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Anti-HIV and Anti-HCV drugs are the putative inhibitors of RNA-dependent-RNA polymerase activity of NSP12 of the SARS CoV-2 (COVID-19)

Abstract

Corona virus is the emerging infectious viral agent that had to threaten the world with its epidemic since 2003 with SARS and 2013 with MERS virus. This virus again stuck the whole world with its robust pandemic in 2019whena novel form of the corona virus was emerged in and infect the local population of Wuhan, China. The virus named as SARS CoV-2 and the disease caused by this infectious virus is introduced as COVID 19. Since December 2019, this virus took more than 432, 973 lives all around the world. This study elaborates the role of HIV and HCV drug in targeting nsp12 gene of SARS CoV 2 that is responsible for RNA dependent RNA polymerase activity. The work employed homology modelling, structure validation and molecular docking analysis to evaluate the binding affinity and interaction analysis between NSP12 (RdRp) protein and HIV/HCV drugs. Outcome of the study impacted on Nelfinavir (NFV), Raltegravir (RAL) and Delavirdine (DLV) among Anti-HIV and Paritaprevir (PTV), Beclabuvir (BCV) and Ledipasvir (LDV) among Anti-HCV as the most effective inhibitors of SARS CoV-2 RdRp ternary complexes. The drugs have a strong binding affinity with the residues that are present in the active site of RdRp of the virus and essential for its replication. This study establishes significant information in the direction of therapeutic development as we are dealing with the situation where we urgently required medication or vaccine to combat COVID-19. Therefore, this study provides essential molecular information about the FDA approved antiviral drugs that can be used to treat this disease. Importantly, the listed drugs had never prioritized for their effectiveness against COVID-19.

Keywords: COVID-19, NSP12 (RdRp), antiviral drug, molecular docking

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Abbreviations: NCBI, National Centre for Biotechnology Information; SARS CoV-2, severe acute respiratory syndrome Corona virus 2; RdRp, RNA dependent RNA polymerase; CoVs, Coronaviruses; NSP, non-structural protein; NSPs, non-structural protein sequences; PDB, protein data bank; 3D, three dimensional; FDA, Food and Drugs Administration; HCV, Hepatitis C virus; HCMV, human cytomegalovirus; HSV, herpes simplex virus; HPV, human papillomavirus; HIV, human immunodeficiency virus; VZV, Varicella zoster virus; +ssRNA, single stranded RNA of positive sense

Introduction

The start of the year 2020 also creates the epidemic situation in the world as a series of confounded influenza-like cases were reported in China in December 2019. In a very short period, this epidemic changed into a dangerous pandemic and spread to other countries. WHO reported that this pandemic is due to novel Corona virus (2019-CoV) which is a new virus in corona virus group that cause COVID-19.[1-3] The virus can invade into the respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and many other wild animals. This COVID-19 outbreak in china had broken all the parameters and measures that occur in 2002 due to severe acute respiratory syndrome (SARS) in 2002/2003 and the Middle East respiratory syndrome (MERS).[4,5] It is enormously conceivable that novel CoVs emergence is inescapable in the future due to changes in the genome, climate and ecology, and the increased interactions of human with animals. These viruses are one of the largest virus group of order *Nidovirales*. *Nidovirales* consists of *Coronaviridae*, *Arteriviridae*, *Mesoniviridae* and *Roniviridae* families. *Coronaviridae* family is further subdivided into Coronavirinae and Toronavirinae. Coronavirinae is comprised of four genera i.e. alpha, beta, gamma and delta. Novel corona virus or SARS CoV-2 is a part of Beta corona virus genera. SARS CoV-2 is closely related to two relatively bat corona viruses known as bat-SL-CoVZC45 and bat-SL-CoVZXC21 with almost 88% similarity. This similarity range is much different from the SARS corona virus (79%) and MERS corona virus (50%). Moreover, one of the recent reports suggests pangolins as a possible virus reservoir. Pangolin-CoV is 91.02% and 90.55% identical to SARS-CoV-2 and one bat corona virus RaTG13 respectively and the S1 protein of CoV is very much identical to the virus samples obtained from dead pangolin lung samples.[6] Although there have been multiple reports are present on the human transmission of the virus, the exact virus reservoir is remained to find.

The genome is single-stranded RNA of positive sense (+ssRNA) of approximately 30kb size.[7,8] There are mainly two types of proteins that are characterized by structural and non-structural proteins. Structural proteins include spikes, nucleocapsids, matrix and envelope proteins whereas non-structural proteins (NSPs) comprise of RNA dependent RNA polymerase protein (RdRp) that is coded by NSP12 gene.[9,10] The first ORFs covers almost two-thirds of the whole genome length that encodes 16 NSPs. Ribosomal frame shifting between ORF1a and ORF1b leads to the production of polyproteins 1a (pp1a) and polyprotein 1b (pp1b) respectively. RdRp is an essential enzyme for running life cycle of various RNA viruses and therefore continuously

been targeted to eradicate RNA viruses. The genome of CoVs contains 6 ORFs, envelope protein, membrane glycoprotein, nucleocapsid phosphoprotein and surface protein. RdRp is a crucial enzyme in the life cycle of RNA viruses, including coronaviruses. RdRp is targeted in different RNA viruses, including Hepatitis C Virus (HCV), Zika Virus (ZIKV), and coronaviruses (CoVs).[11-16]

Suddenly this disease grabs the attention of all due to a tremendous increase in the number of incidences and deaths cases in China. Till 26th May 2020, total 5,631,824 COVID-19 confirmed cases, 2,399,258 recovered cases and 348,965 deaths were reported in around 205 countries areas and territories.[17] The infrequent arrival and epidemics prompt us that this CoVs is an unembellished universal threat to health. Therefore, there is an imperative prerequisite to developed advanced and effective therapies and vaccines against CoVs. The current study provides some essential aspects about NSP12 gene of SARS CoV-2 that codes RNA dependent RNA polymerase enzyme (RdRp). The enzyme is a pronounced target for previous therapeutic approaches to target several RNA viruses. RdRp is a conserved protein in the corona virus family and comprise two conserved aspartate residues in the active site of the enzyme. Controlling RNA virus infection is a critical task because these viruses mutate with greater velocity as compare to any DNA virus. The study includes homology modelling of NSP12 gene using template-based modelling, its validation and molecular docking analysis with Human Immuno Deficiency Virus (HIV) drugs, HCV drugs and anti-malarial drugs.[18,19]

Materials and methods

Homology modelling of SARS CoV-2RdRp

Complete genome sequence of SARS CoV-2 is available in the National Centre for Biotechnology Information (NCBI) with the accession no. (NC_045512.2) was used for homology modelling.[20] The homology modelling was done by using the SWISS-MODEL server which is freely available, and it built the protein model with the given target-template sequence alignment.[20] The identity matrix showed that NSP12 protein from SARS-CoV is 97% identical with the SARS CoV-2 (orf1ab gene sequence). The identical sequence template PDB ID: 6NUR confirmed which is 97.05% identical to NSP12.[17] The predicted 3D model structure validation was done by SAVES meta server of the University of California Los Angles (UCLA) where some server RAMPAGE, Verify3D and ERRAT which predicted different stereochemical properties.[21-23] The final validated model was qualified for protein quality prediction by using ProQ server which was then optimized to find correct models in contrast to other methods. The protein quality prediction measured two types of predicted score LGscore and MaxSub. LGscore is -log of a P-value and MaxSub ranges from 0-1, where 0 is insignificant and 1 most significant.[24-26] Before moving to the molecular docking, the topological properties of protein structures, including binding pockets was determined by using CASTp 3.0. Few residues are responsible for predicted ligand binding site in the protein where the ligand can reversibly bind. However other amino acid residues of the protein were providing correct orientation and confirmation.[27,28]

Molecular docking

Preparation of Ligand and Receptor

Docking studies were accomplished on Acer Laptop with Intel® Core i3 8th Gen, 12 GB RAM and 1 TB hard disk running on Windows 10 operating system. Antiviral compounds which wereFood and Drugs Administration (FDA) approved drugs proposed from the literature and were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in the SDF format.[29] Chem 3D Pro 14.0 was used for making the 3D structure of the antiviral drugs which is enlisted in Supplementary Table S1.[30] The downloaded files were converted by the PyRx 0.8 tool (FastSpring, Amsterdam, Netherlands) were minimize the 3D structure and produce the dock file in PDBQT format. AutoDockVina is an open-source program which was utilized in all docking experiments.[31,32] 74 compounds were tested against SARS CoV-2 RdRp where 70 compounds were antiviral drugs against different viruses like (HCV, HCMV, HIV, HSV, HPV, VZV and Influenza viruses) and rest compounds are in a clinical trial or already published as effective in various manner.

Table S1 Antiviral drugs against SARS COV-2 NSP 12 (RdRp)

S. No	Drug name	Abbreviation	Virus Family
1	Abacavir	ABC	HIV
2	Acyclovir	ACV	HSV,VZV
3	Adefovir	-	HBV
4	Amantadine	AMT	Influenza virus A
5	Amprenavir	APV	HIV-1
6	Asunaprevir	ASV	HCV-1
7	Atazanavir	ATV	HIV
8	Beclabuvir	BCV	HCV-1
9	Boceprevir	BOC	HCV-1
10	Brivudine	BVDU	HSV-1,VZV
11	Catechin	SINE	HPV
12	Cidofovir	CDV	HCMV
13	Cobicistat	COBI	HIV
14	Daclatasvir	DCV	HCV-1
15	Darunavir	DRV	HIV
16	Dasabuvir	DAS	HCV-1
17	Delavirdine	DLV	HIV-1
18	Didanosine	ddI	HIV
19	Dolutegravir	DTG	HIV
20	Docosanol	C22	HSV
21	Efavirenz	EFV	HIV-1
22	Elbasvir	EBR	HCV-1 or 4
23	Elvitegravir	EVG	HIV
24	Emtricitabine	(-) FTC	HIV
25	Entecavir	ETV	HBV
26	Entecavirine	ETR	HIV-1
27	Famciclovir	FCV	HSV,VZV
28	Favipiravir	FPV	Influenza virus A, B & C
29	Fosamprenavir	FPA	HIV-1
30	Foscarnet	PFA	HCMV, HSB
31	Ganciclovir	GCV	HCMV

Table Continued...

S. No	Drug name	Abbreviation	Virus Family
32	Grazoprevir	GZR	HCV-4
33	Idoxuridine	IDU	HSV-1
34	Indinavir	IDV	HIV
35	Lamivudine	3TC	HIV, HBV
36	Laninamivir	-	Influenza virus A &B
37	Ledipasvir	LDV	HCV-1
38	Letermovir	-	HCMV
39	Lopinavir	LPV	HIV
40	Maraviroc	MVC	HIV
41	Nelfinavir	NFV	HIV
42	Nevirapine	NVP	HIV-1
43	Ombitasvir	OBV	HCV-1
44	Oseltamivir	OTV	Influenza virus A & B
45	Paritaprevir	PTV	HCV-1
46	Penciclovir	PCV	HSV
47	Peramivir	PRV	Influenza virus A & B
48	Podofilox	PDX	HPV
49	Raltegravir	RAL	HIV
50	Ribavirin	RBV	HCV-1
51	Rilpivirine	RPV	HIV-1
52	Rimantadine	RIM	Influenza virus A
53	Ritonavir	RTV	HIV
54	Saquinavir	SQV	HIV
55	Simeprevir	SMV	HCV-1
56	Sofosbuvir	SOF	HCV-3
57	Stavudine	d4T	HIV
58	Telaprevir	TVR	HCV-1
59	Telbivudine	LdT	HBV
60	Tenofovir alafenamide	TAF	HIV
61	Tenofovir	-	HIV
62	Tipranavir	TPV	HIV-1
63	Trifluridine	TFT	HSV
64	Valacyclovir	VACV	HSV,VZV
65	Valganciclovir	VGCV	HCMV
66	Vaniprevir	VPV	HC-1
67	Vidarabine	VDR	HSV,VZV
68	Zalcitabine	ddC	HIV
69	Zanamivir	ZAN	Influenza virus A & B
70	Zidovudine	AZT	HIV

Top hit selection against SARS CoV-2 RdRp

Molecular docking analysis of SARS HCoV-2 RdRp was done by determining binding affinity scores (docking scores) based on top 10 hits were selected out of 74 antiviral drugs. The selected drugs further analyzed based on the interactions where false-positive were avoided and highly interactive partners were selected having a binding pocket of SARS CoV-2 RdRp.

Interaction analysis: Visualization and evaluation

The interaction analysis of the protein-ligand and interaction of the binding sites were studied by using PyMOL and Chimera.[33-35] The possible dock conformations of the 2D ligand-receptor interactions was accomplished using Discovery Studio.[36] Further, binding analysis using the visualization approach was carried out to understand the binding pattern of the drug with protein.[37-41]

Result and discussion

Modelling of SARS CoV-2 RdRp

Homology modelling of SARS CoV-2 RdRp was done which showed the sequence identity 97.05% with the template PDB ID: 6NUR (SARS-NSP12) (Figure 1). This 6NUR structure is the complex structure of NSP12 with NSP7 and NSP8 with 3.1 Å resolution.[17] The generated SARS CoV-2 RdRp structure QMEAN (qualitative model energy analysis) score is -0.68 which was the optimized score for further study.[20] The model also includes two zinc ions and it encompasses residues 4501-5315 of the SARS CoV-2 orf1ab. The model was validated by SAVES, the Verify3D server evaluated the scoring as 91.16% of the residues have average 3D-1D score >= 0.2 and the score pass while the quality factor predicted by ERRAT server was 95.9839.[22,23] The Ramachandran plot showed that 92.5% residues were in the allowed region, 7.2% residues in the additional allowed region 0.3% else in the generously allowed region and no residues in the disallowed region (see the Ramachandran plot in Figure S1).[21] The protein quality estimation by ProQ server found the LG score was 6.636 and MaxSub score was 0.610 which was predicted to be asquality of good model.[26] Superimposed cartoon model of SARS-NSP12 and SARS CoV-2 RdRp in red active sites residues region (Figure 2a & 2b) was shown using CASTp 3.0 serve. The SARS CoV-2 RdRp model showed the A chain and two cofactor ions between triphosphate moiety.[27]

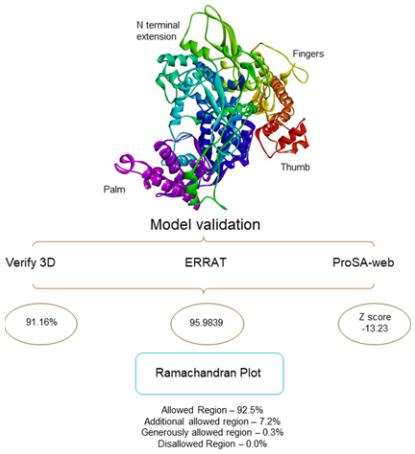

Figure 1 Homology modelling and Model validation: The SARS CoV-2 RdRp model built by Swiss model server with template PDBID: 6NUR and sequence identity is 97.05%. Model validation by SAVES metaserver were stereochemistry of the model was good, with 100% residues are in allowed region.

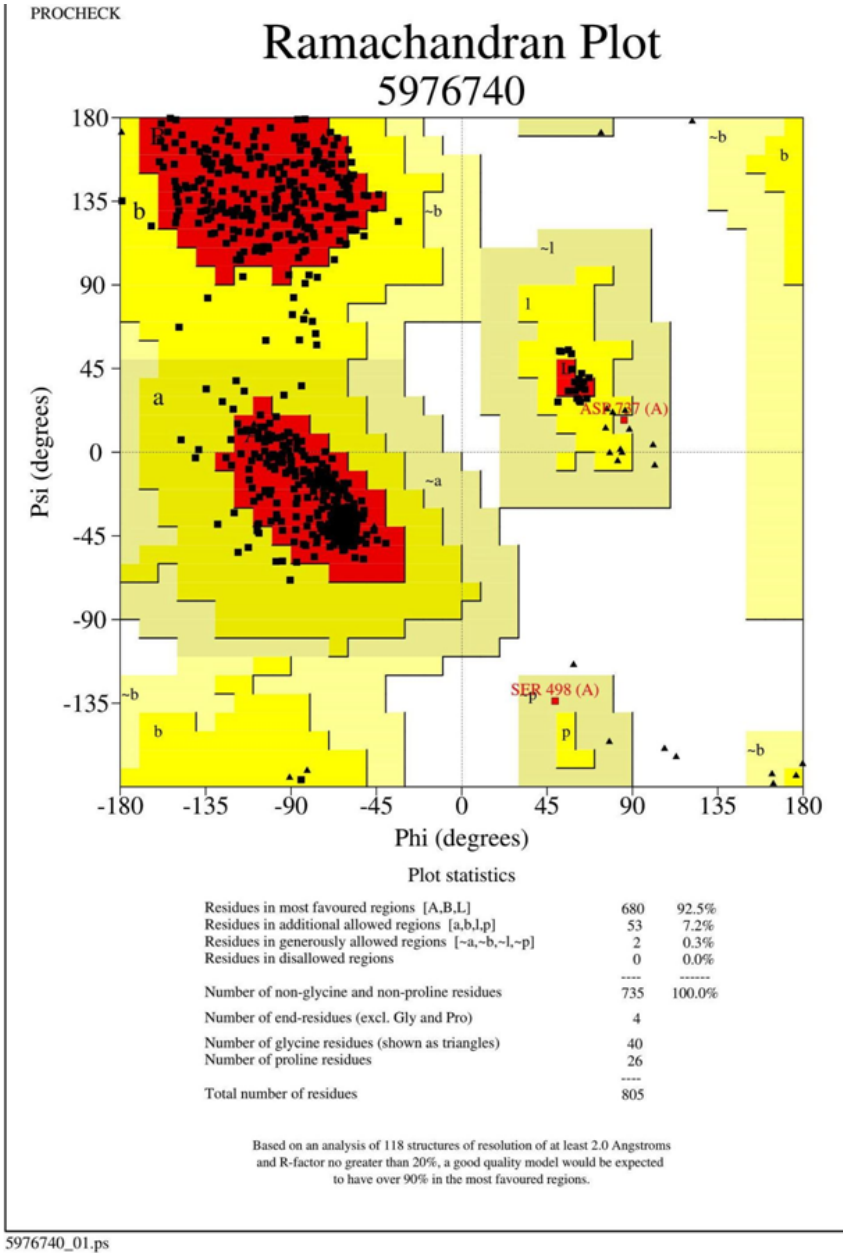

Figure S1 Ramachandran plot by RAMPAGE: In Ramachandran plot shows 100% residues are in allowed region.

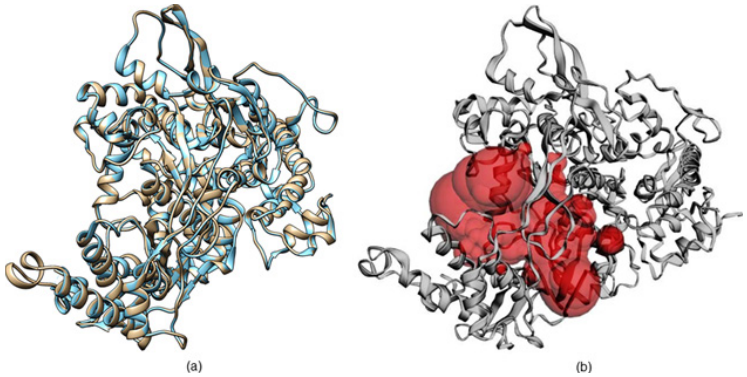

Figure 2 The three-dimensional structure SARS HCoV-2 RpRd: (a) The superimposed three-dimensional cartoon representation of SARS CoV-2 RpRd in (Grey) and the SARS-CoV RdRp in (Sky blue) by using Chimera. (b) Homology model of SARS CoV-2 RpRd predicted binding site residues in (red color) using CASTp 3.0.

Citation: Beg MA, Athar F. Anti-HIV and Anti-HCV drugs are the putative inhibitors of RNA-dependent-RNA polymerase activity of NSP12 of the SARS CoV-2 (COVID-19). *Pharm Pharmacol Int J.* 2020;8(3):163–172. DOI: 10.15406/ppij.2020.08.00292

Table S2 Docking Score (binding affinity) of antiviral drugs against SARS COV-2 NSP 12 (RdRp)

S.No.	Drugs Name	Molecular formula	Molecular weight	Docking score
1	Abacavir	$C_{14}H_{18}N_6O$	286.33	-7.1
2	Acyclovir	$C_8H_{11}N_5O_3$	225.2	-5.9
3	Adefovir	$C_8H_{12}N_5O_4P$	273.19	-6.7
4	Amantadine	$C_{10}H_{17}N$	151.25	-5.5
5	Amprenavir	$C_{25}H_{35}N_3O_6S$	505.6	-7.2
6	Asunaprevir	$C_{35}H_{46}C_lN_5O_9S$	748.3	-7.9
7	Atazanavir	$C_{38}H_{52}N_6O_7$	704.9	-7.5
8	Azithromycin	$C_{38}H_{72}N_2O_{12}$	749	-7.9
9	Beclabuvir	$C_{36}H_{45}N_5O_5S$	659.8	-9.9
10	Boceprevir	$C_{27}H_{45}N_5O_5$	519.7	-8
11	Brivudine	$C_{11}H_{13}BrN_2O_5$	333.13	-6.2
12	Catechin	$C_{15}H_{14}O_6$	290.27	-7.5
13	Cidofovir	$C_8H_{14}N_3O_6P$	279.19	-5.7
14	Cobicistat	$C_{40}H_{53}N_7O_5S_2$	776	-7.8
15	Daclatasvir	$C_{40}H_{50}N_8O_6$	738.9	-8.4
16	Darunavir	$C_{27}H_{37}N_3O_7S$	547.7	-7.9
17	Dasabuvir	$C_{26}H_{27}N_3O_5S$	493.6	-8.8
18	Delavirdine	$C_{22}H_{28}N_6O_3S$	456.6	-8.5
19	Didanosine	$C_{10}H_{12}N_4O_3$	236.23	-6.2
20	Dolutegravir	$C_{20}H_{19}F_2N_3O_5$	419.4	-8
21	Efavirenz	$C_{14}H_9C_lF_3NO_2$	315.67	-7.7
22	Elbasvir	$C_{49}H_{55}N_9O_7$	882	-9.5
23	Elvitegravir	$C_{23}H_{23}C_lFNO_5$	447.9	-7.3
24	Emtricitabine	$C_8H_{10}FN_3O_3S$	247.25	-6
25	Entecavir	$C_{12}H_{15}N_5O_3$	277.28	-7.1
26	Etravirine	$C_{20}H_{15}BrN_6O$	435.3	-7.1
27	Famciclovir	$C_{14}H_{19}N_5O_4$	321.33	-6.3
28	Favipiravir	$C_5H_4FN_3O_2$	157.1	-5.3
29	Fosamprenavir	$C_{25}H_{36}N_3O_9PS$	585.6	-6.9
30	Foscarnet	CH_3O_5P	126.01	-4.8
31	FV 100	$C_{27}H_{35}N_3O_6$	497.6	-7.8
32	Ganciclovir	$C_9H_{13}N_5O_4$	255.23	-6.9
33	Grazoprevir	$C_{38}H_{50}N_6O_9S$	766.9	ND
34	Hydroxychloroquine	$C_{18}H_{26}C_lN_3O$	335.9	-6
35	Idoxuridine	$C_9H_{11}IN_2O_5$	354.1	-6
36	IDX-184	$C_{25}H_{35}N_6O_9PS$	626.6	-7.3
37	Imiquimod	$C_{14}H_{16}N_4$	240.3	-6.8
38	Indinavir	$C_{36}H_{47}N_5O_4$	613.8	-8.4
39	Lamivudine	$C_8H_{11}N_3O_3S$	229.26	-5.6
40	Laninamivir	$C_{13}H_{22}N_4O_7$	346.34	-7
41	Ledipasvir	$C_{49}H_{54}F_2N_8O_6$	889	-9.7
42	Letermovir	$C_{29}H_{28}F_4N_4O_4$	572.5	-8.3
43	Lopinavir	$C_{37}H_{48}N_4O_5$	628.8	-7.9
44	Maraviroc	$C_{29}H_{41}F_2N_5O$	513.7	-8.1
45	Nelfinavir	$C_{32}H_{45}N_3O_4S$	567.8	-8.8
46	Nevirapine	$C_{15}H_{14}N_{4O}$	266.3	-7.1
47	Ombitasvir	$C_{50}H_{67}N_7O_8$	894.1	-7.8
48	Oseltamivir	$C_{16}H_{28}N_2O_4$	312.4	-5.6
49	Paritaprevir	$C_{40}H_{43}N_7O_7S$	765.9	-10
50	Penciclovir	$C_{10}H_{15}N_5O_3$	253.26	-5.4
51	Peramivir	$C_{15}H_{28}N_4O_4$	328.41	-7.3
52	Podofilox	$C_{22}H_{22}O_8$	414.4	-7.3
53	Raltegravir	$C_{20}H_{21}FN_6O_5$	444.4	-8.7
54	Ribavirin	$C_8H_{12}N_4O_5$	244.2	-6.3
55	Rilpivirine	$C_{22}H_{18}N_6$	366.4	-8.4
56	Rimantadine	$C_{12}H_{21}N$	179.3	-6.1
57	Ritonavir	$C_{37}H_{48}N_6O_5S_2$	720.9	-8
58	Saquinavir	$C_{38}H_{50}N_6O_5$	670.8	-9.6
59	Simeprevir	$C_{38}H_{47}N_5O_7S_2$	749.9	-9.4
60	Sofosbuvir	$C_{22}H_{29}FN_3O_9P$	529.5	-8
61	Stavudine	$C_{10}H_{12}N_2O_4$	224.21	-6.1
62	Telaprevir	$C_{36}H_{53}N_7O_6$	679.8	-7.9
63	Telbivudine	$C_{10}H_{14}N_2O_5$	242.23	-6.9
64	Tenofovir alafenamide	$C_{21}H_{29}N_6O_5P$	476.5	-7.1
65	Tenofovir	$C_9H_{14}N_5O_4P$	287.21	-6.1
66	Tipranavir	$C_{31}H_{33}F_3N_2O_5S$	602.7	-8.2
67	Trifluridine	$C_{10}H_{11}F_3N_2O_5$	296.2	-6.7
68	Valacyclovir	$C_{13}H_{20}N_6O_4$	324.34	-6.2
69	Valganciclovir	$C_{14}H_{22}N_6O_5$	354.36	-6.6
70	Vaniprevir	$C_{38}H_{55}N_5O_9S$	757.9	-9.9
71	Vidarabine	$C_{10}H_{13}N_5O_4$	267.24	-6.4
72	Zalcitabine	$C_9H_{13}N_3O_3$	211.22	-5.8
73	Zanamivir	$C_{12}H_{20}N_4O_7$	332.31	-6.4
74	Zidovudine	$C_{10}H_{13}N_5O_4$	267.24	-6.3

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Table 1 Selected antiviral drugs against SARS COV-2 NSP 12 (RdRp)

S.No.	Drug name	Abv.	Docking score	Mode of action
HIV Drugs				
1	Delavirdine	DLV	-8.5	High toxicity not to be used as much
2	Dolutegravir	DTG	-8	Targets HIV integrase to inhibit the integration of viral DNA into human chromosomes
3	Indinavir	IDV	-8.4	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins
4	Maraviroc	MVC	-8.1	Blocks GP120-CCR5 interaction to inhibit HIV entry
5	Nelfinavir	NFV	-8.8	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins
6	Raltegravir	RAL	-8.7	Targets HIV integrase to inhibit the integration of viral DNA into human chromosomes
7	Rilpivirine	RPV	-8.4	Binds directly to HIV RT and inhibits DNA synthesis
8	Ritonavir	RTV	-8	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins
9	Saquinavir	SQV	-9.6	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins
10	Tipranavir	TPV	-8.2	Blocks the active site of HIV protease to prevent cleavage of viral precursor proteins
HCV drugs				
1	Beclabuvir	BCV	-9.9	Inhibits activity of the VZV DNA polymerase
2	Boceprevir	BOC	-8	Protease inhibitor
3	Daclatasvir	DCV	-8.4	Targets NS5A and NS3/4A protease to prevent HCV replication
4	Elbasvir	EBR	-9.5	Inhibit activities of NS5A and NS3/4A protease, respectively
5	Ledipasvir	LDV	-9.7	Harvoni inhibits HCV NS5A and NS5B polymerase to prevent RNA replication
6	Paritaprevir	PTV	-10	Inhibits activities of HCV NS5A, NS5B polymerase, and NS3/4A protease
7	Simeprevir	SMV	-9.4	Target HCV NS5B and NS3/4 protease, respectively
8	Sofosbuvir	SOF	-8	Target HCV NS5B and NS3/4 protease, respectively
9	Vaniprevir	VPV	-9.9	Protease inhibitor

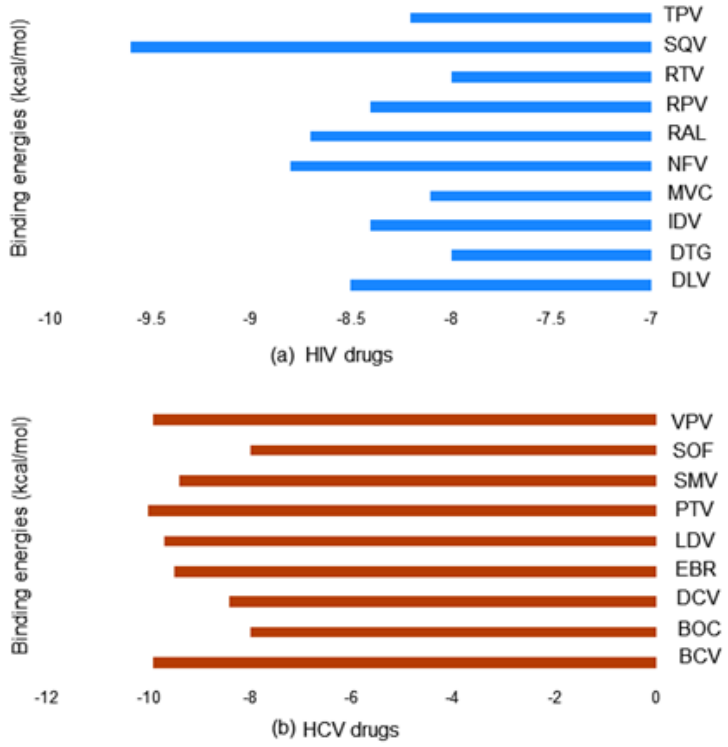

Figure 3 Top hit selected by molecular docking: By using AutoDock Vina molecular docking experiment calculated top binding energies (docking scores) of HIV drugs in (blue) are Tipranavir (TPV), Saquinavir (SQV), Ritonavir (RTV), Rilpivirine (RPV), Raltegravir (RAL), Nelfinavir (NFV), Maraviroc (MVC), Indinavir (IDV), Dolutegravir (DTG), Delavirdine (DLV) and HCV drugs in (brown) are Vaniprevir (VPV), Sofosbuvir (SOF), Simeprevir (SMV), Paritaprevir (PTV), Ledipasvir (LDV), Elbasvir (EBR), Daclatasvir (DCV), Boceprevir (BOC), Beclabuvir (BCV) against SARS CoV-2 RdRp.

Citation: Beg MA, Athar F. Anti-HIV and Anti-HCV drugs are the putative inhibitors of RNA-dependent-RNA polymerase activity of NSP12 of the SARS CoV-2 (COVID-19). *Pharm Pharmacol Int J.* 2020;8(3):163–172. DOI: 10.15406/ppij.2020.08.00292

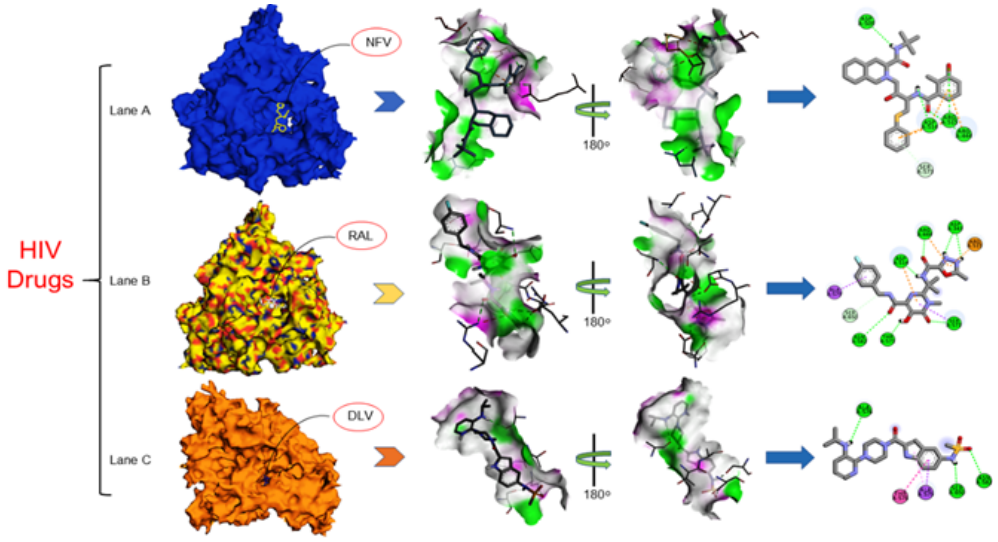

Figure 4 Interaction studies of SARS CoV-2 RdRp against HIV drugs Nelfinavir (NFV), Raltegravir (RAL), Delavirdine (DLV) drugs: Crystal structure of SARS CoV-2in (Lane A) Interactions of active site residues in SCoV 2-NFVcomplex (Lane B) Interactions of active site residues in SCoV 2-RALcomplex (Lane C) Interactions of active site residues in SCoV 2-DLVcomplex and the 2D interaction analysis done by Discovery studio.

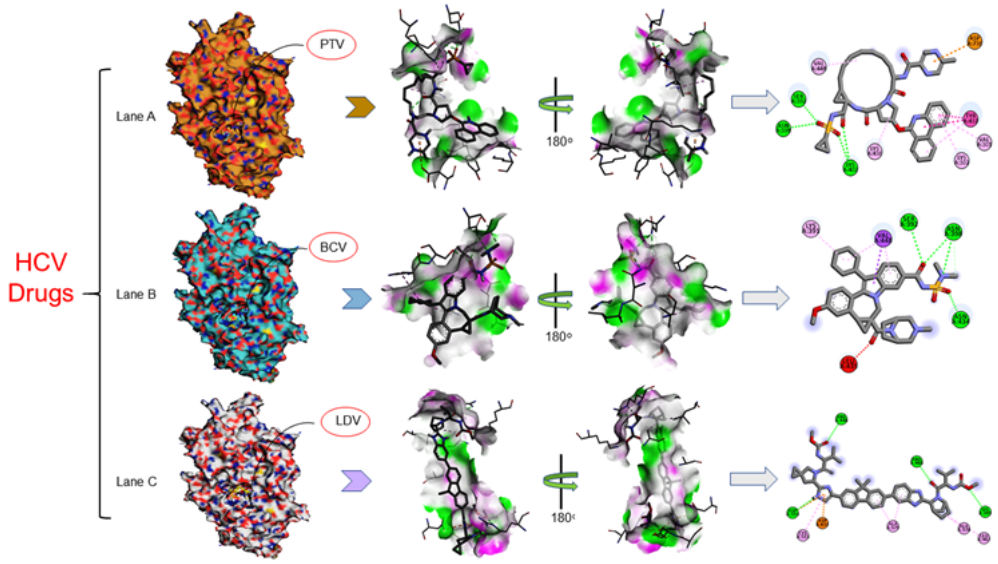

Figure 5 Interaction studies of SARS CoV-2 RdRp against HCV drugs Paritaprevir (PTV), Beclabuvir (BCV), Ledipasvir (LDV) drugs: Crystal structure of SARS CoV-2in (Lane A) Interactions of active site residues in SCoV 2-PTVcomplex (Lane B) Interactions of active site residues in SCoV 2-BCVcomplex (Lane C) Interactions of active site residues in SCoV 2-LDVcomplex and the 2D interaction analysis done by Discovery studio.

Table 2 Selected antiviral drugs with their interacting residues of SARS COV-2 NSP 12 (RdRp)

S.No.	Compound Name	Interacting Residues					
		C-H bond	H-bond	π-Anion	π-Sigma	Amide π stacked	Alkyl
HIV Drugs							
1	Delavirdine		ALA 576		ALA 579	THR 578	
			ASN 582				
			SER 650				
2	Nelfinavir	SER 573	ARG 444				
			ASP 509				
			ASP 514				
			ARG 515				

Citation: Beg MA, Athar F. Anti-HIV and Anti-HCV drugs are the putative inhibitors of RNA-dependent-RNA polymerase activity of NSP12 of the SARS CoV-2 (COVID-19). *Pharm Pharmacol Int J.* 2020;8(3):163–172. DOI: 10.15406/ppij.2020.08.00292

Table Continued...

S.No.	Compound Name	Interacting Residues					
		C-H bond	H-bond	π-Anion	π-Sigma	Amide π stacked	Alkyl
3	Raltegravir	SER 650	ASP 343	ARG 515			
			ARG 444				
			ASP 514				
			THR 571				
			SER 573				
			ASN 582				
HCV Drugs							
1	Beclabuvir		SER 392		VAL 448		LYS 391
			ASN 398				
			ASN 434				
2	Ledipasvir		LYS 391	ASP 651			LEU 467
			ARG 446				CYS 513
			ARG 460				ALA 576
			ASP 514				ALA 579
3	Paritaprevir		SER 392	ASP736		THR 437	VAL 301
			ASN 398				LYS302
			LYS 402				LYS 436
							VAL 448

Docking identifies (+ssRNA) antiviral drugs as a potent inhibitor

In molecular docking, the screening of 74 antiviral drugs produced log files, where the affinity (kcal/mol) obtained and docked poses for discrete compounds were analyzed. This log-file screen-out because of the analysis of binding score or docking score and the docking scores are enlisted in Supplementary Table S2. Molecular docking result having best binding affinity (docking score) was screened based on all the log files and output files and top 19 antiviral drugs were selected that were screened based on binding energies (kcal/mol) (Figure 3).[32,41] HIV drugs (Delavirdine, Dolutegravir, Indinavir, Maraviroc, Nelfinavir, Raltegravir, Rilpivirine, Ritonavir, Saquinavir and Tipranavir) and HCV drugs (Beclabuvir, Boceprevir, Daclatasvir, Elbasvir, Ledipasvir, Paritaprevir, Simeprevir, Sofosbuvir and Vaniprevir) was used in the study were enlisted in Table 1.[29] Furthermore, the interaction analysis of selected drugs with the SARS CoV-2 RdRp on the specific sites highlights that the selected antiviral drug putatively acts as an inhibitor against the respective enzymes.

Interaction studies of antiviral drugs against SARS CoV-2 RdRp

The interaction analysis of SARS CoV-2 RdRp ternary complexes suggested the in HIV-drugs as the putative inhibitor against SARS CoV-2 RdRp isNelfinavir (NFV), Raltegravir (RAL) and Delavirdine (DLV) shown in Figure 4 and in HCV-drugs suggested inhibitor Paritaprevir (PTV), Beclabuvir (BCV) and Ledipasvir (LDV) shown in Figure 5 have closely interacted with active sites and substrate binding domains.[33] The interaction study suggested that the active sites consist of several important active site residues involved in the interaction are VAL_{301}, LYS_{302}, ASN_{434}, ARG_{346}, LYS_{391}, SER_{392}, ASN_{398}, LYS_{402}, LYS_{436}, THR_{437}, ARG_{444}, VAL_{448}, ARG_{460}, LEU_{467}, ASP_{509}, CYS_{513}, ASP_{514}, ARG_{515}, SER_{570}, THR_{571}, SER_{573}, ALA_{576}, THR_{578}, ALA_{579}, ASN_{582}, SER_{650}, ASP_{651} and ASP_{736}. This interaction study confirmed that there was the involvement of Carbon-Hydrogen bond (C-H bond), Hydrogen bond (H-bond), Pi-Anion bond (π-Anion), Pi- Sigma bond (π-Sigma), Amide Pi-stacked bond (Amide π stacked) and Alkyl bond. The important points of interaction study between antiviral drugs against SARS CoV-2 RdRp were enlisted in Table 2.[36] The interaction study also suggested that the interaction between the drug and RdRp enzyme is a strong interaction and therefore targeting this enzyme with the listed inhibitors might be an advantageous step in the direction of therapeutic development.

Concluding remarks

We are currently dealing with the global health emergency of COVID-19 pandemic. The disease almost covers every country with devastating nature in China, Italy, United States of America, Brazil and Spain. The disease had already accounted for almost 432, 973 deaths on the worldwide level. It is the third major outbreak of corona virus after SARS and MERS epidemic. Antiviral drugs have been developing using that target viral RNA polymerase. The present study deals with anti-viral drugs to declare their effectiveness against COVID-19. The study includes Anti-HIV drugs Delavirdine, Nelfinavir and Raltegravir and Anti-HCV drugs Beclabuvir, Ledipasvir and Paritaprevir most effective binding partner among various listed drugs. The binding study establishes a significant platform for further testing the binding parameters in in-vitro condition and beneficial for determining inhibitory effect of the inhibitor against the enzyme. Especially, the advanced therapeutic target generation would need essential clinical and experimental studies for further and strongly confirming drug effectiveness against disease.

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Conflicts of interest

The authors declare that they have no potential conflict of interests.

Author's contributions

Md Amjad Beg: Conceptualization idea, Methodology designing, Software handling, writing manuscript and evaluate results.

Dr Fareeda Athar: Reviewing and corresponding author.

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