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In Silico Identification of Propolis Compounds Potential as COVID-19 Drug Candidates Against SARS-CoV-2 Spike Protein

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Abstract. Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global health issue resulting in mortality and morbidity across the world. There is an urgent need to find treatments to inhibit virus infections and their consequences. Propolis compounds are predicted to have interactions with the SARS-CoV-2 protein since it has various phytochemicals that have been used in medicine. Here, we conducted *in silico* study to analyze the interaction between propolis compounds and SARS-CoV-2 spike protein by performing molecular docking. The target protein of this research is the crystal structure of the SARS-CoV-2 spike receptor-binding domain (RBD) bound with ACE2 (PDB ID: 6M0J). The ligand of this study is the bioactive compounds from Propolis of *Tetragonula sapiens.* The docking analysis revealed that Broussoflavonol F and Glyasperin A were the most promising propolis compounds that potentially block the binding of the SARS-CoV-2 spike protein to the host ACE2 receptor, with the binding affinity of -7.6 kcal/mol and -7.3 kcal/mol and the geometric score of 4582 and 4382, respectively. Based on this finding, those compounds are the potential to be developed as COVID-19 drug candidates.

Keywords: COVID-19; Molecular docking; Propolis compounds; SARS-CoV-2 spike protein; *Tetragonula sapiens*

1. Introduction

The respiratory infectious disease that appeared in late December 2019 in Wuhan, China, has spread widely to other countries and has become a global issue. On February 11, 2020, World Health Organization (WHO) named this disease Coronavirus disease 2019 (COVID-19) and declared this case a pandemic on March 11, 2020. Epidemiological investigations revealed that COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Coronavirus belongs to *Coronaviridae* family and *Orthocoronavirinae* subfamily Wu, Chen, and Chan (2020). Based on phylogenetic analysis,

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SARS-CoV- 2 is related to severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). Lu *et al.* (2020) reported that SARS-CoV-2 had about 79% sequence identity with SARS-CoV and was less similar to MERS-CoV (sequence identity of 50%). Both SARS-CoV and MERS-CoV were caused by a coronavirus.

The entry of SARS-CoV-2 into the human body is mediated by virus surface spike protein. The spike protein of this virus has a receptor-binding domain (RBD) that recognizes Angiotensin-Converting Enzyme 2 (ACE2) as its receptor (Lan *et al*., 2020). The interaction of SARS-CoV-2 RBD with ACE2 has a higher binding affinity than SARS-CoV RBD, with a less accessible RBD area of SARS-CoV-2. The cell entry of SARS-CoV-2 needs furin pre-activation and is less dependent on target cell protease. These properties make SARS-CoV-2 enter the cell efficiently and transmit from human to human easier than SARS-CoV (Shang *et al*., 2020).

The number of COVID-19 cases is growing rapidly and causing problems in various sectors (Al-Doori *et al*., 2021; Asvial, Mayangsari, and Yudistriansyah, 2021). Finding alternative therapeutic candidates is urgently needed. Several studies revealed that chloroquine and hydroxychloroquine might be suggested as potential therapies for COVID-19 patients since they showed antiviral and anti-inflammatory activities (Kearney, 2020; Singh *et al*., 2020), but they were causing renal and hepatic injury as side effects (Gbinigie and Fri, 2020).

For many years, natural products have been contributing to pharmacotherapy as a source of therapeutic agents. One of the potential natural products is propolis, a natural resinous product collected from buds and exudates of certain plants by honey bees (Miyata *et al*., 2019). Various biological activities of propolis have been reported, including antioxidant, anti-inflammatory, antifungal, anticancer, antidiabetic, and antiviral (Dewi *et al*., 2021; Flamandita *et al*., 2020; Sahlan *et al*., 2020; Šabanović *et al*., 2019; Sahlan *et al*., 2019; González-Búrquez *et al*., 2018; Mahadewi *et al*., 2018; Pratami *et al*., 2018). Propolis can exhibit antiviral activity by generating partial blocking of viral penetration, affecting viral replication and causing RNA degradation (Banskota, Tezuka, and Kadota, 2001).

A computational study was conducted to screen the potential pure compounds for the purpose of drug discovery. One of the common methods of virtual screening in drug discovery is molecular docking, a computational approach that is mainly used to forecast the binding affinity and the bound conformations of macromolecule (receptor) and small molecule (ligand) (Trott and Olson, 2010). The important components in a molecular docking program are the docking algorithm, to explore the conformation space of a ligand or protein, and the scoring function, to evaluates the binding modes by considering the binding affinity strength between ligand and protein (Moitessier *et al*., 2008).

This research aims to examine the potential of propolis compounds of *Tetragonula sapiens* as COVID-19 therapy. The target protein of this research is the crystal structure of the SARS-CoV-2 spike receptor-binding domain bound with Angiotensin-Converting Enzyme 2 (ACE2) (PDB ID: 6M0J). The ligand of this research is the bioactive compounds from propolis of *Tetragonula sapiens*. The interaction between bioactive propolis compounds and the crystal structure of SARS-CoV-2 spike protein is determined by molecular docking. It could identify which compounds are bound into the protein's binding site. The propolis compounds potentially being COVID-19 therapy show the lowest molecular docking score toward SARS-CoV-2 spike protein.

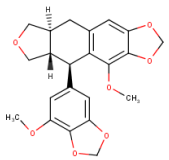
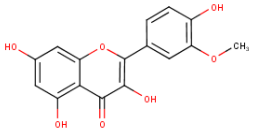
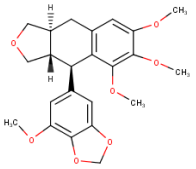
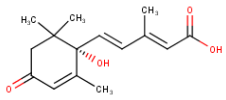
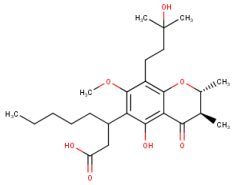
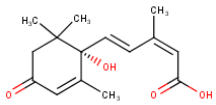
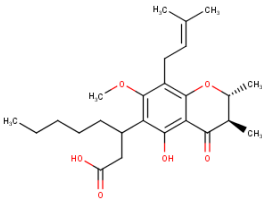
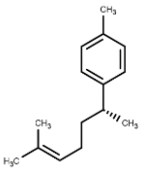
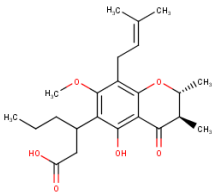
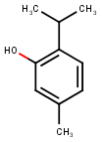
2. Methods

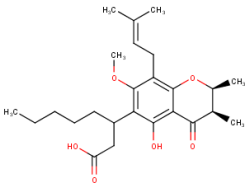
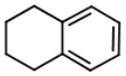
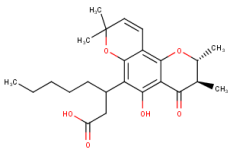
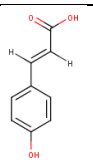
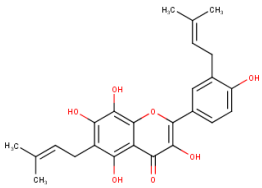
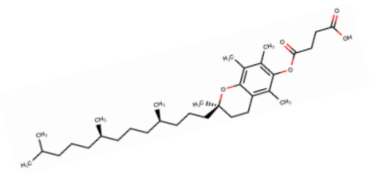
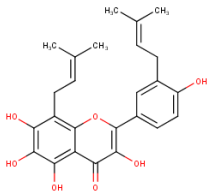
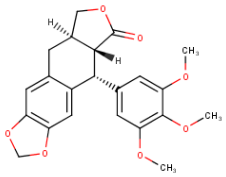
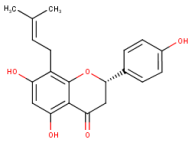
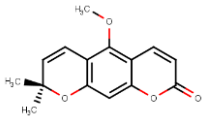
The software used in this research is PyMOL, Autodock Tools 1.5.6 (The Scripps Research Institute, USA), Autodock Vina (The Scripps Research Institute, USA), PatchDock Server, and MarvinSketch (ChemAxon, Budapest, Hungary).

2.1. Propolis Compounds Selection

A total of 20 compounds from the propolis of stingless bees (*Tetragonula sapiens*), here termed as ligands, were obtained from Miyata *et al.* (2020, 2019) publication and suggested from previous studies (Sahlan *et al.*, 2019; Mahadewi *et al.*, 2018). The information about selected compounds was tabulated in Table 1. Each compound was then evaluated based on *Lipinski's Rule of Five* (Lipinski's RO5) and assessed using MarvinSketch. This was used to evaluate the solubility and permeability of propolis compounds as drug candidates. The rule states that poor absorption or permeation of a drug is more probable when it fulfills two or more of the following criteria: molecular weight is greater than 500 g/mol, there are more than five hydrogen bond donors (–NH–, –OH), the number of hydrogen bond acceptors are more than ten, and the partition coefficient (log P) is not greater than five (Lipinski *et al.*, 2012).

Table1 Propolis compounds

Compounds	Molecular Structure	Compounds	Molecular Structure
Sulabiroins A ($C_{22}H_{22}O_7$)		Isorhamnetin ($C_{16}H_{12}O_7$)	
Sulabiroins B ($C_{23}H_{26}O_7$)		(1'S)-2-Trans,4-trans-abscisic acid ($C_{15}H_{20}O_4$)	
2',3'-Dihydro-3'-hydroxypapuanic acid ($C_{25}H_{38}O_7$)		(1'S)-2-Cis,4-trans-abscisic acid ($C_{15}H_{20}O_4$)	
(–)-Papuanic acid ($C_{25}H_{36}O_6$)		Curcumene ($C_{15}H_{22}$)	
(–)-Isocalolongic Acid ($C_{24}H_{34}O_6$)		Thymol ($C_{10}H_{14}O$)	

Compounds	Molecular Structure	Compounds	Molecular Structure
Isopapuanic acid ($C_{25}H_{36}O_6$)		Tetralin ($C_{10}H_{12}$)	
Isocalopolyanic acid ($C_{24}H_{32}O_6$)		P-Coumaric acid ($C_9H_{10}O_3$)	
Glyasperin A ($C_{25}H_{26}O_7$)		α-Tocopherol succinate ($C_{32}H_{52}O_5$)	
Broussoflavonol F ($C_{25}H_{26}O_7$)		Deoxypodophyllotoxin ($C_{22}H_{22}O_7$)	
(2S)-5,7-Dihydroxy-4'-methoxy-8-prenylflavanone ($C_{20}H_{20}O_5$)		Xanthoxyletin ($C_{15}H_{14}O_4$)	

2.2. Protein and Ligand Structure Preparation

The crystal structure of the SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID: 6M0J) was acquired from RCSB Protein Data Bank (http://www.rcsb.org) in the PDB format. The protein structure protein structure has two chains; chain E is SARS-CoV-2 spike protein, and chain A is ACE2. The protein was then separated using PyMOL to get the chain E as a target protein. Furthermore, the 2D structure of 20 propolis compounds was prepared by using MarvinSketch (Csizmadia, 2019) and saved as *.pdb format. The target protein and were ligands then loaded to Autodock Tools 1.5.6 to prepare the *.pdbqt file by adding polar hydrogens and charges.

2.3. Binding Site Determination

Discovering the specific search space in protein involves three criteria; the number of points in x, y, and z dimensions or grid box size, grid box center, and grid spacing. Since the protein structure did not have a co-crystallized ligand inside, the binding domain was obtained by examining the amino acids of the SARS-CoV-2 spike protein that bound to the ACE2 receptor. The grid box mapping parameter considering the existence of amino acids Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe456, Ala475, Phe486, Asn487, Tyr489, Gln493, Gln498, Gly496, Thr500, Asn501, Gly502, Tyr505. Those amino acids contributed to the stability of SARS-CoV-2 RBD and ACE2 complexes (Lan *et al.*, 2020), so the specific search space must contain those amino acids to get binding site coordinates.

2.4. Re-docking

The re-docking step involves separating the native ligand and protein, then docking it back to its place on the protein by setting the size and the center of the search space box (Flamandita *et al*., 2020). Since the protein structure did not have a co-crystallized ligand inside, the redocking was done by docking the ACE-2 back to the SARS-CoV-2 protein structure using PatchDock Server, which is available as a free web service at http://bioinfo3d.cs.tau.ac.il. PatchDock is a molecular docking algorithm based on geometry that aims to perform structure prediction of protein–protein complexes and protein–ligand complexes (Schneidman-Duhovny *et al*., 2005). PatchDock was chosen because of its high-efficiency algorithm, coming out from the local fitting of molecular surface and utilizing the advanced data structure to detect the transformation using Geometric Hashing and Pose Clustering (Duhovny, Nussinov, and Wolfson, 2002).

2.5. Docking and Analysis

We performed protein rigid and ligand flexible molecular docking by AutoDock Vina and PatchDock, using parameters and coordinates that had been obtained from the previous step. AutoDock Vina automatically determines the docking score, also known as binding affinity. The genetic algorithm in AutoDock Vina calculates the affinity or the best conformation of the two molecules binding by adding up all the interactions that contribute to the formation of the binding conformation (Trott and Olson, 2010). Propolis compounds were docked to the protein receptors. The lowest docking score was considered the best conformation used to analyze the ligand-receptor complex interaction.

To perform molecular docking by PatchDock, the molecules had to be uploaded to the server or retrieved from the Protein Data Bank. The patchDock algorithm was similar to assembling a jigsaw puzzle. Two molecules' surfaces were divided into different patches according to the surface shape. These patches were matched with the corresponding generated patterns. Once the patches were identified, they were mapped using the shape-matching algorithm (Schneidman-Duhovny *et al*., 2005). Solution page URL then sent to email address, containing geometric score, interface area size, and desolvation energy of the 20 top solutions.

Interaction profiles of protein-ligand complexes presented by PyMOL, a Python-based software widely used for the three-dimensional (3D) visualization of proteins, nucleic acids, small molecules, electron densities, surfaces, and trajectories (Yuan *et al*., 2017). Here, PyMOL was utilized to identify the interacting residues of docked complexes.

3. Results and Discussion

3.1. Selection of propolis compound

The spike protein that was targeted in this study was presented in the SARS-CoV-2 surface. The virus uses the homotrimeric spike protein to bind to its cellular receptors, comprising an S1 subunit and an S2 subunit in each spike monomer on the envelope. The S1 subunit helps the virus in host receptor binding, while the S2 assists the membrane fusion by forming a six-helical bundle via the two-heptad repeat domain. The specific receptor binding domain (RBD) in the S1 subunit interacts with certain areas of ACE2 to infect the host cells (Lan *et al*., 2020; Huang *et al*., 2020). Its important role makes it considered a target for developing COVID-19 therapeutic candidates, specifically the one that blocks the binding of the SARS-CoV-2 spike protein to the ACE2 receptor. PDB ID 6M0J was chosen because it has a SARS-CoV-2 spike protein structure with RBD, which is bound to ACE2.

Table 2 showed that α-tocopherol succinate violated two out of four Lipinski's RO5. Its molecular weight was greater than 500 g/mol, and the calculated log P was more than five. High molecular weight leads to poor solubility, and it decreases the permeability of drug molecules when it penetrates biological membranes through a passive diffusion process (Qiu *et al*., 2016). Meanwhile, drug candidates with high Log P scores tend to be more non-polar and have poorer aqueous permeability (Templeton *et al*., 2015). Based on these violated rules, α-tocopherol succinate was thrown away from the drug candidate.

Table 2 Propolis Compounds Selection Based on Lipinski's RO5

No.	Compounds	Molecular weight (g/mol)	Log P	H-bond acceptor	H-bond donor	Number of Violations
1	Sulabiroins A	398.41	2.74	7	0	0
2	Sulabiroins B	414.45	2.55	7	0	0
3	2',3'-Dihydro-3'-hydroxypapuanic acid	450.57	4.33	7	3	0
4	(–)-Papuanic acid	432.56	5.57	6	2	1
5	(–)-Isocalolongic Acid	404.50	4.78	6	2	0
6	Isopapuanic acid	432.56	5.57	6	2	1
7	Isocalopolyanic acid	416.51	5.03	6	2	1
8	Glyasperin A	438.48	4.84	7	5	0
9	Broussoflavonol F	438.48	4.84	7	5	0
10	(2S)-5,7-Dihydroxy-4'-methoxy-8-prenylflavanone	340.37	4.19	5	3	0
11	Isorhamnetin	316.26	1.78	7	4	0
12	(1'S)-2-Trans,4-trans-abscisic acid	264.32	2.08	4	2	0
13	(1'S)-2-Cis,4-trans-abscisic acid	264.32	2.08	4	2	0
14	Curcumene	202.34	5.19	0	0	1
15	Thymol	150.22	3.42	1	1	0
16	Tetralin	132.21	3.27	0	0	0
17	P-Coumaric acid	164.16	2.12	3	2	0
18	α-Tocopherol succinate	530.79	9.18	4	1	2
19	Deoxypodophyllo toxin	398.41	2.63	6	0	0
20	Xanthoxyletin	258.27	2.01	3	0	0

3.2. Binding site determination

The specific search space in protein contained amino acids bound to the ACE2 receptor. This step was done by using AutoDock Vina. It found that the binding site apparently had a high probability of being located at the coordinates in Table 3. These coordinates then became an area where the propolis compounds bind to the protein.

Table 3 Grid Box Dimension

Coordinates	Grid box size (Å)	Grid box center	Grid spacing (Å)
x	18	- 36.639	
y	38	29.664	1
z	20	3.978	

3.3. Molecular docking result

Propolis compounds of stingless bees (*Tetragonula sapiens*) were docked onto SARS-CoV-2 Spike RBD (6M0J) by AutoDock Vina and PatchDock. The AutoDock Vina simulation obtained nine ligand poses with different docking scores, also known as binding affinity. The pose with the lowest docking score was considered the best conformation with the

strongest binding affinity. The docking score results of propolis compounds towards SARS-CoV-2 spike RBD bound with ACE2 showed that Broussoflavonol F, followed by Glyasperin A, and (2S)-5,7-dihydroxy-4'-methoxy-8-prenylflavanone were the compounds with the lowest docking score with values of -7.6, -7.3, and -7.2 kcal/mol, respectively.

Table 4 Docking result of propolis compounds towards SARS CoV-2 spike RBD

No	Propolis Compounds	AutoDock Vina (kcal/mol)	PatchDock
1	ACE2*	-	12716
2	Broussoflavonol F	**-7.6**	**4582**
3	Glyasperin A	**-7.3**	**4382**
4	(2S)-5,7-dihydroxy-4'-methoxy-8-prenylflavanone	**-7.2**	4056
5	Isocalopolyanic acid	-6.6	3780
6	Isorhamnetin	-6.4	3384
7	Sulabiroins A	-6.2	3908
8	(1'S)-2-trans,4-trans-abscisic acid	-6.2	3056
9	Deoksipodophyllotoksin	-6.1	3794
10	Isocalolongic acid	-6.1	4182
11	(1'S)-2-cis,4-trans-abscisic acid	-6.0	3412
12	Xanthoxyletin	-6.0	3478
13	Curcumene	-6.0	3088
14	Sulabiroins B	-5.9	4262
15	Papuanic acid	-5.9	4290
16	Isopapuanic acid	-5.7	4246
17	2',3'-dihydro-3'-hydroxypapuanic acid	-5.5	**4464**
18	α tocopherol succinate	-5.3	5368
19	Thymol	-5.3	2528
20	p-coumaric acid	-5.0	2426
21	Tetralin	-4.7	2346

*ACE2 bound with SARS-CoV-2 spike receptor-binding domain in 6M0J crystal structure

On the other hand, based on geometry fit and atomic desolvation energy, PatchDock simulation results generated the top 20 solutions, arranged by geometric score. The highest geometric score presented by α tocopherol succinate with a value of 5368. Unfortunately, based on Table 2, α-tocopherol succinate was thrown away from the drug candidate. Hence the propolis compounds with the highest geometric score were Broussoflavonol F, followed by 2',3'-dihydro-3'-hydroxypapuanic acid and Glyasperin A with values of 4582, 4464, and 4382, respectively. Both AutoDock Vina and PatchDock showed that Broussoflavonol F and Glyasperin A could be promising drug candidates for COVID-19. Those compounds were categorized as flavonoids, which have antiviral activity against various types of viruses (Badshah *et al*., 2021; Ninfali *et al*., 2020; Zakaryan *et al*., 2017). Furthermore, the molecular interaction of propolis compounds and SARS-CoV-2 spike protein RBD needs to be evaluated to explore this antiviral activity.

3.4. Propolis and SARS-CoV-2 spike protein interaction

Amino acid residues that comprised molecular interactions of propolis compounds and SARS-CoV-2 spike protein RBD were presented in Table 5. Based on AutoDock Vina simulation, the most promising propolis compounds, as well as ACE2, formed interaction with Lys417, Tyr453, Leu455, Gln493, Gly496, Gln498, Asn501, Gly502, and Tyr505. Supporting this finding, eight residues, Lys417, Tyr449, Tyr453, Leu455, Gly496, Gln498, Asn501, and Tyr505, have been previously reported to be the key binding sites on SARS-CoV-2 spike protein RBD (Lan *et al*., 2020; Wang *et al*., 2020). Those residues were crucial for the affinity of SARS-CoV-2 spike protein RBD to ACE2. As the most promising drug

candidates, Broussoflavonol F and Glyasperin A also formed interaction with Arg403, Tyr495, and Glu406, which did not involve in spike protein RBD and ACE2 complex. Those results were completely different from the PatchDock simulation. Different docking algorithms and scoring functions of each simulation were the most possible reason that lead to different results. AutoDock creates ligand poses by using a genetic algorithm (Trott and Olson, 2010), while the PatchDock algorithm works on the principles of shape complementarity (Duhovny, Nussinov, and Wolfson, 2002).

Table 5 Molecular interactions of various ligands and spike protein RBD

No	Ligands/ Protein	Binding analysis	
		AutoDock Vina	PatchDock
1	ACE2	* Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe456, Ala475, Phe486, Asn487, Tyr489, Gln493, Gly496, Gln498, Thr500, Asn501, Gly502, Tyr505,	Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe456, Ala475, Phe486, Asn487, Tyr489, Gln493, Gly496, Gln498, Thr500, Asn501, Gly502, Tyr505,
2	Broussoflavonol F	Arg403, Glu406, Lys417, Tyr453, Leu455, Gln493, Ser494, Tyr495, Gly496, Phe497, Gln498, Asn501, Gly502, Tyr505, Gln506	Thr345, Arg346, Phe347, Asn440, Asn439, Leu441, Asp442, Ser443, Lys444, Asn448, Tyr449, Asn450, Tyr451, Arg509
3	Glyasperin A	Arg403, Glu406, Lys417, Ile418, Tyr453, Leu455, Gln493, Tyr495, Gly496, Phe497, Gln498, Asn501, Gly502, Tyr505,	Arg346, Thr345, Phe347, Asn439, Asn440, Leu441, Asp442, Ser443, Lys444, Val445, Gly447, Asn448, Tyr449, Asn450, , Pro499,

*Amino acid residues that comprise the ACE2 and spike protein RBD interaction were obtained from Lan *et al.* (2020) publication. Blue residues form hydrogen bonds; Red residues form hydrophobic interactions; Green residues form salt bridge interactions.

PyMOL was used to analyze the interaction between propolis compounds and spike protein RBD. The visual examination results of the two promising propolis compounds, Broussoflavonol F and Glyasperin, are presented in Figure 1. Ligand molecules, represented by sticks structure, showed molecular interaction with polar (blue line structure) and non-polar (red line structure) amino acid residues of SARS-CoV-2 spike protein RBD. The molecular interaction of polar residues and ligands formed hydrogen bonds that are illustrated by yellow dashed lines. Meanwhile, non-polar amino acid residues were considered to form hydrophobic interactions with the ligand.

Most of the molecular interactions of propolis compounds with SARS-CoV-2 spike protein RBD comprise hydrophobic interactions, both AutoDock Vina and PatchDock simulation. This interaction is important to increase the binding affinity between target-drug interfaces; it also keeps the protein folding stable and increases the biological activities of the drug by increasing the number of hydrophobic atoms in the active core (Varma *et al.*, 2010). Meanwhile, hydrogen bond intensified receptor-ligand binding when both donor and acceptor had either significantly stronger or weaker hydrogen bond capabilities than the hydrogen and oxygen atoms in water (Chen *et al.*, 2016).

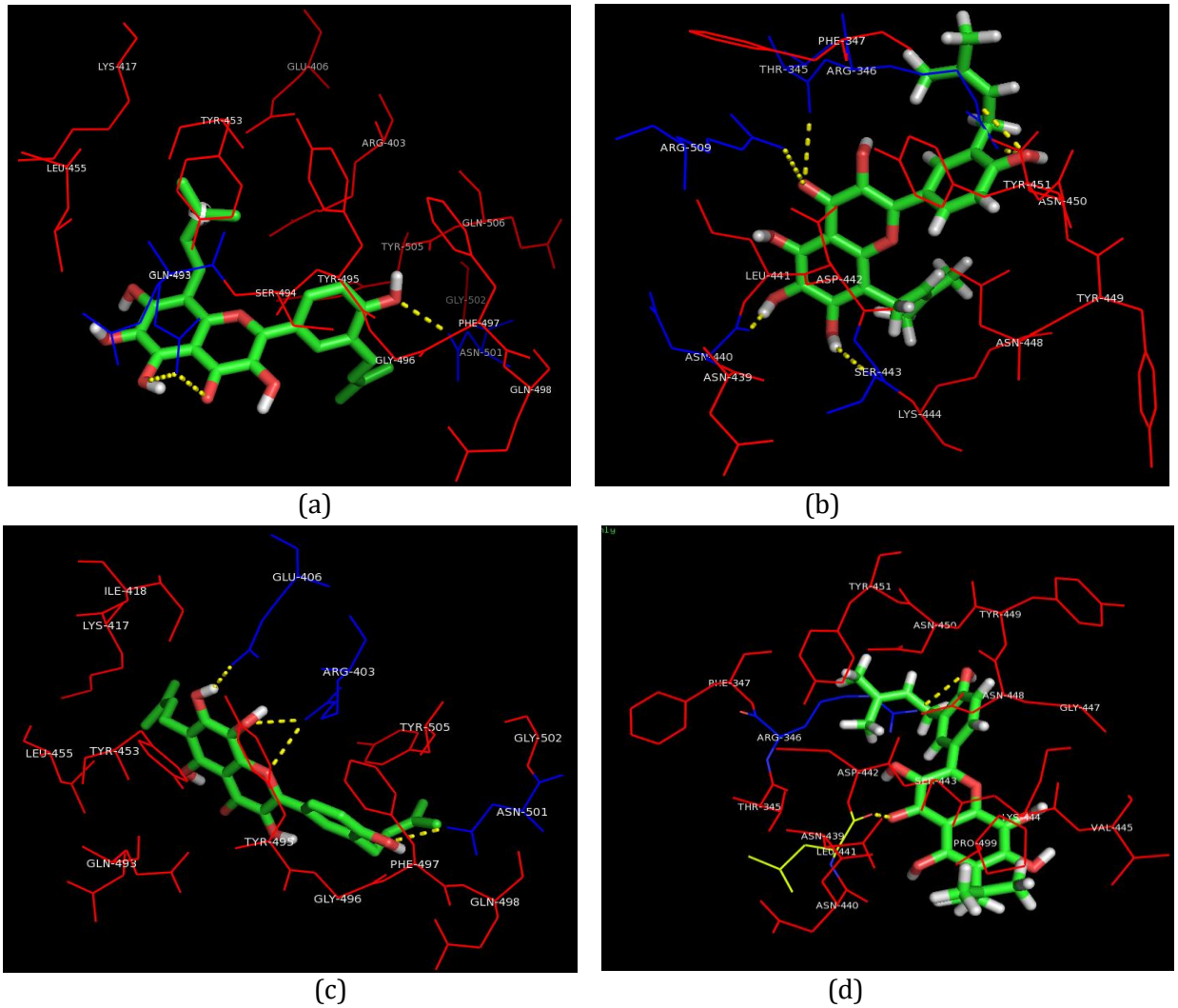


Figure 1 Interaction visualization of spike protein RBD with various ligands. (a) Broussoflavonol F (AutoDock Vina), (b) Broussoflavonol F (PatchDock), (c) Glyasperin A (AutoDock Vina), (d) Glyasperin A (PatchDock)

4. Conclusions

Molecular docking results suggested that propolis compounds of *Tetragonula sapiens* had the potential to be developed as SARS-CoV-2 spike protein inhibitors. Two compounds, namely Broussoflavonol F and Glyasperin A, were the most promising propolis compounds for COVID-19 drug candidates. The study results suggested that these propolis compounds could bind to the key binding site residues of SARS-CoV-2 spike protein and could potentially suppress viral attachment to the host cell. In the present study, Autodock Vina was more accurate in predicting the molecular binding of propolis compounds and SARS-CoV-2 spike protein. Further studies should be conducted to determine the safety of these propolis compounds for COVID-19 therapy.

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