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Molecular Docking Study to Identify the Best among the Approved Anti-Viral Drugs

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Abstract: ***Background: The mortality rate was increasing day by day and as of march 2020 the reported deaths are 21,031. In a novel and life threatening condition when there is no medicine or vaccine available a drug repurposing technique can be used. Currently, there are few antivirals available for COVID-19 and many of the potent drugs of antivirals, repurposed drugs are under urgent investigation. Aims: To identify the potential of some approved antiviral drugs for COVID-19 using molecular docking based virtual screening. Methods: The binding energy of various anti viral drugs are determined from xray crystallaographic data using autodock vina, binding energy for the anti viral drugs that have potential against COVID 19. Results: Hydroxychloroquine, the reference drug was predicted to have a binding energy of (-5.7 Kcal/mol). In contrast 10 Anti viral drugs exhibited dock score greater than (-5.7 kcal/mol). Famiciclovir exhibited high binding energy of (-8.5kcal/mol) followed by ritonavir with the binding energy of (8.4 kcal/mol). Conclusion: This confirms the reports that some of approved antiviral drugs have potential for treatment of COVID-19. As per the study Famiciclovir and Ritonavir were identified as the effective drugs for COVID-19 therapy based on molecular docking of clinically approved anti-viral drugs in comparison with Hydroxychloroquine which can be useful to interpret the results and for selection of candidate drugs in ongoing clinical trials against COVID-19.***

Keywords: COVID-19, Hydroxycholoroquine, anti virals, binding energy, molecular docking

1. Introduction

The novel coronavirus disease 2019 (COVID-19) is highly pathogenic and large-scale epidemic during the 21st century. According to WHO as of 26th march 2020 they are about 465,915 cases globally and 21,031 reported deaths. Corona viruses (CoVs), belonging to the family Coronaviridae, are positive-sense enveloped RNA viruses and can cause infections in humans. Two infamous infectious coronaviruses in the genus Betacoronavirus are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[1] associated with fever, cough, and respiratory complications, the illness usually accompanied by high mortality rates (9.6% for SARS-CoV and 34.4% for MERSCoV).[2] Scientists are endeavouring to discover drugs for it however; this cannot be achieved with our present drug development process, that may take several years for a new drugs moiety to come into the market.

In a new and life threatening condition where there is no approved medicine or vaccine a drug repurposing technique can be used. Drug repositioning/repurposing, is an effective process to combat novel diseases caused by rapidly spreading infectious agents where the effectiveness of drugs against the required disease can be established from the drugs that have been approved and are safe for other indication in humans.[3]

Chloroquine (hydroxychloroquine), an anti malarial drug was approved by the US Food and Drug Administration (FDA) as a treatment for COVID-19 on 19th March 2020.[4] In general, Chloroquine possesses the antiviral effects against HIV type 1, hepatitis B virus, and herpes simplex virus type. Moreover, chloroquine was reported to inhibit the replication of HCoV-229E and SARS-CoV in vitro.[5] Several clinical trials are assessing the potential of protease inhibitors such as Lopinavir and Ritonavir that have been approved for treatment of other viral infections.[6,7] According to the latest edition (the 6th edition) of National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19 that was issued on February 18, 2020 the recommended antivirals are IFN-α, lopinavir/ritonavir, and ribavirin for treatment of COVID-19.[8]

Currently, there are also few other antivirals available for COVID-19 and many of the potent drugs of antivirals, repurposed drugs are under urgent investigation.[9] Hence the study was aimed to identify the potential of some approved antiviral drugs for COVID-19 using molecular docking based virtual screening so as to provide the information that can be used for choosing the drugs for in vivo, in vitro studies and clinical trials. The recent availability of the high resolution experimental structure, the main protease of SARS-CoV-2, was utilized as the target.[10]

2. Method and Methodology

2.1 Protein preparation

The X-Ray Diffraction crystal structureof SARS-CoV-2 main protease in complex with PCM-0102389 (PDB ID - 5RFL)with resolution 1.64 Å was obtained from RSCB Protein Data Bank (PDB). The hetero atoms present in the crude PDB file were removed. Kollman charges and polar hydrogen atoms are added to satisfy their appropriate charges in AutodockVina and the file is converted to Protein Data Bank, Partial Charge (Q), & Atom Type (T) (PDBQT) format .pymol is used for visualization

2.2 Identification of Binding Pockets

Active pockets in 5RFL receptor molecule were predicted using Computed Atlas of Surface Topography of Proteins (CASTp) program[9] (http://sts.bioe.uic.edu/castp/).One binding pocket was predicted with solvent accessible surface area and volume of 248.401 and 237.159respectively. These

catalytic sites are further used for recognising ligands with best affinity to the receptor

2.3 Preparation of Ligands

The list of approved antiviral drugs was considered for molecular docking analysis. these drugs were approved for other indications3D and 2Dstructures of ligands were retrieved from PubChem compound database at NCBI (National Centre for Biotechnology Information) (https://pubchem.ncbi.nlm.nih.gov/). Ligands were downloaded in SDF (structure data file) format subsequently the structures were converted PDB format using pymol(https://pymol.org/2/) gastgeir charges and hydrogens were added using Auto Dock Vina. structures were converted to pdbqt format for use in docking calculations with vina.

2.4 Molecular Docking

Following protein and ligand preparation, molecular docking analysis was Carried using AutodockVina.a grid box wasset at 11×-2.1×20A^0A^0 along the X, Y and Z axes respectively at grid resolution of 0.4 A^0which predicts the best binding site on the protein surface.initially docking was carried out using hydroxycholoroquine ,which have been found to be efficient on SARS-CoV-2 And Reported to be efficient on Chinese COV-19 which is taken as reference drug. The binding affinity of ligands were compared with reference drug. The compound that has equal or higher binding affinity than the reference drug is considered.

3. Results and Discussion

The binding energy of various anti viral drugs are determined from X-ray crystallaographic data using autodock vina, binding energy for the anti viral drugs that have potential against COVID 19 are depicted in the (table: 1) Hydroxychloroquine, the reference drug was predicted to have a binding energy of (-5.7 Kcal/mol) . In contrast to Anti viral drugs exhibited dock score greater than (-5.7 kcal/mol). Ritonavir with the binding energy of (8.4 kcal/mol) and Entecavir with (7.0Kcal/mol), which was almost similar to the study conducted by Wang et al., 2020 where the binding energies of Lopinavir and Ritonavir are (-7.4 to -7.7 kcal/mol). This confirms initial reports that drugs approved for treatment of other viral infections also have the potential for treating the COVID-19 similar to Chloroquine (hydroxychloroquine),

Despite the results of previous studies, Famiciclovir exhibited high binding energy of(-8.5kcal/mol, was identified as the drug with the best binding energy (Table 1) and the binding energies of other drugs are Zanamavir (-6.8 Kcal/mol), Trifluridine (-6.8Kcal/mol), acyclovir (-6.4 Kcal/mol), Idoxuridene (-6.4Kcal/mol), Ribavarin(-6.1 kcal/mol) cidofovir(-5.8 Kcal.mol) and Vidarabine (-5.8 Kcal/mol).

Even though the same scoring function and target receptor structure are used, the differences in predicted binding constants can arise the results may vary due to the variation in charges assigned, the method used for relaxation, flexibility of the receptor, charge type added to the ligand, differences in use of united atoms, calculation the molecular potential, as well as due to the randomness of the search procedure. Despite these limitations, the estimates of binding energy provide valuable information that can inform and guide further studies (Kontoyianni, 2017; Li et al., 2019).

4. Conclusion

Famiciclovir and Ritonavir were identified as the drugs with more affinity for COVID-19 therapy using virtual screening based molecular docking of clinically approved anti-viral drugs in comparison with Hydroxychloroquine. The results of this study can be useful to interpret the results and also can provide information for selection of candidate drugs in ongoing clinical trials against COVID-19.

5. Acknowledgements

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6. Conflicts of Interest

We hereby declare that the authors have no conflicts of interest

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Drugs	Binding affinity
Zanamavir	-6.8 Kcal/mol
Vidarabine	-5.8 Kcal/mol
Trifluridine	-6.8 Kcal/mol
Ritonavir	-8.4 Kcal/mol
Ribavarin	-6.1 Kcal/mol
Remantadine	-5.1 Kcal/mol
Oseltamavir	-5.6 Kcal/mol
Lamavudine	-5.6 Kcal/mol
Idoxurudiene	-6.4 Kcal/mol
Hydroxychloroquine	-5.7 Kcal/mol
Ganciclovir	-5.4 Kcal/mol
Foscarnet	-4.3 Kcal/mol
Famiciclovir	-8.5 Kcal/mol
Entecavir	-7.0 Kcal/mol
Cidofovir	-5.8 Kcal/mol
Amantadine	-4.4 Kcal/mol
Acyclovir	-6.4 Kcal/mol

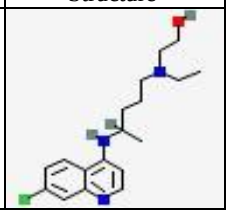
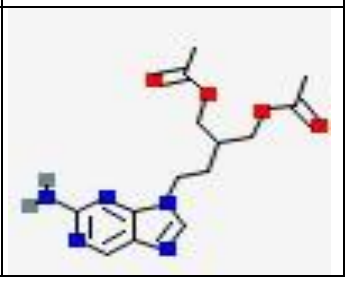
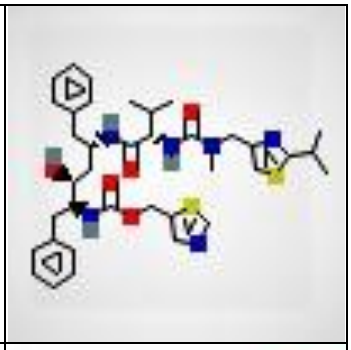
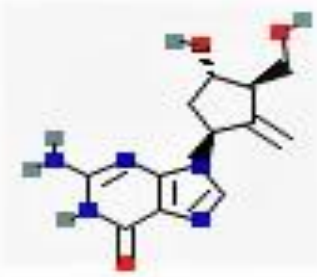
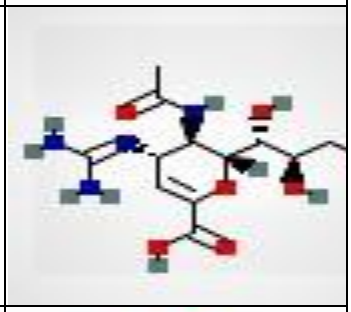
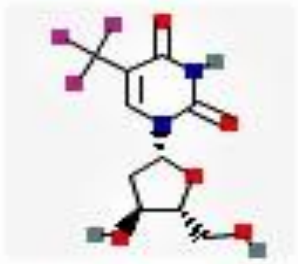
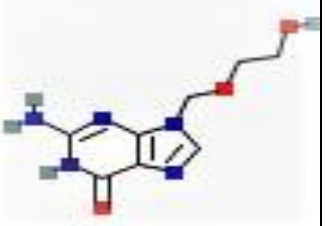
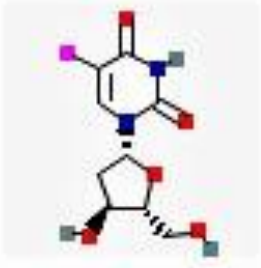
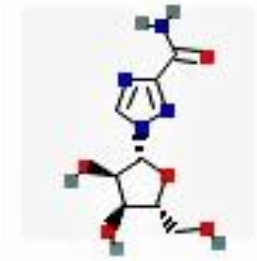
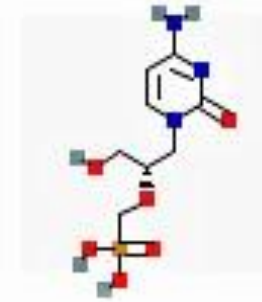
Reference Drug	Binding affinity	Structure
hydroxychloroquine	-5.7 Kcal/mol	

Table 2:

Anti viral drugs	Binding affinity	structure
Famciclovir	-8.5 Kcal/mol	

Ritonavir	-8.4 Kcal/mol	
Entecavir	-7.0 Kcal/mol	
zanamavir	-6.8 Kcal/mol	
Trifluridine	-6.8 Kcal/mol	
acyclovir	-6.4 Kcal/mol	
idoxuridene	-6.4 Kcal/mol	

Ribavarin	-6.1 Kcal/mol	
cidofovir	-5.8 Kcal/mol	

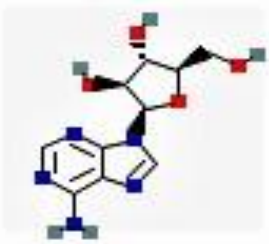
vidarabine	-5.8 Kcal/mol	

Table 3:

Potential drugs	Vina score	category	Approved for
Conformer3D_CID_3324 Famciclovir	-8.5 Kcal/mol	Guanosine analouge	Varicella zoster, Mucocutaneous or genital herpes simplex infections
Structure2D_CID_392622 Ritonavir	-8.4 Kcal/mol	Protease inhibitor	HIV
Structure2D_CID_135398508 Entecavir	-7.0 Kcal/mol	Nucleoside reverse transcriptase inhibitors	Chronic hepatitis B virus
Conformer3D_CID_60855 zanamavir	-6.8 Kcal/mol	Neuraminidase inhibitor	Influenza A &B
Conformer3D_CID_6256 Trifluridine	-6.8 Kcal/mol	Pyramidine nucleoside	Herpes simplex virus type 1 &2
Structure2D_CID_135398513 acyclovir	-6.4 Kcal/mol	Synthetic nucleoside anlogue	Herpes simplex virus,chicken pox&shingles
Conformer3D_CID_5905 idoxuridene	-6.4 Kcal/mol	nucleoside anlogue	Herpes simplex virus
Conformer3D_CID_37542 Ribavarin	-6.1 Kcal/mol	nucleoside anlogue	Hepatitis c virus
Conformer3D_CID_60613 cidofovir	-5.8 Kcal/mol	nucleoside anlogue	Herpes Cytomegalovirus in HIV patients
Conformer3D_CID_21704 vidarabine	-5.8 Kcal/mol	nucleoside anlogue	Herpes simplex virus
Conformer3D_CID_3652 hydroxychloroquine	-5.7 Kcal/mol	4-aminoquinoline	Malaria,lupus erythematous,rheumatoid arthritis

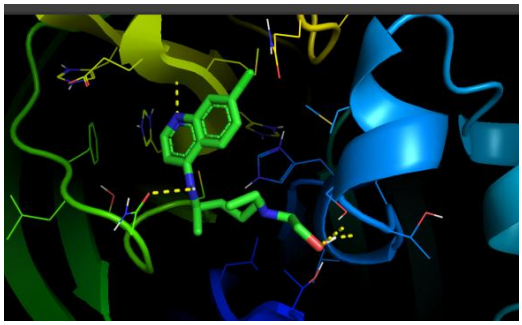


Figure 1: Interaction of 5RFL and Hydroxychloroquine

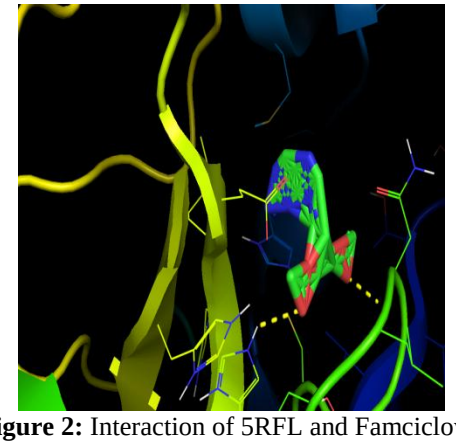


Figure 2: Interaction of 5RFL and Famciclovir

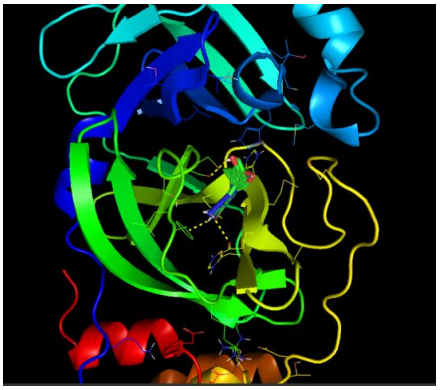


Figure 3: Interaction of 5RFL and Entecavir