Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

Autumn 2021. Vol 25. Num 3

Research Paper

Identification of Anti-HIV/Migraine Drugs as Potential Inhibitors of SARS-Cov2 Main Protease Using in Silico Assessments

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Citation Shariatifar H, Hooshmand A, Gheibi N, Farasat AR. Identification of Anti-HIV/Migraine Drugs as Potential Inhibitors of SARS-Cov2 Main Protease Using in Silico Assessments. Journal of Inflammatory Diseases. 2021; 25(3):153-160. http://dx.doi.org/10.32598/JQUMS.25.3.1

doi http://dx.doi.org/10.32598/JQUMS.25.3.1

Article info:
Received: 25 Apr 2022
Accepted: 29 Dec 2021
Publish: 01 Oct 2021

Keywords:
Mpro 3Clpro, Anti-migraine, Anti-HIV, Rimegepant, SARS-CoV-2

ABSTRACT

Background The acute respiratory syndrome named "COVID-19" is caused by a novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Lack of specific antiviral drugs or proper vaccination has led to the development of new therapeutic methods against this virus.

Objective The Mpro 3Clpro is the main protease of the SARS-CoV-2 which plays an important role in replication and transcription of the virus. Therefore, targeting this enzyme is a valuable approach for drug development.

Methods In the present study, the structural properties of 69 anti-migraine and 212 anti-HIV drugs were first obtained from Drug Bank database. To select the appropriate drugs for the enzyme inhibition, the AutoDock Vina software was used. The molecular dynamics (MD) simulation method was applied for better recognition of the structural changes.

Results We identified Rimegepant (PubChem ID: 51049968), Dihydroergotamine (PubChem ID: 10531) and Ergotamine (PubChem ID: 8223) as potential inhibitors of Mpro 3Clpro. These complexes were equilibrated after 70 ns.

Conclusion Among these compounds, the anti-migraine drug "Rimegepant" showed the highest affinity for binding to the Mpro 3Clpro (-60.8 kJ/mol). This study provides enough evidence for further accomplishment of the identified compounds in the development of effective therapeutics methods against COVID-19.

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1. Introduction

In December 2019, several cases of pneumonia with unknown reason were reported to the World Health Organization (WHO) in Wuhan, China. Three days later, in January 2020, Chinese government officials reported that 44 people were affected by the disease, some of them were linked to the sea food market in Wuhan [1]. The cause of the disease was a new type of coronavirus family called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the pneumonia caused by the disease was called Coronavirus-2019 (Covid-19) [2, 3]. This is the third widespread outbreak of the SARS-CoV-2 coronavirus in the last 20 years, following the SARS epidemic in 2002-2003 and Middle East Respiratory Syndrome (MERS) in 2012 [4-6]. Up to now, over 80 million people worldwide have been affected by the virus, of whom more than 1.5 million have died from the disease [7, 8].

Coronaviruses are the largest group belonging to the Nidovirales order. All viruses in this order are non-segmented positive-sense RNA [9]. Replicase gene translation from the RNA genome of the virus is an important stage in the life cycle of coronaviruses. The replicase gene possesses two open reading frames (ORFs) called "rep1a" and "rep1b" which are expressed as two co-terminal poly proteins named "pp1a" and "pp1ab". Coronaviruses encode three proteases including Papain-Like protease (PLpro), serine protease, and the Main protease (Mpro) which is also called "3CLpro". The PLpro separates the first four non-structural proteins of the polyprotein by cleaving the nsp1/2, nsp 2/3, and nsp 3/4 boundaries while the Mpro is responsible for cleavage at 11 remaining positions [9].

Currently, there is no specific treatment for COVID-19 [10]. Therefore, one of the proposed options is to inhibit the main protease of the virus [11, 12]. Rimegepant is one of the FDA-approved and effective drugs in treatment of migraine. Calcitonin gene-related peptide receptor is one of the effective factors in migraine pathogenesis [13, 14]. Rimegepant is a small molecule in the group of "gepants" which inhibits this receptor and reduces migraine-induced pain. It has 64% bioavailability and can be used in cases where the migraine could not be treated by triptans. This is an effective drug and is safe for consumption [15, 16]. Ergotamine is a vasoconstrictor and alpha adrenoreceptor antagonist. Ergotamine can be absorbed by 60%-70% orally, although it has low bioavailability. It has various functions and interacts with several receptors. It works by narrowing the blood vessels around the brain [17]. It also affects the blood flow patterns which is associated with certain types of headaches.

Dihydroergotamine is a derivative of ergotamine and similar to Ergotamine. It has a vasoconstrictive role, especially for the treatment of migraine. Dihydroergotamine is used to treat migraine and cluster headaches. Both ergotamine and dihydroergotamine tend to bind to 5-HT, dopamine, and noradrenaline receptors [17, 18]. Molecular docking is a calculative method to predict the binding energies of the molecules and their conformations [19]. The Molecular Dynamics (MD) simulation process has a great role in diagnosis of protein-ligand interactions and conformational changes of the protein at the atomic level with more details in comparison with the above mentioned drugs. In the present study, we aim to assess the effects of anti HIV/Migraine drugs on the main protease of the COVID-19 virus (Mpro, 3Clpro) using molecular docking and MD simulation.

2. Materials and Methods

Protein-ligand docking

The characteristics of Rimegepant, Ergotamine, and Dihydroergotamine were obtained from PubChem and the Mpro 3Clpro (Coronavirus main proteinase). Crystal structure (entry code: 6M03) was obtained from the Protein Data Bank (PDB) (http://www.rcsb.org). The molecular docking process of Rimegepant, Dihydroergotamine, and Ergotamine to Mpro 3Clpro were assessed through a changeable docking process. The receptor and ligand side chain had sufficient flexibility and the potential to interact together using AutoDock Vina 1.1.2 software. This tool was used to evaluate the allowable torsions for ligand and polar hydrogen atoms to the protein [19]. The docking procedure was then carried out at a grid size of 40×66×64 along the X, Y, and Z axes with 1 Å spacing. AutoDock software has the capability to specify the lowest binding energy of Rimegepant-Mpro 3Clpro, Ergotamine-Mpro 3Clpro and Dihydroergotamine-Mpro 3Clpro complexes for docking conformation which were considered as primary structures for MD simulation process.

Molecular dynamics simulation

To estimate the conformational modifications of the receptor-ligand complex, the MD simulation method was carried out using the GROMACS 5.1 package [20]. The Prodrug program was applied to provide the topological characteristics of Rimegepant, Dihydroer-

gotamine ,and Ergotamine [21]. The complexes which were prepared by the method were located in a simulation box full of water molecules. In the next step, a box (gmx editconf-f protein-processed.gro-o protein-newbox.gro-c-d 1.0-bt cubic) was used. It is at least 1 nm from the edge box (-d 1.0) of simple point charge water molecules which was provided for the immersion of the aforementioned complexes.

To minimize the energy, the steepest descent method (10,000 steps), followed by the conjugate gradient method (10,000 steps), were applied for incompatible contact releases. The system equilibration (Position-restrained dynamics simulation, NVT/NPT) was carried out at 310 K for 100 ps, followed by MD production run for 100 ns [22, 23]. The atomic coordinates were recorded every 2.0 ps within the MD simulation process. Then, for a better recognition of the MD process, the Root mean Square Deviation (RMSD) was measured [24]. Then, the Pymol software was used to design the final PDB file of MD simulation process [25]. Consequently, the LigPlot software was used to analyze the H-bond and hydrophobic interactions of the complexes [26].

Molecular mechanics Poisson-Boltzmann surface area measurement

To assess the affinities of the molecular models including protein-protein and protein-ligand interactions, the molecular mechanics poisson-boltzmann surface area (MMPBSA) method was applied [27, 28]. For measuring binding affinity of Rimegepant/ Dihydroergotamine/ Ergotamine to Mpro 3Clpro, binding free energies were measured by the MMPBSA method in GROMACS software [29].

3. Results

Molecular docking and MD simulation

In the present study, to assess the interaction of 212 anti-HIV and 69 anti-migraine drugs with Mpro 3Clpro, the molecular docking process was performed. Binding drugs to Mpro 3Clpro and estimating their interaction are important, because the protein-ligand binding interaction can provide beneficial knowledge about their structures as potential therapeutic agents [12]. In the current study, the AutoDock Vina software was used to provide the selective side chain residue flexibility which is a valuable option [13]. The main superiority of this method is that it provides practical approach to ligand-protein interaction without a remarkable increase in processing time. The docking results demonstrated that the drugs bound to the Mpro 3Clpro with the lowest binding energies (Table 1). Figures 1-3 show the 2D and 3D images of the Rimegepant/ Dihydroergotamine/ Ergotamine-Mpro 3Clpro complexes after 100 ns of MD simulation process. As illustrated in 2D image, in Rimegepant-Mpro 3Clpro complex, the Rimegepant had two hydrogenic interactions with Tyr154 and ser158 residues and hydrophobic interactions with Gln110, Val104, Asn151, Ile152, Asn153, Phe294, Val297, Arg298, Val303, Thr 304, and Phe305 residues (Figure 1B).

The 2D and 3D illustrations of Dihydroergotamine-Mpro 3Clpro complex were shown in Figure 2. As can be seen, the Dihydroergotamine had hydrophobic interactions with Phe8, Gln110, Thr111, Asn151, Ile152,

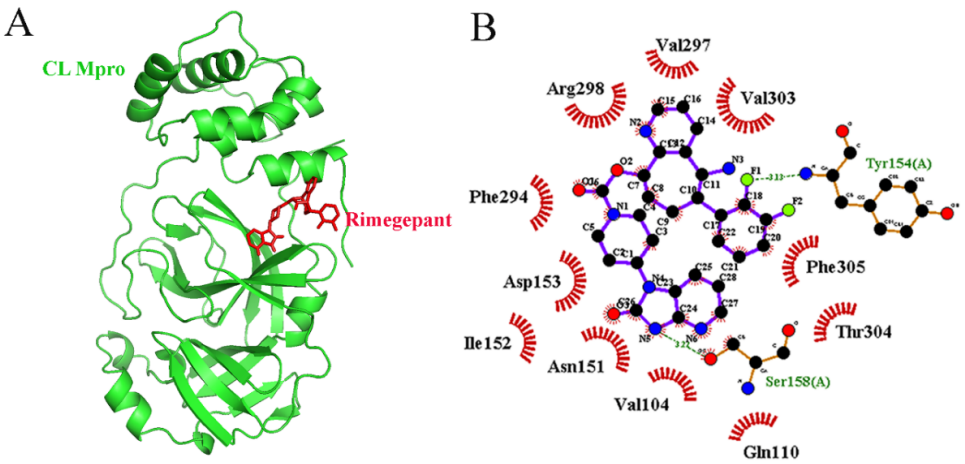

Figure 1. The 3D illustration of the Rimegepant-Mpro 3Clpro complex in Pymol software (A), and the 2D illustration of Rimegepant-Mpro 3Clpro complex in LigPlot software (B)

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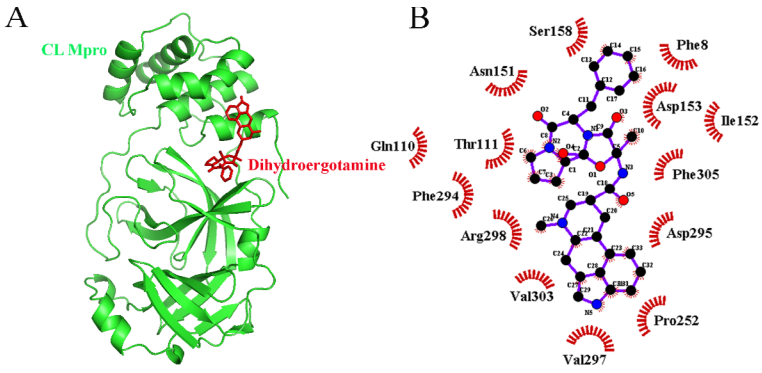

Figure 2. The 3D illustration of the Dihydroergotamine-Mpro 3Clpro complex in Pymol software (A) and the 2D illustration of Dihydroergotamine-Mpro 3Clpro complex in LigPlot software (B)

Asp153, Ser158, Pro252 Phe294, Asp295, Val297, Arg298, Val303, and Phe305 residues (Figure 2B).

Figure 3 illustrates the 2D/3D illustrations of Ergotamine- Mpro 3Clpro complex. In Ergotamine- Mpro 3Clpro complex, the Ergotamine had four hydrogen interactions with Lys137, Ala194, and Asp289 residues and hydrophobic interactions with Arg131, Asn133, Val171, Gly195, Asp197, Thr199, Tyr239, Leu286, Leu287, Glu288, and Glu290 residues (Figure 3B).

The RMSD is a useful parameter to predict the equilibration of the systems during the simulation process [30, 31]. In this study, the RMSD profiles of Rimegepant-Mpro 3Clpro, Dihydroergotamine-Mpro 3Clpro, and Ergotamine-Mpro 3Clpro complexes were evalu-

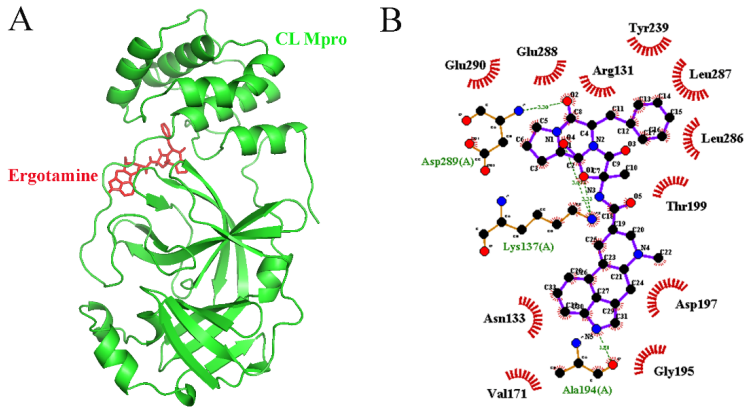

Figure 3. The 3D illustration of the Ergotamine-Mpro 3Clpro complex in Pymol software (A), and the 2D illustration of Ergotamine-Mpro 3Clpro complex in LigPlot software (B)

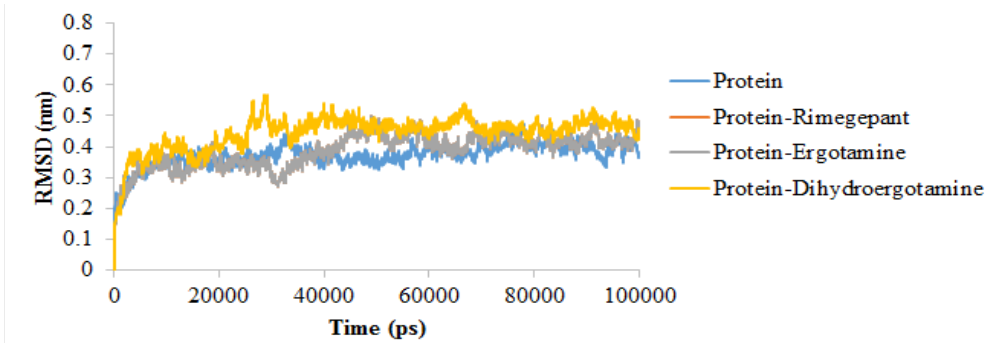

Figure 4. The RMSD values of Rimegepant-Mpro 3Clpro, Dihydroergotamine-Mpro 3Clpro, and Ergotamine-Mpro 3Clpro complexes

Table 1. Docking scores of the compounds binding to the Mpro 3Clpro

No.	Generic Name	PDB ID	Binding Energy (Kcal/moL)	Application
1	Rimegepant	DB12457	-9.6	Anti-migraine
2	Dihydroergotamine	DB00320	-9.5	Anti-migraine
3	Ergotamine	DB00696	-9.4	Anti-migraine
4	Ubrogepant	DB15328	-9.3	Anti-migraine
5	Bictegravir	DB11799	-9.2	Anti-HIV-1 and anti-HIV-2
6	Dolutegravir	DB08930	-9.0	Anti-HIV-1
7	Raltegravir	DB06817	-9.0	Anti-HIV
8	Dasabuvir	DB09183	-8.3	Anti-hepatitis C virus
9	Baloxavir marboxil	DB13997	-8.1	Anti-influenza
10	Indinavir	DB00224	-8.1	Anti-HIV
11	Maraviroc	DB04835	-8.1	Anti-HIV-1
12	Nelfinavir	DB00220	-8.1	Anti-HIV
13	Rilpivirine	DB08864	-8.1	Anti-HIV-1
14	Doravirine	DB12301	-8.0	Anti-HIV-1
15	Etravirine	DB06414	-8.0	Anti-HIV-1
16	Delavirdine	DB00705	-7.9	Anti-HIV-1
17	Letermovir	DB12070	-7.8	Anti-cytomegalovirus
18	Elvitegravir	DB09101	-7.7	Anti-HIV-1
19	Tipranavir	DB00932	-7.6	Anti-HIV-1
20	Sofosbuvir	DB08934	-7.5	Anti- hepatitis C virus
21	Boceprevir	DB08873	-7.4	Anti- hepatitis C virus
22	Darunavir	DB01264	-7.3	Anti-HIV
23	Entecavir	DB00442	-7.2	Anti- hepatitis B virus
24	Amprenavir	DB00701	-7.1	Anti-HIV

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Table 2. The MMPBSA of protein-rimegepant, protein-dihydroergotamine and protein-ergotamine complexes

Row	Type	Van der Waal Interaction (kJ/moL)	Electrostatic Interaction (kJ/moL)	Polar Salvation Energy (kJ/moL)	Non-polar Salvation Energy (kJ/moL)	Binding Energy (kJ/moL)
1	Protein-rimegepant	-148.1	-356.5	475.5	-31.2	-60.8
2	Protein-dihydroergotamine	-151.4	-330.3	461.1	-37.5	-58.1
3	Protein-ergotamine	-148.6	-372.7	499.2	-36.00	-58.1

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ated during the 100-ns simulation. Their RMSD are illustrated in Figure 4. As can be seen, the equilibration of the systems was done after 70 ns. The average RMSD of the Rimegepant-Mpro 3Clpro, Dihydroergotamine-Mpro 3Clpro, and Ergotamine-Mpro 3Clpro complexes in the final stages of the simulation was 0.2, 0.25, and 0.29 nm, respectively.

Binding energy calculation using the MMPBSA method

The MMPBSA can be used for evaluating the binding free energy [32]. The binding free energy of the complexes and Mpro 3Clpro was measured using g-MMPBSA command in GROMACS software [29]. The results showed that the Protein-Rimegepant complex had the highest negative binding free energy (-60.8 kJ/mol). The Protein-Dihydroergotamine and Protein-Ergotamine complexes had an energy of -58.1 and -58.1 kJ/mol, respectively. It should be noted that the van der Waals and electrostatic interactions and non-polar solvation energy contributed negatively to the total free binding energy, while the polar solvation energy contributed positively. Moreover, in the three complexes, electrostatic interactions contributed more than van der Waals interactions and the non-polar free energy was lower (Table 2).

4. Discussion

The prevalence of SARS-CoV-2 threatens the global public health. Lack of specific treatment methods against this virus indicates the necessity of new drug compounds in which in silico assessments offer fast and cost-effective approaches. Sencanski et al. evaluated the effects of 57 drugs on SARS-Cov2 protease and confirmed that the Raltegravir binds to the allosteric site of the enzyme with the highest binding energy [33]. Our study verified that the aforementioned drug is attached to the enzyme with binding energy of -90 kcal/mol ranked as the seventh docked drug to the enzyme. Taj Mohammad et al. evaluated the effects of 4802 compounds on the main enzyme of SARS-CoV-2 in AutoDock Vina software [34]. Their results showed that, all the above compounds bound to the enzyme with a binding energy ranged from -8.1 to -8.7 kcal/mol. In our study, the binding energies ranged from -7.1 to -9.6 kcal/mol which confirmed that the selected compounds had a higher affinity for binding to the enzyme. In another study, Fischer et al. assessed many compounds on the aforementioned enzyme [35]. They showed that the Nelfinavir and Amprenavir had the highest and lowest binding affinities to the Mpro 3Clpro, respectively [35]. It should be noted that in the current study, the above compounds ranked 12th and 24th places with binding energies of -8.1 and -7.1 kcal/mol, respectively.

5. Conclusion

Some anti HIV and anti-migraine drugs can bind to the main protease of SARS-CoV-2 efficiently and therefore they can considered as appropriate inhibitors of the enzyme. Among these drugs, the anti-migraine drug "Rimegepant" is a good candidate for in vitro and in vivo evaluations.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the University of Qazvin University of Medical Sciences (Code: IR.QUMS.REC.1399.041).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank the Research Council of Qazvin University of Medical Sciences.

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