



Original Article

Multitarget-based *in silico* screening from phytoactive compounds of *Garcinia linii* fighting toward severe acute respiratory syndrome coronavirus-2

Ting-Hsu Chen^{a†}, Zi-Han Shen^{b†}, May-Jywan Tsai^c, Ching-Feng Weng^{d*}, Max K. Leong^{e*}

^aGraduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan,

^bDepartment of Clinical Medicine, Xiamen Medical College, Xiamen, Fujian, China,

^cDepartment of Neurosurgery, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ^dFunctional Physiology Section, Department of Basic Medical Science, Xiamen Medical College, Fujian, China, ^eDepartment of Chemistry, National Dong Hwa University, Hualien, Taiwan

[†]Both authors contributed equally to this work.

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ABSTRACT

Objectives: The recent global coronavirus disease 2019 (COVID-19) pandemic, resulting from infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), can cause severe and fatal pneumonia along with other life-threatening complications. **Materials and Methods:** The rare and limited accessibility of approved therapeutic agents or vaccines is of great distress. Swiftly working on designing and identifying inhibitors against all possible viral key protein targets, seven key SARS-CoV-2 viral enzymes were selected as targets, particularly in the action on the virus-entry, viral replication, and immune evasion of COVID-19. Papain-like protease, main protease, RNA-dependent RNA polymerase, endoribonuclease (nsp15), receptor-binding domain-angiotensin-converting enzyme 2, transmembrane serine protease 2 (TMPRSS2), and 2'-O-ribose methyltransferase (2'MTase), which were subjected to an unbiased *in silico* screening against 22 small molecules originating from *Garcinia linii* concomitantly with Remdesivir, Nirmatrelvir, and Molnupiravir were approved by Food and Drug Administration as repurposing drugs against SARS-CoV-2 invasion. **Results:** The *in silico* results showed that natural bioactive compounds containing α -Tocopherylquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin and Quercetin have a high binding affinity with seven selected viral protein targets concurrently with the preference of absorption, distribution, metabolism, excretion, and toxicity and drug-likeness. **Conclusion:** This study provides potential phytoactive compounds from *G. linii* through multi-target screen with molecular dynamic simulation for combating COVID-19 pandemics that need further experimental validation to confirm the prospective efficacy.

KEYWORDS: *Garcinia linii*, Immune evasion, Severe acute respiratory syndrome coronavirus-2, Viral proliferation, Virus entry

INTRODUCTION

At the end of 2019, the novel human coronavirus has been found in Wuhan, China; furthermore, this etiological agent was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], World Health Organization (WHO) notably announced this infectious coronavirus disease 2019 as (COVID-19) [2]. According to the COVID-19 dashboard from WHO, as of September 9, 2022, the total confirmed cases were 6.121 billion around 212 countries and localities which included 6.518 million deaths, and further analysis of 119 billion vaccine doses have been administered (WHO COVID-19 Dashboard. covid19. who. int; 2021). Unpredictably, due to rapid mutation rate, those of variant strains would collapse the public health system;

hence, drug development should stick on the fighting of SARS-CoV-2 character (virus entry, virus proliferation, and immune evasion). Of note, the human angiotensin converting enzyme 2 (ACE2) transmembrane receptor and transmembrane protease serine 2 (TMPRSS2) play the vital role for virus entry [3]. In terms of the primary route of entry, the spike protein (S protein) could be fused into the outer plasma membrane through TMPRSS2-mediated priming; hereafter,

*Address for correspondence: Prof. Max K. Leong, Department of Chemistry, National Dong Hwa University, 1, Section 2, Da Hsueh Road, Hualien, Taiwan. E-mail: leong@gms.ndhu.edu.tw
Prof. Ching-Feng Weng, Functional Physiology Section, Department of Basic Medical Science, Xiamen Medical College, Xiamen 361023, Fujian, China. E-mail: cfwengcf@gmail.com

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the fused S protein will become an endosome to assist the virus entering host cells [3]. With respect to transcription and replication of SARS-CoV-2, the major function of main protease (M^{pro} , nsp5) and papain-like protease (PL^{pro} , nsp3) is that cleaving the polyprotein replicase of SARS-CoV-2 into non-structure protein (nsp) [4-6]. Interestingly, nsp3 has been suggested that it could inhibit host immune response. Especially, RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 is composed by three nsp subunits (nsp7, nsp8, and nsp12); in addition, RdRp has been investigated in the replication of viral RNA [7]. The other translational molecule of SARS-CoV-2 is methyltransferase (MTase), which is consisted by two nsps (nsp10 and nsp16), and it also could improve viral protein translation by methylation Cap-0 viral mRNAs; of note, the MTase could avoid the dictation from host immune system [1]. Considered the immune evasion of SARS-CoV-2, the endoribonuclease plays an essential role to avoid the detection from host cell dsRNA sensors through degrading the 5'-polyuridines of the producing of anti-genome during the poly (A) region of viral genomic and subgenomic RNAs [8,9].

There are currently several repurposed drugs granted emergency use authorization for the treatment of COVID-19. Remarkably, the emergency authorization use drugs such as Remdesivir, Molnupiravir, and Paxlovid (a combination is composed by Nirmatrelvir and Ritonavir) have presented to reduce a dramatic rate of mortality and severity [10]. Whereas according to COVID-19 treatment guidelines, some adverse effects have been scrutinized from all of the above-mentioned medicines. Taking Remdesivir for instance, the common undesirable effects are gastrointestinal symptoms, elevated transaminase levels an increase in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions. Furthermore, molnupiravir might cause diarrhea, nausea, and dizziness; additionally, the side effects of Paxlovid are dysgeusia, diarrhea, hypertension, and myalgia (<https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>). There are currently several repurposed drugs granted emergency use authorization for the treatment of COVID-19. Remdesivir, a nucleoside analogue that inhibits the RdRp of SARS-CoV-2, has taken a premier role in treatment since early 2020. Other drugs that are currently being used to treat COVID-19 cases are the rheumatoid arthritis drug baricitinib and the corticosteroid dexamethasone, which act to reduce the inflammation associated with severe infection [11]. There are at least two newly approved drugs for the treatment of COVID-19 such as Paxlovid and Molnupiravir [10], but the real efficacy in practice remains to be put forth a significant effect for further investigation. Specially, the medicinal extract or phytochemicals from herbs have been illustrated as an anti-viral regime through different potential infectious pathway such as virus entry, virus proliferation, and immune evasion [12]. Moreover, the physical and chemical characteristics of phytochemicals showed moderate adverse effects and high safety for patients when compared with repurposed or reference drugs; hereafter, the phytochemicals would be considered into the potential therapeutic strategy [12]. Based on accumulating evidence

of Rutin and Quercetin against COVID-19, the inhibitory effects of these compounds on the viral proteins M^{pro} , PL^{pro} , and RdRp of SARS-CoV-2 have been investigated through *in silico* studies [13-15]. To validate the docking results, Rutin and Quercetin are docked on M^{pro} of SARS-CoV-2 with *in vitro* inhibition assays IC_{50} values ranged from 0.125 to 12.9 μ M of M^{pro} activity [16]. One report has shown that Rutin and Quercetin could bind to ACE2 receptors [17]. It is worth to mention that Quercetin was also treated in multi-target (ACE2 and M^{pro}) and multi-pathway therapeutic regimes such as inhibiting inflammatory mediators, regulating immunity, and eliminating free radicals [18]. Especially, one more article also elucidated the binding affinity of Rutin ($\sim 10^{-6}$ M) was much higher than those of Chloroquine ($\sim 10^{-3}$ M) and Hydroxychloroquine ($\sim 10^{-4}$ M), and the reference drug Remdesivir ($\sim 10^{-5}$ M) [19]. Notably, *Garcinia linii* is endemic evergreen tree in outlying islands-Langyu land and Green island of Taiwan; furthermore, a previous research has reported the fruit, seed, leave, and stem could treat several illnesses such as abdominal pain, food allergies, arthritis, diarrhea, dysentery, wound infections, and diabetes [20]. Especially, there contained 15 xanthenes, 6 biphenyls, 2 benzopyran, and 13 known compounds which were isolated from the root extract, and further five of Xanthenes (Linixanthone B and C, Globulixanthone D, 1,6-Dihydroxy-5-methoxyxanthone, and 1,7-Dihydroxyxanthone) have revealed the cytotoxicity effect of mouse lymphocytic leukemia and human colon carcinoma [21]. Interestingly, some compounds (α -Tocopherylquinone, Squalene, and 6 β -Hydroxystigmast-4-en-3-one) isolated from *G. linii* have been further exemplified some biological and medical properties such as anti-cancer, anti-oxidant, drug carrier, detoxifier, skin hydrating, and anti-mycobacterial [22-24]. Mostly, Squalene has been applied as an adjuvant of COVID-19 vaccine to augment protective immunity [25] whereas an unmet medical need of Squalene for both the prevention and treatment of SARS-CoV-2 infection. To overcome lack of knowledge in those natural products has been directly treated the COVID-19 pandemics. The researchers around the world are swiftly working on the design and identification of inhibitors against all possible viral key protein targets. To promptly and efficiently screen targets phytomedicine via pharmacokinetics, druglikeness and medicinal chemistry rules, absorption, distribution, metabolism, excretion and toxicity (ADMET) profiling of phytochemicals, this process depicts the probability of the potential drug candidates to undergo a profitable interaction with specific protein targets for the success of drug discovery and development. Furthermore, the relationship between potential drug pharmacokinetics and physicochemical parameters can be demonstrated by the criteria of Lipinski rule-of-five. First, the molecular weight is advised to be below 500 daltons, as larger molecules may struggle to cross cell membranes, impacting bioavailability. Lipophilicity, measured by the LogP value, should ideally be <5 to avoid complications associated with poor water solubility and absorption difficulties. The number of hydrogen bond donors is recommended to be <5, as an excess may hinder membrane penetration. Similarly, the count of hydrogen bond acceptors should be kept below 10 to ensure optimal

oral bioavailability [26]. Based on the anti-inflammation and anti-viral activities of *Garcinia* family, a previous study has elucidated the peel extract of *Garcinia indica* could forbid the activity of histone acetyltransferase suppressed the proliferation of influenza A as well as human immunodeficiency virus [27]. In terms of anti-inflammatory activities, a plethora of research has evidenced anti-inflammation of *Garcinia kola* extraction [28,29]. Furthermore, taking deep insight of the mechanism of anti-inflammatory activities, the extraction could inhibit Cyclo-oxygenase 2 (COX-2) and inducible nitric oxide synthase expressions [30]. It is worth noting that, the phytomedicine from *Garcinia mangostana* has been reported the properties in antiviral (hepatitis C virus, dengue virus, and HIV etc.) and anti-inflammation [31]. Moreover, one of phytocompounds, α -Tocopherylquinone, has been evidenced against SARS-CoV-2 via computational screening with the targeting protein of COVID-19 (Angiotensin-converting enzyme 2 - Receptor-binding domain (ACE2-RBD), RdRp, PL^{pro}, and endoribonuclease) [32]. While the other compounds of *G. linnii* has not been fully investigated for antiviral and anti-inflammatory activities.

Computer-aided drug discovery enhances modern drug development by accelerating the identification of potential drug candidates. It leverages computational models to predict molecular interactions, optimize compounds, and reduce costs. This technology streamlines the research process, improves accuracy, and ultimately shortens the time needed to bring effective treatments to market [33]. Hence, according to aforementioned literatures, this study aimed to elucidate the phytoactive compounds, particularly in *G. linnii* virtually targeting SARS-CoV-2 through multi-target-based *in silico* screening for treating COVID-19 pandemics.

MATERIALS AND METHODS

Pharmacokinetics and ADME/toxicity profiling

The pharmacokinetic properties such as the Absorption, Distribution, Metabolism, Excretion, and Toxic behavior of ligands to human body are screened using the SwissADME (<http://www.swissadme.ch/index.php>) and admetSAR prediction tool webserver (<http://lmmd.ecust.edu.cn/admetSar2>). This plays a significant role in proffering the “druglikeness”, “medicinal chemistry,” and “lead likeness” and toxicity potential of new drugs, phytochemicals, food additives, and industrial chemicals candidates. It serves as a prerequisite establishment for a valid complementary method before *in vivo/in vitro* analysis [34,35].

Molecule docking

After conducting a literature review, the 36 bioactive compound 3D structures from *Ophioglossum vulgatum* were downloaded from the PubChem database website (<https://pubchem.ncbi.nlm.nih.gov/>), while the source of 3D structure potential proteins molecules was retrieved from the RCSB PDB (<https://www.rcsb.org/>). The docking process was conducted by CCDC Gold Suite V5.3 (Cambridge Crystallographic Data Centre, Cambridge, UK) [36]. Through Gold platform, the docking parameter was followed by GA run 10, GA search efficiency 200%, and removing

water as well as co-crystallized ligands. In addition, the scoring function was conducted by ChemPLP that uses the ChemScore hydrogen bonding and multiple linear potentials to model van der Waals and repulsive. In GOLD molecular docking, ChemPLP (Chemical Properties and Ligand Pose) and ChemScore are scoring functions used to evaluate ligand-binding affinity. ChemPLP focuses on the chemical properties and binding poses of molecules, while ChemScore is based on energy calculations and geometric similarity. The ligand and proteins of those high chemical score structures were acted the molecular docking process via Discovery Studio (version 2019) and performed the visual analysis. In the process of molecular docking on Discovery Studio, the docking-binding sites were defined and edited as the active sites corresponding to the protein as the previous literature from the RCSB website.

Ligand-protein complex visualization

Discovery Studio was used to visualize the completed docking complexes, allowing for an in-depth analysis of the interactions between the receptors and ligands. The tools available in the receptor-ligand interactions module facilitated the calculation of binding bond distances, providing insights into the strength and nature of these interactions. In addition, the docking images of the complexes were presented in a 2D diagram, which clearly illustrates the spatial arrangement of the ligands within the binding sites. This comprehensive visualization aids in understanding the binding mechanisms and can help guide further optimization of the ligands for improved affinity and specificity.

Molecular dynamic simulation

To further investigate the stability of protein complexes from molecular docking; hence, the major docked complexes were subjected to molecular dynamic (MD) simulation. Moreover, the MD simulation was also reported that it is seen to be more profoundly fundamental molecular analysis of ligand recognition. Calculations of ligand-protein complexes were applied with the CHARMM force field Discovery Studio 2019. In addition, to prepare the MD simulation module, the ligand-protein complexes from molecular docking were applied the solvation process via Discovery Studio 2019; then, the solvent model was set as explicit periodic boundary. The protocol of standard dynamic cascade was followed default setting; except, the simulation time of production step was set 100 ns (temperature 300K, time step 2 fs) as well as we turned on the SHAKE step at advantage section. Finally, the root-mean-square deviation (RMSD) mappings were generated from the outcome of MD simulation.

Ethics statement

All of our results were obtained through *in silico* methods; therefore, this study did not require IRB or IACUC approval.

RESULTS

It is imperative that efforts be dedicated to the development of small-molecule inhibitors which target various parts of the viral life cycle, by direct action upon either viral proteins or host factors required for viral replication.

Absorption, distribution, metabolism, excretion, and toxicity

All candidates in this study fall within the acceptable range of oral drug candidates with few violations by α -Tocopherylolquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin, which violate two leadlikeness parameter. The blood-brain barrier (BBB) interference is attributed with some neurological dysfunction such as amyotrophic lateral sclerosis, epilepsy, edema, brain traumas, and Parkinson's disease [37]. Therefore, drug candidates reflecting this BBB crossing with a TPSA <79 Å² and WLogP <6 as reported by Ishola *et al.* [38] is suitably important in the development of central nervous system (CNS)-acting therapeutics [Table 1]. Thus, five phytochemical candidates used in this study, α -Tocopherylolquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin can transverse the BBB, however, the last two candidates exhibit carcinogenic properties. This barricade is essential for restricted CNS microenvironment in/outflux, for adequate neuronal function [38]. While α -Tocopherylolquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and

Quercetin possess a considerable binding affinity for the seven SARS-CoV-2 protein targets, its significant BBB permeation could be employed for anti-neurodegenerative diseases drugs development. The acute oral toxicity profile of the drug candidates shows they are within the category II to III (Moderate-slightly toxic), except medicagenate which is in the category I (extremely toxic).

Furthermore, all candidates are readily absorbed into the intestine which are negative. Accessibility of the drug candidates through the membrane are determined by their Caco2 permeation. Hence, this attribute is better in the case of α -Tocopherylolquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin. Three phytochemicals in potential drug candidates substantially passed the profiling test, as shown in Table 1 and Table 2. Thus, these phytochemicals fulfill all the enlisted criteria similar to Kushwaha *et al.* [39] findings, and it is suggestively determined to be suitable for the development of potent anti-diabetic drugs. While acknowledging the limitations of traditional ADMET parameters, this study provides a nuanced perspective on the selected compounds, emphasizing their potential in CNS-acting therapeutics. The

Table 1: Absorption, distribution, metabolism, excretion, and toxicity of selected phytoactive compounds from *Garcinia linii*

Biological ability	CID/compound name				
	2734086 α -Tocopherylolquinone	5280343 Quercetin	5280805 Rutin	638072 Squalene	71307329 6 β -Hydroxystigmast-4-en-3-one
<i>In vivo</i> BBB penetration (C. brain/C. blood)	12.96	0.17	0.03	27.46	13.89
<i>In vitro</i> Caco-2 cell permeability (nm/s)	53.00	3.41	7.91	23.40	51.40
<i>In vitro</i> CYP 3A4 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
<i>In vitro</i> CYP 3A4 substrate	Substrate	Non	Weakly	Substrate	Substrate
<i>In vitro</i> MDCK cell permeability (nm/s)	0.72	13.35	54.77	68.01	6.81
<i>In vitro</i> skin permeability (logKp, cm/h)	-0.51	-4.43	-4.67	-0.48	-0.83
MDDR-like rule	Mid-structure	Mid-structure	Drug-like	Mid-structure	Mid-structure
Rule of five	Suitable	Suitable	Violated	Suitable	Suitable
Ames test	Nonmutagen	Mutagen	Nonmutagen	Mutagen	Nonmutagen
Carcino mouse	Negative	Negative	Negative	Positive	Positive
GPCR ligand [#]	0.13	-0.06	-0.05	0.04	0.07
Ion channel modulator [#]	0.07	-0.19	-0.52	0.01	0.05
Kinase inhibition [#]	-0.15	0.28	-0.14	-0.10	-0.67
Nuclear receptor ligand [#]	0.17	0.36	-0.23	0.19	0.79
Protease inhibitor [#]	0.16	-0.25	-0.07	-0.03	0.10
Enzyme inhibitor [#]	0.28	0.28	0.12	0.16	0.55

[#]Molinspiration bioactivity score. BBB: Blood-brain barrier

Table 2: Chemoinformatics of selected phytoactive compounds from *Garcinia linii*

Biological ability	CID/compound name				
	2734086 α -Tocopherylolquinone	528034 Quercetin	5280805 Rutin	638072 Squalene	71307329 6 β -Hydroxystigmast-4-en-3-one
Molecular weight (g/mol)	446.7	302.23	610.5	410.7	428.7
XLogP3	8.8	1.5	-1.3	11.6	8
HBD	1	5	10	0	1
HBA	3	7	16	0	2
Rotatable bond count	15	1	6	15	6
TPSA (Å ²)	54.4	127	266	0	37.7
Covalently-bonded unit count	1	1	0	1	1
nviolations (violations from RO5)	1	0	3	1	1
LogP (LogP <5)	8.12	1.68	-1.06	9.62	7.76

HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor, TPSA: Topological polar surface area

results section now offers a more detailed and contextualized understanding of compound pharmacokinetic profiles, guiding further considerations in the drug development pipeline.

In silico screening with various proteins of severe acute respiratory syndrome coronavirus-2

Furthermore, the ability of α -Tocopherylolquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin bind effectively to the seven protein targets (PL^{pro}, M^{pro}, RdRp, endoribonuclease (nsp15), RBD-ACE2, TMPRSS2, and MTase) could be pivotal in the treatment of COVID-19 pandemic, coupled with the link ability of the phytochemical candidates to interact strongly than the standard inhibiting drugs to individual receptors. A therapeutic drug can be inferred from this collection [Table 3]. The 2D and 3D mapping of docking results showed that α -Tocopherylolquinone [Figure 1a], 6 β -Hydroxystigmast-4-en-3-one [Figure 1b], Squalene [Figure 1c], Rutin [Figure 1d], and Quercetin [Figure 1e] bind effectively to the seven protein targets (PL^{pro}, M^{pro}, RdRp, endoribonuclease (nsp15), RBD-ACE2, MPRSS2, and MTase) of SARS-CoV-2. The docking results with high chemical scores are presented through 3D diagrams. Squalene with Endoribonuclease [Figure 2a], Squalene with M^{pro} [Figure 2b], Squalene with PL^{pro} [Figure 2c], Squalene with RdRp [Figure 2d], Squalene with TMPRSS2 [Figure 2e], α -Tocopherylolquinone with MTase [Figure 2f], and

α -Tocopherylolquinone with RBD-ACE2 [Figure 2g]. The docking analysis revealed significant interactions of α -Tocopherylolquinone, Squalene, 6 β -Hydroxystigmast-4-en-3-one, Rutin, and Quercetin with key SARS-CoV-2 proteins, including papain-like protease, main protease, RNA-dependent RNA polymerase, endoribonuclease (nsp15), receptor-binding domain of the spike protein interacting with angiotensin-converting enzyme 2 (ACE2), transmembrane serine protease 2 (TMPRSS2), and 2'-O-ribose methyltransferase (MTase) [Figure 3].

The validation of molecular dynamics simulation

MD simulations are additionally conducted to evaluate the dynamic behavior and stability of SARS-CoV-2 proteins in complex with the best hits of above-docking experiments. Furthermore, previous computational research has shown that the RMSD value between the target ligand and protein molecule can provide the evidence for whether the docking complex is a close match or not through MDs simulation. In addition, an RMSD value of ≤ 2 Å has been found to indicate a good conformation [45]. Based on the docking results, the best complex with each COVID-19-related protein had been further investigated by MD simulation. As shown in the supplementary file [Figure S1], the complex of α -Tocopherylolquinone and MTase showed a stable

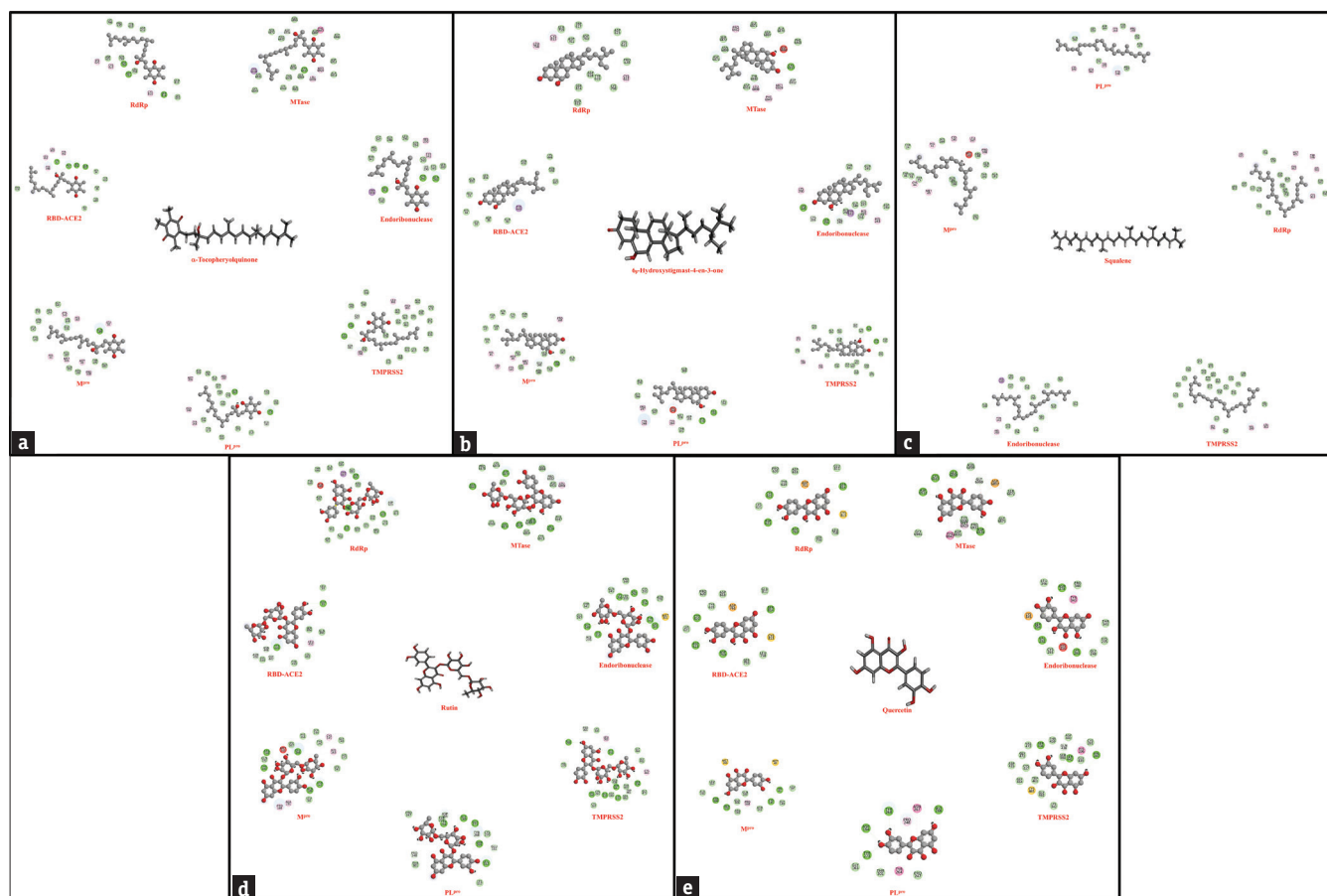


Figure 1: Two-dimensional snapshot of α -Tocopherylolquinone (a), 6 β -Hydroxystigmast-4-en-3-one (b), Squalene (c), Rutin (d), and Quercetin (e) interacted with certain amino acid residues of papain-like protease, main protease, RNA dependent RNA polymerase, endoribonuclease (nsp15), receptor binding domain-angiotensin-converting enzyme 2, transmembrane serine protease 2 (TMPRSS2), and 2'-O-ribose methyltransferase (MTase) of severe acute respiratory syndrome coronavirus-2

trajectory with clear fluctuations from the early stages of the simulation. Moreover, the system of this complex maintained an RMSD value between 2 and 4 Å. However, the AEC2-RBD complex with α -Tocopherylquinone did not reach a stable state before 80 ns, which was later than the previously mentioned conformation. In addition, this complex presented a higher RMSD value, indicating that the ligand moved slightly away from the protein. The trajectory of Squalene with M^{pro} displayed a similar trend to that of the AEC2-RBD complex with α -Tocopherylquinone, and the RMSD value of conformation was approximately 4 Å. Furthermore, the conformation of squalene with TMPRSS2 shown relatively stable and the RMSD value was close to 2 Å. However, the PL^{pro} complex, RdRP complex, and endoribonuclease complex displayed more drastic fluctuations when compared to other four MD conformations.

DISCUSSION

In the postpandemic era, the sequelae and complication of recovery patients have played a pivotal character of prognostic treatment in COVID-19. In addition, those symptoms usually manifest persistent postacute phase of COVID-19 [46]. According to a previous study, the long-term complications of COVID-19 could be roughly divided into nine categories such as neuropsychiatric, cardiovascular, musculoskeletal, dermatologic, pulmonary, hematologic, gastrointestinal, renal, and endocrine disease [47]. Furthermore, the common symptoms of above-mentioned phase are fatigue, breathlessness, cough, joint pain, chest pain, muscle aches, and headache. While this persistent syndrome has not been well defined; therefore, the mild disease for 2 weeks, moderate disease to worsened illness for 4 weeks, and 6 weeks for severe ill should be considered as “long COVID” [48]. It

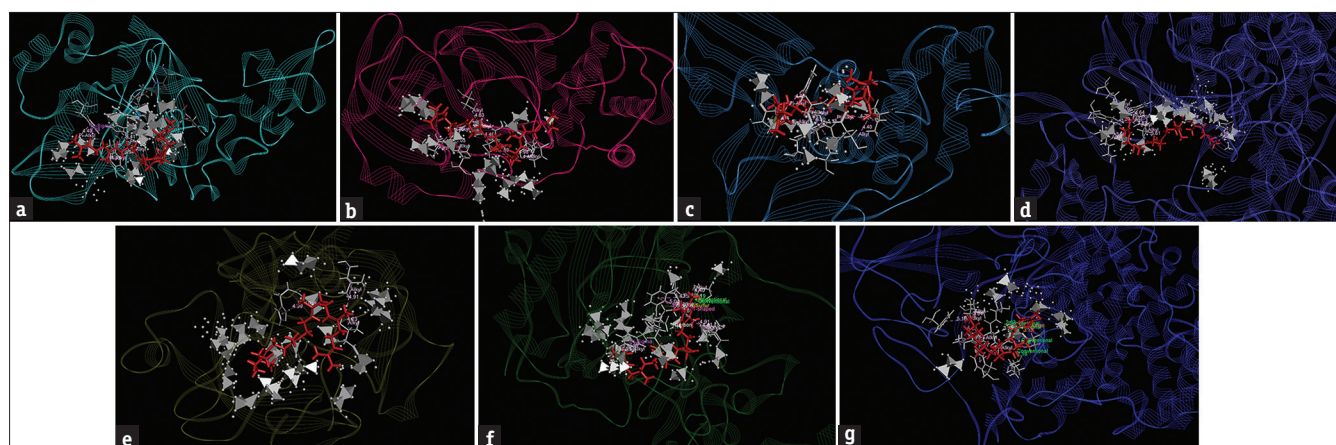


Figure 2: 3D structure diagram of complexes, Squalene with Endoribonuclease (a), Squalene with main protease (b), Squalene with papain-like protease (c), Squalene with RNA dependent RNA polymerase (d), Squalene with TMPRSS2 (e), α -Tocopherylquinone with MTase (f), and α -Tocopherylquinone with receptor binding domain-angiotensin-converting enzyme 2 (g)

Table 3: The binding affinity of drug inhibitors and selected phytoactive compounds from *Garcinia linii* with papain-like protease, main protease, RNA dependent RNA polymerase, endoribonuclease (nsp15), receptor binding domain-angiotensin-converting enzyme 2, transmembrane serine protease 2, and 2'-O-ribose methyltransferase from Severe Acute Respiratory Syndrome Coronavirus-2

CID name	ChemPLP						
	COVID-19 M ^{pro} [40]	COVID-19 PL ^{pro} [41]	COVID-19 Endoribonuclease [9]	COVID-19 RdRp [42]	RBD-ACE2 [43]	COVID-19 MTase [1]	TMRSS2 [44]
121304016 Remdesivir	74.06	67.94	70.06	55.23	48.64	69.33	60.26
145996610 Molnupiravir	45.80	53.96	50.11	42.05	41.50	45.24	49.00
155903259 Nirmatrelvir	61.81	57.16	60.89	45.51	46.64	46.57	47.39
2536 Camostat (TMPRSS2 inhibitor)	57.96	60.65	63.25	50.23	51.17	52.88	62.56
2734086 α -Tocopherylquinone	70.18	64.71	74.20	62.07	52.68	73.11	54.98
4413 Nafamostat (TMPRSS2 inhibitor)	54.18	55.35	56.35	44.02	49.28	53.10	70.63
5280343 Quercetin	48.51	55.43	56.87	46.45	46.47	60.39	54.49
5280805 Rutin	70.85	65.85	60.31	52.76	48.34	52.66	56.08
53277 Chaetochromin	56.05	59.34	51.85	51.26	51.65	44.39	39.38
6323266 Tipiracil (Endoribonuclease inhibitor)	36.18	47.02	47.49	36.97	36.86	49.35	41.12
638072 Squalene	81.39	76.67	83.15	70.03	0.00	70.37	63.80
65482 Sinefungin (O-methyltransferase inhibitor)	52.18	61.61	65.38	53.53	47.52	72.68	62.45
71307329 6 β -Hydroxystigmast-4-en-3-one	70.26	66.27	59.86	52.73	43.96	46.23	54.70
8655 Syringaldehyde	37.45	42.97	38.10	36.23	34.20	46.32	42.98

M^{pro}: Main protease, RdRp: RNA dependent RNA polymerase, PL^{pro}: Papain-like protease, MTase: Methyltransferase, RBD-ACE2: Receptor-binding domain-angiotensin-converting enzyme, TMPRSS2: Transmembrane serine protease 2, COVID-19: Coronavirus disease 2019, ChemPLP: Chemical properties and ligand pose

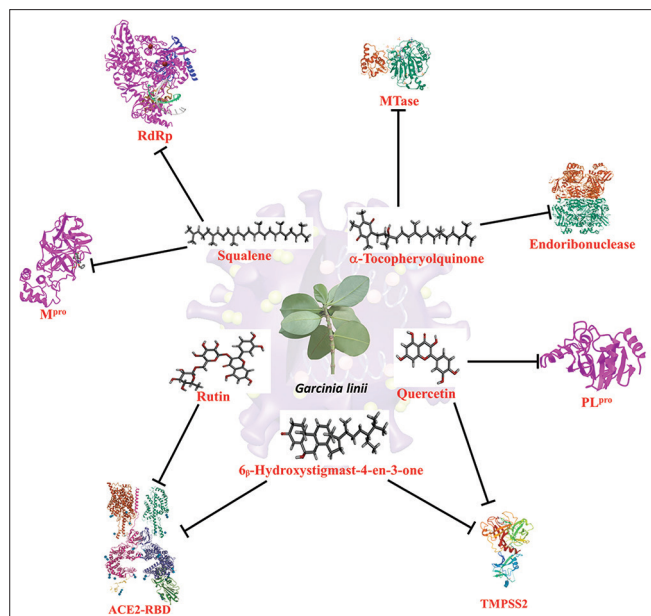


Figure 3: Three-dimensional depiction of α -Tocopherolquinone, Squalene, 6 β -Hydroxystigmast-4-en-3-one, Rutin, and Quercetin docked with papain-like protease, main protease, RNA-dependent RNA polymerase, endoribonuclease (nsp15), receptor-binding domain-angiotensin-converting enzyme 2, transmembrane serine protease 2 (TMPRSS2), and 2'-O-ribose methyltransferase (MTase) of severe acute respiratory syndrome coronavirus-2

is worth noting that the neuropsychiatric complication and sequelae of COVID recovering patients. The hallmark of neuropsychiatric illness has been demonstrated that loss of smell and taste; both of them are feature syndromes of SARA-CoV-2 patients [47]. Moreover, the other threatening illness, acute respiratory distress syndrome, which could perturb memory, verbal fluency, and executive function [49]. Due to encephalitis and cerebrovascular damage of COVID-19 patients, those two persistent impairments may subtly cause impairment in concentration and cognition [50]. In addition, other investigations also evidenced the systemic inflammation should cause the development of neurocognition complication of COVID-19 patients [51]. Taking deep insight of neurological symptoms, the term of brain fog has been portrayed mentally slow, fuzzy, or spaced out [50,52]. With regarding to long-term psychiatric sequelae, a research showed the COVID-19 discharged patients should manifest posttraumatic stress disorder, depression, anxiety, and insomnia [53]. A previous evidence indicated that long COVID frequently manifests in aged population as well as the elder usually got muscle pain even ICU admission [54]. Moreover, the COVID poses of children are usually asymptomatic or mild symptoms, even the rate of hospitalization and life-threatening complication presents relatively low than adults [55]. Although most of children and adolescent patients have shown no symptoms, the clinical manifestation is wide spectrum of COVID-19 diagnosis [56]. Especially, the recent research has demonstrated the severe illness of children which would develop a postinfectious multisystem hyperinflammatory syndrome as well as this well-known syndrome is named as multisystem inflammatory syndrome in children (MIS-C) [57]. The rough definition of MIS-C is damage more than one

system organ such as cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological; to further investigate the prevalence of MIS-C, the obesity is a high risk factor for COVID children [58].

Extraordinarily, phytoactive molecules such as (polyphenol, flavonoid, alkaloid, and triterpenoid etc.) have been well investigated at anti-oxidation, anti-inflammation, anti-tumor, and anti-virus etc. [59]. Notably, the phytomedicines could be a potential therapeutic regime to reduce the ratio of hospitalization or death of COVID-19 patents. Accumulative evidence from numerous studies have demonstrated the multiple pharmacological activities in the fruit, leaf, and seed extracts of *Garcinia* family, including anti-bacterial, anti-cancer, anti-depressant, anti-diabetes, anti-inflammatory, anti-fungal, anti-oxidant, anti-HIV, anti-nociceptive, anti-histaminic, anti-ulcerogenic, anti-viral, vasodilator, hypolipidemic, hepatoprotective, nephroprotective, cardioprotective, and larvicidal properties are particularly in bioactive compounds, containing xanthenes, flavonoids, phenolic acids, organic acids, and terpenoids such as *Garcinia morella*, *Garcinia porrecta*, and *G. linii* [20,60-63]. Furthermore, the root extract from *G. linii* presented anti-tubercular activity against *Mycobacterium tuberculosis* infection [64].

In this study, the high docked score compounds (at least 5 candidates after molecular docking and MD simulation) could be applied as a direct action on virus replicative apparatus (viral entry or replication, acting on the viral enzymatic system), and collateral action of phytocompounds on the immune system or vaccine adjuvant. For example, COVID-19 patients receiving a natural bee product known as propolis show earlier viral clearance, enhanced symptom recovery, quicker discharge from hospitals, and a reduced mortality rate relative to other patients has been reported. This could be due to the effects of flavonoids in propolis on including anti-oxidant, immunomodulatory, anti-inflammatory, and anti-viral activities to reduce viral replication [65]. In terms of adjuvant, it contributes to alleviate the symptoms of the disease, enhance vaccine action, and increase effective immune response; moreover, adjuvant might not cause the undesirable effects, toxicity, even change immune system function. Vaccine adjuvants usually are chosen to boost the immune response against a simultaneously administered antigen. In this perspective, β -(1,3) bond linked to a β -(1,6)-(1,6) glucans are considered to be the most effective due to their immunomodulatory activity and biosafety according to the list issued by the European Commission. This implies the possible effects of β -glucans as an adjuvant in the efficacy of vaccines against SARS-CoV-2 virus [66]. The other evidence for vaccine adjuvant, Squalene, a medicinal terpene, plays diverse biological roles as an antioxidant and anticancer agent and is used as a vaccine adjuvant to improve the efficacy of vaccines, including pandemic COVID-19 vaccines [67]. The phytocompounds of *G. linii* act directly as an anti-SARS-CoV-2 reagent or/and vaccine adjuvant need to be further verified.

For the further investigation of TMPRSS2, this protease is co-localized with ACE2 at the cell membrane; moreover, both of them are extremely expressed in the aero-digestive

tract, liver, kidneys and sex organs as well as the TMPRSS2 has also been reported as the dominant proteolytic driver of S protein activation [68-70]. Since protective antibodies through vaccination could not cross the BBB, leading to neuro-inflammation and contributing to long-COVID, currently possible interventions using small natural molecules such as flavonoids luteolin and quercetin [71] to mitigate S-protein-related detrimental effects to the brain even liposomal luteolin [72] to hinder mast cells and microglia for ameliorating the manifestation of COVID-19.

As far as nsp3, it could cleave interferon regulatory factor 3; hereafter, the type-I IFN response would be suppressed during SARS-CoV-2 infection [73]. Moreover, rendering inflammatory pathways, nsp5 could regulate NLRP12 and TAB1 to cause the production of cytokines and inflammatory response [73]. Taking deep insights to inflammatory process, the neuro-inflammation caused neurogenesis as well as downsized the hippocampus of patient, decline the amount of granule neurons and neural progenitor cells. Those inflammatory manifestations could further develop the exacerbation of pre-existing dementia even above-mentioned long COVID symptoms [74]. To further investigated the anti-inflammatory effect of Chinese medicine as well as regulating immunity, the multi-component of Chinese medicine could eliminate free radicals through COX-2, CASP3, IL-6, MAPK1, MAPK14, MAPK8, and REAL in the signaling pathways of IL-17, arachidonic acid, HIF-1, NF- κ B, Ras, and TNF [18]. *In silico* screening has significantly advanced drug discovery by enabling efficient identification of potential candidates. Studies show that computational methods can predict binding affinities and optimize lead compounds, leading to successful drug development [75-77]. Prospectively, multicomponents are virtually concomitant with multi-target proteins and multisignal pathways could play a latent role in discovery and development of phytomedicines for the treatment of COVID-19 pandemics.

CONCLUSIONS

Based on the anti-inflammation and anti-viral activities of Garcinia family, *in silico* results showed that natural bioactive compounds containing α -Tocopherylquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin have a high-binding affinity with 7 selected SARS-CoV-2 viral protein targets (PL^{pro}; M^{pro}; RdRp; endoribonuclease (nsp15), RBD-ACE2; transmembrane serine protease 2, TMPRSS2; and 2'-O-ribose methyltransferase, MTase) concurrently with the preference of ADMET and drug-likeness. The study exhibits several strengths, enhancing its contribution to the field. A standout feature is the comprehensive ADMET analysis, which meticulously evaluates the pharmacokinetic and toxicological profiles of selected compounds, encompassing crucial factors such as BBB permeation, acute oral toxicity, intestinal absorption, and Caco2 permeation. The emphasis on CNS-acting therapeutics underscores the strategic importance of the compounds, particularly α -Tocopherylquinone, 6 β -Hydroxystigmast-4-en-3-one, Squalene, Rutin, and Quercetin, presenting a nuanced

approach to neurological disorder treatments. The study broadens its scope by delving into COVID-19 treatment potential, utilizing *in silico* screening and MDs simulations. The visual confirmation of strong binding interactions and the identification of three phytochemicals as potential antidiabetic drug candidates further enrich the study's findings. This study affords potential phytoactive compounds from *G. linii* via multi-target screen with MD simulations for combating COVID-19 pandemics that need further experimental validation (*in vitro* and *in vivo*) to confirm the impending efficacy.

Data availability statement

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

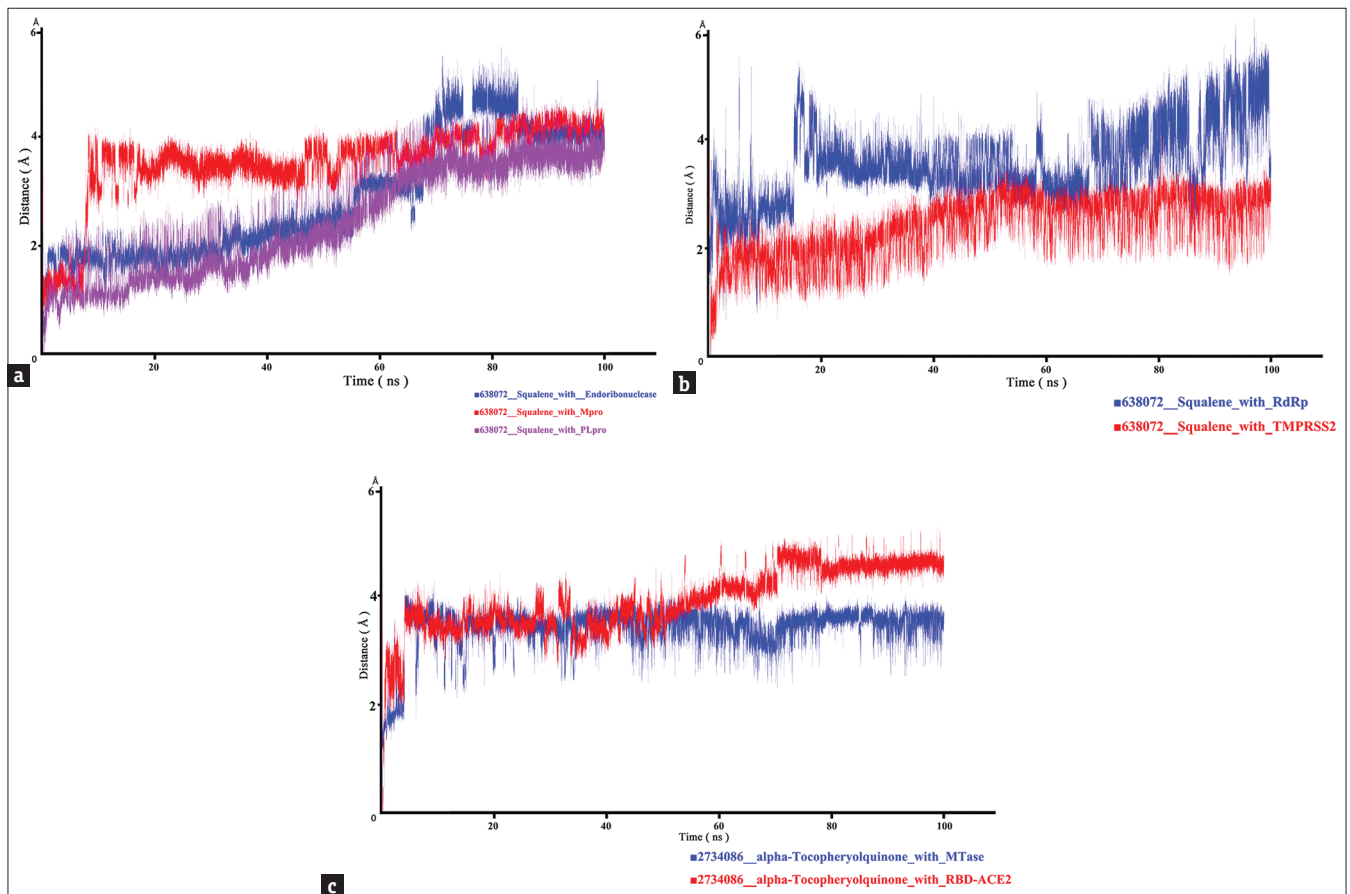


Figure S1: The root mean square deviation trajectory values obtained from MD simulation analyses of the major target conformations of a) squalene with Endoclease, Mpro, and PLpro, b) squalene with RdRp and TMPRSS2, and c) alpha-Tocopherylquinone with MTase and RBD-ACE2