Potential of Plant Bioactive Compounds as SARS-CoV-2 Main Protease (Mpro) and Spike (S) Glycoprotein Inhibitors: A Molecular Docking Study

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Abstract

Background: Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, researchers have been trying to investigate several active compounds found in plants that have the potential to inhibit the proliferation of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the cause of COVID-19. The search for plant-based antivirals against the SARS-CoV-2 is promising, as several plants have been shown to possess antiviral activities against betacoronaviruses (beta-CoVs) **Objective:** The present study aimed to evaluate bioactive compounds found in plants by using a molecular docking approach to inhibit Main Protease (Mpro) (PDB code: 6LU7) and Spike (S) Glycoprotein (PDB code: 6VXX) of SARS-CoV-2. **Methods:** Evaluation was performed on the docking scores calculated using AutoDock Vina as a docking engine. For each compound that was docked, a rule of five was calculated to determine whether a compound with certain pharmacological or biological activities might have chemical and physical properties that would make it an active

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drug orally in humans. Determination of the docking score was done by selecting the conformation of the ligand that has the lowest binding free energy (best pose). As a comparison, nelfinavir (an antiretroviral drug), chloroquine and hydroxychloroquine sulfate (anti-malarial drugs recommended by the FDA as emergency drugs) were used. **Results:** The results showed that hesperidine, cannabinoids, pectolinarin, epigallocatechin gallate, and rhoifolin had better poses than nelfinavir, chloroquine and hydroxychloroquine sulfate as spike glycoprotein inhibitors. Hesperidin, rhoifolin, pectolinarin, and cannabinoids had about the same pose as nelfinavir, but were better than chloroquine and hydroxychloroquine sulfate as $M^{pro}/3CL^{pro}$ inhibitors. These plant compounds have the potential to be developed as specific therapeutic agents against COVID-19. **Conclusion**: Several natural compounds of plants evaluated in this study showed better binding free energy compared to nelfinavir, chloroquine and hydroxychloroquine sulfate which so far are recommended in the treatment of COVID-19.

Keywords

Medicinal plants, M^{pro}, $3CL^{pro}$, spike (S) glycoprotein, COVID-19, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by a new type of transmissible pathogenic human betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of Betacoronaviruses (Beta-CoVs) (Lai et al., 2020; Shereen et al., 2020). As of March 11, 2020, WHO has stated that COVID-19 has been characterized as a pandemic. The World Health Organization (2020), as of 3 April 2020, has reported 932,166 confirmed cases and 46,764 deaths in 206 countries (WHO, 2020). While in Indonesia, the death toll of COVID-19 reached 170 with the number of positive cases of 1,790 people as of 3 April 2020 (COVID-19, 2020).

COVID-19 infection is characterized by symptoms of acute respiratory distress such as fever $38.1^{o}C$ - $39^{o}C$, dry cough, and shortness of breath with an incubation period of about 5 days (average 2-14 days) (Kamps & Hoffmann, 2020). Until now there is no specific therapy or vaccine available to treat and prevent COVID-19 (NCIRD & Diseases, 2020; WHO, 2020). Therefore, there has been an increase in demand for the availability of medicines, vaccines, diagnostics and reagents, all related to COVID-19. This can lead to opportunities for irresponsible people to distribute falsified medical products.

Several agents are being used in clinical trials and protocols based on *in vitro* activity against SARS-CoV-2 or related viruses with limited clinical experience, however, the effectiveness of therapy for any type of drug has not been established (Smith et al., 2020). Xu et al. (2020) examined the effectiveness of tocilizumab (atlizumab, an immunosuppressive drug) in a retrospective analysis with the results such as reduced fever, oxygen demand, radiological features and decreased C-reactive protein (CRP) (Xu et al., 2020). Bian et al. (2020) in an open-labeled clinical trial (concurrent controlled add-on clinical trial) of meplazumab found a median virus clearance time, discharge time, and a better repair time (Bian et al., 2020). As study based on molecular dynamics simulation (MDS) of a docked protein-ligand compound, nelfinavir (a selective inhibitor of HIV protease) was predicted to be COVID-19 drug candidates as the best potential inhibitor against Main Protease (M^{pro}) (Xu et al., 2020). On the other hand, despite little evidence on the effectivity of chloroquine and hydroxychloroquine, these two antimalarial agents has approved by Food and Drug Administration (FDA) for emergency coronavirus treatment (NCIRD, 2020).

Because COVID-19 is a new disease with serious global health problems, research is still needed, including finding specific therapeutic regimens to overcome the morbidity and mortality it causes. Plant is one of the medicinal active compound sources that have been widely used to treat disease caused by microbes (Estevam et al., 2015; Ningsih et al., 2019; Nuraskin et al., 2020). There are many plant bioactive compounds reported to have activities as antifungal (Sardi et al., 2013), antibacterial (Nuraskin et al., 2019; Pratiwi et al., 2015; Rahmad et al., 2019), and antiviral (Calland et al., 2012; Hu et al., 2013). The natural products that have been reported to have antiviral activity can be used as a starting point in finding potential bioactive compound candidates against SARS-CoV-2. Molecular docking can be used to predict how receptor protein interact with bioactive compounds (ligands) (Earlia et al., 2019a; Earlia et al., 2019b). Several previous studies have been performed to investigate bioactive compounds in plants that have the potential to inhibit the proliferation of viruses (Khaerunnisa et al., 2020; Shaghaghi, 2020; ul Qamar et al., 2020). A recent study reported that nelfinavir (a selective inhibitor of HIV protease) was predicted by using molecular docking to be COVID-19 drug candidate as the best potential inhibitor against Main Protease (M^{pro}) (Xu et al., 2020).

Referring to the importance of early screening for the potential of bioactive compounds to find drug candidates or prevention of viral infections, this study aimed to evaluate various bioactive compounds found in several plants known by the community with

a molecular docking approach. The results of the study are expected to be one of the references for further research in finding specific regimens to overcome COVID-19.

Methods

Determination of ligands

The compounds to be docked (ligands) are active compounds from plants that have been known to have antiviral activities. These compounds are quinine, cannabinoids, hesperidin, rhoifolin, pectolinarin, morin, epigallocatechin gallate, herbacetin, ethyl cholate, kaempferol, tangeretin, chalcone, nobiletin, bis (3,5,5-trimethylhexyl) phthalate, 6-gingerol, 6-shogaol, hydroxychloroquine sulfate, myristicin, and eugenol.

Determination of receptors

Two SARS-CoV-2 proteins were chosen as drug discovery targets : Main Protease (M^{pro}) (PDB code: 6LU7) and Spike Glycoprotein (S) (PDB code: 6VXX).

Ligand and receptor preparation

Three-dimensional (3D) structures M^{pro} (3C-like protease - 3CL^{pro}) of SARS-CoV-2 were retrieved from Protein Data Bank (http://www.rcsb.org//pdb) in .pdb formats. These proteins were served as receptors in docking process. The files were opened using BIOVIA Discovery Studio Visualizer 2020. Water molecules and ligand that were still attached to the receptor were removed, and the receptor was stored in the .pdb format. Next, using Autodock Tools, polar hydrogen atoms were added to the receptors. Next, polar hydrogen atoms were added to the receptors. The file was saved in .pdbqt format.

Ligand structures were obtained from the PubChem site (http://pubchem.ncbi.nlm.nih.gov). The search was done by entering the name of the ligand in the search option. Each ligand's file was downloaded and saved. Files in the .sdf format were converted to .pdb using Open Babel. The .pdb format ligand was opened using the Autodock Tools tool. Torque adjustment was done by detecting root and adjusted as desired. The file was saved in .pdbqt format. Properties of active compounds were calculated using Lipinski's rule of five calculated on SWISSADME prediction (http://www.swissadme.ch/) (Lipinski, 2004).

Active site determination

The location of the amino acids as active sites in the receptor region where the ligand was docked was determined using Autodock Tools. For this reason, a three-dimensional map of the gridbox was made in the receptor region where the ligand was docked. Determination of this map can be based on the type of docking used. A three-dimensional map was made as wide as the size of the receptor (Spike glycoprotein) itself so that the ligand was likely to be docked to all parts of the receptor (blind docking). In $M^{pro}/3CL^{pro}$ docking, the three-dimensional map was only the size of the area to be docked (targeted docking).

Receptor-ligand docking

The docking was performed using Autodock Vina. Ligands and receptors that have been saved in the .pdbqt format were copied into the Vina folder. Then the vina configuration file was typed into notepad, saved with the name 'conf.txt'. Vina program was run through command prompt.

Analysis and visualization

The results of the docking calculation were shown in the output in notepad format. Determination of the docking conformation of the ligand was done by selecting the pose with the highest affinity (most negative Gibbs free energy).

Results

The estimation of free energies of binding between potential inhibitors and receptors was calculated using a docking experiment. Table 1 shows the Lipinski's Rule of Five (RO5) of the docking compounds.

Table1. Lipinski's Rule of Five (RO5) of SARS-CoV-2 $M^{pro}/3CL^{pro}$ and S protein potential inhibitors

Compounds	Molecular Formula	Lipinski's Rule of Five	
		Properties	Value
Nelfinavir	$C_{32}H_{45}N_3O_4S$	Molecular weight (<500 g/mol)	567.78
		LogP (<5)	4.41
		H-bond donor (<5)	4
		H-bond acceptor (<10)	5
		Violation	1
		Meet RO5 criteria	Yes

Chloroquine	$C_{18}H_{26}ClN_3$	Molecular weight (<500 g/mol)	319.87
		LogP (<5)	4.15
		H-bond donor (<5)	1
		H-bond acceptor (<10)	2
		Violation	0
		Meet RO5 criteria	Yes
Hydroxy-chloroquine sulfate	$C_{18}H_{28}ClNO_5S$	Molecular weight (<500 g/mol)	439.95
		LogP (<5)	2.13
		H-bond donor (<5)	4
		H-bond acceptor (<10)	7
		Violation	0
		Meet RO5 criteria	Yes
Hesperidin	$C_{28}H_{34}O_{15}$	Molecular weight (<500 g/mol)	610.56
		LogP (<5)	-1.06
		H-bond donor (<5)	8
		H-bond acceptor (<10)	15
		Violation	3
		Meet RO5 criteria	No
Cannabinoids	$C_{42}H_{60}O_4$	Molecular weight (<500 g/mol)	628.92
		LogP (<5)	9.12
		H-bond donor (<5)	3
		H-bond acceptor (<10)	4
		Violation	2
		Meet RO5 criteria	Yes
Pectolinarin	$C_{29}H_{34}O_{15}$	Molecular weight (<500 g/mol)	622.57
		LogP (<5)	-0.09
		H-bond donor (<5)	7
		H-bond acceptor (<10)	15
		Violation	3
		Meet RO5 criteria	No
Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	Molecular weight (<500 g/mol)	458.37
		LogP (<5)	0.95
		H-bond donor (<5)	8
		H-bond acceptor (<10)	11
		Violation	2
		Meet RO5 criteria	Yes
Rhoifolin	$C_{27}H_{30}O_{14}$	Molecular weight (<500 g/mol)	578.52
		LogP (<5)	-0.81
		H-bond donor (<5)	8
		H-bond acceptor (<10)	14
		Violation	3
		Meet RO5 criteria	No
Morin	$C_{15}H_{10}O_7$	Molecular weight (<500 g/mol)	302.24
		LogP (<5)	1.2
		H-bond donor (<5)	5
		H-bond acceptor (<10)	7
		Violation	0
		Meet RO5 criteria	Yes

Kaempferol	$C_{15}H_{10}O_6$	Molecular weight (<500 g/mol)	286.24
		LogP (<5)	1.58
		H-bond donor (<5)	4
		H-bond acceptor (<10)	6
		Violation	0
		Meet RO5 criteria	Yes
Herbacetin	$C_{15}H_{10}O_7$	Molecular weight (<500 g/mol)	302.24
		LogP (<5)	1.33
		H-bond donor (<5)	5
		H-bond acceptor (<10)	7
		Violation	0
		Meet RO5 criteria	Yes
Ethyl Cholate	$C_{26}H_{44}O_5$	Molecular weight (<500 g/mol)	436.62
		LogP (<5)	3.5
		H-bond donor (<5)	3
		H-bond acceptor (<10)	5
		Violation	0
		Meet RO5 criteria	Yes
Quinine	$C_{20}H_{24}N_2O_2$	Molecular weight (<500 g/mol)	324.42
		LogP (<5)	2.81
		H-bond donor (<5)	1
		H-bond acceptor (<10)	4
		Violation	0
		Meet RO5 criteria	Yes
Nobiletin	$C_{21}H_{22}O_8$	Molecular weight (<500 g/mol)	402.39
		LogP (<5)	3.02
		H-bond donor (<5)	0
		H-bond acceptor (<10)	8
		Violation	0
		Meet RO5 criteria	Yes
Tangeretin	$C_{20}H_{20}O_7$	Molecular weight (<500 g/mol)	372.37
		LogP (<5)	3.02
		H-bond donor (<5)	0
		H-bond acceptor (<10)	7
		Violation	0
		Meet RO5 criteria	Yes
Chalcone	$C_{15}H_{12}O$	Molecular weight (<500 g/mol)	402.39
		LogP (<5)	3.30
		H-bond donor (<5)	0
		H-bond acceptor (<10)	1
		Violation	0
		Meet RO5 criteria	Yes
6-Gingerol	$C_{17}H_{26}O_4$	Molecular weight (<500 g/mol)	294.38
		LogP (<5)	3.02
		H-bond donor (<5)	2
		H-bond acceptor (<10)	4
		Violation	0
		Meet RO5 criteria	Yes

Bis(3,5,5-trimethylhexyl) phthalate	$C_{26}H_{42}O_4$	Molecular weight (<500 g/mol)	418.61
		LogP (<5)	6.47
		H-bond donor (<5)	0
		H-bond acceptor (<10)	4
		Violation	1
		Meet RO5 criteria	Yes
Myristicin	$C_{11}H_{12}O_3$	Molecular weight (<500 g/mol)	192.21
		LogP (<5)	2.49
		H-bond donor (<5)	0
		H-bond acceptor (<10)	3
		Violation	0
		Meet RO5 criteria	Yes
Eugenol	$C_{10}H_{12}O_2$	Molecular weight (<500 g/mol)	164.20
		LogP (<5)	2.25
		H-bond donor (<5)	1
		H-bond acceptor (<10)	2
		Violation	0
		Meet RO5 criteria	Yes
6-Shogaol	$C_{17}H_{24}O_3$	Molecular weight (<500 g/mol)	176.37
		LogP (<5)	3.76
		H-bond donor (<5)	1
		H-bond acceptor (<10)	0
		Violation	0
		Meet RO5 criteria	Yes

Table 2 shows the results of docking between the selected compounds with $M^{pro}/3CL^{pro}$ and S protein. The docking results showed that some compounds from plants which had better binding positions with S protein compared to nelfinavir were hesperidine, cannabinoids, pectolinarin, epigallocatechin gallate, and rhoifolin. Other compounds tend to be better positioned compared to chloroquine and hydroxychloroquine sulfate, except for 6-Shogaol. Binding poses to $M^{pro}/3CL^{pro}$ that were better or equivalent to nelfinavir were hesperidin, rhoifolin, and pectolinarin. Some compounds showed better binding poses than chloroquine and hydroxychloroquine on $M^{pro}/3CL^{pro}$.

Table 2. Molecular docking analysis of several plant compounds against S protein (6VXX) and $M^{pro}/3CL^{pro}$ (6LU7)

Ligand Properties	PubChem CID	Binding Energy With Protein 6VXX	Binding Energy With Protein 6LU7
Nelfinavir	64143	-8.8	-8.2
Hydroxychloroquine sulfate	12947	-7.3	-6.6
Chloroquine	2719	-6.1	-5.3
Hesperidin	10621	-10.4	-8.3

Cannabinoids	9852188	-10.2	-8
Pectolinarin	168849	-9.8	-8.2
Epigallocatechin gallate	65064	-9.8	-7.8
Rhoifolin	5282150	-9.5	-8.2
Morin	5281670	-8.8	-7.8
Kaempferol	5280863	-8.5	-7.8
Herbacetin	5280544	-8.3	-7.2
Ethyl Cholate	6452096	-8.1	-6.7
Nobiletin	72344	-8.1	-6.4
Tangeretin	68077	-7.9	-6.5
Chalcone	637760	-7.5	-6.2
Quinine	3034034	-7.5	-6.9
6-Gingerol	442793	-6.3	-5.8
Bis(3,5,5-trimethylhexyl) phthalate	34277	-6.1	-5.6
Myristicin	4276	-6.1	-5.3
Eugenol	3314	-6.1	-5.4
6-Shogaol	5281794	-5.5	-5.8
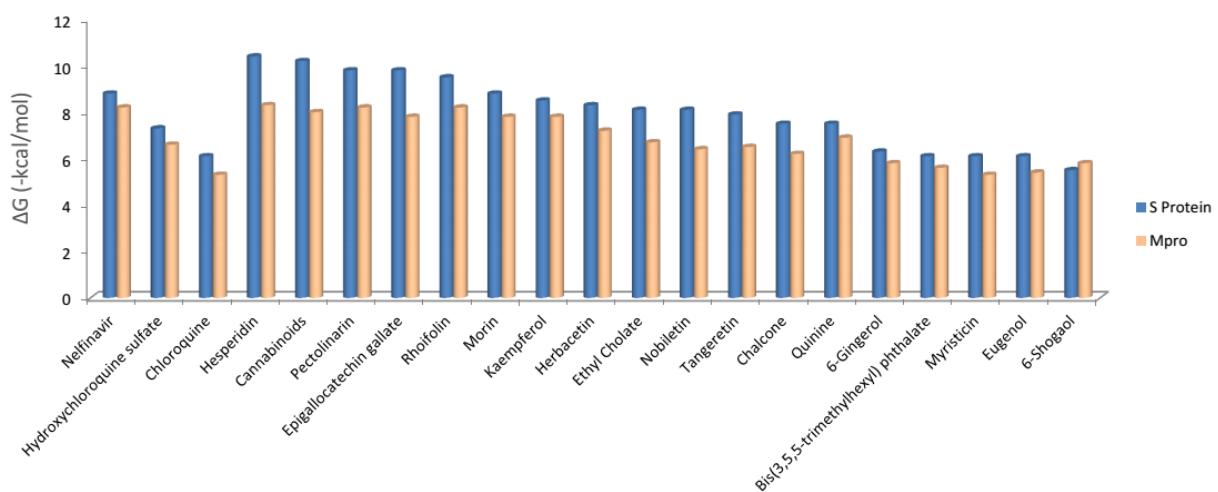
Figure 1. Histogram showing the energy binding value of ΔG (-kcal/mol) of S protein and $M^{pro}/3CL^{pro}$ with several inhibitor compound candidates

The list of plants that have active compounds used as ligands is presented in Table 3. It can be seen that Citrus fruit has many active compounds which are potential as anti-SARS-CoV-2, including hesperidin, rhoifolin, nobiletin, tangeretin, and chalcone. From this table it can be seen that only pectolinarin, epigallocatechin gallate, myristicin and eugenol have high bioavailability when administered orally.

Table 3. List of plants that have active compounds used as ligands and their bioavailability

Compounds	Oral Bioavailability	Sources
Hesperidin	Low	Citrus fruit (*Citrus* spp.), Peppermint (*Mentha* spp.), Yellow Toadflax (*Linaria vulgaris*)
Cannabinoids	Low	Marijuana (*Cannabis* spp.)
Pectolinarin	High	Plume thistles (*Cirsium* spp.), Yellow toadflax (*Linaria vulgaris*)
Epigallocatechin gallate	High	Tea (*Camellia sinensis*) (green tea), skin of Apple (*Malus domestica*), Plum (*Prunus domestica*), Onion (*Allium cepa*), Hazelnut (*Corylus avellana*)
Rhoifolin	Low	Rhus plant (*Rhus succedanea*), Bitter orange (*Citrus aurantium*), Bergamot (*Citrus bergamia*), Grapefruit (*Citrus paradisi*), Lemon (*Citrus limon*), Lablab beans (*Lablab purpureus*), Tomato (*Lycopersicon esculentum*), Artichoke (*Cynara scolymus*), Bananas (Musa spp.), Grape (*Vitis vinifera*)
Morin	Very low	Osage orange (*Maclura pomifera*), Almond (*Prunus dulcis*), Old fustic (*Chlorophora tinctoria*), Guava (*Psidium guajava*)
Kaempferol	Low to good	Kale (*Brassica oleracea* var. *sabellica*), Beans (*Phaseolus vulgaris*), Tea (*Camellia sinensis*), Spinach (*Spinacia oleracea*), Broccoli (*Brassica oleracea* var. *Italica*)
Herbacetin	Good	Golden root (*Rhodiola* spp.), Gossypium (*Gossypium hirsutum*), Common horsetail (*Equisetum arvense*), Common boneset (*Eupatorium perfoliatum*)
Ethyl Cholate	N/A	Leaf of football fruit / keluak (*Pangium edule*)
Nobiletin	Low	Citrus fruit (*Citrus* spp.)
Tangeretin	Low	Citrus fruit (*Citrus* spp.)
Chalcone	Very good	Citrus fruit (*Citrus* spp.)
6-Gingerol	Low	Fresh Ginger (*Zingiber officinale*)
Bis (3,5,5-trimethylhexyl) phthalate	Low	Leaf of football fruit / keluak (*Pangium edule*)
Myristicin	High	Nutmeg (*Myristica fragrans*)
Eugenol	High	Clove (*Syzygium aromaticum*)
6-Shogaol	Low	Ginger (*Zingiber officinale*)

Discussion

In determining that a compound has the potential as a drug, one of which is to follow the rule of five (RO5). Therefore, each docking compound was checked whether it met the Lipinski's RO5. Some compounds that show violations towards RO5 are nelfinavir (1), hesperidin (3), cannabinoids (2), pectolinarin (3), epigallocatechin gallate (2), rhoifolin (3), and bis(3,5,5-trimethylhexyl) phthalate (1) (Tabel 1). The rule is used for the evaluation the drug-likeness, as well as determination if any certain chemical compound possesses chemical

and physical properties to be used as an active drug which can be consumed orally in humans (Lipinski, 2004). This rule is very useful because it acts as a basis for the prediction of high probability of success or failure of one compound with certain pharmacological or biological activity to be developed as a drug. This rule also suggests that if a compound shows two or more RO5 violations, then the compound shows low solubility or permeability (Benet, Hosey, Ursu, & Oprea, 2016)

Dozens of proteins are coded by coronavirus, some of which are involved in viral replication and entry into cells. Main protease (M^{pro}/3CL^{pro}) is a key enzyme for coronavirus replication (X. Liu & Wang, 2020), and surface Spike (S) glycoprotein (S protein) is an important binding protein for fusion of the virus and cellular membrane via cellular receptor angiotensin-converting enzyme 2 (ACE2) (Song et al., 2018). SARS-Cov-2 is easily transmitted because the S protein on the surface of the virus binds very efficiently to ACE2 on the surfaces of human cells. Therefor, M^{pro}/3CL^{pro} and S protein are ideal targets for drug design and development.

Efforts have been made globally to obtain vaccines or drugs for the prevention or treatment of COVID-19 infections. So far, remdesivir is the most promising COVID-19 drug, although the FDA has approved the use of chloroquine and hydroxychloroquine. Coutard et al. (2020) suggested finding an inhibitor for furin, because the S protein sequence has a specific furin-like cleavage (Coutard et al., 2020). In addition, some researchers have targeted 3CL^{pro} (3-chymotrypsin-like protease) which is also one of the main proteases of SARS-CoV-2 (Qamar et al., 2020; Wu et al., 2020). The function of this main protease together with M^{pro} is to form a viral replication complex. So targeting one or both of these main proteases will inhibit the replication of the virus.

The results of this study aimed at predicting the inhibition of compounds found in some plants against M^{pro} and S proteins have revealed several results showing that these these compounds have a better docking pose than nelfinavir, chloroquin, and hydroxychloroquine sulfate (Tabel 2 and Figure 1). If the results are juxtaposed, the potential candidates to become drugs targeting S protein and M^{pro} are hesperidin, cannabinoids, rhoifolin, pectolinarin, morine, epigallocatechin gallate, and herbacetin. Some of the plants producing compounds which are docked with the target protein can be seen in Table 3. Table 3 also contains information on oral bioavailability of the compounds used as ligands in this analysis. Only a few compounds have high bioavailability when administered orally, i.e. pectolinarin, epigallocatechin gallate, myristicin and eugenol. The low oral bioavailability has become a common problem in drug design, since it may pose failure to a new drug in a clinical trials,

eventhough the compounds have high eficacy in *in vitro* and/or *in vivo* tests (Kim et al., 2014). This may incure problem faced by scientists in the pharmaceutical industry (Lin & Wong, 2017). Therefore, oral bioavailability of a compound is essential to be taken into account when predicting the compound as a drug candidate. Oral availability of some compounds can be low if administered together with food.

The major flavanone glycosides in the citrus peel is hesperidin (Brett et al., 2008). Docking scores in this study of S protein and M^{pro} were -10.4 and -8.3, respectively. Utomo et al. (2020) have docked this compound against S protein (-9.6) and M^{pro} (-13.51) (Utomo et al., 2020). Chen et al (2020) revealed that the best hesperidin position against SARS-CoV-2 3C-like protease ($3CL^{pro}$) was -10.1 (Chen et al., 2020). Adem et al. (2020) found that the ability of hesperidin was better than nelfinavir (Adem et al., 2020).

Cannabinoids are active compounds of *Cannabis sativa* and *C. indica*. Docking score of this compound against M^{pro} and S protein was -8 and -10.2, respectively. Besides being known as an anti-herpes simplex virus (Blevins & Dumic, 1980), this compound also has an anti-inflammatory activity (Reiss, 2010). However, some researches show that this compound can increase the pathogenesis of the virus to the host (Liu et al., 2020; Reiss, 2010; Tahamtan et al., 2018).

The docking results using rhoifolin as ligan were -9.5 and -8.2 for S protein and M^{pro}, respectively. Rhoifolin is a flavon that was first discovered in fresh leaves of Rhus succedanea in 1952 (Hattori & Matsuda, 1952). In addition, this compound was also found in *Citrus grandis* (Rao et al., 2011). The results of rhoifolin docking on S protein were -9.5 and M^{pro} was -8.2. The rhoifolin binding score for SARS-CoV $3CL^{pro}$ shows a value of -9.565 (Jo et al., 2020).

The induced-fit docking result of pectolinarin against SARS-CoV $3CL^{pro}$ was -8.054 (Jo et al., 2020). In this study, the best pose between pectolinarin and S protein was -9.8 and -8.2 with M^{pro}. Pectolinarin can be found in Plume thistles (*Cirsium* spp). Morin docking results by Jo et al (2020) against SARS-CoV $3CL^{pro}$ was -8,930. In this study, the best docking scores of morin against S protein and M^{pro} were -8.8 and -7.8, respectively. Almond, Old fustic, and Guava contain high quantity of this compound. Kaempferol can be found in spinach and kale. The best position of kaempferol against S protein was -8.5 and -7.8 against Mpro, while Jo et al. (2020) found that -8,526 was the best binding position of this compound against SARS-CoV $3CL^{pro}$.

Epigallocatechin gallate is found in high quiantity in tea (*Camellia sinensis*), especially in the form of green tea. The best binding position of this compound against S

protein was -9.8 and against M[pro] was -7.8. It has ben reported previously that this compound was able to inhibit the proteolytic activity of SARS-CoV 3CL[pro] (Nguyen et al., 2012). Herbacetin which can be found *Rhodiola* sp. (golden root) has antiviral activity against vesicular stomatitis virus (VSV), a prototype of negative-strand RNA viruses, such as rabies and influenza viruses (Ahmed et al., 2015). The best binding pose of this compound against SARS-3CL[pro] was -9.263 as reported by Jo et al. (2020), while in this study, binding score of -8.3 against S protein and -7.2 against M[pro] were obtained. Jo et al. (2019) also stated that herbacetin might act as an MERS-CoV/3CL[pro] inhibitor (Jo et al., 2019).

In a very limited time, we have been able to assess some potential M[pro] and S protein of SARS-CoV-2 plant-derived inhibitors using molecular docking method. These results are only preliminary screening to facilitate subsequent tests starting from *in vitro* and *in vivo* (in animal models or human clinical trials).

Conclusion

Our study revealed that natural compounds hesperidine, cannabinoids, pectolinarin, epigallocatechin gallate, and rhoifolin had better binding free energies with M[pro] and S protein of SARS-CoV-2. These compounds have a potential as anti-viral phytochemicals that may inhibit the replication of the virus. However, further *in vitro* and later *in vivo* tests are needed to evaluate these potential inhibitors as clinical drugs. The oral bioavailability of several compounds were indicated low, therefore this also needs attention.

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