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RESEARCH ARTICLE

Virtual screening as therapeutic strategy of COVID-19 targeting angiotensin-converting enzyme 2

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Abstract: Objective: The receptor-binding domain (RBD) of the S1 domain of the SARS-CoV-2 Spike protein performs a key role in the interaction with Angiotensin-converting enzyme 2 (ACE2), leading to both subsequent S2 domain-mediated membrane fusion and incorporation of viral RNA in host cells. Methods: In this study, we investigated the inhibitor's targeted compounds through existing human ACE2 drugs to use as a future viral invasion. 54 FDA approved drugs were selected to assess their binding affinity to the ACE2 receptor. The structure-based methods via computational ones have been used for virtual screening of the best drugs from the drug database. Key Findings: The ligands "Cinacalcet" and "Levomefolic acid" high-affinity scores can be a potential drug preventing Spike protein of SARS-CoV-2 and human ACE2 interaction. Levomefolic acid from vitamin B family was proved to be a potential drug as a spike protein inhibitor in previous clinical and computational studies. Besides that, in this study, the capability of Levomefolic acid to avoid ACE2 and Spike protein of SARS-CoV-2 interaction is indicated. Therefore, it is worth to consider this drug for more in vitro investigations as ACE2 and Spike protein inhibition candidate. Conclusion: Cinacalcet and Levomefolic acid are the two ligands that have highest energy binding for human ACE2 blocking among 54 FDA approved drugs.

Keywords: SARS-CoV-2, COVID-19, ACE2 inhibitor, docking VINA, docking SMINA

1 Introduction

In the year 2019, an outbreak of a new coronavirus was identified in Wuhan, China [1]. It appears to be more transmissible than the Severe Acute Respiratory Syndrome coronavirus (SARS) and the Middle East Respiratory Syndrome coronavirus (MERS). Full-length genome sequence analysis showed that 2019-nCoV holds 79.5 percent sequence similarity with SARS-CoV, and sequence analysis of pairwise protein showed that it belongs to the SARS-related coronavirus class [2]. Both of 2019-nCoV and SARS-CoV viruses enter into the host cell through the same receptor, ACE2 [2]. Although the mortality rate of COVID-19 from SARS-CoV-2 is lower than SARS and MERS, organ failures such as acute respiratory distress syndrome (ARDS), acute heart injury, acute liver injury, and acute kidney injury in severe cases, are very common. ACE2, expressed in a number of human organs and tissues, has widespread biological activity and can counteract the renin-angiotensin (RAS) system's negative function in many disorders [3, 4]. Human SARS coronavirus infection is known to be closely related to the association of the viral spike protein (S-protein), which has a favorable binding affinity for angiotensin converting enzyme 2 (ACE2) [5, 6]. ACE2 is an integral type I membrane protein having a residue containing 805 amino acids with a Zn^{2+} which is necessary for enzyme activity. ACE2 is involved in the regulation of cardiac function and as a functional coronavirus receptor associated with extreme acute respiratory syndrome (SARS). ACE2 is a novel cellular coronavirus receptor (SARS-CoV-2) that causes a severe COVID-19 pandemic [7, 8]. SARS-CoV-2 binds to the human ACE2 receptor via a glycosylated spike protein as an initiation step entering the human cells [9]. The spike protein of the virus consists of two active regions: S1 region including ACE2 RBD and the S2 region, which is responsible for membrane fusion. An analysis of the X-Ray structure of RBD domain of protein S of SARS-CoV-2 with ACE2 indicates that the RBD has a flat surface, which is not suitable for drug targeting. However, we could identify the transient pockets where small molecules can bind to the protein S through protein dynamic [10]. Since RBD binding ACE2 is the first step in viral disease, a strong therapeutic technique is to prevent the interaction between Spike receptor-binding domain and

ACE2, and the use of previous zoonotic coronavirus SARS and MERS has been demonstrated as a proof of concept for this process [11]. The presence of this metal ion allows the virus to bind to the surface of the target cells. Zinc ions act as an intracellular second messenger, which can induce apoptosis and effectively interfere with the replication of various viruses based on direct inhibition. ACE2 exists in all humans but in varying quantities. Patients with hypertension, diabetes, or cardiovascular disease have a high level of ACE2 enzymes in their blood [12]. Compared to children with low ACE2 enzyme concentrations, these types of people can easily be infected with coronavirus easily, with an infection rate of just two percent [13]. Blocking ACE2 by an effective pharmaceutical substance prevents the virus from entering human cells. Therefore, the synthesis of such medicines is highly in demand. Many scientists are trying to synthesize new drugs to avoid the spread of new COVID-19 infectious diseases. Consequently, the use of FDA-approved drugs is a shortcut to resolve this problem. Chloroquine was Introduced as a successful inhibitor of SARS-CoV-2 infection in 2005 and it was suggested that the new coronavirus could be treated with hydroxychloroquine [14]. The hydroxychloroquine, however, was labeled red by the USFDA for use as a prophylactic step because of its cardiotoxicity. In this study, we selected 54 FDA-approved drugs [10] to evaluate their binding with the ACE2 receptor in order to find the potential drugs as an ACE2 inhibitor.

2 Materials and methods

We conducted our researches using Web of Sciences, Google Scholar, PubMed, and WHO website. In addition, through the following steps, the potential effective medicines are found to achieve the purpose, blocking human ACE2 receptor cellular.

2.1 The target PDB structure selection

All the stages for the docking process are shown in Figure 1. The target protein structure of angiotensin-converting enzyme2 (ACE2) was downloaded from Protein Data Bank (https://www.rcsb.org/structure/1R42) .1R42 is Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) of the human organism. (Figure 2) The requirement is to find potential sites of this protein that play the most important role in the interaction between 1R42 and the Spike protein of SARS. For this reason, the protein complex structure of the SARS-CoV-2 spike receptor-binding domain bound with ACE2 (6M0J) was used to find the target protein (1R42) potential binding sites for different compounds. This protein complex includes two chains A and E, which A is from ACE2 and E is from the Spike protein receptor domain of SARS-CoV-2. In NCC Finder software, chain A was defined to access the most involved residues of ACE2, which are in connection to the Spike protein in the protein complex 6M0J. (Figure 3)

2.2 Target preparation

The 1R42 preparation was carried out through the software Auto Dock tools. Polar Hydrogens were added and the target protein structure format (pdb) was converted to the (pdbqt).

2.3 Ligand preparation

The Drug Bank database is a comprehensive, free-to-access database of drugs and drug targets, which also contains small molecules, biologics, nutrients, and a few thousands of experimental drugs. In our work, the FDA-approved small molecules that are suitable for IR42 were selected. 3D-SDF format files of these approved drugs were obtained from the drug bank database and then prepared as pdb format via https://cactus.nci.nih.gov/translate. Therefore, ligands format was converted to pdbqt format via Auto Dock tool. This step of ligand preparation is an essential step for the docking process. Then the ligands were entered one after another to detect root and to save as pdbqt. 36 chemical compounds were prepared for the next steps.

2.4 Molecular docking

It is necessary to identify the docking region as a grid in Auto Dock tool, and to enter the grid dimension in “config” file. The grid’s information was extracted via NCC Finder. The config file is one of the requirements for the docking process. The docking process was applied through VINA [15] and SMINA [16] methods with a good scoring function for the interaction between the potential ligands and ACE2 receptor. Auto dock VINA considerably improves

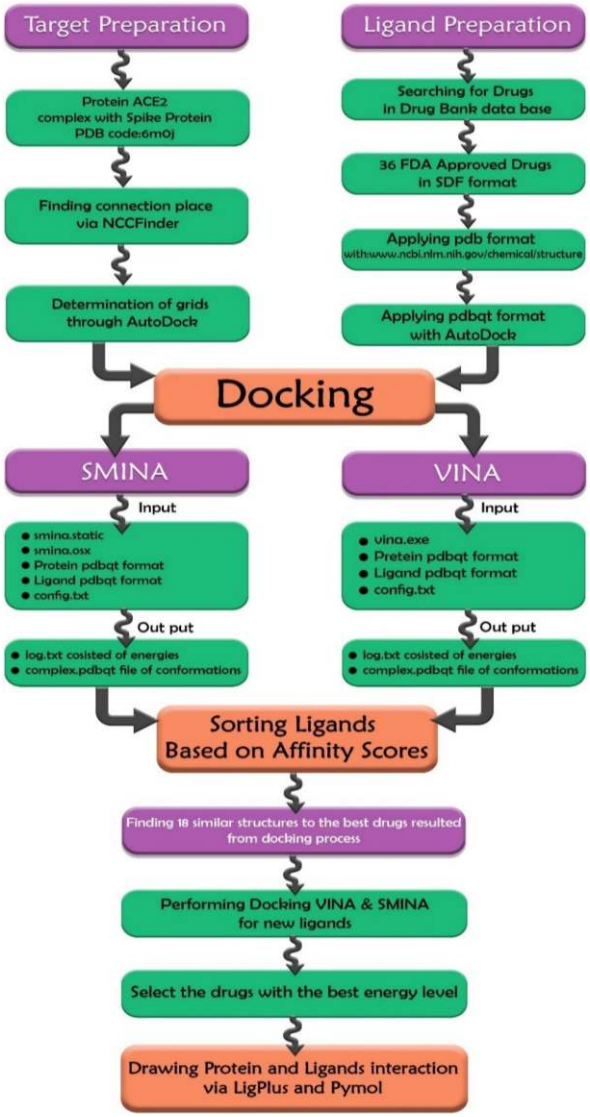

Figure 1 Docking Process in different stages. After the preparation of the target protein and the ligand; the docking process was performed through two methods VINA and SMINA. The results were sorted according to the binding energy levels (docking scores) to the target protein. LigPlot program generated schematic diagrams of protein-ligand interactions for a given ligand.

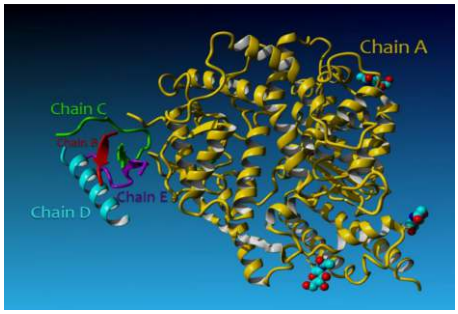

Figure 2 The structure of target protein (1R42). Native human angiotensin converting enzyme related carboxypeptidase (ACE2) includes five chains A,B,C,D, and E which chain A is responsible for interaction with Spike protein of SARS-CoV-2 in protein complex 6M0J.

the accuracy of the binding state predictions. Parallelism using multi-threading has led to the highly fast performance of this method. In addition, SMINA is a version of VINA which is optimized to support user-specified common scoring function [16]. Finally, the results were

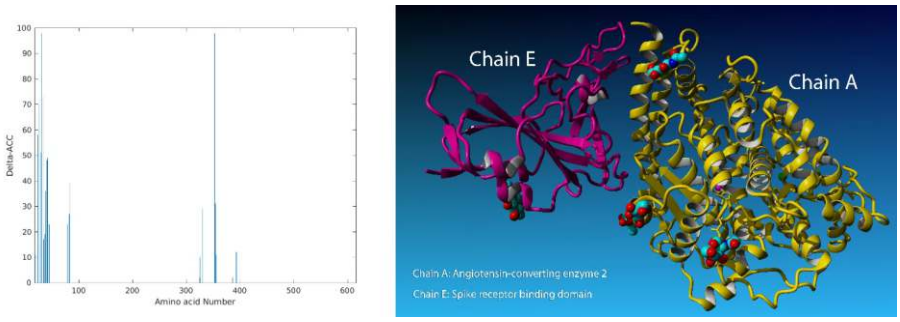

Figure 3 The protein complex structure of the SARS-CoV-2 spike receptor-binding domain bound with ACE2 (6M0J) was used to find target protein (1R42) potential binding sites for different ligands. Protein complex 6M0J is included two chains A and E, which A is from ACE2 and E is from Spike protein receptor domain of SARS-CoV-2 Defining the target protein and its related chain, which is in connection to the protein Spike of SARS-CoV-2 We have the critical residues. These residues play an important role in protein 1R42 and the Spike protein interaction. It can be seen that in NCC Finder software, LYS 353, GLN 24, THR 27, LYS 31, and HIS 34 are the most involved residues of ACE2, which interacted with the Spike protein in the complex 6M0J.

sorted according to the binding energy levels to the target protein.

The LigPlot program automatically generates a schematic of protein-ligand interactions for specific ligands in PDB files. At first, running the below code in the command prompt, several files based on different conformations were available which the first one was the best ligand conformation to continue the drawing process. (vina-split –input filename.pdbqt)

After that, the target protein ACE2 and the ligand were selected in Pymol program at the same time and saved in pdb format. The LigPlot program drew the protein-ligand interaction and provided output in pdf format.

3 Results

Table 1 All the ligands with the docking affinity scores for AutoDock VINA docking method against the respected grid are reported here. The sorted docking results indicated that the best drug is Methotrexate with an affinity score of -8 kcal/mol.

Drug	Accession Number in Drug Bank	VINA Affinity Score (kcal/mol)
Methotrexate	DB00563	-8.0
Arbutamine	DB01102	-7.7
Enalaprilat	DB09477	-7.7
Ketorolac	DB00465	-7.6
Zofenopril	DB13166	-7.6
Butenafine	DB01091	-7.5
Cholecalciferol	DB00169	-7.5
Dobutamine	DB00841	-7.4
Enalaprilat	DB09477	-7.4
Nylidrin	DB06152	-7.4
Eplerenone	DB00700	-7.3
Sacubitril	DB09292	-7.2
Candesartan cilexetil	DB00796	-7.1
Flavastatin	DB01095	-7.0
Rescinnamine	DB01180	-6.9
Eprosartan	DB00876	-6.8
Torasemide	DB00214	-6.8
Losartan	DB00678	-6.7
Atenolol	DB00335	-6.7
Cilazapril	DB01340	-6.7
Ramipril	DB00178	-6.6
Trandolapril	DB00519	-6.6
Fenoldopam	DB00800	-6.5
Moexipril	DB00691	-6.5
Spirapril	DB01348	-6.3
Isoetharine	DB00221	-6.3
Macitentan	DB08932	-6.3
Nadolol	DB01203	-6.2
Perindopril	DB00790	-6.0
Oxilofrine	DB11610	-5.8
Etafedrine	DB11587	-5.8
Oxprenolol	DB01580	-5.8
Amlodipine	DB00381	-5.8
Palmitic Acid	DB03796	-5.5
Nisoldipine	DB00401	-5.3
Captopril	DB01197	-5.3

Table 2 All the ligands with the docking affinity scores for SMINA docking method against the respected grid are reported here. The sorted docking results indicated that the best drugs are Nylidrine and Butenafine with affinity score of -8.4 and -8.1 kcal/mol respectively.

Drug	Accession Number in Drug Bank	SMINA Affinity Score (kcal/mol)
Nylidrin	DB06152	-8.4
Butenafine	DB01091	-8.1
Enalaprilat	DB09477	-7.9
Ketorolac	DB00465	-7.8
Methotrexate	DB00563	-7.8
Arbutamine	DB01102	-7.7
Cholecalciferol	DB00169	-7.7
Zofenopril	DB13166	-7.7
Sacubitril	DB09292	-7.5
Candesartan cilexetil	DB00796	-7.5
Enalaprilat	DB09477	-7.4
Flavastatin	DB01095	-7.4
Cilazapril	DB01340	-7.4
Eplerenone	DB00700	-7.3
Dobutamine	DB00841	-7.3
Fenoldopam	DB00800	-7.3
Rescinnamine	DB01180	-6.9
Losartan	DB00678	-6.9
Atenolol	DB00335	-6.9
Ramipril	DB00178	-6.8
Eprosartan	DB00876	-6.7
Torasemide	DB00214	-6.6
Trandolapril	DB00519	-6.6
Macitentan	DB08932	-6.6
Isoetharine	DB00221	-6.5
Nadolol	DB01203	-6.5
Spirapril	DB01348	-6.4
Perindopril	DB00790	-6.3
Oxilofrine	DB11610	-5.9
Oxprenolol	DB01580	-5.9
Etafedrine	DB11587	-5.8
Moexipril	DB00691	-5.7
Palmitic Acid	DB03796	-5.6
Captopril	DB01197	-5.5
Amlodipine	DB00381	-5.2
Nisoldipine	DB00401	-5.2

Table 3 Table of similar structures to the Nylidrine, Methotrexate, and Butenafine as ligands to the target protein (ACE2), which are applied to VINA docking method. The sorted results are reported here. Obviously, the best drug is Cinacalcet with -9 kcal/mol affinity score.

Drug	Accession Number in Drug Bank	Vina Affinity Score (kcal/mol)
Cinacalcet	DB01012	-9.0
Naftifine	DB00735	-8.3
Buclizine	DB00354	-8.3
Levomefolic Acid	DB11256	-8.1
Pemetrexed	DB00642	-8.0
Levoleucovorin	DB11596	-7.9
Acalabrutinib	DB11703	-7.9
Leucovorine	DB00650	-7.8
Plerixafor	DB06809	-7.8
Arbutamine	DB01102	-7.7
Raltitrexed	DB00293	-7.7
Dobutamine	DB00841	-7.4
Cyclizine	DB01176	-7.2
Isoetharine	DB00221	-6.3
Oxilofrine	DB11610	-5.8
Etafedrine	DB11587	-5.8
Benzododecinium	DB13282	-5.7
Pargyline	DB01626	-5.6

It is obvious, in Figure 3 NCC Finder indicated that LYS 353, GLN 24, THR 27, LYS 31, and HIS 34 are the most involved residues of ACE2, which have more interaction with the Spike protein in the complex 6M0J. These residues help to consider the appropriate region of our target protein for the docking process.

All the ligands with docking affinity scores for methods VINA and SMINA against the respected grid are shown in Table 1 for VINA and Table 2 for the SMINA docking methods. Drugs with a higher affinity score were Nylidrine, Methotrexate, and Butenafine. Then we searched for the similar structures to these drugs from the Drug Bank database with a threshold of 0.7, in order to perform the docking process between target protein ACE2 and drugs with the similar structures.

We performed two methods of docking process VINA and SMINA on the similar structures to the best ligands Nylidrine, Methotrexate, and Butenafine. Table 3 and Table 4 reported

Table 4 Table of similar structures to the Nylidrine, Methotrexate, and Butenafine as ligands to the target protein, which are applied to SMINA docking method. The sorted results are reported here. Obviously, the best drug is Cinacalcet with a -8.8 kcal/mol affinity score.

Drug	Accession Number in Drug Bank	Smina Affinity Score (kcal/mol)
Cinacalcet	DB01012	-8.8
Naftifine	DB00735	-8.4
Levomefolic Acid	DB11256	-8.4
Buclizine	DB00354	-8.3
Pemetrexed	DB00642	-8.3
Levoleucovorin	DB11596	-8.3
Acalabrutinib	DB11703	-8.0
Leucovorine	DB00650	-7.9
Raltitrexed	DB00293	-7.8
Plerixafor	DB06809	-7.8
Arbutamine	DB01102	-7.7
Dobutamine	DB00841	-7.3
Isoetharine	DB00221	-6.5
Cyclizine	DB01176	-6.1
Benzododecinium	DB13282	-6.0
Oxilofrine	DB11610	-5.9
Etafedrine	DB11587	-5.8
Pargyline	DB01626	-5.6

the docking sorted scores from the best binding energy to the lowest one. It can be seen that Cinacalcet, Naftifine, Buclizine, Levomefolic Acid, Pemetrexed, Levoleucovorin, and Acalabrutinib are the drugs with higher affinity scores through both mentioned docking methods.

Schematic diagrams of protein-ligand interactions for the ligands, which have higher affinity scores among other drugs have been extracted from Drug Bank database are shown in Figure 4 and Figure 5. In addition, these drugs' 2D structures are presented in Figure 6.

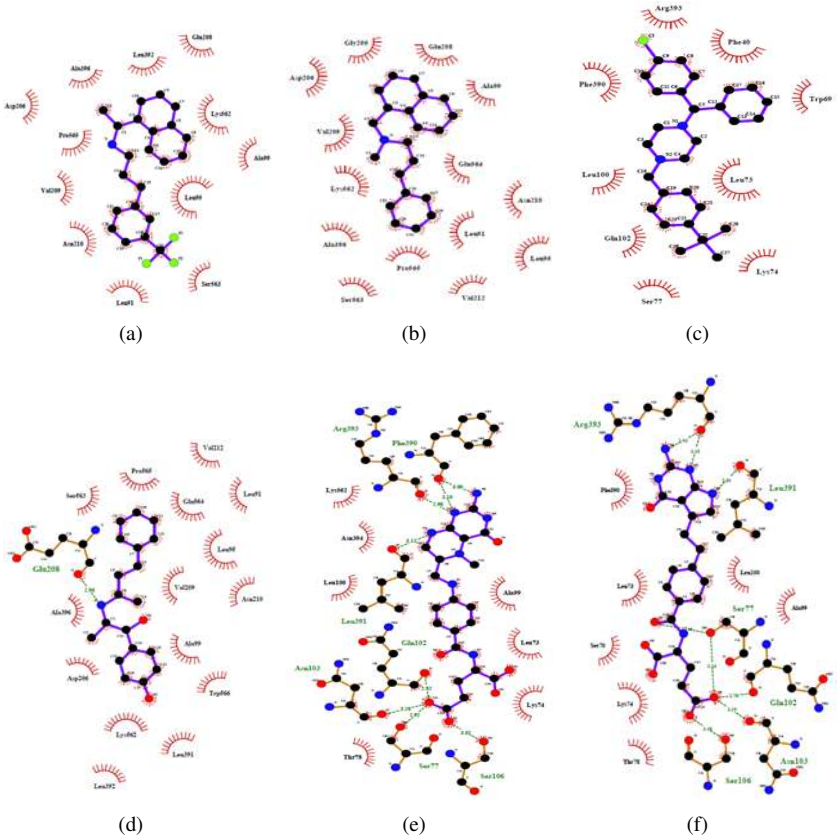

Figure 4 LigPlot Schematic diagrams of protein-ligand interactions. ACE2 interaction with ligands: (a) Cinacalcet with Drug Bank code DB01012, (b) Naftifine with Drug Bank code DB00735, (c) Buclizine with Drug Bank code DB00354, (d) Nylidrine with Drug Bank code DB06152, (e) Levomefolic Acid with Drug Bank code DB11256 and (f) Pemetrexed with Drug Bank code DB00642.

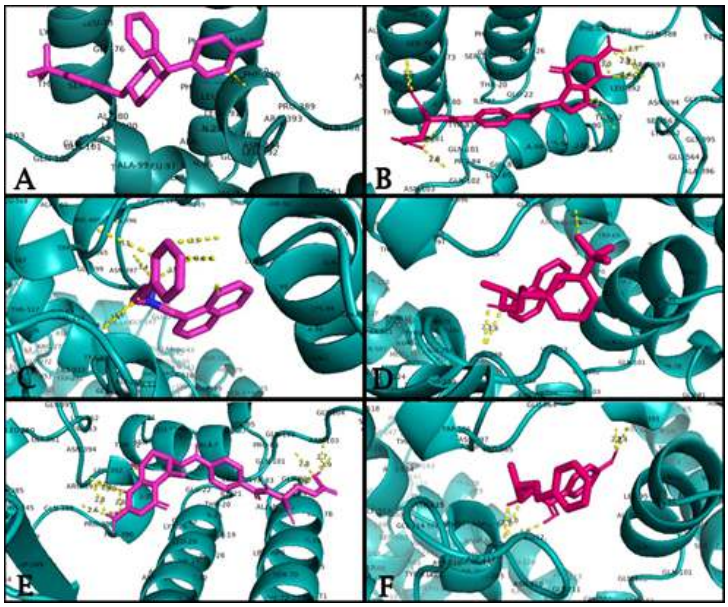

Figure 5 Pymol Schematic diagrams of protein-ligand interactions. ACE2 interaction with ligands: A) Buclizine-DB00354, B) Pemetrexed-DB00642, C) Naftifine-DB00735, D) Cinacalcet-DB01012, E) Levomefolic Acid-DB11256, F) Nylidrine-DB06152 which are the potential drugs introduced as ACE2 inhibitors in our study.

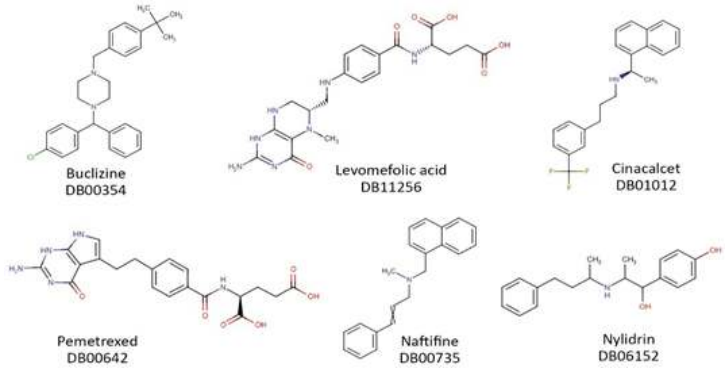

Figure 6 2D structure of the drugs with higher affinity scores to ACE2 through VINA docking methods Cinacalcet with a higher affinity score of -9 kcal/mol, Buclizine with an affinity score of -8.3 kcal/mol, Levomefolic acid with an affinity score of -8.1 kcal/mol, Pemetrexed with an affinity score of -8 kcal/mol, Naftifine with an affinity score of -8.3 kcal/mol, and Nylidrine with an affinity score of -8.4 kcal/mol.

4 Discussion

The results of SARS-CoV-2 clinical investigations may provide deep insight into the differences among drug groups (ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, statins) or drug differences in the same class (lipophilicity, tissue ACE inhibition) or if the outcome of SARS-CoV-2 pneumonia differs from other types of virus-based pneumonia in patients treated with RAAS modulators [17]. Thus, maintaining high levels of ACE2 activity appears to be advantageous to avoid enhanced inflammatory responses during SARS-CoV-2 infections, while high ACE2 plasma levels are related to cardiovascular complications [18].

In this study, we searched for a new treatment of covid-19 based on ACE2 blockade. The strategy is inhibiting ACE2 with potential drugs not to allow Spike protein of SARS-CoV-2 interaction with the host cell. Our drugs were screened through VINA and SMINA docking method in the best region, which includes the involved amino acid residues in the complex between Spike protein and ACE2 protein. Therefore, drugs with high-affinity scores introduced as potential drugs in covid-19 treatment. Since our drugs are FDA-approved chemical compounds, their side effects and their particular consumption are determined. As a result, using these drugs

would lead the fewer problems with medication.

The best drug in our study was **Cinacalcet** with a high binding energy score of -9 kcal/mol resulted from VINA docking method and -8.8 kcal/mol resulted from SMINA docking method. This drug works by the reduction of parathyroid hormone, calcium, and phosphorus in your body. The right amount of the mentioned substances in your body helps to avoid bone disease. Treatment of hyperparathyroidism patients with Cinacalcet can reduce all-cause mortality and cardiovascular mortality in patients with sustained dialysis. This drug can decrease serum calcium, accompanied by a serum phosphate reduction [19]. Clinical studies showed that mortality rates from all causes and cardiovascular disease were significantly lower for patients treated with Cinacalcet than for those who were not [20, 21]. Another medicine with a high-affinity score of -8.4 kcal/mol resulted from SMINA and -8.1 kcal/mol resulted from VINA is **Levomefolic acid**. This drug is the active form of Folic acid (vitamin B9) with minor side effects. It is interesting referring to the previous clinical and computational studies on Levomefolic acid in COVID 19 disease. In clinical studies, low Levomefolic acid serum levels have led to more severe cases of the disease in patients with COVID 19 infection [22]. Folic acid causes decreasing the level of homocysteine [23]. Hyper-homocystinemia as well causes more severe COVID 19 disease [24]. Through in silico studies, Folic acid was capable to bind to the active site of SARS-CoV-2 main protease efficiently [25]. In addition, several computational docking studies indicated that Levomefolic acid has the potential to avoid the binding of Spike protein of SARS-CoV-2 to human ACE2 receptor and then COVID 19 infection [26]. Comparing to our study, Levomefolic acid has interaction with important residues of S1 domain of Spike protein including Glu 406, Ile 418, Lys 417, Tyr 453 with a lower affinity score of -5.3 kcal/mol. Among these residues, Lys 417 and Tyr 453 play an effective role in the interaction of human ACE2 and Spike protein [27]. In another recent research, resolution X-ray crystal structures of SARS-CoV-2 Spike protein in complex with ACE-2, structural rigidity, and a high degree of sequence similarity of RBDs warrants us to produce reliable homology models for drug screening. In this study, screening a lot of approved compounds were screened against an optimized homology model of the SARS-CoV-2 Spike protein RBD [28]. Digitoxin, an FDA approved drug was bound with four critical residues in RBD-ACE-2 interaction formation. This lowest energy pose had a binding energy or affinity score of -7.6 kcal/mol indicating its potential as an RBD-ACE-2 interaction inhibitor.

Low expression of ACE2 due to virus infection activates the renin-angiotensin system, which aggravates respiratory lesions [29]. Thus, the patient may have benefited from activation Ace2-Ang-(1-7) -Mas receptors or inhibiting receptor pathway of AceAngII-AT1R. The inhibitory effect of ACEI or AT1R blockers on the renin-angiotensin system would increase the expression level of ACE2 mRNA and ACE2 activeness, however, did not increase the concentration of ACE2. Furthermore, the ACE2 expression level is inconsistent with the coronavirus attack in the body.

A mixture of nature-based products with conventional anti SARS-CoV-2 medicines may create a promising inhibitor and therapeutic option to be evaluated. Different traditional herbal medicines have been used with appropriate health effects among patients who are infected with SARS-CoV-2 mainly in China [30]. Various plant-based products are used for direct inhibition of the virus replication or virus entry to the human cells. Among these, some of the drugs may block the ACE-2 receptor or the Serine protease TMPRRS2 needed by SARS-CoV-2 to infect the target cells. Although anti SARS-CoV-2 effects of plant-based medicines are not enough, some natural products with efficient IC50 below 10 μm may be considered as promising agents to inhibit SARS-CoV-2 life cycle dependent proteins including the ACE-2 receptor cells, papain-like, or chymotrypsin-like proteinases. Researchers provided 405 traditional Chinese medicine ingredients against ACE2 as target protein and molecularly docked the binding region with SARS-CoV. Virtual screening has identified 46 active components of traditional medicine that are able to interact with Spike protein binding region with ACE2 through high Binding energy. These ingredients mainly attributed to mulberry leaves, honeysuckle, Atractylodes chinensis, grass fruit, Fritillaria cirrhosa, ginger, forsythia, and other Traditional Chinees Medicine components [31, 32]. Astragaloside would be able to activate the ACE2-Ang- (1-7) -Mas pathway; increase levels of ACE2, Ang- (1-7), and Mas; and play an important role in the regulation of lung function and effectively respiratory failure inhibition. The defensive impact of ginsenoside Rg3 on the kidney is mainly due to the upregulation of ACE2 expression, enhancement of AngII degradation, reduction of AngII-mediated oxidative stress, and reduction of lesions. ACE2 is downregulated after virus infection and it increases the inflammatory response in the body. It reduces the production of Ang- (1-7) which stimulates blood vessels, improves endothelial function, and reduces proliferation [33]. An imbalance between the AngII-AT1R / AT2R and ACE2 Ang (1–7) - Mas axes leads to target organ damage in humans. The strategy should be designed to develop ACE2-targeted drugs that block the virus from

integrating with the host cell, explore some effective drugs to activate the ACE2-Ang- (1-7) -Mas receptor pathway or inhibit the receptor pathway ACE-AngII-AT1R to suppress inflammation and decrease organ damage [34].

In one study, the ligands with good affinity scores resulted from the docking process were introduced as potential drugs in COVID 19 infectious disease. The drugs with higher affinity scores were Ergotamine -9.8 kcal/mol, Bromocriptine -9.6 kcal/mol, Tadalafil -9.5 kcal/mol, Dihydroergotamine -9.2 kcal/mol, Perampanel -9.2 kcal/mol, Nilotinib -9.2 kcal/mol, Rolapitant -9.1 kcal/mol binding energy to the ACE2 target protein [35]. In previous studies, Nilotinib decreases SARS-CoV-2 infection by 50%. This well-tolerated drug interferes with the replication of SARS-CoV-2 in both Calu-3 and Vero-E6 cells. It binds to the RBD domain of protein S of SARS-CoV-2 to avoid entry to the host cells through ACE2 receptor [36]. We performed docking VINA and SMINA on these ligands to compare our results with the results of the previous study in Table 5 [35]. The results are presented in which the affinity scores of Tadalafil, Bromocriptine, Perampanel, and Rolapitant is more different from the scores of the previous resource.

Table 5 Docking results through SMINA and VINA for the introduced ligands of the previous study, which had the higher binding energies. The reported results in a recent research were different from our reports.

Drug Name	Accession Number	SMINA	VINA
Dihydroergotamine	DB00320	-9.2	-9.2
Nilotinib	DB04868	-8.9	-9.6
Ergotamine	DB00696	-8.3	-9.0
Tadalafil	DB00820	-8.0	-8.3
Bromocriptine	DB01200	-8.0	-8.3
Perampanel	DB08883	-7.3	-7.6
Rolapitant	DB09291	-7.2	-8.3

5 Conclusion

ACE2 is not just an “entryway” for infection attack but also a key substance that causes organ/tissue failures. Discovering conceivable treatment techniques based on ACE2 has wide application possibilities and clinical worth. Obstructing the ACE2 active site via effective inhibitor drug substance keeps the virus away from penetrating relative cells. The synthesis of such a pharmaceutical substance is therefore highly in demand.

In our study, the potential FDA-approved medicines as ACE2 inhibitors are presented with their affinity scores. Since we can use FDA approved drugs in clinical trial step efficiently, these drugs are more advantageous. Results suggest the potential of these compounds as prophylactic medication or use in preventive countermeasures. In this study during the two docking methods VINA and SMINA, Cinacalcet showed the best interaction of this medicine with ACE2 receptor. Furthermore, Levomefolic acid from vitamin B family was the drug with higher affinity score among the rest of the medicines in our dataset. According to our study and the previous clinical and computational studies, Levomefolic acid may Point with a double arrow including ACE2 blockade and Spike protein of SARS-CoV-2 inhibitor. We need in vitro evidence of investigations for these known agents to discover a likely inhibitor of Spike protein: ACE2 cooperation.

Authors contribution

Z. S., S. A., and M.I. carried our molecular docking experiments and writing the draft. A.A. checked the data and edited the manuscript. A.A. provided the funds.

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