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Full length article

In silico molecular docking analysis for repurposing therapeutics against multiple proteins from SARS-CoV-2

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ABSTRACT

SARS-CoV-2 has devastated the world with its rapid spread and fatality. The researchers across the globe are struggling hard to search a drug to treat this infection. Understanding the time constraint, the best approach is to study clinically approved drugs for control of this deadly pandemic of COVID 19. The repurposing of such drugs can be supported with the study of molecular interactions to enhance the possibility of application. The present work is a molecular docking study of proteins responsible for viral propagation namely 3Clpro, Nsp10/16, Spike protein, SARS protein receptor binding domain, Nsp 9 viral single strand binding protein and viral helicase. The protein through virus enters the host cell-human angiotensin-converting enzyme 2 (ACE2) receptor, is also used as a target for molecular docking. The docking was done with most discussed drugs for SARS-CoV-2 like Ritonavir, Lopinavir, Remdesivir, Chloroquine, Hydroxychloroquine (HCQ), routine antiviral drugs like Oseltamivir and Ribavirin. In addition, small molecules with anti-inflammatory actions like Mycophenolic acid (MPA), Pemirolast, Isoniazid and Eriodictyol were also tested. The generated data confirms the potential of Ritonavir, Lopinavir and Remdesivir as a therapeutic candidate against SARS-CoV-2. It is observed that Eriodictyol binds to almost all selected target proteins with good binding energy, suggesting its importance in treatment of COVID 19. Molecular interactions of Ritonavir, Lopinavir and Remdesivir against SARS-CoV-2 proteins enhanced their potential as a candidate drug for treatment of COVID-19. Eriodictyol had emerged as a new repurposing drug that can be used in COVID-19.

1. Introduction

The current outbreak of the novel coronavirus disease, COVID-19, is in headlines globally because of its threat to public health. This disease is caused by a novel severe acute respiratory syndrome-related coronavirus SARS-CoV-2 that emerged from Wuhan, China, in December 2019 (Lai et al., 2020; Wu et al., 2020). The disease has spread in 215 countries and territories with 31,81,642 confirmed cases and about 2,24,301 deaths to date (www.who.int). The symptoms of COVID-19 range from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death. The virus is highly transmissible among humans, with clusters occurring among close contacts forcing many countries to impose a lockdown on all activities which had already

affected the global economy, and the situation will be worse if this disease is not controlled in time. Unfortunately, there is no effective medication for this novel SARS-CoV-2 at present (Liu et al., 2020).

In an attempt to fight against coronavirus, scientists are coming up with different strategies. Drug repurposing, an effective drug discovery strategy, could significantly shorten the time and reduce the cost compared to *de novo* drug discovery and randomized clinical trials (Cheng et al., 2016, 2017; Cheng, 2019; Zhou et al., 2020). Computational methods to understand the ligand protein interaction is one of the fastest ways to identify the candidate drug and target. Scientists are screening existing molecules from the database, which might be effective against coronavirus as a strategy (Zhou et al., 2020; Chauhan, 2020; Wu et al., 2020). In case of SARS-CoV-2, inputs from this traditional way

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were lacking because of unavailability of protein structure. But 3D structures of different proteins of this novel SARS-CoV-2 are constantly being deposited in the database and hence in the present study we decided to do molecular docking analysis of these newly deposited proteins against some repeatedly discussed drugs as a repurposing therapeutic approach. We had selected those proteins for docking which play an important role in propagation of virus. We selected 3CLpro which is the main protease of the virus, envelope anchored spike protein from virus and receptor binding domain of this protein, SARS-CoV-2 helicase, Nsp10/16 complex a nonstructural protein and a single strand or RNA binding protein as target because of their importance in viral life cycle (Wu et al., 2020). Virus enters the cell via angiotensin receptor converting enzyme 2 therefore blocking this enzyme could be of immense importance (Li et al., 2003; Han et al., 2006; Ge et al., 2013). This enzyme is also selected as one of the target proteins.

In the present study, some known antiviral drugs like Ritonavir, Lopinavir, Remdesivir, Oseltamivir and Ribavirin, along with some small molecules like Mycophenolic acid (MPA), Chloroquine, Hydroxychloroquine (HCQ), Pemirolast, Isoniazid and Eriodictyol which are being discussed as therapeutic agents against COVID-19, are used as candidate ligands for docking. Molecular docking was done using PyRx version 0.8 (Trott and Olson, 2010).

2. Materials and methods

2.1. Proteins/macromolecules

Different proteins from SARS-CoV-2 were selected which include main protease of SARS-CoV-2 Mpro/3CLpro [PDB ID: 6Y84] (Owen et al., 2020), the crystal structure of COVID-19 main protease in apo form [PDB ID: 6M03] (Zhang et al., 2020) and crystal structure of COVID-19 main protease [PDB ID: 6LU7] (Xu et al., 2020), Nsp10 [PDB ID: 6W75 B and D] and Nsp 16 [PDB ID: 6W75 A and C] (Minasov et al., 2020) the complex which plays a pivotal role in viral transcription; separate chains A, B and C of spike glycoprotein [PDB ID: 6VSB A,B and C chains] (Wrapp et al., 2020), SARS protein receptor binding domain [PDB ID: 2GHV] (Cao et al., 2020), Nsp9 RNA binding protein of SARS-CoV-2 [PDB ID: 6W4B] (Tan et al., 2020) and ADP ribose phosphatase of NSP3 from SARS CoV-2 [PDB ID: 6VXS] (Kim et al., 2020). We have also selected the protein from host cell, i.e. human cell, which is responsible for host virus interaction. Virus enters the cell through angiotensin-converting enzyme 2 (ACE2) receptor [PDB ID: 6M18] chains B and D (Yan et al., 2020) by binding with its spike protein. 3D structures were obtained from Protein Data Bank (<https://www.rcsb.org/>), in .pdb format (Berman et al., 2000).

2.2. Ligand/drug structures

Known antiviral drugs like Ritonavir, Lopinavir, Remdesivir, Oseltamivir and Ribavirin as well as Mycophenolic acid (MPA), Chloroquine, Hydroxychloroquine (HCQ), Pemirolast, Isoniazid and Eriodictyol, which are used to treat other ailments, were selected as a candidate ligands for docking against viral proteins.

The drug/ligand structures were obtained from the DrugBank database which is a comprehensive, freely accessible, online database containing information on drugs and drug targets (Wishart et al., 2018).

2.3. Determination of active sites

The Computed Atlas for Surface Topography of Proteins (CASTp) (Tian et al., 2018) and Biovia Discovery Studio 4.5 (Biovia, D.S 2019) were used to determine the amino acids in the active site of a protein (<http://sts.bioe.uic.edu/castp/index.html?2011>).

2.4. Molecular docking

Ligand and protein optimization were done using PyMOL version 2.3.3 [The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC]. For ligand optimization, the geometry of ligands was cleaned, whereas for protein, the water was removed. The docking was performed by using PyRx 0.8 (Trott and Olson, 2010). The docking analyses were performed using both Pymol as well as Biovia Discovery Studio 4.5 (Biovia, D.S 2019).

3. Results

Table 1 represents proteins along with their PDB ID and structure which were used as targets for molecular docking. These proteins play an important role in viral replication and virus entry. Table 2 gives the details of ligands which were selected for molecular docking. Traditional structure-based method of molecular docking was done because of availability of 3D structures of SARS-CoV-2 virus. Table 3 A and 3 B shows molecular docking data represented in terms of binding energy (ΔG) in Kcal/mole for selected viral target proteins (Table 3 A) and human receptor protein ACE-2 (Table 3 B) with all selected drugs. Result presented in this table clearly show that all these compounds are binding to all viral proteins as well as human ACE 2 to some extent. Different ligands are showing highest binding against different proteins and this data are presented in Table 4. It was observed that Ritonavir is giving efficient binding energy for Nsp16, 6W75D, 6VSB and 2GHV whereas Remdesivir is more active against 6M03, 6LU7, 6VSB, 6W75B. It was observed that Lopinavir shows a highly efficient binding with key viral proteins like 6Y84, 6W4B, 6VSB, 6VXS and ACE 2 receptor protein 6M18B and 6M18D. Out of the small molecules tested here, Eriodictyol has high binding efficiencies against all selected proteins. Nevertheless, Pemirolast also shows high binding efficiencies against 6M03 and 6W4B. Fig. 1 represents the graph of binding energy in $-Kcal/mol$ of different drug ligands against 6Y84. It was observed that all ligands are binding to this target with good binding energies but binding of Lopinavir, Remdesivir, Eriodictyol and Ritonavir is more favorable than others (Fig. 1). Same drug ligands also show good binding energy against human ACE-2 suggesting their high potential for repurposing. We further analyzed only those docking poses which have binding energy less than $-7.5 kcal/mol$ to understand the molecular interactions. Docking poses with less than $-7.5 kcal/mol$ binding energy were shown in Fig. 2 along with the active site of respective protein. The docking analysis of these poses was done to check the interaction as amino acid level. The comparison of amino acids from specific protein which are binding to ligand and amino acids present in active site of that protein is shown in Table 5. It was observed that in case of 6Y84 almost all drugs which are binding to this protein are binding to 3 amino acids from active site GLN127, GLU290 and PHE 191. In case of 6VXS, helicase of corona virus, Lopinavir and Pemirolast are binding with $-7.9 kcal/mol$ and $-7.6 kcal/mol$ respectively but both contain only one common amino acid LYS44 with protein active site. Eriodictyol has binding energy of $-7.9 kcal/mol$ against 6VXS and the interactions involves ALA38, ASN40, GLY46, GLY47, GLY48, VAL49, ALA50, PRO125, LEU126, LEU127, SER128, ALA129, ILE131, PHE132 amino acids. All these amino acids are present in the active site of 6VXS protein. Remdesivir and Pemirolast are binding to 6M03, the apo form of main protease, but not involving any amino acid from active site. In case of Ritonavir binding to 2GHV, the receptor binding domain of spike protein of the virus PHE361, SER362 GLY368 amino acids from the active site are involved in the interaction. The 6VSB is a spike protein of the virus to which Eriodictyol is binding with the energy of $-7.6 kcal/mol$. This interaction involves ASN544, VAL576, PHE543, LEU546, PHE565, ALA522, ARG577, PRO521, PRO579, GLN564 amino acids from the active site.

In case of 6W75 Nsp10/16 complex, Remdesivir and Eriodictyol are binding to the protein but only Eriodictyol is directly interacting with

Table 1

Structure of viral proteins which were used as a targets for molecular docking with PDB ID (4-character unique identifier of every entry in the Protein Data Bank) and source organism.


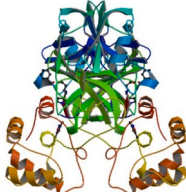


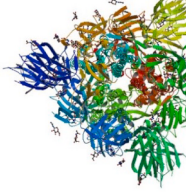
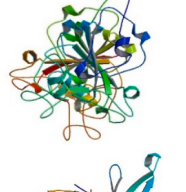
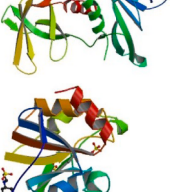


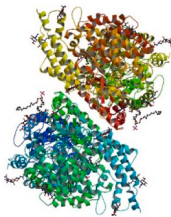
Name of the protein and description	Source	PDB ID	Structure of protein
Mpro/3CLpro (Main protease of SARS CoV 2)	SARS CoV 2	6Y84	
The crystal structure of COVID-19 main protease	SARS CoV 2	6LU7	
The crystal structure of COVID-19 main protease in apo form	SARS CoV 2	6M03	
Nsp10 (Plays a crucial role in viral transcription by stimulating both nsp14 3'-5' exoribonuclease and nsp16 2'-O-methyltransferase activities.)	SARS CoV 2	6W75 B	
Nsp 16 (S-adenosylmethionine-dependent (nucleoside-2'-O)-methyltransferase only active in the presence of its activating partner nsp10)	SARS CoV 2	6W75 D 6W75 A 6W75D	
SARS protein receptor binding domain	SARS CoV 2	6VSBA 6VSBB 6VSBC	
Nsp9 (RNA binding protein of SARS CoV 2) and SARS CoV 2 helicase	SARS CoV 2	2GHV	
ADP ribose phosphatase of NSP3 from SARS CoV-2	SARS CoV 2	6W4B	
Angiotensin-converting enzyme 2 (ACE2) receptor (Receptor through which virus enters the cell)	Human	6VXS 6M18B 6M18D	

Table 1 (continued)

Name of the protein and description	Source	PDB ID	Structure of protein
			

amino acids TYR4329, HIS 4336, PRO4337 which are present in active site of 6W75 chain C. Lopinavir, Ritonavir, Eriodictyol are binding at 6M18B and Lopinavir, Ritonavir, Remdesivir are binding at 6M18D but their binding but is not in the active site.

The comparison of anti SARS-CoV-2 potential of different drugs is summarized in Table 6. It was observed that all drug ligands except Oseltamivir and Isoniazid are binding to 6Y84, the main protease in virus, in active site. Based on this study all drug ligands except Oseltamivir and Isoniazid have anti-SARS-CoV-2 potential. Lopinavir and Pemirolast are binding in the active site of 6VXS other than 6Y84 and Ritonavir is binding in active site of 2GHV along with 6Y84. Among all these ligands, Eriodictyol has the highest potential to be repurposed as an antiviral against SARS-CoV-2 since it is binding to 6VXS, 6VSB C, 6W75D along with 6Y84.

4. Discussion

Since the current outbreak of viral epidemic, scientists around the world are taking enormous efforts to understand this new virus and pathophysiology of the disease. Overall current knowledge of the SARS-CoV-2 virus as well as previous understanding of SARS-CoV 2003 and MERS-CoV 2012 is helpful to discover new therapeutic agents, targets and vaccines (Wu et al., 2020; Jiang et al., 2020). Considering the nature of SARS-CoV-2 and its high infection rate, finding new therapeutic target and development of a vaccine is actually a race against time. There is no treatment available to kill the virus or to stop the infection till date. Therefore, finding broad-spectrum inhibitors which may reduce the effects of human coronavirus infection is challenging (Liu et al., 2020). The fastest strategy for such a widely spreading infectious diseases is to utilize the existing medication of other diseases i.e. repurposing of drug. Such drugs are already approved for their safety and it's ADME properties are already known (Smith and Smith, 2020). Unavailability of protein structures of SARS-CoV-2 was one of the major hurdles to curate the huge bulk of antivirals for studying molecular interaction. As 3D structures of many proteins from SARS-CoV-2 are reconstructed and deposited in protein databases, we decided to use these structures to study the molecular interactions of known antivirals.

We have selected viral proteins which are important for viral replication and viral entry to host cell. One such key protein is 3CLpro which is the main protease of the virus. It is continuously discussed as a potential target for drug development (Khaerunnisa et al., 2020; Xu et al., 2020; Zhang et al., 2020). The first long polypeptides of virus become functional only when they are cut into smaller pieces by 3CLpro proteases. Thus, the propagation of Coronavirus is highly dependent on proteases. This protease cuts the long polypeptide at the recognition sequence at most sites is Leu-Gln↓(Ser,Ala,Gly) (↓ marks the cleavage site). Since no human proteases with a similar cleavage specificity are known, blocking this protease would be beneficial without disturbing host cell activities (Zhang et al., 2020). Another important target we selected was the envelope anchored spike protein from the virus and receptor binding domain of this protein. The spike protein is a glycoprotein which binds with human cell receptor by its receptor binding domain, and enters in the cells (Wan et al., 2020; Li, 2016). SARS-CoV-2

Table 2

Ligands which were selected for molecular docking along with its structure obtained from DrugBank and the important activities.

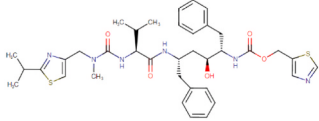
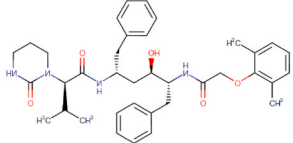
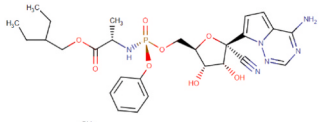
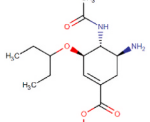
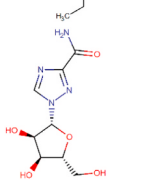
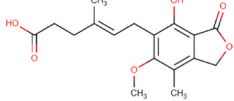
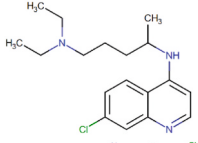
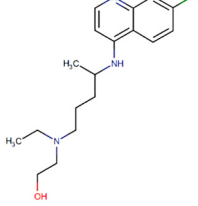
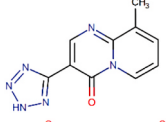
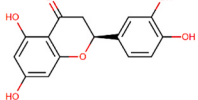
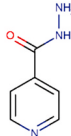
Sr. No.	Name	Structure	Function
1	Ritonavir		Antiretroviral protease inhibitor, used as common anti HIV in combination with other protease inhibitors
2	Lopinavir		Antiretroviral protease inhibitor, used as common anti HIV in combination with other protease inhibitors
3	Remdesivir		Nucleotide analog, novel antiviral treatment for Ebola virus disease and Marburg virus infections, antiviral activity against other single stranded RNA viruses including MERS and SARS viruses
4	Oseltamivir		An antiviral medication used to treat and prevent influenza A and influenza B (flu)
5	Ribavirin		An antiviral medication used to treat RSV infection, hepatitis C and some viral hemorrhagic fevers
6	Mycophenolic acid (MPA)		An immunosuppressant medication
7	Chloroquine		Medication primarily used to prevent and treat malaria, used in compassionate treatment of patients with coronavirus infections during Covid19 pandemic
8	Hydroxychloroquine (HCQ)		Prevent and treat malaria, an experimental treatment for coronavirus disease 2019 (COVID-19)
9	Pemirolast		Pyrimidinone derivative with anti-allergic activity, anti-inflammatory
10	Eriodictyol		Anti-inflammatory
11	Isoniazid		Antituberculosis, anti HIV

Table 3AMolecular docking data represented in terms of binding energy (ΔG) in Kcal/mole for viral target proteins with drug ligands.

Sr. No	Drug	Binding energy ΔG (Kcal/Mol)												
		6M03	6LU7	6Y84	6W4b	6VSBA	6VSBB	6VSBC	2GHV	6VXS	6W75A	6W75C	6W75B	6W75D
1	Ritonavir	-7.2	-6.6	-8.7	-5.8	-6.2	-5.6	-7	-7.6	-6.3	-7.3	-7.2	-6.1	-7.3
2	Lopinavir	-7.3	-5.9	-9.9	-6.4	-6.9	-6.2	-6.6	-7.1	-7.9	-6.9	-7.3	-6.5	-6.9
3	Remdesivir	-7.8	-7.2	-9.4	-6.2	-6.5	-6.8	-6.2	-6.9	-6.9	-6.9	-7.6	-7	-6.9
4	Oseltamivir	-6.1	-5.2	-6.6	-4.3	-5.3	-6	-5.4	-5.8	-5.7	-5.7	-6.2	-5.6	-5.7
5	Ribavirin	-6	-6.3	-8.2	-5.6	-5.5	-5.5	-5.4	-6.5	-6.2	-6.6	-6.6	-5.9	-6.6
6	Mycophenolic acid	-6.4	-6.4	-8	-5.3	-4.7	-4.8	-5.4	-6.6	-6.3	-6.5	-6.9	-6.3	-6.5
7	Chloroquine	-6.5	-5.4	-7.8	-5.2	-4.8	-5.4	-4.8	-5.4	-6.4	-6.7	-7.1	-5.9	-6.7
8	Hydroxychloroquine	-6.1	-5.6	-7.9	-5.5	-5.8	-5.6	-5.5	-5.8	-5.8	-6.5	-7	-6.4	-6.5
9	Pemirolast	-7.7	-6.4	-8.2	-6.5	-6.6	-6.2	-6.3	-6.7	-7.6	-6.7	-6.9	-6.4	-6.7
10	Eriodictyol	-7.4	-6.7	-8.8	-6.5	-7	-6.7	-7.6	-7.3	-7.8	-7.5	-7.5	-7	-7.5
11	Isoniazid	-4.8	-4.6	-5.6	-4.4	-5	-4.4	-5	-5.1	-5	-5.2	-5.1	-4.8	-5.2

Table 3BMolecular docking data represented in terms of binding energy (ΔG) in Kcal/mole for ACE2 protein with drug ligands.

Sr. No.	Drug	Binding energy ΔG (Kcal/Mol)	
		6M18B	6M18D
1	Ritonavir	-8.2	-8.1
2	Lopinavir	-8.6	-8.9
3	Remdesivir	-8.2	-7.7
4	Oseltamivir	-6	-5.8
5	Ribavirin	-6.2	-6.3
6	Mycophenolic acid	-6.5	-6.4
7	Chloroquine	-5.8	-5.2
8	Hydroxychloroquine	-6.2	-6.5
9	Pemirolast	-7.3	-7
10	Eriodictyol	-7.5	-7.4
11	Isoniazid	-5.2	-5.2

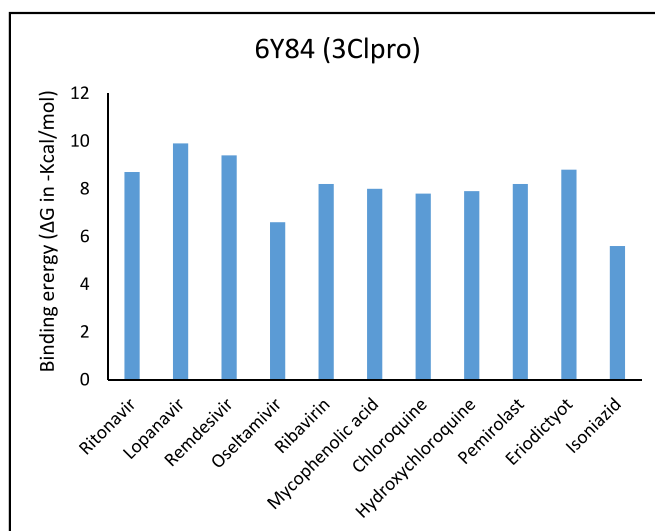
Table 4

Drug giving lowest binding energy in Kcal/mole for a particular protein.

Sr.No.	Protein	Drug	Binding energy in Kcal/mol
1	6M03	Remdesivir	-7.8
2	6LU7	Remdesivir	-7.2
3	6Y84	Lopinavir	-9.9
4	6W4b	Eriodictyol and Pemirolast	-6.5
5	6VSBA	Eriodictyol	-7
6	6VSBB	Remdesivir	-6.8
7	6VSBC	Eriodictyol	-7.6
8	2GHV	Ritonavir	-7.6
9	6VXS	Lopinavir	-7.9
10	6W75A	Eriodictyol	-7.5
11	6W75C	Remdesivir	-7.6
12	6W75B	Remdesivir	-7
13	6W75D	Eriodictyol	-7.5
14	6M18B	Lopinavir	-8.6
15	6m18D	Lopinavir	-8.9

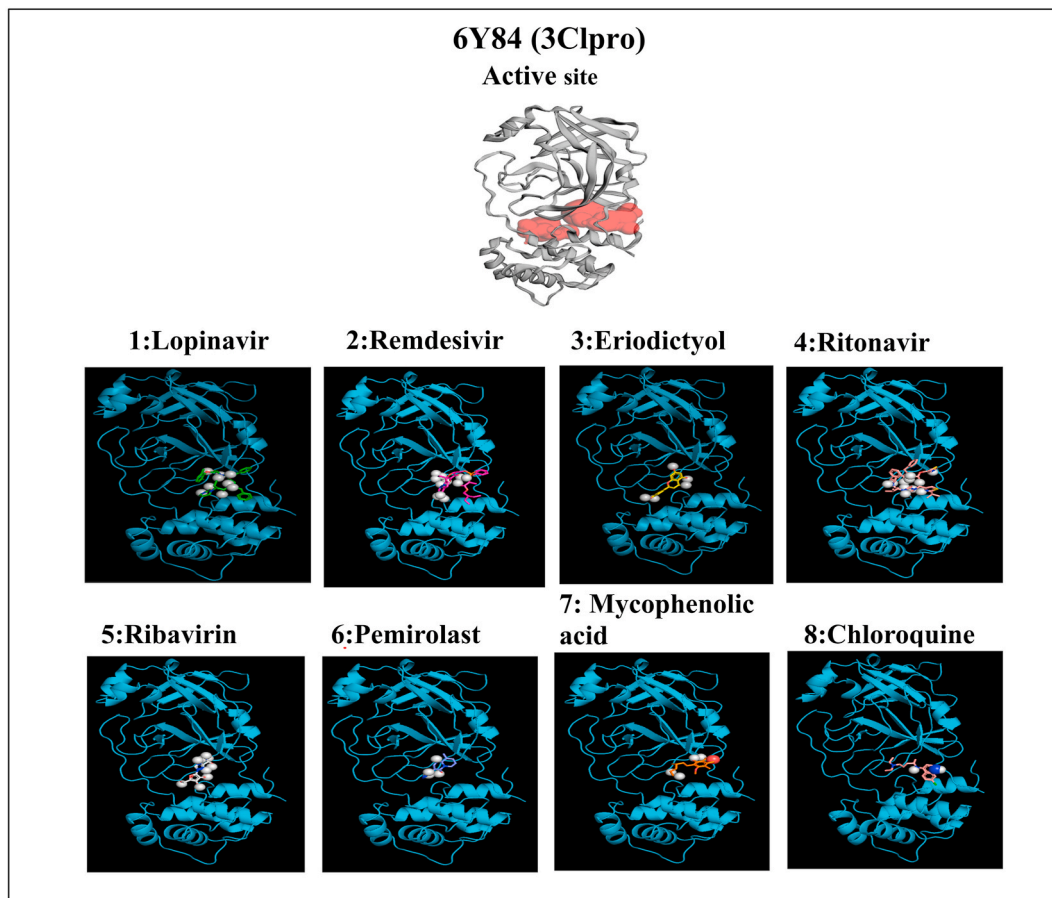
helicase is used as another target. This is responsible for unwinding RNA-DNA duplex during virus replication (Jiang et al., 2020). Nsp10/16 complex is a nonstructural protein that plays an important role in viral translation and could be of importance as a target for drug development (Wang et al., 2015; Decroly et al., 2011). A single strand or RNA binding protein was also selected as target. Virus enters the cell via angiotensin receptor converting enzyme 2 therefore blocking this protein could be of immense importance (Wan et al., 2020).

During docking it was observed that all drug ligands except Oseltamivir and Isoniazid are binding to 6Y84 with binding energy between binding energy between -7.5 kcal/mol and -9.9 kcal/mol but interaction includes only 3 amino acids. As expected, Lopinavir is showing minimum energy for binding the 6Y84 target followed by Remdesivir. This supports the idea of repurposing the two drugs for the treatment of COVID-19. It was reported that Remdesivir is more effective as

**Fig. 1.** Represents the binding energy in - Kcal/mole of all ligand molecules against 6Y84, the main protease of SARS-CoV-2.

compared to the combination of Lopinavir, Ritonavir and interferon beta in improvement of pulmonary function in MERS-CoV in mouse model (Sheahan et al., 2020). Lopinavir and Ritonavir combination treatment trials were reported by Cao et al., (2020) in total 99 patients with no benefit (Cao et al., 2020). In our study we observed that Ritonavir, Lopinavir as well as Remdesivir are binding with main protease of SARS-CoV-2 virus. High quality randomized clinical trials are needed to find the efficacy of these drugs in COVID-19. Ritonavir, Lopinavir and Remdesivir are also binding with 6M18 i.e. ACE-2 receptor of human cell but this binding is not at active site. As all three drugs are binding to viral main protease and ACE 2, these drugs might be the important candidates for repurposing if mechanism of action is known. Wan et al. recently reported that Remdesivir and Chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro (Wang et al., 2020). Ritonavir, apart from having the individual protease inhibitor activity, is also a protease inhibitor booster which increases the pharmacokinetics of another protease inhibitor if used in combination (Hull and Montaner, 2011). Pulmonary discomfort is one of the important symptoms in COVID-19. Pemirolast, is a mast cell stabilizer used in anti-allergy medication for treating chronic asthma (Kemp et al., 1992). Eriodictyol, is a flavanone found in Yerba Santa a plant native to North America and is a traditional herbal remedy used for asthma and treating common colds (Bown and America, 1995). Asthma drugs may act locally to get control over the respiratory system. This will reduce the hospitalization time and improve the general health of the patient. Therefore, these drugs were tested to check their potential role in suppressing the viral replication via interacting with viral proteins. One interesting

A:



B:

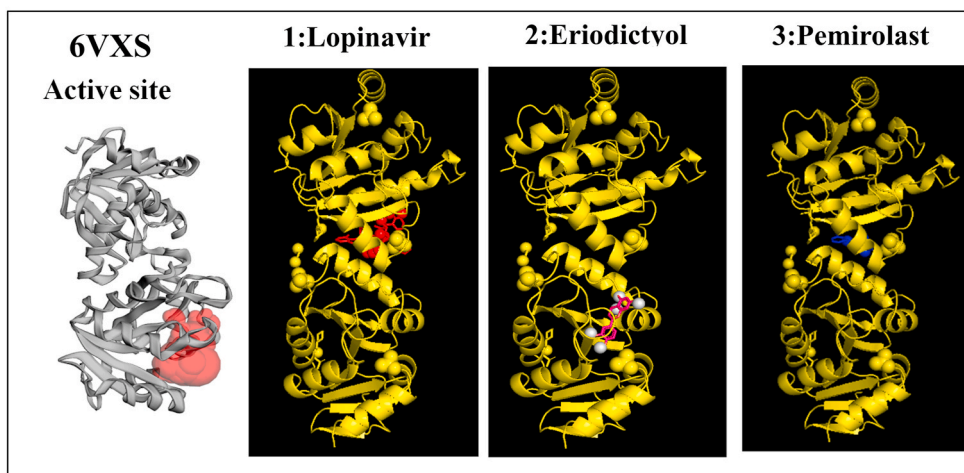
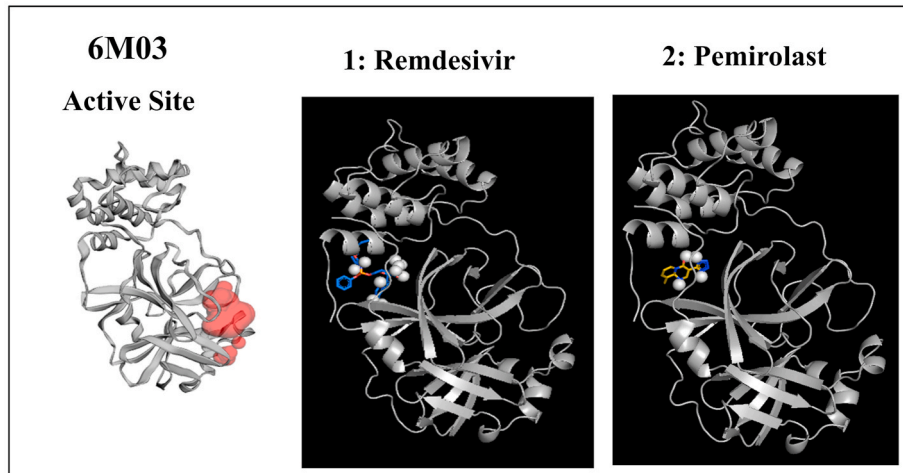
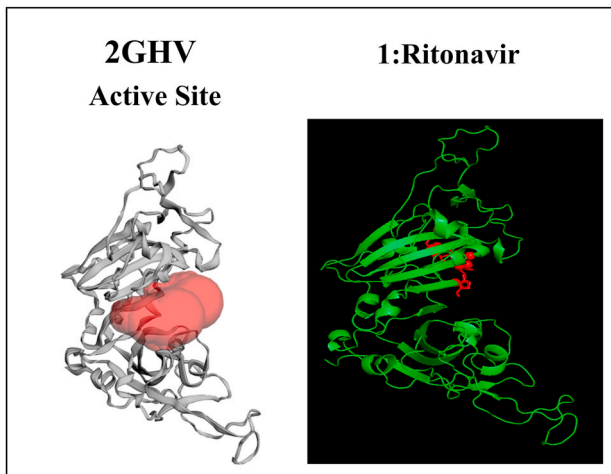


Fig. 2. A to J: Represents the active site of a particular protein and binding poses of drug ligands showing binding energy less than -7.5 Kcal/mol. A: 3Clpro (6Y84) with 1: Lopinavir, 2: Remdesivir, 3: Eriodictyol, 4: Ritonavir, 5: Ribavirin, 6: Pemirolast, 7: Mycophenolic acid (MPA), 8: Chloroquine, B: Helicase (6VXS) with 1: Lopinavir, 2: Eriodictyol 3: Pemirolast, C: 3Clpro (6M03) with 1: Remdesivir, 2: Pemirolast, D: Receptro binding domain of S protein (2GHV) with 1: Ritonavir, E : S protein (VSB C chain) with 1: Eriodictyol, F: NsP10/16 complex (6W75A) with 1: Eriodictyol, G: NsP10/16 complex (6W75D) with 1: Eriodictyol, H: NsP10/16 complex (6W75C) with 1: Remdesivir, 2: Eriodictyol, I: ACE 2 receptor (6M18B) with 1: Lopinavir, 2: Ritonavir, 3: Remdesivir, 4: Eriodictyol, J: ACE 2 receptor (6M18D) with 1: Lopinavir, 2: Ritonavir, 3: Remdesivir.

C:



D:



E:

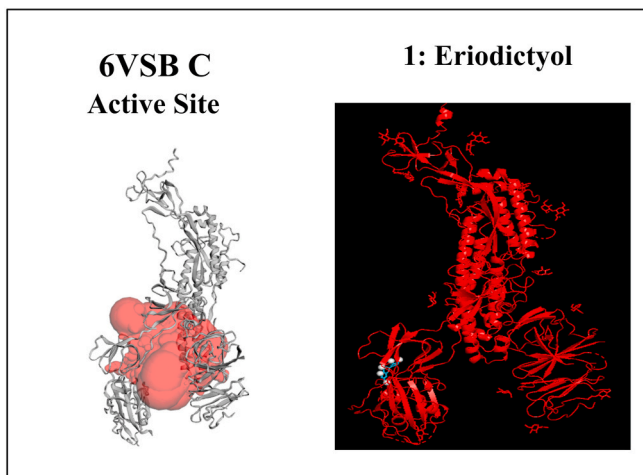
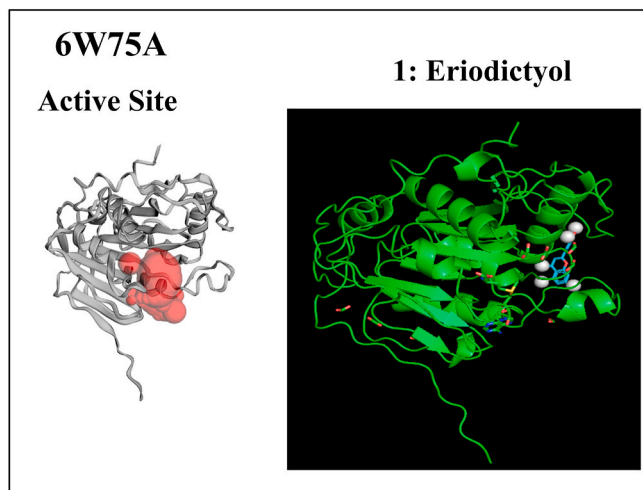


Fig. 2. (continued).

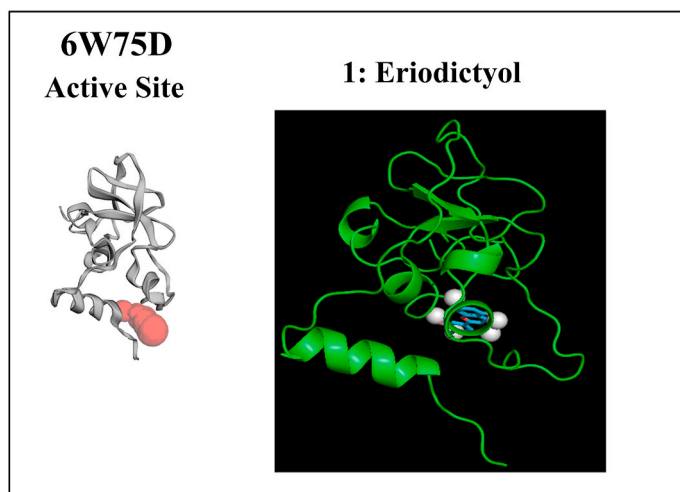
observation here is that the drug Eriodictyol is binding with all selected proteins with the binding energy between -6.7 kcal/mol and 8.8 kcal/mol. In case of 6VXS, the viral helicase, the Eriodictyol is binding

with amino acids ALA38, ASN40, GLY46, GLY47, GLY48, VAL49, ALA50, PRO125, LEU126, LEU127, SER128, ALA129, ILE131, PHE132. All these amino acids are present in the active site of helicase. This

F:



G:



H:

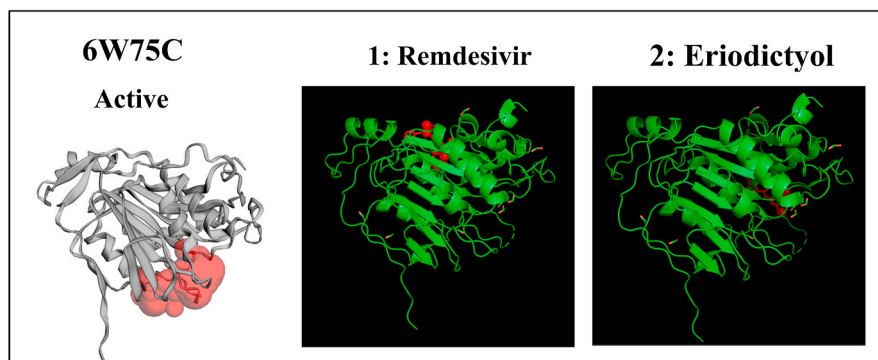
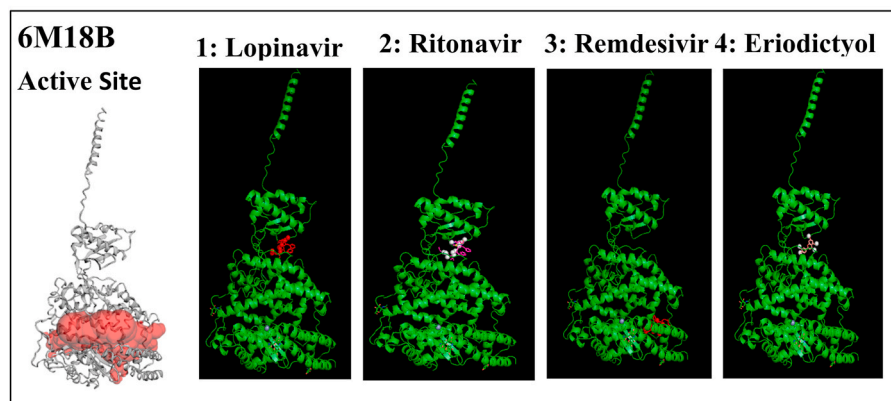


Fig. 2. (continued).

binding has 2 van der Waals interactions and 6 hydrogen bonds. There is locking at left terminal oxygen with amino acids 126, 127, 128 and 129 making it a strong interaction (Table 5). This strong interaction may affect the activity of enzyme. Eriodictyol is binding to 6VSB C viral spike protein, 6W75D Nsp10/16 complex and 6Y84 main protease along with 6VXS viral helicase with efficient binding energy and within active site.

The prediction of protein functioning based on mere molecular docking in case of small molecules is difficult. Eriodictyol, bitter taste masker and is known to have anti-inflammatory, antioxidant, cytotoxic, antidiabetic properties (Shukla et al., 2019; Rossato et al., 2011; Habtemariam and Dagne, 2009; Zhang et al., 2012) It is reported to suppress the lipopolysaccharide (LPS)-induced inflammatory responses in macrophages

I:



J:

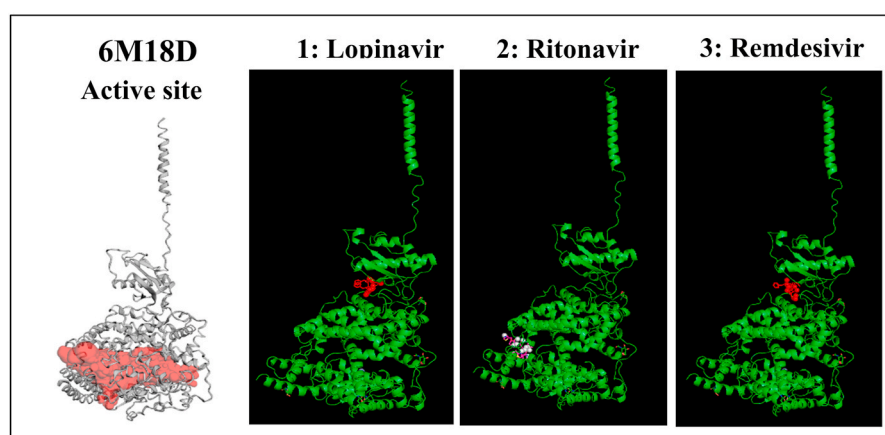


Fig. 2. (continued).

by reducing nitric oxygen, pro-inflammatory cytokines in Raw 264.7 cells (Lee, 2011). Zhu et al. had reported anti-inflammatory action of it against LPS induced acute lung injury (Zhu et al., 2015). This data definitely suggests that Eriodictyol might affect the virus lifecycle by interacting with multiple proteins. With its anti-inflammatory, antioxidant activity and positive drug score Eriodictyol could be a strong candidate for repurposing in case of SARS-CoV-2. Antimalarial drugs Hydroxychloroquine and Chloroquine are discussed for the treatment against this virus (Al-bari, 2017; Lai et al., 2020; Kumar et al., 2020). A recent preprint in BioRxiv indicates that Chloroquine, and azithromycin, another drug of interest in COVID-19 context, work by altering pH of intracellular compartments in respiratory epithelial cells with potential effects on viral life cycle and additional anti-inflammatory effect. Chloroquine also seems to act as a zinc ionophore, that allows extracellular zinc to enter the cell and inhibit viral RNA-dependent RNA polymerase (Xue et al., 2014; Velthuis et al., 2010). Hydroxychloroquine is also suggested to work in the same manner as that of Chloroquine. In this study Chloroquine and Hydroxychloroquine drugs are interacting with main protease 6Y84 in active site but are not showing efficient binding energy with any selected proteins. This suggests that their role is not to kill the virus directly but to change the cells environment which is consistent with previous reports (Vincent et al., 2005; Salata et al., 2017).

RNA viruses are subject to genetic mutations and recombination which leads to cross contamination and emergence of novel infectious diseases. The world is still not prepared for effective management of such diseases. This increases the need of research and development of new drugs for coronaviruses. This work is a small attempt in the process

of repurposing the existing drugs for treatment of SARS-CoV-2. The data shows efficient binding of Ritonavir, Lopinavir and Remdesivir with 3CLpro, the main protease of the virus and ACE 2 receptor of human cell. This supports the need of more randomized trials of these drugs against COVID-19 in spite of discouraging results in the preliminary clinical trial. We also impart the need of clinical trials of one more flavonoid drug - Eriodictyol which is showing very good binding energies with all viral proteins as well as ACE 2. In case of SARS-CoV-2 helicase Eriodictyol binding is stronger as compared to other interactions. SARS-CoV-2 helicase is a potential drug target as it recognizes the RNA: DNA duplex which is unique feature of virus (Jang et al., 2020). It also binds within the active site of viral spike glycoprotein C chain with 10 amino acids. It is binding with ACE 2 receptor on human cells. Since all these proteins are important in viral replication, Eriodictyol can become a multi-target molecule which can be a strong candidate for repurposing against SARS- CoV- 2.

5. Conclusion

Drug repurposing is the best approach for finding out solution for treatment of novel coronavirus infection. If the targets and mechanism of action of these drugs are known then formulating treatment would be easier. Therefore, the extensive work carried out in this study to understand the interaction of multiple viral proteins and different drug ligands which are discussed for treatment in COVID-19. Proteins important in viral replication were selected in the study because inhibiting these proteins might be useful to block the initiation of infection and chain of replication. *In silico* molecular docking study

Table 5

Specific binding site for a particular drug ligand for a specific protein with binding energy less than -7.5 kcal/mol. Binding site was compared with active site and common amino acids are listed.

Sr. No.	Active site	Name of the drug with binding energy in $-Kcal/mol$	Binding with drug with binding energy
1.	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)) MET6, ALA7, PHE8, PRO9, VAL104, ILE106, GLN107, PRO108, GLY109, GLN110, THR111, GLN 127, PRO132, ASN151, ILE152, ASP153, TYR154, CYS156, SER158, ILE200, THR201, VAL202, ASN203, GLU240, PRO241, ASP245, HIS246, ILE 249, GLU290, PHE291, THR292, PRO293, PHE294, ASP295, ARG298, GLN299, GLY302, VAL303, THR304	Lopinavir (-9.9) GLN 127, GLU290, PHE291	
		Remdesivir (-9.4) GLN 127, GLU290, PHE291	
		GLN 127, GLU290	
		Eriodictyol (-8.8)	
		Ritonavir (-8.7) GLN 127, GLU290, PHE291	
		Ribavirin (-8.2) GLN127, GLU290	
		Pemirolast (-8.2) GLN127, GLU290	
		Mycophenolic acid (-8) GLN127, GLU290	
		Hydroxychloroquine (-7.9) GLN 127, GLU290, PHE291	

(continued on next page)

Table 5 (continued)

Sr. No.	Active site	Name of the drug with binding energy in -Kcal/mol	Binding with drug with binding energy
6	<p>6W75A (NSP10 – NSP16 Complex from SARS-CoV-2) ASN6841, LYS6844, TYR6845, HIS6867, PHE6868, GLY6869, ALA6870, GLY6871, SER6872, ASP6873, PRO6878, GLY6879, SER6896, ASP6897, LEU6898, ASN6899, ASP6900, PHE6901, GLY6911, ASP6912, CYS6913, ASP6928, MET6929, TYR6930, ASP6931, PRO6932, LYS6933, GLY6946, PHE6947, LYS6968</p>	Eriodictyol (-7.8)	
7	<p>6W75C (NSP10 – NSP16 Complex from SARS-CoV-2) ASN6841, LYS6844, TYR6845, HIS6867, PHE6868, GLY6869, ALA6870, GLY6871, SER6872, ASP6873, PRO6878, GLY6879, SER6896, ASP6897, LEU6898, ASN6899, ASP6900, PHE6901, GLY6911, ASP6912, CYS6913, ASP6928, MET6929, TYR6930, ASP6931, PRO6932, LYS6933, GLY6946, PHE6947, LYS6968</p>	Remdesivir (-7.6)	
8	<p>6W75D (NSP10 – NSP16 Complex from SARS-CoV-2) ALA4273, VAL4274, ASP4275, ALA4276, ALA4277, TYR4329, ILE4334, ASP4335, HIS 4336, PRO4337</p>	Eriodictyol (-7.5)	
9	<p>6M18B (Angiotensin-converting enzyme 2 (ACE2) receptor) SER623, LYS625, SER626, ALA627, LEU628, GLY629, ASP630, LYS631, ARG678, ARG705, ARG708, SER709, ASN712, ASP713, ARG716, LEU717, ASN718, ASP719, ASN720, SER721, GLU723, ILE727, GLN728, PRO729, THR730, LEU731, GLY732, PRO733, PRO734, ASN735, GLN736, PRO737, PRO738, VAL739, ILE741, ILE744, VAL745, VAL748, VAL749, VAL752, ILE753, VAL755, GLY756, VAL758, ILE759, LEU760, PHE762, THR763, ARG766, ASP767, ARG768, SER623</p>	Lopinavir (-8.6)	
		Ritonavir(-8.2)	
		Remdesivir (-8.2)	

(continued on next page)

Table 5 (continued)

Sr. No.	Active site	Name of the drug with binding energy in -Kcal/mol	Binding with drug with binding energy
10	<p>6M18D (Angiotensin-converting enzyme 2 (ACE2) receptor) SER623, LYS625, SER626, ALA627, LEU628, GLY629, ASP630, LYS631, ARG678, ARG705, ARG708, SER709, ASN712, ASP713, ARG716, LEU717, ASN718, ASP719, ASN720, SER721, GLU723, ILE727, GLN728, PRO729, THR730, LEU731, GLY732, PRO733, PRO734, ASN735, GLN736, PRO737, PRO738, VAL739, ILE741, ILE744, VAL745, VAL748, VAL749, VAL752, ILE753, VAL755, GLY756, VAL758, ILE759, LEU760, PHE762, THR763, ARG766, ASP767, ARG768</p>	Eriodictyol (-7.5)	
		Lopinavir (-8.9)	
		Ritonavir (-8.1)	
		Remdesivir (-7.7)	

Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Unfavorable Positive-Positive
- Unfavorable Donor-Donor
- Pi-Sigma
- Alkyl
- Pi-Alkyl
- Pi-Cation
- Pi-Anion
- Pi-Sulfur

Table 6
Summary of anti-SARS-CoV-2 potential of drug ligands.

Sr. No	Name	Name of Protein to which binding is in active site	anti-SARC-CoV-2 potential
1	Ritonavir	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2) 2GHV (SARS spike protein receptor binding domain)	Yes
2	Lopinavir	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2) 6VXS (ADP ribose phosphatase of NSP3 from SARS CoV-2)	Yes
3	Remdesivir	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)	Yes
4	Oseltamivir	–	No
5	Ribavirin	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)	Yes
6	Mycophenolic acid (MPA)	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)	Yes
7	Chloroquine	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)	Yes
8	Hydroxychloroquine (HCQ)	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2)	Yes
9	Pemivrolast	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2) 6VXS (ADP ribose phosphatase of NSP3 from SARS CoV-2)	Yes
10	Eriodictyol	6Y84 (Mpro/3CLpro (Main protease of SARS-CoV-2) 6VXS (ADP ribose phosphatase of NSP3 from SARS CoV-2) 6VSB C (Spike glycoprotein) 6W75D (NSP10 – NSP16 Complex from SARS-CoV-2)	Yes
11	Isoniazid	–	No

enhanced the potential of Lopinavir, Ritonavir, Remdesivir as a candidate drugs for treatment of COVID-19. Eriodictyol is binding to multiple targets like 6Y84, 6VXS, 6VSB C, 6W75D with efficient binding energy and within the active site. Its strong interaction in active site of SARS-CoV-2 helicase (6VXS) reinforces its application. This small molecule with its anti-inflammatory activity has emerged as a promising candidate for treatment of corona infection.

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CRedit authorship contribution statement

Rujuta R. Deshpande: Methodology, Software, Validation, Data curation, Writing - original draft, Visualization. **Arpita Pandey Tiwari:** Conceptualization, Investigation, Resources, Writing - original draft. **Narendra Nyayanit:** Conceptualization, Methodology, Formal analysis, Data curation. **Manisha Modak:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Supervision.

Declaration of competing interest

The authors declare “No conflict of interest”.

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