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Affinity of Chlorogenic Acid as COVID-19 Antiviral with Molecular Docking Method

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ABSTRACT

Due to the continued presence of and impact of COVID-19 on our modern world, the benefit and necessity of alternative treatment options and effective antiviral compounds is readily apparent. This study seeks to explore the utility of chlorogenic acid as a COVID-19 antiviral. The in-silico experimental study was conducted using a laptop and publicly-available freeware. Key compounds used in this study are the comparative drugs favipiravir (CID 492405), oseltamivir (CID 65028), nafamostat (CID 4413), and spironolactone (CID 5833), to be tested against our subject, chlorogenic acid (CID 1794427). Compunds used in this study were docked with specific target proteins, such as ACE2, TMPRSS2, RdRp, dan 3Clpro, using AutoDock Vina. The visualization of molecular interactions was performed with Discovery Studio v21. Our results showed that chlorogenic acid has one Lipinski's Rule of Five violation in H-bond Donor parameter. Chlorogenic acid had a higher affinity towards ACE2 and 3CLpro and lower affinity towards TMPRSS2 and RdRp, if compared to competing drugs, with a binding energy of -7.8, -6.9, -7.0, and -7.4 kcal/mol respectively, for ACE2, TMPRSS2, RdRp, and 3CLpro. We conclude that chlorogenic acid shows promise as oral drug candidate based on these results, and that further studies into the realm of molecular dynamics, in-vitro, or in-vivo studies are warranted in order to explore this underutalized compound and possibly bring it to human trials.

KEYWORDS:
COVID-19, Affinity, Molecular Docking, Chlorogenic Acid

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INTRODUCTION

COVID-19 is an infectious disease caused by SARS-CoV-2, that first founded in Wuhan City, Hubei, China, in December 2019 (1). COVID-19 become fifth pandemic that happened in the world. COVID-19 first symptom onset happened at December 1st 2019, with some symptoms like fever, malaise, dry cough and dispnea (2). SARS-CoV-2 is an enveloped positive single strain-RNA virus that looked like solar corona (3). SARS-CoV-2 has 4 main structural protein, such as spike(S) protein, envelope(E) protein, membrane(M) protein, and nucleocapsid(N) protein. Other than that, SARS-CoV-2 also has 16 nonstructural proteins and 5-8 accessories proteins (4,5). SARS-CoV-2 enters host cells by binding ACE2 receptors with its S1 subunit protein and priming process of S2 subunit protein which is facilitated by TMPRSS2 protease. After that, SARS-CoV-2 genome will be translated by host ribosomes, making polypeptide chain that will be auto-proteolitically cleaved by 3CLpro and PLpro. Those cleavage will making 16 nonstructural proteins, which will be formed into RTC by rough endoplasmic reticulum. This complex has a central enzyme named RdRp, and will be needed for SARS-CoV-2 replication (6,7). Based on each protein roles in SARS-CoV-2 life cycle, there are some proteins that are potential to become COVID-19 treatments, which are ACE2, TMPRSS2, RdRp, dan 3CLpro (8,9). Chlorogenic acid is an polyphenol found in food and herbal plant like apple, betel, burdock, coffee bean, carrot,

eggplant, potato, and many else (10). Several studies shows some of chlorogenic acid benefits like antioxidant, anticancer, and antiinflammation. Moreover, chlorogenic acid also benefit in type 2 diabetes, obesity, Alzheimer disease, stroke, and can lower blood pressure. But, some studies also shows the adverse effects of chlorogenic acid, such as headache and diarrhea (11–13). Until now, the only COVID-19 drug approved by FDA is remdesivir, while WHO still don't approve any drugs as COVID-19 drug, including remdesivir (14,15). Therefore, researcher keep finding COVID-19 drug candidate and developing COVID-19 therapy. This study aim to look chlorogenic acid's affinity as COVID-19 antiviral. Therefore, it is necessary to conduct this research using molecular docking to predict chlorogenic acid's affinity with some COVID-19 drugs target proteins such as ACE2, TMPRSS2, RdRp, and 3CLpro.

METHODS

This experimental study was conducted experimentally using *molecular docking* method with some software and databases that are freely accessible online. In this study, RSCB Protein Data Bank and PubChem database were used to retrieve some ligands and COVID-19 therapy target proteins.

Data retrieval

The process starts by retrieving ligands and some COVID-19 therapy target proteins. Target proteins used in this study were based from some COVID-19 drug target proteins that used until now. These target proteins structural data downloaded from RSCB Protein Data Bank (https://www.rcsb.org/) in pdb format which named ACE2(PDB ID : 7A91), TMPRSS2(PDB ID : 7MEQ), RdRp(PDB ID : 7BV1), dan 3CLpro(PDB ID: 6M2Q). Ligands used in this study were chlorogenic acid(CID 1794427) and some comparative drugs such as remdesivir(CID 121304016), oseltamivir (CID 65028), nafamostat (CID 4413), and spironolactone (CID 5833). These ligands were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in sdf format.

Preparation of target protein and ligand

The preparation of target protein structures were done by removing water (H_2O) molecules, adding polar hydrogen atoms, and removing natural ligand and non-target protein exists in the structure downloaded. After that, the prepared target protein structures will be saved as pdbqt format. This preparation were done using *AutoDockTools-1.5.6* and *Discovery Studio v21* software. The preparation of ligand structures were done by change its format become pdb with *DiscoveryStudiov21* and change its format again become pdbqt with *AutoDockTools-1.5.6*. The results of the protein targets and ligands preparation will be used in the molecular docking process.

Target protein active sites prediction

Active sites of each target protein predicted using *CASTp 3.0* (*Computed Atlas of Surface Topography of proteins*) (http://sts.bioe.uic.edu/castp/calculation.html). *CASTp*

3.0 is a web server which provide comprehensive identification of protein topography including surface pockets of the protein, which will be used to validate target protein active sites in this study (16).

Molecular docking

The next process is molecular docking, which were carried out to predict binding energies between ligands toward COVID-19 therapy target proteins using *AutoDock Vina* software via Command Prompt (17). This study using blind docking in the molecular docking process, so the gridbox parameters of each target protein were set to cover the whole target protein, using *AutoDockTools-1.5.6*. The best binding affinity pose was selected based on the lowest *binding energy* pose, which choosen from nine conformation poses formed in the output of *AutoDock Vina*. After that, the molecular interactions of each pose choosen were analyzed using *Discovery Studiov21*.

Drug-likeness properties

This study uses Lipinski's Rule of Five to assess drug-likeness properties of chlorogenic acid. Lipinski's violation and each Lipinski's Rule of Five parameter such as H-bond donor, H-bond acceptor, molecular weight, and logP, were screened by using SwissADME tools (http://www.swissadme.ch/index.php) (18).

RESULTS AND DISCUSSION

Target protein active sites prediction

Table 1. Active sites of each target protein

Target protein	Active site residues
ACE2	Asp30, Phe32, Asn33, His34, Glu37, Asp38, Phe40, Ser43, Ser44, Ala46, Ser47, Tyr50, Asn51, Val59, Met62, Asn63, Ala65, Gly66, Asp67, Trp69, Ser70, Ala71, Leu73, Lys74, Ser77, Thr78, Gln81, Leu85, Gln86, Leu91, Lys94, Leu95, Gln98, Ala99, Leu100, Gln101, Gln102, Asn103, Gly104, Ser105, Ser106, Leu108, Ser109, Glu110, Ser113, Lys114, Leu116, Asn117, Leu120, Asn121, Met123, Ser124, Thr125, Tyr127, Ser128, Leu144, Glu145, Pro146, Asn149, Glu150, Met152, Ala153, Asn154, Lys187, Met190, Ala193, Asn194, His195, Tyr196, Tyr199, Tyr202, Trp203, Arg204, Gly205, Asp206, Tyr207, Glu208, Val209, Asn210, Val212, Arg219, Leu222, Gly268, Asp269, Met270, Trp271, Arg273, Phe274, Thr276, Asn277, Asn290, Ile291, Leu320, Pro321, Thr324, Gln325, Gly326, Phe327, Phe329, Asn330, Lys341, Val343, Cys344, His345, Pro346, Thr347, Ala348, Trp349, Asp350, Leu351, Gly352, Lys353, Gly354, Asp355, Phe356, Leu359, Met360, Cys361, Lys363, Thr365, Met366, Asp367, Asp368, Leu370, Thr371, His374, Glu375, His378, Gln380, Asp382, Met383, Ala384, Tyr385, Ala386, Ala387, Gln388, Pro389, Phe390, Leu391, Leu392, Arg393, Asn394, Gly395, Ala396, Asn397, Glu398, Gly399, His401, Glu402, Glu406, Ser409, Leu410, Ala413, Thr414, Pro415, Phe428, Glu430, Asp431, Thr434, Glu435, Phe438, Lys441, Gln442, Thr445, Ile446, Thr449, Glu457, Trp461, Leu503, Phe504, His505, Ser507, Asn508, Asp509, Tyr510, Ser511, Ile513, Arg514, Tyr515, Arg518, Thr519, Gln522, Gln526, Leu539, His540, Lys541, Cys542, Phe555, Arg559, Lys562, Ser563, Glu564, Pro565, Trp566, Tyr587
TMPRSS2	Asn247, Leu248, Asn249, Glu260, Ser261, Ala262, Leu263, Ala266, Trp267, His274, Val275, Gln276, Asn277, Trp306, His307, Thr309, Phe311, Met320, Tyr322, Gly323, Gly325, Gln327, Trp380, Ala399, Ser436, Ser438, Ser441, Cys465
RdRp	Tyr32, Arg33, Ala34, Phe35, Asp36, Ile37, Tyr38, Asn39, Lys50, Lys47, Tyr122, Asp126, Tyr129, Ala130, Arg132, His133, Phe134, Asp135, Asn138, Cys139, Thr141, Leu142, Val204, Thr206, Asp208, Asn209, Asp218, Gly220, Asp221, Ser236, Asn705, Ala706, Ser709, Tyr728, Arg733, Ala771, Gly774, Val776, Ser778, Lys780, Asn781, Ser784, Val785, Tyr788,
3CLpro	Phe8, Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Met49, Ile106, Gln107, Pro108, Gly109, Gln110, Thr111, Arg131, Pro132, Lys137, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, Asn151, Ile152, Asp153, His163, His164, Met165, Glu166, Leu167, Pro168, Arg188, Gln189, Thr190, Gln192, Asp197, Thr199, Ile200, Thr201, Val202, Asn203, Glu240, Pro241, Leu242, Asp245, His246, Ile249, Leu286, Leu287, Glu288, Asp289, Thr292, Pro293, Phe294, Asp295, Arg298, Phe305

Active sites of each target protein identified using *CASTp 3.0* web server. There are 195 active sites of ACE2, 28 active sites of TMPRSS2, 44 active sites of RdRp, and 60 active sites of 3CLpro. Each active sites amino acid shown at **Table 1**.

Molecular docking study

We conducted molecular docking of chlorogenic acid to four target proteins used, and docking of comparative drugs to its receptor. The docking result are represented in **Table 2**.

Table 2. Molecular Docking Result

Ligand	Binding energy (kcal/mol)			
	ACE2	TMPRSS2	RdRp	3CLpro
Chlorogenic Acid	-7.8	-6.9	-7.0	-7.4
Spironolactone	-5.1	-	-	-
Nafamostat	-	-7.6	-	-
Remdesivir	-	-	-7.7	-
Oseltamivir	-	-	-	-6.4

The molecular interactions formed and involved amino acid residue in each pose are shown in **Figure 1.**

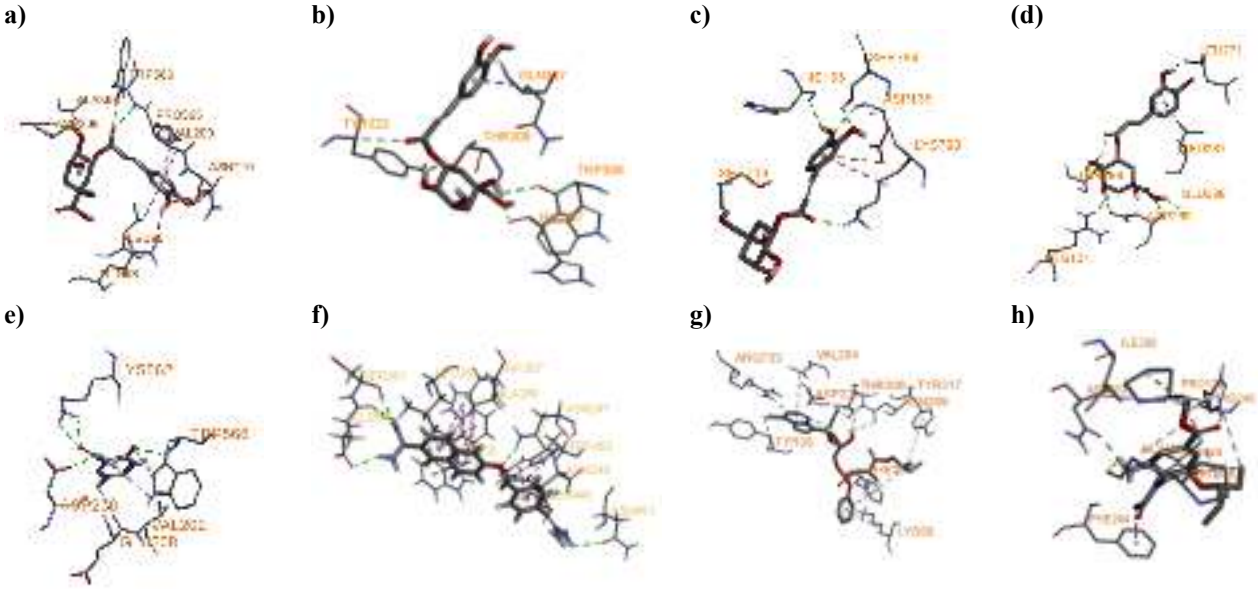
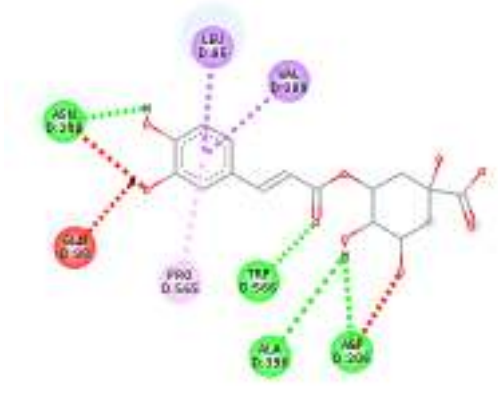


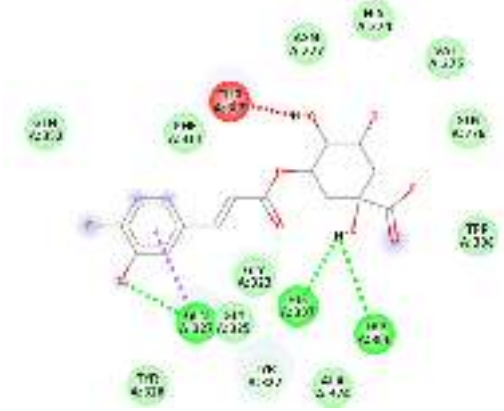
Figure 1. 3D molecular interaction diagram. (a) ACE2 and chlorogenic acid (b) TMPRSS2 and chlorogenic acid (c) RdRp and chlorogenic acid (d) 3CLpro and chlorogenic acid (e) ACE2 and spironolactone (f) TMPRSS2 and nafamostat (g) RdRp and remdesivir (h) 3CLpro and oseltamivir.

and **Figure 2,**

(a)



(b)



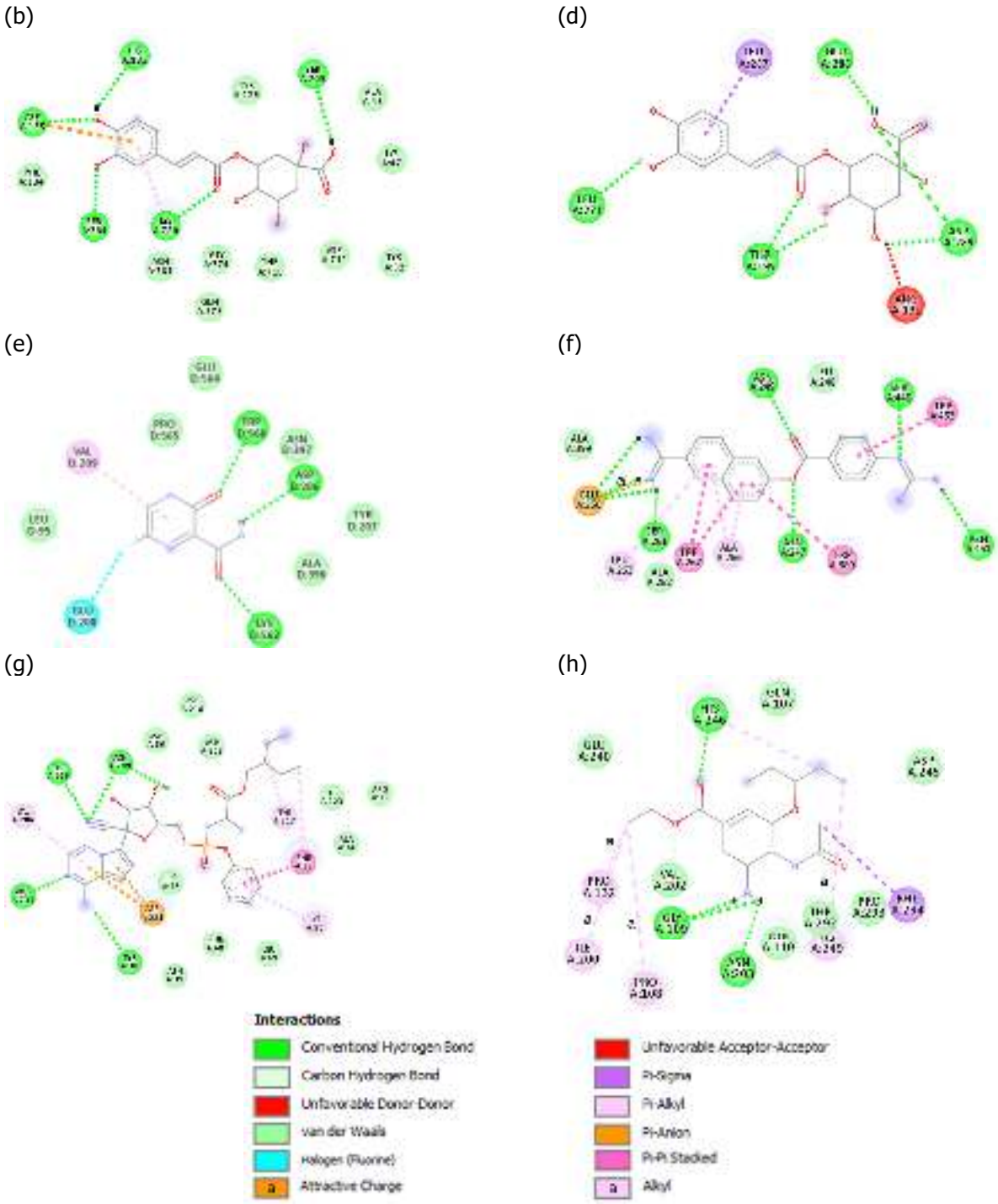


Figure 2. 2D molecular interaction diagram. (a) ACE2 and chlorogenic acid (b) TMPRSS2 and chlorogenic acid (c) RdRp and chlorogenic acid (d) 3CLpro and chlorogenic acid (e) ACE2 and spironolactone (f) TMPRSS2 and nafamostat (g) RdRp and remdesivir (h) 3CLpro and oseltamivir.

and summarized in **Table 3**.

Table 3. Molecular interactions and involved amino acid residues in each pose.

Ligand	Interactions	Amino acid residues involved in interactions		
		Hydrogen bonds	Hydrophobic bonds	Unfavorable bonds
Chlorogenic Acid	ACE2	Asp206, Asn210, Ala396, Trp566	Leu95, Val209, Pro565	Gln98, Asp206, Asn210
	TMPRSS2	Trp306, His307, Tyr322, Gln327	Gln327	Thr309
	RdRp	His133, Asp135, Ser709, Lys780, Ser784	Lys780	-
	3CLpro	Thr199(2), Leu271, Glu288, Asp289(2)	Leu287	Arg131

Spironolactone	ACE2	Asp206, Lys562, Trp566	Val209	-
Nafamostat	TMPRSS2	Asn247, Asn249, Glu260(3), Ser261, Ser448, Asn451	Leu263, Ala266(2), Trp267(2), Trp380, Trp453	-
Remdesivir	RdRp	Tyr38, Thr206, Asn209(2), Arg733	Phe35(2), Lys50, Val204, Tyr217, Asp221(2)	Asn209
Oseltamivir	3CLpro	Gly109(2), Asn203, His246	Pro108, Gly109, Pro132, Ile200, His246, Ile249, Phe294	-

The result show that chlorogenic acid have an affinity for all receptor targets. This is characterized by energy released when ligand form complexes with the target protein, which called as binding energy. The lower the binding energy of a complex obtained shows the stronger affinity of the ligand with the target protein (19).

ACE2

Chlorogenic acid was found to have higher affinity with ACE2, with a binding energy of -7.8 kcal/mol, compared to spironolactone with a binding energy of -5.1 kcal/mol. From the interactions, chlorogenic acid was found to have 4 hydrogen bonds with the residues Asp206, Asn210, Ala396, and Trp566; and 3 hydrophobic bonds with the residues Leu95, Val209, Pro565. But there is also 3 unfavorable bonds with the residues Gln98, Asp206, and Asn210. Unfavorable bonds can affect activity stability of the ligand towards the target protein, because it indicates there are repulsion force that occured within 2 molecules and an atom (20). Besides, spironolactone as drug that founded can target ACE2 in COVID-19, had 3 hydrogen bonds with the residues Asp206, Lys562, and Trp566; and an hydrophobic bond with the residue Val209. There are 3 residues that involved in both interaction with ACE2, which are Asp206, Asn210, and Val209. From ACE2 active sites results in *CASTp 3.0* and these results, we can concluded that all amino acids involved in both ligand interactions with ACE2 is active sites.

TMPRSS2

Molecular docking results shows that chlorogenic acid have lower affinity with TMPRSS2, with a binding energy of –6.9 kcal/mol, compared to nafamostat with a binding energy of -7.6 kcal/mol. From the interactions, chlorogenic acid was found to have 4 hydrogen bonds with the residues Trp306, His307, Tyr322, and Gln327; and an hydrophobic bond with the residue Gln327. But there is also an unfavorable bond with the residue Thr309. Besides, nafamostat as current COVID-19 drug that targeted TMPRSS2, had 8 hydrogen bonds with the residues Asn247, Asn249, Glu260(3), Ser261, Ser448, and Asn451; and 7 hydrophobic bonds with the residues Leu263, Ala266(2), Trp267(2), Trp380, and Trp453. All residues involved in chlorogenic acid and nafamostat were different, which means there were different binding sites between chlorogenic acid

and nafamostat. From TMPRSS2 active sites results and amino acids involved in these results, we can concludedthat almost all amino acids involved in both ligand interactions with TMPRSS2 is active sites, except Tyr322 in chlorogenic acid and Ser448, Asn451, and Trp453 in nafamostat.

RdRp

Chlorogenic acid was found to have lower affinity with RdRp, with a binding energy of -6.9 kcal/mol, compared to current drug, remdesivir with a binding energy of -7.7 kcal/mol. Molecular interactions showed that chlorogenic acid had 4 hydrogen bonds with the residues His133, Asp135, Ser709, Lys780, and Ser784; and an hydrophobic bond with the residue Lys780. Besides, remdesivir as current COVID-19 drug that target RdRp, had 5 hydrogen bonds with the residues Tyr38, Thr206, Asn209(2), and Arg733; and 7 hydrophobic bonds with the residues Phe35(2), Lys50, Val204, Tyr217, and Asp221(2). Other than that, there is also an unfavorable bond with a residue Asn209. There were different residues involved in chlorogenic acid and remdesivir interactions with RdRp. However, all those residues were active sites of RdRp based on the results gained by *CASTp 3.0*.

3CLpro

Docking results showed that chlorogenic acid have higher affinity with 3CLpro, with a binding energy of -7.4 kcal/mol, compared to current drug, oseltamivir with a binding energy of -6.4 kcal/mol. Results showed that chlorogenic acid had 6 hydrogen bonds with the residues Thr199(2), Leu271, Glu288, and Asp289(2); and 1 hydrophobic bond with the residue Leu287. There is also an unfavorable bond with the residue Arg131, which can affect its activity stability toward 3CLpro. Besides, oseltamivir as current COVID-19 drug that target 3CLpro, had 4 hydrogen bonds with the residues Gly109(2), Asn203, and His246; and 7 hydrophobic bonds with the residues Pro108, Gly109, Pro132, Ile200, His246, Ile249, and Phe294. All residues involved in chlorogenic acid and oseltamivir were different, which means they interact with different binding sites toward 3CLpro. Although, almost all residues were active sites of 3CLpro based on the results gained by *CASTp 3.0*, except Leu271 in chlorogenic acid.

Drug-likeness properties

Chlorogenic acid compound was virtually screened against Lipinski's Rule of Five using SWISSADME website. Lipinski's Rule of Five stated that to be considered as a drug-like, a compound must obey minimum three of these four criteria: molecular weight >500 gr/mol, H-bond donor >5, H-bond acceptor >10, and ClogP >5(or MlogP >4,15). These criteria based on Lipinski's study that predicts that any compounds violate more than two criteria, is more likely have poor absorption or permeation (22). Lipinski's Rule of Five results showed at **Table 4**. Results showed

that chlorogenic acid obey Lipinski's Rule of Five with an violation at H-bond donor.

Table 4. Lipinski's Rule of Five results

Compounds	Mr	H-bond Donor	MlogP	H-bond Acceptor	Lipinski's Violation
Chlorogenic acid	354.31	6	-1.05	9	1

DISCUSSION

Based on our study, chlorogenic acid showed an affinity for all target receptors, characterized by the binding energy released when the ligand forms complexes with the target protein. The lower the binding energy, the stronger the affinity between the ligand and the target protein. Chlorogenic acid demonstrated higher affinity for ACE2, with a binding energy of -7.8 kcal/mol, compared to spironolactone's -5.1 kcal/mol. This interaction included four hydrogen bonds and three hydrophobic bonds, but also three unfavorable bonds, which can impact the stability of the ligand's activity due to repulsion forces within the molecules. For TMPRSS2, chlorogenic acid had a lower affinity (-6.9 kcal/mol) compared to nafamostat (-7.6 kcal/mol). It formed four hydrogen bonds and one hydrophobic bond, alongside an unfavorable bond. This indicates different binding sites from nafamostat, which had numerous hydrogen and hydrophobic bonds contributing to its higher affinity. With RdRp, chlorogenic acid's binding energy was -6.9 kcal/mol, less than remdesivir's -7.7 kcal/mol. Chlorogenic acid formed four hydrogen bonds and one hydrophobic bond, while remdesivir formed five hydrogen bonds and seven hydrophobic bonds, indicating stronger interactions. The residues involved in the interactions were different, suggesting unique binding sites but still within the active sites of RdRp. For 3CLpro, chlorogenic acid showed higher affinity (-7.4 kcal/mol) compared to oseltamivir (-6.4 kcal/mol), forming six hydrogen bonds and one hydrophobic bond. An unfavorable bond was also present, potentially affecting the interaction stability. Oseltamivir interacted with different binding sites, evidenced by its different residues involved. The molecular interactions of chlorogenic acid were analyzed based on hydrogen bonds, hydrophobic bonds, and unfavorable bonds. Hydrogen bonds are critical for specific and strong ligand-protein interactions, enhancing stability and binding affinity. Hydrophobic bonds contribute to the proper alignment and interaction within the hydrophobic regions of target proteins, playing a crucial role in binding affinity and drug activity. Unfavorable bonds, however, indicate repulsive forces that can destabilize the ligand-protein complex, reducing the efficacy and stability of the drug candidate. Furthermore, chlorogenic acid adheres to Lipinski's Rule of Five, with only one violation concerning hydrogen bond donors. This suggests that chlorogenic acid retains drug-like properties, making it a promising candidate for drug development despite the presence of some

unfavorable interactions. The identified unfavorable bonds highlight the need for further studies, such as molecular dynamics simulations, to understand the molecular mechanisms and optimize the interaction stability (21). Overall, chlorogenic acid's potential as a COVID-19 drug candidate lies in its strong interactions with ACE2 and 3CLpro, while further optimization could enhance its affinity for TMPRSS2 and RdRp.

CONCLUSION

Chlorogenic acid has the ability to become drug candidate based on Lipinski's Rule of Five. Based on molecular docking study, chlorogenic acid is potent to become COVID-19 drug candidate, which this compound has multiple target proteins of COVID-19 therapy targets, which some stronger than current drug(spironolactone and oseltamivir) and some weaker than current drug (nafamostat and remdesivir). But further studies like molecular dynamics study, in-vitro or in-vivo studies are needed in order to analyze this compound further and bring it at the clinical settings.

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