ORIGINAL ARTICLE

Molecular Docking Based Drug Repurposing Study of Antiviral Drugs against COVID-19 Virus Spike Receptor Binding Domain

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ABSTRACT

Background: Coronavirus disease (COVID-19) has affected more than 30 million people from all over the world. The SARS-CoV-2 is the pathogen of Coronavirus disease (COVID-19). Its infection may cause mild illness, but in certain susceptible persons, it may cause critical condition leading to respiratory failure and even multi-organ failure. The finding of effective curative medicine for the Coronavirus disease (COVID-19) is a huge challenge to the scientists. The drug repurposing with the help of computational simulation may be a one positive step towards the development of an effective curative therapeutic agent for this pathogen.
Aim: To evaluate the binding affinity of four antiviral drugs with this COVID-19 virus spike receptor binding domain with the application of molecular docking.
Methods: In the present study, four antiviral agents have been selected for the evaluation of binding affinity with the COVID-19 virus spike receptor binding domain. The antiviral drugs included in the study are sofosbuvir, dasabuvir, ledipasvir and daclatasvir while remdesivir is used as standard. The binding affinity was evaluated with the application of molecular docking.
Results: In the present study, four antiviral drugs have been evaluated for drug repurposing which included sofosbuvir, dasabuvir, ledipasvir and daclatasvir while remdesivir is used as standard for the result comparison. The docking score (binding affinity) of ledipasvir (-8.12 kcal/mol) and daclatasvir (-7.47 kcal/mol) was more than remdesivir (-6.54 kcal/mol).
Conclusion: The antiviral agents used for the management of HCV (positive sense - RNA virus) could also be a potential candidate drugs for the management of Coronavirus disease (COVID-19).
Keywords: Molecular Docking; Drug Repurposing; COVID-19

INTRODUCTION

Coronavirus disease (COVID-19) has affected a vast population of the world. More than half of millions of people have died due to this disease in less than one year. The SARS-CoV-2 is the causative pathogen of this ailment. It is a member of the genus beta-coronavirus, which is included in the family of Coronaviridae and the order of Nidovirales. The other members of the genus beta-coronavirus are SARS-CoV and MERS-CoV. The Coronaviruses are enveloped viruses. These viruses have positive-sense single-stranded RNA. The SARS-CoV-2 enters the host cell by binding the receptor with its spike protein[1]. The spike protein of SARS-CoV-2 attaches to the ACE2 receptor[2]. The size of the viral particle varies from 66 to 81 nm in diameter[3]. The mode of transmission of this virus is mainly through respiratory droplets[4-6]. The SARS-CoV-2 may cause mild illness, or the person may remain asymptomatic, but in certain susceptible persons, it may cause critical condition leading to respiratory failure and even multi-organ failure[7-8]. The overall mortality of COVID-19 is low, but it is high in patients with increased age, hypertension, diabetes mellitus, and cardiovascular diseases[9]. The incubation period is 2–14 days[10]. The standard clinical features of Coronavirus disease (COVID-19) include elevated body temperature, tiredness, dry cough, loss of appetite, muscle pains, dyspnea, and sputum production[11]. The envelope of SARS-CoV-2 contains three essential proteins, which include spike protein (S), membrane protein M and envelope protein E. After entering into the human body through the respiratory tract, the virus binds to the columnar epithelial cells of the bronchial tree and the type 2 pneumocytes present in the alveoli. The SARS-CoV-2 attaches to the cells through its spike protein, which binds to ACE 2 receptors.

The interruption in the binding of spike protein of SARS-CoV-2 with the ACE 2 receptors may be helpful in stopping the viral entry into the human cells. The chemical substance which may bind to the COVID-19 virus spike receptor binding domain, could also interfere with its binding to ACE 2 receptors and may result in reduction in the viral entry and subsequent replication in the human cells. The binding affinity of some antiviral drugs with this COVID-19 virus spike receptor binding domain may be evaluated with the help of molecular docking.

Molecular docking is used to predict the preferred orientation of a ligand (drug or chemical compound) when it binds to the active site of a target (receptor or enzyme). It helps to identify the best compound against a target protein or enzyme and also aids in the drug repurposing of the existing approved drugs[12]. Accordingly, the titled study was performed to evaluate the binding affinity of four antiviral drugs, which are indicated for the positive sense single-stranded viruses such as the hepatitis C virus, with the COVID-19 virus spike receptor binding domain.

MATERIALS AND METHODS

The MOE software (Molecular Operating Environment, 2019.0102, Chemical Computing Group Inc., Canada) was utilized for the docking analysis. The 7BZ5 protein was downloaded from the PDB website [https://www.rcsb.org/structure/7BZ5][13]. This protein contains three chains, chain A, chain H, and chain L. The longest chain was chain A (229 amino acid), and it also included a natural ligand (2-acetamido-2-deoxy-β-D-glucopyranose, NAG) in it. Therefore, the 7BZ5 protein was truncated, and chain A was selected for the docking study. The original 7BZ5 protein was uploaded in the MOE program. The chain H and chain L, along with their water molecules, were deleted from it. The water molecules of chain A were also deleted. The chain, A without its associated water molecules, was prepared for the docking study by using the Quickprep feature of the MOE program. The default setting of the Quickprep was used for this purpose. The preparation of the ligands, their docking with the purified protein, and the calculation of the inhibition constant (K_i) were done as described in our earlier publication[14].

Four antiviral agents have been selected for the evaluation of binding affinity with the COVID-19 virus spike receptor binding domain. The antiviral drugs included in the study are sofosbuvir, dasabuvir, ledipasvir and daclatasvir while remdesivir is used as standard. These are antiviral drugs and used to treat hepatitis C virus infection. The hepatitis C virus is a positive sense RNA virus while SARS-CoV-2 is also a positive sense RNA virus. It has been postulated that these drugs may be a potential therapeutic drug for the treatment COVID-19.

Remdesivir has been conditionally approved in many countries, including the USA, Europe, China, Singapore, Australia, and Canada, for the COVID-19 treatment[15]. Accordingly, remdesivir was used as a standard drug for a comparative analysis of the docking results. The 7BZ5 was used for the docking analysis of the selected antiviral drugs. The chain A of 7BZ5 protein was selected for the docking purpose because it was the longest chain of this protein with the natural ligand (NAG = 2-acetamido-2-deoxy-β-D-glucopyranose) attached with it. The three parameters were checked with the molecular docking, namely, docking score (DS/binding affinity expressed as kcal/mol), Root mean square deviation (RMSD expressed as Å), and the inhibition constant (K_i expressed as µM). The docking score (DS) is an indicator of binding of the molecules with the receptor/protein. Lower values of the DS indicate better binding of a molecule with the receptor/protein and ultimately better potency. The RMSD values are indicators of the fit quality of the ligand with the receptor/binding site. A lower value of RMSD (< 2 Å) indicates a better fit quality of the ligand with the receptor/binding site. The inhibition constant (K_i) is an indicator of the potency of a ligand or compound.

RESULTS

In the present study, four antiviral drugs have been evaluated for drug repurposing which included sofosbuvir, dasabuvir, ledipasvir and daclatasvir while remdesivir is used as standard for the result comparison.

The docking score (binding affinity) of ledipasvir (-8.12 kcal/mol) and daclatasvir (-7.47 kcal/mol) was more than remdesivir (-6.54 kcal/mol). This shows that ledipasvir and daclatasvir are more potent than remdesivir. Our understanding is also supported by the calculated K_i values of ledipasvir (0.0026 uM) and daclatasvir (0.0042 uM) in contrast to remdesivir (0.0083). This increase in the potency may be because ledipasvir and daclatasvir interact with more amino acid residues of the chain A of 7BZ5 protein**.** The data of the molecular docking is provided in Table 1.

The NAG (natural ligand) shows interactions with the Cys 336, Phe 374, Val 367, Phe 342, Gly 339, Phe 338, Leu 368, Asn 343, and Ser 371 of the chain A of 7BZ5 protein. It is quite interesting to know that remdesivir, daclatasvir, dasabuvir, ledipasvir, and sofosbuvir also showed interaction with these amino acid residues. This indicates that these drugs bind in the same region of the chain A of 7BZ5 protein, and they might be sharing a similar mechanism of action.

Figure 1: 2D interaction of remdesivir with the amino acid residues of the chain A of 7BZ5 protein

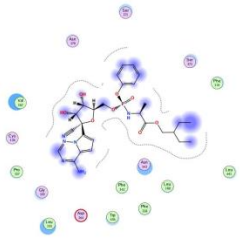

Figure 2: 2D interaction of daclatasvir with the amino acid residues of the chain A of 7BZ5 protein

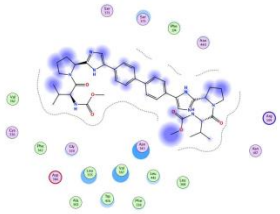

Figure 3: 2D interaction of dasabuvir with the amino acid residues of the chain A of 7BZ5 protein

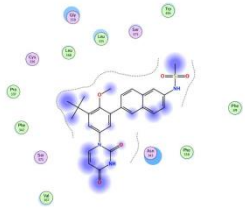

Figure 4: 2D interaction of ledipasvir with the amino acid residues of the chain A of 7BZ5 protein

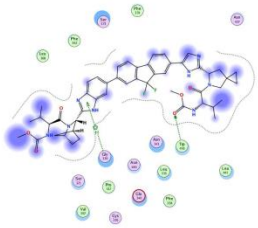

Figure 5: 2D interaction of sofosbuvir with the amino acid residues of the chain A of 7BZ5 protein

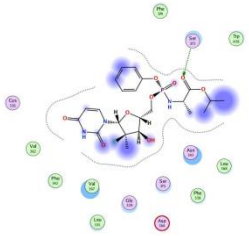

Figure 6: 2D interaction of **NAG** (natural ligand) with the amino acid residues of the chain A of 7BZ5 protein

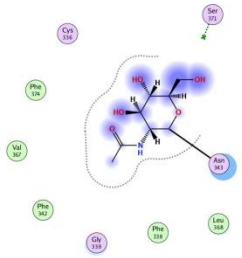

Table 1: The molecular docking data of remdesivir, daclatasvir, dasabuvir, ledipasvir, and sofosbuvir

S. No.	Drug	Chain A of 7BZ5			Interacting Amino Acid Residues
		DS	RMSD	K_i	
1	Remdesivir (Figure 1)	-6.54	1.24	0.0083	Ser 371, Ser 373, Phe 374, Leu 441, Leu 368, Asn 343, Phe 338, Phe 342, Trp 436, Asp 364, Leu 335, Gly 339, Pro 337, Cys 336, Val 367, Asn 370
2	Daclatasvir (Figure 2)	-7.47	1.33	0.0042	Ser 371, Ser 373, Phe 374, Asn 440, Arg 509, Asn 437, Leu 368, Leu 441, Asn 343, Phe 338, Val 367, Trp 436, Leu 335, Ala 363, Gly 339, Asp 364, Phe 342, Cy 336, Val 362
3	Dasabuvir (Figure 3)	-6.12	1.38	0.0113	Val 367, Ser 371, Phe 342, Pro 337, Cys 336, Leu 368, Gly 339, Leu 335, Ser 373, Trp 436, Phe 374, Phe 338, Asn 343
4	Ledipasvir (Figure 4)	-8.12	1.16	0.0026	Ser 371, Val 367, Gly 339, Pro 337, Cys 336, Asn 440, Glu 340, Asn 343, Leu 335, Phe 338, Trp 436, Leu 441, Asn 437, Phe 374, Ser 373, Phe 342, Leu 368
5	Sofosbuvir (Figure 5)	-6.32	1.48	0.0097	Cys 336, Val 362, Phe 342, Val 367, Leu 335, Gly 339, Asp 364, Ser 371, Phe 338, Asn 343, Leu 368, Trp 436, Ser 373, Phe 374
6	NAG (Figure 6)	-4.58	1.38	0.0349	Cys 336, Phe 374, Val 367, Phe 342, Gly 339, Phe 338, Leu 368, Asn 343, Ser 371

DISCUSSION

The analysis of this study showed that the binding affinity of ledipasvir (-8.12 kcal/mol) and daclatasvir (-7.47 kcal/mol) was better than the remdesivir (-6.54 kcal/mol). While other antiviral drugs sofosbuvir and dasabuvir revealed the binding affinity -6.32 kcal / mol and – 6.12 kcal / mol respectively which is less the binding affinity of the drug (remdesivir) used as standard.

The study conducted by Elfiky AA revealed the binding affinity of sofosbuvir against the COVID –19 RdRp is– 7.5kcal/mol[16].

Since at present, we do not have a standard treatment for the Coronavirus disease (COVID-19). It would be quite useful to perform drug repurposing analysis which could be an important step towards the development or identification of most appropriate antimicrobial agent for the management of Coronavirus disease (COVID-19). The drug repurposing saves a lot of time and financial resources.

The process of drug repurposing is characterized by evaluation of existing drugs for purpose of new therapeutic purpose. This strategy has got many benefits such as reduction in the financial cost and time with rapid availability of the medicinal drug for therapeutic purpose which could be due to limitation of clinical trials and presence of drug supply chains. In the current scenario of pandemic of Coronavirus disease (COVID-19), it would be of paramount importance to apply the strategy of drug repurposing for the discovery of therapeutic drug for Coronavirus disease (COVID-19). Since HCV is a RNA virus and the antiviral drugs used for the management of HCV infection may be evaluated for the purpose of therapeutic effects on SARS-CoV-2.

For the discovery of new drugs, molecular docking has emerged as an important technique. The molecular docking is quite popular computational strategy for the purpose of drug repositioning. With the help of molecular docking, large number of approved drugs may be evaluated in a short span of time for the purpose of specific biological target[17].

The remdesivir is the drug which has been used in the clinical trial for the management of COVID-19. This medicine acts by blocking the RNA-dependent RNA polymerase of the virus and causes inhibition of viral replication[18]. In the present study, the molecular docking analysis revealed the binding affinity of (-6.54 kcal/mol) of remdesivir with COVID-19 virus spike receptor binding domain.

Another direct antiviral agent is dasabuvir which revealed a binding affinity of -6.12 kcal/mol. Dasabuvir is used in treatment of chronic HCV infection. The drug checks the HCV replication by blocking the action of NS5B polymerase[19]. Sofosbuvir is another drug which is used for the management of HCV infection in case of chronic hepatitis. It is a nucleotide analogue inhibiter which inhibits NS5B polymerase and interferes with the HCV replication[20]. In the present study the binding affinity of Sofosbuvir is -6.32 kcal/mol.

The findings of the present study suggest that some of the direct acting antiviral drugs which are used to treat HCV infection may also play a role in limiting the disease caused by SARS-CoV-2.

The present study used the in silico pathway for the drug experimentation. The in silico process for the therapeutic

agent experimentation is performed by computer simulation which is easier than the in vivo and in vitro pathways. But this process has got certain limitations as well, such as dearth of synergistic computational models and constraints in the assessment of multi drug effects.
Further studies with the applications of deep learning (artificial intelligence) are recommended along with the in vivo and in vitro studies for the identification of a suitable drug for the treatment of Coronavirus disease (COVID-19).

CONCLUSION

The antiviral agents used for the management of hepatitis C virus infection could be a potential candidate drugs for the management of Coronavirus disease (COVID-19).
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