Active constituents and Molecular Analysis of *Psidium guajava* Against Multiple Protein of SARS-CoV-2

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Research article

Keywords: Molecular analysis, Psidium guajava, 3CLPro, MPro, ACE2, Spike, PLPro, SARS-CoV-2

Posted Date: March 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-271919/v1

Abstract

Background

The severe acute respiratory syndrome COVID-19 declared as a global pandemic by the World Health Organization has become the present wellbeing worry to the whole world. The latest development of COVID-19 spread in Indonesia has reached 1.024.298 cases, with 28.855 patients died, updated on January 28, 2021. Unfortunately, these numbers continue to overgrow, and no drug has yet been approved for effective treatment. There is an emergent need to search for possible medications and explore the potential of Indonesian herbal compounds. Ministry of Health Indonesia stated that *Psidium guajava* can be use as daily nutritional supplement during COVID-19 pandemic. This study aims to determine the potential active constituents in *Psidium guajava* as an inhibitor for multiple SARS-CoV-2 proteins using molecular analysis.

Methods

Molecular docking was performed by using Autodocktools 1.5.6. We performed a structure-based virtual screening of fourteen 3D structure of *Psidium guajava* compounds, three antivirals (lopinavir, remdesivir, and ritonavir) against multiple SARS-CoV-2 proteins. We download the main protease (3CLPro), Papain Like Protease (PL Pro), MPro, Spike and ACE2 as protein target from human against from Protein Data Bank (PDB). We used PyMOL to analyse the interactions between the SARS-CoV-2 proteins and 14 compounds from *Psidium guajava* and three antiviral (lopinavir, remdesivir and ritonavir) used as positive control.

Results

Based on the molecular docking analysis, it was found there are two potential compounds that showed higher binding affinity score namely gamma sitosterol and peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl).

Conclusions

Gamma sitosterol and peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) from *Psidium guajava* have potential as antiviral candidates for SARS-CoV-2 multiple proteins such as main protease (3CLPro), Papain Like Protease (PL Pro), MPro, Spike and ACE2.

Introduction

The new coronavirus, called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), was first identified in Wuhan, China, in December 2019 [1]. SARS-CoV-2 belongs to the Coronaviridae family, a single-stranded RNA virus (+ ssRNA) that is widespread among humans and other mammals, causing a wide range of infections from common cold symptoms to fatal illnesses, such as severe respiratory syndrome [2, 3]. The latest development of COVID-19 spread in Indonesia has reached 1.024.298 cases, with 28.855 patients died, updated on January 28, 2021 (data taken from https://covid19.go.id). The infected numbers continue to overgrow and reached more than 10.000 new case per day. Unfortunately, there are no drugs approved yet as an effective treatment. Therefore, the need to discover and develop drugs to treat the Coronavirus Disease 2019 (COVID-19) is become more urgent.

There are two categories of anti-coronavirus therapy depending on the target, one act on the human immune system or human cells, and the other one is on the coronavirus itself. In terms of the human immune system, the innate immune system response plays an essential role in controlling the replication and infection of coronavirus and to enhance the immune response [4]. Blocking the signalling pathways of human cells required for virus replication may exhibit a specific antiviral effect. The therapies that work on the coronavirus itself include preventing the synthesis of viral RNA by acting on the genetic material of the virus, inhibiting virus replication through acting on critical enzymes of the virus, and blocking the virus from binding to human cell receptors or inhibiting the viral assembly process by working on several structural proteins [5].

In an attempt to fight against coronavirus, scientists are coming up with different strategies. One of the strategy is exploring natural compounds to find out their activity against the multiple SARS-CoV-2 protein targets. Especially, in Indonesia, people are more familiar with using herbal to care their health in daily life, we also need to consider developing agents from herbal. Erlina et al.

(2020), found that *Psidium guajava* is potential as a candidate of SARS-CoV-2 therapeutic agent. By using combination studies of machine learning, pharmacophore modelling and molecular docking, some of *Psidium guajava* compounds such as myricetin, quercetin, luteolin, kaempferol, isorhamnetin [6], and Hesperidin [7] shown good activity for 3CL Pro inhibition [8].

Computational methods to understand the ligand protein interaction is one of the fastest ways to identify the candidate drug and target. Scientists are screening existing molecules from the database, which might be effective against coronavirus as a strategy [9–11]. In case of SARS-CoV-2, inputs from this traditional way were lacking because of unavailability of protein structure. But 3D structures of different proteins of this novel SARS-CoV-2 are constantly being deposited in the database and hence in the present study we decided to do molecular docking analysis of these newly deposited proteins against some repeatedly discussed drugs as a repurposing therapeutic approach. We had selected those proteins for docking which play an important role in propagation of virus. We selected 3CLpro and Mpro which are the main protease of the virus, spike protein from virus, and Papain like protease (PL pro) [11]. Virus enters the cell via angiotensin receptor converting enzyme 2 therefore blocking this enzyme could be of immense importance [12–14]. This enzyme is also selected as one of the target proteins. In this study, some known antiviral drugs like Ritonavir, Lopinavir, and Remdesivir, which are being used as therapeutic agents against COVID-19, are used as candidate ligands for docking. Molecular docking was performed using Autodocktools 1.5.6.

Materials And Methods

Proteins (macromolecules)

Different proteins from SARS-CoV-2 were selected which include main protease of SARS-CoV-2 3CLpro [PDB ID: 6LU7] [15], the crystal structure of COVID-19 main protease in apo form [PDB ID: 6M03] [16], Spike protein receptor binding domain [PDB ID: 2GHV] [17], Papain Like Protease from SARS CoV-2 [PDB ID: 6WX4] [18]. We have also selected the protein from host cell, i.e. human cell, which is responsible for host virus interaction. Virus enters the cell through angiotensin-converting enzyme 2 (ACE2) receptor [PDB ID: 6M18] chains D [19] by binding with its spike protein. 3D structures were obtained from Protein Data Bank (https://www.rcsb.org/), in .pdb format [20].

Ligand (*Psidium guajava* and antiviral) structures

Fourteen *Psidium guajava* active constituents were prepared as ligand (Table 1). Known antiviral drugs like ritonavir, lopinavir, and remdesivir, which are used to SARS-CoV-2 therapeutic agents, also selected as a candidate ligands for docking against viral proteins. The 2D or 3D structures were downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/), save in .sdf format file and structures optimization (checking torsion, and angles) were done using MarvinSketch.

Molecular docking validation

Molecular docking validation was done using redocking methods by Autodocktools 1.5.6. 3CL Pro (PDB ID: 6LU7) has native ligand namely inhibitor N3 and PL pro (PDB ID: 6WX4) has native ligand namely peptide inhibitor VIR251. Grid box for 6LU7 and 6WX4 develop into three set (40x40x40 Å, 50x50x50 Å and 60x60x60 Å). Run Genetic Algorithm (GA) was set to 100 times. Binding energy (Kcal/mol) and RMSD will evaluate per each docking results.

Molecular docking analysis and visualization

AutoDock software was utilized in all the docking experiments, with the optimized model as the docking target. Ligand and protein optimization were done using Autodocktools 1.5.6. For ligand optimization, the geometry of ligands was cleaned and torsion were set to fewest. For protein optimization, the water was removed, hydrogen polar only were added, hydrogen non polar were merged and Gasteiger charge were added. The docking was performed by using AutoDock4. Run Genetic Algorithm (GA) was set to 10 times. The docking analysis were performed using PyMOL version 2.4.1 for 3D visualization [The PyMOL Molecular Graphics System, Version 2.1 Schrödinger, LLC].

Results And Disscussion

Molecular docking validation

6LU7 (PDB ID) was choose as 3CL Pro receptor because it has a resolution value of 2.16 Å. Based on molecular docking validation with a re-docking method between 6LU7 and its native ligand (N3), the optimum grid box is 40x54x40 Å with binding energy value – 8.72 kcal/mol, RMSD value 3.96 Å and inhibition constant value 408.59 nM. The optimum grid center is x= -9.768; y = 11.424; z = 68.935 with 0.375 Å spacing for default setting.

6WX4 (PDB ID) was choose as PL Pro receptor because it has a resolution value of 1.66 Å. Based on molecular docking validation with a re-docking method between 6WX4 and its native ligand (VIR251), the optimum grid box is 40x40x40 Å with binding energy value – 6.96 kcal/mol, RMSD value 2.94 Å and inhibition constant value 7.91 uM. The optimum grid center is x = 9.508; y= -27.455; z= -37.252 with 0.375 Å spacing for default setting.

6M03 (PDB ID) was choose as M Pro receptor because it has a resolution value of 2.00 Å. Based on molecular docking validation with a docking method between 6M03 and antivirals (lopinavir, remdesivir and ritonavir), the optimum grid box is 70x70x70 Å. The optimum grid center is x = 10.393; y= -12.893; z = 23.623 with 0.375 Å spacing for default setting.

2GHV (PDB ID) was choose as Spike receptor because it has a resolution value of 2.2 Å. Based on molecular docking validation with a docking method between 2GHV and antivirals (lopinavir, remdesivir and ritonavir), the optimum grid box is 60x60x60 Å. The optimum grid center is x = 1.933; y= -20.911; z = 26.065 with 0.375 Å spacing for default setting.

6M18 (PDB ID) was choose as ACE2 receptor because it has a resolution value of 2.9 Å. Based on molecular docking validation with a docking method between 6M18 and antivirals (lopinavir, remdesivir and ritonavir), the optimum grid box is 100x100x100 Å. The optimum grid center is x = 164.699; y = 162.987; z = 201.537 with 0.375 Å spacing for default setting.

Binding energy of molecular docking

Table 2. Molecular docking data represented in terms of binding energy (ΔG) in Kcal/mol for viral target proteins with Psidium guajava compounds

Compounds	3CL Pro		PL Pro		Spike		M Pro		ACE2	
	ΔG(Kcal/Mol)	IC	ΔG(Kcal/Mol)	IC	ΔG(Kcal/Mol)	IC	ΔG(Kcal/Mol)	IC	ΔG(Kcal/Mol)	IC
1,2-benzenedicarboxylic-acid	-3,33	3.64 mM	-3,04	5.94 mM	-4,82	293.01 uM	-3,42	3.13 mM	-3,72	1.89 mM
2-cyclohexene-1-carboxylic-acid-1-methyl-4-oxo-ethyl-ester	-5,88	48.58 uM	-5,30	131.09 uM	-4,17	879.47 uM	-5,16	163.84 uM	-6,20	28.67 uM
2-Furancarboxaldehyde_5-hydroxymethyl	-4,32	680.75 uM	-4,59	434.94 uM	-3,58	2.37 mM	-3,86	1.48 mM	-4,61	461.62 uM
2-methyl-Z-Z-3-13-octadecadienol	-4,90	254.95 uM	-5,81	54.76 uM	-2,91	7.32 mM	-5,11	179.68 uM	-4,65	392.05 uM
3-methylmannoside	-4,22	811.54 uM	-3,77	1.71 mM	-2,91	7.37 mM	-3,41	3.14 mM	-4,02	1.12 mM
14-methyl-8-hexadecyn-1-ol	-4,74	336.75 uM	-5,37	116.44 uM	-3,55	2.5 mM	-5,12	175.86 uM	4,84	283.51 uM
gamma sitosterol	-9,06	228.82 nM	-7,50	3.2 uM	-6,65	13.38 uM	-9,35	139.06 nM	-10,41	23.35 nM
geranyl acetate	-5,25	142.52 uM	-5,85	51.32 uM	-4,65	388.33 uM	-5,59	79.46 uM	-4,98	225.36 uM
hexadenoic acid	-4,26	754.77 uM	-5,04	201.08 uM	-3,63	2.2 mM	-3,26	4.11 mM	-3,66	2.09 mM
hexadenoic acid ethyl ester	-4,81	296.02 uM	-6,13	32.3 uM	-2,90	7.54 mM	-4,37	629.60 uM	-4,40	598.94 uM
hexadenoic acid methyl ester	-5,15	168.23 uM	-5,91	46.31 uM	-3,39	3.3 mM	-4,26	751.39 uM	-4,35	642.60 uM
methyl (8E,11E)-8,11-octadecadienoate	-5,25	141.25 uM	-6,56	15.61 uM	-3,71	1.9 mM	-4,28	725.81 uM	-4,80	301.85 uM
peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl)	-11,49	3.79 nM	-8,65	456.49 nM	-8,10	1.16 uM	-8,82	343.99 nM	-10,26	30.05 nM
(R)-(-)-14-methyl-8-hexadecyn-1-ol	-5,36	116.97 uM	-5,49	94.66 uM	-3,98	1.22 mM	-4,77	321.50 uM	-4,60	421.67 uM
lopinavir	-8,20	968.24 nM	-7,80	1.93 uM	-4,74	337.08 uM	-8,38	721.86 nM	-8,21	966.21 nM
remdesivir	-7,10	6.2 uM	-5,33	124.83 uM	-4,76	321.63 uM	-7,41	3.70 uM	-7,75	2.1 uM
ritonavir	-6,25	26.07 uM	-3,34	3.34 mM	-6,65	13.37 uM	-7,17	5.56 uM	-6,72	11.95 uM

Based on the docking results of 14 compounds of *Psidium guajava* against the 3CL Pro, Pl Pro, M Pro, Spike and ACE2 receptors (Table 2), two compounds with the best docking results were obtained, namely gamma sitosterol and peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl). For antiviral docking results, lopinavir become the best binding energy value against 3CL Pro, PL Pro, M pro and ACE2 and show the worst binding energy value against spike protein.

Table 3. Amino acid interactions in 3CL Pro binding site

Amino acid	gamma sitosterol	Peri-xantheno	lopinavir	remdesivir	ritonavir	Native ligand (N3)
His41						
Met49	(3.6)					
Arg188	(3.0)	(2.8)				
Gln189			(2.2)	(3.1), (3.1), (3.2) and (3.5)	(2.8)	(3.2)
Gly143		(2.2)				
Leu141						
Phe140						
Glu166		(2.2)	(2.5) and (2.1), (2.4) and (2.5)	(1.8), (1.9) and (2.9)	(2.4)	(3.4)
Leu167				(2.1) and (3.4)		
Asn142			(2.8) and (2.3)	(3.6)	(2.8)	
Met165						
Asp187						(3.5)
Ser144						
Cys145						
Gly170						
Pro168						(2.8)
Thr169						
Ala173						
His163					(2.0)	
Leu27						
His164						
Thr190						
Gln192						

*colored box means there are interaction and number in () represent distance of hydrogen bond in Å

N3 inhibitor is the native ligand molecule isolated from the crystal structure of 3CLpro (6LU7), which was used as the binding site control. According to the analysis of docking results (Table 3), N3 have several amino acid interactions such as His41, Met49, Gln189, Gly143, Glu166, Leu167, Met165, Asp187, Gly170, Pro168, Thr169, Thr190 and Gln192. There are 4 hydrogen bond interaction with Gln189, Glu166, Asp187 and Pro168.

According to Fig. 1 and Table 3, ligand gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and lopinavir have the same amino acid interaction in position Met49, Arg188, Gln189, Gly143, Leu141, Glu166, Asn142, and Met165.

Table 4. Amino acid interactions in PL Pro binding site

Amino acid	gamma sitosterol	Peri-xantheno	lopinavir	remdesivir	ritonavir	native ligand (VIR251)
Pro248						
Pro247						
Thr301						
Asp164						(3.2)
Gly163				(3.3) and (1.9)	(3.3)	(3.5)
Leu162			(2.6)		(3.2)	
Tyr264				(2.6) and (2.6)		
Cys270						
Gln269		(3.5) and (3.0)			(3.9)	
Tyr268			(2.6) and (3.3)	(2.7) and (3.3)	(2.9)	
Gly271						
His272						
Tyr273		(2.5)				(3.1)
Tyr112						
Glu161						
Lys157			(3.6)			
Arg166						
Val165						
Glu167						(3.4)
Asp302						(2.9) and (3.1)

*colored box means there are interaction and number in () represent distance of hydrogen bond in Å

VIR251 inhibitor is the native ligand molecule isolated from the crystal structure of PL Pro (6WX4), which was used as the binding site control. According to the analysis of docking results (Table 4), VIR251 have several amino acid interactions such as Thr301, Asp164, Gly163, Leu162, Cys270, Gln269, Gly271, His272, Tyr273, Tyr112, Arg166, val165, Glu167 and Asp302. There are 6 hydrogen bond interaction with Asp164, Gly163, Tyr273, Glu167 and Asp302.

According to Fig. 2 and Table 4, ligand gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and lopinavir have the same amino acid interaction in position Asp164, Gly163, Leu162, Cys270, and Gln269.

Table 5. Amino acid interactions in Spike binding site

Amino acid	gamma sitosterol	Peri-xantheno	lopinavir	remdesivir	ritonavir
Gly368					
Val369	(2.7)				
Tyr367		(2.8)		(2.0) and (3.5)	(2.2) and (3.1)
Cys366					
Lys365				(3.4)	
Ala398					
Ile397		(2.5)			
Arg395			(3.4)	(3.1)	(3.5)
Val394					
Gly391					
Ser362				(2.6)	
Thr363		(3.0)		(2.0)	
Gln401					
Asp414					
Asp415					
Pro399			(2.5)		(2.0)
Gly400					(2.7) and (3.1)
Thr402					
Asp393					
Asp392					(3.0)

*colored box means there are interaction and number in () represent distance of hydrogen bond in Å

According to the analysis of docking results (Table 5), gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl), lopinavir, remdesivir and ritonavir have essential amino acid interactions such as Arg395 and Val394. Lopinavir, remdesivir and ritonavir have one hydrogen bond interaction with Arg395.

According to Fig. 3 and Table 5, ligand gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and ritonavir have the same amino acid interaction in position Tyr367 and Arg395, Val394. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and ritonavir have hydrogen bond interaction with Tyr367.

Table 6. Amino acid interaction in M Pro binding site

Amino acid	gamma sitosterol	Peri-xantheno	lopinavir	remdesivir	ritonavir
Met165					
Glu166	(2.8)	(3.2)		(2.7)	
Phe140	(2.3)		(2.3)	(3.3)	
Leu141				(2.4), (3.5)	
Ser144					
Asn142			(3.1), (3.2), (2.7) and (3.5)		
Gly143			(2.9)		(3.5)
Cys145					
Met49					
Thr45					
Thr24					
Thr25					(2.8)
Thr26					
Cys44					
Leu167					
Val42					
Ile43					
His41		(2.9)			
Arg188					
Thr190					
Tyr118					
Asn119					
Ser46					(3.3)
Gln189				(3.4)	(2.7), (2.5) and (3.4)
Glu47					
Leu27					

*colored box means there are interaction and number in () represent distance of hydrogen bond in Å

According to the analysis of docking results (Table 6), gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl), lopinavir, remdesivir and ritonavir have essential amino acid interactions such as Met165, Glu166, Asn142, Gly143, and Met49.

According to Fig. 4 and Table 6, ligand gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and lopinavir have the same amino acid interaction in position Met165, Glu166, Asn142, Gly143, Thr25, Thr26 and Met49. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and gamma sitosterol have hydrogen bond interaction with Glu166.

Table 7. Amino acid interactions in ACE2 binding site

Amino acid	gamma sitosterol	Peri-xantheno	lopinavir	remdesivir	ritonavir
Leu675					
Asn674					
Ala673					
Val672			(3.1)		(3.5)
Arg671					
Val670					
Glu668					
Pro492				(2.7) and (2.2)	
Asp494				(3.6)	(3.1)
His493		(3.0) and (2.9)	(3.0)	(3.4)	
Met474					
Lys475	(3.5)				
Trp477					
Trp478					
Lys476					
Glu479					
Met480					
Met640					
Asp637					
Glu639					
Glu495			(2.8)		(3.3)
Asp471			(2.5) and (2.3)		
Lys676					
Gln472					
Arg644				(3.0)	
Glu667					

*colored box means there are interaction and number in () represent distance of hydrogen bond in Å

According to the analysis of docking results (Table 7), gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl), lopinavir, remdesivir and ritonavir have essential amino acid interactions such as Ala673, Val672, Pro492, Asp494, and His493.

According to Fig. 5 and Table 7, ligand gamma sitosterol, peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and lopinavir have the same amino acid interaction in position Leu675, Trp478, Ala673, Val672, Pro492, Asp494, and His493. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl), lopinavir and remdesivir have hydrogen bond interaction with His493.

After we got molecular docking results, we further checked the previous studies to find the biological activities of each compound. So that this research can be useful for the community, we also tried to find from commodity crops. One of the commodity crops in Indonesia is Guava (*Psidium guajava*) that can be harvested continuously in one year. In Indonesia, production of guava in the year 2018 is 230,697 tons, with growth rate from the year 2017 to 2018 is 15.06% [21]. Guava is consumed not only as food but also as a traditional medicine in subtropical areas around the world due to its pharmacologic activities. Based on Herbal Regulation as Healthy Supplement for Fighting COVID-19 in Indonesia published by The Indonesian Food and Drug Authority (BPOM) (May, 2020), we can consume *Psidium guajava* (Guava) 1–4 fruits per day (55–100 gram/fruit) which contain vitamin C 228.3 mg in 100 gram fruit. For the administration, Guava can be eaten directly or processed as juice. There is no case for toxicity for long term consumption, overall this herbal is safe to use as daily nutritional supplement [22]. Phenolic compound from Guajava has been proved as immunomodulator and antioxidant [23].

Guava is well known has several flavonoids compounds, i.e. myricetin, quercetin, luteolin, kaempferol, isorhamnetin [6], and Hesperidin [7]. These compounds were also shown in our result, although without the aglycones. Luteolin is known as a furin protein inhibitor [24] which is predicted to be one of the enzymes that break down Coronavirus S (spike) protein as in MERS into units S1 and S2 [25]. In the S1 unit, there is a Receptor Binding Domain (RBD) where the ACE2 peptidase binds so that the virus can bind to the host [25]. Hesperidin / Hesperitin compounds in the *in silico* study are known to inhibit RBD domain binding of the SARS-COV-2 Spike protein with ACE2 receptors in humans so that it is predicted to inhibit the entry of the SARS-COV-2 potentially [5]. It is also

known that luteolin is a neuraminidase inhibitor as well as oseltamivir which is currently one of the drugs used in the CDC protocol. Hesperitin (the form of hesperidin aglycone) and quercetin are known to also act as inhibitors of 3Clpro [26, 27]. Other compounds in guava such as myricetin are known to act as SARS coronavirus helicase inhibitors [28]. The kaempferol has the potential to be a non-competitive inhibitor of 3CLPro and PLpro as well as quercetin [29]. Another interesting thing is that kaempferol acts as a modulator of autophagy, which can be utilized in strategies to inhibit SARS-COV-2 virus.

Conclusions

Based on the molecular docking analysis, it was found there are two potential compounds from *Psidium guajava* that showed higher binding affinity score namely gamma sitosterol and peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl). Therefore, the extensive work carried out in this study to understand the interaction of multiple viral proteins and different drug ligands which are discussed for treatment in COVID-19. Proteins important in viral replication were selected in the study because inhibiting these proteins might be useful to block the initiation of infection and chain of replication.

Abbreviations

ACE2: Angiotensin-Converting Enzyme 2; 3CLPro: 3C-like protease; COVID-19: Coronavirus Disease 2019; MPro: Main protease; PDB: Protein Data Bank; PLPro: Papain-like Protease; RBD: Receptor Binding Domain; RMSD: Root Mean Square Deviation; SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus 2.

Declarations

Funding

This research funded by Universitas Indonesia Grant year 2020.

Authorship contribution statement

Fadilah: Conceptualization, Investigation, Methodology, Software, Validation, Data curation, Supervision. **Linda Erlina:** Conceptualization, Investigation, Resources, Formal analysis, Visualization, Writing - original draft. **Rafika Indah Paramita:** Conceptualization, Methodology, Formal analysis, Data curation. **Khaerunissa Anbar Istiadi:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Raden Rara Diah Handayani:** Conceptualization and Supervision.

Declaration of competing interest

The authors declare “No conflict of interest”.

Acknowledgement

All authors are thankful to Universitas Indonesia to give us grant to complete this research.

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Table 1

Due to technical limitations, Table 1 is only available as a download in the supplemental files section

Figures

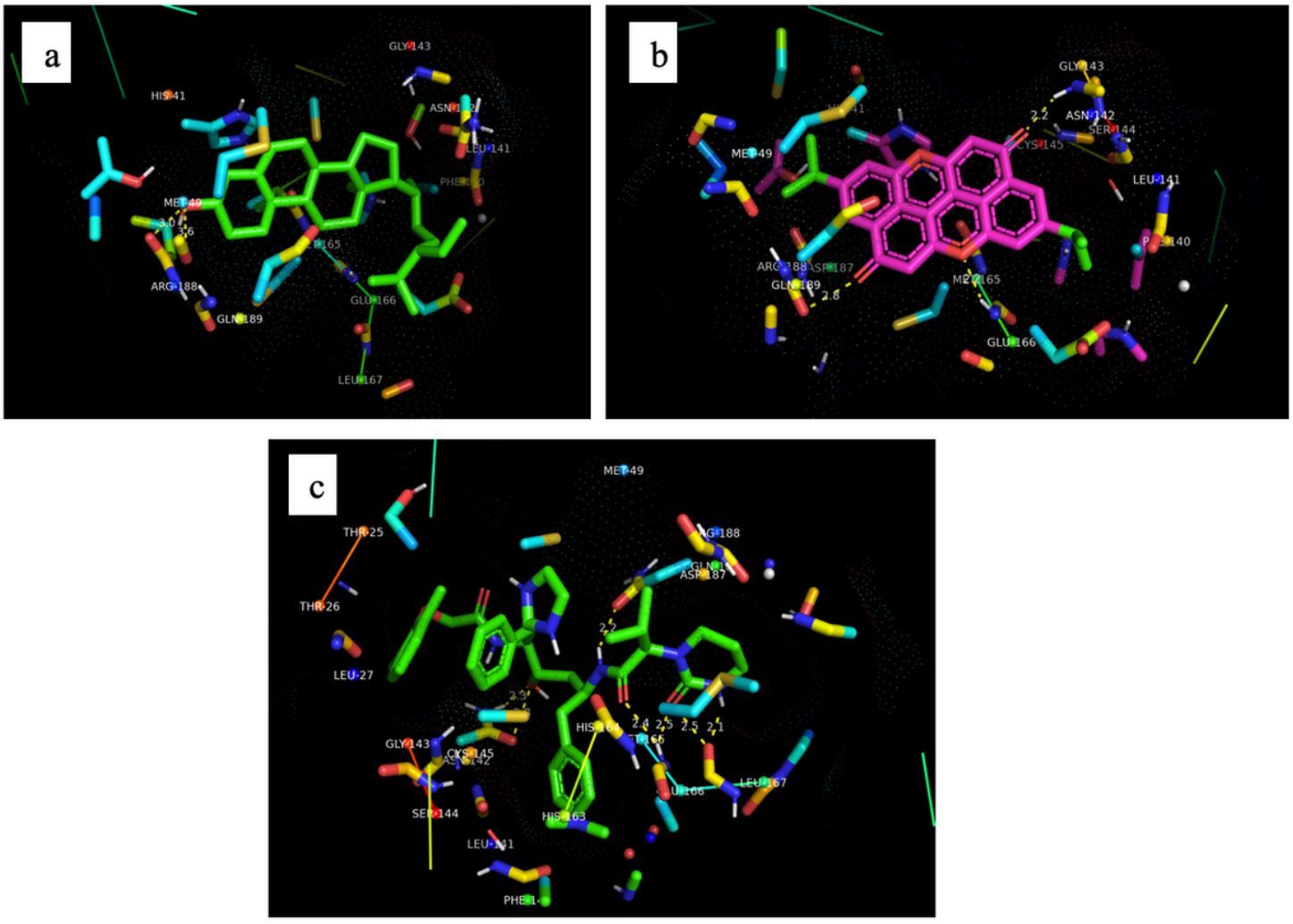

Figure 1

Amino acid interaction 3CL Pro with a. gamma sitosterol, b. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and c. lopinavir

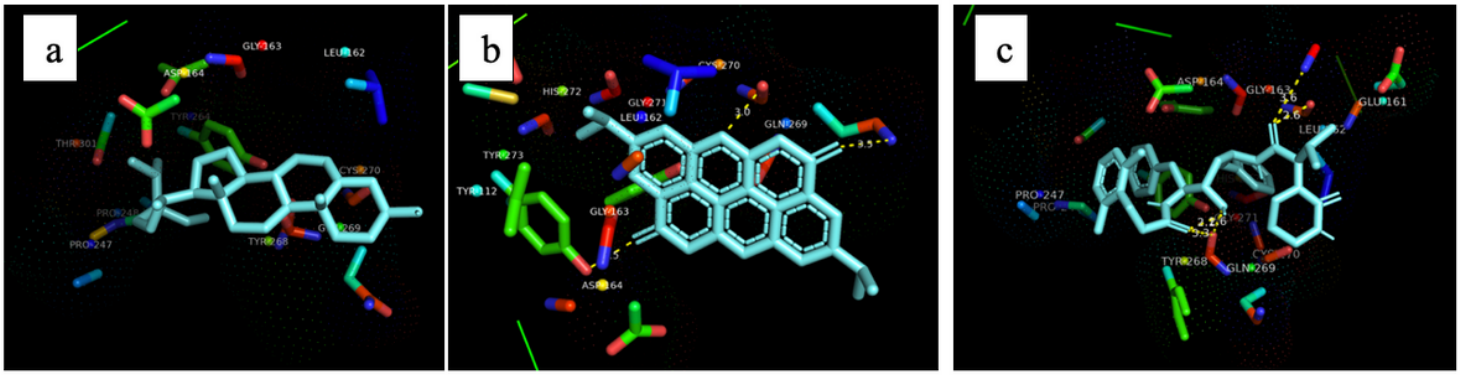

Figure 2

Amino acid interaction PL Pro with a. gamma sitosterol, b. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and c. lopinavir

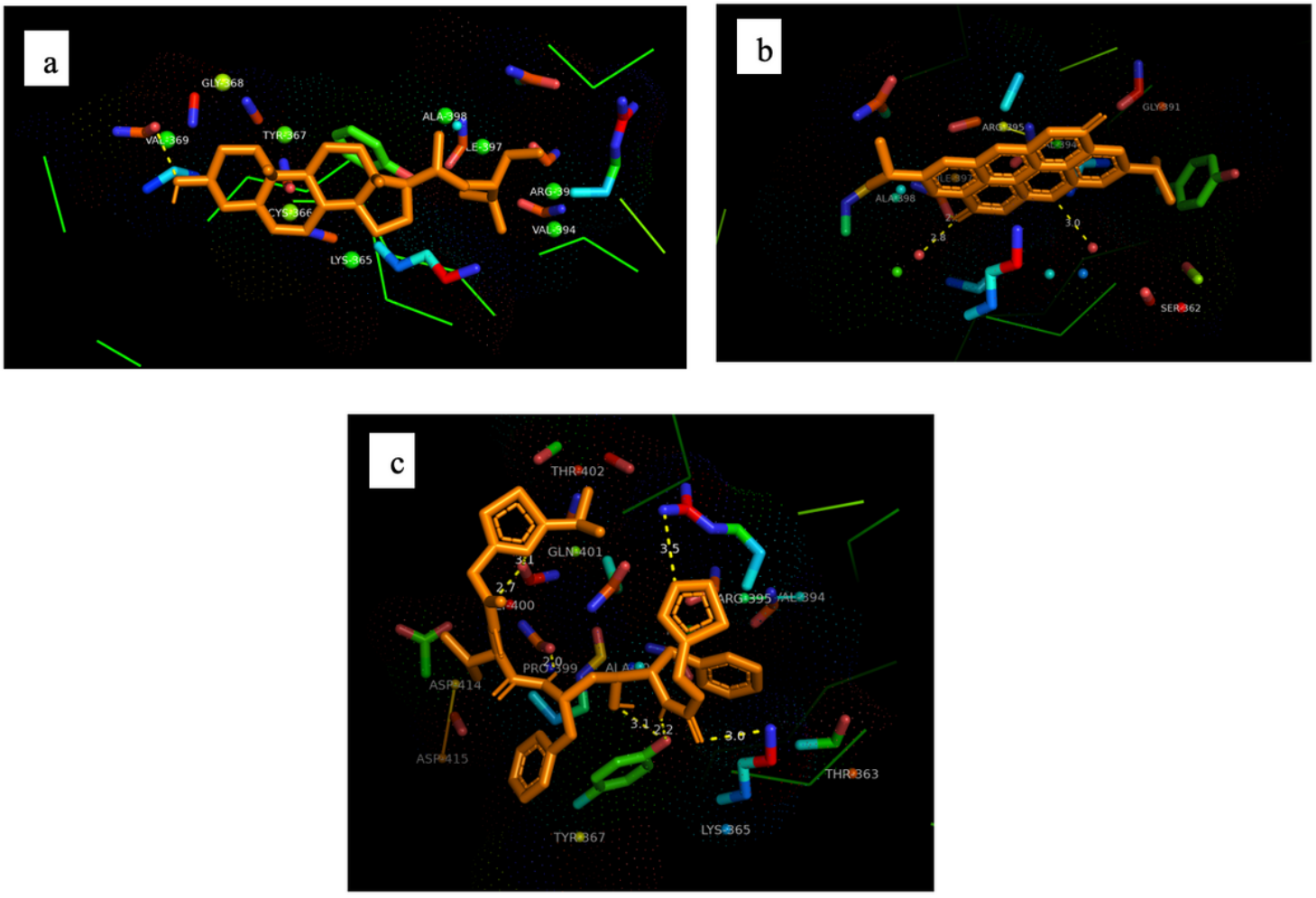

Figure 3

Amino acid interaction Spike with a. gamma sitosterol, b. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and c. ritonavir

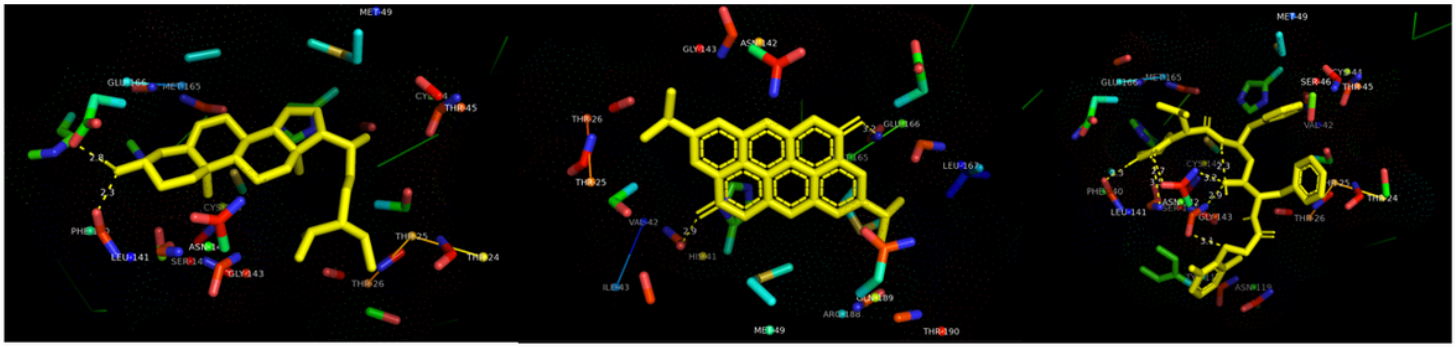

Figure 4

Amino acid interaction M Pro with gamma sitosterol (left), peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) (middle) and lopinavir (right)

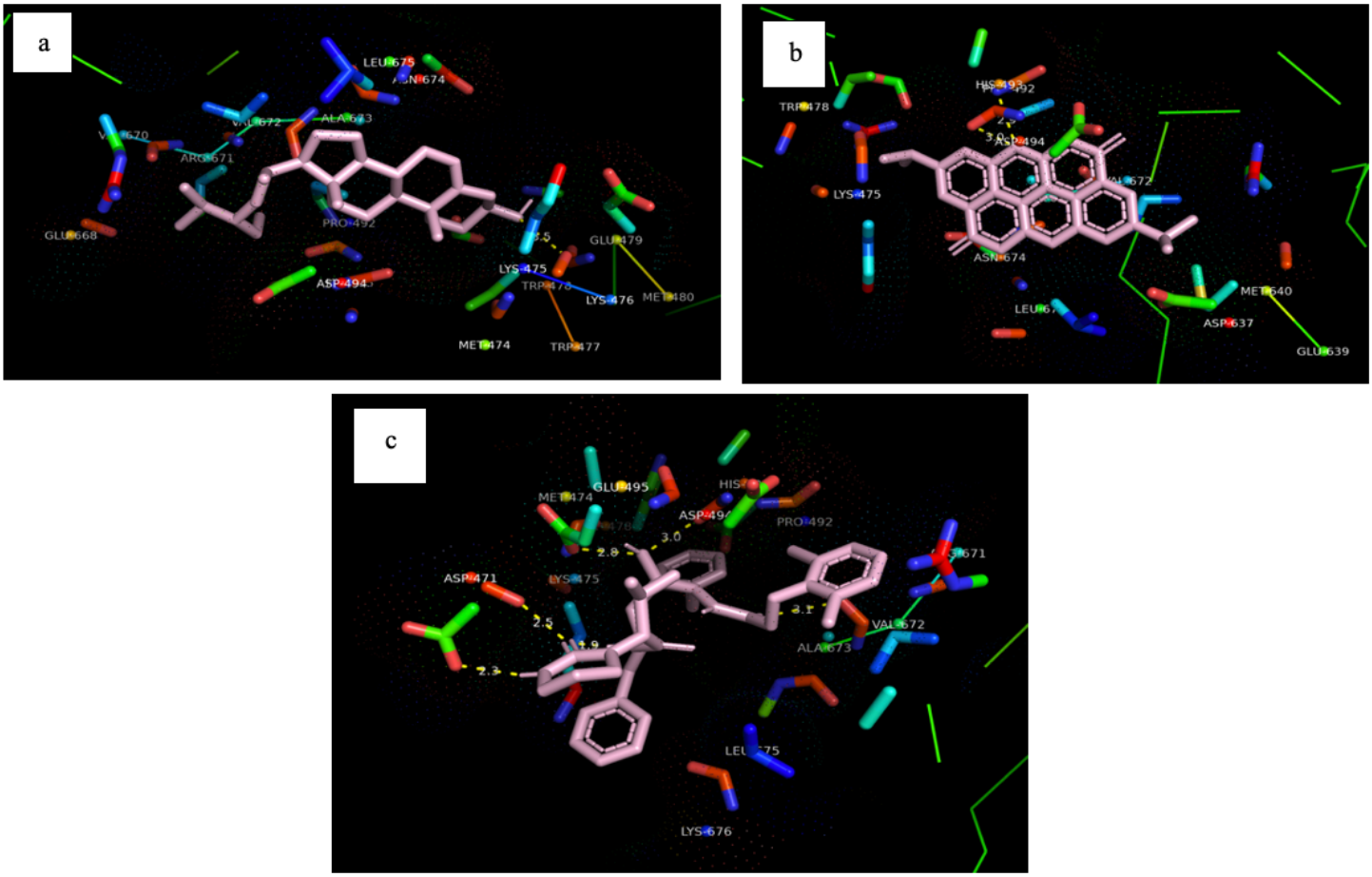

Figure 5

Amino acid interaction ACE2 with a. gamma sitosterol, b. peri-xanthenoxanthene-4,10-dione,2,8-bis (1-methylethyl) and c. lopinavir

Supplementary Files

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- Table1.docx