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Original article

In silico prediction of mozenavir as a potential drug for SARS-CoV-2 infection via binding multiple drug targets

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ABSTRACT

Since the epidemic began in November 2019, no viable medicine against SARS-CoV-2 has been discovered. The typical medication discovery strategy requires several years of rigorous research and development as well as a significant financial commitment, which is not feasible in the face of the current epidemic. Through molecular docking and dynamic simulation studies, we used the FDA-approved drug mezonavir against the most important viral targets, including spike (S) glycoprotein, Transmembrane serine protease 2 (TMPRSS2), RNA-dependent RNA polymerase (RdRp), Main protease (Mpro), human angiotensin-converting enzyme 2 (ACE-2), and furin. These targets are critical for viral replication and infection propagation because they play a key role in replication/transcription and host cell recognition. Molecular docking revealed that the antiviral medication mozenavir showed a stronger affinity for SARS-CoV-2 target proteins than reference medicines in this investigation. We discovered that mozenavir increases the complex's stability and validates the molecular docking findings using molecular dynamics modeling. Furin, a target protein of COVID-19, has a greater binding affinity (-12.04 kcal/mol) than other COVID-19 target proteins, forming different hydrogen bonds and polar and hydrophobic interactions, suggesting that it might be used as an antiviral treatment against SARS-CoV-2. Overall, the present *in silico* results will be valuable in identifying crucial targets for subsequent experimental investigations that might help combat COVID-19 by blocking the protease furin's proteolytic activity.
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1. Introduction

In Central China's Hubei region, a new virus has been discovered, named SRAS-CoV-2, which belongs to the human coronavirus family (The, 2020). Though the cause of zoonotic infection still has to be identified; recombination of bat coronavirus and the pangolin coronavirus is most likely to result in the new virus. In humans with a substantial fatality rate, SRAS-CoV-2 causes serious respiratory illness (Li, 2020). According to the WHO Coronavirus Disease 2021 situation report of July 11; 2021, there were 185,291,530 confirmed cases, with 4,010,834 fatalities worldwide, COVID-19 has rapidly expanded to over 212 states, and on 11 March 2020, it was labeled a global health emergency by the World Health Organization (MOHEW, 2020; Bedford et al., 2020).

In the Coronavirinae subfamily of the Nidoviral order, SARS-CoV-2 belongs to the CoV genus (Chan et al., 2020). It is closest to the coronavirus strain SARS-CoV-1 (2002-03), that led to the two recent epidemics of furin and angiotensin-converting enzyme-2 (ACE-2) cells' surface proteins, with a 79.5 percent identification sequence and a host cell entrance mechanism (Zhou et al., 2020). Researchers focus on drug repositioning because effective therapies are urgently needed to halt the course of the illness and since the development of new drugs takes time. The bulk of medicines licensed or developed for other reasons proposed for

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the treatment of SARS-CoV-2 are enzyme inhibitors that tackle RNA polymerase (RDRP) reliant on the Virus or protease. Favipinavir, ribavirin, remdesivir and galidesivir are inhibitors of RDRP, while lopinavir, ritonavir, and danoprevir are the viral protease inhibitors (Mamidala, 2020). In addition, it has been proposed to prevent the input of viral particulate matter in medicines like chloroquine, hydroxychloroquine (Mamidala et al., 2020), or APN01 (UBC, 2021).

The receptor-binding region's three-dimensional SARS-CoV 2 structures have led to the creation of several methods to identify a potential goal for a SARS-CoV-2 therapeutic applicant including furine, ACE2, TMPRSS2, Spike protein, primary protease (MDP), and RdRp. The S1 domain is the receptor-binding region of the Coronavirus Spike protein, while in the earlier stages of viral infection the S2 domain promotes membrane fusion (Belouzard et al., 2009). The process of host SARS-CoV requires key cleaving mechanisms that change the ability of SARS-infectious CVs. The S1 and S2 subunit spike protein is broken down by Type II Serine Protease (TMPRSS2) (Hoffmann et al., 2020). The second is responsible for fusing the viral envelope to the cell membrane, while the first is attached to a receptor at the surface of the host cell. Furin is some kind of proprotein convertase (PC), which may split precursor proteins into physiologically active mature proteins with specific patterns. Furine-like enzymes divide the glycoprotein virus envelope into a functional receptor of the binding virus and the fusogenic transmembrane protein, crucial to the entry into the infection of the virus cells (Ajoy et al., 2009). No furin inhibitor small molecules that have both good actions and excellent specificity have yet been found. For RNA replication and transcription (Lu et al., 2020), RNA-dependent polymerase (RdRp; nsp12) is also needed.

No licensed viral therapy has yet been produced, despite significant research on SARS-CoV-2. Consequently, there is an urgent need for sensible and effective antiviral medications, such as SARS-CoV-2, against zoonotic coronaviruses. Since it takes a long time to license new antiviral drugs, many studies to evaluate the efficacy of SARS-CoV-2 licensed drugs have been carried out. Several antiviral drugs against SARS-CoV-2 have been found. Old antimalarials, including anthelmintic (ivermectin) (Wang et al., 2020; Caly et al., 2020), viral inhibitors of RNA polymerase (remdesivir and favipiravir) (Wang et al., 2020), viral protease inhibitors (remdesive and favipiravir) (Mugisha et al., 2020), etc. Mozenavir (DMP-450) has been developed as an antiviral drug for HIV/AIDS treatment. It acts as an HIV protease inhibitor and is tied to the target with a high affinity selected for this research (Nugiel et al., 1996; Patel et al., 1998). The study now uses molecular docking and dynamic simulations to explore the binding affinity of many viral proteins to mozenavir with potential antiviral efficacy against SARS-CoV-2.

2. Materials and methods

2.1. Protein retrieval and Preparation:

The 3D structures of the S glycoprotein (PDB ID = 2AJF), TMPRSS2 (PDB ID = 7MEQ), RdRp (PDB ID = 7B3C), Mpro (PDB ID = 6Y2E), human ACE-2 (PDB ID = 7DF4), and Furin (PDB ID = 5JXH) from the RCSB (Research Collaboratory for Structural Bioinformatics) Protein Data Bank (Accessed). All of the proteins found were employed in molecular docking experiments with the medication Mozenavir.

2.2. Ligand preparation

The 3D structure of Mozenavir (Fig. 2), as well as arbidol, camostat, remdesivir, indinavir, chloroquine phosphate, and decanoyl-

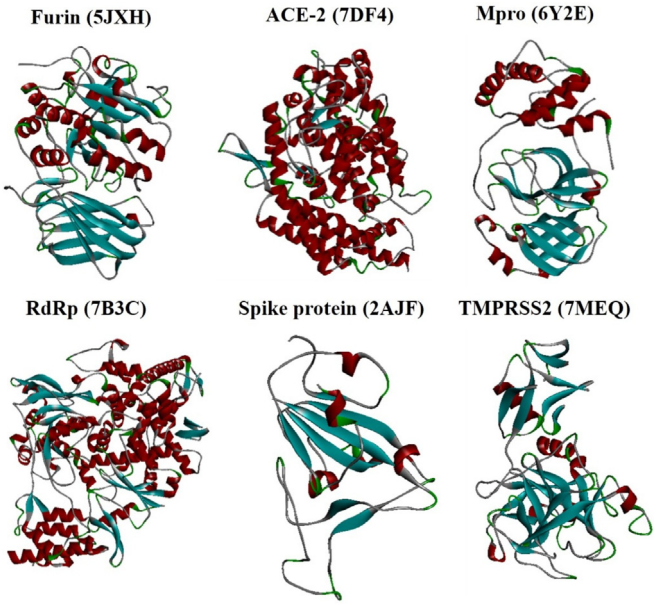

Fig. 1. 3-Dimentional structures of SARS-CoV-2 target proteins.

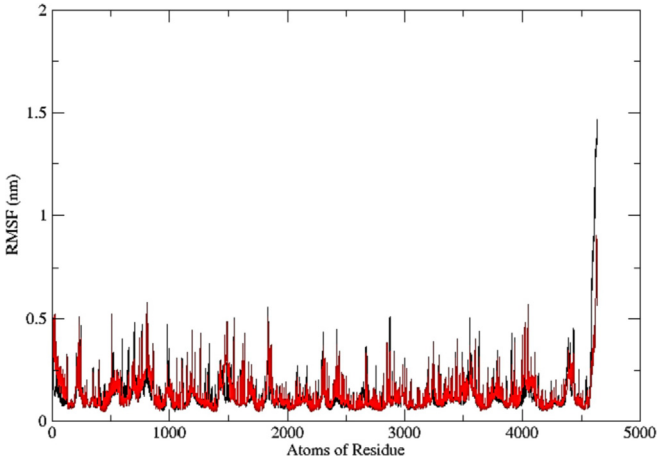

Fig. 2. 2-Dimentional structure of Mozenavir drug.

RVKR-chloromethylketone, which are all proposed drug candidates for treating COVID-19, were obtained in .sdf format from the PubChem database (http://www.pubchem.ncbi.nlm.nih). Open babul software was used to transform their three-dimensional (3D) structures to PDB format, and all of the structures were energy reduced and converted to PDBQT format using AutoDock Tools.

2.3. Molecular docking

Computer-based approaches were employed to examine the structure of ligand–protein complexes and metabolic pathways in the docking investigation of possible therapeutic medication candidates employed against COVID-19 across the globe. AutoDock 4.2 was used for all docking tests since it has a faster running time due to multiple core processors and better accuracy for ligands with more than 20 rotatable bonds. Using AutoDock tools 1.5.6, the protein molecules and ligands were transformed to their correct readable file format (pdbqt). The blind docking approach was used in all of the docking studies, which included creating a grid box big enough to encompass the whole protein structure

and include any potential protein–ligand interactions. Each docking operation had a total of ten runs. Furthermore, the maximum iterations were 2000, with a 100 Kcal/mol energy barrier. The default settings for all other program settings were used. The lowest docked binding energy was used to choose the optimal conformations for each docking procedure. Discovery Studio Visualizer 2.5 and UCSF-Chimera were used to create the final representation of the docked structure.

2.4. Molecular dynamic simulation

Molecular dynamics (MD) simulation for individually of the anticipated protein–ligand complexes was performed to confirm the correctness of the binding interaction findings. GROMACS 2018 Abraham et al., 2015 was used to run all simulations, which used the AMBER 99SB-ILDN force field (Mamidala et al., 2021). Energy minimization; equilibration, and MD simulation with two-femtosecond integration steps for 10 ns were all followed as usual. The system was neutralized by introducing ions and then relaxing using the energy minimization method. MD simulations with an acceptable beginning velocity descend to a local minimum via the sharpest descent route on the potential energy surface. A one-nanosecond temperature and pressure equilibrium step were taken before the 10 ns manufacturing simulation. The root mean square deviation (RMSD), the root mean square luctuation (RMSF), and gyrate radius were employed in the determination of root gyration, g rmsf, and gyrate (Rg). Moreover, hydrogen bonds were generated between the protein–ligand and the protein solvent. It was considered to be fixed on a protein alone, or with a ligand, that could maintain its RMSD under 1 nm, stable below 2 nm, and stabilized beyond 2 nm.

3. Results

Six coronavirus targeting proteins, comprising spike glycoprotein, TMPRSS2, Mpro, human ACE-2, RdRp, and furin, were docked with the antiviral medication mozenavir to investigate a possible treatment target. Because hydrogen bonds (H-bonds) are important for ligand-target protein interactions and binding affinity, we investigated the binding affinity of mozenavir among SARS-CoV-2 target proteins using H-bond interactions (Table 1). Molecular docking studies results are matched to previously reported drug candidates (Decanoyl-RVKR-chloromethyl ketone, Arbidol, Camostat, Remdesivir, Indinavir, and Chloroquine phosphate) that inhibit the furin, Spike glycoprotein, TMPRSS2, RdRp, mpro, and ACE-2 target proteins of coronavirus that obstruct the furin (Table 2).

The virtual screening of mozenavir against the coronavirus target proteins using molecular docking demonstrated a significant interaction with greater docking energy and binding affinities, as shown in Fig. 3. The antiviral medication mozenavir docked with COVID-19′s therapeutic targets in the active region of the protein. Table-1 shows the binding energy values for all COVID-19 targets, which vary between (7.08) and −12.04 kcal per mole. Furin, the COVID-19 target protein, had higher binding affinities (lowest binding energy) (−12.04 kcal per mole), which were higher than the binding affinities of the other COVID-19 target proteins. According to the findings of the molecular docking investigations, mozenavir was discovered to be a candidate that inhibits all of the COVID-19 target proteins.

Discovery Studio Visualizer and UCSF Chimera were used to showing and assessing mozenavir docking with all protein targets binding affinities. Figs. 4–9 depict the surface structure, 2D, and 3D interactions of mozenavir with all target sites (see Fig. 10).

Based on binding energy acquired through molecular docking against chosen COVID-19 targets, Furin (-12.04 kcal per mole), ACE-2 (-9.71 kcal per mole), Mpro (-8.79 kcal per mole), RdRp (-7.32 kcal per mole), Spike glycoprotein (-7.09 kcal per mole), and TMPRSS2 (-7.08 kcal per mole) with chosen antiviral medication mozenavir, it is predicted that the furin is to be the best target for COVID-19 infection.

4. Docking of the mozenavir with the furin

Interfering with the cleavage of the coronavirus S protein processing by compounds might be a promising antiviral strategy. As a reference chemical, decanoyl-RVKR-chloromethyl ketone, a well-known medication that has previously been described as a furin inhibitor, was investigated. Tables 1 and 2 show the docking score of mozenavir in comparison to the reference chemical. We employed bioinformatics methods to identify licensed and experimental drugs (Mozenavir) as probable furin inhibitors in the current study.

Fig. 2 depicts docking studies of the mozenavir-furin interaction. Furin with mozenavir had the lowest binding energy of −12.05 kcal/mol. Furin discovered that the binding energy of the reference medication decanoyl-RVKR-chloromethyl ketone is −6.89 kcal/mol, which is greater than the binding affinity of the test medication mozenavir. Even though Furin-mozenavir has the most hydrogen bonds (five) (Fig. 4, green colored). With mozenavir, Tyr308, Gly265, Gly255, Asp154, and Val231 showed a strong hydrogen interaction. In the development of a hydrophobic contact with mozenavir, the amino acid residues Glu236, Pro256, Trp254, Leu227, His194, Gly229, Asp264, Asp191, Glu230, and Gly229 were

Table 1
Binding energy (kcal/mol) and intermolecular interactions of mozenavir drug against various protein targets involved in SARS-CoV-2 infection by molecular docking study.

Sl No	Target proteins	Intermolecular interactions against SARS-CoV-2 target proteins			
		Binding Energy (kcal/mol)	Number of Hydrogen bonds	Hydrogen bonding interactions	Hydrophobic interactions
1	Furin (5JXH)	−12.04	5	TYR308, GLY265, GLY255, ASP154, VAL231	GLU236, PRO256, TRP254, LEU227, HIS194, GLY229, ASP264, ASP191, GLU230, GLY229
2	ACE-2 (7DF4)	−9.71	4	ARG393, TYR385, HIS378, GLU375	ASN394, ASP350, HIS401, ALA348, HIS374, PRO346, HIS345, PHE504, THR347, PHE40
3	Mpro (6Y2E)	−8.79	2	ASP153, ASP245	ILE249, PHE294, HIS246, GLY109, ILE200, GLN110, THR292, ASN203, VAL202, THR111, ASN151
4	RdRp (7B3C)	−7.32	–	–	TYR515, TRP509, ALA375, LEU371, MET380, TYR374, PHE340, PHE368, PHE506, LEU372
5	Spike protein (2AJF)	−7.09	2	ASP415, SER370	VAL369, GLY368, TYR367, ASP414, CYS366, LYS365, PRO399, GLN401
6	TMPRSS2 (7MEQ)	−7.08	1	TYR337	ALA490, GLN487, PRO335, HIS334, ILE332, SER333, ASN303, VAL298, VAL331, LYS330

Table 2
Binding energy in kcal/mol for the test drug mozenavir along with the reference drugs against each protein target of SARS-CoV-2.

Sl. No	Name of the Drug	Binding energy (kcal/mol) against SARS-CoV-2 target proteins					
		Furin	ACE2	Mpro	RdRp	Spike	TMPRSS2
1	Mozenavir	−12.04	−9.71	−8.79	−7.32	−7.09	−7.08
Ref	Decanoyl-RVKR-chloromethylketone	−6.89					
Ref	Chloroquine phosphate		−7.88				
Ref	Indinavir			−7.11			
Ref	Remdesivir				−4.7		
Ref	Arbidol					−7.86	
Ref	Camostat						−5.9

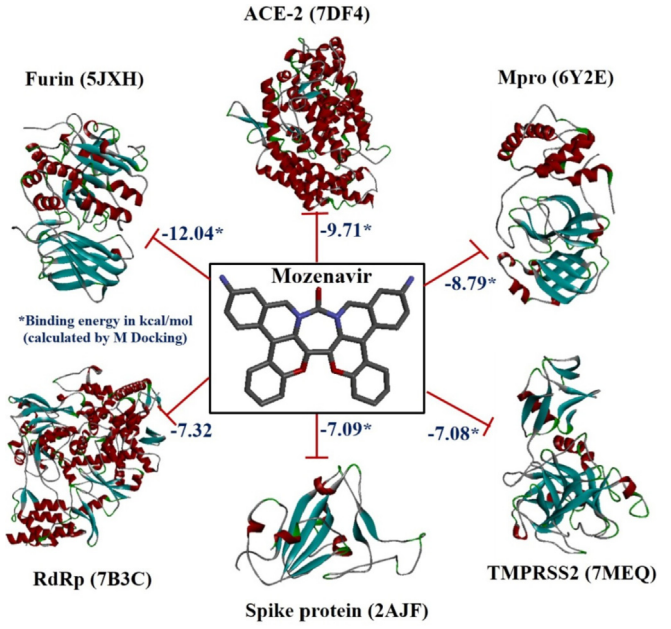

Fig. 3. Illustration of mozenavir inhibition against the SARS-CoV-2 target proteins: Furin, ACE2, Mpro, RdRp, Spike Glycoprotein, and TMPRSS2.

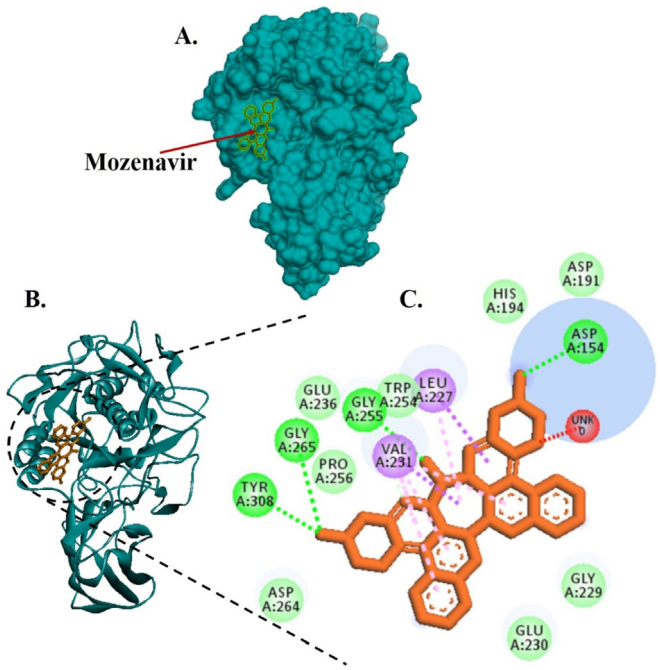

Fig. 4. Docking interactions of Mozenavir with furin protease (PDB ID: 5JXH). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with amino acid with a hydrogen bond (green dashed line).

implicated. As a result, mozenavir might be regarded a possible furin inhibitor.

5. Docking of the mozenavir with the ACE-2

As a result, we looked at the FDA-approved medication mozenavir for suppressing human ACE2. As a reference chemical, chloroquine phosphate, a well-known medication that has previously been claimed to be an ACE2 inhibitor, was investigated. Table 2 shows the docking score of mozenavir in comparison to the reference molecule.

6. Docking of the mozenavir with the SARS-CoV-2 Mpro

Table 2 shows the docking score of mozenavir in comparison to the reference molecule. When compared to the reference medication Indinavir (-7.11 kcal/mol), docking studies indicated that mozenavir had the greatest binding affinity (lowermost binding energy) to the protein active site with − 8.79 kcal/mol against Mpro. Furthermore, mozenavir established two H-bonds with Asp153 and Asp245 amino acid residues found in the protein's predicted active site, as well as hydrophobic interactions with Ile249, Phe294, His246, Gly109, Ile200, Gln110, Thr292, Asn203, Val202, Thr111, and Asn151.

7. Docking of the mozenavir with the SARS-CoV-2 RdRp

In comparison to the reference drug remdesivir (-4.7 kcal/mol), we conducted molecular docking tests of the antiviral medicine mozenavir against the RdRp protein of the coronavirus and found that mozenavir had the lowermost binding energy (−7.32 kcal/mol) and the greatest binding affinity (−7.32 kcal/mol). Mozenavir binds to the active site of RdRp with −7.32 kcal/mol and forms several interactions with residues such as Tyr515, Trp509, Ala375, Leu371, Met380, Tyr374, Phe340, Phe368, Phe506, and Leu372 without creating any hydrogen bonds, according to the current research (Fig. 7). Based on these findings, the antiviral medication mozenavir might be a promising RdRp inhibitor in the fight against coronavirus.

8. Docking of the mozenavir with the SARS-CoV-2 splike glycoprotein

Mozenavir has a docking score of −7.09 kcal/mol with spike glycoprotein. Mozenavir, on the other hand, has the lowest binding affinity for SARS-CoV-2 spike proteins when compared to other protein targets such as furin, ACE-2, and RdRp. However, this target

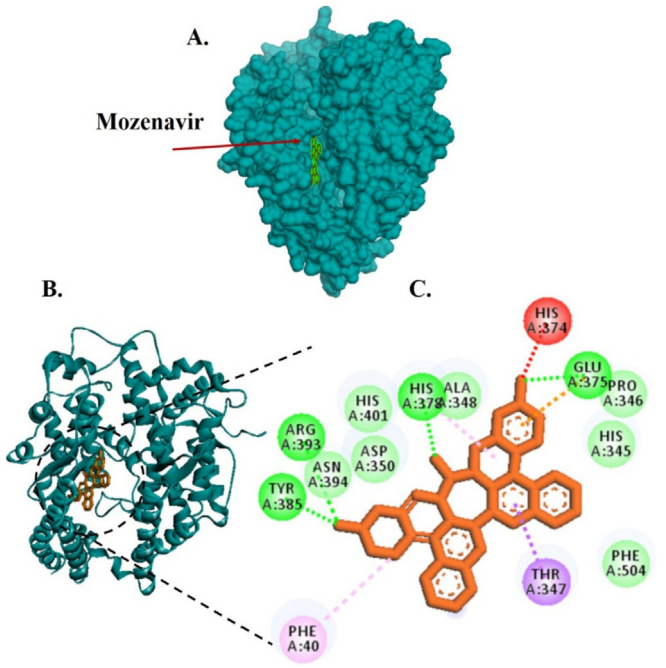

Fig. 5. Docking interactions of Mozenavir with ACE-2 (PDB ID: 7DF4). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with amino acid with a hydrogen bond (green dashed line).

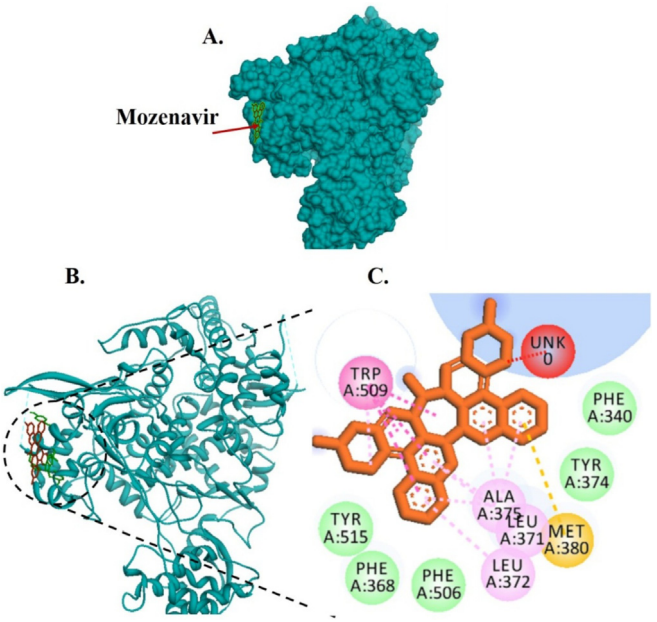

Fig. 7. Docking interactions of Mozenavir with the SARS-CoV-2 RdRp (PDB ID: 7B3C). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with an amino acid with a hydrogen bond (green dashed line).

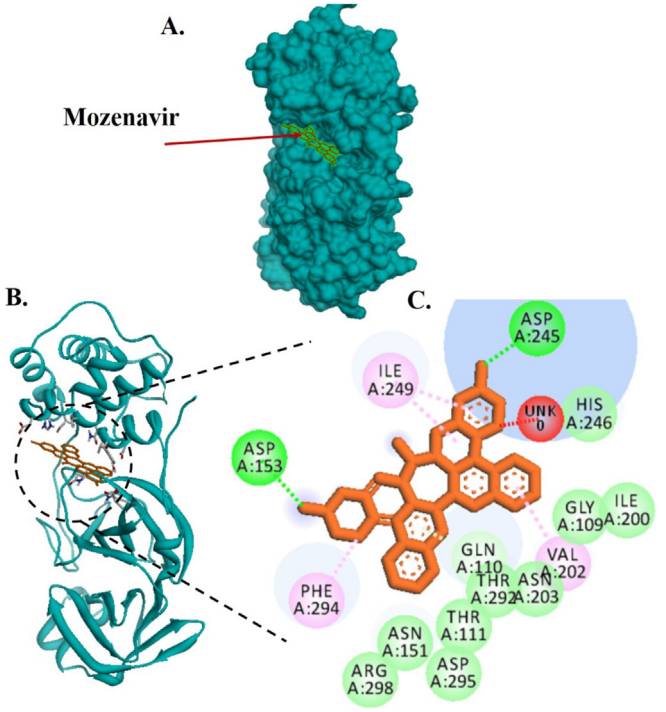

Fig. 6. Docking interactions of Mozenavir with the SARS Main protease (Mpro) (PDB ID: 6YTE). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with amino acid with a hydrogen bond (green dashed line).

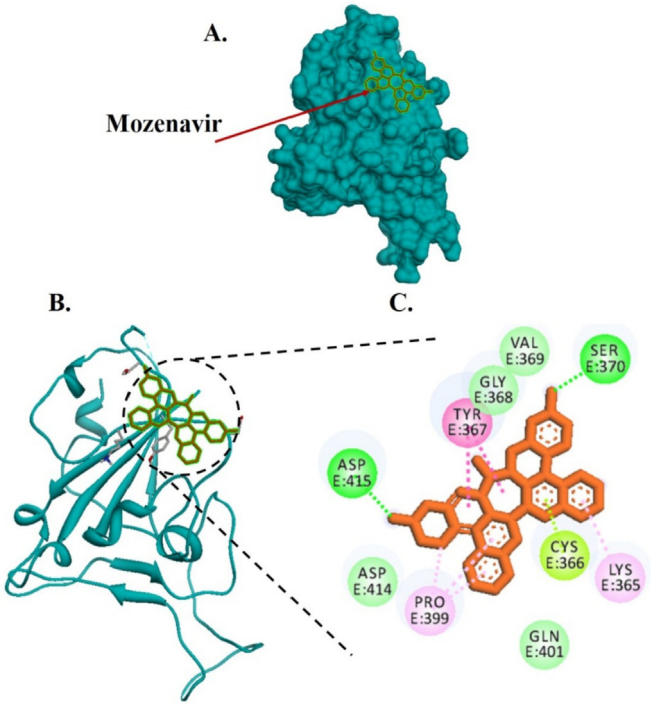

Fig. 8. Docking interactions of Mozenavir with the SARS-CoV-2 spike glycoprotein (PDB ID: 2AJF). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with an amino acid with a hydrogen bond (green dashed line).

protein generated two hydrogen bonds with Asp415 and Ser370, as well as electrostatic interactions with Val369, Gly368, Tyr367, Asp414, Cys366, Lys365, Pro399, and Gln401 (ig 8). When these data are analyzed, it can be shown that mozenavir has a relatively low binding energy with Spro of the SARS-CoV-2, indicating that

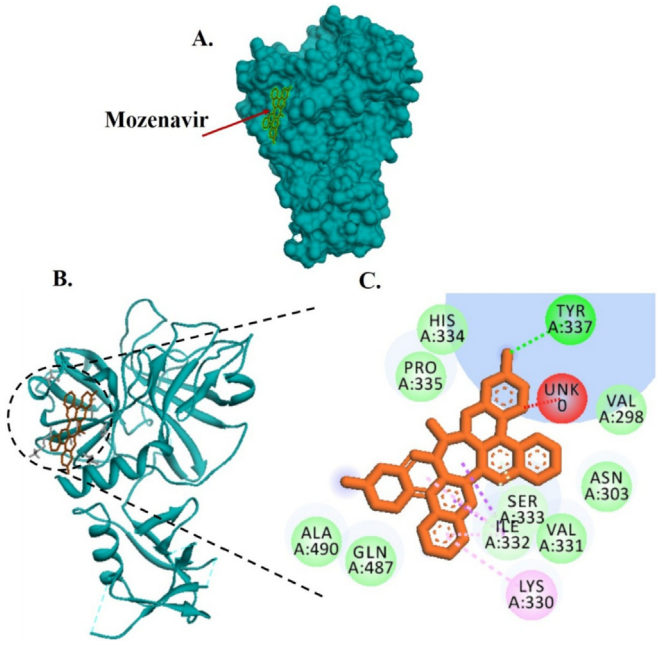

Fig. 9. Docking interactions of Mozenavir with TMPRSS2 (PDB ID: 7MEQ). (a) Surface structure of best binding mode in the protein pocket (ligand illustrated as orange sticks), (b) 3D structure of amino acid residues involved in the interaction with mozenavir ligand (ligand as orange sticks), and (c) 2D structure of mozenavir binding interaction with an amino acid with a hydrogen bond (green dashed line).

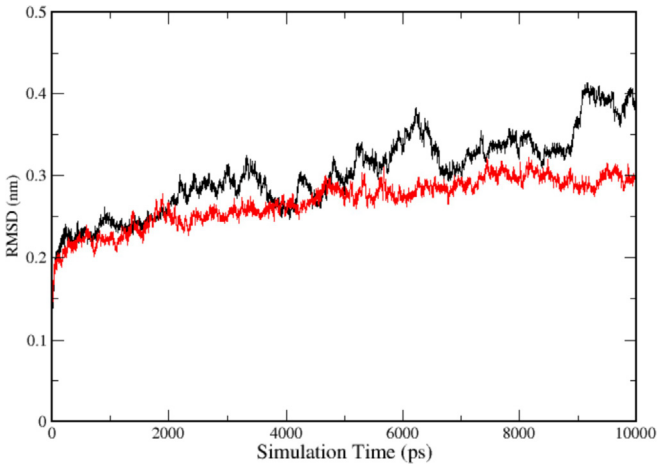

Fig. 10. A plot of root mean square deviation (RMSD) during 10 ns MD simulation of SARS-CoV-2 target protein furin alone (black color) in complex with mozenavir (red colour).

further in vitro and in vivo research is needed before they can be considered as prospective COVID-19 medicines.

9. Docking of the mozenavir with TMPRSS2

When compared to the reference molecule camostat (-5.9 kcal/mol), docking studies indicated that mozenavir had the greatest binding affinity and lowest binding energy (-7.08 kcal/mol) to the active site of the TMPRSS2 protein. Mozenavir also formed one H-bond with Tyr337, an amino acid residue found in the TMPRSS2 protein's predicted active site, as well as ten hydrophobic interactions with Ala490, Gln487, Pro335, His334, Ile332, Ser333, Asn303, Val298, Val331, and Lys330, making it a promising TMPRSS2 inhibitor candidate (Figure-9).

10. Molecular dynamics simulation

According to a molecular docking investigation of mozenavir with several COVID-19 targets, mozenavir had the greatest binding affinity for furin. As a result, a molecular dynamics simulation was used to assess the stability of the target protein furin alone and in combination with mozenavir.

11. Estimation of root mean square deviations (RMSDs)

Fig. 4A shows the root mean square deviations (RMSDs) in the backbone of furin alone or combination with mozenavir as a function of simulation duration as compared to the start frame. Due to the equilibration of the initial protein structure, substantial fluctuations in RMSD values (up to 0.3 nm or 3.0) of protein alone were seen over the first 2000 ps (2 ns). As a result, the simulation period was increased from 2000 to 6000 ps, and the RMSD values were altered and exceeded the allowed limit of 0.2 nm. Throughout the simulation duration, the RMSD values of furin with bound ligand mozenavir were under the top limit of 0.2 nm (2 Ao) (1000 ps). As a result of the creation of complementary connections between protein and ligands, a stable protein–ligand complex was formed, as shown by steady RMSD values.

12. Root mean square fluctuations (RMSFs) determination:

Furthermore, the root means square fluctuations (RMSFs) along the furin side chains were monitored to track any conformational changes caused by mozenavir binding (Fig. 11). The data demonstrated that the binding site residues exhibited less variation when furin with 472 amino acids was complexed with mozenavir medication candidate. The average RMSF values for furin alone and complex with mozenavir were 0.21 and 0.23 nm, respectively (Fig. 5b, 6b & 7b). As a consequence of the RMSFs, the creation of a stable protein–ligand complex was verified.

The closeness of the ligand mozenavir to active site residues of the target protein furin may imply greater binding, according to dynamic modeling studies. As shown in Fig. 1, mozenavir was able to sustain a low ligand mobility root-mean-square deviation (RMSD) of less than 0.3 nm (Fig. 11). This graph was created by superimposing the furin receptor on its reference structure. Finally, a molecular dynamics study has shown that Mozenaivr may experience greater conformational changes over simulation time.

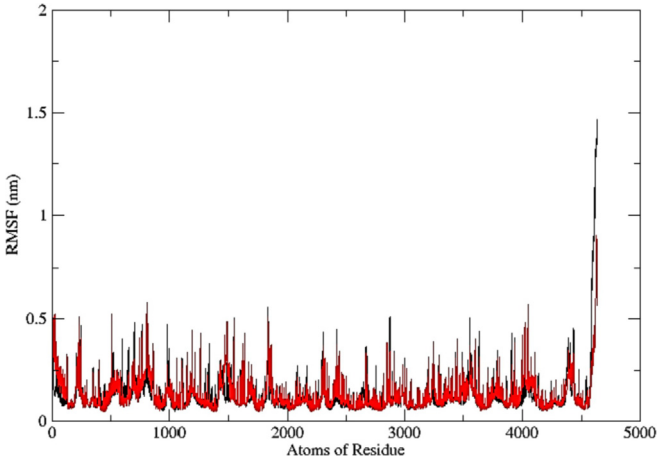

Fig. 11. A plot of root mean square fluctuation (RMSF) values, during 10 ns MD simulation of SARS CoV-2 target protein furin alone (black color) and in complex with mezanovir (red color).

13. Discussions

The coronavirus spike protein features a furin cleavage position that was not seen in any other betacoronavirus subtype B. Based on our findings, we believe that SARS-greater CoV-2′s infectious nature than other coronaviruses is due to the existence of a redundant furin cut site in its Spike protein, which leads to increased membrane fusion efficiency (Coutard, 2020). As a result, the SARS-CoV-2 may take advantage of the great manifestation of furin and other furin-like enzymes present in human lung, liver, and brain tissues to activate S protein, resulting in increased infection, virulence, and viral transmission (Tang et al., 2020).

We reasoned that blocking viral entrance into the host cell would limit the viral burden. One of the enzymes on the host cell surface that allows coronavirus to enter the host is ACE2. As a result, we chose this receptor protein for our research. The COVID-19 spike protein (S) binds to ACE2, which may aid in the transfer of COVID-19 from humans to humans (Wrapp et al., 2020). ACE2 also aids endocytosis and endosome-containing coronaviruses. Targeting as a viral entry inhibitor is a unique anti-COVID-19 therapeutic strategy.

When compared to other target proteins such as Mpro, Spike glycoprotein, and RdRp, as well as the reference medication Chloroquine phosphate (-7.88 kcal/mol), docking data indicated that mozenavir had the greatest binding affinity to the active site of the ACE-2 protein (-9.71 kcal/mol). It also established 4H-bonds with Arg393, Tyr385, His378, and Glu375 amino acid residues found in the protein's putative active site. ACE-2′s Asn394, Asp350, His401, Ala348, His374, Pro346, His345, Phe504, Thr347, and Phe40 amino acid residues reacted hydrophobically with mozenavir. When these data are analyzed, it is clear that the antiviral medicine mozenavir has low binding energy with ACE-2, indicating that it should be investigated further in vitro and in vivo before being considered as a possible COVID-19 medication.

Coronavirus Mpro, also recognized as 3C-like proteins, is a cysteine protease with 3 domains (domains I-III) and a 33.8 kDa size (Jin et al., 2020). Mpro is implicated in polyprotein cleavage at 11 preserved sites, resulting in mature and transitional non-structural proteins (Jin et al., 2020). Coronavirus Mpro has a non-canonical dyad of Cys145 and His41 between domains I and II, which is related to domain III through a loop (Quimque et al., 2020). The amino acids Cys145 and His41 are important for substrate recognition (Mirza and Froeyen, 2020). As a result, this protein was chosen as a potential COVID-19 therapeutic target, and intermolecular interactions, including binding energy, were tallied in Table 1 and shown in Fig. 6. Indinavir was used as a reference molecule since it is a well-known medicine that has previously been linked to Mpro inhibitors.

Two more subunits, nsp7 and nsp8 (Jin et al., 2020), are included in RdRp, commonly known as nsp12. The nucleotidyltransferase (NiRAN) domain linked to the N-terminal *nido*-virus RdRp and an interface domain forms the structural structure of RdRp (Shannon et al., 2020). The main function of RdRp is to catalyze viral replication from the 3′-poly-A point of view. RdRp catalyses RNA-genome replication utilizing RNA-string (+) for the creation of an additional RNA-strand as a template (Yin et al., 2020). RdRp's active site is made up of -helices, an antiparallel -strand, and catalytic aspartate (Wang et al., 2020). RdRp is an important antiviral therapeutic target because of its function in the replication cycle of coronaviruses (Ivanov and Ziebuhr, 2004). Remdesivir was used as a reference chemical since it is a well-known medicine that has previously been identified as an RdRp inhibitor.

Virtual screening aided molecular docking was used on the binding pocket of spike proteins to examine a possible antiviral medication targeting the spike protein of SARS-CoV-2. The viral entrance into the host's cellular system with the help of the ACE-2 receptor has been thoroughly documented (Liu et al., 2020). Glycosylated spike 1 (S1) interacts with the ACE-2 receptor on the surface of the human host cell and mediates viral entry (Hoffmann et al., 2018). Table 1 shows the docking scores of mozenavir, which were chosen for the research of Spro inhibition in SARS-CoV-2. Arbidol was used as a reference drug since it is a well-known medicine that has been shown to increase glycoprotein inhibitors in the past.

The spike S1 subunit binds first to the cell receptor and then to the ACE-2 priming S protein, which is supported via irreversible conformational modifications, by host transmembrane serine protease 2 (TMPRSS2) [37]. Inhibition of TMPRSS2 may assist to prevent the SARS-CoV-2 virus from infecting human cells. A reduction in TMPRSS2 expression and activity has also been shown in previous studies to be a safe and effective technique for treating viral infection caused by viruses (Liu et al., 2020; Hoffmann et al., 2018). As a result, several researchers are working to find an effective drug to suppress TMPRSS2, which has been chosen as a coronavirus target protein. Camostat was used as a reference molecule since it is a well-known medication that has previously been described as a TMPRSS2 inhibitor.

14. Conclusion

In conclusion**,** COVID-19 is a worldwide illness that has a significant fatality rate. The antiviral medication mozenavir was chosen to interact with various SARS-CoV-2 targets, including spike glycoprotein, TMPRSS2, RdRp, Mpro, human ACE-2, and furin, in this investigation. Our goal was to find a chemical that might bind several SARS-CoV-2 targets since viral drug targets are more prone to alterations. Mozenaivr was discovered to interact with various targets and to be particularly effective at blocking all six SARS-CoV-2 targets (spike glycoprotein, TMPRSS2, RdRp, Mpro, human ACE-2, and furin) with considerable binding affinities as compared to reference medicines. When compared to other COVID-19 targets, we chose six target proteins for molecular docking with mozenaivr, and the medication has the greatest binding affinity (lowest binding energy), which is −12.04 kcal/mol with furin. The RMSD of the furin-mozenavir complex in the upper limit was 0.2 nm, suggesting that the mozenaivr underwent excellent conformational changes during binding and retained tight affinity with the furin's binding site. Together, we think that mozenavir has the potential to suppress SARS-CoV-2 by binding to various pharmacological targets, including furin, and that additional in vitro and in vivo research is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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