Drug repurposing of approved drugs Elbasvir, Ledipasvir, Paritaprevir, Velpatasvir, Antrafenine and Ergotamine for combating COVID19

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Abstract

Pneumonia of unknown cause detected in Wuhan, China was first reported to the WHO Country Office in China on 31 December 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. Currently, there is no Vaccine against COVID-19 pandemic and infection is spreading worldwide vary rapidly there is an exigent requirement of practicable drug treatment. Drug repurposing is one of the most promising approaches for that. Many reports are available with *in silico* drug repurposing but the majority of them engrossed on a single target. The present study aimed at screening the approved against Covid19 protein and extract the combination of operational comprehensively. A total of 1735 drug molecules against all COVID19 protein structures and sequential screening recognize the better potential of anti-HCV drugs over anti-HIV drugs. The study designated Elbasvir, Ledipasvir, Paritaprevir, Velpatasvir, Antrafenine Ergotamin as promising drug candidates for covid19 treatment. The computational analysis also reveled the better potential of proposed drugs over the currently used drug combination for COVID19 drugs.

Keywords

Drug-repurposing, Molecular Docking, COVID 19, Elbasvir, Ledipasvir, Paritaprevir, Velpatasvir, Antrafenine, Ergotamine.

Introduction

The World Health Organization announced in February 2020 that COVID-19 is the official name of the disease. World Health Organization chief Tedros Adhanom Ghebreyesus explained that CO stands for corona, VI for virus and D for disease, while 19 is for the year that the outbreak was first identified; 31 December 2019 ("Updated rapid risk assessment from ECDC on the novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK," 2020). Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) previously referred to as the 2019 novel coronavirus (2019-nCoV) (Gorbalenya, 2020). In 2019 in Wuhan, the capital of Hubei, China, and disease was first reported and then it spread worldwide, resulting in the 2019-20 coronavirus pandemic. (Hui *et al.*, 2020; Organization, 2020).

At present, there is no clinically proven vaccines and medicine for COVID-19 prevention and treatment as per U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) (National Center for Immunization and Respiratory Diseases (NCIRD) & Prevention, 2020). On an interactive web-based dashboard to track COVID-19 in real-time as on April 03, 2020, in the entire world more than 200 countries/territories

are having 1 Million confirmed cases and 53,280 deaths worldwide and more than 50000 increase daily reported since March 26, 2020. (Dong, Du, & Gardner, 2020). There is an immediate need for exploring approved drugs for managing COVID-19. Due to a shortage of time drug repurposing with various computation approaches against the COVID-19 target is the best strategy.

Recovery observed in patients of Covid19 treated with the mixture of Anti-HIV drugs like Libonavir & Ritonavir, Anti-SARS drugs Oseltamivir and Anti-malarial drug Chloroquine in India (Wadhawan, 2020). In South Korea, human MERS-CoV successfully revokes the viral clearance using a combination of Lopinavir/Ritonavir (LPV/RTV) (Anti-HIV drugs) pegylated interferon and ribavirin (N. Chen *et al*., 2020). Still, the treatment of anti-HIV is a mystery for the Patients and Researchers as well (Lu, 2020).

Molecular docking of lopinavir darunavir and Ritonavir reported against homology model of Structure models of two severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteases, coronavirus endopeptidase C30 (CEP_C30) and papain-like viral protease (PLVP)(Lin, Shen, He, Li, & Guo, 2020). MM-PBSA-WSAS (Molecular dynamics simulations followed by binding free energy calculations using an endpoint method) employed for Fast Identification of Possible Drug against COVID-19 protease(Vinet & Zhedanov, 2010). Anti-HCV drugs inspected with docking approach against modelled COVID-19 RNA dependent RNA polymerase (RdRp) and Sofosbuvir, IDX-184, Ribavirin, and Remidisvir reported promising drug candidate (Elfiky, 2020). Hirokawa *et al.*, (2020) identified one hundred and several dozen potentially candidate drugs for 3CL protease inhibitors, which are already approved as antiviral, HIV protease inhibitors, antibacterial or antineoplastic agents with *in silico* docking-based screening approach, which combines molecular docking with a protein-ligand interaction fingerprint (PLIF) scoring method.

The present study designed for docking all Drugbank compounds with molecular weight less than 700 against all COVID-19 experimentally and computationally generated protein. The AnCOVID19 online database created to share the output with other researchers and doctors for immediate excess and exploration for research and possible clinical application.

Materials and Methods

Target preparation

Crystal structure of COVID-19 main protease in complex with an inhibitor N3 (PDB ID: 6LU7) (Jin *et al*., 2020), SARS-Coronavirus NSP12 bound to NSP7 and NSP8 co-factors(6NUR) (Kirchdoerfer & Ward, 2019) and Pre-fusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up (6VSB)(Wrapp *et al*., 2020) were retrieved from the Protein Data Bank available at https://www.rcsb.org/. I-TASSAR online server provided 24 modelled structures based on protein

sequences translated from the complete genome of Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu1 (GenBank Accession: MN908947.3)(Yang & Zhang, 2015). All resulted 27 receptors three-dimensional structures were subjected addition of hydrogens for pH 7.0 and gasteiger charges were using Open Babel (O'Boyle *et al*., 2011). The resulting structures were converted to PDBQT format using python script "prepare_receptor.py" from AutoDockTools 4.2(Morris *et al*., 2010). (Table: 2)

Ligand preparation

Total of 1735 approved drug molecules having a molecular weight of less than 700 MW downloaded from Drugbank (Wishart *et al*., 2018). The drug structures downloaded in 2D-SDF format. The Ligand molecules subjected to optimization of Gasteiger charges and MMFF94 force-field using steepest descents followed by conjugate gradient minimization at 400 modes using OpenBabel and customized python script "prepare_ligand.py" script provided by AutoDockTool 4.0 utilities. Subsequently, the structures were converted to 3D-PDBQT format using MGL Tools for Autodock provided by The Scripps Research Institute.

Virtual Screening

Molecular docking of all 27 protein receptors against the approved 1735 drug Library performed with Autodock Vina v4.2 software (Trott & Olson, 2010). Due to the lack of information regarding binding pocket, blind-docking was performed as suggested by Vaque *et al*., 2006 (Vaque, Arola, Aliagas, & Pujadas, 2006). The virtual screening performed on two separate servers, High-Performance Computing Server (HPC) and ParamShavak Server (PSS). The exhaustiveness was set to 48, CPU utilization set to 48 and separate grid size was set for each 27 receptor molecules in Autodock Vina config file.

Data Analysis

The Binding energy for each drug ligand exported for analysis from the Autodock Vina v4.2 software and need-based analysis performed manually using python script and excel software. Drug target interaction analysed with Ligplot^{+} (Laskowski & Swindells, 2011).

Results and Discussion

Drug repurposing study for FDA approves 1735 drug molecules with less than 700 MW included in the present study virtual screening performed against total 24 modelled proteins and 3 PDB structures in seven stage to predict the best combination for COVID19 treatment.

Library creation and Docking

In the first stage, a total of 4,68,650 docking solutions obtained from Molecular docking of approved 1735 drug molecules against 27 COVID19 proteins (Table 1).

Best pose selection

From Autodock Vina output, one best pose was extracted from out of 10 poses in the second stage and 46,865 pose data utilized for further analysis (Table 1).

Top 20 drug selection

In stage 3rd screening step, the top 20 drug molecules based on binding energy were separated for each COVID19 Protein. Which lead to 540 drugs with a potential range of docking scores (Table 1 & 2, Figure 1).

Removal of redundant drug

The merger of the top 20 dock score for all COVID19 protein together yields 133 unique drugs from the 540 drugs (Supplementary material).

Safe Drug selection

All the 133 drugs were manually inspected for pharmacological activity reported in Drugbank. Consequently, 18 anticancer drugs, 6 anti-inflammatory, 7 anti-HIV, 8 anti-HCV, 6 drugs for lung disease, 3 drugs for anti-parasitic activity, 2 anti-migraine and few other activities reported.

Drugs with anti-cancer activity and clinically major side effects contained drugs were omitted. The remaining 35 drugs were selected for further comparative analysis. This included anti-HIV, anti-HCV, anti-Inflammatory, Lung disease, anti-migraine activity and anti-parasitic activity. Along with nine clinically reported promising anti-COVD19 drugs also merged for further analysis.

The binding energy of selected 35 compounds was graded in five grades displaying dark green, light green, yellow, orange and red for easy comparison. Concerning anti-COVID19 activity against single and multiple target analysis, the best results obtained for 8 drugs from anti-HCV followed by 7 anti-HIV and 3 currently clinically used drugs. In addition to that, 1 drug from an anti-inflammatory and anti-migraine group also had a good docking score. The overall analysis also showed the comparatively better scoring of the selected drug in this study over currently clinically applied drugs for COVID19 treatment. (Figure 1).

Dock score based Rank analysis

To narrow down the number of drug combinations and removing drug acting on the same target dock score were replaced with the top 20 docking rank. Based on dock rank 10 drug selected. (Figure 2)

Drug combination creation

To reduce the drug for treatment and avoid the duplication of a drug acting on the same target drug acting on similar target remove. Combination of Elbasvir, Ledipasvir, Paritaprevir, Velpatasvir, Antrafenine Ergotamin drug figured out as a potential cocktail for COVID19 treatment. (Figure: 3)

Comparative drug interaction of drugs against HCV and COVID19

To investigate the similarity with the HCV targets for anti-COVID19 receptors, three similar targets of HCV NS3 Helicase, NS5B RNA-dependent RNA polymerase and NS3/4A S168A protease docked against 26 potential drugs along with the already known inhibitors against all three receptors used as control molecules. The results indicate, Chloroquine anti-plasmodial drug computationally significant for three HCV receptors but the same is not much significant for COVID19. (Figure 4)

Similarly, anti-HIV drugs Dolutegravir and Maraviroc showed considerable binding against HCV targets but less potential with COVID19 receptors. However, some of the drugs used to treat Hepatitis C shown similar results in all 3 proteins of HCV and well as COVID19. Elbasvir, Ledipasvir reacted with similar potential against Helicase, RdRp and Protease from both virus HCV and COVID19. This clearly stated the importance of anti-HCV drugs might beneficial to treat the COVID19 infection. While ergotamine used in the present study proposes significant binding against all three COVID19 proteins but no promising binding evident with HCV. This suggests the presence of a specific binding site present in COVID19 which might be absent in HCV.

Discussion

The earlier report of drug repurposing mainly focused on a single target option we represented the holistic approach of targeting all the viral proteins for effective anti-COVID19 activity. The combination suggested will effective on the nonstructural protein, a structural protein of COVID19 and also including drug the anti-inflammatory and anti-COVID19 activity. As the comparative computational analysis of the proposed drug is better than currently clinically used drug combination results. Which, reflects the possibility of the most promising effect of proposed drug combination in clinical application.

Ledipasvir is an inhibitor of the Hepatitis C Virus (HCV) Non-Structural Protein 5A (NS5A)(Keating, 2015). This protein is crucial for viral RNA replication and assembly of HCV virions. Ledipasvir and

Vepatasvir were reported promising in one of the recent studies in virtual screening (Y. W. Chen, Yiu, & Wong, 2020). Clinical trials against anti-HCV suggest the Ledipasvir treatment significantly improves the patients within one to twelve weeks (Waheed, 2015; Younossi *et al*., 2015).

Similarly, Velpatasvir acts as a defective substrate for NS5A (Non-Structural Protein 5A) sharing a similar function as Ledipasvir (Mogalian *et al*., 2017). The preclinical study conducted by, shown the patient having an infection of HCV genotype 1 to 6 can be treated with Velpatasvir(Mogalian *et al*., 2017). Currently, very few reports were identified for the usage of these drugs against COVID19.

Elbasvir was primarily used for the treatment of HCV. However, some trials are also carried out for using Elbasivir in the treatment of covid19 (Asselah *et al*., 2018). Paritaprevir reported as inhibitor of COVID19 Protease. (Alamri, Tahir ul Qamar, & Alqahtani, 2020). No reports are available for anti-COVD19 effectively of Antrafenine and Ergotamine.

As COVID19 and HCV both are positive-strand RNA virus and possess a similar mechanism for the creation of viral protein in the host cells. The drugs effective against HCV can have a similar mode of inhibition for the viral protein synthesis mechanism. The lesser effectively of the anti-HIV drugs are due to differential mechanism for synthesis of viral protein. Recently, Chen *et al.,* (2020) reported the clinical study using HCV protease inhibitor Danoprevir to treat naive and experienced COVID-19 patients which are supportive of our hypothesis of using the anti-HCV drugs for anti-COID19 treatment.

Conclusion

There is an urgent need for anti-COVID-19 drugs to address the global medical emergency. Many drugs are currently tried with empirical clinical knowledge and few of them are in practice along with some contradictions. Many Drug repurposing reports are available but those are mainly focused on a single target. The study represented the holistic approach of targeting multiple targets with a combination of FDA approved drugs. The proposed blend drugs includes, Elbasvir, Ledipasvir, Paritaprevir and Velpatasvir which currently used for HCV treatment. Inclusion anti-inflammatory Antrafenine and anti-migraine Ergotamine drugs can be effective for dual action of inflammation reduction and COVID19 inhibition. The proposed combination of drugs targeted for both non-structural and structural proteins which will be able to reduce COVID19 infection process and also manage viral multiplication process. The present study can be immediacy explore further by medical, pharm and research experts effectively to find out the best strategy for anti-COVID19 treatment.

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Table 1: Process flow for screening

Stage	Process	Targets included	Drugs included	Remarks
1	Library creation and Docking	27	1735	Obtained total of 468650 docking solutions
2	Selection of best pose for each drug	27	1735	46865 docking solutions
3	Selection of top 20 drugs for each target	27	1735	540 drugs molecules screened
4	Removal of drug redundancy	27	540	Obtained 133 unique drugs
5	Safe Drug selection	27	133	Screening of 35 less toxic and anti–Covid19 drugs
6	Dock score based Rank analysis	27	35	8 drugs
7	Drug combination creation	27	8	6 drugs

Table 2: Receptor molecules and their binding energy

No.	Source	Code	Description	Binding Energy (kcal/mol)	
				Overall range	Range of top 20 molecules
1	Modeled	QHD43415_1	Host translation inhibitor (nsp1)	-9.3 to -0.5	-9.3 to -8
2	Modeled	QHD43415_2	Non-structural protein 2 (nsp2)	-11.6 to -0.3	-11.6 to -10.8
3	Modeled	QHD43415_3	Papain-like proteinase	-12.4 to 1	-12.4 to -11.1
4	Modeled	QHD43415_4	Non-structural protein 4 (nsp4)	-13.4 to -0.1	-13.4 to -10.9
5	Modeled	QHD43415_5	Proteinase 3CL-PRO	-10.2 to -1	-10.2 to -9
6	Modeled	QHD43415_6	Non-structural protein 6 (nsp6)	-10 to -1	-10 to -8.8
7	Modeled	QHD43415_7	Non-structural protein 7 (nsp7)	-7.1 to 5	-7.1 to -6.3
8	Modeled	QHD43415_8	Non-structural protein 8 (nsp8)	-8.3 to 5	-8.3 to -7
9	Modeled	QHD43415_9	Non-structural protein 9 (nsp9)	-9.1 to -1	-9.1 to -7.7
10	Modeled	QHD43415_10	Non-structural protein 10 (nsp10)	-9.8 to -1	-9.8 to -8.8
11	Modeled	QHD43415_11	RNA-directed RNA polymerase (RdRp)	-11.5 to -1	-11.5 to 9.8
12	Modeled	QHD43415_12	Helicase (Hel)	-12.4 to -1.2	-12.4 to -9.8
13	Modeled	QHD43415_13	Guanine-N7 methyltransferase (ExoN)	-12 to -1.1	-12 to -10.9
14	Modeled	QHD43415_14	Endoribonuclease (NendoU)	-10.9 to -0.8	-10.9 to -9.8
15	Modeled	QHD43415_15	2'-O-methyltransferase (2'-O-MT)	-10.9 to -1.2	-10.9 to -9.8
16	Modeled	QHD43416	Surface glycoprotein (S)	-10.8 to -0.6	-10.8 to -9.8
17	Modeled	QHD43417	Potassium sensitive ion channels	-9.8 to -1	-9.8 to -8.9
18	Modeled	QHD43418	E-Component (Self Assembly)	-8.2 to -0.8	-8.2 to -7.4
19	Modeled	QHD43419	M-Component (Morphogenesis)	-10 to -1.1	-10 to -8.9
20	Modeled	QHD43420	ORF6(Virulence)	-7.8 to -0.8	-7.8 to -7
21	Modeled	QHD43421	ORF7a (Tethering Suppression)	-8.5 to -1.1	-8.5 to -7.6
22	Modeled	QHD43422	ORF8 (Hypothetical)	-9.4 to -0.7	-9.4 to -7.9
23	Modeled	QHD43423	N-Component	-12.1 to -1.2	-12.1 to -10.6
24	Modeled	QHI42199	ORF10	-4.5 to 5	-4.5 to -3.8
25	PDB	6LU7	COVID-19 main protease	-9.7 to -0.9	-9.7 to -9.1
26	PDB	6NUR	SARS-Coronavirus NSP12	-10.8 to -0.7	-10.8 to -9.7
27	PDB	6VSB	2019-nCoV spike glycoprotein	-9.5 to -0.6	-9.5 to -8.3

			Binding Energy from AnCOVID-19 for Drugs used clinically workdwide									Hepatitis C								HIV							Anti-Inflametry						*
No	Protein Code	Name of Tagrget	Chloroquine	Oseltamivir	Lopinavir	Hydroxychloroquine	Remdesivir	Darunavir	Ribavarin	Danoprevir	Azithromycin	Elbasvir	Ledipasvir	Eltrombopag	Paritaprevir	Velpatasvir	Daclatasvir	Simeprevir	Ombitasvir	Saquinavir	Ritonavir	Dolutegravir	Maraviroc	Tipranavir	Etravirine	Rilpivirine	Antrafenine	Diflunisal	Flufenamic acid	Nabumetone	Rosiglitazone	Naproxen	Ergotamine
1	QHD43415_1	Host translation inhibitor (nsp1)	-5.5	-5	-6	-5.6	-6.7	-5.4	-5.8	-7.9	-5.9	-8.3	-8.2	-8	-7.4	-7.2	-7.7	-6.9	-7.3	-7.4	-6.8	-7.6	-6	-8.1	-7.2	-7.3	-8.7	-7.1	-6.9	-5.9	-7	-6.7	-9.3
2	QHD43415_2	Non-structural protein 2 (nsp2)	-6.2	-6.8	-9.2	-7.2	-9.9	-9.7	-7.4	-8.4	-8.5	-10.8	-10.7	-10.9	-10.9	-10.1	-9.9	-10.3	-9.8	-9.8	-9.7	-10.8	-11	-11	-9.4	-9.5	-10.5	-8.2	-8.7	-7.3	-8.1	-7.8	-11.2
3	QHD43415_3	Papain-like proteinase	-7.7	-7.3	-9	-7.7	-8.8	-9.1	-7.4	-9.9	-9.9	-11.9	-11.8	-12.2	-11.7	-11.8	-10.9	-9.7	-10.5	-10.7	-10.4	-10.6	-10.2	-10.2	-9.3	-10.1	-10.2	-8.8	-9.1	-7.9	-8.2	-9	-11.8
4	QHD43415_4	Non-structural protein 4 (nsp4)	-6.4	-7.1	-9.6	-6.9	-8.6	-8.8	-6.5	-10.3	-8.1	-11.9	-11.1	-10.3	-10.8	-10.7	-10.8	-9.2	-9.4	-11	-9.2	-10	-10.7	-9.6	-9.7	-9.8	-9.5	-8	-8.5	-7.4	-7.1	-7.3	-11.2
5	QHD43415_5	Proteinase 3CL-PRO	-5.6	-5.4	-8.7	-5.7	-7.5	-7.6	-5.8	-10.9	-6.8	-9.9	-9.4	-9.5	-8.5	-9.2	-8.9	-7.7	-8.9	-8.1	-8.6	-8.3	-8.4	-8.1	-7.9	-7.7	-7.8	-7.3	-7.1	-6.1	-5.9	-6.8	-10.2
6	QHD43415_6	Non-structural protein 6 (nsp6)	-6.1	-5.4	-7.7	-6.4	-6.1	-7.5	-5.7	-10.1	-5.9	-9.2	-9.6	-8.7	-9.1	-8.9	-8.6	-7.7	-8.3	-7.8	-6.6	-8	-7.5	-7.7	-8	-8.2	-9.5	-7	-6.9	-7.2	-5.9	-7.1	-9
7	QHD43415_7	Non-structural protein 7 (nsp7)	-4.2	-3.7	-4.5	-4.5	-5.2	-5.2	-4.6	-8.3	-4.1	-5.8	-4.5	-6.1	-6.5	-5.5	-5.2	-5.2	-4.2	-5.1	-4.9	-5.9	-4.7	-4.6	-5.8	-5.8	-4.8	-5.6	-5.3	-4.8	-5.4	-5	-6.2
8	QHD43415_8	Non-structural protein 8 (nsp8)	-3.7	-4	-5.5	-4.3	-5.7	-5.1	-4.9	-10.1	-5.7	-7.2	-8.2	-7.3	-8.3	-6.6	-7.1	-6.8	-6.3	-6.7	-5.8	-6.1	-5.7	-6.4	-6.1	-5.9	-5.5	-5.3	-5.5	-5.1	-5.4	-5.4	-8.1
9	QHD43415_9	Non-structural protein 9 (nsp9)	-5.2	-4.8	-6.5	-5	-5.6	-6.2	-5.4	-10.7	-5.7	-7.8	-7.8	-7.5	-7.7	-7.5	-7.6	-7.7	-7.4	-6.6	-6.2	-6.8	-7.4	-7.2	-7.9	-7.7	-7.3	-6.4	-7.9	-5.8	-6.5	-5.6	-7.3
10	QHD43415_10	Non-structural protein 10 (nsp10)	-5.6	-5.5	-7.6	-5.7	-6.9	-6.7	-6.1	-9.4	-7.8	-8.3	-7.9	-8.5	-8.5	-9.4	-8.4	-7.9	-7.5	-7.7	-7.5	-8.4	-7.8	-8.2	-7.6	-7.4	-8.3	-6.3	-7.1	-6.1	-6.6	-5.9	-9.5
11	QHD43415_11	RNA-directed RNA polymerase (RdRp)	-5.4	-6.1	-8.3	-6	-7.7	-7.2	-6.6	-8.8	-7.7	-9.8	-10.7	-10.8	-11.4	-9.3	-8.6	-9	-9.1	-9.2	-8.8	-9	-9.4	-9.2	-8.8	-8.5	-8.5	-7.5	-7.7	-6.8	-6.8	-7.4	-10.4
12	QHD43415_12	Helicase (Hel)	-6.4	-6.3	-8.1	-6	-7.8	-7.8	-7.2	-8.8	-8.1	-11.1	-11.2	-9.4	-11.5	-10.3	-10.4	-9.4	-9.3	-9.8	-8.6	-9.2	-8.2	-9	-8.6	-8.3	-8.1	-7.4	-8.3	-6.4	-7.4	-6.5	-10.5
13	QHD43415_13	Guanine-N7 methyltransferase (ExoN)	-6.4	-6.2	-9.3	-6.3	-9	-8.5	-6.3	-5.6	-8	-11.8	-11.8	-10.3	-10.4	-11.2	-10.9	-11.1	-10.3	-10.3	-9.7	-9.4	-9.8	-9.5	-9.2	-8.7	-9.1	-7.6	-7.7	-6.7	-7.8	-6.9	-12
14	QHD43415_14	Endoribonuclease (NendoU)	-6.9	-5.8	-9.3	-6.6	-7.9	-8.6	-7.3	-6.2	-6.9	-9.5	-9.7	-9.3	-10.3	-10	-8.8	-9.2	-8.7	-9.8	-10	-8.2	-9.7	-9.2	-8.3	-8.5	-9.3	-7.6	-7.7	-6.5	-7.8	-6.5	-9.2
15	QHD43415_15	2'-O-methyltransferase (2'-O-MT)	-6.5	-6	-8.8	-6.3	-8.4	-8.6	-6.3	-7.1	-7	-9.4	-9.2	-9	-10.1	-8.3	-8.7	-9.5	-8.9	-8.7	-8.2	-9.6	-8.7	-6.9	-8.1	-8	-8.2	-7.6	-7.6	-6.7	-7	-7.4	-9.9
16	QHD43416	Surface glycoprotein (S)	-5.5	-6.2	-8.4	-6.8	-7.3	-8.3	-6.7	-8.8	-7.2	-10.5	-10.2	-9.6	-9.8	-9.6	-9.4	-9.3	-8.7	-8.4	-7.8	-8.6	-8.7	-9.4	-9.1	-7.9	-7.9	-7.5	-7.9	-6.7	-7.3	-7	-9.8
17	QHD43417	Potassium sensitive ion channels	-5.5	-5.5	-7.5	-6.2	-7.3	-7	-6.6	-8.8	-6.6	-8.4	-9.4	-9.3	-8.8	-8.3	-8.1	-8.7	-7.9	-7.9	-7.4	-9.5	-7.8	-7.9	-8.3	-8.9	-8.3	-7.6	-7.3	-7	-8.2	-7.1	-9.5
18	QHD43418	E-Component (Self Assembly)	-4.5	-4.5	-5.2	-5.1	-5.2	-6.1	-4.8	-6.9	-5.2	-7.7	-7.4	-7.9	-6.7	-7.4	-7.4	-6.2	-6.9	-5.9	-6.2	-6.3	-6.9	-7.2	-6.2	-7.3	-8	-6.1	-6	-5.3	-5.2	-5.8	-7.9
19	QHD43419	M-Component (Morphogenesis)	-5.8	-5.8	-7.7	-5.7	-7.1	-7.4	-6.6	-7.9	-7.4	-9.1	-9.2	-9.1	-8.8	-8.9	-8.4	-8.9	-9	-8.4	-6.9	-8.3	-8.9	-7.3	-8.3	-7.6	-9.5	-7.1	-7.2	-6.8	-7	-6.2	-9.7
20	QHD43420	ORF6(Virulance)	-4.5	-4.4	-5.5	-4.7	-5.7	-5.7	-4.1	-7.2	-6	-7.3	-7.4	-7.1	-6.7	-6.9	-6.7	-6.6	-6.6	-6.7	-5.5	-6.5	-5.8	-6.1	-5.8	-6.7	-5.8	-5.3	-5.4	-4.9	-4.5	-4.9	-7.6
21	QHD43421	ORF7a (Tethering Supression)	-4.7	-5.1	-5.8	-5.6	-6.9	-5.8	-5.2	-6.5	-5.5	-7.2	-7	-8.5	-7.2	-7.3	-6.7	-6.2	-6.7	-6.4	-5.5	-7.9	-6.4	-5.5	-7	-7.3	-6.8	-6.2	-6.3	-6.1	-5.5	-6.1	-8.2
22	QHD43422	ORF8 (Hypothetical)	-5.2	-5.2	-6.6	-5.7	-6.4	-6.8	-5.4	-7.2	-5.2	-9.4	-8	-8.4	-8	-8.5	-7.7	-6.8	-6.4	-7.5	-6	-7.4	-6.5	-6.9	-7.3	-6.9	-6.3	-6.9	-7.1	-6.6	-6.2	-6.5	-8.5
23	QHD43423	N-Component	-6.8	-6	-9.6	-7.2	-9	-9	-7.2	-10.7	-8.5	-11.1	-10.2	-10.6	-12	-10.1	-9.4	-9.8	-9	-10.4	-9.1	-9.6	-10.9	-10.3	-9	-9.5	-10.2	-8.2	-8.3	-7.7	-8	-7.6	-10.8
24	QHI42199	ORF10	-2.3	-1.1	-1.9	-2.5	0.1	-2.3	-2.5	5	-0.8	1	1.3	-3.8	1	-1.1	-1	1	-0.6	-0.7	-1.8	-3	-1.8	-1.7	-3.2	-3.3	0	-3.9	-3.1	-3.8	-4	-3.9	0
25	6LU7	COVID-19 main protease	-5.5	-6.1	-8	-6.1	-7.5	-8.3	-6.3	-7.9	-7	-9.2	-9.5	-8.5	-8.5	-8.5	-8.7	-7.9	-8.1	-8.7	-7.6	-8	-8.7	-7.4	-7.7	-7.9	-7.2	-7	-6.9	-6.1	-6.8	-6.5	-8.7
26	6NUR	SARS-Coronavirus NSP12	-5.8	-6	-7.7	-6.4	-8.1	-7.8	-6.8	-9.2	-7.4	-10.2	-10.8	-10.3	-10.8	-9.9	-8.9	-9.7	-8.9	-9.2	-8	-8.9	-8.6	-8.2	-9.1	-8.4	-8.3	-7.6	-8.1	-7.4	-7	-7.6	-9.1
27	6VSB	2019-nCoV spike glycoprotein	-5.3	-5.3	-7	-5.2	-7.1	-7.8	-5.9	-8	-6.8	-8.8	-8.5	-8.6	-9.5	-8.7	-8.2	-8	-7.9	-7.9	-7.6	-7.6	-8	-7.7	-8	-6.8	-7.7	-6.5	-6.6	-6	-6.3	-5.8	-9

*- Anti-migraine

Figure 1: Comparative analysis of 35 drug molecules against 27 COVID19 proteins based on binding energy

The Green colored cell contains the lowest binding energy for each row followed by the greenish-yellow, yellow, orange and red color. The lowest binding energy represents the firm binding of ligand and protein molecules. The Comparative analysis establishes the drugs used for the treatment of Hepatitis C represented a more number of greenish cells. This indicates these drugs stay on top throughout the library used in the present study. The Elbasvir, Ledipasvir, Paritaprevir, Velpatasvir from Anti-HCV followed by Anti-HIV drugs Saquinavir, Ritonavir, Dolutegravir, Maraviroc, Tipranavir, Etravirine and Rilpivirine having good binding energy one or more targets. Only one drug, Antrafenine used for anti-inflammatory and Ergotamine used for anti-migraine activity shown significant activity against the different targets. However, the drugs used worldwide for clinical purposes except for Danoprevir and Lopinavir have shown poor binding with receptor molecules used in the study.

			Anti-HCV					Anti-HIV			**	*
No	Protein Code	Name of Tagrget	Elbasvir	Ledipasvir	Eltrombopag	Paritaprevir	Velpatasvir	Dolutegravir	Maraviroc	Tipranavir	Antrafenine	Ergotamin
1	QHD43415_1	Host translation inhibitor (nsp1)	11	13	22	97	157	62	884	16	4	1
2	QHD43415_2	Non-structural protein 2 (nsp2)	22	25	13	15	64	20	8	6	37	4
3	QHD43415_3	Papain-like proteinase	6	8	3	12	9	61	120	114	117	7
4	QHD43415_4	Non-structural protein 4 (nsp4)	4	17	55	31	34	86	33	139	164	14
5	QHD43415_5	Proteinase 3CL-PRO	2	7	5	55	15	81	64	114	193	1
6	QHD43415_6	Non-structural protein 6 (nsp6)	9	3	31	11	18	121	281	186	5	12
7	QHD43415_7	Non-structural protein 7 (nsp7)	103	1078	43	13	232	74	855	924	748	26
8	QHD43415_8	Non-structural protein 8 (nsp8)	14	2	7	1	59	147	319	78	462	3
9	QHD43415_9	Non-structural protein 9 (nsp9)	12	10	33	19	38	177	44	66	54	51
10	QHD43415_10	Non-structural protein 10 (nsp10)	62	128	35	37	5	48	148	68	58	3
11	QHD43415_11	RNA-directed RNA polymerase (RdRp)	22	4	3	2	56	97	46	61	198	7
12	QHD43415_12	Helicase (Hel)	4	3	37	2	12	63	270	78	312	8
13	QHD43415_13	Guanine-N7 methyltransferase (ExoN)	3	2	42	37	10	166	88	137	236	1
14	QHD43415_14	Endoribonuclease (NendoU)	34	26	47	6	12	267	25	57	44	56
15	QHD43415_15	2'-O-methyltransferase (2'-O-MT)	35	6	76	7	289	18	145	955	311	12
16	QHD43416	Surface glycoprotein (S)	2	4	28	20	30	182	150	37	449	16
17	QHD43417	Potassium sensitive ion channels	66	5	6	31	95	3	228	172	81	2
18	QHD43418	E-Component (Self Assembly)	11	17	7	88	21	207	55	29	3	6
19	QHD43419	M-Component (Morphogenesis)	13	5	11	33	23	81	19	369	3	2
20	QHD43420	ORF6(Virulance)	9	7	14	57	28	91	286	164	281	3
21	QHD43421	ORF7a (Tethering Supression)	65	98	1	62	48	10	321	1008	141	3
22	QHD43422	ORF8 (Hypothetical)	1	11	5	13	4	62	381	152	497	3
23	QHD43423	N-Component	10	45	20	2	54	139	15	36	44	17
24	QHI42199	ORF10	1583	1584	19	6	1528	422	1406	1425	1562	5
25	6LU7	COVID-19 main protease	14	3	57	63	64	162	36	396	496	34
26	6NUR	SARS-Coronavirus NSP12	9	1	6	2	16	78	140	265	228	10
27	6VSB	2019-nCoV spike glycoprotein	5	10	8	1	7	75	29	52	55	2
		Total Drug Score	2131	3122	634	723	2928	3000	6396	7104	6783	309

*=Anti-migraine **= Anti-Inflammatory

Figure 2: Selected drugs having significant docking score (≤10)

All the 35 drug molecules screened based on their docking score/rank and selected molecules that lie in the range of 1 to 10. These molecules were marked with having a yellow background in cells. Total 10 drugs found having a lesser docking score. This includes 5 drugs of Anti-HCV followed by 3 Anti-HIV and 1 for anti-inflammatory and anti-migraine.

			Anti-HCV				**	*
No	Protein Code	Name of Tagrget	Elbasvir	Ledipasvir	Paritaprevir	Velpatasvir	Antrafenine	Ergotamin
1	QHD43415_1	Host translation inhibitor (nsp1)	11	13	97	157	4	1
2	QHD43415_2	Non-structural protein 2 (nsp2)	22	25	15	64	37	4
3	QHD43415_3	Papain-like proteinase	6	8	12	9	117	7
4	QHD43415_4	Non-structural protein 4 (nsp4)	4	17	31	34	164	14
5	QHD43415_5	Proteinase 3CL-PRO	2	7	55	15	193	1
6	QHD43415_6	Non-structural protein 6 (nsp6)	9	3	11	18	5	12
7	QHD43415_7	Non-structural protein 7 (nsp7)	103	1078	13	232	748	26
8	QHD43415_8	Non-structural protein 8 (nsp8)	14	2	1	59	462	3
9	QHD43415_9	Non-structural protein 9 (nsp9)	12	10	19	38	54	51
10	QHD43415_10	Non-structural protein 10 (nsp10)	62	128	37	5	58	3
11	QHD43415_11	RNA-directed RNA polymerase (RdRp)	22	4	2	56	198	7
12	QHD43415_12	Helicase (Hel)	4	3	2	12	312	8
13	QHD43415_13	Guanine-N7 methyltransferase (ExoN)	3	2	37	10	236	1
14	QHD43415_14	Endoribonuclease (NendoU)	34	26	6	12	44	56
15	QHD43415_15	2'-O-methyltransferase (2'-O-MT)	35	6	7	289	311	12
16	QHD43416	Surface glycoprotein (S)	2	4	20	30	449	16
17	QHD43417	Potassium sensitive ion channels	66	5	31	95	81	2
18	QHD43418	E-Component (Self Assembly)	11	17	88	21	3	6
19	QHD43419	M-Component (Morphogenesis)	13	5	33	23	3	2
20	QHD43420	ORF6(Virulance)	9	7	57	28	281	3
21	QHD43421	ORF7a (Tethering Supression)	65	98	62	48	141	3
22	QHD43422	ORF8 (Hypothetical)	1	11	13	4	497	3
23	QHD43423	N-Component	10	45	2	54	44	17
24	QHI42199	ORF10	1583	1584	6	1528	1562	5
25	6LU7	COVID-19 main protease	14	3	63	64	496	34
26	6NUR	SARS-Coronavirus NSP12	9	1	2	16	228	10
27	6VSB	2019-nCoV spike glycoprotein	5	10	1	7	55	2

*=Anti-migraine **=Anti-Inflammatory

Figure 3: Suggested best combination for multi-target approach against COVID-19

The drugs from the list removed having overlapping target applicability. The removal identified 6 unique drugs acting on the multiple targets. The combination of these drugs overcomes the lower affinity of the drug molecules to the specific receptors targeting all the proteins available in the present study. Ergotamine shown good binding against 18 receptors, followed by Lepidasvir, Elbasivir and Pariptapevir respectively against 16, 12 and 9 receptors. While velpatasvir and anterafenine showed binding against 5 which might be very useful in a multi-drug combinatorial approach.

					BInding Energy from AnCOVID-19 for Drugs used clinically workdwide									Hepatitis C								HIV							**	*
No	Name of Organism	Name of Tagrget	Protein Code	Control inhibitor	Chloroquine	Oseltamivir	Lopinavir	Hydroxychloroquine	Remdesivir	Darunavir	Ribavarin	Danoprevir	Azithromycin	Elbasvir	Ledipasvir	Eltrombopag	Paritaprevir	Velpatasvir	Daclatasvir	Simeprevir	Ombitasvir	Saquinavir	Ritonavir	Dolutegravir	Maraviroc	Tipranavir	Etravirine	Rilpivirine	Antrafenine	Ergotamine
1	HVC	NS3 Helicase	4WXR	-8.9	-9.9	-6.7	-6.2	-8.3	-8.2	-8.2	-8.4	-9.9	-7.9	-10.6	-10	-8.9	-9.6	-6.9	-10	-8.2	-10.1	-7.7	-5.8	-11.3	-10.1	-8.5	-9.1	-9.1	-8.5	-6.4
2	COVID19	Helicase (Hel)	qhd43415_11		-6.4	-6.3	-8.1	-6	-7.8	-7.8	-7.2	-8.8	-8.1	-11.1	-11.2	-9.4	-11.5	-10.3	-10.4	-9.4	-9.3	-9.8	-8.6	-9.2	-8.2	-9	-8.6	-8.3	-8.1	-10.4
3	HVC	NS5B RNA-dependent RNA polymerase	5QJ0	-10	-11.1	-6.2	-6.8	-9.2	-8.6	-10.3	-8.8	-10.3	-8	-10.5	-10.2	-10.7	-9.4	-7.5	-9.1	-9.5	-11	-7.6	-5.8	-11.6	-9.8	-10.1	-9.8	-9.5	-9	-6.4
4	COVID19	RNA-directed RNA polymerase (RdRp)	qhd43415_12		-5.4	-6.1	-8.3	-6	-7.7	-7.2	-6.6	-8.8	-7.7	-9.8	-10.7	-10.8	-11.4	-9.3	-8.6	-9	-9.1	-9.2	-8.8	-9	-9.4	-9.2	-8.8	-8.5	-8.5	-10.5
5	HVC	NS3/4A D168A protease	6PIV	-11.7	-9.1	-5.7	-6	-7.9	-7.7	-7	-6.5	-7.9	-6.5	-9	-8.7	-7.6	-7.6	-7.8	-8	-7.9	-9.4	-7.2	-5.1	-9.7	-8.7	-7.6	-7.8	-7.9	-6.6	-6.2
6	COVID19	Proteinase 3CL-PRO	qhd43415_5		-5.6	-5.4	-8.7	-5.7	-7.5	-7.6	-5.8	-10.9	-6.8	-9.9	-9.4	-9.5	-8.5	-9.2	-8.9	-7.7	-8.9	-8.1	-8.6	-8.3	-8.4	-8.1	-7.9	-7.7	-7.8	-10.2

**=Anti-Inflametry

*=Anti- Migraine

Figure 4: Comparison of HCV targets as a reference against COVID19.

The results graded on five color green for lowest binding energy followed by greenish-yellow, yellow, orange and red for the highest binding energy for each receptor.