6.83	139.24
6.	Gartanine	396.43	4	6	4.96	115.52

Table 4. Toxicity

No.	Compounds	Carcinogenecity	Ames mutagenesis	Acute oral toxicity
1.	8-Desoxygartanin	- (0.9571)	+ (0.6200)	III (0.6305)
2.	α-Mangostin	- (0.9571)	- (0.6200)	III (0.6336)
3.	β-Mangostin	- (0.9571)	- (0.7000)	III (0.8250)
4.	γ-Mangostin	- (0.9571)	- (0.6700)	III (0.5700)
5.	Garcinon E	- (0.9571)	- (0.5600)	III (0.5700)
6.	Gartanine	- (0.9571)	+ (0.6400)	III (0.6305)

4. Discussion

There is no particular drug with a direct effect againts COVID-19 has been discovered. Molecular docking study has become a strategy in screening of bioactive components and has been utilized as a tool to predict the effect of many antiviral drugs on SARS-CoV-2.[19] In our study, potential mangosteen compounds were chosen to be investigated againts SARS-CoV-2.

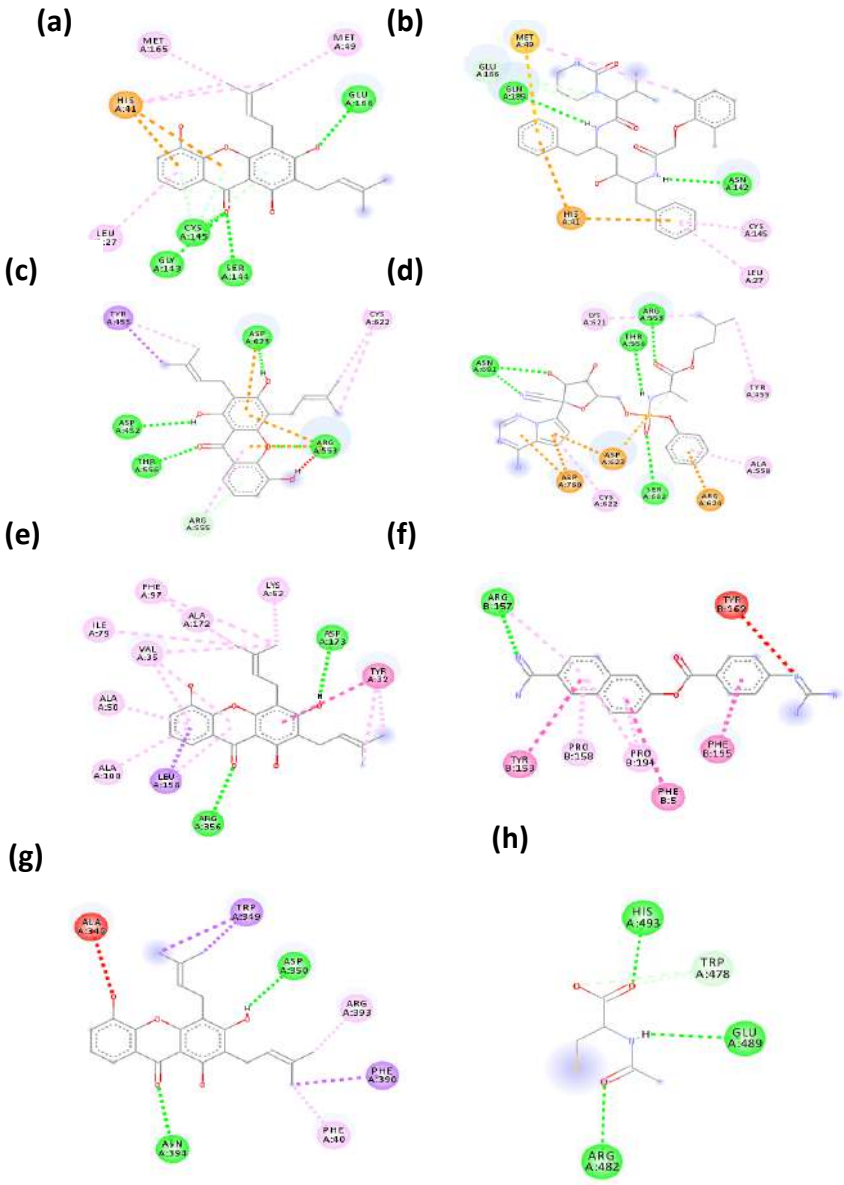

Figure 1. Molecular interaction in 2D between (a) 8-desoxygartanin and Mpro; (b) lopinavir and Mpro; (c) 8-desoxygartanin and TMPRSS2; (d) nafamostat and TMPRSS2; (e) 8-desoxygartanin and RdRp; (f) remdesivir and RdRp; (g) 8-desoxygartanin and ACE2; (h) NAC and ACE2.

Based on docking simulation, the docking scores of 8-desoxygartanin was comparable to all comparative drugs because the docking score of 8-desoxygartanin was higher than that of all comparative drugs in each protein target. In **Figure 1**, the interactions of 8-desoxygartanin with four protein targets are presented while **Figure 2** described the amino acid residues which involved in the interactions. The binding energy value that is more negative than the comparison compound indicates a more robust and better ligand.[20]

Previous in silico study reported that the binding pocket of Mpro were amino acid residues of His41, Met49, Phe140, Leu141, Asn142, Gly143, His163, His,164, Met165, Glu166, Leu167, Pro168, His172, Gln189, Thr190, and Ala191.[21] In another study, His41 and Cys145 were found in the catalytic dyad (active sites) of the enzyme in which this sites play a key role to inhibit the enzyme.[22] His41, Met49, Glu166, and Cys145 were found in the interaction of 8-desoxygartanin and lopinavir shown in **Figure 2**. Therefore, 8-desoxygartanin binds in the active sites of Mpro as well as lopinavir.

8-Desoxygartanin and remdesivir posed several similar amino acid recidues such as Tyr455, Asp623, Cys622, Arg553, and Thr556. These residues were found in the active sites of RdRp based on previous molecular docking study.[23] Thus, 8-desoxygartanin and remdesivir bound in the active sites of RdRp.

In TMPRSS2, no residues were same between 8-desoxygartanin and nafamostat. Thus, both of them bound in the different binding sites of TMPRSS2. Several compounds were reported to have interactions in ACE2 to treat COVID-19. A molecular docking study revealed that flavonoid bind to residues of Ala348, Asp350, and Arg393.[6] The compound rutin well occupied the receptor with residues of Ala348, Asp350, Asp382, Phe390, Asn394, and Glu402 whereas hesperidin showed interaction with Ala348, Asp350, Trp69, and Tyr385.[24,25,26] Those residues were also found in the interaction of 8-desoxygartanin. Thus, they targeted similar binding pocket in ACE2. Nevertheless, there were no same residues between the interaction of 8-desoxygartanin and nafamostat.

Lipinski's rule of five describes a relationship between pharmacokinetics and physicochemical parameters.[27] The Lipinski rule of five can help to distinguish between drug-like compounds and non-drug-like compounds. The rules consist of molecular weight less than 500 Dalton, number of H-bond acceptors less than 10, number of H-bond donors less than 5, LogP less than 5, and molar refractivity should be between 40-130.[20] In this study, all compounds are considered drug-like compounds.

Toxicity assessment in this study used admetSAR. We used three indicators in assessing toxicity, namely carcinogenecity, ames mutagenesis, and acute oral toxicity. Carcinogenecity test means whether a compound is carcinogenic or not. In this study, all compounds showed negative results, so all compounds were non-carcinogenic. Ames mutagenesis test is helpful to determine whether a compound is mutagenic or not. Almost all compounds showed negative results, which means non-mutagenic. Acute oral toxicity has four categories to state whether the compound is oral toxic or not. Category I ($LD_{50} \leq 50$ mg/kg) and category II (50 mg/kg $< LD_{50} \leq 500$ mg/kg) considered as toxic while category III (500 mg/kg $< LD_{50} \leq 5000$ mg/kg) and category IV ($LD_{50} > 5000$ mg/kg) considered as non-toxic.[17,28] All compounds in this study had category III which was non-toxic.

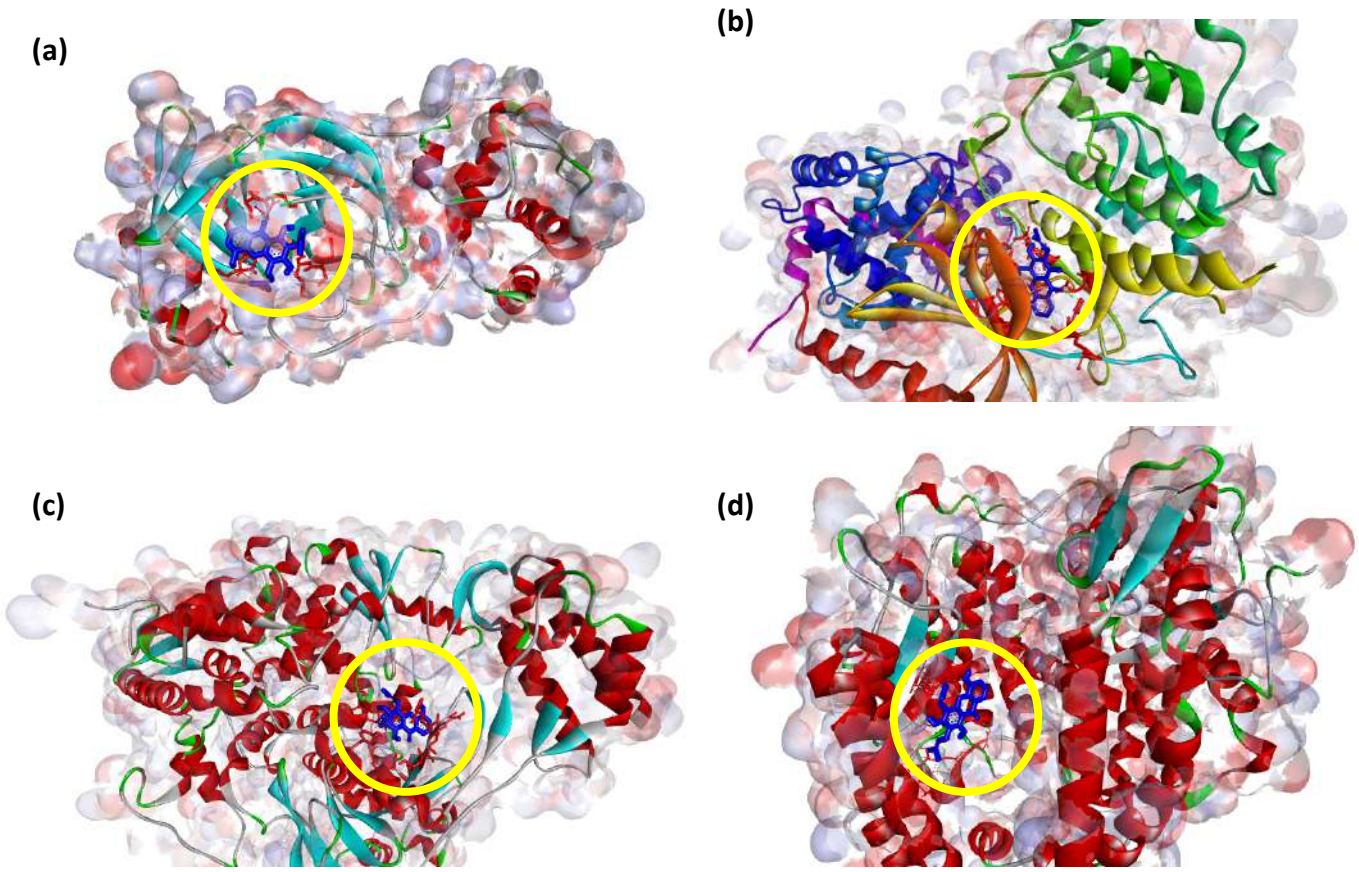

Figure 2. Molecular interaction in 3D between 8-desoxygartanin and protein targets: (a) Mpro; (b) TMPRSS2; (c) RdRp: (d) ACE2.

In vivo study conducted by Kasem et al., showed that Crude methanolic extract from mangosteen pericarp after a single-dose administration of as much as 1000 mg/kg orally produces a toxic effect in mice. Meanwhile, Chivapat et al., reported that mangosteen pericarp extract does not produce a toxic effect after being given as much 1000 mg/kg for wistar rats in 6 months orally. Moreover, after a single oral administration of an ethanolic extract from mangosteen in rats up to 5,000 mg/kg, it still does not produce a toxic effect.[29,30] Thus, the results of the toxicity analysis in this study were in line with previous studies where mangosteen did not produce a toxic effect significantly that tested in vivo.

Previous studies reported that mangosteen have been proven as antiviral. A randomized controlled trial study by Amanah et al. reported the HIV patients after 2400 mg/day for 30 days of mangosteen peel extract (MPE) treatment shown a significant increase in CD4+ T cells and resulting in decreased levels of IL-2. Moreover, $CD8^+$ T cells decreased in line with a decrease of CD38 expression in HIV patients which have high reactive oxygen species (ROS), MPE also play a role in inhibiting the high levels of ROS by protecting cell damage and suppresses apoptosis that would maintain the number of $CD4^+$ T lymphocytes.[14]

In vitro study by Choi et al. shown that the ethanol from mangosteen fruit peels (MG-EtOH) was able to inhibit HCV genome replication Inhibition by MG-EtOH caused subsequent down-regulation of HCV proteins expression with α-mangostin and Y-

mangostin as the most potential xanthones compounds for its antiviral effects.[8] Moreover, Patil et al. reported in vitro research using CHIKV replication in Vero E6 cells with α-mangostin completely inhibited CHIKV infectivity under pre-treatment and co-treatment conditions. In addition, in vivo study using CHIKV-infected mice can reduce viral burden and relieve disease symptoms in mice.[15] Gopalakrishnan et al. reported in vitro research using several xanthones from fruit hulls of mangosteen against three phytopathogenic fungi such as *Fusarium oxysporum vasinfectum, Alternaria tenuis,* and *Dreschlera oryzae* showed all the compounds showed inhibitory activity against the fungi and 8-desoxygartanin showed best effects compared other xanthones.[9]

5. Conclusion

In conclusion, based on the docking scores and the interactions with four protein targets, namely Mpro, TMPRSS2, RdRp, and ACE2. 8-Desoxygartanin appeared to be the most potential compound in inhibiting SARS-CoV-2 although there were many compounds from mangosteen shown better results than comparative drugs. All of the compounds also had drug-likeness properties and less toxicity. Therefore, mangosteen has a potential effect to inhibit SARS-CoV-2. Further in vitro and in vivo investigations are needed to bring mangosteen compounds to the clinical trial.

References

1. Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol [Internet]. 2020;41(12):1100–15. Available from: https://doi.org/10.1016/j.it.2020.10.004
2. Di Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, et al. Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. Int J Environ Res Public Health. 2020;17(8).
3. World Health Organization (WHO). WHO Coronavirus (COVID-19) Dashboard [Internet]. 2021. Available from: https://covid19.who.int/
4. World Health Organization. WHO COVID-19 Dashboard [Internet]. 2021 [cited 2021 Jul 24]. Available from: https://covid19.who.int/
5. Trougakos IP, Stamatelopoulos K, Terpos E, Tsitsilonis OE, Aivalioti E, Paraskevis D, et al. Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. J Biomed Sci [Internet]. 2021;28(1):1–18. Available from: https://doi.org/10.1186/s12929-020-00703-5
6. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B [Internet]. 2020;10(5):766–88. Available from: https://doi.org/10.1016/j.apsb.2020.02.008
7. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA - J Am Med Assoc. 2020;324(8):782–93.
8. Choi M, Kim YM, Lee S, Chin YW, Lee C. Mangosteen xanthones suppress hepatitis C virus genome replication. Virus Genes. 2014;49(2):208–22.
9. Ovalle-Magallanes B, Eugenio-Pérez D, Pedraza-Chaverri J. Medicinal properties of mangosteen (Garcinia mangostana L.): A comprehensive update. Food Chem Toxicol [Internet]. 2017;109:102–22.

Available from: http://dx.doi.org/10.1016/j.fct.2017.08.021

10. Widowati W, Darsono L, Suherman J, Yelliantty Y, Maesaroh M. High Performance Liquid Chromatography (HPLC) Analysis, Antioxidant, Antiaggregation of Mangosteen Peel Extract (Garcinia mangostana L.). Int J Biosci Biochem Bioinforma. 2014;4(6):458–66.
11. Do HTT, Cho J. Mangosteen pericarp and its bioactive xanthones: Potential therapeutic value in alzheimer's disease, parkinson's disease, and depression with pharmacokinetic and safety profiles. Int J Mol Sci. 2020;21(17):1–23.
12. Feng Z, Lu X, Gan L, Zhang Q, Lin L. Xanthones, A Promising Anti-Inflammatory Scaffold: Structure, Activity, and Drug Likeness Analysis. Molecules. 2020;2.
13. Kang HH, Zhang H Bin, Zhong MJ, Ma LY, Liu DS, Liu WZ, et al. Potential antiviral xanthones from a coastal saline soil fungus Aspergillus iizukae. Mar Drugs. 2018;16(11):1–9.
14. Amanah A, Komala I, Kurniasari MD, Dharmana E, Gasem MH. Effect of mangosteen (Garcinia mangostana) PEEL Extract towards CD4+, CD8+ T LYMPHOCYTES, CD38 Expression, NK Cells, IL-2 and IFNγ in HIV Patients with Antiretroviral Therapy. Hiroshima J Med Sci. 2018;67(24):56–62.
15. Patil P, Agrawal M, Almelkar S, Jeengar MK, More A, Alagarasu K, et al. In vitro and in vivo studies reveal α-Mangostin, a xanthonoid from Garcinia mangostana, as a promising natural antiviral compound against chikungunya virus. Virol J [Internet]. 2021;18(1):1–12. Available from: https://doi.org/10.1186/s12985-021-01517-z
16. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2012;64(SUPPL.):4–17.
17. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, et al. ADMET-score-a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm. 2019;10(1):148–57.
18. Forli S, Huey R, Pique ME, Sanner M, Goodsell DS, Arthur J. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. Nat Protoc. 2016;11(5):905–19.
19. Luo J, Wei W, Waldispühl J, Moitessier N. Challenges and current status of computational methods for docking small molecules to nucleic acids. Eur J Med Chem. 2019;168:414–25.
20. Aamir M, Singh VK, Dubey MK, Meena M, Kashyap SP, Katari SK, et al. In silico prediction, characterization, molecular docking, and dynamic studies on fungal SDRs as novel targets for searching potential fungicides against fusarium wilt in tomato. Front Pharmacol. 2018;9(OCT):1–28.
21. Agrawal A, Jain NK, Kumar N, Kulkarni GT. Molecular Docking Study to Identify Potential Inhibitor of COVID-19 Main Protease Enzyme: An In-silico Approach. ChemRxiv. 2020;(April).
22. Khalifa I, Zhu W, Nafie MS, Dutta K, Li C. Anti-COVID-19 effects of ten structurally different hydrolysable tannins through binding with the catalytic-closed sites of COVID-19 main protease: An in-silico approach. Preprint. 2020;(December):1–21.
23. Poustforoosh A, Hashemipour H, Tüzün B, Pardakhty A, Mehrabani M, Nematollahi MH. Evaluation of potential anti-RNA-dependent RNA polymerase

(RdRP) drugs against the newly emerged model of COVID-19 RdRP using computational methods. Biophys Chem [Internet]. 2021;272:254–66. Available from: www.elsevier.com/locate/cca Review

24. Haggag YA, El-Ashmawy NE, Okasha KM. Is hesperidin essential for prophylaxis and treatment of COVID-19 Infection? Med Hypotheses. 2020;144(January).
25. Huang F, Li Y, Leung EL-H, Liu X, Liu K, Wang Q, et al. A review of therapeutic agents and Chinese herbal medicines against SARS COV-2 (COVID-19). Pharmacol Res. 2020;158.
26. Goyal RK, Majeed J, Tonk R, Dhobi M, Patel B, Sharma K, et al. Current targets and drug candidates for prevention and treatment of SARS-CoV-2 (COVID-19) infection. Rev Cardiovasc Med. 2020;21(3):365–3984.
27. Ansori ANM, Susilo RJK, Hayaza S. Biological activity investigation of phytocomponents in mangosteen (Garcinia mangostana l.): In silico study. Indian J Forensic Med Toxicol. 2021;15(1):847–51.
28. Nisha CM, Kumar A, Nair P, Gupta N, Silakari C, Tripathi T, et al. Molecular docking and in silico admet study reveals acylguanidine 7a as a potential inhibitor of β -secretase. Adv Bioinformatics. 2016;2016.
29. Chivapat S, Chavalittumrong P, Wongsinkongman P. Chronic Toxicity Study of Garcinia mangostana Linn. pericarp Extract. Thai J Vet Med. 2011;41(1):45–53.
30. Kosem N, Ichikawa K, Utsumi H, Moongkarndi P. In vivo toxicity and antitumor activity of mangosteen extract. J Nat Med. 2013;67(2):255–63.