Evaluation of certain medicinal plants compounds as new potential inhibitors of novel corona virus (COVID-19) using molecular docking analysis

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Abstract

SARS-CoV-2 is a new strain of coronavirus that appeared in China in December 2019, in recent years, great progress has been made in developing new antiviral drugs, and natural products, are important sources of potential and new antiviral drugs. The present study aimed to assess some biologically active compounds present in medicinal plants as potential COVID-19 inhibitors, using molecular docking methods. The Docking study was performed by Molecular Operating Environment software (MOE). About 20 Compounds were screened in this study; these compounds were selected based on classification of their chemical origin and their antiviral activity from literature. These compounds might be used to inhibit COVID-19 infection. The results demonstrate the effectiveness of this screening strategy, which can lead to rapid drug discovery in response to new infectious diseases. The results showed that many compounds isolated from medicinal plants such as; Gallic acid (− 17.45), Quercetin (− 15.81), Naringin (− 14.50), Capsaicin (− 13.90), and Psychotrine (− 13.5) are important sources for novel antiviral drugs targeting COVID-19.

Keywords COVID-19 · Anti-viral · Medicinal plants · Docking study · Sudan

Abbreviations

COVID-19	Corona virus disease-2019
MOE	Molecular Operating Environment software
M.W	Molecular weight
LD_{50}	Lethal dose that inhibit 50%

Introduction

The world faces a severe and acute public health emergency due to the ongoing global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wu and McGoogan 2020). SARS-CoV-2 is a new strain of coronavirus that appeared in China in December 2019 (Guo et al. 2020). Symptoms of COVID-19 can be relatively non-specific and infected people may be asymptomatic. People infected with COVID-19 generally develop signs and symptoms including mild respiratory symptoms and fever, dry cough, fatigue, shortness of breath, and loss of smell on an average of 5–6 days after infection but may range from two to fourteen days. Complications may include pneumonia and acute respiratory distress syndrome which may lead to death (Singhal 2020; Pal et al. 2020). There has been no noticeable progress in managing this disease so far and the patient is being given treatment based on his observable and diagnosed symptom (Organization et al. 2009). Until now, there is no known vaccine or specific antiviral treatment (Sheahan et al. 2020). The Human Genome Project helped to increase the number of new therapeutic targets for drug discovery. Meanwhile, high-throughput protein purification techniques, crystallography, and nuclear magnetic resonance spectroscopy techniques have contributed to the structural details of proteins and protein complexes. These developments allow computational strategies to penetrate in all its aspects (Jorgensen 2004; Bajorath 2002; Langer and Hoffmann 2001; Walters et al. 1998 and Kitchen et al. 2004), such as virtual

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screening techniques (VS) (Gohlke and Klebe 2002) to determine results and methods for improving molecules. Molecular docking, a computational technique used to estimate the affinity of association between two molecules such as ligand–protein and protein–protein. The use of molecular docking became an essential component in drug discovery. These techniques also help in predicting the side and toxic effects of compounds (Bacha et al. 2008). A number of conventional drugs such as chloroquine, hydroxychloroquine, remediffer have been tested and found with a specific therapeutic effect in the laboratory. However, the clinical pharmacological response is not very encouraging and toxicity remains an inevitable problem that causes serious adverse effects (Otitoloju et al. 2020). The lack of a specific treatment for COVID-19 led most researchers in many regions of the world, to use medicinal herbs known in the science of ethnopharmacology as an antiviral (Rajabian and Hosseinzadeh 2020). The development of viral resistance to current

antiviral agents reinforces the need for new effective compounds against viral infections (Chattopadhyay et al. 2009). In this study, some of the active compounds present in some medicinal plants used in Sudan traditional medicine to treat viral diseases were selected based on literature review for docking studies and the interactions of these compounds have been clarified to determine the preferred molecules for the treatment of COVID-19 via the inhibition of SARS-CoV-2 main protease enzyme, and compare the results with the proposed drugs such as chloroquine and hydroxychloroquine. Furthermore, the toxicity of these compounds was performed in order to assess their safety for human use. The study of the crystal structure of therapeutic targets is crucial for knowing how the drugs will be discovered in the future. Alkaloids are a rich source of important chemical compounds which can be used for development of new antiviral agents. Alkaloids have a wide distribution in the plant kingdom and are mainly found in higher plants, some viral diseases can be treated with approved antiviral, but for others they still have no any vaccines or drugs available. Most of the approved antiviral are directly or indirectly related to side effects, which ultimately leads to an increased need to develop antiviral based on natural phytochemicals. Globally, antiviral are shifting toward plant-derived products because they are less toxic and have less chance of developing resistance (Ghildiyal et al. 2020). All selected compounds from different groups were selected based on their chemical origin were used to treat many diseases such as antiviral activity. The present paper aimed to evaluate the antiviral activity of some compounds from medicinal plants against COVID-19 using Molecular Docking Analysis.

Table 2 Molecular docking analysis of several compounds against SARS-CoV-2 main protease

No.	Name	Energy (kcal/mol)	LD_{50} class	Predicted LD_{50} mg/kg
1	Gallic acid	− 17.45	5	2260
2	Quercetin	− 15.81	3	159
3	Naringin	− 14.50	5	2300
4	Capsaicin	− 13.90	2	47
5	Psychotrine	− 13.50	4	480
6	Curcumin	− 12.80	5	4000
7	Plicamine	− 12.75	3	230
8	Narciclasine	− 12.67	3	80
9	Catechin	− 11.48	6	10,000
10	Lycoricidine	− 11.47	4	460
11	Cryptopleurine	− 11.28	3	100
12	Oliverine	− 11.06	4	450
13	Papaverine	− 10.43	3	69
14	Hyoscyamine	− 10.10	3	75
15	Lycorenine	− 9.99	4	795
16	Galantamine	− 9.44	2	19
17	Mesembrine	− 9.43	4	369
18	Cystin	− 8.20	3	156
19	Hydroxychloroquine	− 12.25	4	1240
20	Chloroquine	− 10.04	4	311
	RZG (standard)	− 10.30		

Class I: fatal if swallowed ($LD_{50} \leq 5$ mg/kg), Class II: fatal if swallowed ($5 < LD_{50} \leq 50$ mg/kg)

Class III: toxic if swallowed ($50 < LD_{50} \leq 300$ mg/kg), Class IV: harmful if swallowed ($300 < LD_{50} \leq 2000$ mg/kg), Class V: may be harmful if swallowed ($2000 < LD_{50} \leq 5000$ mg/kg), Class VI: non-toxic ($LD_{50} > 5000$ mg/kg)

RZG: methyl 4-sulfamoylbenzoate

Methodology

Ligands preparation and optimization

Ligands for this study were drawn using ChemDraw Professional 15.0, then three- dimensional structures of ligands were generated by Open babel (O'Boyle et al. 2011) and saved as SDF format for further preparation and molecular docking study.

The COVID-19 receptor preparation and optimization

The crystallographic structure of SARS-CoV-2 main protease (M^{pro}) (PDB ID: 5R80) in complex with Z18197050, was retrieved from protein data bank with a resolution: 1.93 Å. Interactive visualization and analysis of molecular structures were done using MOE and PyMol software for better understanding of protein-ligands interactions.

Geometry optimization and pre-docking procedure

Hydrogens and Gasteiger charges were added and all the hetero-atoms and water molecules were removed from protein structure. The protonated protein initially optimized in order to remove all the bad steric clashes using AMBER99 force field (Cornell et al. 1996), while MMFF94s force field parameters (Halgren 1996) and (Halgren 1999) were performed for small molecules. The protonated and optimized structures were saved for further preparation and analysis. All the minimizations were performed with MOE (grade < 0.001).

Docking strategy and setup

Docking studies were performed by MOE with 10 poses for each ligand (other parameters were kept default). The unnecessary chain was deleted. Ligand interactions were computed for the X-rayco-crystallized protein to reveal the different types of interaction as a validation for the coming docking procedure. The docking was done with the default settings of the MOE–DOCK as following: The scoring function was London d G. & 10 conformers of the ligand were retained with highest and best score by default. The scoring configuration of the ligand–Target complexes was selected on energetic grounds (MM/GBVI); best poses with the lowest binding energy was chosen for each compound.

The docking scores, docking binding energy, and chemical structures of selected ligands were then presented. ProTox (Drwal et al. 2014) a webserver was used for acute oral toxicity prediction based on chemical similarities between compounds with known toxic effects and the presence of toxic fragments. Toxic doses are often given as LD_{50} values in mg/kg body weight, whereas toxicity classes are defined according to the globally harmonized system of classification of labelling of chemicals (Cheng et al. 2012).

Results and discussion

Natural products are among the most important major resources for drug research and development in the past decades, especially for treating infectious diseases. Contagious disease treatment and control is widely demonstrated by effectiveness of medicinal herbs (Bouchentouf and Missoum 2020; Asadbeigi et al. 2014; Bouredja et al. 2020). A large number of diverse chemical structure compounds isolated from medicinal plants possessing antiviral activity and in this study only highly effective compounds were registered (Table 1). Twenty-one compounds were screened for in silico analysis using MOE Docking software. The best compounds interacting with SARS-CoV-2 M^pro are shown in Table 2.

The results showed that the compounds have a rank scores ranged from − 17.45 to − 8.20 kcal/mol. The docking

Table 1 Compounds of medicinal plants screened for antiviral activity targeting COVID-19

No.	Compound	Formula	M.W	Type of compound
1	Gallic acid	$C_7H_6O_5$	170.12 g/mol	Phenol
2	Quercetin	$C_{15}H_{10}O7$	302.23 g/mol	Flavonoid glycoside
3	Naringin	$C_{27}H_{32}O_{14}$	580.5 g/mol	Flavonoid glycoside
4	Capsaicin	$C_{18}H_{27}NO_3$	305.4 g/mol	Pyridine Alkaloid
5	Psychotrine	$C_{28}H_{36}N_2O_4$	464.6 g/mol	Phenyl and phenylpropyl Alkaloid
6	Curcumin	$C_{21}H_{20}O_6$	368.4 g/mol	Phenol
7	Plicamine	$C_{26}H_{26}N_2O_6$	462.5 g/mol	Amaryllidaceae Alkaloid
8	Narciclasine	$C_{14}H_{13}NO_7$	307.25 g/mol	Amaryllidaceae Alkaloid
9	Catechin	$C_{15}H_{14}O_6$	290.27 g/mol	Flavonoid glycoside
10	Lycoricidine	$C_{14}H_{13}NO_6$	291.26 g/mol	Amaryllidaceae Alkaloid
11	Cryptopleurine	$C_{24}H_{27}NO_3$	377.5 g/mol	Phenanthroindolizidine and phenanthroquinolizidine Alkaloid
12	Oliverine	$C_{20}H_{22}ClNO_4$	375.8 g/mol	Aporphinoid Alkaloid
13	Papaverine	$C_{20}H_{21}NO_4$	339.4 g/mol	Benzylisoquinoline Alkaloid
14	Hyoscyamine	$C_{17}H_{23}NO_3$	289.4 g/mol	Tropane Alkaloid
15	Lycorenine	$C_{18}H_{23}NO_4$	317.4 g/mol	Amaryllidaceae Alkaloid
16	Galantamine	$C_{17}H_{21}NO_3$	287.35 g/mol	Amaryllidaceae Alkaloid
17	Mesembrine	$C_{17}H_{23}NO_3$	289.4 g/mol	Tropane ester Alkaloid
18	Cysteine	$C_3H_7NO_2S$	121.16 g/mol	Opium Alkaloid
19	Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	335.9 g/mol	Standard (Alkaloid)
20	Chloroquine	$C_{18}H_{26}ClN_3$	319.9 g/mol	Standard (Alkaloid)

Gallic Acid (ZINC14775732)

Quercetrin (ZINC4175638)

Naringin (ZINC8143604)

Capsaicin (ZINC1530575)

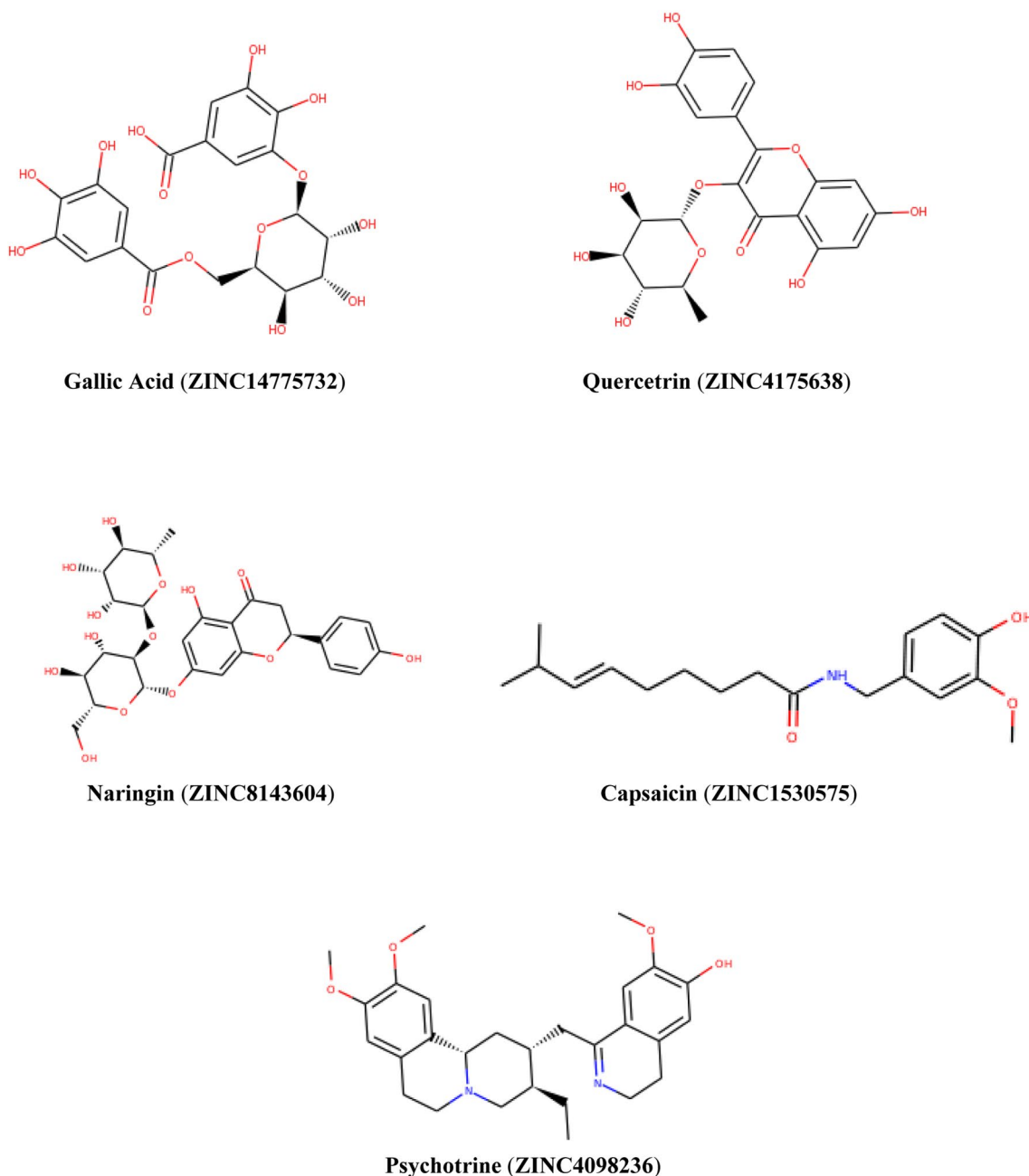**Psychotrine (ZINC4098236)**

Fig. 1 Chemical structure of the top ranked compounds

simulations resulted in five compounds that were assigned as the most potential candidate among the docked ones; the compounds' poses were ranked with respect to their binding energy values. We noted that the inhibition potentials of the Gallic acid (1) are very encouraging. The compounds including Quercetin (2), Naringin (3), Capsaicin (4), and Psychotrine (5) (Fig. 1), have larger inhibition potentials than that of chloroquine as a reference too. The standard was docked to protomer A of the dimeric COVID-19 Mpro (Fig. 2a). The co-crystallized ligand (RZG; methyl 4-sulfamoylbenzoate) is interacting with the enzyme residues in the substrate-binding site located in a cleft between domain I and II (Fig. 2b). Figure 2c shows the interaction of RZG. The other compounds also possess certain inhibition properties against SARS-COV2 M^{pro}.

Gallic acid revealed the highest docking score − 17.45 kcal/mol, the depiction of the key interactions is displayed in Table 1 and Fig. 3d. The compound revealed
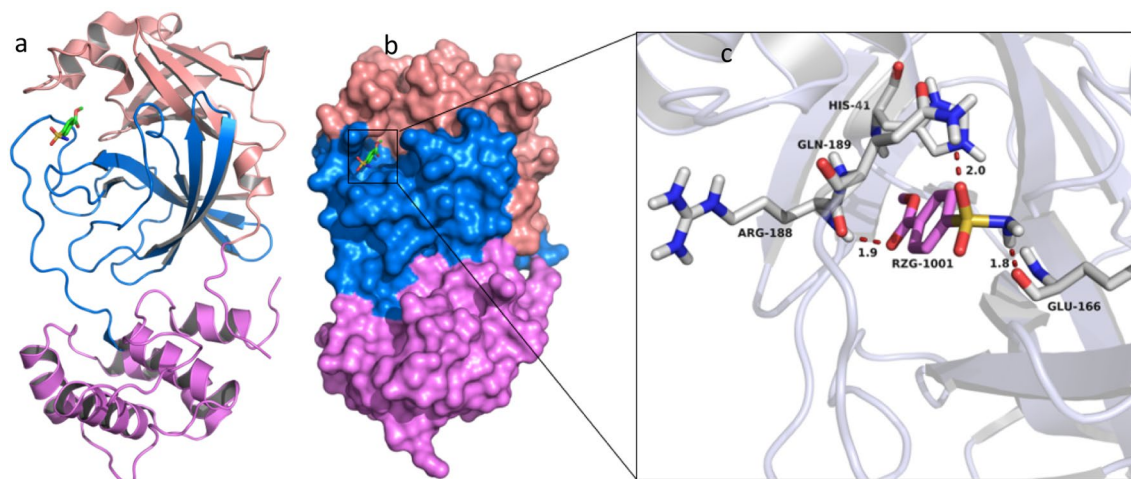
Fig. 2 The crystal structure of COVID-19 M^pro in complex with RZG (methyl 4-sulfamoylbenzoate). **a** Cartoon representation of protomer A of the dimeric M^pro-inhibitor complex. **b** Surface representation of the Protomer A. Domain I is in purple, domain II is in blue, and domain III is in salmon-red. RZG is presented as green sticks. **c** A close view of the substrate-binding pocket. The key residues forming the binding pocket are shown as grey sticks
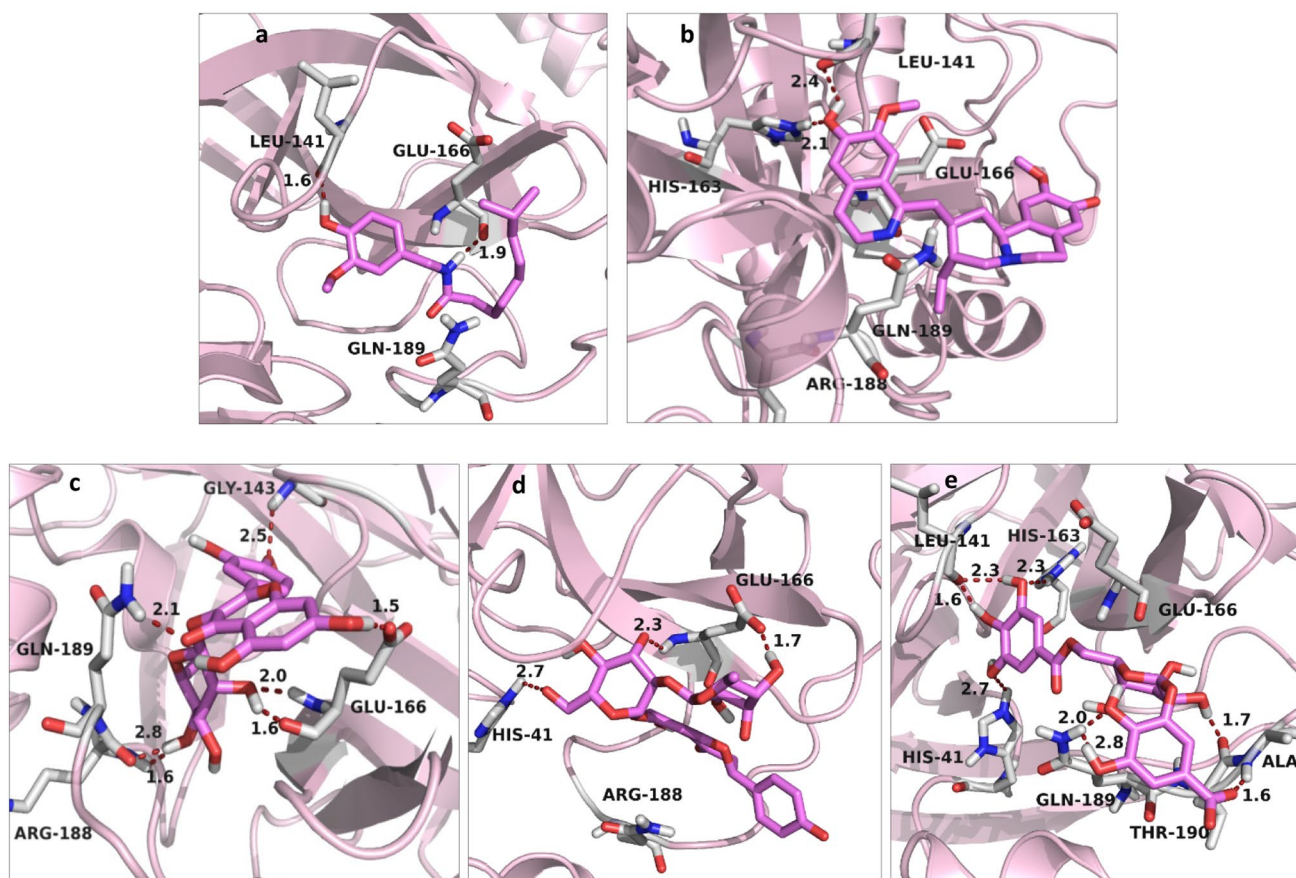

Fig. 3 3D view of the interaction of the top ranked compounds in the binding site of COVD-19 M^pro. The compounds shown as pink sticks, and residues as gray sticks, the rest of the enzyme structure is represented as faint pink cartoons. The red dashed lines indicate the hydrogen bonds which are labeled with their lengths

an interaction profile better that displayed by HCQ. It is completely trapped in the binding site of the enzyme by a complicated network of strong hydrogen bonding generated by His41, Leu141, His163, Gln189, Thr190, and Ala191, with distances ranging between 1.6 Å to 2.8 Å as shown in Fig. 3e. Quercetin with a docking score − 15.80 kcal/mol is connected to the enzyme's residues Gly143, Glu166, Arg188, and Glu189, through strong hydrogen bonding with distances range 1.5–2.8 Å (Fig. 3c). Naringin, Capsaicin and Psychotrine (Fig. 3a, b, and d) are interacting with most of these amino acid residues with potential hydrogen bonding, however, they revealed binding scores − 14.50, − 13.90, − 13.50 kcal/mol respectively, which are much smaller than that displayed by compounds 5.

Throughout human history, thousands of biologically active plants have been discovered, identified and used in medicine. Most cultures around the world rely on medicinal plants for disease treatment (Halberstein 2005). Plants possess the ability to produce a wide range of compounds including flavonoids, alkalis, lignans and tannins, and are responsible for the primary functions of plant growth and development (Saxena et al. 2013). Molecular docking studies and explores the interaction mechanism between ligands and receptors. Interactions between the compound and the receptor play a crucial role in the discovery of drugs. All these 21 molecules were docked against the target enzyme SARS-COV2 M^{pro} and ranked based on their dock scores. Flavonoids are important natural compounds with diverse biologic activities. Citrus flavonoids constitute an important series of flavonoids. Naringin and its aglycone naringenin belong to this series of flavonoids and were found to display strong anti-in flammatory and antioxidant activities (Alam et al. 2014). Naringenin (flavanones), quercetin (flavonols) and Catechins (flavans) which are found in *Citrus* spp and different plants showed the highest result against COVID-19, flavonoids are widely distributed as secondary metabolites produced by plants and play important roles in plant physiology, and they have a variety of potential biological benefits such as antioxidants, anti-inflammatory, anti-cancer, antibacterial, antifungal and antiviral agents. Various flavonoids have been investigated for their potential antiviral activities and many have shown important antiviral properties in the laboratory and even in live studies (Zakaryan et al. 2017). Recent research has shown that Amaryllidaceae alkaloids represent a rich reservoir of potential small chemical molecules that display many medicinal properties through various mechanisms. Among the many *Amaryllidaceae* compounds, galanthamine has been given a lot of attention since it has a strong inhibitory activity of acetylcholine esterase (Habartova et al. 2016). Among the many species investigated for components of small molecules with treatment potential, the *Amaryllidaceae* family plants were particularly fruitful (Evidente et al. 2009). Psychotrine Occurs in *ipecacuanha*

root *Cephaelis acuminata* (Rubiaceae); active against HIV-1 (Manske and Brossi 1985). Capsaicin is an alkaloid from Capsicum genus is one of the principle substances which have many important biological activities in food and medicine (Reyes-Escogido et al. 2011).

Conclusion

To combat the life-threatening corona virus infection, several studies are ongoing using antiviral drug therapies. This study will be useful in recent and future for designing novel drugs for the treatment of COVID-19. In this study, docking analyses showed that the COVID-19 protease (6LU7) may be inhibited by some compounds from herbal plants, based on the binding energy score, we suggest that these compounds such as; Naringin, Quercetin, Capsaicin, Psychotrine and Gallic acid can be tested against Corona virus and used to develop effective antiviral drugs. These molecules could be utilized for further innovation and development of antiviral compounds against Corona virus. However, further researches warranted to investigate the potential uses of the medicinal plants containing these compounds.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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