Molecular Docking Studies of SARS-Cov-2 Mainprotease Potential Inhibitors

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Abstract

BACKGROUND : SARS-Cov-2 causes an coronavirus disease 2019 (COVID-19), and the vaccines or drugs of this disease have not been found to inhibit this replication of the virus. Researchers are engaged in all fields of study to discover new potential inhibitors. This study aimed to compute the binding energy (BE) and interactions between the new potential inhibitors and the SARS-Cov-2 Mainprotease (Mpro).

METHODS: In this study, we docked between twenty-seven patented drugs and the Mpro receptor (PDB ID: 6W63). The molecular docking calculation was performed using AutoDock Tools 1.5.6. software. Moreover, the information about the biological activity of ligands was calculated using the PASS online server. The result of the calculation was then analyzed and visualized using Biovia Discovery Studio Visualizer. Further calculation, such as the ligand-protein interaction using STITCH database and Lipinski's rule five were employed in this research.

RESULTS: The molecular docking calculation results showed that nelfinavir was strongly bound to Mpro with BE of -9,51 kcal/mol, followed by lopinavir, vitamin D, ritonavir, and dexamethasone. From these ligands, we considered dexamethasone because this ligand works as an anti-inflammatory agent.

CONCLUSIONS: Following the calculation, nelfinavir, lopinavir, and dexamethasone are proposed as a potential inhibitor of the Mpro receptor, but there is a need for further investigation.

Background

At the end of 2019, the 2019-nCov viruses invade Wuhan city ¹, Hubei Province, China. World Health Organization (WHO) then officially named the virus SARS-Cov-2 and the disease caused by it as coronavirus disease 2019 (COVID-19). Because this disease was spread worldwide, the WHO announced the condition as an international pandemic in March 2020 ². As of 18 July 2020, there have been over 13.575.158 confirmed cases globally (WHO, 2020).

The previous study has reported that the SARS-Cov-2 is one of the β -coronavirus with RNA particle causing an acute infection of human respiratory system, and uses angiotensin-converting enzyme 2 (ACE2) to penetrate the human cell membrane ³⁻⁵. The transmission of this virus from infected people could happen through droplets, saliva, or liquid ⁶. The SARS-Cov-2 has a similar genomic structure with other β -coronavirus, but it is distinctly different from MERS-Cov and SARS-Cov. The β -coronavirus group has a ~800 kDa polypeptide, which can split into several proteins. Polypeptide splitting is a critical step in the virus replication process ¹. The degradation of the polypeptide is mediated by papain-like protease (PLPro) and 3-chymotrypsin-like protease (3CLPro). Therefore, one way to resolve SAR-Cov-2 infection is to inhibit this enzyme.

Previous studies have shown that hesperidine, rutin, nelfinavir, lopinavir, kaempferol, and diosmin may be strongly bound to the active of 3CL^{Pro} receptor site ^{2,7}. Presently, chloroquine is widely used as a potential cure for COVID-19 patients globally ⁸. The inhibition mechanism of chloroquine interferes with the ACE2

receptor glycosylation, so it prevents the SARS-Cov-2 binding the cell target ⁹. Other than 3CLpro, the virus replication can also be inhibited by inhibiting Mpro.

The crystal structure of the SARS-Cov-2 Mpro has been identified and stored at Protein Data Bank, and one of them is a liganded 6W63 receptor with X77, which is a novel inhibitor. The previous study reported that nelfinavir, ritonavir, and darunavir may interact with this receptor ⁶. Because the vaccines or cures for COVID-19 have not yet been identified, patented drugs have been used as a calculation input for this research. The information on the drug was used in this study was collected from the previous research ¹⁰. Thus we performed molecular docking calculation to identify candidates as potential inhibitors of Mpro.

Method

Molecular Docking Calculation

The molecular docking calculation was conducted using 27 compounds which are Nelfinavir, Lopinavir, Vitamin D ¹¹⁻¹³, Ritonavir, Dexamethasone, Baloxivir Marboxil, Alpha Tocopherol Acetate (Vitamin E), Vitamin A, Umifenovir, Darunavir, Cobicistat ⁶, Meropenem ¹⁰, Midazolam, Levofloxacin, Chloroquine Phosphate, Chloroquine ¹⁴, Oseltamivir, Chloroquine Sulfate, Hydroxychloroquine, Cefotaxime, Salbutamol Sulfate, Remdesivir, Acetaminophen, Ribavirin, Favipiravir, Ascorbic acid (Vitamin C), and Acetylcysteine that were retrieved from pubchem.ncbi.nlm.nih.gov, and the receptor is obtained from www.rcsb.org with PDB ID: 6W63. Before molecular docking calculation was performed, the receptor and ligand were prepared using Chimera 1.14 ¹⁵. The redocking calculation was conducted between native ligand (X77) and the active site of the 6W63 receptor. The molecular docking calculation was performed utilizing AutodockTools 1.5.6 sized the grid box 40 x 40 x 40 points, spacing 0,375 Å. For searching the parameter, we used the Lamarckian Genetic Algorithm (LGA) in 100 runs ¹⁶. The result of the calculation with the best conformation was visualized using Biovia Discovery Studio Visualizer to observe molecular interactions.

Biological Activity Analysis

Twenty-seven ligands were analyzed using the PASS server online (<http://www.pharmaexpert.ru/passonline>) to determine their biological activity. This analysis is based on Structure-Activity Relationship (SAR). This step yielded a probability of active (Pa) and the probability of inactive (Pi) with range 0-1. If the Pa value is greater than 0.7, so the compound has a biology activity ^{17,18}.

Lipinski's Rule and STITCH Database

The drug-like properties of the 27 potential inhibitors were calculated by using Drug Likeness Tools (DruLiTo) software based on the Lipinski's rule five. The potential inhibitors were then further analyzed using a server online Search Tool for Interactions of Chemical (STITCH) (<http://stitch.embl.de/>) to predict ligand-protein interaction.

Result

In this study, we use the 6W63 receptor liganded to X77. The redocking calculation was conducted for standard data and method validations, and then further calculation was performed on a new potential inhibitor with the same parameter as the redocking process. The result of redocking between receptor and the native ligand is depicted in Figure 1. The result of the molecular docking calculation between the Mpro receptor and 27 drugs is given in Table 1. The potential inhibitors were selected from the previous studies such as Nelfinavir, Lopinavir, Vitamin D Ritonavir, Dexamethasone, Baloxivir Marboxil, Vitamine E, Vitamin A, Umifenovir, Darunavir, Cobicistat, Meropenem, Midazolam, Levofloxacin, Chloroquine Phosphate, Chloroquine, Oseltamivir, Chloroquine Sulfate, Hydroxychloroquine, Cefotaxime, Salbutamol Sulfate, Remdesivir, Acetaminophen, Ribavirin, Favipiravir, Ascorbic acid (Vitamin C), and Acetylcysteine^{6,10–14}. Following Table 1, there is a ligand with BE comparable or better than native ligand, nelfinavir.

Table 1.

The result of molecular docking calculation some potential inhibitors and Mproreceptor

No.	Compounds	Binding Energy (Kcal/mol)	Amino Acids Residu
1	Native ligand (X77)	-9.24	GLY143, GLU166, CYS145
2	Nelfinavir	-9.51	GLN189, HIS164, PHE140, GLU166
3	Lopinavir	-9.13	HIS41
4	Vitamin D	-9.12	GLU166
5	Ritonavir	-8.68	GLU166
6	Dexamethasone	-8.30	GLN192, THR190, ARG188
7	Baloxivir Marboxil	-8.25	GLU166, GLY143, ASN142
8	Vitamine E	-8.10	GLY143
9	Vitamin A	-7.99	GLU166
10	Umifenovir	-7.84	GLU166, ASN142
11	Darunavir	-7.83	GLU166, MET49, ASP187
12	Cobicistat	-7,43	GLU166, GLY143
13	Meropenem	-7.57	GLN192, GLN189, GLU166, THR190, ARG188
14	Midazolam	-7.15	-
15	Levofloxacin	-7.00	HIS41, ARG188
16	Chloroquine Phosphate	-6.55	HIS164
17	Chloroquine	-6.40	GLU166, HIS164
18	Oseltamivir	-6.37	GLU166
19	Choloroquine Sulfate	-6.37	GLU166
20	Hydroxychloroquine	-6.42	THR190, GLN192
21	Cefotaxime	-5.84	GLY143, GLN189, HIS163
22	Salbutamol Sulfate	-5.69	GLU166, PHE140
23	Remdesivir	-5.38	ARG188
24	Acetaminopen	-5.05	GLY143
25	Ribavirin	-4.97	-

26	Favipiravir	-4.14	GLY143, CYS145, SER144
27	Vitamin C	-4.08	GLU166, GLY143, HIS163, LEU141
28	Acetylcysteine	-3.51	SER144, GLU166, ASN142

Table 1 shows that several ligands interact with the same amino acid residues compared to the native ligands through conventional hydrogen bond and other secondary interactions. The potential inhibitors that bind to one amino acid residue are nelfinavir, vitamin D, ritonavir, vitamin E, vitamin A, umifenovir, darunavir, meropenem, chloroquine, oseltamivir, chloroquine sulfate, cefotaxime, salbutamol sulfate, acetaminophen, and acetylcysteine. There are also other potential inhibitors that bind two amino acid residues, such as baloxivir marboxil, cobicistat, favipiravir, and Vitamin C. Other ligands such as lopinavir, dexamethasone, midazolam, levofloxacin, chloroquine phosphate, hydroxychloroquine, remdesivir, and ribavirin do not form the same interaction with native ligand. In addition, Table 1 also shows BE information of its ligands with the active site of Mpro receptor. Nelfinavir is the lowest BE compared to native ligand, while the other potential inhibitors are higher than native ligand. In addition to the BE calculations, amino acid residues are crucial information to discuss a potential inhibitor of Mpro receptor inhibition.

Figure 1 shows that the native ligand binds three amino acid residues via conventional hydrogen bonds such as GLU166, CYS145, and GLY143, even as non-classical hydrogen bonds are LEU141, SN142, and THR26. Native ligand also has secondary interactions such as electrostatic (HIS164) and hydrophobic (MET165, LEU141, CYS145, HIS41, and LEU27). Nelfinavir attaches the residues of amino acids GLN189, GLU166, PHE140, and HIS164. The interaction with GLU166 amino acid residue shows that nelfinavir has the same interaction with native ligand. Hydrophobic interaction with MET165 amino acid residue has also occurred in this complex. Nelfinavir also interacts with CYS145 through sulphur interaction (see pic. 1.c. and 1.d.). Referring to Figure 1.d, nelfinavir binds four amino acid residues such as HIS164, PHE140, GLU166, and GLN189. HIS164 is bound to hydroxyl, PHE140 hydroxyl, and aromatic, GLU166 to a ketone, and GLN189 to an amide. Other potential inhibitors that included on the top seven BE are depicted in Figure 2. Figure 2 shows 2-dimensional visualization of several Mpro receptor inhibitors, namely Lopinavir, vitamin D, ritonavir, dexamethasone, baloxivir marboxil, vitamin E, which have BE of -9.13 to -8.10 kcal/mol. Lopinavir is tied to HIS41 on the Mpro receptor through a conventional hydrogen bond. Vitamin D and ritonavir bind the same amino acid residue, GLU166. Dexamethasone has different interactions with the native ligand. Baloxivir marboxil interacts with GLU166 and GLY143, while vitamin E interacts with GLY143. The Pa analysis, Lipinski's rule, and ligand-protein interactions were performed to explain the potential inhibitors of Mpro.

Table 2.
Analysis of the probability of active (Pa) potential inhibitors

No	Compounds	Pa value	Activity
1	Nelfinavir	0.590	Antiviral
2	Lopinavir	0.482	Antiviral
3	Vitamin D	0.508	Antiviral (Rhinovirus)
4	Ritonavir	0.602	Antiviral
5	Dexamethasone	0.420	Antiviral (Rhinovirus)
6	Baloxivir Marboxil	-	-
7	Vitamine E	0.386	Antiviral (Rhinovirus)
8	Vitamin A	0.421	Antiviral (Herpes)
9	Umifenovir	0.740	Antiviral (Influenza)
10	Darunavir	0.878	Antiviral (HIV)
11	Cobicistat	0.403	Antiviral
12	Meropenem	-	-
13	Midazolam	-	-
14	Levofloxacin	0.291	Antiviral (Adenovirus)
15	Chloroquine Phosphate	-	-
16	Chloroquine	-	-
17	Oseltamivir	0.932	Antiviral (Influenza)
18	Choloroquine Sulfate	-	-
19	Hydroxychloroquine	0.323	Antiviral (Rhinovirus)
20	Cefotaxime	0.382	Antiviral (Rhinovirus)
21	Salbutamol Sulfate	0.391	Antiviral (Picornavirus)
22	Remdesivir	0.814	Antiviral
23	Acetaminopen	0.588	Antiviral (Influenza)
24	Ribavirin	0.829	Antiviral
25	Favipiravir	0.662	Antiviral
26	Vitamin C	0.567	Antiviral (Rhinovirus)
27	Acetylcysteine	0.658	Antiviral (Picornavirus)

To ensure of molecular docking data, we use the PASS server online to perform a Pa value analysis. The Pa value was obtained from the SMILE of each of the potential inhibitors. The SMILE of each potential inhibitors was used to calculate Pa value. The results of this analysis are Pa and Pi values, which can be considerable discussion of this study. The Pa analysis of inhibitors is used to explore a specific activity as an antiviral agent based on SAR. Table 2 shows the Pa of antiviral activity in the range 0-1. Based on Table 2, the Pa values for umifenovir, darunavir, oseltamivir, remdesivir, and ribavirin are 0.740; 0.878; 0.932; 0.814; and 0.829, respectively. Although the BE calculation of 5 inhibitors are low, these inhibitors are still used as drugs for COVID-19 treatment ¹⁹.

There is a crucial analysis in drug design, i.e., Lipinski's rule of five. Table 3 shows that the 27 simulated potential inhibitors do not display more than two violations of Lipinski's rule of five. Among the potential inhibitors on Table 3, it can be observed that dexamethasone, umifenovir, meropenem, midazolam, levofloxacin, chloroquine, oseltamivir, hydroxychloroquine, salbutamol sulfate, acetaminophen, ribavirin, favipiravir, vitamin C, and acetylcysteine do not violate. At the same time, the remaining shows contravention of 1 namely nelfinavir, lopinavir, vitamin D, E, A, and cefotaxime. Ritonavir, darunavir, cobicistat, and remdesivir are in violation 2.

Table 3.
Properties of 27 potential inhibitor based on Lipinski' rule of five

No.	Compounds	Lipinski's Rule				
		MW (Da)	LogP	HBA	HBD	Violation
1	Nelfinavir	567.31	3.948	7	4	1
2	Lopinavir	628.36	3.688	9	4	1
3	Vitamin D	384.34	9.896	1	1	1
4	Ritonavir	720.31	3.546	11	4	2
5	Dexamethasone	392.2	1.138	5	3	0
6	Baloxivir Marboxil	571.12	0.579	10	0	2
7	Vitamine E	430.38	10.695	2	1	1
8	Vitamin A	286.23	6.158	1	1	1
9	Umifenovir	476.08	3.328	5	1	0
10	Darunavir	547.24	1.154	10	3	2
11	Cobicistat	775.35	3.309	12	3	2
12	Meropenem	383.15	-0.778	8	3	0
13	Midazolam	325.08	1.835	3	0	0
14	Levofloxacin	361.14	1.995	7	1	0
15	Chloroquine Phosphate	-	-	-	-	-
16	Chloroquine	319.18	2.68	3	1	0
17	Oseltamivir	312.2	1.052	6	2	0
18	Choloroquine Sulfate	-	-	-	-	-
19	Hydroxychloroquine	335.18	1.548	4	2	0
20	Cefotaxime	455.06	-2.712	10	3	1
21	Salbutamol Sulfate	239.15	0.469	4	4	0
22	Remdesivir	602.23	0.3336	14	4	2
23	Acetaminopen	151.06	0.314	3	2	0
24	Ribavirin	244.08	-2.433	9	4	0
25	Favipiravir	157.03	-0.822	5	2	0
26	Vitamin C	176.03	-0.178	6	4	0

27	Acetylcysteine	163.03	-0.133	4	2	0
MW: molecular weight						
HBA: H-bond acceptor						
HBD : H-bond donor						

Calculations for the chemical-protein interaction of four (4) potential inhibitors of *Homo sapiens* are shown in Figure 3. Drugs are depicted as shaped pills, while the proteins are represented as a sphere. The nodes describe a drug action to protein such as green (activation), red (inhibition), blue (binding), cyan (phenotype), purple (catalysis), black (reaction), pink (posttranslational modification), and yellow (transcriptional regulation). Based on the STITCH database, the interaction scores are divided into three (3) clusters, namely medium confidence (0.40-0.70), high confidence (0.70-0.90), and the highest confidence (0.90-1.00). The most important interaction that contributing to this prediction is binding, inhibition, and activation²⁰, so the discussions in this article are based on three clusters.

Discussion

The previous studies have shown that nelfinavir may bind with other Mpro receptors such as 6LU7 and 3M3V. The BE results of these studies were -10.72 and -17.31 kcal/mol for 6LU7 and 3M3V. Although their tendency to interact poses was similar, the interactions of these complexes with each protein were different. In this study, nelfinavir interacts with the residues of amino acids GLN189, HIS164, PHE140, and GLU166, while it was bound with CYS145, MET49, MET165, GLU166, LEU167, PRO168, GLY170, GLN189, THR190, ALA191 and HIS41 in the active site of the 3M3V receptor¹. As a result, nelfinavir is often used as a standard for molecular docking research^{6,7}

Previous studies have shown that, lopinavir also has a functional inhibition of the Mpro receptor. In this research lopinavir is one of the top four, -9.13 kcal/mol. Although the BE score is higher than native ligand, this drug is reported as an inhibitor of the SARS-Cov-2 on Vero E6 cells with EC₅₀ below 100 µM²¹. This drug may be used in vitro against SARS-Cov, MERS-Cov, and hCov-229E⁷. Lopinavir is often combined with ritonavir for inhibiting the Mpro receptor. This step causes the uses of lopinavir in a mixture that is not too much^{7,22,23}. The previous data showed that twenty-seven COVID-19 patients have treated with lopinavir 400 mg/ritonavir 100 mg¹⁴. These drugs have also been reported to inhibit HIV protease, a member of β-coronavirus, due to their therapeutic benefits as antivirals. Lopinavir was shown to have the best therapeutic benefit compared to ritonavir²⁴. In addition to nelfinavir and lopinavir, the results of this study show that vitamin D is potent as an inhibitor of Mpro.

Vitamin D has the lowest BE among vitamins in this study, -9.12 kcal/mol. This vitamin is used in the treatment to improve the immune system of patients and as a preventive measures. Previous studies

have reported that the use of vitamin D in therapy may reduce T helper cell type 1 (Th1) cytokines (tumor necrosis factor- α and interferon- γ) and expression of pro-inflammatory²⁵⁻²⁷. The use of vitamin D in the Mpro receptor inhibitor reduces the expression of the dipeptidyl peptidase-4 receptor (DPP-4), a molecular virulent that reacts with the SARS-Cov-2 spike glycoprotein²⁸. However, there is no firm evidence of the relationship between vitamin D and the death of patients^{12,13}. Vitamin A has BE -7.99 kcal/mol and may also increase the immune system in the human body. This vitamin is included in the list of drugs used to treat and to maintain immune system stabilization in patients^{29,30}.

Vitamin E and C are also used as immune boosters for treatment with COVID-19 globally. The BE for vitamin E and C is -8.1 dan -4.08 kcal/mol, respectively. Both compounds are antioxidants that can be obtained from fruit and vegetables in our dietary menu. Also these antioxidants may be obtained from supplements. The BE of Vitamin E is lower than Vitamin C, so vitamin E is expected to be more strongly bound to the Mpro receptor. The previous study explained that this antioxidant might increase T-cell subsets, lymphocyte reactions to mitogen, interleukin-2 production, potentiated natural killer cell activity, and influenza virus response compared with placebo. The use of antioxidants in the therapy process is essential to maintain physical and spiritual conditions during the quarantine period, and the healing process is quickly completed^{31,32}.

The anti-inflammatory agent is included in the list of the drugs used for therapy because the immune response of COVID-19 patients has increased such as the number of leukocytes, platelets, lymphocytes, and neutrophils^{33,34}. Dexamethasone is one of the corticosteroid groups used to cure a patient of SARS-Cov infection in patients^{19,35}. Oxford University recently researched the use of dexamethasone to chronic patients in the United Kingdom (UK), and the WHO has accepted the results of the. Based on the previous research review, the corticosteroid group has been shown to have clinical benefit. Critically, genomic SARS-Cov-2 and SARS-Cov are similar, so a literature review is conducted to gather data and evidence on the efficacy of the drug in the treating of patients. The use of this drug is better than Non-steroidal Anti-Inflammation Drugs (NSAIDs)^{35,36}. In general, NSAIDs are used as a pain killer for acute to chronic inflammation. Long-term consumption of this drug may cause adverse cardiovascular events in the human body¹⁶. Ibuprofen is one NSAIDs, and the use of these drugs causes an increase in ACE2 expression. The treatment of patients with co-morbid (diabetic) using NSAIDs may increase the incidence of SARS-Cov-2 infection³⁷. Researchers are still discussing COVID-19, followed co-morbid. The previous study reported that co-morbid (cancer) is not directly related to acute inflammation³⁸.

In addition to previous ligands, there are a number of other potential inhibitors such as umifenovir, darunavir, cobicistat, meropenem, midazolam, and levofloxacin. The BE of these ligands shall be between -7.83 and -7.0 kcal/mol. Generally, the BE of these potential inhibitors is higher than that of native ligand, but these inhibitors are still used for therapy. Umifenovir's function is to inhibit the interaction of the virus with the host cell membrane¹⁴. Umifenovir (arbidol) is used *in vitro* to cure influenza A infection. Applications of this drug to SAR-Cov-2 therapy still require advanced research to complete the information³⁹. Darunavir is also known as an inhibitor of HIV-1 protease, and this drug may prevent the

dimerization of HIV-1 protease⁴⁰. In Atlanta, at dose of 800 mg darunavir/Cobicistat 150 mg, darunavir/cobicistat was used for 2 weeks (one daily) of patients¹⁴. In addition to antioxidants, antibiotics are also used in the treatment of patients. Earlier work described that almost all patients received antibiotics, antiviral, and glucocorticoid. Meropenem and levofloxacin are mostly antibiotics used in the medication of COVID-19 victims^{41–44}.

Chloroquine phosphate, chloroquine, oseltamivir, chloroquine sulfate, hydroxychloroquine, cefotaxime, salbutamol sulfate, remdesivir, acetaminophen, ribavirin, favipiravir, vitamin C, and acetylcysteine have BE -6.55 to -3.51 kcal/mol. The BE of these potential inhibitors is higher than native ligand, so these drugs are expected to interact weakly with the active site of the Mpro receptor. Newly, chloroquine phosphate has an excellent clinical effect on the treatment of this viral virus, while the molecular docking calculation of this study is -6.55 kcal mol⁻¹. Based on this score, this drug is weakly bound to the Mpro receptor⁴⁵.

Recently, a viral inhibitor has been used to treat patients with chloroquine, an antimalaria agent. The inhibition chloroquine mechanism on SARS-Cov-2 has not yet been invented. The previous study recommended that this drug be developed to treat COVID-19 with diabetes in India. The therapy was designed with a view to minimizing the risk, prolonged use, cost, and source of raw material¹⁴. The coronavirus seems to be using hemagglutinin-esterase, which binds sialic acid to the surface of the glycoprotein. There is an indication that this virus interacts with ACE2. When this virus binds to ACE2, so this process will continue to replicate the virus. Chloroquine could well interfere with the mechanism of ACE2, and this drug inhibits the reaction with the target cell. Chloroquine may interfere with the biosynthesis of sialic acid. This drug also modulates the acidity of the endosome to prevent the formation of autophagosomes. When mitogen-activated protein (MAP) kinase activation is reduced, virus replication may be managed to stop. This potential inhibitor interfere in the maturation of protein M and the creation of virion before entering the host cell⁹. The efficacy of this drug is to increase the pH of the endosome, a condition for the fusion virus²³.

Previous study reported that chloroquine demonstrated inhibition of Mpro receptor performance by indirect immunofluorescence assay. Inhibition of infection with this drug has been used to destabilize the terminal glycosylation of the cellular receptor, ACE2⁴⁶. Chloroquine is known to have been cheap and widely used^{8,45}. This drug may react with ritonavir/lopinavir in patient therapy^{22,47}. Eventually, chloroquine provides a good prediction for inhibition of Mpro receptor. This drug is generally used as an antimalarial drug⁸. The previous study concluded that chloroquine was known as an antiviral agent for several viruses, including coronavirus OC43, enterovirus EV-A71, Zika virus, influenza A H5NI, SARS coronavirus, chikungunya virus (CHIKV), and Ebola virus. However, HIV therapy has not been recommended for this drug^{8,23,48}. In this study, chloroquine is not the best choice as a new potential inhibitor Mpro. It can not be considered a new potential inhibitor through the Mpro pathway because the BE of this ligand is bad.

Besides the potential inhibitor explained above, there are ligands that have to BE higher than native ligands such as oseltamivir, chloroquine sulfate, hydroxychloroquine, cefotaxime, salbutamol sulfate, remdesivir, acetaminophen, ribavirin, favipiravir, vitamin C, and acetylcysteine. Oseltamivir with the trademark Tamiflu was recognized as an antiviral agent that alters free carboxylate as an active metabolism^{22,49}. Apart from oseltamivir, many researchers suggest hydroxychloroquine as opposed to chloroquine because hydroxychloroquine has a low toxin level. In vitro, hydroxychloroquine was the most proposed drug than chloroquine^{22,50}. Since then, the USA has claimed that remdesivir can be used in the treatment of COVID-19 patients in their country. Subsequently, the recent study claimed that remdesivir had no clinical benefit from chronic COVID-19⁵¹. This overview reveals that finding drugs or vaccines for this viral virus still requires a long research in all field studies.

Based on Table 1, favipiravir has a BE value of $-4.14 \text{ kcal mol}^{-1}$. This value is higher than native ligand, so this compound is estimated to be weakly constrained to the Mpro receptor relative to a native ligand. China and Japan used this drug to diagnose and treat influenza⁵². Favipiravir has not shown a binding effect under $100 \mu\text{M}$ ²¹. Recent studies have suggested that favipiravir has been used to treat influenza infection (A, B, C). This drug was also used to treat H5N1, Ebola (EBOV), human norovirus, and human arenavirus^{49,53}. The inhibition of RNA-dependent polymerase is a mechanism of favipiravir in the healing process¹⁴. The further research in order to obtain more comprehensive data^{54,55}. Chloroquine sulfate, cefotaxime, salbutamol sulfate, acetaminophen, and acetylcysteine do not show any results that could be considered from BE results.

According to Table 1, the native ligand is well-posed at the binding site of GLU166, CYS145, and GLY143 due to conventional hydrogen bonds. Subsequently, this novel inhibitor also interacts with residues of amino acids in the hydrophobic regions MET165, LEU141, CYS145, HIS41, and LEU27. In addition to hydrogen bond and hydrophobic interaction, the X77 also forms electrostatic interaction through HIS164 to strengthen its position. The existence of a hydrogen bond is crucial to the inhibition mechanism between drug candidates and Mpro receptors. This finding by the authors is compromised by a previous study⁵⁶. Almost all molecular docking calculations between ligands and Mpro receptor always react with the amino acid residues of GLY143, next CYS145, GLU166, and HIS163, so the amino acid residues are hypothesized as a priority in inhibiting Mpro receptor⁵⁷.

According to BE calculation, nelfinavir is the most potent potential candidate in this study, but this drug was compared to native ligand only via GLU166 for inhibiting the Mpro receptor. Nelfinavir is only attached to MET65 in the hydrophobic region and shows sulfur interaction with CYS145. A conventional hydrogen bond is a primary interaction in this discussion, but the hydrophobic also contributes to the stabilization of the drug-receptor complex⁵⁵.

Lopinavir unveils a different interaction with native ligand and interacts with HIS41 via conventional hydrogen bonds. This potential inhibitor binds to MET49, PRO52, ARG188, MET165, and LEU27 in the hydrophobic environment. Sulfur interaction also presents in this complex, CYS145. The previous study

showed that this drug was used as an experimental standard. This drug was also successful in inhibiting HIV, SARS, and MERS treatments^{7,36}. Lopinavir is used in combination with ritonavir to cure COVID-19 patients in several countries⁵¹. Lopinavir is also co-formulated with ribavirin for an inhibitor of SARS-Cov³⁶. The routine use of this drug has received a weak recommendation because it does not have sufficient evidence in the case of this pandemic⁵⁸. According to the interaction of amino acids, nelfinavir is still considered an excellent potential inhibitor of the Mpro receptor. Beside lopinavir, ligand from vitamin group is regarded as a new potential inhibitor, vitamin D. Vitamin D, an immune system booster, is used to protect COVID-19 patients. It shows hydrogen bond interaction with GLU166 and is useful in agreement with the native ligand. Although it does not show 100% the same interaction relative with the native ligand, with a vitamin D hydrophobic environment to stabilize the complex, namely MET165, HIS41, CYC145, MET49, LEU27, and CYS44. In order to clarify the explanation, we conducted a Pa analysis, Lipinski's rule, and ligand-protein interaction of potential inhibitors to explore their therapeutic benefits and drug-like properties.

In Pa calculation, umifenovir has specific activity an influenza antiviral. This result is consistent with the previous study that umifenovir was antiviral influenza in Russia and China¹⁹. To contribute, the new potential inhibitor is simulated by an online analysis using the PASS server to identify therapeutic candidates as antiviral agents. According to Table 2, umifenovir, darunavir, oseltamivir, remdesivir, and ribavirin have Pa values between 0.1 to 1. Compounds with an antiviral activity value of Pa in a computational or laboratory analysis^{17,18}. The Pa value of the PASS analysis results is not specific to SARS-Cov-2. This can be used as a material for further research consideration. In this result, Pa value nelfinavir has a low antiviral activity score, while oseltamivir shows the highest score.

Lipinski's rule of five gives us an overview of the drug-like inhibitor candidate. Overall, in Table 2, compounds with the violation value of more than one do not meet the criteria for the drug-likeness⁵⁹. The value of MV is a parameter for the penetration of drugs in the human body's cell membrane. If the MV is more than 500 Da, the drugs hardly enter into the cell membrane. Nelfinavir, lopinavir, ritonavir, baloxivir marboxil, darunavir, cobicistat, and remdesivir have MV greater than 500 Da, and may interfere with the diffusion of the cell membrane. It was also the case for logP, the H-bond donor, and the acceptor. If the limit of Lipinski's rule of five is violated by a candidate inhibitor, the candidates may not be suitable for laboratory synthesis⁶⁰. Lipinski's rule of five still shows that nelfinavir has good criteria to be a drug candidate for this viral virus.

In Figure 3.a. we can observe the nelfinavir-protein interaction on Homo sapien. Activation mechanism of nelfinavir, e.g., ATP-binding cassette, sub-family B (MDR/TAP), member 1 (ABCB1), while inhibition action of protein cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4); cyclin-dependent kinase 2 (CDK2); cytochrome P450, family 3, subfamily A, polypeptide 5 (CYP3A5); v-akt murine thymoma viral oncogene homolog 1 (AKT1); ATP-binding cassette, sub-family G (WHITE), member 2 (ABCG2); cytochrome P450, family 2, subfamily B, polypeptide 6 (CYP2B6); and heat shock protein 90kDa alpha (cytosolic), class A member 1 (HSP90AA1). The binding action of this drug is CYP34A and ABCB1.

Following to Figure 3.b. lopinavir has ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2) with score of 0.726. Then, inhibition action to cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4); zinc metalloproteinase STE24 (ZMPSTE24); and ATP-binding cassette, sub-family B(MDR/TAP), member 11 (ABCB11) with score 0.968; 0.942; 0.700, respectively. Binding action to protein CYP3A4 with score of 0.968. The vitamin D-protein interaction prediction on Figure 3.c. This vitamin shows an activation process to bone gamma-carboxyglutamate (gla) protein (BGLAP); vitamin D (1,25- dihydroxyvitamin D3) receptor (VDR); fibroblast growth factor 23 (FGF23); parathyroid hormone (PTH); cyclin-dependent kinase 2 (CDK2); and klotho (KL) with score 0.996;0.996; 0.800; 0.986; 0.943, and 0.917, respectively. BGLAP, PTH, and CDK2 also experience inhibition route with score 0.786; 0.986; and 0.700, singly. Despite binding activity of this vitamin is on VDR (0.800) and group-specific component (GC, 0.900).

Ritonavir also produces activation, inhibition, and binding pathways prediction on the protein of *Homo sapiens*, namely activation mechanism on the protein of ATP-binding cassette, sub-family B (MDR/TAP); member 1 (ABCB1), cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP22C9); scavenger receptor class B, member 1 (SCARB1); thrombospondin receptor (CD36); and scavenger receptor class B, member 2 (SCARB2). Protein CYP3A4; ZMPSTE24; CYP3A5; cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6); and caspase 1 (CASP1) are employed an inhibition mode, while CYP3A4 and CYP2C9 predict binding schema (see Figure 3.d.). This pathway prediction is in good agreement with the previous study ⁶¹.

Conclusion

Calculation of molecular docking using 27 potential inhibitors and the Mpro receptor yields several data. The BE of these potential inhibitors shows that nelfinavir is the best Mpro receptor complex supported by amino acid residue interaction. Other potential inhibitors in this study is lopinavir, and vitamin D. Previous study reported that, there was no direct evidence between vitamin D and COVID-19 infection. The analysis of Lipinski's rule of five shows that nelfinavir, lopinavir, and vitamin D do not display more than one violation. Dexamethasone as an anti-inflammatory agent may also be considered in this study because there is no violation of the result of Lipinski's rule of five. Based on the calculation and analysis data in this study, nelfinavir, lopinavir, and dexamethasone are recommended as candidates for a new potential Mpro receptor inhibitor. However, further research needs to be conducted to obtain more accurate data.

Abbreviations

BE	Binding Energy
Mpro	Mainprotease
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
ACE2	Angiotensin-converting enzyme 2
MERS-Cov	Middle east respiratory syndrome coronavirus
SARS-Cov	Severe acute respiratory syndrome coronavirus
PLPro	Papain-like protease
3CLPro	3-chymotrypsin-like protease
LGA	Lamarckian Genetic Algorithm
Drulito	Drug Likeness Tools
hCov-229E	Human coronavirus 229E
Th1	T helper cell type 1
DPP-4	Dipeptidyl peptidase-4 receptor
NSAIDs	Non-steroidal Anti-Inflammation Drugs
MAP	Mitogen-activated protein
SMILE	Simplified molecular-input line-entry
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
CDK2	Cyclin-dependent kinase 2
CYP3A5	Cytochrome P450, family 3, subfamily A, polypeptide 5
AKT1	V-akt murine thymoma viral oncogene homolog 1
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2
CYP2B6	Cytochrome P450, family 2, subfamily B, polypeptide 6
HSP90AA1	Heat shock protein 90kDa alpha (cytosolic), class A member 1
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2
ZMPSTE24	Zinc metallopeptidase STE24
ABCB11	ATP-binding cassette, sub-family B(MDR/TAP), member 11
BGLAP	Bone gamma-carboxyglutamate (gla) protein
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor

FGF23	Fibroblast growth factor 23
PTH	Parathyroid hormone
CDK2	Cyclin-dependent kinase 2
KL	Klotho
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP); member 1
CYP22C9	Vytochrome P450, family 2, subfamily C, polypeptide 9
SCARB1	Scavenger receptor class B, member 1
CD36	Thrombospondin receptor
SCARB2	Savenger receptor class B, member 2
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6
CASP1	Caspase 1

Declarations

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The authors declare that they have no conflict interests

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Figures

Figure 1

(a,b,c)2-dimensional visualization of native ligand, (d)nelfinavir

Figure 2

Interaction of potential inhibitors on the Mpro receptor based on complexes(d)

Figure 3

Ligand- protein interactions (a) nelfinavir, (b) lopinavir, (c) vitamin D, dan (d) ritonavir

Supplementary Files

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